"FORMULATION, OPTIMIZATION & EVALUATION OF MOUTH DISSOLVING TABLET OF AMLOPDIPINE BESYLATE. "

A THESIS SUBMITTED TO

NIRMA UNIVERSITY

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR

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IN

PHARMACEUTICAL TECHNOLOGY &

BIOPHARMACEUTICS

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CERTIFICATE

*This is to certify that **Mr./Ms. XYZ** has prepared his thesis entitled "Formulation and Development of … drug delivery system", in partial fulfillment for the award of M. Pharm. degree of the Nirma University, under our guidance. He/She has carried out the work at the Department of Pharmaceutics & Pharmaceutical Technology, Institute of Pharmacy, Nirma University.*

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DECLARATION

I declare that the thesis "Formulation and Development of … drug delivery system" has been prepared by me under the guidance of Dr. Tejal A. Mehta, Professor, and Mr./Ms. ABC, Assistant Professor, Department of Pharmaceutics & Pharmaceutical Technology, Institute of Pharmacy, Nirma University. No part of this thesis has formed the basis for the award of any degree or fellowship previously.

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AIM OF PRESENT INVESTIGATION

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine had a strong blocking action on both the L-type and N-type Ca2+ channels expressed in the oocyte.

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. Approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Elimination half-life is about 30 to 50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Following administration of therapeutic doses to patients with hypertension, Amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

Conventional amlodipine besylate tablets available in the market are not suitable for acute hypertension conditions where quick onset of action is required. Besides, the conventional tablets also show poor patient compliance particularly by the geriatric & pediatric patients who experience difficulty in swallowing tablets or capsules which is a common problem among all age group. For these reason, tablet that can dissolve or disintegrate in oral cavity, have attracted a great deal of attention to provide the patients with the most conventional mode of administration and to overcome the problems of poor bioavailability.

A solid oral dosage form that dissolves or disintegrates rapidly in oral cavity resulting in a solution or suspension with out need for water is known as fast dispersing

dosage form or Mouth dissolving tablets. When this type of tablet is placed in to the mouth, the saliva will rapidly dissolve tablet.

Thus present work was aimed to formulate MDT of amlodipine besylate using super disintegrants which provide better dissolution.

Identification of amlodipine was carried out by using melting point estimation, by UV spectrophotometrically, and by IR spectroscopy & drug was identified as pure amlodipine besylate. Estimation of amlodipine was carried out by standard curve in 0.01 N HCl media.

A direct compression technique was used to prepare MDT as it is economical, simple, less time consuming. The formulations were evaluated for % friability, wetting time, disintegration time, & in-vitro drug release study.

3^2 factorial design was employed to study the effect of independent variables, concentration of crospovidone & HPC-EXF on disintegration time & friability by using contour plot & 3 D surface plot

Amlodipine besylate MDTs was compared with Amlodipine besylate conventional release tablets. By experiments, it was estimated that Amlodipine besylate MDT was dissolved more rapidly than Amlodipine besylate conventional release tablets

Accelerated Stability study of Amlodipine besylate MDT was carried out, and no higher degradation was seen in studies.

An attempt was made to prepare MDT of Amlodipine besylate with appropriate mechanical strength which would disintegrate in oral cavity in less than 30 secs & provide immediate control over hypertension due to faster release of amlodipine in to GI tract & total drug would be released in with in 5 mins

1. MOUTH DISSOLVE TABLETs

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desire therapeutics concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. This is possible through administration of conventional dosage form in a particular dose and at a particular frequency.[1] Thus drug may be administered by variety of routes in a variety of dosage forms.

Drugs are more frequently taken by oral administration. Although a few drugs taken orally are intended to be dissolved within the mouth, the vast majority of drugs taken orally are swallowed. Compared with alternate routes, the oral route of drug administration is the most popular and has been successfully used for conventional delivery of drug. It is considered most natural, uncomplicated, convenient, safe means of administering drugs, greater flexibility in dosage form design, ease of production and low cost.[2]

Tablets and hard gelatin capsules constitute a major portion of the drug delivery systems that are currently available. However, many patient groups such as elderly, children, and patients mentally retarted, uncooperative, nauseated, or on reduced liquid intake diets have difficulty in swallowing these dosage forms. Many elderly persons face difficulties in administering conventional oral dosage forms because of hand tremors and dysphasia. Swallowing problem is common in children because of their underdeveloped muscular and nervous systems. In some cases like motion sickness, sudden episodes of allergic attack or coughing, and during unavailability of water, swallowing conventional tablets is difficult. To fulfill these medical needs, formulators have devoted considerable efforts for developing a novel type of dosage form for oral administration known as ***MOUTH DISSOLVING TABLETs (MDT).***[3]

MOUTH DISSOLVING TABLET [4, 5]

This is an innovative tablet technology where the dosage form containing active pharmaceutical ingredients disintegrates rapidly, usually in a matter of seconds, without the need for water, providing optimal convenience to the patient. Innovators and inventor companies have given these tablets various names such as orally disintegrating tablets (ODT), mouth dissolving (MD), fast melting, fast dissolving or Orodisperse.

The European Pharmacopoeia defines Orodisperse as a tablet that can be placed in the mouth where it disperses rapidly before swallowing. Researchers have formulated MDT for various categories of drugs, which are used for therapy in which rapid peak plasma concentration is required to achieve desired pharmacological response. These include neuroleptics, cardiovascular agents, analgesics, anti-allergic and drugs for erectile dysfunction.

MOUTH DISSOLVING TABLET (MDT) is a solid unit dosage form containing drugs that disintegrates rapidly and dissolves in the mouth without taking water within 60seconds or less. Drug absorption through local oral–mucosal and through pre and post gastric parts of G.I.T. MDTs are also called as Oro-disperse, mouth dissolving, rapidly disintegrating, fast melt, quick dissolve and freeze dried wafers.

MDT are generally classified into two types

ORAL SUBLINGUAL TABLET:

- MDT as a solid dosage form which disintegrates rapidly, within a matter of seconds, under the tongue.

ORAL DELAYED RELEASE:

- when place upon the tongue, releases a drug (or drugs) at a time other than promptly after administration.

CHARACTERISTICS OF MOUTH DISSOLVING TABLET:

- Convenient and easy to administer as does not require water for oral administration
- Durable and sufficient strength to withstand the rigors of the manufacturing process and manufacturing handling
- Pleasant mouth feel
- Insensitive to environmental conditions such as humidity and temperature.
- Improved taste without any residue in the mouth after disintegration
- Adaptable and amenable to existing processing and packaging machinery
- Cost effective
- Compatible with taste masking

BENEFITS OF MOUTH DISSOLVING TABLET:

- Administered without water, anywhere, any time.
- Suitability for geriatric and pediatric patients, who experience difficulties in swallowing and for the other groups that may experience problems using conventional oral dosage form, due to being mentally ill, the developmentally disable and the patients who are un-cooperative, or are on reduced liquid intake plans or are nauseated
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid on set of action required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

LIMITATIONS OF MOUTH DISSOLVING TABLET:

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

SELECTION OF DRUG :

The ideal characteristics[1] of a drug for in vivo dissolution from an MDT include

- No bitter taste
- Dose lower than 20mg
- Small to moderate molecular weight
- Good stability in water and saliva
- Partially non ionized at the oral cavities pH
- Ability to diffuse and partition into the epithelium of the upper GIT (logp>1, or preferably>2)
- Ability to permeate oral mucosal tissue

UNSUITABLE DRUG CHARACTERSTICS FOR MDT;

- Short half-life and frequent dosing
- Very bitter or otherwise unacceptable taste because taste masking cannot be achieved
- Required controlled or sustained release.

➢ *Taste masking Methods:*

The success of this delivery system is because of good taste. Taste is a chemical reaction derived from sensory responses from the four main taste perceptions salt, sour, bitter and sweet[5]. The drugs are mostly bitter in nature. Skillful taste masking is needed to hide the bitter taste in MDT formulations. This can be achieved by using combination of right flavour and right sweetners. The taste masking in MDT has more influences on dissolution method development, specifications, and testing. Following methods are used in Taste masking is given as follows:

- Simple wet granulation method or roller compaction[6] of other excipients. Spray drying can also employed to shroud the drug.
- Co-sifting method the large quantities of water soluble polymers are used as an excipient. Drugs can be sifted twice or thrice in small particle size mesh with excipients such as sweeteners and flavors etc.
- Hydroxy propyl methyl cellulose, Ethyl cellulose, Methacrylates, Kollicoat, Polyvinyl pyrollidone polymers can be used to coat to mask the taste.
- Cyclodextrins can be used to trap or complex, cyclodextrin help to solubilze many drugs.
- Drug complexation[7] with resinates are insoluble and no taste in oral cavity. With the correct selection of the ion exchange resin, the drug will not be released in the mouth so that the patient does not taste the drug when it is swallowed. When the drug resinate comes into contact with the gastrointestinal fluids, such as the acid of the stomach, the drug is released from the resinate, directly into solution and then absorbed in the usual way. The resin passes through the GI tract without being absorbed. Examples of drugs where this technique has been successfully demonstrated include ranitidine, risperidone and paroxetine.
- Other methods include hot melt and supercritical fluids.

TECHNIQUES USED FOR THE FORMULATION OF MOUTH DISSOLVING TABLET:

Many techniques have been reported by various researchers for the formulation of MOUTH DISSOLVING TABLET.

1. Freeze-Drying or Lyophilization: [6, 7, 8]

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of MDT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is dosed by weight and poured in the wells of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminium foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophillization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

2. Tablet Molding: [9, 10]

Molding process is of two types i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydroalcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is than removed by air-drying. The tablets manufactured in this manner are less compact than the compressed

tablets and posses a porous structure that hastens dissolution. The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°C under vacuum. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology. The taste masked drug particles were prepared by spray congealing, a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol, and an active ingredient, into a lactose based tablet triturate form. Compared to the lyophillization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture.

3. Spray Drying: [11, 12]

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose or crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate & croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

4. Sublimation: [13, 14, 15]

To generate a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride may be compressed

along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane, benzene can be used as pore forming agents.

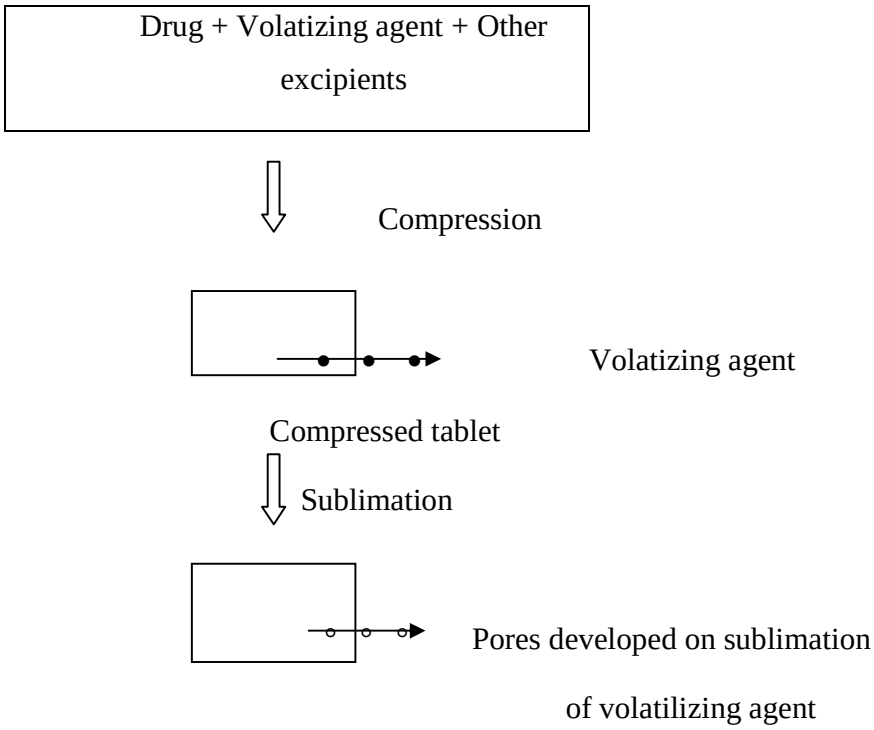


Fig. 1: Steps involved in Sublimation

5. Direct Compression: [16, 17]

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied for the preparation of MDT because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

(a) Superdisintegrants:

In many mouth dissolving tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

Factors to be considered for selection of superdisintegrants[9]:

- It should produce rapid disintegration(hydrophilic) when tablet meets saliva in the mouth
- It should be **compactable** enough to produce less-friable tablets.
- It can able to produce good mouth feel to the patient. Thus, small **particle size** are preferred to achieve patient compliance.
- It should has good flow since it improve the **flowability** of the total blend.
- **Super disintegrants:** Crosspovidone, Microcrystalline cellulose, sodium starch glycollate, sodium carboxy methyl cellulose, pregelatinzed starch, calcium carboxy methyl cellulose, and modified corn starch. Sodium starch glycollate has good flowability than crosscarmellose sodium. Cross povidone is fibrous nature and highly compactable.
- **Flavors:** Peppermint flavor, cooling flavor, flavor oils and flavoring aromatic oil, peppermint oil, clove oil, bay oil, anise oil, eucalyptus oil thyme oil, oil of bitter almonds. Flavoring agents include, vanilla, citrus oils, fruit essences
- **Sweeteners:** Aspartame, Sugars derivatives
- **Fillers:** Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulfate, pregelatinized starch, magnesium trisilicate, aluminum hydroxide.

- **Surface active agents:** sodiumdoecylsulfate, sodiumlaurylsulfate, polyoxyethylene sorbitan fatty acid esters (Tweens), sorbitan fatty acid esters (Spans), polyoxyethylene stearates.
- **Lubricants:** Stearic acid, Magnesium stearate, Zinc state, calcium state, talc, polyethylene glycol, liquid paraffin, magnesium laury sulfate, colloidal silicon dioxide.

(b) Sugar Based Excipients:

This is another approach to manufacture MDT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel. Mizumito et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate.

Type 1 saccharides (lactose and mannitol) exhibit low mould ability but high dissolution rate.

Type 2 saccharides (maltose and maltilol) exhibit high mould ability and low dissolution rate.

6. Cotton Candy Process: [18]

The cotton candy process is also known as the “candy floss” process and forms on the basis of the technologies such as Flash Dose30 (Fuisz Technology). An MDT is formed using a candy floss or shear form matrix; the matrix is formed from saccharides or polysaccharides processed into amorphous floss by a simultaneous action of flash melting and centrifugal force. The matrix is then cured or partially recrystallised to provide a compound with good flow properties and compressibility. The candy floss can then be milled and blended with active ingredients and other excipients and subsequently compressed into MDT.

However, the high processing temperature limits the use of this technology to thermo-stable compounds only.

7. Mass-Extrusion: [19, 20]

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

PATENTED TECHNOLOGIES FOR MOUTH DISSOLVING TABLET:[21 -25]

1) Zydis Technology.
2) Durasolve Technology.
3) Orasolve Technology.
4) Flash Dose Technology.
5) Wow Tab Technology.
6) Flash Tab Technology.
7) Oraquick Technology.
8) Quick –Dis Technology.
9) Nanocrystal Technology.

1) Zydis Technology:

Zydis, the best known of the mouth-dissolving/disintegrating tablet preparations, was the first marketed new technology tablet. A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile, and must be dispensed in a special blister pack. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds. A major claim of the Zydis product is increased bioavailability compared to traditional tablets. Because of its dispersion and dissolution in saliva while still in the oral cavity, there can be a substantial amount of pre-gastric absorption from this formulation. Any pre-gastric absorption avoids first-pass metabolism and can be an advantage in drugs that undergo a great deal of hepatic metabolism. There are some disadvantages to the Zydis technology. As mentioned earlier, the Zydis formulation is very lightweight and fragile, and therefore should not be stored in backpacks or the bottom of purses. Finally, the Zydis formulation has poor

stability at higher temperatures and humidities. It readily absorbs water, and is very sensitive to degradation at humidities greater than 65%.

2) Orasolv Technology:

OraSolv was Cima's first mouth-dissolving/disintegrating dosage form. The OraSolv technology, unlike Zydis, disperses in the saliva with the aid of almost imperceptible effervescence. The OraSolv technology is best described as a mouth disintegrating tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The major disadvantage of the OraSolv formulations is its mechanical strength. The OraSolv tablet has the appearance of a traditional compressed tablet. However, the OraSolv tablets are only lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets. For that reason, Cima developed a special handling and packaging system for OraSolv. An advantage that goes along with the low degree of compaction of OraSolv is that the particle coating used for taste masking is not compromised by fracture during processing. These formulations can accommodate single or multiple active ingredients and tablets containing more that 1.0 g of drug have been developed. Their disintegration time is less than 30 seconds. The OraSolv formulations are not very hygroscopic.

3) Durasolv Technology:

DuraSolv is Cima's second-generation mouth-dissolving/disintegrating tablet formulation. Produced in a fashion similar to OraSolv, DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. DuraSolv tablets are prepared by using conventional tabletting equipment and have good rigidity (friability less than that 2%). The DuraSolv product is thus produced in a mouther and more cost-effective manner. DuraSolv is so durable that it can be packaged in traditional blister packaging, pouches or vials. One disadvantage of DuraSolv is that the technology

is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction.

4) Flash Dose Technology:

The FlashDose technology utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. This procedure has been patented by Fuisz and is known as Shear form. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue. Flash dose tablets consist of self–binding shear form matrix termed as “floss”. Shear form matrices are prepared by flash heat processing and are of two types.

5) Wowtab Technology

The Wowtab mouth-dissolving/disintegrating tablet formulation has been on the Japanese market for a number of years. The WOW in Wowtab signifies the tablet is to be given “With Out Water”. The Wowtab technology utilizes sugar and sugar-like (e.g., mannitol) excipients. This process uses a combination of low mouldability saccharides (rapid dissolution) and high mouldability saccharide (good binding property).The two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and mouth dissolution rate. Due to its significant hardness, the Wowtab formulation is a bit more stable to the environment than the Zydis or OraSolv. It is suitable for both conventional bottle and blister packaging. The Wowtab product dissolves quickly in 15 seconds or less.

6) Flashtab Technology

Prographarm laboratories have patented the Flashtab technology. This technology involves the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, extrusion-spheronization, simple pan coating methods and microencapsulation. The microcrystals of microgranules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation, and compressed into tablets. All the processing utilized the conventional tabletting technology, and the tablets produced are reported to have good mechanical strength and disintegration time less than one minute.

7) Oraquick Technology

The Oraquick mouth-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. The taste masking process does not utilize solvents of any kind, and therefore leads to mouther and more efficient production. Also, lower heat of production than alternative mouth-dissolving/disintegrating technologies makes Oraquick appropriate for heat-sensitive drugs. KV Pharmaceutical claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking. Oraquick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the Oraquick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives.

8) Quick –Dis Technology

Lavipharm has invented an ideal intra-oral mouth dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intra-oral drug delivery system, trademarked Quick-Dis™, is Lavipharm's proprietary patented technology and is a thin, flexible, and quick-dissolving film. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. The typical disintegration time is only 5 to 10 seconds for the Quick-Dis™ film with a thickness of 2 mm. The dissolving time is around 30 seconds for Quick Dis™ film with a thickness of 2 mm.

9) Nanocrystal Technology

For MOUTH DISSOLVING TABLETs, Elan's proprietary NanoCrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using NanoCrystal technology. NanoCrystal particles are small particles of drug substance, typically less than 1000 nm in diameter, which are produced by milling the drug substance using a proprietary wet milling technique. NanoCrystal colloidal dispersions of drug substance are combined with water-soluble ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds.

2. SUPERDISINTEGRANTS:

To achieve rapid disintegration, direct-compression MDT formulations typically contain high levels of a superdisintegrant. Depending on the level and characteristics of the active pharmaceutical ingredient (API) and the desired release profile, the levels of superdisintegrant used can be 8–10 wt % of the formulation, and it can be higher or lower in some cases. Thus, in developing an MDT formulation for direct compression, choosing the optimal superdisintegrant is critical.

SELECTING THE SUPERDISINTEGRANTS[26,27]**:**

Although the superdisintegrant primarily affects the rate of disintegration, when used at high levels it can also affect mouth feel, tablet hardness, and friability. Thus, several factors must be considered when selecting a superdisintegrant.

- ***Disintegration*:** The disintegrant must quickly wick saliva into the tablet to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration in the mouth.

- ***Compactability*:** When manufacturing an ODT, it is desirable to have tablets with acceptable hardness at a given compression force to produce robust tablets that avoid the need to use specialized packaging while maximizing production speed. Thus, a more compactable disintegrant will produce stronger, less-friable tablets.

- ***Mouth feel:*** To achieve patient compliance, ODTs must provide a palatable experience to the patient. Large particles can result in a gritty feeling in the

mouth. Thus, small particles are preferred. If the tablet forms a gel-like consistency on contact with water, however, it produces a gummy texture that many consumers find objectionable.

- ***Flow:*** As with all direct-compression tablet formulations, attaining good flow and content uniformity is important to achieving the required dosage per unit. In typical tablet formulations, superdisintegrants are used at 2–5 wt % of the tablet formulation. With ODT formulations, disintegrant levels can be significantly higher. At these higher use levels, the flow properties of the disintegrant are more important because it makes a greater contribution to the flow characteristics of the total blend.

MECHANISM OF SUPERDISINTEGRANTS [28,29,30]

The tablet breaks to primary particles by one or more of the mechanisms listed below

1. Because of heat of wetting (air expansion)

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and can not describe the action of most modern disintegrating agents.

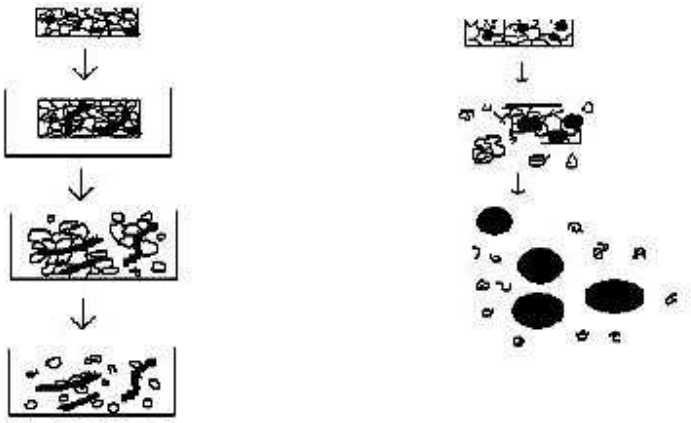
2. Swelling:

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

3. Porosity and capillary action (Wicking):

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

WICKING **SWELLING**



Water is pulled into pores by disintegrant and reduced the physical bonding force between particles.

Particles swell and break up the matrix form within; swelling setup; localized stress spreads throughout the matrix.

Fig. 2: Disintegration of Tablet by Wicking and Swelling

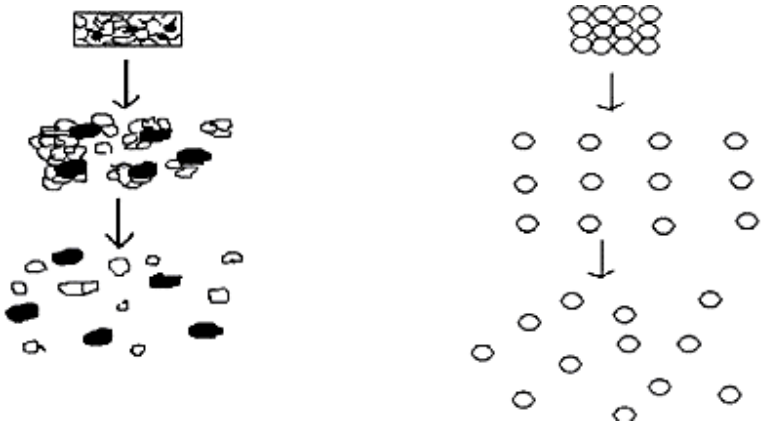
4. Due to disintegrating particle/particle repulsive forces:

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

5. Due to deformation.

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a break up of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

DEFORMATION **REPULSION**



Particles swell to precompression size and break up the matrix

Water is drawn into pores and particles repel each other because of the resulting electrical force

Fig. 3: Disintegration of Tablet by Deformation and Repulsion

6. Due to release of gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

***Table 1*: List of Superdisintegrants**

Superdisintegrants	Example	Mechanism of action	Special comment
Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose® Solutab® Vivasol® L-HPC	Crosslinked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation -Starch free
Crosspovidone Crosspovidon M® Kollidon® Polyplasdone®	Crosslinked PVP	-Swells very little and returns to original size after compression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab® Primogel®	Crosslinked starch	-Swells 7-12 folds in < 30 seconds	-Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine®	Crosslinked alginic acid	-Rapid swelling in aqueous medium or wicking action	-Promote disintegration in both dry or wet granulation
Soy polysaccharides Emcosoy®	Natural super disintegrant		-Does not contain any starch or sugar. Used in nutritional products.

Table 2: *Commercially Available MOUTH DISSOLVING TABLETs*[30]

TECHNOLOGIES	***TRADE NAME***	***ACTIVE INGREDIENT***	***MANUFACTURER***
Freeze Drying	Feldene Fast Melt	Piroxicam	Pfizer, USA
	Claritin Redi Tab	Loratidine	Schering plough, USA
	Maxalt MLT	Rizatriptan	Merck, USA
	Zyprexia	Olanzepine	Eli Lilly, USA
	Pepcid RPD	Famotidine	Merck, USA
	Zofran ODT	Ondansetron	Glaxo, UK
	Zooming ZMT	Zolmitriptan	AstraZeneca, USA
	Zelapar TM	Selegilline	Amarin,UK
Disintegrant Addition	Tempra Quicklets	Acetaminophen	Bristol Myers, USA
	Febrectol	Paracetamol	Prographarma, France
	Nimulid MDT	Nimesulide	Panacea Biotech, India
	Torrox MT	Rofecoxib	Torrent pharma, India
	Olanex Instab	Olanzapine	Ranbaxy, India
	Romilast	Montelukast	Ranbaxy, India
Sugar Based Excipient	Benadryl Fastmelt	Diphenhydramine & Pseudoephedrine	WarnerLambert, USA

- ***Evaluating physical characteristics of commercial superdisintegrants***[26,32,33]

  Currently available disintegrants were evaluated for particle size, particle-size distribution, flowability, compactability, particle shape, and morphology.

The following superdisintegrants were studied:

- **Crosspovidone A1** (standard particle-size grade) (Polyplasdone XL, International Specialty Products, Wayne, NJ);
- **Crosspovidone A2** (fine particle-size grade) (Polyplasdone XL-10, ISP);
- **Crosspovidone B** (Kollidon CL, BASF, Ludwigshafen, Germany);
- **sodium starch glycolate** (Explotab, JRS Pharma, Patterson, NY);
- **Crosscarmellose sodium**(Ac-Di-Sol, FMC, Philadelphia, PA).

- Crospovidone is an insoluble, neutral cross-linked homopolymer of N-vinyl-2-pyrrolidone. It is available in various particle sizes.
- The *US Pharmacopeia* defines sodium starch glycolate as the sodium salt of a carboxymethyl ether of starch or of a cross-linked carboxymethyl ether of starch, and crosscarmellose sodium is defined as the sodium salt of a cross-linked, partly O-(carboxymethylated) cellulose.

The selection of the optimal disintegrant for a formulation depends on a consideration of the combined effects of all of these factors:

(a) Particle size and distribution. A comparison of particle sizes of various disintegrants is shown in Table I and Figure 1.

Table I: Particle size and flowability index.

Superdisintegrant	Typical average particle size (μm)	Flowability index
Crospovidone A1	115	50
Crospovidone A2	30	47
Crospovidone B	110	44
Croscarmellose sodium	50	31
Sodium starch glycolate	50	58

Table: Particle size and flowability index.

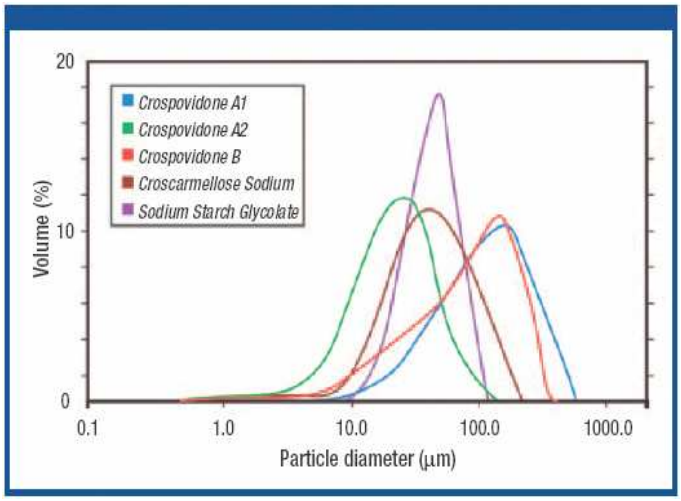


Figure I

Sodium starch glycolate and crosscarmellose sodium show similar average particle sizes; however, sodium starch glycolate has a narrower distribution, which contributes to the good flow properties. The particle size differences between the various types of crospovidone are shown. Because crospovidone

A2 offers the smallest average particle size (~30 μm), it is often preferred because small particles result in a smoother mouth feel.

(b) Flowability. Flowability index results are shown in Table I. Sodium starch glycolate provides the best flow as a result of its spherical particle morphology and narrow particle size distribution.

(c) Particle shape and morphology. When examined under a scanning electron microscope, sodium starch glycolate particles are spherical (Figure 2). Crospovidone particles appear granular and highly porous, although crospovidone B particles appear less porous. This porous particle morphology facilitates rapid wicking of liquid into both particle and tablet and contributes to the compactability of the material. Crosscarmellose sodium particles have a fibrous structure.

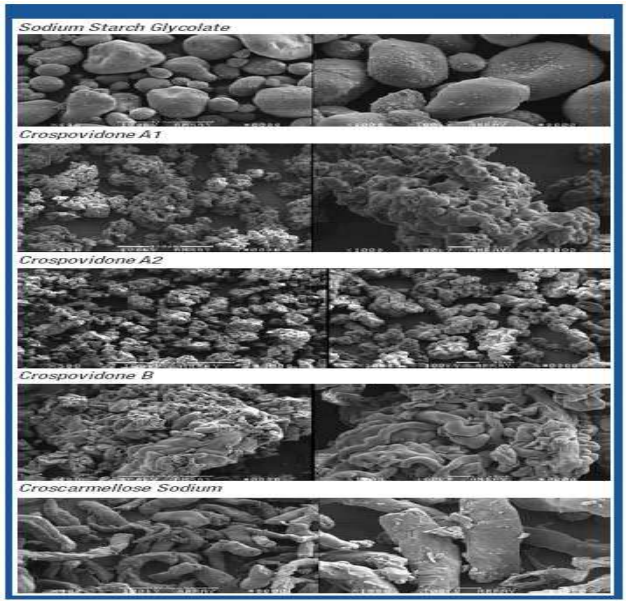


Figure II

(d) Compactability. The compactability of each of the disintegrants was evaluated by comparing the breaking force, at various compression forces, of pure compacts of each disintegrant with small amounts of lubricant and glidant added (see Figure 3). Results indicate that crospovidone is the most highly compactable disintegrate tested, thus producing the highest tablet-breaking force at a given compression force.

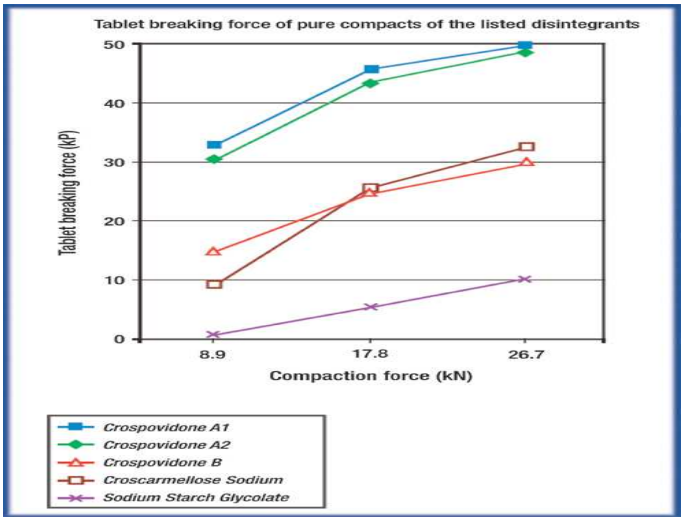
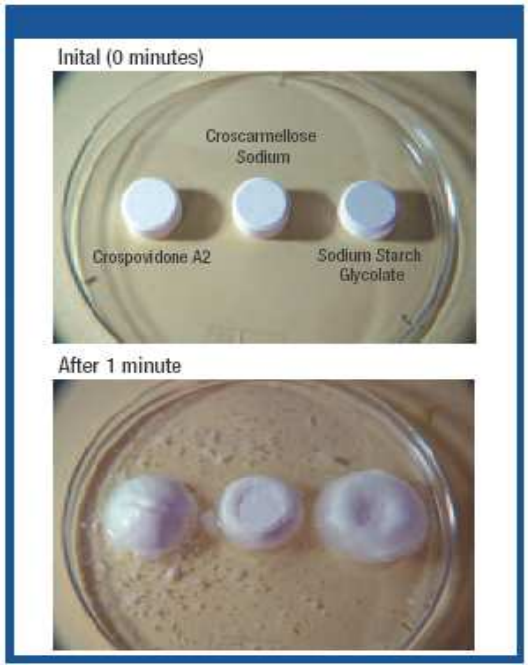


Figure III

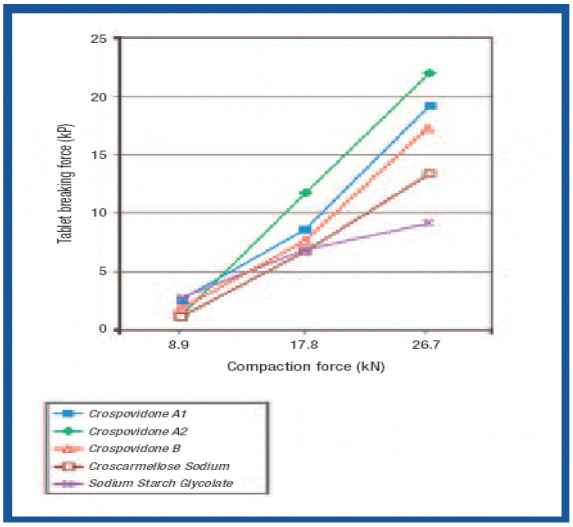
Nonetheless, the results also show that crospovidone A1 and B, with similar particle size, perform significantly differently. Crospovidone A1 is more compactable than crospovidone B.



When representative placebo tablets with crospovidone A2, sodium starch glycolate, and croscarmellose sodium were placed in a Petri dish with a small amount of water, the relative ability of the various disintegrants to wick water into the tablet was observed. One minute after contact with water, the tablet containing crospovidone A2 was fully hydrated and soft throughout because crospovidone quickly wicks water into the tablet. Meanwhile, the centers of the tablets made with sodium starch glycolate and croscarmellose sodium remained dry and hard. Although the tablet with sodium starch glycolate swelled, the outer edge appeared gel-like.

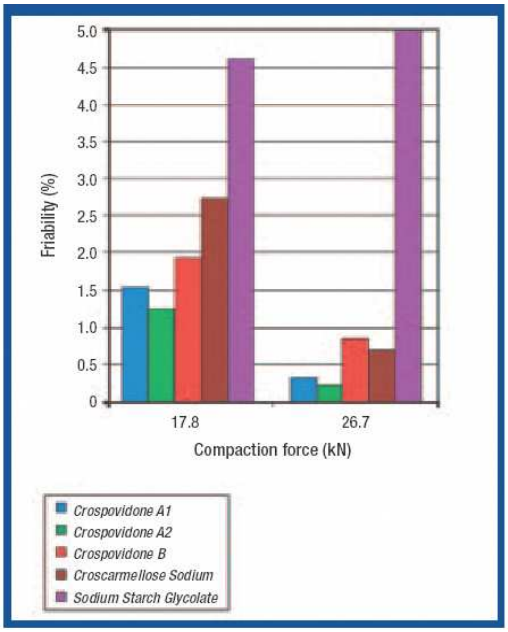
Relation between different pharmaceutical properties[26,34,35]*:*

(1) Relation between compaction force & tablet breaking force:



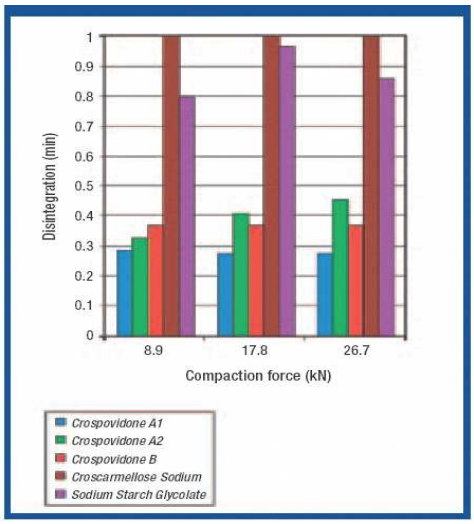
As per graph, it is concluded that, as compaction force increases tablet breaking force also increases. Crosspovidone has highest linearity between compaction force & tablet breaking force

(2) Relation between compaction force & friability:



As per graph, as compaction force increases, friability decreases. Minimum friability is of Crosspovidone A2 at compaction force 26.7 kN.

(3) Relation between compaction force & Disintegration:



As compaction force increases, disintegration time increases.

3. AMLODIPINE BESYLATE:

Drug Profile:

1. Drug class: Antihypertensive

2. Category: second generation dihydropyridamol Ca++ channel blocker

3. CAS number[36]: 88150-42-9

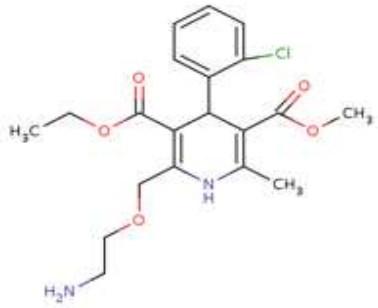
4. Official status: Drug is official in USP, IP, BP and EP.

5. Chemical name[36]***:*** 3-Ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate.

6. Molecular formula[36]: $C_{20}H_{25}ClN_2O_5$

7. Molecular weight[36]: 408.879 g/mol

8. Structural formula[36]***:***



9. Physicochemical properties:

a) Description and Solubility[3]: a white powder. It is slightly soluble in water and isopropanol; freely soluble in methanol; and sparingly soluble in dehydrated alcohol.

b) Melting point: 178-179^{o}C

c) Experimental Water Solubility- 75.3 mg/L

d) Predicted Water Solubility- 7.40e-03 mg/mL

e) Experimental LogP/Hydrophobicity- 1.9

f) Predicted LogP- 2.22

g) Optical rotation4: Between -0.10° & +0.10° at 20°C (solution 10mg/ml in methanol).

h) Dissociation constant (Pka)5: 8.6

i) Partition coefficient (log p)5: (o/w) 3.0

10. Storage condition[39]:

Preserve in tight container, protected from light, store at room temperature.

11. Pharmacological action and clinical pharmacology:

a) Mechanism of action[37]:

- Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle.
- Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites.

- Amlodipine had a strong blocking action on both the L-type and N-type Ca2+ channels expressed in the oocyte. The potency of the amlodipine block on the N-type Ca2+ channel was comparable to that on the L-type Ca2+ channel.
- The blocking action of amlodipine on the N-type Ca2+ channel was dependent on holding potential and extracellular pH, as has been observed with amlodipine block on the L-type Ca2+ channel. A depolarized holding potential and high pH enhanced the blocking action of amlodipine,
- Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa = 8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.
- The time course of block development by amlodipine was similar for L-type and N-type Ca2+ channels. However, it was slower than the time course of block development by nifedipine for the L-type Ca2+ channel.
- Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.
- The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

    - ✓ *Exertional Angina*: In patients with exertional angina, amlodipine reduces the total peripheral resistance (after load) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

- ✓ *Vasospastic Angina*: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A_2 analog in experimental animal models and in human coronary vessels *in vitro*. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in vasospastic (Prinzmetal's or variant) angina.

b) Pharmacokinetics and Metabolism:

- After oral administration of therapeutic doses of amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%.
- The bioavailability of amlodipine is not altered by the presence of food.
- Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.
- *Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients.
- Elimination from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours.
- Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.
- The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.
- Elderly patients and patients with hepatic insufficiency have decreased clearance of Amlodipine with a resulting increase in AUC of approximately 40 to 60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

c) Pharmacodynamics:

- *Hemodynamic*[36]*:*

  - Following administration of therapeutic doses to patients with hypertension, Amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.
  - Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.
  - With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients.
  - The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105 to 114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90 to 104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/–2 mmHg).
  - In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

- As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co administered with beta blockers to man. Similar findings, however, have been observed in normals or well compensated patients with heart failure with agents possessing significant negative inotropic effects.

➢ *Electro physiologic Effects*[37]:

- Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing.
- Similar results were obtained in patients receiving amlodipine and concomitant beta blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

❖ *Clinical Studies*

➢ Effects in Hypertension:

✓ *Adult Patients*:

- The antihypertensive efficacy of amlodipine has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on Amlodipine and 538 on placebo. Once daily administration produced statistically significant placebo corrected reductions in supine and standing blood pressures at 24 hours post dose, averaging about 12/6 mmHg in the standing position and 13/7 mmHg in the supine position in patients with mild to moderate hypertension. Maintenance of the blood pressure effect over the 24-hour dosing interval was observed, with little difference in peak and trough effect. Tolerance was not demonstrated in patients studied for up to 1 year.
- The 3 parallel, fixed dose, dose response studies showed that the reduction in supine and standing blood pressures was dose-related within the recommended dosing range.
- Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure. Effects were similar in black patients and in white patients.

✓ *Pediatric Patients:*

Two-hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to amlodipine besylate 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 5 mg at the end of 8 weeks had lower blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5-mg dose. Adverse events were similar to those seen in adults.

➢ **Effects in Chronic Stable Angina:**

- The effectiveness of 5 to 10 mg/day of amlodipine in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind clinical trials of up to 6 weeks duration involving 1038 patients (684 amlodipine, 354 placebo) with chronic stable angina. In 5 of the 8 studies significant increases in exercise time (bicycle or treadmill) were seen with the 10 mg dose.
- Increases in symptom-limited exercise time averaged 12.8% (63 sec) for amlodipine 10 mg, and averaged 7.9% (38 sec) for amlodipine 5 mg. Amlodipine 10 mg also increased time to 1 mm ST segment deviation in several studies and decreased angina attack rate.
- The sustained efficacy of amlodipine in angina patients has been demonstrated over long-term dosing. In patients with angina there were no clinically significant reductions in blood pressures (4/1 mmHg) or changes in heart rate (+0.3 bpm).

➢ **Effects in Vasospastic Angina:**

In a double-blind, placebo-controlled clinical trial of 4 weeks duration in 50 patients, Amlodipine therapy decreased attacks by approximately 4/week compared with a placebo decrease of approximately 1/week ($p<0.01$). Two (2) of 23 amlodipine and 7 of 27 placebo patients discontinued from the study due to lack of clinical improvement.

❖ ***INDICATIONS AND USAGE[40]:***

1. Hypertension:

Amlodipine Orally Disintegrating Tablets is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

2. Coronary Artery Disease:

- *Chronic Stable Angina:*

Amlodipine Orally Disintegrating tablets are indicated for the symptomatic treatment of chronic stable angina. Amlodipine Orally Disintegrating Tablets may be used alone or in combination with other antianginal agents.

- *Vasospastic Angina (Prinzmetal's or Variant Angina):*

Amlodipine Orally Disintegrating Tablets are indicated for the treatment of confirmed or suspected vasospastic angina. It may be used as monotherapy or in combination with other antianginal drugs.

❖ *CONTRAINDICATIONS*[41]

Amlodipine Orally Disintegrating Tablets is contraindicated in patients with known sensitivity to amlodipine.

❖ *WARNINGS:*

➢ **Increased Angina and/or Myocardial Infarction:**

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

❖ *PRECAUTIONS*[37]

➢ General:

Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, caution, as with any other peripheral vasodilator, should be exercised when administering amlodipine, particularly in patients with severe aortic stenosis.

❖ *DRUG INTERACTIONS:*

In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

➢ Effect of other agents on amlodipine[37]:

- *CIMETIDINE:* Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.
- *GRAPEFRUIT JUICE*: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.
- *MAALOX (antacid):* Co-administration of the antacid Maalox with a single dose of Amlodipine had no significant effect on the pharmacokinetics of amlodipine.
- *SILDENAFIL:* A single 100 mg dose of sildenafil (Viagra®) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When Amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

➢ Effect of amlodipine on other agents[37]:

- *ATORVASTATIN:* Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.
- *DIGOXIN:* Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.
- *ETHANOL (alcohol*): Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.
- *WARFARIN:* Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time. In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

➢ Pediatric Use:

The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

➢ Geriatric Use:

- Clinical studies of amlodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.
- In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40 to 60%, and a lower initial dose may be required.

❖ *ADVERSE REACTIONS[38]:*

- **Cardiovascular:**

arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.

- **Central and Peripheral Nervous System:**

hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.

- **Gastrointestinal:**

anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

- **General:**

allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

- **Musculoskeletal System:**

arthralgia, arthrosis, muscle cramps, myalgia.

- **Psychiatric:**

sexual dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

- **Respiratory System:**

dyspnea, epistaxis.

- **Skin and Appendages:**

angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular..

- **Special Senses:**

abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

- **Urinary System:**

micturition frequency, micturition disorder, nocturia.

❖ OVERDOSAGE[39]

- Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral Amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more time times the maximum recommended human dose on a mg/m^2 basis) caused a marked peripheral vasodilation and hypotension.

- Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited.

❖ DOSAGE AND ADMINISTRATION[39]

- **Adults:**

  The usual initial antihypertensive oral dose of Amlodipine Orally Disintegrating Tablets is 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly individuals, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding Amlodipine Orally Disintegrating tablets to other antihypertensive therapy. The recommended dose for chronic stable or vasospastic angina is 5 to 10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency.

- **Children:**

  The effective antihypertensive oral dose in pediatric patients ages 6 to17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients.

Mannitol

1. Nonproprietary Names

- BP: Mannitol
- JP: D-Mannitol
- PhEur: Mannitolum
- USP: Mannitol

2. Synonyms

Cordycepic acid; E421; manna sugar; D-mannite; mannite;

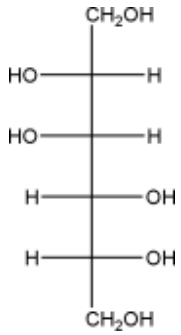
3. Chemical Name and CAS Registry Number

D-Mannitol [69-65-8]

4. Empirical Formula and Molecular Weight

$C_6H_{14}O_6$ 182.17

5. Structural Formula



6. Functional Category

Diluent; diluent for lyphilized preparations; sweetening agent; tablet and capsule diluent; tonicity agent.

7. Applications in Pharmaceutical Formulation or Technology

Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients.

Mannitol may be used in direct-compression tablet applications, for which the granular and spray-dried forms are available, or in wet granulations. Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel'.

Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (<7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations, and as a carrier in dry powder inhalers. It is also used as a diluent in rapidly dispersing oral dosage forms. It is used in food applications as a bulking agent.

8. Description

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol.

Mannitol occurs as a white, odorless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism.

9. Pharmacopeial Specifications

Table: Pharmacopeial specifications for mannitol.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
Solution appearance	+	+	—
Melting range	166–169°C	165–170°C	164–169°C
Loss on drying	≤0.3%	≤0.5%	≤0.3%
Chloride	≤0.007%	—	≤0.007%
Sulfate	≤0.01%	—	≤0.01%
Arsenic	≤1.3 ppm	—	≤1 ppm
Microbial contamination	—	≤100/g	—
Assay (dried basis)	≥ 98.0%	98.0–102.0%	96.0–101.5%

10. Typical Properties

- ✓ *Density (bulk):*

  0.430 g/cm^3 for powder;

- ✓ *Density (tapped):*

  0.734 g/cm^3 for powder;

- ✓ *Density (true):*

  1.514 g/cm^3

- ✓ *Flowability:*

  powder is cohesive, granules are free flowing.

- ✓ *Melting point:*

  166–168°C

11. Stability and Storage Conditions

Mannitol is stable in the dry state and in aqueous solutions. Solutions may be sterilized by filtration or by autoclaving and if necessary may be autoclaved repeatedly with no adverse physical or chemical effects. The bulk material should be stored in a well-closed container in a cool, dry place.

12. Incompatibilities

Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride. Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic. Sodium cephapirin at 2 mg/mL and 30 mg/mL concentration is incompatible with 20% w/v aqueous mannitol solution.

13. Method of Manufacture

Mannitol may be extracted from the dried sap of manna and other natural sources by means of hot alcohol or other selective solvents. It is commercially produced by the catalytic or electrolytic reduction of monosaccharides such as mannose and glucose.

14. Safety

Mannitol is a naturally occurring sugar alcohol found in animals and plants; it is present in small quantities in almost all vegetables. Laxative effects may occur if mannitol is consumed orally in large quantities. If it is used in foods as a bodying agent and daily ingestion of over 20 g is foreseeable, the product label should bear the statement ‘excessive consumption may have a laxative effect’. After intravenous injection, mannitol

is not metabolized to any appreciable extent and is minimally reabsorbed by the renal tubule, about 80% of a dose being excreted in the urine in 3 hours.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Mannitol may be irritant to the eyes; eye protection is recommended

Aspartame

1. Nonproprietary Names

- BP: Aspartame
- USPNF: Aspartame

2. Synonyms

3-Amino-*N*-(α-carboxyphenethyl)succinamic acid *N*-methyl ester;

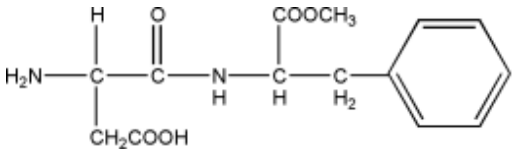
3. Chemical Name and CAS Registry Number

N-α-L-Aspartyl-L-phenylalanine 1-methyl ester [22839-47-0]

4. Empirical Formula and Molecular Weight

$C_{14}H_{18}N_2O_5$ 294.31

5. Structural Formula



6. Functional Category

Sweetening agent.

7. Applications in Pharmaceutical Formulation or Technology

Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations. It enhances flavor systems and can be used to mask

some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose.

8. Description

Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.

9. Pharmacopeial Specifications

Table: Pharmacopeial specifications for aspartame.

Test	PhEur 2005	USPNF 23
Characters	+	—
Identification	+	+
Heavy metals	≤10 ppm	≤0.001%
Loss on drying	≤4.5%	≤4.5%
Assay	98.0–102.0%	98.0–102.0%

10. Typical Properties

- ✓ *Acidity/alkalinity:*

  pH = 4.5–6.0 (0.8% w/v aqueous solution).

- ✓ Flowability:

  44% (Carr compressibility index)

- ✓ Density (bulk):

  0.5–0.7 g/cm^3 for granular grade;

- ✓ Density (tapped):

  0.29 g/cm^3 (Spectrum Quality Products)

- ✓ Melting point:

  246–247°C

- ✓ Solubility:

  slightly soluble in ethanol (95%); sparingly soluble in water. At 20°C the solubility is 1% w/v at the isoelectric point (pH 5.2). Solubility increases at higher temperature and at more acidic pH, e.g., at pH 2 and 20°C solubility is 10% w/v.

11. Stability and Storage Conditions

Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form the degradation products L-aspartyl-L-phenylalanine and 3-benzyl-6-carboxymethyl-2,5-diketopiperazine. The bulk material should be stored in a well-closed container, in a cool, dry place.

12. Incompatibilities

Differential scanning calorimetry experiments with some directly compressible tablet excipients suggests that aspartame is incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate. Reactions between aspartame and sugar alcohols are also known.

13. Method of Manufacture

Aspartame is produced by coupling together L-phenylalanine (or L-phenylalanine methyl ester) and L-aspartic acid, either chemically or enzymatically. The former procedure yields both the sweet α-aspartame and nonsweet β-aspartame from which the α-aspartame has to be separated and purified. The enzymatic process yields only α-aspartame.

14. Safety

Aspartame is widely used in oral pharmaceutical formulations, beverages, and food products as an intense sweetener and is generally regarded as a nontoxic material. However, the use of aspartame has been of some concern owing to the formation of the potentially toxic metabolites methanol, aspartic acid, and phenylalanine.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Measures should be taken to minimize the potential for dust explosion. Eye protection is recommended.

Microcrystalline Cellulose

1. Nonproprietary Names

- BP: Microcrystalline cellulose
- USPNF: Microcrystalline cellulose

2. Synonyms

Avicel PH; *Celex*; cellulose gel; *Celphere*; *Ceolus KG*; crystalline cellulose; E460;

3. Chemical Name and CAS Registry Number

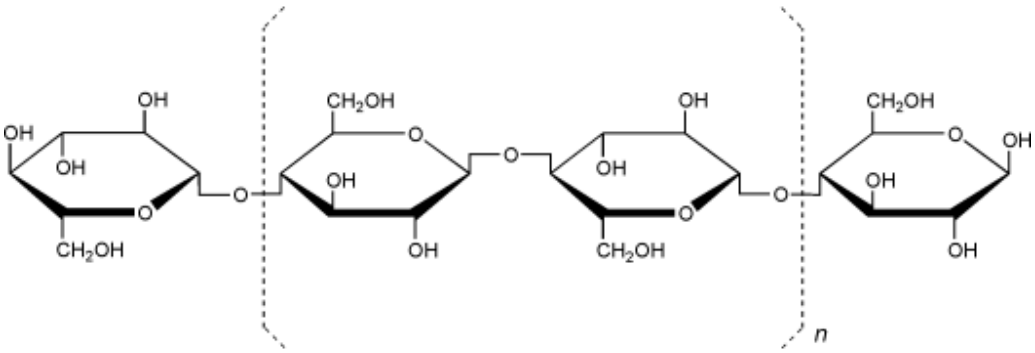
Cellulose [9004-34-6]

4. Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ ≈36 000

where $n \approx 220$.

5. Structural Formula



6. Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

7. Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.[1–7] In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant[8] and disintegrant properties that make it useful in tableting.

Microcrystalline cellulose is also used in cosmetics and food products;

Table I: Uses of microcrystalline cellulose.

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluent	20–90
Tablet disintegrant	5–15
Tablet binder/diluent	20–90

8. Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

9. Pharmacopeial Specifications

Table : Pharmacopeial specifications for microcrystalline cellulose.

Test	JP 2001	PhEur 2005 (Suppl 5.1)	USPNF 23
Identification	+	+	+
Characters	+	+	—
pH	5.0–7.0	5.0–7.5	5.0–7.5
Bulk density	+	—	+
Loss on drying	≤7.0%	≤7.0%	≤7.0%
Residue on ignition	≤0.05%	—	≤0.1%

10. Typical Properties

- ✓ Angle of repose:

  49° for *Ceolus KG*;

- ✓ Density (bulk):

  0.337 g/cm^3;

- ✓ Density (tapped):

  0.478 g/cm^3;

- ✓ Melting point:

  chars at 260–270°C.

- ✓ Solubility:

  slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

11. Stability and Storage Conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

12. Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

13. Method of Manufacture

Microcrystalline cellulose is manufactured by controlled hydrolysis with dilute mineral acid solutions of α-cellulose, obtained as a pulp from fibrous plant materials. Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spray-dried to form dry, porous particles of a broad size distribution.

14. Safety

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

Silicified Microcrystalline

1. Nonproprietary Names

None adopted.

2. Synonyms

ProSolv.

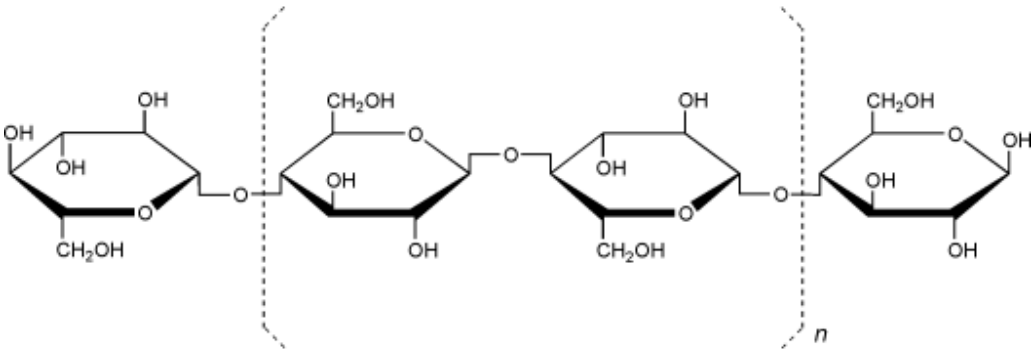
3. Chemical Name and CAS Registry Number

Section 8.

4. Empirical Formula and Molecular Weight

Section 8.

5. Structural Formula



6. Functional Category

Tablet and capsule diluent.

7. Applications in Pharmaceutical Formulation or Technology

Silicified microcrystalline cellulose is used as a filler in the formulation of capsules and tablets. It has improved compaction properties in both wet granulation and direct compression compared to conventional microcrystalline cellulose. Silicified microcrystalline cellulose was specifically developed to address the loss of compaction that occurs with microcrystalline cellulose after wet granulation.

8. Description

Silicified microcrystalline cellulose is a synergistic, intimate physical mixture of two components: microcrystalline cellulose and colloidal silicon dioxide (for further information *see* Cellulose, Microcrystalline and Colloidal Silicon Dioxide). Silicified microcrystalline cellulose contains 2% w/w colloidal silicon dioxide.

9. Pharmacopeial Specifications

-

10. Typical properties

- ✓ Acidity/alkalinity:
  pH = 5.0–7.5 (10% w/v suspension)
- ✓ Density:
  1.58 g/cm^3
- ✓ Density (bulk):
  0.31 g/cm3
- ✓ Density (tapped):
  0.39 g/cm^3

- ✓ Moisture content:

  typically less than 6% w/w.

- ✓ Solubility:

  Practically insoluble in water, dilute acids, and most organic solvents. The microcrystalline cellulose component is slightly soluble in 5% w/w sodium hydroxide solution.

11. Stability and Storage Conditions

Silicified microcrystalline cellulose is stable when stored in a well-closed container in a cool,dry place.

12. Method of Manufacture

- Silicified microcrystalline cellulose is manufactured by co-drying a suspension of microcrystalline cellulose particles and colloidal silicon dioxide so that the dried finished product contains 2% w/w colloidal silicon dioxide.
- The colloidal silicon dioxide appears physically bound onto the surface and inside the silicified microcrystalline cellulose particles. Extensive studies using different spectroscopic methods have failed to show any form of chemical interaction.4,6,7

13. Safety

See Cellulose, Microcrystalline and Colloidal Silicon Dioxide.

Hydroxy propyl Cellulose

1. Nonproprietary Names:

- BP: Hydroxy propyl cellulose
- USPNF: Hydroxy propyl cellulose

2. Synonyms:

Cellulose, hydroxy propyl ether; E463; hyprolose; *Klucel*; *Methocel*; *Nisso HPC*;

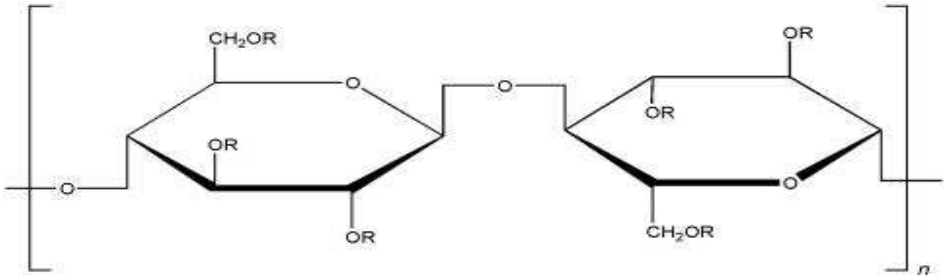
3. Chemical Name and CAS Registry Number:

Cellulose, 2-hydroxy propyl ether [9004-64-2]

4. Empirical Formula and Molecular Weight:

The PhEur 2005 and USPNF 23 describe hydroxy propyl cellulose as a partially substituted poly(hydroxy propyl) ether of cellulose. It may contain not more than 0.6% of silica or another suitable anticaking agent. Hydroxy propyl cellulose is commercially available in a number of different grades that have various solution viscosities. Molecular weight has a range of 50 000–1 250 000;

5. Structural Formula:



R is H or $[CH_2CH(CH_3)O]_mH$

6. Functional Category:

Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology:

Hydroxy propyl cellulose is widely used in oral and topical pharmaceutical formulations;

Uses of hydroxy propyl cellulose.

Use	Concentrations(%)
Extended release-matrix former	15–35
Tablet binder	2–6
Tablet film coating	5

- In oral products, hydroxy propyl cellulose is primarily used in tableting as a binder, filmcoating, and extended-release-matrix former. Concentrations of hydroxy propyl cellulose of 2–6% w/w may be used as a binder in either wet-granulation or dry, direct-compression tableting processes. Concentrations of 15–35% w/w of hydroxy propyl cellulose may be used to produce tablets with an extended drug release. Typically, a 5% w/w solution of hydroxy propyl cellulose may be used to filmcoat tablets.

8. Description:

Hydroxy propyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder.

9. Pharmacopeial Specifications:

Table II: Pharmacopeial specifications for hydroxy propyl cellulose.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Apparent viscosity	+	+	+
Appearance of solution	+	+	—
pH (1 in 100)	5.0–7.5	5.0–8.5	5.0–8.0
Loss on drying	5.0%	7.0%	5.0%
Residue on ignition	0.5%	—	0.2%

10. Typical Properties

- ✓ Acidity/alkalinity:

  pH = 5.0–8.5 for a 1% w/v aqueous solution.

- ✓ Density (bulk):

  0.5 g/cm3

- ✓ Melting point:

  softens at 130°C; chars at 260–275°C.

- ✓ Solubility:

  Soluble 1 in 10 parts dichloromethane; 1 in 2.5 parts ethanol (95%); 1 in 2 parts methanol; 1 in 5 parts propan-2-ol; 1 in 5 parts propylene glycol; and 1 in 2 parts water. Practically insoluble in aliphatic hydrocarbons; aromatic hydrocarbons; carbon tetrachloride; petroleum distillates; glycerin; and oils.

11. Stability and Storage Conditions:

Hydroxy propyl cellulose powder is a stable material, although it is hygroscopic after drying. Aqueous solutions of hydroxy propyl cellulose are stable at pH 6.0–8.0, with the viscosity of solutions being relatively unaffected.

Crospovidone

1. Nonproprietary Names

- BP: Crospovidone
- USPNF: Crospovidone

2. Synonyms

Crosslinked povidone; E1202; *Kollidon CL*; *Kollidon CL-M*; *Polyplasdone XL*; *Polyplasdone XL-10*;

3. Chemical Name and CAS Registry Number

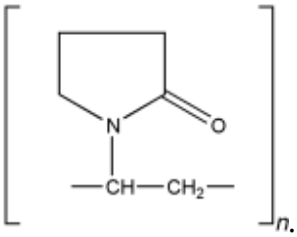
1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4. Empirical Formula and Molecular Weight

$(C_6H_9NO)_n$ >1 000 000

The USPNF 23 describes crospovidone as a water-insoluble synthetic crosslinked homopolymer of *N*-vinyl-2-pyrrolidinone. An exact determination of the molecular weight has not been established because of the insolubility of the material.

5. Structural Formula



6. Functional Category

Tablet disintegrant.

7. Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels.

8. Description

Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

See SEM 1.

9. Pharmacopeial Specifications

Table I

Table I: Pharmacopeial specifications for crospovidone.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
pH (1% suspension)	—	5.0–8.0
Water	—	≤5.0%
Residue on ignition	≤0.1%	≤0.4%

10. Typical Properties

- ✓ Acidity/alkalinity:

  pH = 5.0–8.0 (1% w/v aqueous slurry)

- ✓ Moisture content**:**

  maximum moisture sorption is approximately 60%.

- ✓ Solubility:

  practically insoluble in water and most common organic solvents.

11. Stability and Storage Conditions

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

12. Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials

13. Method of Manufacture

Acetylene and formaldehyde are reacted in the presence of a highly active catalyst to form butynediol, which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acetylene are reacted under pressure. The monomer vinylpyrrolidone is then polymerized in solution, using a catalyst. Crospovidone is prepared by a ‘popcorn polymerization’ process.

14. Safety

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. Short-term animal toxicity studies have shown no adverse effects associated with crospovidone. However, owing to the lack of available data, an acceptable daily intake in humans has not been specified by the WHO.

Vanillin

1. Nonproprietary Names

- BP: Vanillin
- USPNF: Vanillin

2. Synonyms

4-Hydroxy-*m*-anisaldehyde; *p*-hydroxy-*m*-methoxybenzaldehyde

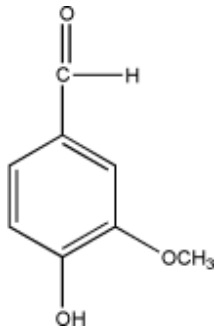
3. Chemical Name and CAS Registry Number

4-Hydroxy-3-methoxybenzaldehyde [121-33-5]

4. Empirical Formula and Molecular Weight

$C_8H_8O_3$ 152.15

5. Structural Formula



6. Functional Category

Flavoring agent.

7. Applications in Pharmaceutical Formulation or Technology

Vanillin is widely used as a flavor in pharmaceuticals, foods, beverages, and confectionery products, to which it imparts a characteristic taste and odor of natural

vanilla. It is also used in perfumes, as an analytical reagent and as an intermediate in the synthesis of a number of pharmaceuticals, particularly methyldopa. Additionally, it has been investigated as a potential therapeutic agent in sickle cell anemia and is claimed to have some antifungal properties.

8. Description

White or cream, crystalline needles or powder with characteristic vanilla odor and sweet taste.

9. Pharmacopeial Specifications

Table

Table I: Pharmacopeial specifications for vanillin.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Loss on drying	≤1.0%	≤1.0%
Sulfated ash	≤0.05%	—
Residue on ignition	—	≤0.05%

10. Typical Properties

- ✓ Acidity/alkalinity:

  aqueous solutions are acid to litmus.

- ✓ Density (bulk):

  0.6 g/cm^3

11. Stability and Storage Conditions

Vanillin oxidizes slowly in moist air and is affected by light.The bulk material should be stored in a well-closed container, protected from light, in a cool, dry place.

12. Incompatibilities

Incompatible with acetone, forming a brightly colored compound.[7] A compound practically insoluble in ethanol is formed with glycerin.

13. Method of Manufacture

Vanillin occurs naturally in many essential oils and particularly in the pods of Vanilla planifolia and Vanilla tahitensis. Industrially, vanillin is prepared from lignin, which is obtained from the sulfite wastes produced during paper manufacture. Lignin is treated with alkali at elevated temperature and pressure, in the presence of a catalyst, to form a complex mixture of products from which vanillin is isolated. Vanillin is then purified by successive recrystallizations.

14. Safety

There have been few reports of adverse reactions to vanillin, although it has been speculated that cross-sensitization with other structurally similar molecules, such as benzoic acid, may occur.

Magnesium Stearate

1. Nonproprietary Names

- BP: Magnesium stearate
- USPNF: Magnesium stearate

2. Synonyms

Magnesium octadecanoate; octadecanoic acid,

3. Chemical Name and CAS Registry Number

Octadecanoic acid magnesium salt [557-04-0]

4. Empirical Formula and Molecular Weight

$C_{36}H_{70}MgO_4$ 591.34

The USPNF 23 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$)..

5. Structural Formula

$[CH_3(CH_2)_{16}COO]_2Mg$

6. Functional Category

Tablet and capsule lubricant.

7. Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams. *See also* Section 18.

8. Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

See SEM: 1, SEM: 2.

9. Pharmacopeial Specifications

Table: Pharmacopeial specifications for magnesium stearate.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Microbial limits	+	+	+
Aerobic microbes	≤1000/g	$\leq 10^3$/g	$\leq 10^3$/g
Assay (dried, as Mg)	4.0–5.0%	4.0–5.0%	4.0–5.0%

10. Typical Properties

- ✓ Crystalline forms:

  high-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.

- ✓ Density (bulk):

  0.159 g/cm^3

- ✓ Density (tapped):

  0.286 g/cm^3

- ✓ Density (true):

  1.092 g/cm^3

11. Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

12. Incompatibilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

13. Method of Manufacture

Magnesium stearate is prepared either by the interaction of aqueous solutions of magnesium chloride with sodium stearate or by the interaction of magnesium oxide, hydroxide, or carbonate with stearic acid at elevated temperatures.

14. Safety

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.

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4. LITERATURE REVIEW

4.1 Mouth Dissolving Tablets

- Gohel[42] et al (2004) prepared the mouth dissolved tablets of Nimesulide using vaccum drying technique. Granules containing Nimesulide, camphor, crorospovidone and lactose were prepared by wet granulation technique. Camphor was sublimed from the dried granules by exposure to vacuum. The tablets were evaluated for % friability, wetting time and disintegration time. In the present investigation a 3^2 full factorial design was used to investigate combined effect of two formulation variables: amount of camphor and amount of superdisintegrant. The results of multiple linear regression analysis revealed that for obtaining a rapidly disintegrating dosage form, tablets should be prepared using optimum concentration of camphor and higher percentage of crospovidone.

- Ahmed S. Zidan[43] et al (2006) formulated and optimized mouth dissolving tablets containing Rofecoxib using solid dispersion. The purpose of the present investigation was to increase the solubility and dissolution rate of Rofecoxib by the preparation of its solid dispersion with polyvinyl pyrrolidone K30 (PVP K30) using solvent evaporation method. For the preparation of Rofecoxib mouth dissolve tablets, its 1: 9 solid dispersion with PVP K30 was used with various disintegrants and sublimable materials. The obtained results showed that dispersion of the drug in the polymer considerably enhanced the dissolution rate. The drug-to-carrier ratio was the controlling factor for dissolution improvement.

- Keith J. Simons[44] et al (2006) prepared fast-disintegrating sublingual tablets. Four tablet formulations, A, B, C, and D, containing 0%, 6%, 12%, and 24% of Epinephrine bitartrate, respectively, and microcrystalline cellulose: low-substituted hydroxypropyl cellulose (9:1), were prepared by direct compression,

at a range of compression forces. Tablet weight variation, content uniformity, hardness, disintegration time, wetting time, and friability were measured for each formulation at each compression force. All 4 tablet formulations at each compression force were within the USP limits for weight variation and content uniformity. At a mean ± SD hardness of ≤ 2.3 ± 0.2 kg, all tablet formulations passed the USP friability test. At a mean ± SD hardness of ≥ 3.1 ± 0.2 kg, all tablet formulations resulted in disintegration and wetting times of <10 seconds and <30 seconds, respectively.

- Abdelbary[45] et al (2004) prepared orally disintegrating tablets using a hydrophilic waxy binder. The incorporation of Superpolystate® in the formulation of RDT was realised by means of two different granulation methods: wet granulation by using an emulsion of this waxy binder as granulating liquid and melt granulation where the molten form of the binder was used. The potential of the intragranular addition of croscarmellose sodium as a disintegrating agent was also evaluated. An improvement in tablet hardness and friability was observed with both granulation methods where we were able to obtain RDT with a disintegration time of 40 ± 2 seconds and a hardness of 47.9 ± 2.5N.

- Koizumi[46] et al (1997) presented an invention, which related to rapidly saliva tablets using sublimation technique. Compressed tablets of Mannitol did not dissolve in water due to the low porosity. To increase the porosity of tablets sublimation was done. Tablets were prepared by direct compression containing mannitol and camphor. A high porosity was achieved due to formation of many pores due to camphor sublimation. The compressed tablets have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva.

- Shawn A. Mitchell[47] et al studied a compaction process to enhance dissolution of poorly water soluble drugs using low-viscosity HPMC. The purpose of this study was to develop a technique to enhance the dissolution rate of poorly water-soluble drugs with low-viscosity HPMC without the use of solvent or heat addition. The

compaction processes enhanced drug dissolution relative to drug alone and also relative to corresponding loosely mixed physical mixtures. The roller compaction and slugging method produced comparable dissolution enhancement. The mechanism for dissolution enhancement is believed to be a microenvironment HPMC surfactant effect facilitated by keeping the HPMC and drug particles in close proximity during drug dissolution.

- Abdelbary[48] et al (2005) determined the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration. In the present study, they evaluated the disintegration profile of RDT manufactured by main commercialised technologies, using the texture analyzer. In order to simulate as much as possible the oral disintegration of these dosage forms, a new operating structure was developed. This structure mimics the situation in the patient's mouth and provides a gradual elimination of the detached particles during the disintegration process. Moreover, the oral disintegration time of the same products was evaluated by 14 healthy volunteers. Results obtained when artificial saliva at 37^{o}C was employed as disintegration medium were used to correlate the in vitro and oral disintegration times. Excellent correlation was found and in addition, we were able to achieve a qualitative measure of the mouth feel by comparing the thickness of the tablets and the penetration distance obtained from the disintegration profile.

- Fukami[49] et al (2006) formulated a rapidly disintegration tablet in the oral cavity using a Glycine as a disintegrant. Wetting time prepared from carboxymethylcellulose (NS-300) having the hardness of 4kg was 3 seconds. Tablets containing NS-300 showed fastest disintegration compared to other formulations. These results suggest that NS-300 possessed excellent wetting nature and resulted in the rapid disintegration of tablet. Ethenzamide and ascorbic acid were added to the formulation, and their disintegration behaviors were evaluated. Ethenzamide did not affect the disintegration property; however, ascorbic acid prolonged disintegration time. It was suggested that the tablet

formulation containing NS-300 and Glycine was highly applicable to water-insoluble drug, such as Ethenzamide.

- Shirwaiker[50] et al (2004) prepared fast disintegrating tablets of Atenolol. The preparation contained an active ingredient, sugar (mannitol), superdisintegrant and dicalcium phosphate. Required quantities of each ingredient were weighed, mixed and prepared the tablets by dry granulation. All the formulation had disintegration time of less than 70 seconds. Among the three superdisintegrant Ac-Di-Sol showed the highest efficacy. Formulation containing 10 % Ac-Di-Sol showed the least disintegration time of 30 ± 2 seconds compare to Explotab and Polyplasdone XL.

- Mishra [51] et al (2005) prepared rapidly disintegrating tablets of Valdecoxib. The poor aqueous solubility of the drug results in variable dissolution rate and poor bioavailability. In the present, invention tablets were prepared using various superdisintegrant following direct compression. All formulation showed disintegration time of less than 60 seconds along with rapid *in vitro* dissolution. All the formulation showed more than 70 % dissolution in 30 min.

- Amin[52] et al (2005) presented an invention, which relates to fast disintegration tablets for oral administration. Taste masked adsorbents of Ofloxacin were prepared using cationic exchange resins. Taste evaluation of tablets showed complete masking of the bitterness of Ofloxacin. The taste-masked complex of the Ofloxacin was further incorporated into mouth dissolve tablets in combination with Metronidazole benzoate. All the formulation exhibited an in vitro dispersion time less than 50 seconds.

- Remon[53] et al (1997) prepared the rapidly disintegrating tablets by lyophillization. Tablets contained hydrochlorothiazide, Maltrodextrin, hydroxyethylcellulose and gelatin. The solutions were poured into blisters and freeze dried. Maltrodextrin

could be a filler of choice for the production of lyophilized tablets as freeze-drying due to amorphous network, which dissolved in the water with seconds. They evaluated gelatin, xanthan gum and hydroxyethylcellulose a binding agents in the formulation of freeze dried tablets with Maltrodextrin as filling agents.

- Chaudhari[54] et al (2005) prepared fast dissolving tablets of Famotidine. In this study the bitter taste of Famotidine was masked using drug: Eudragit E 100 in different ratios (1:1 to 1:10). For taste masking the ratio was optimized to 1:4 by time intensity. The different superdisintegrant (Ac-Di-Sol, Polyplasdone) with their varying concentration were used for disintegration of tablets in mouth. The formulation containing 2 % of Ac-Di-Sol and Polyplasdone showed 91.89 % and 101.07 % release respectively in 12 min.

- Vijaya[55] et al (2006) prepared Meloxicam rapidly disintegrating tablets by direct compression. The tablets were prepared with three superdisintegrant like SSG, Ac-Di-Sol and L-HPMC. The hardness of tablets was found to be less than 10% and disintegration time of tablets was found to be less than 1 minute, except L-HPMC. In-vitro drug release study showed enhance dissolution rate compared to pure Meloxicam.

- Sreenivas[56] et al (2006) prepared mouth dissolve tablets of Ondansetron by direct compression. In this study a varity of disintergrant like crospovidone, croscarmelose, pregelatinized starch, sodium starch glycolate and L-HPC were selected at 5 % and 10 % concentration. The friability of all the formulation between 0.16 to 0.36 %. The in vitro disintegration time for all formulation varied from 10 to 15 seconds. In all the formulation the drug release was almost up to 80-100% after 15 min.

- Shirwaikar A[57] et al (2006) formulated and evaluated fast dissolving tablets of Granisetron hydrochloride by direct compression method using superdisintegrants. A combination of mannitol and silicified microcrystalline

cellulose (SMCC) in the ration 70:30 was used in the study. Study concluded that crospovidone and croscarmellose sodium are better disintegrants for formulation of fast dissolving tablets of Granisetron HCl.

- Halakatti P.K.[58] et al (2006) formulated rapidly disintegrating tablets of Domperidone by applying two methods. Sodium starch glycolate and treated agar used as superdisintegrants in mass extrusion technique and treated agar method respectively.

- Mahajan H.S.[59] et al (2004) formulated mouth dissolving tablets of Salbutamol sulphate by direct compression method. SSG, croscarmellose sodium, treated agar were used as superdisintegrants while microcrystalline cellulose used as diluents. Formulation containing SSG along with other superdisintegrants showed rapid in-vitro and in-vivo dispersion time, as compared to other formulation.

- Nayak S.M.[60] et al (2004) prepared fast dissolving tablets of Promethazine theoclate using effervescent melt, super disintegration addition and melt technologies. Tablets from effervescent melt and super disintegration addition technique released 92 % and 89 % of the drug at the end of 10 min.

- Kaushik D.[61] et al (2004) prepared mouth dissolving tablets of Olanzepine by effervescent approach. Sodium bicarbonate and citric acid were used as effervescent agent and their ratio was optimized. The study revealed that 10:8 ratio of sodium bicarbonate and citric acid in the Olanzepine mouth dissolving tablets gave a soothing fizz, excellent mouth feel, good palatability and quick dissolution profile.

- Devi V. K.[62] et al (2006) prepared orodispersible tablets of Fluconazole with two different volatilizable compounds viz. ammonium chloride and camphor by wet granulation method. The best formulations were compared with marketed conventional tablets.

- Mahajan H.S.[63] et al (2004) studied on mouth dissolving tablets of Sumatriptan succinate. Tablets were prepared by using disintegrants like sodium starch glycolate, carboxymethyl cellulose sodium and treated agar by direct compression method. The tablets were evaluated for various tests. The study showed that formulation containing sodium starch glycolate and carboxymethyl cellulose was found to give the best results.

- Patel D.M.[64] et al (2004) formulated orodispersible tablets of Rofecoxib by granulation method that carried out by solid deposition method using three superdisintegrants namely SSG, crospovidone, croscarmellose sodium. From that crospovidone giving lowest disintegration time and wetting time as compared to remain superdisintegrants.

- Kuchekar B. S.[65] et al (2006) prepared orodissolving tablets of Promethazine hydrochloride by direct compression method using superdisintegrants, sodium starch glycolate, croscarmellose sodium. Study revealed that formulation containing 4% of SSG and 1-3 % of croscarmellose sodium were found to give the best results.

- Patel D. M.[66] et al (2006) prepared fast dissolving tablets containing solid dispersion of Valdecoxib. They were prepared solid dispersion with mannitol polyethylene glycol 4000, and PVP K12. Valdecoxib solid dispersion with PVP K12 showed maximum drug release hence, the tablet formulation containing Valdecoxib PVP K12 solid dispersion was prepared with a view to improve its water solubility.

- Poornima D. Amin [67] et al (2004) formulated patient compliant dosage form for Roxithromycin. The present study deals with various techniques utilized for taste masking of roxithromycin viz granulation with udragit E100 and complexation with ion exchange resins. Of these, complexation with ion exchange resin yielded complete test masking. The test masked complex was then formulated in to palatable mouth dissolve tablet.

- Amin Purnima[68] et al studied that Indion 414 as superdisintegrant in formulation of mouth dissolve tablets. The present research paper introduces Indion 414, an ion exchange resin, as a new superdisintegrant for pharmaceutical dosage forms. Model drugs belonging to various classes were taste masked and formulated into palatable mouth dissolve tablets. Experiments were carried out to evaluate the disintegrant property of Indion 414 by incorporating Indion 414 in fast disintegrating dosage form like mouth dissolve tablets.

- Mane Avinash[69] et al (2003) formulated highly porous, mouth dissolving tablets of Domperidone using meltable binder polyethylene glycol-4000, a diluent-mannitol and sublimable material like camphor and ammonium bicarbonate. The amounts of volatilizable material were varied from 10% to 60% w/w to obtain various formulations. Two of the formulations having 40% w/w of ammonium bicarbonate and 20% w/w of camphor exhibiting least disintegration time.

- Shishu[70] et al (2006) prepared rapidly disintegrating Diazepam tablets by using microcrystalline cellulose as directly compressible filler and sodium starch glycolate as super disintegrants.

- Gordan[71] et al found that aging decrease the dissolution efficiency of superdisintegrant in wet granulated tablets. The formulation that initially exhibited faster dissolution showed decrease in dissolution after storage. So out of sodium starch glycolate, croscarmellose and crospovidone, croscarmellose is most affected.

4.3 AMLODIPINE BESYLATE

- D.M. McDaid[78] were prepared Amlodipine base from its besylate salt and various physicochemical properties relevant to transdermal delivery determined. Permeation of the drug from a range of hydrophilic and hydrophobic bases through hairless mouse skin was studied and the influence of the penetration enhancers sodium lauryl sulphate 1% and propylene glycol 20% in a sodium carboxymethylcellulose 3% gel base was examined. The flux of drug could be further enhanced using variable percentage of ethanol in the donor phase. The influence of various rate controlling membranes and a contact adhesive on drug permeation was examined. In vivo studies using rabbits were performed to assess the suitability of a reservoir-type device. Employing data obtained from in vitro studies involving human abdominal skin, it was possible to predict the plasma profile resulting from the application of a similar device onto human skin over a period of 1 week and was found to be inadequate for clinical use. No adverse local effects in the animal model arising from the application of the transdermal device were observed by them.

- Dong-Jin Janga[79] had improve the bioavailability and photostability of poorly water-soluble and photosensitive amlodipine, dry emulsion (DE) which was prepared by spray-drying the oil-in-water emulsion of amlodipine. Labrafil M 1944 CS and dextrin were employed as oil phase and matrix material, respectively. Dispersing DE in distilled water formed an emulsion with a mean droplet size 1.4-fold larger than that of the homogenized amlodipine emulsion before spray-drying (0.24±0.30 _m versus 0.17±0.02 _m). The mean droplet size of DE remained unchanged during 6-month storage at room temperature. 94.4% versus 33.1% of amlodipine remained intact after 24-h UV irradiation of amlodipine as DE formulation or as powder. These data suggest that DE formulation greatly improved the photostability of amlodipine, as well as

increasing the physical stability of emulsion systems. *In vitro* release of DE was higher than that of amlodipine powder (66% versus 48% release at 60 min). Consequently, DE formulation resulted in 2.6- and 2.9-fold higher *C*max and AUC0–24h of amlodipine compared after oral administration of amlodipine powder in rats. Their data suggest that the DE may be a potential oral dosage form for amlodipine to improve its bioavailability.

- Yinghua Suna[80] had developed and evaluated a drug-in-adhesive transdermal patch for S-amlodipine (S-AM) free base. Initial in vitro experiments were conducted to optimize the formulation parameters before transdermal delivery in rats. The effects of the type of adhesive and the content of permeation enhancers on S-AM free base transport across excised rat skin were evaluated. For in vivo studies, patches were administered transdermally to rats while orally administered S-AM in suspension and intravenously administered S-AM solution were used as controls. The plasma level of SAM following transdermal application could be maintained for 72 h. After transdermal administration to rats, the absolute bioavailability was 88.8% for S-AM free base. After dose normalization, the areas under the plasma concentration–time curve (AUC) and mean residence times (MRT) were evidently increased and extended, respectively. This suggests that the transdermal application of S-AM in a drug-in-adhesive transdermal patch may be used for the treatment for hypertension.

- Atram SC[81] had developed an optimized bilayer tablet for antihypertension patients using Metoprolol succinate and Amlodipine besylate as a model drug candidate by optimization technique. A 3^2 factorial design was employed in formulating bilayer tablet with individual release layer i.e. sustained release layer and immediate release layer. The independent variables selected both cases HPMC(X1), Starch 1500 (X2) and SSG (X1), MCC (X2), respectively. Two dependent variables were considered: t50 (Y1), Q12 (Y2) and t50 (Y1), Q2 (Y2),

respectively. The main effect and interaction terms were quantitatively evaluated using mathematical model. Bilayer tablets were evaluated for thickness, hardness, friability, drug content and in vitro dissolution studies. The drug release of Amlodipine besylate and Metoprolol succinate depicted non-fickian diffusion and Super Case II transport mechanism, respectively.

- Menger Chung[82] had studied bioequivalence of combination tablets containing amlodipine besylate/atorvastatin calcium with coadministered matching doses of amlodipine besylate and atorvastatin. calcium tablets was investigated in randomized, 2-way crossover studies in healthy volunteers (N = 126). Subjects received a single dose of the amlodipine/atorvastatin tablet or coadministered matching doses of amlodipine and atorvastatin at the highest (10/80 mg; n = 62) and lowest (5/10 mg; n = 64) dose strengths. Atorvastatin geometric mean ratios for maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve (AUC) for the highest and lowest dose strengths were 94.1 and 98.8, and 104.5 and 103.8, respectively. Amlodipine geometric mean ratios for C_{max} and AUC for the highest and lowest dose strengths were 100.8 and 103.4, and 100 and 102.7, respectively. The 90% confidence intervals for all comparisons were within 80% to 125%, demonstrating bioequivalence for amlodipine and atorvastatin at both dose strengths. Use of amlodipine/atorvastatin combination tablets may provide a more integrated approach to treatment of cardiovascular risk.

- Abdoh[83] studied the compatibility of amlodipine besylate in its solid formulations with various drug excipients. The various factors affecting amlodipine besylate stability were studied using high-performance liquid chromatography (HPLC). It has been found that binary 1:1 mixtures of amlodipine besylate and an excipient are stable at 65°C and 40°C/75% RH. Further investigations were conducted to

study the stability of amlodipine besylate in multicomponent mixtures, including mixtures with actual formulations. The study reveals that mixtures of lactose, magnesium stearate, and water induce some instability on amlodipine besylate. The major degradation product confirmed by HPLC-mass spectrometry is amlodipine besylate glycosyl. This is in conformity with the well-known Maillard reaction between primary amines and lactose. Thus, lactose-free amlodipine formulations were recommended by them from the safety, quality, efficacy, and process cost points of view.

- Nahata MC[84] had determined the stability of amlodipine besylate in two liquid dosage forms under refrigeration and at room temperature. Commercially available amlodipine tablets (Norvasc-Pfizer) were used to prepare two suspensions: one in extemporaneously prepared 1% methylcellulose in syrup (1:1), and another in equal volumes of commercially available OraPlus/OraSweet. Each suspension containing amlodipine 1 mg/mL was stored in 10 plastic prescription bottles; 5 were stored at 4 degrees C and 5 at 25 degrees C. Samples were collected immediately after preparation (day 0) and on days 7, 14, 28, 42, 56, 70, and 91. Amlodipine concentration was measured by stability-indicating HPLC method. Physical and chemical stability (> 90% of the initial concentration) of amlodipine in the two extemporaneously prepared suspensions during storage in plastic prescription bottles at 4 degrees C and 25 degrees C. Observed mean concentrations exceeded 90% of the initial concentrations in both suspensions for 91 days at 4 degrees C and 56 days at 25 degrees C. No noticeable change in physical appearance or odor was observed; pH changed slightly in the methylcellulose-containing formulation stored at 25 degrees C. So Amlodipine was stable in two suspensions when stored in plastic prescription bottles for 91 days at 4 degrees C or 56 days at 25 degrees C. These formulations may be considered for pediatric or elderly patients who are unable to swallow tablets. The liquid dosage form would also permit accurate administration of amlodipine doses to infants and young children based on their body weight.

- Fiorenzo Mignini[85] has investigated open, randomized, two-period crossover trial in 24 healthy volunteers over a 144 h period the bioequivalence of amlodipine maleate tablets 10 mg versus amlodipine besylate tablets (Norvasc® 10 mg). Plasma amlodipine concentrations were assessed by ultra performance liquid chromatography interfaced with a double quadrupole mass spectrometer. The area under the curve total (AUC_t) and the area under the curve to infinity (AUC_{inf}) values, peak plasma concentration (C_{max}), and time to attain peak (t_{max}) were not statistically different between the two drugs. AUC_t and AUC_{inf} values were higher ($p < 0.05$) in females than in males. The tolerability profile was comparable for the two salts of amlodipine. These findings indicate that amlodipine maleate and besylate are bioequivalent and were well tolerated, which suggests that the plasma kinetics of amlodipine depend on the properties of the molecule itself. Hence, the two salts investigated could be used interchangeably in clinical practice.

AIM OF PRESENT INVESTIGATION

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine had a strong blocking action on both the L-type and N-type Ca2+ channels expressed in the oocyte.

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. Approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Elimination half-life is about 30 to 50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Following administration of therapeutic doses to patients with hypertension, Amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

Conventional amlodipine besylate tablets available in the market are not suitable for acute hypertension conditions where quick onset of action is required. Besides, the conventional tablets also show poor patient compliance particularly by the geriatric & pediatric patients who experience difficulty in swallowing tablets or capsules which is a common problem among all age group. For these reason, tablet that can dissolve or disintegrate in oral cavity, have attracted a great deal of attention to provide the patients with the most conventional mode of administration and to overcome the problems of poor bioavailability.

A solid oral dosage form that dissolves or disintegrates rapidly in oral cavity resulting in a solution or suspension with out need for water is known as fast dispersing

dosage form or Mouth dissolving tablets. When this type of tablet is placed in to the mouth, the saliva will rapidly dissolve tablet.

Thus present work was aimed to formulate MDT of amlodipine besylate using super disintegrants which provide better dissolution.

Identification of amlodipine was carried out by using melting point estimation, by UV spectrophotometrically, and by IR spectroscopy & drug was identified as pure amlodipine besylate. Estimation of amlodipine was carried out by standard curve in 0.01 N HCl media.

A direct compression technique was used to prepare MDT as it is economical, simple, less time consuming. The formulations were evaluated for % friability, wetting time, disintegration time, & in-vitro drug release study.

3^2 factorial design was employed to study the effect of independent variables, concentration of crospovidone & HPC-EXF on disintegration time & friability by using contour plot & 3 D surface plot

Amlodipine besylate MDTs was compared with Amlodipine besylate conventional release tablets. By experiments, it was estimated that Amlodipine besylate MDT was dissolved more rapidly than Amlodipine besylate conventional release tablets

Accelerated Stability study of Amlodipine besylate MDT was carried out, and no higher degradation was seen in studies.

An attempt was made to prepare MDT of Amlodipine besylate with appropriate mechanical strength which would disintegrate in oral cavity in less than 30 secs & provide immediate control over hypertension due to faster release of amlodipine in to GI tract & total drug would be released in with in 5 mins

1. MOUTH DISSOLVE TABLETs

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desire therapeutics concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. This is possible through administration of conventional dosage form in a particular dose and at a particular frequency.[1] Thus drug may be administered by variety of routes in a variety of dosage forms.

Drugs are more frequently taken by oral administration. Although a few drugs taken orally are intended to be dissolved within the mouth, the vast majority of drugs taken orally are swallowed. Compared with alternate routes, the oral route of drug administration is the most popular and has been successfully used for conventional delivery of drug. It is considered most natural, uncomplicated, convenient, safe means of administering drugs, greater flexibility in dosage form design, ease of production and low cost.[2]

Tablets and hard gelatin capsules constitute a major portion of the drug delivery systems that are currently available. However, many patient groups such as elderly, children, and patients mentally retarted, uncooperative, nauseated, or on reduced liquid intake diets have difficulty in swallowing these dosage forms. Many elderly persons face difficulties in administering conventional oral dosage forms because of hand tremors and dysphasia. Swallowing problem is common in children because of their underdeveloped muscular and nervous systems. In some cases like motion sickness, sudden episodes of allergic attack or coughing, and during unavailability of water, swallowing conventional tablets is difficult. To fulfill these medical needs, formulators have devoted considerable efforts for developing a novel type of dosage form for oral administration known as ***MOUTH DISSOLVING TABLETs (MDT).***[3]

MOUTH DISSOLVING TABLET [4, 5]

This is an innovative tablet technology where the dosage form containing active pharmaceutical ingredients disintegrates rapidly, usually in a matter of seconds, without the need for water, providing optimal convenience to the patient. Innovators and inventor companies have given these tablets various names such as orally disintegrating tablets (ODT), mouth dissolving (MD), fast melting, fast dissolving or Orodisperse.

The European Pharmacopoeia defines Orodisperse as a tablet that can be placed in the mouth where it disperses rapidly before swallowing. Researchers have formulated MDT for various categories of drugs, which are used for therapy in which rapid peak plasma concentration is required to achieve desired pharmacological response. These include neuroleptics, cardiovascular agents, analgesics, anti-allergic and drugs for erectile dysfunction.

MOUTH DISSOLVING TABLET (MDT) is a solid unit dosage form containing drugs that disintegrates rapidly and dissolves in the mouth without taking water within 60seconds or less. Drug absorption through local oral–mucosal and through pre and post gastric parts of G.I.T. MDTs are also called as Oro-disperse, mouth dissolving, rapidly disintegrating, fast melt, quick dissolve and freeze dried wafers.

MDT are generally classified into two types

ORAL SUBLINGUAL TABLET:

- MDT as a solid dosage form which disintegrates rapidly, within a matter of seconds, under the tongue.

ORAL DELAYED RELEASE:

- when place upon the tongue, releases a drug (or drugs) at a time other than promptly after administration.

CHARACTERISTICS OF MOUTH DISSOLVING TABLET:

- Convenient and easy to administer as does not require water for oral administration
- Durable and sufficient strength to withstand the rigors of the manufacturing process and manufacturing handling
- Pleasant mouth feel
- Insensitive to environmental conditions such as humidity and temperature.
- Improved taste without any residue in the mouth after disintegration
- Adaptable and amenable to existing processing and packaging machinery
- Cost effective
- Compatible with taste masking

BENEFITS OF MOUTH DISSOLVING TABLET:

- Administered without water, anywhere, any time.
- Suitability for geriatric and pediatric patients, who experience difficulties in swallowing and for the other groups that may experience problems using conventional oral dosage form, due to being mentally ill, the developmentally disable and the patients who are un-cooperative, or are on reduced liquid intake plans or are nauseated
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid on set of action required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

LIMITATIONS OF MOUTH DISSOLVING TABLET:

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

SELECTION OF DRUG :

The ideal characteristics[1] of a drug for in vivo dissolution from an MDT include

- No bitter taste
- Dose lower than 20mg
- Small to moderate molecular weight
- Good stability in water and saliva
- Partially non ionized at the oral cavities pH
- Ability to diffuse and partition into the epithelium of the upper GIT (logp>1, or preferably>2)
- Ability to permeate oral mucosal tissue

UNSUITABLE DRUG CHARACTERSTICS FOR MDT;

- Short half-life and frequent dosing
- Very bitter or otherwise unacceptable taste because taste masking cannot be achieved
- Required controlled or sustained release.

➢ *Taste masking Methods:*

The success of this delivery system is because of good taste. Taste is a chemical reaction derived from sensory responses from the four main taste perceptions salt, sour, bitter and sweet[5]. The drugs are mostly bitter in nature. Skillful taste masking is needed to hide the bitter taste in MDT formulations. This can be achieved by using combination of right flavour and right sweetners. The taste masking in MDT has more influences on dissolution method development, specifications, and testing. Following methods are used in Taste masking is given as follows:

- Simple wet granulation method or roller compaction[6] of other excipients. Spray drying can also employed to shroud the drug.
- Co-sifting method the large quantities of water soluble polymers are used as an excipient. Drugs can be sifted twice or thrice in small particle size mesh with excipients such as sweeteners and flavors etc.
- Hydroxy propyl methyl cellulose, Ethyl cellulose, Methacrylates, Kollicoat, Polyvinyl pyrollidone polymers can be used to coat to mask the taste.
- Cyclodextrins can be used to trap or complex, cyclodextrin help to solubilze many drugs.
- Drug complexation[7] with resinates are insoluble and no taste in oral cavity. With the correct selection of the ion exchange resin, the drug will not be released in the mouth so that the patient does not taste the drug when it is swallowed. When the drug resinate comes into contact with the gastrointestinal fluids, such as the acid of the stomach, the drug is released from the resinate, directly into solution and then absorbed in the usual way. The resin passes through the GI tract without being absorbed. Examples of drugs where this technique has been successfully demonstrated include ranitidine, risperidone and paroxetine.
- Other methods include hot melt and supercritical fluids.

TECHNIQUES USED FOR THE FORMULATION OF MOUTH DISSOLVING TABLET:

Many techniques have been reported by various researchers for the formulation of MOUTH DISSOLVING TABLET.

1. Freeze-Drying or Lyophilization: [6, 7, 8]

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of MDT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is dosed by weight and poured in the wells of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminium foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophillization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

2. Tablet Molding: [9, 10]

Molding process is of two types i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydroalcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is than removed by air-drying. The tablets manufactured in this manner are less compact than the compressed

tablets and posses a porous structure that hastens dissolution. The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°C under vacuum. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology. The taste masked drug particles were prepared by spray congealing, a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol, and an active ingredient, into a lactose based tablet triturate form. Compared to the lyophillization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture.

3. Spray Drying: [11, 12]

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose or crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate & croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

4. Sublimation: [13, 14, 15]

To generate a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride may be compressed

along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane, benzene can be used as pore forming agents.

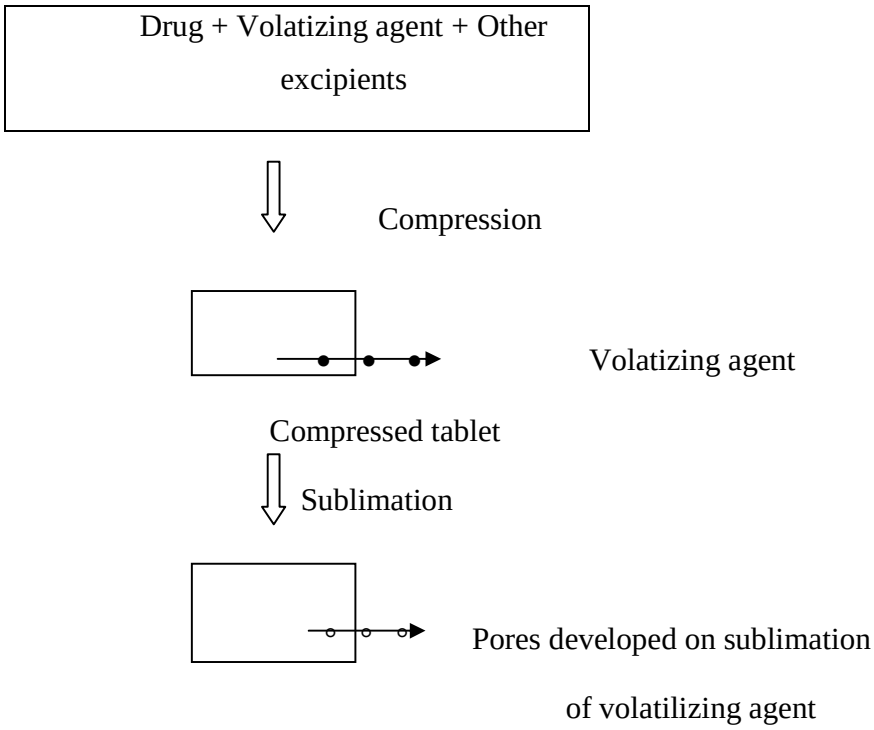


Fig. 1: Steps involved in Sublimation

5. Direct Compression: [16, 17]

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied for the preparation of MDT because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

(a) Superdisintegrants:

In many mouth dissolving tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

Factors to be considered for selection of superdisintegrants[9]:

- It should produce rapid disintegration(hydrophilic) when tablet meets saliva in the mouth
- It should be **compactable** enough to produce less-friable tablets.
- It can able to produce good mouth feel to the patient. Thus, small **particle size** are preferred to achieve patient compliance.
- It should has good flow since it improve the **flowability** of the total blend.
- **Super disintegrants:** Crosspovidone, Microcrystalline cellulose, sodium starch glycollate, sodium carboxy methyl cellulose, pregelatinzed starch, calcium carboxy methyl cellulose, and modified corn starch. Sodium starch glycollate has good flowability than crosscarmellose sodium. Cross povidone is fibrous nature and highly compactable.
- **Flavors:** Peppermint flavor, cooling flavor, flavor oils and flavoring aromatic oil, peppermint oil, clove oil, bay oil, anise oil, eucalyptus oil thyme oil, oil of bitter almonds. Flavoring agents include, vanilla, citrus oils, fruit essences
- **Sweeteners:** Aspartame, Sugars derivatives
- **Fillers:** Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulfate, pregelatinized starch, magnesium trisilicate, aluminum hydroxide.

- **Surface active agents:** sodiumdoecylsulfate, sodiumlaurylsulfate, polyoxyethylene sorbitan fatty acid esters (Tweens), sorbitan fatty acid esters (Spans), polyoxyethylene stearates.
- **Lubricants:** Stearic acid, Magnesium stearate, Zinc state, calcium state, talc, polyethylene glycol, liquid paraffin, magnesium laury sulfate, colloidal silicon dioxide.

(b) Sugar Based Excipients:

This is another approach to manufacture MDT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel. Mizumito et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate.

Type 1 saccharides (lactose and mannitol) exhibit low mould ability but high dissolution rate.

Type 2 saccharides (maltose and maltilol) exhibit high mould ability and low dissolution rate.

6. Cotton Candy Process: [18]

The cotton candy process is also known as the “candy floss” process and forms on the basis of the technologies such as Flash Dose30 (Fuisz Technology). An MDT is formed using a candy floss or shear form matrix; the matrix is formed from saccharides or polysaccharides processed into amorphous floss by a simultaneous action of flash melting and centrifugal force. The matrix is then cured or partially recrystallised to provide a compound with good flow properties and compressibility. The candy floss can then be milled and blended with active ingredients and other excipients and subsequently compressed into MDT.

However, the high processing temperature limits the use of this technology to thermo-stable compounds only.

7. Mass-Extrusion: [19, 20]

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

PATENTED TECHNOLOGIES FOR MOUTH DISSOLVING TABLET:[21 -25]

1) Zydis Technology.
2) Durasolve Technology.
3) Orasolve Technology.
4) Flash Dose Technology.
5) Wow Tab Technology.
6) Flash Tab Technology.
7) Oraquick Technology.
8) Quick –Dis Technology.
9) Nanocrystal Technology.

1) Zydis Technology:

Zydis, the best known of the mouth-dissolving/disintegrating tablet preparations, was the first marketed new technology tablet. A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile, and must be dispensed in a special blister pack. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds. A major claim of the Zydis product is increased bioavailability compared to traditional tablets. Because of its dispersion and dissolution in saliva while still in the oral cavity, there can be a substantial amount of pre-gastric absorption from this formulation. Any pre-gastric absorption avoids first-pass metabolism and can be an advantage in drugs that undergo a great deal of hepatic metabolism. There are some disadvantages to the Zydis technology. As mentioned earlier, the Zydis formulation is very lightweight and fragile, and therefore should not be stored in backpacks or the bottom of purses. Finally, the Zydis formulation has poor

stability at higher temperatures and humidities. It readily absorbs water, and is very sensitive to degradation at humidities greater than 65%.

2) Orasolv Technology:

OraSolv was Cima's first mouth-dissolving/disintegrating dosage form. The OraSolv technology, unlike Zydis, disperses in the saliva with the aid of almost imperceptible effervescence. The OraSolv technology is best described as a mouth disintegrating tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The major disadvantage of the OraSolv formulations is its mechanical strength. The OraSolv tablet has the appearance of a traditional compressed tablet. However, the OraSolv tablets are only lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets. For that reason, Cima developed a special handling and packaging system for OraSolv. An advantage that goes along with the low degree of compaction of OraSolv is that the particle coating used for taste masking is not compromised by fracture during processing. These formulations can accommodate single or multiple active ingredients and tablets containing more that 1.0 g of drug have been developed. Their disintegration time is less than 30 seconds. The OraSolv formulations are not very hygroscopic.

3) Durasolv Technology:

DuraSolv is Cima's second-generation mouth-dissolving/disintegrating tablet formulation. Produced in a fashion similar to OraSolv, DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. DuraSolv tablets are prepared by using conventional tabletting equipment and have good rigidity (friability less than that 2%). The DuraSolv product is thus produced in a mouther and more cost-effective manner. DuraSolv is so durable that it can be packaged in traditional blister packaging, pouches or vials. One disadvantage of DuraSolv is that the technology

is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction.

4) Flash Dose Technology:

The FlashDose technology utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. This procedure has been patented by Fuisz and is known as Shear form. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue. Flash dose tablets consist of self–binding shear form matrix termed as “floss”. Shear form matrices are prepared by flash heat processing and are of two types.

5) Wowtab Technology

The Wowtab mouth-dissolving/disintegrating tablet formulation has been on the Japanese market for a number of years. The WOW in Wowtab signifies the tablet is to be given “With Out Water”. The Wowtab technology utilizes sugar and sugar-like (e.g., mannitol) excipients. This process uses a combination of low mouldability saccharides (rapid dissolution) and high mouldability saccharide (good binding property).The two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and mouth dissolution rate. Due to its significant hardness, the Wowtab formulation is a bit more stable to the environment than the Zydis or OraSolv. It is suitable for both conventional bottle and blister packaging. The Wowtab product dissolves quickly in 15 seconds or less.

6) Flashtab Technology

Prographarm laboratories have patented the Flashtab technology. This technology involves the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, extrusion-spheronization, simple pan coating methods and microencapsulation. The microcrystals of microgranules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation, and compressed into tablets. All the processing utilized the conventional tabletting technology, and the tablets produced are reported to have good mechanical strength and disintegration time less than one minute.

7) Oraquick Technology

The Oraquick mouth-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. The taste masking process does not utilize solvents of any kind, and therefore leads to mouther and more efficient production. Also, lower heat of production than alternative mouth-dissolving/disintegrating technologies makes Oraquick appropriate for heat-sensitive drugs. KV Pharmaceutical claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking. Oraquick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the Oraquick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives.

8) Quick –Dis Technology

Lavipharm has invented an ideal intra-oral mouth dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intra-oral drug delivery system, trademarked Quick-Dis™, is Lavipharm's proprietary patented technology and is a thin, flexible, and quick-dissolving film. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. The typical disintegration time is only 5 to 10 seconds for the Quick-Dis™ film with a thickness of 2 mm. The dissolving time is around 30 seconds for Quick Dis™ film with a thickness of 2 mm.

9) Nanocrystal Technology

For MOUTH DISSOLVING TABLETs, Elan's proprietary NanoCrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using NanoCrystal technology. NanoCrystal particles are small particles of drug substance, typically less than 1000 nm in diameter, which are produced by milling the drug substance using a proprietary wet milling technique. NanoCrystal colloidal dispersions of drug substance are combined with water-soluble ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds.

2. SUPERDISINTEGRANTS:

To achieve rapid disintegration, direct-compression MDT formulations typically contain high levels of a superdisintegrant. Depending on the level and characteristics of the active pharmaceutical ingredient (API) and the desired release profile, the levels of superdisintegrant used can be 8–10 wt % of the formulation, and it can be higher or lower in some cases. Thus, in developing an MDT formulation for direct compression, choosing the optimal superdisintegrant is critical.

SELECTING THE SUPERDISINTEGRANTS[26,27]**:**

Although the superdisintegrant primarily affects the rate of disintegration, when used at high levels it can also affect mouth feel, tablet hardness, and friability. Thus, several factors must be considered when selecting a superdisintegrant.

- ***Disintegration*:** The disintegrant must quickly wick saliva into the tablet to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration in the mouth.

- ***Compactability*:** When manufacturing an ODT, it is desirable to have tablets with acceptable hardness at a given compression force to produce robust tablets that avoid the need to use specialized packaging while maximizing production speed. Thus, a more compactable disintegrant will produce stronger, less-friable tablets.

- ***Mouth feel:*** To achieve patient compliance, ODTs must provide a palatable experience to the patient. Large particles can result in a gritty feeling in the

mouth. Thus, small particles are preferred. If the tablet forms a gel-like consistency on contact with water, however, it produces a gummy texture that many consumers find objectionable.

- ***Flow:*** As with all direct-compression tablet formulations, attaining good flow and content uniformity is important to achieving the required dosage per unit. In typical tablet formulations, superdisintegrants are used at 2–5 wt % of the tablet formulation. With ODT formulations, disintegrant levels can be significantly higher. At these higher use levels, the flow properties of the disintegrant are more important because it makes a greater contribution to the flow characteristics of the total blend.

MECHANISM OF SUPERDISINTEGRANTS [28,29,30]

The tablet breaks to primary particles by one or more of the mechanisms listed below

1. Because of heat of wetting (air expansion)

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and can not describe the action of most modern disintegrating agents.

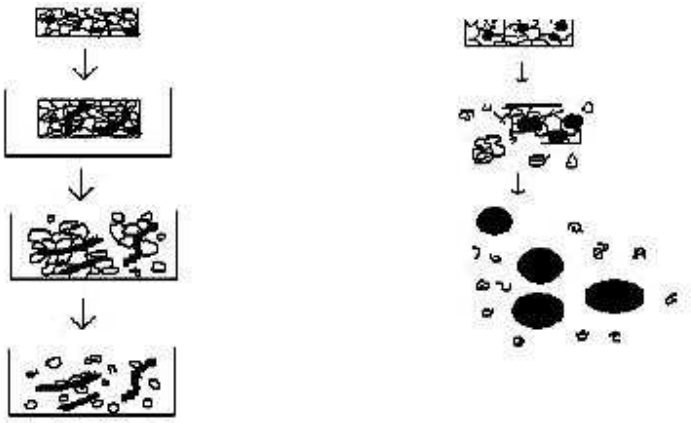
2. Swelling:

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

3. Porosity and capillary action (Wicking):

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

WICKING **SWELLING**



Water is pulled into pores by disintegrant and reduced the physical bonding force between particles.

Particles swell and break up the matrix form within; swelling setup; localized stress spreads throughout the matrix.

Fig. 2: Disintegration of Tablet by Wicking and Swelling

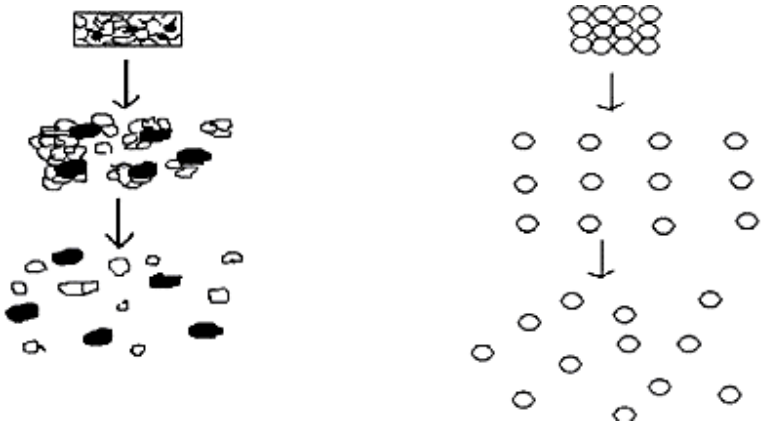
4. Due to disintegrating particle/particle repulsive forces:

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

5. Due to deformation.

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a break up of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

DEFORMATION **REPULSION**



Particles swell to precompression size and break up the matrix

Water is drawn into pores and particles repel each other because of the resulting electrical force

Fig. 3: Disintegration of Tablet by Deformation and Repulsion

6. Due to release of gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

***Table 1*: List of Superdisintegrants**

Superdisintegrants	Example	Mechanism of action	Special comment
Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose® Solutab® Vivasol® L-HPC	Crosslinked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation -Starch free
Crosspovidone Crosspovidon M® Kollidon® Polyplasdone®	Crosslinked PVP	-Swells very little and returns to original size after compression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab® Primogel®	Crosslinked starch	-Swells 7-12 folds in < 30 seconds	-Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine®	Crosslinked alginic acid	-Rapid swelling in aqueous medium or wicking action	-Promote disintegration in both dry or wet granulation
Soy polysaccharides Emcosoy®	Natural super disintegrant		-Does not contain any starch or sugar. Used in nutritional products.

Table 2: *Commercially Available MOUTH DISSOLVING TABLETs*[30]

TECHNOLOGIES	***TRADE NAME***	***ACTIVE INGREDIENT***	***MANUFACTURER***
Freeze Drying	Feldene Fast Melt	Piroxicam	Pfizer, USA
	Claritin Redi Tab	Loratidine	Schering plough, USA
	Maxalt MLT	Rizatriptan	Merck, USA
	Zyprexia	Olanzepine	Eli Lilly, USA
	Pepcid RPD	Famotidine	Merck, USA
	Zofran ODT	Ondansetron	Glaxo, UK
	Zooming ZMT	Zolmitriptan	AstraZeneca, USA
	Zelapar TM	Selegilline	Amarin,UK
Disintegrant Addition	Tempra Quicklets	Acetaminophen	Bristol Myers, USA
	Febrectol	Paracetamol	Prographarma, France
	Nimulid MDT	Nimesulide	Panacea Biotech, India
	Torrox MT	Rofecoxib	Torrent pharma, India
	Olanex Instab	Olanzapine	Ranbaxy, India
	Romilast	Montelukast	Ranbaxy, India
Sugar Based Excipient	Benadryl Fastmelt	Diphenhydramine & Pseudoephedrine	WarnerLambert, USA

- ***Evaluating physical characteristics of commercial superdisintegrants***[26,32,33]

  Currently available disintegrants were evaluated for particle size, particle-size distribution, flowability, compactability, particle shape, and morphology.

The following superdisintegrants were studied:

- **Crosspovidone A1** (standard particle-size grade) (Polyplasdone XL, International Specialty Products, Wayne, NJ);
- **Crosspovidone A2** (fine particle-size grade) (Polyplasdone XL-10, ISP);
- **Crosspovidone B** (Kollidon CL, BASF, Ludwigshafen, Germany);
- **sodium starch glycolate** (Explotab, JRS Pharma, Patterson, NY);
- **Crosscarmellose sodium**(Ac-Di-Sol, FMC, Philadelphia, PA).

- Crospovidone is an insoluble, neutral cross-linked homopolymer of N-vinyl-2-pyrrolidone. It is available in various particle sizes.
- The *US Pharmacopeia* defines sodium starch glycolate as the sodium salt of a carboxymethyl ether of starch or of a cross-linked carboxymethyl ether of starch, and crosscarmellose sodium is defined as the sodium salt of a cross-linked, partly O-(carboxymethylated) cellulose.

The selection of the optimal disintegrant for a formulation depends on a consideration of the combined effects of all of these factors:

(a) Particle size and distribution. A comparison of particle sizes of various disintegrants is shown in Table I and Figure 1.

Table I: Particle size and flowability index.

Superdisintegrant	Typical average particle size (μm)	Flowability index
Crospovidone A1	115	50
Crospovidone A2	30	47
Crospovidone B	110	44
Croscarmellose sodium	50	31
Sodium starch glycolate	50	58

Table: Particle size and flowability index.

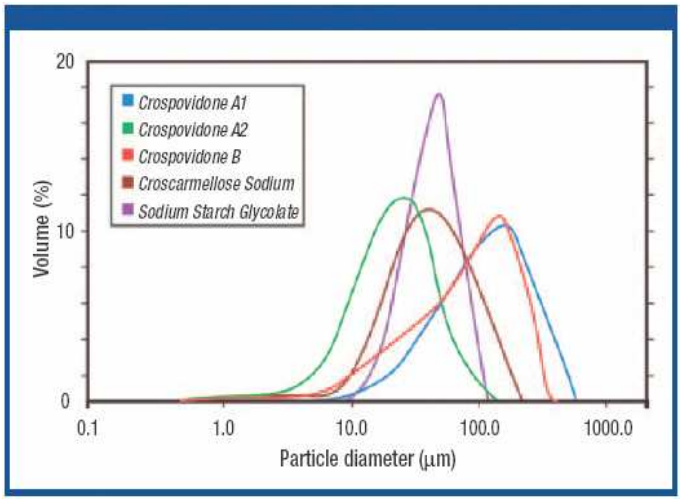


Figure I

Sodium starch glycolate and crosscarmellose sodium show similar average particle sizes; however, sodium starch glycolate has a narrower distribution, which contributes to the good flow properties. The particle size differences between the various types of crospovidone are shown. Because crospovidone

A2 offers the smallest average particle size (~30 μm), it is often preferred because small particles result in a smoother mouth feel.

(b) Flowability. Flowability index results are shown in Table I. Sodium starch glycolate provides the best flow as a result of its spherical particle morphology and narrow particle size distribution.

(c) Particle shape and morphology. When examined under a scanning electron microscope, sodium starch glycolate particles are spherical (Figure 2). Crospovidone particles appear granular and highly porous, although crospovidone B particles appear less porous. This porous particle morphology facilitates rapid wicking of liquid into both particle and tablet and contributes to the compactability of the material. Crosscarmellose sodium particles have a fibrous structure.

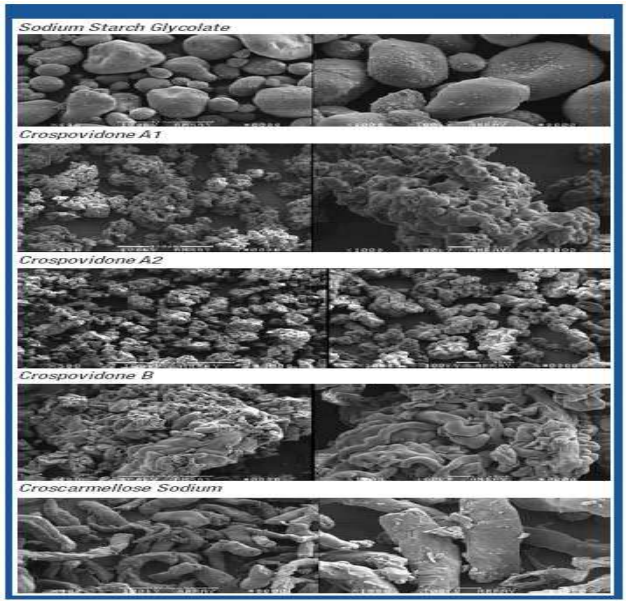


Figure II

(d) Compactability. The compactability of each of the disintegrants was evaluated by comparing the breaking force, at various compression forces, of pure compacts of each disintegrant with small amounts of lubricant and glidant added (see Figure 3). Results indicate that crospovidone is the most highly compactable disintegrate tested, thus producing the highest tablet-breaking force at a given compression force.

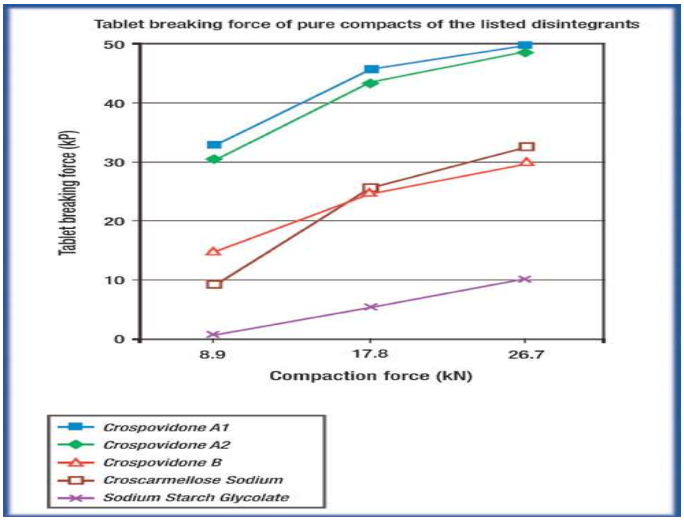
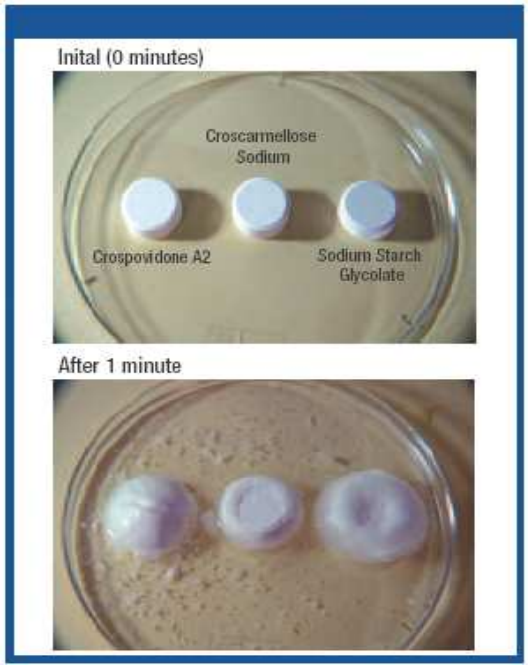


Figure III

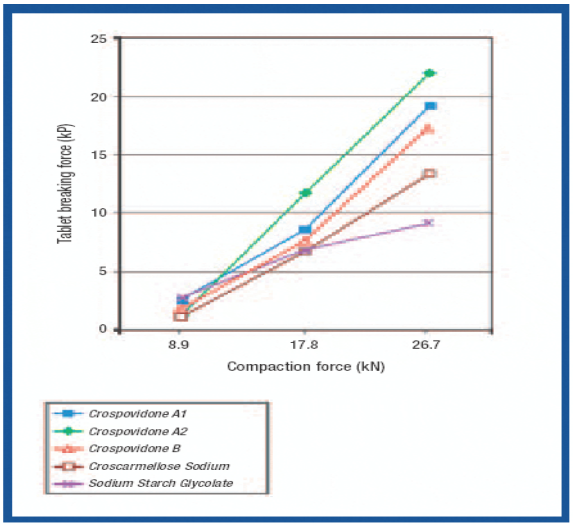
Nonetheless, the results also show that crospovidone A1 and B, with similar particle size, perform significantly differently. Crospovidone A1 is more compactable than crospovidone B.



When representative placebo tablets with crospovidone A2, sodium starch glycolate, and croscarmellose sodium were placed in a Petri dish with a small amount of water, the relative ability of the various disintegrants to wick water into the tablet was observed. One minute after contact with water, the tablet containing crospovidone A2 was fully hydrated and soft throughout because crospovidone quickly wicks water into the tablet. Meanwhile, the centers of the tablets made with sodium starch glycolate and croscarmellose sodium remained dry and hard. Although the tablet with sodium starch glycolate swelled, the outer edge appeared gel-like.

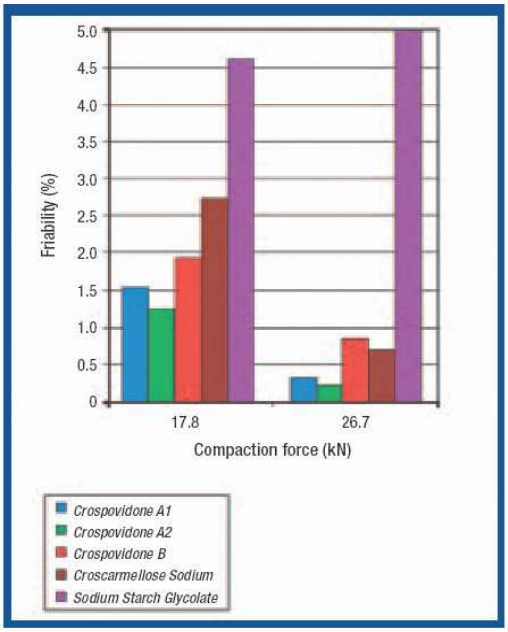
Relation between different pharmaceutical properties[26,34,35]*:*

(1) Relation between compaction force & tablet breaking force:



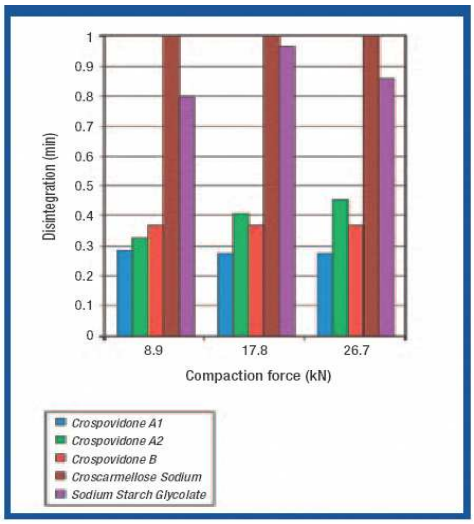
As per graph, it is concluded that, as compaction force increases tablet breaking force also increases. Crosspovidone has highest linearity between compaction force & tablet breaking force

(2) Relation between compaction force & friability:



As per graph, as compaction force increases, friability decreases. Minimum friability is of Crosspovidone A2 at compaction force 26.7 kN.

(3) Relation between compaction force & Disintegration:



As compaction force increases, disintegration time increases.

3. AMLODIPINE BESYLATE:

Drug Profile:

1. Drug class: Antihypertensive

2. Category: second generation dihydropyridamol Ca++ channel blocker

3. CAS number[36]: 88150-42-9

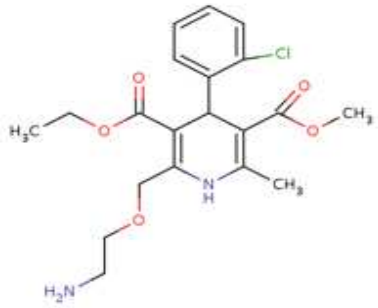
4. Official status: Drug is official in USP, IP, BP and EP.

5. Chemical name[36]***:*** 3-Ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate.

6. Molecular formula[36]: $C_{20}H_{25}ClN_2O_5$

7. Molecular weight[36]: 408.879 g/mol

8. Structural formula[36]***:***



9. Physicochemical properties:

a) Description and Solubility[3]: a white powder. It is slightly soluble in water and isopropanol; freely soluble in methanol; and sparingly soluble in dehydrated alcohol.

b) Melting point: 178-179^{o}C

c) Experimental Water Solubility- 75.3 mg/L

d) Predicted Water Solubility- 7.40e-03 mg/mL

e) Experimental LogP/Hydrophobicity- 1.9

f) Predicted LogP- 2.22

g) Optical rotation4: Between -0.10° & +0.10° at 20°C (solution 10mg/ml in methanol).

h) Dissociation constant (Pka)5: 8.6

i) Partition coefficient (log p)5: (o/w) 3.0

10. Storage condition[39]:

Preserve in tight container, protected from light, store at room temperature.

11. Pharmacological action and clinical pharmacology:

a) Mechanism of action[37]:

- Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle.
- Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites.

- Amlodipine had a strong blocking action on both the L-type and N-type Ca2+ channels expressed in the oocyte. The potency of the amlodipine block on the N-type Ca2+ channel was comparable to that on the L-type Ca2+ channel.
- The blocking action of amlodipine on the N-type Ca2+ channel was dependent on holding potential and extracellular pH, as has been observed with amlodipine block on the L-type Ca2+ channel. A depolarized holding potential and high pH enhanced the blocking action of amlodipine,
- Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa = 8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.
- The time course of block development by amlodipine was similar for L-type and N-type Ca2+ channels. However, it was slower than the time course of block development by nifedipine for the L-type Ca2+ channel.
- Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.
- The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

    - ✓ *Exertional Angina*: In patients with exertional angina, amlodipine reduces the total peripheral resistance (after load) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

- ✓ *Vasospastic Angina*: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A_2 analog in experimental animal models and in human coronary vessels *in vitro*. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in vasospastic (Prinzmetal's or variant) angina.

b) Pharmacokinetics and Metabolism:

- After oral administration of therapeutic doses of amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%.
- The bioavailability of amlodipine is not altered by the presence of food.
- Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.
- *Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients.
- Elimination from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours.
- Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.
- The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.
- Elderly patients and patients with hepatic insufficiency have decreased clearance of Amlodipine with a resulting increase in AUC of approximately 40 to 60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

c) Pharmacodynamics:

- *Hemodynamic*[36]*:*

  - Following administration of therapeutic doses to patients with hypertension, Amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.
  - Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.
  - With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients.
  - The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105 to 114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90 to 104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/–2 mmHg).
  - In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

- As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co administered with beta blockers to man. Similar findings, however, have been observed in normals or well compensated patients with heart failure with agents possessing significant negative inotropic effects.

➢ *Electro physiologic Effects*[37]:

- Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing.
- Similar results were obtained in patients receiving amlodipine and concomitant beta blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

❖ *Clinical Studies*

➢ Effects in Hypertension:

✓ *Adult Patients*:

- The antihypertensive efficacy of amlodipine has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on Amlodipine and 538 on placebo. Once daily administration produced statistically significant placebo corrected reductions in supine and standing blood pressures at 24 hours post dose, averaging about 12/6 mmHg in the standing position and 13/7 mmHg in the supine position in patients with mild to moderate hypertension. Maintenance of the blood pressure effect over the 24-hour dosing interval was observed, with little difference in peak and trough effect. Tolerance was not demonstrated in patients studied for up to 1 year.
- The 3 parallel, fixed dose, dose response studies showed that the reduction in supine and standing blood pressures was dose-related within the recommended dosing range.
- Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure. Effects were similar in black patients and in white patients.

✓ *Pediatric Patients:*

Two-hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to amlodipine besylate 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 5 mg at the end of 8 weeks had lower blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5-mg dose. Adverse events were similar to those seen in adults.

➢ **Effects in Chronic Stable Angina:**

- The effectiveness of 5 to 10 mg/day of amlodipine in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind clinical trials of up to 6 weeks duration involving 1038 patients (684 amlodipine, 354 placebo) with chronic stable angina. In 5 of the 8 studies significant increases in exercise time (bicycle or treadmill) were seen with the 10 mg dose.
- Increases in symptom-limited exercise time averaged 12.8% (63 sec) for amlodipine 10 mg, and averaged 7.9% (38 sec) for amlodipine 5 mg. Amlodipine 10 mg also increased time to 1 mm ST segment deviation in several studies and decreased angina attack rate.
- The sustained efficacy of amlodipine in angina patients has been demonstrated over long-term dosing. In patients with angina there were no clinically significant reductions in blood pressures (4/1 mmHg) or changes in heart rate (+0.3 bpm).

➢ **Effects in Vasospastic Angina:**

In a double-blind, placebo-controlled clinical trial of 4 weeks duration in 50 patients, Amlodipine therapy decreased attacks by approximately 4/week compared with a placebo decrease of approximately 1/week ($p<0.01$). Two (2) of 23 amlodipine and 7 of 27 placebo patients discontinued from the study due to lack of clinical improvement.

❖ ***INDICATIONS AND USAGE[40]:***

1. Hypertension:

Amlodipine Orally Disintegrating Tablets is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

2. Coronary Artery Disease:

- *Chronic Stable Angina:*

Amlodipine Orally Disintegrating tablets are indicated for the symptomatic treatment of chronic stable angina. Amlodipine Orally Disintegrating Tablets may be used alone or in combination with other antianginal agents.

- *Vasospastic Angina (Prinzmetal's or Variant Angina):*

Amlodipine Orally Disintegrating Tablets are indicated for the treatment of confirmed or suspected vasospastic angina. It may be used as monotherapy or in combination with other antianginal drugs.

❖ *CONTRAINDICATIONS*[41]

Amlodipine Orally Disintegrating Tablets is contraindicated in patients with known sensitivity to amlodipine.

❖ *WARNINGS:*

➢ **Increased Angina and/or Myocardial Infarction:**

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

❖ *PRECAUTIONS*[37]

➢ General:

Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, caution, as with any other peripheral vasodilator, should be exercised when administering amlodipine, particularly in patients with severe aortic stenosis.

❖ *DRUG INTERACTIONS:*

In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

➢ Effect of other agents on amlodipine[37]:

- *CIMETIDINE:* Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.
- *GRAPEFRUIT JUICE*: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.
- *MAALOX (antacid):* Co-administration of the antacid Maalox with a single dose of Amlodipine had no significant effect on the pharmacokinetics of amlodipine.
- *SILDENAFIL:* A single 100 mg dose of sildenafil (Viagra®) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When Amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

➢ Effect of amlodipine on other agents[37]:

- *ATORVASTATIN:* Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.
- *DIGOXIN:* Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.
- *ETHANOL (alcohol*): Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.
- *WARFARIN:* Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time. In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

➢ Pediatric Use:

The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

➢ Geriatric Use:

- Clinical studies of amlodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.
- In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40 to 60%, and a lower initial dose may be required.

❖ *ADVERSE REACTIONS[38]:*

- **Cardiovascular:**

arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.

- **Central and Peripheral Nervous System:**

hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.

- **Gastrointestinal:**

anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

- **General:**

allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

- **Musculoskeletal System:**

arthralgia, arthrosis, muscle cramps, myalgia.

- **Psychiatric:**

sexual dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

- **Respiratory System:**

dyspnea, epistaxis.

- **Skin and Appendages:**

angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular..

- **Special Senses:**

abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

- **Urinary System:**

micturition frequency, micturition disorder, nocturia.

❖ OVERDOSAGE[39]

- Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral Amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more time times the maximum recommended human dose on a mg/m^2 basis) caused a marked peripheral vasodilation and hypotension.

- Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited.

❖ DOSAGE AND ADMINISTRATION[39]

- **Adults:**

  The usual initial antihypertensive oral dose of Amlodipine Orally Disintegrating Tablets is 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly individuals, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding Amlodipine Orally Disintegrating tablets to other antihypertensive therapy. The recommended dose for chronic stable or vasospastic angina is 5 to 10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency.

- **Children:**

  The effective antihypertensive oral dose in pediatric patients ages 6 to17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients.

Mannitol

1. Nonproprietary Names

- BP: Mannitol
- JP: D-Mannitol
- PhEur: Mannitolum
- USP: Mannitol

2. Synonyms

Cordycepic acid; E421; manna sugar; D-mannite; mannite;

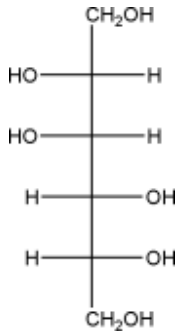
3. Chemical Name and CAS Registry Number

D-Mannitol [69-65-8]

4. Empirical Formula and Molecular Weight

$C_6H_{14}O_6$ 182.17

5. Structural Formula



6. Functional Category

Diluent; diluent for lyphilized preparations; sweetening agent; tablet and capsule diluent; tonicity agent.

7. Applications in Pharmaceutical Formulation or Technology

Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients.

Mannitol may be used in direct-compression tablet applications, for which the granular and spray-dried forms are available, or in wet granulations. Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel'.

Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (<7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations, and as a carrier in dry powder inhalers. It is also used as a diluent in rapidly dispersing oral dosage forms. It is used in food applications as a bulking agent.

8. Description

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol.

Mannitol occurs as a white, odorless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism.

9. Pharmacopeial Specifications

Table: Pharmacopeial specifications for mannitol.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
Solution appearance	+	+	—
Melting range	166–169°C	165–170°C	164–169°C
Loss on drying	≤0.3%	≤0.5%	≤0.3%
Chloride	≤0.007%	—	≤0.007%
Sulfate	≤0.01%	—	≤0.01%
Arsenic	≤1.3 ppm	—	≤1 ppm
Microbial contamination	—	≤100/g	—
Assay (dried basis)	≥ 98.0%	98.0–102.0%	96.0–101.5%

10. Typical Properties

- ✓ *Density (bulk):*

  0.430 g/cm^3 for powder;

- ✓ *Density (tapped):*

  0.734 g/cm^3 for powder;

- ✓ *Density (true):*

  1.514 g/cm^3

- ✓ *Flowability:*

  powder is cohesive, granules are free flowing.

- ✓ *Melting point:*

  166–168°C

11. Stability and Storage Conditions

Mannitol is stable in the dry state and in aqueous solutions. Solutions may be sterilized by filtration or by autoclaving and if necessary may be autoclaved repeatedly with no adverse physical or chemical effects. The bulk material should be stored in a well-closed container in a cool, dry place.

12. Incompatibilities

Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride. Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic. Sodium cephapirin at 2 mg/mL and 30 mg/mL concentration is incompatible with 20% w/v aqueous mannitol solution.

13. Method of Manufacture

Mannitol may be extracted from the dried sap of manna and other natural sources by means of hot alcohol or other selective solvents. It is commercially produced by the catalytic or electrolytic reduction of monosaccharides such as mannose and glucose.

14. Safety

Mannitol is a naturally occurring sugar alcohol found in animals and plants; it is present in small quantities in almost all vegetables. Laxative effects may occur if mannitol is consumed orally in large quantities. If it is used in foods as a bodying agent and daily ingestion of over 20 g is foreseeable, the product label should bear the statement ‘excessive consumption may have a laxative effect’. After intravenous injection, mannitol

is not metabolized to any appreciable extent and is minimally reabsorbed by the renal tubule, about 80% of a dose being excreted in the urine in 3 hours.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Mannitol may be irritant to the eyes; eye protection is recommended

Aspartame

1. Nonproprietary Names

- BP: Aspartame
- USPNF: Aspartame

2. Synonyms

3-Amino-*N*-(α-carboxyphenethyl)succinamic acid *N*-methyl ester;

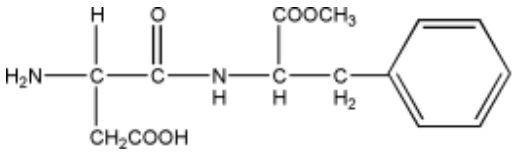
3. Chemical Name and CAS Registry Number

N-α-L-Aspartyl-L-phenylalanine 1-methyl ester [22839-47-0]

4. Empirical Formula and Molecular Weight

$C_{14}H_{18}N_2O_5$ 294.31

5. Structural Formula



6. Functional Category

Sweetening agent.

7. Applications in Pharmaceutical Formulation or Technology

Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations. It enhances flavor systems and can be used to mask

some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose.

8. Description

Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.

9. Pharmacopeial Specifications

Table: Pharmacopeial specifications for aspartame.

Test	PhEur 2005	USPNF 23
Characters	+	—
Identification	+	+
Heavy metals	≤10 ppm	≤0.001%
Loss on drying	≤4.5%	≤4.5%
Assay	98.0–102.0%	98.0–102.0%

10. Typical Properties

- ✓ *Acidity/alkalinity:*

  pH = 4.5–6.0 (0.8% w/v aqueous solution).

- ✓ Flowability:

  44% (Carr compressibility index)

- ✓ Density (bulk):

  0.5–0.7 g/cm^3 for granular grade;

- ✓ Density (tapped):

  0.29 g/cm^3 (Spectrum Quality Products)

- ✓ Melting point:

  246–247°C

- ✓ Solubility:

  slightly soluble in ethanol (95%); sparingly soluble in water. At 20°C the solubility is 1% w/v at the isoelectric point (pH 5.2). Solubility increases at higher temperature and at more acidic pH, e.g., at pH 2 and 20°C solubility is 10% w/v.

11. Stability and Storage Conditions

Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form the degradation products L-aspartyl-L-phenylalanine and 3-benzyl-6-carboxymethyl-2,5-diketopiperazine. The bulk material should be stored in a well-closed container, in a cool, dry place.

12. Incompatibilities

Differential scanning calorimetry experiments with some directly compressible tablet excipients suggests that aspartame is incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate. Reactions between aspartame and sugar alcohols are also known.

13. Method of Manufacture

Aspartame is produced by coupling together L-phenylalanine (or L-phenylalanine methyl ester) and L-aspartic acid, either chemically or enzymatically. The former procedure yields both the sweet α-aspartame and nonsweet β-aspartame from which the α-aspartame has to be separated and purified. The enzymatic process yields only α-aspartame.

14. Safety

Aspartame is widely used in oral pharmaceutical formulations, beverages, and food products as an intense sweetener and is generally regarded as a nontoxic material. However, the use of aspartame has been of some concern owing to the formation of the potentially toxic metabolites methanol, aspartic acid, and phenylalanine.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Measures should be taken to minimize the potential for dust explosion. Eye protection is recommended.

Microcrystalline Cellulose

1. Nonproprietary Names

- BP: Microcrystalline cellulose
- USPNF: Microcrystalline cellulose

2. Synonyms

Avicel PH; *Celex*; cellulose gel; *Celphere*; *Ceolus KG*; crystalline cellulose; E460;

3. Chemical Name and CAS Registry Number

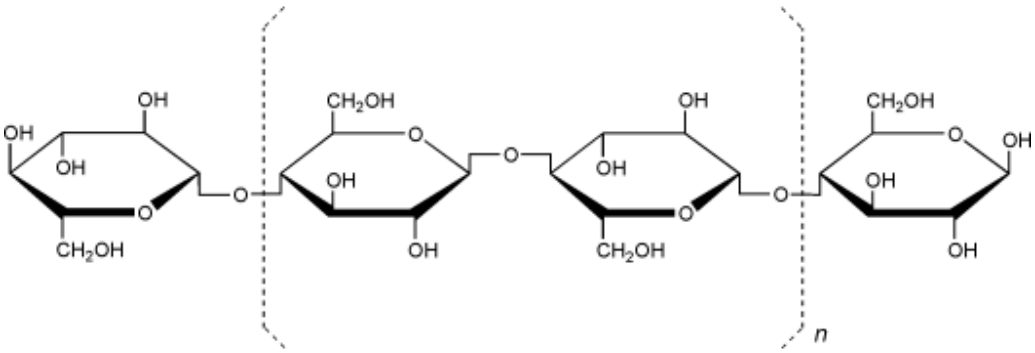
Cellulose [9004-34-6]

4. Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ ≈36 000

where $n \approx 220$.

5. Structural Formula



6. Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

7. Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.[1–7] In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant[8] and disintegrant properties that make it useful in tableting.

Microcrystalline cellulose is also used in cosmetics and food products;

Table I: Uses of microcrystalline cellulose.

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluent	20–90
Tablet disintegrant	5–15
Tablet binder/diluent	20–90

8. Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

9. Pharmacopeial Specifications

Table : Pharmacopeial specifications for microcrystalline cellulose.

Test	JP 2001	PhEur 2005 (Suppl 5.1)	USPNF 23
Identification	+	+	+
Characters	+	+	—
pH	5.0–7.0	5.0–7.5	5.0–7.5
Bulk density	+	—	+
Loss on drying	≤7.0%	≤7.0%	≤7.0%
Residue on ignition	≤0.05%	—	≤0.1%

10. Typical Properties

- ✓ Angle of repose:

  49° for *Ceolus KG*;

- ✓ Density (bulk):

  0.337 g/cm^3;

- ✓ Density (tapped):

  0.478 g/cm^3;

- ✓ Melting point:

  chars at 260–270°C.

- ✓ Solubility:

  slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

11. Stability and Storage Conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

12. Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

13. Method of Manufacture

Microcrystalline cellulose is manufactured by controlled hydrolysis with dilute mineral acid solutions of α-cellulose, obtained as a pulp from fibrous plant materials. Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spray-dried to form dry, porous particles of a broad size distribution.

14. Safety

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

Silicified Microcrystalline

1. Nonproprietary Names

None adopted.

2. Synonyms

ProSolv.

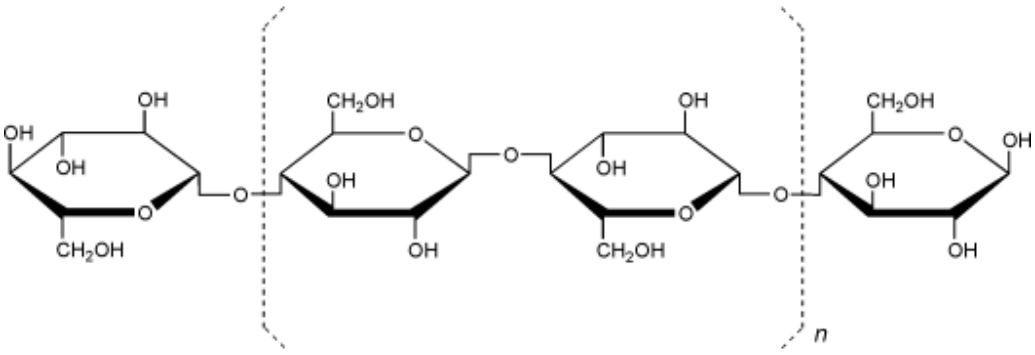
3. Chemical Name and CAS Registry Number

Section 8.

4. Empirical Formula and Molecular Weight

Section 8.

5. Structural Formula



6. Functional Category

Tablet and capsule diluent.

7. Applications in Pharmaceutical Formulation or Technology

Silicified microcrystalline cellulose is used as a filler in the formulation of capsules and tablets. It has improved compaction properties in both wet granulation and direct compression compared to conventional microcrystalline cellulose. Silicified microcrystalline cellulose was specifically developed to address the loss of compaction that occurs with microcrystalline cellulose after wet granulation.

8. Description

Silicified microcrystalline cellulose is a synergistic, intimate physical mixture of two components: microcrystalline cellulose and colloidal silicon dioxide (for further information *see* Cellulose, Microcrystalline and Colloidal Silicon Dioxide). Silicified microcrystalline cellulose contains 2% w/w colloidal silicon dioxide.

9. Pharmacopeial Specifications

-

10. Typical properties

- ✓ Acidity/alkalinity:
  pH = 5.0–7.5 (10% w/v suspension)
- ✓ Density:
  1.58 g/cm^3
- ✓ Density (bulk):
  0.31 g/cm3
- ✓ Density (tapped):
  0.39 g/cm^3

- ✓ Moisture content:

  typically less than 6% w/w.

- ✓ Solubility:

  Practically insoluble in water, dilute acids, and most organic solvents. The microcrystalline cellulose component is slightly soluble in 5% w/w sodium hydroxide solution.

11. Stability and Storage Conditions

Silicified microcrystalline cellulose is stable when stored in a well-closed container in a cool,dry place.

12. Method of Manufacture

- Silicified microcrystalline cellulose is manufactured by co-drying a suspension of microcrystalline cellulose particles and colloidal silicon dioxide so that the dried finished product contains 2% w/w colloidal silicon dioxide.
- The colloidal silicon dioxide appears physically bound onto the surface and inside the silicified microcrystalline cellulose particles. Extensive studies using different spectroscopic methods have failed to show any form of chemical interaction.4,6,7

13. Safety

See Cellulose, Microcrystalline and Colloidal Silicon Dioxide.

Hydroxy propyl Cellulose

1. Nonproprietary Names:

- BP: Hydroxy propyl cellulose
- USPNF: Hydroxy propyl cellulose

2. Synonyms:

Cellulose, hydroxy propyl ether; E463; hyprolose; *Klucel*; *Methocel*; *Nisso HPC*;

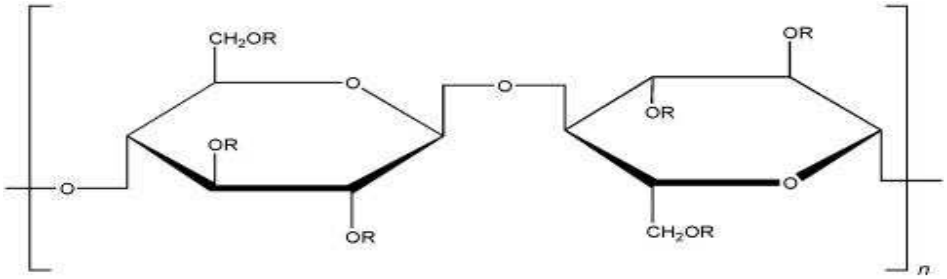
3. Chemical Name and CAS Registry Number:

Cellulose, 2-hydroxy propyl ether [9004-64-2]

4. Empirical Formula and Molecular Weight:

The PhEur 2005 and USPNF 23 describe hydroxy propyl cellulose as a partially substituted poly(hydroxy propyl) ether of cellulose. It may contain not more than 0.6% of silica or another suitable anticaking agent. Hydroxy propyl cellulose is commercially available in a number of different grades that have various solution viscosities. Molecular weight has a range of 50 000–1 250 000;

5. Structural Formula:



R is H or $[CH_2CH(CH_3)O]_mH$

6. Functional Category:

Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology:

Hydroxy propyl cellulose is widely used in oral and topical pharmaceutical formulations;

Uses of hydroxy propyl cellulose.

Use	Concentrations(%)
Extended release-matrix former	15–35
Tablet binder	2–6
Tablet film coating	5

- In oral products, hydroxy propyl cellulose is primarily used in tableting as a binder, filmcoating, and extended-release-matrix former. Concentrations of hydroxy propyl cellulose of 2–6% w/w may be used as a binder in either wet-granulation or dry, direct-compression tableting processes. Concentrations of 15–35% w/w of hydroxy propyl cellulose may be used to produce tablets with an extended drug release. Typically, a 5% w/w solution of hydroxy propyl cellulose may be used to filmcoat tablets.

8. Description:

Hydroxy propyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder.

9. Pharmacopeial Specifications:

Table II: Pharmacopeial specifications for hydroxy propyl cellulose.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Apparent viscosity	+	+	+
Appearance of solution	+	+	—
pH (1 in 100)	5.0–7.5	5.0–8.5	5.0–8.0
Loss on drying	5.0%	7.0%	5.0%
Residue on ignition	0.5%	—	0.2%

10. Typical Properties

- ✓ Acidity/alkalinity:

  pH = 5.0–8.5 for a 1% w/v aqueous solution.

- ✓ Density (bulk):

  0.5 g/cm3

- ✓ Melting point:

  softens at 130°C; chars at 260–275°C.

- ✓ Solubility:

  Soluble 1 in 10 parts dichloromethane; 1 in 2.5 parts ethanol (95%); 1 in 2 parts methanol; 1 in 5 parts propan-2-ol; 1 in 5 parts propylene glycol; and 1 in 2 parts water. Practically insoluble in aliphatic hydrocarbons; aromatic hydrocarbons; carbon tetrachloride; petroleum distillates; glycerin; and oils.

11. Stability and Storage Conditions:

Hydroxy propyl cellulose powder is a stable material, although it is hygroscopic after drying. Aqueous solutions of hydroxy propyl cellulose are stable at pH 6.0–8.0, with the viscosity of solutions being relatively unaffected.

Crospovidone

1. Nonproprietary Names

- BP: Crospovidone
- USPNF: Crospovidone

2. Synonyms

Crosslinked povidone; E1202; *Kollidon CL*; *Kollidon CL-M*; *Polyplasdone XL*; *Polyplasdone XL-10*;

3. Chemical Name and CAS Registry Number

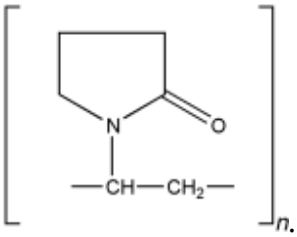
1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4. Empirical Formula and Molecular Weight

$(C_6H_9NO)_n$ >1 000 000

The USPNF 23 describes crospovidone as a water-insoluble synthetic crosslinked homopolymer of *N*-vinyl-2-pyrrolidinone. An exact determination of the molecular weight has not been established because of the insolubility of the material.

5. Structural Formula



6. Functional Category

Tablet disintegrant.

7. Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels.

8. Description

Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

See SEM 1.

9. Pharmacopeial Specifications

Table I

Table I: Pharmacopeial specifications for crospovidone.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
pH (1% suspension)	—	5.0–8.0
Water	—	≤5.0%
Residue on ignition	≤0.1%	≤0.4%

10. Typical Properties

- ✓ Acidity/alkalinity:

  pH = 5.0–8.0 (1% w/v aqueous slurry)

- ✓ Moisture content**:**

  maximum moisture sorption is approximately 60%.

- ✓ Solubility:

  practically insoluble in water and most common organic solvents.

11. Stability and Storage Conditions

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

12. Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials

13. Method of Manufacture

Acetylene and formaldehyde are reacted in the presence of a highly active catalyst to form butynediol, which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acetylene are reacted under pressure. The monomer vinylpyrrolidone is then polymerized in solution, using a catalyst. Crospovidone is prepared by a ‘popcorn polymerization’ process.

14. Safety

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. Short-term animal toxicity studies have shown no adverse effects associated with crospovidone. However, owing to the lack of available data, an acceptable daily intake in humans has not been specified by the WHO.

Vanillin

1. Nonproprietary Names

- BP: Vanillin
- USPNF: Vanillin

2. Synonyms

4-Hydroxy-*m*-anisaldehyde; *p*-hydroxy-*m*-methoxybenzaldehyde

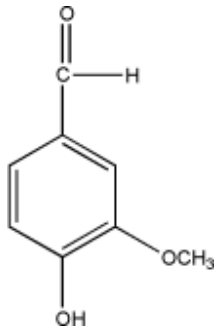
3. Chemical Name and CAS Registry Number

4-Hydroxy-3-methoxybenzaldehyde [121-33-5]

4. Empirical Formula and Molecular Weight

$C_8H_8O_3$ 152.15

5. Structural Formula



6. Functional Category

Flavoring agent.

7. Applications in Pharmaceutical Formulation or Technology

Vanillin is widely used as a flavor in pharmaceuticals, foods, beverages, and confectionery products, to which it imparts a characteristic taste and odor of natural

vanilla. It is also used in perfumes, as an analytical reagent and as an intermediate in the synthesis of a number of pharmaceuticals, particularly methyldopa. Additionally, it has been investigated as a potential therapeutic agent in sickle cell anemia and is claimed to have some antifungal properties.

8. Description

White or cream, crystalline needles or powder with characteristic vanilla odor and sweet taste.

9. Pharmacopeial Specifications

Table

Table I: Pharmacopeial specifications for vanillin.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Loss on drying	≤1.0%	≤1.0%
Sulfated ash	≤0.05%	—
Residue on ignition	—	≤0.05%

10. Typical Properties

- ✓ Acidity/alkalinity:

  aqueous solutions are acid to litmus.

- ✓ Density (bulk):

  0.6 g/cm^3

11. Stability and Storage Conditions

Vanillin oxidizes slowly in moist air and is affected by light.The bulk material should be stored in a well-closed container, protected from light, in a cool, dry place.

12. Incompatibilities

Incompatible with acetone, forming a brightly colored compound.[7] A compound practically insoluble in ethanol is formed with glycerin.

13. Method of Manufacture

Vanillin occurs naturally in many essential oils and particularly in the pods of Vanilla planifolia and Vanilla tahitensis. Industrially, vanillin is prepared from lignin, which is obtained from the sulfite wastes produced during paper manufacture. Lignin is treated with alkali at elevated temperature and pressure, in the presence of a catalyst, to form a complex mixture of products from which vanillin is isolated. Vanillin is then purified by successive recrystallizations.

14. Safety

There have been few reports of adverse reactions to vanillin, although it has been speculated that cross-sensitization with other structurally similar molecules, such as benzoic acid, may occur.

Magnesium Stearate

1. Nonproprietary Names

- BP: Magnesium stearate
- USPNF: Magnesium stearate

2. Synonyms

Magnesium octadecanoate; octadecanoic acid,

3. Chemical Name and CAS Registry Number

Octadecanoic acid magnesium salt [557-04-0]

4. Empirical Formula and Molecular Weight

$C_{36}H_{70}MgO_4$ 591.34

The USPNF 23 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$)..

5. Structural Formula

$[CH_3(CH_2)_{16}COO]_2Mg$

6. Functional Category

Tablet and capsule lubricant.

7. Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams. *See also* Section 18.

8. Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

See SEM: 1, SEM: 2.

9. Pharmacopeial Specifications

Table: Pharmacopeial specifications for magnesium stearate.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Microbial limits	+	+	+
Aerobic microbes	≤1000/g	$\leq 10^3$/g	$\leq 10^3$/g
Assay (dried, as Mg)	4.0–5.0%	4.0–5.0%	4.0–5.0%

10. Typical Properties

- ✓ Crystalline forms:

  high-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.

- ✓ Density (bulk):

  0.159 g/cm^3

- ✓ Density (tapped):

  0.286 g/cm^3

- ✓ Density (true):

  1.092 g/cm^3

11. Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

12. Incompatibilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

13. Method of Manufacture

Magnesium stearate is prepared either by the interaction of aqueous solutions of magnesium chloride with sodium stearate or by the interaction of magnesium oxide, hydroxide, or carbonate with stearic acid at elevated temperatures.

14. Safety

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.

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4. LITERATURE REVIEW

4.1 Mouth Dissolving Tablets

- Gohel[42] et al (2004) prepared the mouth dissolved tablets of Nimesulide using vaccum drying technique. Granules containing Nimesulide, camphor, crorospovidone and lactose were prepared by wet granulation technique. Camphor was sublimed from the dried granules by exposure to vacuum. The tablets were evaluated for % friability, wetting time and disintegration time. In the present investigation a 3^2 full factorial design was used to investigate combined effect of two formulation variables: amount of camphor and amount of superdisintegrant. The results of multiple linear regression analysis revealed that for obtaining a rapidly disintegrating dosage form, tablets should be prepared using optimum concentration of camphor and higher percentage of crospovidone.

- Ahmed S. Zidan[43] et al (2006) formulated and optimized mouth dissolving tablets containing Rofecoxib using solid dispersion. The purpose of the present investigation was to increase the solubility and dissolution rate of Rofecoxib by the preparation of its solid dispersion with polyvinyl pyrrolidone K30 (PVP K30) using solvent evaporation method. For the preparation of Rofecoxib mouth dissolve tablets, its 1: 9 solid dispersion with PVP K30 was used with various disintegrants and sublimable materials. The obtained results showed that dispersion of the drug in the polymer considerably enhanced the dissolution rate. The drug-to-carrier ratio was the controlling factor for dissolution improvement.

- Keith J. Simons[44] et al (2006) prepared fast-disintegrating sublingual tablets. Four tablet formulations, A, B, C, and D, containing 0%, 6%, 12%, and 24% of Epinephrine bitartrate, respectively, and microcrystalline cellulose: low-substituted hydroxypropyl cellulose (9:1), were prepared by direct compression,

at a range of compression forces. Tablet weight variation, content uniformity, hardness, disintegration time, wetting time, and friability were measured for each formulation at each compression force. All 4 tablet formulations at each compression force were within the USP limits for weight variation and content uniformity. At a mean ± SD hardness of ≤ 2.3 ± 0.2 kg, all tablet formulations passed the USP friability test. At a mean ± SD hardness of ≥ 3.1 ± 0.2 kg, all tablet formulations resulted in disintegration and wetting times of <10 seconds and <30 seconds, respectively.

- Abdelbary[45] et al (2004) prepared orally disintegrating tablets using a hydrophilic waxy binder. The incorporation of Superpolystate® in the formulation of RDT was realised by means of two different granulation methods: wet granulation by using an emulsion of this waxy binder as granulating liquid and melt granulation where the molten form of the binder was used. The potential of the intragranular addition of croscarmellose sodium as a disintegrating agent was also evaluated. An improvement in tablet hardness and friability was observed with both granulation methods where we were able to obtain RDT with a disintegration time of 40 ± 2 seconds and a hardness of 47.9 ± 2.5N.

- Koizumi[46] et al (1997) presented an invention, which related to rapidly saliva tablets using sublimation technique. Compressed tablets of Mannitol did not dissolve in water due to the low porosity. To increase the porosity of tablets sublimation was done. Tablets were prepared by direct compression containing mannitol and camphor. A high porosity was achieved due to formation of many pores due to camphor sublimation. The compressed tablets have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva.

- Shawn A. Mitchell[47] et al studied a compaction process to enhance dissolution of poorly water soluble drugs using low-viscosity HPMC. The purpose of this study was to develop a technique to enhance the dissolution rate of poorly water-soluble drugs with low-viscosity HPMC without the use of solvent or heat addition. The

compaction processes enhanced drug dissolution relative to drug alone and also relative to corresponding loosely mixed physical mixtures. The roller compaction and slugging method produced comparable dissolution enhancement. The mechanism for dissolution enhancement is believed to be a microenvironment HPMC surfactant effect facilitated by keeping the HPMC and drug particles in close proximity during drug dissolution.

- Abdelbary[48] et al (2005) determined the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration. In the present study, they evaluated the disintegration profile of RDT manufactured by main commercialised technologies, using the texture analyzer. In order to simulate as much as possible the oral disintegration of these dosage forms, a new operating structure was developed. This structure mimics the situation in the patient's mouth and provides a gradual elimination of the detached particles during the disintegration process. Moreover, the oral disintegration time of the same products was evaluated by 14 healthy volunteers. Results obtained when artificial saliva at 37^{o}C was employed as disintegration medium were used to correlate the in vitro and oral disintegration times. Excellent correlation was found and in addition, we were able to achieve a qualitative measure of the mouth feel by comparing the thickness of the tablets and the penetration distance obtained from the disintegration profile.

- Fukami[49] et al (2006) formulated a rapidly disintegration tablet in the oral cavity using a Glycine as a disintegrant. Wetting time prepared from carboxymethylcellulose (NS-300) having the hardness of 4kg was 3 seconds. Tablets containing NS-300 showed fastest disintegration compared to other formulations. These results suggest that NS-300 possessed excellent wetting nature and resulted in the rapid disintegration of tablet. Ethenzamide and ascorbic acid were added to the formulation, and their disintegration behaviors were evaluated. Ethenzamide did not affect the disintegration property; however, ascorbic acid prolonged disintegration time. It was suggested that the tablet

formulation containing NS-300 and Glycine was highly applicable to water-insoluble drug, such as Ethenzamide.

- Shirwaiker[50] et al (2004) prepared fast disintegrating tablets of Atenolol. The preparation contained an active ingredient, sugar (mannitol), superdisintegrant and dicalcium phosphate. Required quantities of each ingredient were weighed, mixed and prepared the tablets by dry granulation. All the formulation had disintegration time of less than 70 seconds. Among the three superdisintegrant Ac-Di-Sol showed the highest efficacy. Formulation containing 10 % Ac-Di-Sol showed the least disintegration time of 30 ± 2 seconds compare to Explotab and Polyplasdone XL.

- Mishra [51] et al (2005) prepared rapidly disintegrating tablets of Valdecoxib. The poor aqueous solubility of the drug results in variable dissolution rate and poor bioavailability. In the present, invention tablets were prepared using various superdisintegrant following direct compression. All formulation showed disintegration time of less than 60 seconds along with rapid *in vitro* dissolution. All the formulation showed more than 70 % dissolution in 30 min.

- Amin[52] et al (2005) presented an invention, which relates to fast disintegration tablets for oral administration. Taste masked adsorbents of Ofloxacin were prepared using cationic exchange resins. Taste evaluation of tablets showed complete masking of the bitterness of Ofloxacin. The taste-masked complex of the Ofloxacin was further incorporated into mouth dissolve tablets in combination with Metronidazole benzoate. All the formulation exhibited an in vitro dispersion time less than 50 seconds.

- Remon[53] et al (1997) prepared the rapidly disintegrating tablets by lyophillization. Tablets contained hydrochlorothiazide, Maltrodextrin, hydroxyethylcellulose and gelatin. The solutions were poured into blisters and freeze dried. Maltrodextrin

could be a filler of choice for the production of lyophilized tablets as freeze-drying due to amorphous network, which dissolved in the water with seconds. They evaluated gelatin, xanthan gum and hydroxyethylcellulose a binding agents in the formulation of freeze dried tablets with Maltrodextrin as filling agents.

- Chaudhari[54] et al (2005) prepared fast dissolving tablets of Famotidine. In this study the bitter taste of Famotidine was masked using drug: Eudragit E 100 in different ratios (1:1 to 1:10). For taste masking the ratio was optimized to 1:4 by time intensity. The different superdisintegrant (Ac-Di-Sol, Polyplasdone) with their varying concentration were used for disintegration of tablets in mouth. The formulation containing 2 % of Ac-Di-Sol and Polyplasdone showed 91.89 % and 101.07 % release respectively in 12 min.

- Vijaya[55] et al (2006) prepared Meloxicam rapidly disintegrating tablets by direct compression. The tablets were prepared with three superdisintegrant like SSG, Ac-Di-Sol and L-HPMC. The hardness of tablets was found to be less than 10% and disintegration time of tablets was found to be less than 1 minute, except L-HPMC. In-vitro drug release study showed enhance dissolution rate compared to pure Meloxicam.

- Sreenivas[56] et al (2006) prepared mouth dissolve tablets of Ondansetron by direct compression. In this study a varity of disintergrant like crospovidone, croscarmelose, pregelatinized starch, sodium starch glycolate and L-HPC were selected at 5 % and 10 % concentration. The friability of all the formulation between 0.16 to 0.36 %. The in vitro disintegration time for all formulation varied from 10 to 15 seconds. In all the formulation the drug release was almost up to 80-100% after 15 min.

- Shirwaikar A[57] et al (2006) formulated and evaluated fast dissolving tablets of Granisetron hydrochloride by direct compression method using superdisintegrants. A combination of mannitol and silicified microcrystalline

cellulose (SMCC) in the ration 70:30 was used in the study. Study concluded that crospovidone and croscarmellose sodium are better disintegrants for formulation of fast dissolving tablets of Granisetron HCl.

- Halakatti P.K.[58] et al (2006) formulated rapidly disintegrating tablets of Domperidone by applying two methods. Sodium starch glycolate and treated agar used as superdisintegrants in mass extrusion technique and treated agar method respectively.

- Mahajan H.S.[59] et al (2004) formulated mouth dissolving tablets of Salbutamol sulphate by direct compression method. SSG, croscarmellose sodium, treated agar were used as superdisintegrants while microcrystalline cellulose used as diluents. Formulation containing SSG along with other superdisintegrants showed rapid in-vitro and in-vivo dispersion time, as compared to other formulation.

- Nayak S.M.[60] et al (2004) prepared fast dissolving tablets of Promethazine theoclate using effervescent melt, super disintegration addition and melt technologies. Tablets from effervescent melt and super disintegration addition technique released 92 % and 89 % of the drug at the end of 10 min.

- Kaushik D.[61] et al (2004) prepared mouth dissolving tablets of Olanzepine by effervescent approach. Sodium bicarbonate and citric acid were used as effervescent agent and their ratio was optimized. The study revealed that 10:8 ratio of sodium bicarbonate and citric acid in the Olanzepine mouth dissolving tablets gave a soothing fizz, excellent mouth feel, good palatability and quick dissolution profile.

- Devi V. K.[62] et al (2006) prepared orodispersible tablets of Fluconazole with two different volatilizable compounds viz. ammonium chloride and camphor by wet granulation method. The best formulations were compared with marketed conventional tablets.

- Mahajan H.S.[63] et al (2004) studied on mouth dissolving tablets of Sumatriptan succinate. Tablets were prepared by using disintegrants like sodium starch glycolate, carboxymethyl cellulose sodium and treated agar by direct compression method. The tablets were evaluated for various tests. The study showed that formulation containing sodium starch glycolate and carboxymethyl cellulose was found to give the best results.

- Patel D.M.[64] et al (2004) formulated orodispersible tablets of Rofecoxib by granulation method that carried out by solid deposition method using three superdisintegrants namely SSG, crospovidone, croscarmellose sodium. From that crospovidone giving lowest disintegration time and wetting time as compared to remain superdisintegrants.

- Kuchekar B. S.[65] et al (2006) prepared orodissolving tablets of Promethazine hydrochloride by direct compression method using superdisintegrants, sodium starch glycolate, croscarmellose sodium. Study revealed that formulation containing 4% of SSG and 1-3 % of croscarmellose sodium were found to give the best results.

- Patel D. M.[66] et al (2006) prepared fast dissolving tablets containing solid dispersion of Valdecoxib. They were prepared solid dispersion with mannitol polyethylene glycol 4000, and PVP K12. Valdecoxib solid dispersion with PVP K12 showed maximum drug release hence, the tablet formulation containing Valdecoxib PVP K12 solid dispersion was prepared with a view to improve its water solubility.

- Poornima D. Amin [67] et al (2004) formulated patient compliant dosage form for Roxithromycin. The present study deals with various techniques utilized for taste masking of roxithromycin viz granulation with udragit E100 and complexation with ion exchange resins. Of these, complexation with ion exchange resin yielded complete test masking. The test masked complex was then formulated in to palatable mouth dissolve tablet.

- Amin Purnima[68] et al studied that Indion 414 as superdisintegrant in formulation of mouth dissolve tablets. The present research paper introduces Indion 414, an ion exchange resin, as a new superdisintegrant for pharmaceutical dosage forms. Model drugs belonging to various classes were taste masked and formulated into palatable mouth dissolve tablets. Experiments were carried out to evaluate the disintegrant property of Indion 414 by incorporating Indion 414 in fast disintegrating dosage form like mouth dissolve tablets.

- Mane Avinash[69] et al (2003) formulated highly porous, mouth dissolving tablets of Domperidone using meltable binder polyethylene glycol-4000, a diluent-mannitol and sublimable material like camphor and ammonium bicarbonate. The amounts of volatilizable material were varied from 10% to 60% w/w to obtain various formulations. Two of the formulations having 40% w/w of ammonium bicarbonate and 20% w/w of camphor exhibiting least disintegration time.

- Shishu[70] et al (2006) prepared rapidly disintegrating Diazepam tablets by using microcrystalline cellulose as directly compressible filler and sodium starch glycolate as super disintegrants.

- Gordan[71] et al found that aging decrease the dissolution efficiency of superdisintegrant in wet granulated tablets. The formulation that initially exhibited faster dissolution showed decrease in dissolution after storage. So out of sodium starch glycolate, croscarmellose and crospovidone, croscarmellose is most affected.

4.2 SUPERDISINTEGRANTS

- Na Zhao[72] et al compared the disintegration efficiency and to develop a discriminating test model for the classes of superdisintegrants represented by Ac-Di-sol, Primojel, and Polyplasdone XL 10. Using a digital video camera to examine the disintegration process of tablets containing the same Wt/Wt percentage concentration of the superdisintegrants, Ac-Di-Sol was found to disintegrated tablets rapidly into apparently primary particles; Primojel also apparently disintegrated tablets into primary particles but more slowly; polyplasdone XL 10 disintegrated tablets rapidly but into larger masses of aggregated particles. The differences in the size distribution generated in the disintegrated tablets likely contributed to the drug dissolution rate differences found for aspirin tablets with similar disintegration rate.

- Di martino[73] et al studied a central composite design for evaluation of different fast melting disintegrants. The main factors included were he concentration of disintegrants(X1) and the compression force (X2). These factors were studied for tablets containing either Zeparox or Pearlitol 200 as soluble diluents and six different disintegrants ; L-HPC, LH11 and LH31, Lycatab PGS, Vivasol, Kollidon Cl, and Explotab. The response variables were disintegration time (Y1), tensile strength (Y2) and porosity (Y3). Whatever the diluent, the longest disintegration time is obtained with Vivasol as the disintegrant, while kollidon Cl leads to the shortest disintegration time. Exceptions are Lycatab PGS and L-HPC LH-11. Almost the same results are obtained with porosity; no relevant effect of disintegrant concentration is observed.

- Gohel[74] et al prepare and evaluate of coprocessed disintegrant containing crospovidone and sodium starch glycolate. Crospovidone are selected because of better compressibility compared with other superdisintegrant, high capillary activity, pronounced hydration capacity, and little tendancy to form gels. Rate and extent of liquid uptake and swelling of crospovidone (Polyplasdone XL10) are not reduced in 0.1 N hydrochloric acid when compared with aqueous medium. The aqueous medium represents disintegration medium and 0.1 N represents gastric environment. The bulk density of crospovidone and sodium starch glycolate is 0.4 and 0.756 gm/cm3. SSG were selected because of its high swelling capacity. It exhibits good flow. The coprocessed superdisintegrant was to avoid the problems of segregation.

- Massimo[75] et al evaluated disintegrant propensity of tablets by means of disintegrant force kinetics. Because of the experimental set up, the disintegration force measured was result of the force generated by disintegrant swelling and dissipated by tablets disintegration. The disintegration force vs. time curves had shapers ranging from a skewed distribution curve to a bell shaped curve, depending on slow or rapid disintegration of tablets, respectively. The disintegration force curve allows for the clear identification to be used.

- Gorden[76] et al found that aging decreases the dissolution efficiency of superdisintegrant in wet granulated tablets. The formulation that initially exhibited faster dissolution showed decrease in dissolution after storage. So out of sodium starch glycolate, croscarmellose and crospovidone, croscarmellose is most affected.

- Thibert[77] et al analyzed hydration behavior of superdisintegrant powders using an environmental scanning microscope. The researchers observed that at 40% RH croscarmellose sodium and sodium starch glycolate comprised twisted fibers and oblate particles respectively. Up on exposure to elevated relative humidity (80% RH), irreversible change in the structured of croscarmellose sodium and sodium starch glycolate was observed even after the reduction of relative humidity to 40%. In the case of crospovidone, the particles main tan their physical integrating up on dehydration and repeated hydration and rehydration cycling.

4.3 AMLODIPINE BESYLATE

- D.M. McDaid[78] were prepared Amlodipine base from its besylate salt and various physicochemical properties relevant to transdermal delivery determined. Permeation of the drug from a range of hydrophilic and hydrophobic bases through hairless mouse skin was studied and the influence of the penetration enhancers sodium lauryl sulphate 1% and propylene glycol 20% in a sodium carboxymethylcellulose 3% gel base was examined. The flux of drug could be further enhanced using variable percentage of ethanol in the donor phase. The influence of various rate controlling membranes and a contact adhesive on drug permeation was examined. In vivo studies using rabbits were performed to assess the suitability of a reservoir-type device. Employing data obtained from in vitro studies involving human abdominal skin, it was possible to predict the plasma profile resulting from the application of a similar device onto human skin over a period of 1 week and was found to be inadequate for clinical use. No adverse local effects in the animal model arising from the application of the transdermal device were observed by them.

- Dong-Jin Janga[79] had improve the bioavailability and photostability of poorly water-soluble and photosensitive amlodipine, dry emulsion (DE) which was prepared by spray-drying the oil-in-water emulsion of amlodipine. Labrafil M 1944 CS and dextrin were employed as oil phase and matrix material, respectively. Dispersing DE in distilled water formed an emulsion with a mean droplet size 1.4-fold larger than that of the homogenized amlodipine emulsion before spray-drying (0.24±0.30 _m versus 0.17±0.02 _m). The mean droplet size of DE remained unchanged during 6-month storage at room temperature. 94.4% versus 33.1% of amlodipine remained intact after 24-h UV irradiation of amlodipine as DE formulation or as powder. These data suggest that DE formulation greatly improved the photostability of amlodipine, as well as

increasing the physical stability of emulsion systems. *In vitro* release of DE was higher than that of amlodipine powder (66% versus 48% release at 60 min). Consequently, DE formulation resulted in 2.6- and 2.9-fold higher *C*max and AUC0–24h of amlodipine compared after oral administration of amlodipine powder in rats. Their data suggest that the DE may be a potential oral dosage form for amlodipine to improve its bioavailability.

- Yinghua Suna[80] had developed and evaluated a drug-in-adhesive transdermal patch for S-amlodipine (S-AM) free base. Initial in vitro experiments were conducted to optimize the formulation parameters before transdermal delivery in rats. The effects of the type of adhesive and the content of permeation enhancers on S-AM free base transport across excised rat skin were evaluated. For in vivo studies, patches were administered transdermally to rats while orally administered S-AM in suspension and intravenously administered S-AM solution were used as controls. The plasma level of SAM following transdermal application could be maintained for 72 h. After transdermal administration to rats, the absolute bioavailability was 88.8% for S-AM free base. After dose normalization, the areas under the plasma concentration–time curve (AUC) and mean residence times (MRT) were evidently increased and extended, respectively. This suggests that the transdermal application of S-AM in a drug-in-adhesive transdermal patch may be used for the treatment for hypertension.

- Atram SC[81] had developed an optimized bilayer tablet for antihypertension patients using Metoprolol succinate and Amlodipine besylate as a model drug candidate by optimization technique. A 3^2 factorial design was employed in formulating bilayer tablet with individual release layer i.e. sustained release layer and immediate release layer. The independent variables selected both cases HPMC(X1), Starch 1500 (X2) and SSG (X1), MCC (X2), respectively. Two dependent variables were considered: t50 (Y1), Q12 (Y2) and t50 (Y1), Q2 (Y2),

respectively. The main effect and interaction terms were quantitatively evaluated using mathematical model. Bilayer tablets were evaluated for thickness, hardness, friability, drug content and in vitro dissolution studies. The drug release of Amlodipine besylate and Metoprolol succinate depicted non-fickian diffusion and Super Case II transport mechanism, respectively.

- Menger Chung[82] had studied bioequivalence of combination tablets containing amlodipine besylate/atorvastatin calcium with coadministered matching doses of amlodipine besylate and atorvastatin. calcium tablets was investigated in randomized, 2-way crossover studies in healthy volunteers (N = 126). Subjects received a single dose of the amlodipine/atorvastatin tablet or coadministered matching doses of amlodipine and atorvastatin at the highest (10/80 mg; n = 62) and lowest (5/10 mg; n = 64) dose strengths. Atorvastatin geometric mean ratios for maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve (AUC) for the highest and lowest dose strengths were 94.1 and 98.8, and 104.5 and 103.8, respectively. Amlodipine geometric mean ratios for C_{max} and AUC for the highest and lowest dose strengths were 100.8 and 103.4, and 100 and 102.7, respectively. The 90% confidence intervals for all comparisons were within 80% to 125%, demonstrating bioequivalence for amlodipine and atorvastatin at both dose strengths. Use of amlodipine/atorvastatin combination tablets may provide a more integrated approach to treatment of cardiovascular risk.

- Abdoh[83] studied the compatibility of amlodipine besylate in its solid formulations with various drug excipients. The various factors affecting amlodipine besylate stability were studied using high-performance liquid chromatography (HPLC). It has been found that binary 1:1 mixtures of amlodipine besylate and an excipient are stable at 65°C and 40°C/75% RH. Further investigations were conducted to

study the stability of amlodipine besylate in multicomponent mixtures, including mixtures with actual formulations. The study reveals that mixtures of lactose, magnesium stearate, and water induce some instability on amlodipine besylate. The major degradation product confirmed by HPLC-mass spectrometry is amlodipine besylate glycosyl. This is in conformity with the well-known Maillard reaction between primary amines and lactose. Thus, lactose-free amlodipine formulations were recommended by them from the safety, quality, efficacy, and process cost points of view.

- Nahata MC[84] had determined the stability of amlodipine besylate in two liquid dosage forms under refrigeration and at room temperature. Commercially available amlodipine tablets (Norvasc-Pfizer) were used to prepare two suspensions: one in extemporaneously prepared 1% methylcellulose in syrup (1:1), and another in equal volumes of commercially available OraPlus/OraSweet. Each suspension containing amlodipine 1 mg/mL was stored in 10 plastic prescription bottles; 5 were stored at 4 degrees C and 5 at 25 degrees C. Samples were collected immediately after preparation (day 0) and on days 7, 14, 28, 42, 56, 70, and 91. Amlodipine concentration was measured by stability-indicating HPLC method. Physical and chemical stability (> 90% of the initial concentration) of amlodipine in the two extemporaneously prepared suspensions during storage in plastic prescription bottles at 4 degrees C and 25 degrees C. Observed mean concentrations exceeded 90% of the initial concentrations in both suspensions for 91 days at 4 degrees C and 56 days at 25 degrees C. No noticeable change in physical appearance or odor was observed; pH changed slightly in the methylcellulose-containing formulation stored at 25 degrees C. So Amlodipine was stable in two suspensions when stored in plastic prescription bottles for 91 days at 4 degrees C or 56 days at 25 degrees C. These formulations may be considered for pediatric or elderly patients who are unable to swallow tablets. The liquid dosage form would also permit accurate administration of amlodipine doses to infants and young children based on their body weight.

- Fiorenzo Mignini[85] has investigated open, randomized, two-period crossover trial in 24 healthy volunteers over a 144 h period the bioequivalence of amlodipine maleate tablets 10 mg versus amlodipine besylate tablets (Norvasc® 10 mg). Plasma amlodipine concentrations were assessed by ultra performance liquid chromatography interfaced with a double quadrupole mass spectrometer. The area under the curve total (AUC_t) and the area under the curve to infinity (AUC_{inf}) values, peak plasma concentration (C_{max}), and time to attain peak (t_{max}) were not statistically different between the two drugs. AUC_t and AUC_{inf} values were higher ($p < 0.05$) in females than in males. The tolerability profile was comparable for the two salts of amlodipine. These findings indicate that amlodipine maleate and besylate are bioequivalent and were well tolerated, which suggests that the plasma kinetics of amlodipine depend on the properties of the molecule itself. Hence, the two salts investigated could be used interchangeably in clinical practice.

SUMMARY

Many patients, especially elderly find it difficult in swallowing tablets, capsules, fluids and thus do not comply with prescription, which results in high incidence of non-compliance oriented research has resulted in bringing out many safer and newer drug delivery systems. Rapidly disintegrating/dissolving tablet is one of such example, for the reason of rapid disintegration or even with saliva. Significance of this drug delivery system includes administration without water, accuracy of dosage, ease of portability, alternative to liquid dosage forms, ideal for pediatric and geriatric patients and rapid onset of action

Identification of amlodipine was carried out by using melting point estimation, by UV spectrophotometrically, and by IR spectroscopy & drug was identified as pure amlodipine besylate. Estimation of amlodipine was carried out by standard curve in 0.01 N HCL media.

A direct compression technique was used to prepare MDT as it is economical, simple, less time consuming. The formulations were evaluated for % friability, wetting time, disintegration time, & in-vitro drug release study

MDT were initially formulated with mannitol, considering its advantages in terms of easy availability, cost-effectiveness, negative heat of dissolution and relative rapid dissolution, but poor weight uniformity due to poor flowability & diverse sticking to die cavity limits its alone application in MDT. SO combination of Mannitol SD 200 & MCC in 50 : 30 ratio was used which is investigated by formulation trials. SMCC was selected in formulation instead of MCC because of presence of 2 % Silicon dioxide which decreases friability & also decrease wetting & disintegration time. As crospovidone XL 10 was costlier than crospovidone XL & it was not added any advantage to formulation so, crospovidone XL was selected. By varying amount of crospovidone, 8% was

optimized as optimum concentration as higher amount leads to higher friability & lesser amount results in low wetting & disintegration time. HPC & HPC-EXF were used in formulation trials but HPC-EXF (4%) was selected in final formulation development as HPC being higher binding effect decreases wetting & disintegration time. Tablets were compressed by varying compression force to obtain tablets with different hardness. 4-5 kp hardness was selected as best hardness as lower hardness (2 kp) results in higher friability & higher hardness (6 kp) leads to lower wetting & disintegration time.

Thus present work was aimed to formulate MDT of amlodipine besylate using super disintegrants which provide better dissolution.

3^2 full factorial design was employed to study the effect of independent variables, concentration of crospovidone & HPC-EXF on disintegration time & friability by using contour plot & 3 D surface plot.

Amlodipine besylate MDT was compared with Amlodipine besylate IR tablet. By experiments, it was estimated that Amlodipine besylate MDT was dissolved more rapidly than Amlodipine besylate IR tablets.

The accelerated stability study was conducted as per ICH guideline & the formulations were found to be stable, with insignificant changes in physical characteristic, drug content, disintegration time & drug release property.

An attempt was made to prepare MDT of Amlodipine besylate with appropriate mechanical strength which would disintegrate in oral cavity in less than 30 secs & provide immediate control over hypertension due to faster release of amlodipine in to GI tract & total drug would be released in with in 5 mins.

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"FORMULATION, OPTIMIZATION & EVALUATION OF MOUTH DISSOLVING TABLET OF AMLOPDIPINE BESYLATE. "

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BIOPHARMACEUTICS

BY

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CERTIFICATE

*This is to certify that **Mr./Ms. XYZ** has prepared his thesis entitled "Formulation and Development of … drug delivery system", in partial fulfillment for the award of M. Pharm. degree of the Nirma University, under our guidance. He/She has carried out the work at the Department of Pharmaceutics & Pharmaceutical Technology, Institute of Pharmacy, Nirma University.*

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DECLARATION

I declare that the thesis "Formulation and Development of … drug delivery system" has been prepared by me under the guidance of Dr. Tejal A. Mehta, Professor, and Mr./Ms. ABC, Assistant Professor, Department of Pharmaceutics & Pharmaceutical Technology, Institute of Pharmacy, Nirma University. No part of this thesis has formed the basis for the award of any degree or fellowship previously.

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AIM OF PRESENT INVESTIGATION

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine had a strong blocking action on both the L-type and N-type Ca2+ channels expressed in the oocyte.

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. Approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Elimination half-life is about 30 to 50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Following administration of therapeutic doses to patients with hypertension, Amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

Conventional amlodipine besylate tablets available in the market are not suitable for acute hypertension conditions where quick onset of action is required. Besides, the conventional tablets also show poor patient compliance particularly by the geriatric & pediatric patients who experience difficulty in swallowing tablets or capsules which is a common problem among all age group. For these reason, tablet that can dissolve or disintegrate in oral cavity, have attracted a great deal of attention to provide the patients with the most conventional mode of administration and to overcome the problems of poor bioavailability.

A solid oral dosage form that dissolves or disintegrates rapidly in oral cavity resulting in a solution or suspension with out need for water is known as fast dispersing

dosage form or Mouth dissolving tablets. When this type of tablet is placed in to the mouth, the saliva will rapidly dissolve tablet.

Thus present work was aimed to formulate MDT of amlodipine besylate using super disintegrants which provide better dissolution.

Identification of amlodipine was carried out by using melting point estimation, by UV spectrophotometrically, and by IR spectroscopy & drug was identified as pure amlodipine besylate. Estimation of amlodipine was carried out by standard curve in 0.01 N HCl media.

A direct compression technique was used to prepare MDT as it is economical, simple, less time consuming. The formulations were evaluated for % friability, wetting time, disintegration time, & in-vitro drug release study.

3^2 factorial design was employed to study the effect of independent variables, concentration of crospovidone & HPC-EXF on disintegration time & friability by using contour plot & 3 D surface plot

Amlodipine besylate MDTs was compared with Amlodipine besylate conventional release tablets. By experiments, it was estimated that Amlodipine besylate MDT was dissolved more rapidly than Amlodipine besylate conventional release tablets

Accelerated Stability study of Amlodipine besylate MDT was carried out, and no higher degradation was seen in studies.

An attempt was made to prepare MDT of Amlodipine besylate with appropriate mechanical strength which would disintegrate in oral cavity in less than 30 secs & provide immediate control over hypertension due to faster release of amlodipine in to GI tract & total drug would be released in with in 5 mins

1. MOUTH DISSOLVE TABLETs

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desire therapeutics concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. This is possible through administration of conventional dosage form in a particular dose and at a particular frequency.[1] Thus drug may be administered by variety of routes in a variety of dosage forms.

Drugs are more frequently taken by oral administration. Although a few drugs taken orally are intended to be dissolved within the mouth, the vast majority of drugs taken orally are swallowed. Compared with alternate routes, the oral route of drug administration is the most popular and has been successfully used for conventional delivery of drug. It is considered most natural, uncomplicated, convenient, safe means of administering drugs, greater flexibility in dosage form design, ease of production and low cost.[2]

Tablets and hard gelatin capsules constitute a major portion of the drug delivery systems that are currently available. However, many patient groups such as elderly, children, and patients mentally retarted, uncooperative, nauseated, or on reduced liquid intake diets have difficulty in swallowing these dosage forms. Many elderly persons face difficulties in administering conventional oral dosage forms because of hand tremors and dysphasia. Swallowing problem is common in children because of their underdeveloped muscular and nervous systems. In some cases like motion sickness, sudden episodes of allergic attack or coughing, and during unavailability of water, swallowing conventional tablets is difficult. To fulfill these medical needs, formulators have devoted considerable efforts for developing a novel type of dosage form for oral administration known as ***MOUTH DISSOLVING TABLETs (MDT).***[3]

MOUTH DISSOLVING TABLET [4, 5]

This is an innovative tablet technology where the dosage form containing active pharmaceutical ingredients disintegrates rapidly, usually in a matter of seconds, without the need for water, providing optimal convenience to the patient. Innovators and inventor companies have given these tablets various names such as orally disintegrating tablets (ODT), mouth dissolving (MD), fast melting, fast dissolving or Orodisperse.

The European Pharmacopoeia defines Orodisperse as a tablet that can be placed in the mouth where it disperses rapidly before swallowing. Researchers have formulated MDT for various categories of drugs, which are used for therapy in which rapid peak plasma concentration is required to achieve desired pharmacological response. These include neuroleptics, cardiovascular agents, analgesics, anti-allergic and drugs for erectile dysfunction.

MOUTH DISSOLVING TABLET (MDT) is a solid unit dosage form containing drugs that disintegrates rapidly and dissolves in the mouth without taking water within 60seconds or less. Drug absorption through local oral–mucosal and through pre and post gastric parts of G.I.T. MDTs are also called as Oro-disperse, mouth dissolving, rapidly disintegrating, fast melt, quick dissolve and freeze dried wafers.

MDT are generally classified into two types

ORAL SUBLINGUAL TABLET:

- MDT as a solid dosage form which disintegrates rapidly, within a matter of seconds, under the tongue.

ORAL DELAYED RELEASE:

- when place upon the tongue, releases a drug (or drugs) at a time other than promptly after administration.

CHARACTERISTICS OF MOUTH DISSOLVING TABLET:

- Convenient and easy to administer as does not require water for oral administration
- Durable and sufficient strength to withstand the rigors of the manufacturing process and manufacturing handling
- Pleasant mouth feel
- Insensitive to environmental conditions such as humidity and temperature.
- Improved taste without any residue in the mouth after disintegration
- Adaptable and amenable to existing processing and packaging machinery
- Cost effective
- Compatible with taste masking

BENEFITS OF MOUTH DISSOLVING TABLET:

- Administered without water, anywhere, any time.
- Suitability for geriatric and pediatric patients, who experience difficulties in swallowing and for the other groups that may experience problems using conventional oral dosage form, due to being mentally ill, the developmentally disable and the patients who are un-cooperative, or are on reduced liquid intake plans or are nauseated
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid on set of action required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

LIMITATIONS OF MOUTH DISSOLVING TABLET:

- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

SELECTION OF DRUG :

The ideal characteristics[1] of a drug for in vivo dissolution from an MDT include

- No bitter taste
- Dose lower than 20mg
- Small to moderate molecular weight
- Good stability in water and saliva
- Partially non ionized at the oral cavities pH
- Ability to diffuse and partition into the epithelium of the upper GIT (logp>1, or preferably>2)
- Ability to permeate oral mucosal tissue

UNSUITABLE DRUG CHARACTERSTICS FOR MDT;

- Short half-life and frequent dosing
- Very bitter or otherwise unacceptable taste because taste masking cannot be achieved
- Required controlled or sustained release.

➢ *Taste masking Methods:*

The success of this delivery system is because of good taste. Taste is a chemical reaction derived from sensory responses from the four main taste perceptions salt, sour, bitter and sweet[5]. The drugs are mostly bitter in nature. Skillful taste masking is needed to hide the bitter taste in MDT formulations. This can be achieved by using combination of right flavour and right sweetners. The taste masking in MDT has more influences on dissolution method development, specifications, and testing. Following methods are used in Taste masking is given as follows:

- Simple wet granulation method or roller compaction[6] of other excipients. Spray drying can also employed to shroud the drug.
- Co-sifting method the large quantities of water soluble polymers are used as an excipient. Drugs can be sifted twice or thrice in small particle size mesh with excipients such as sweeteners and flavors etc.
- Hydroxy propyl methyl cellulose, Ethyl cellulose, Methacrylates, Kollicoat, Polyvinyl pyrollidone polymers can be used to coat to mask the taste.
- Cyclodextrins can be used to trap or complex, cyclodextrin help to solubilze many drugs.
- Drug complexation[7] with resinates are insoluble and no taste in oral cavity. With the correct selection of the ion exchange resin, the drug will not be released in the mouth so that the patient does not taste the drug when it is swallowed. When the drug resinate comes into contact with the gastrointestinal fluids, such as the acid of the stomach, the drug is released from the resinate, directly into solution and then absorbed in the usual way. The resin passes through the GI tract without being absorbed. Examples of drugs where this technique has been successfully demonstrated include ranitidine, risperidone and paroxetine.
- Other methods include hot melt and supercritical fluids.

TECHNIQUES USED FOR THE FORMULATION OF MOUTH DISSOLVING TABLET:

Many techniques have been reported by various researchers for the formulation of MOUTH DISSOLVING TABLET.

1. Freeze-Drying or Lyophilization: [6, 7, 8]

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of MDT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is dosed by weight and poured in the wells of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminium foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophillization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

2. Tablet Molding: [9, 10]

Molding process is of two types i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydroalcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is than removed by air-drying. The tablets manufactured in this manner are less compact than the compressed

tablets and posses a porous structure that hastens dissolution. The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°C under vacuum. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology. The taste masked drug particles were prepared by spray congealing, a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol, and an active ingredient, into a lactose based tablet triturate form. Compared to the lyophillization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture.

3. Spray Drying: [11, 12]

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose or crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate & croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

4. Sublimation: [13, 14, 15]

To generate a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride may be compressed

along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane, benzene can be used as pore forming agents.

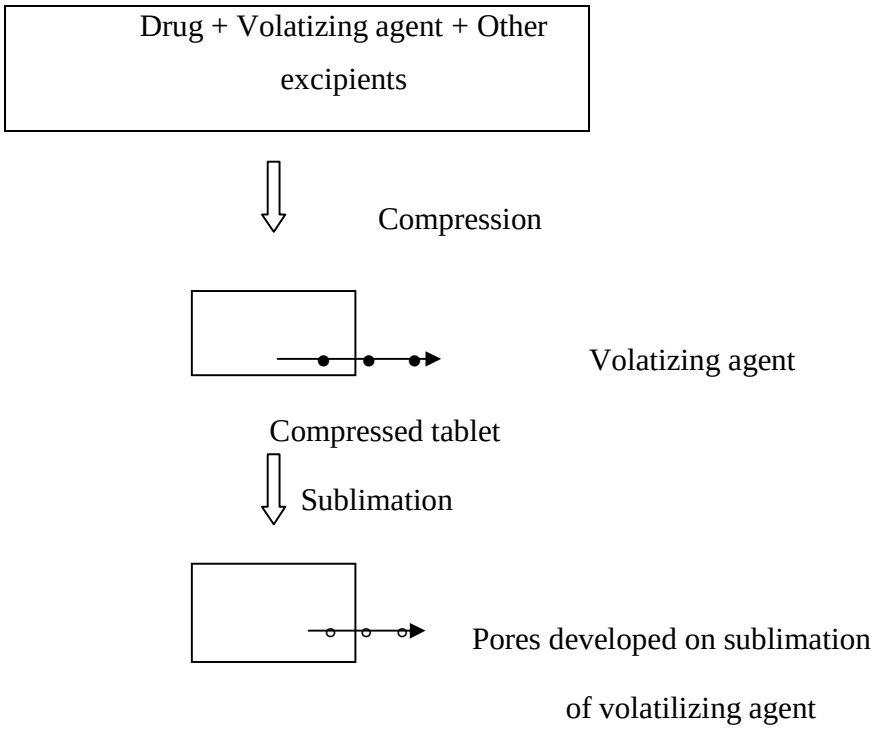


Fig. 1: Steps involved in Sublimation

5. Direct Compression: [16, 17]

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied for the preparation of MDT because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

(a) Superdisintegrants:

In many mouth dissolving tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

Factors to be considered for selection of superdisintegrants[9]:

- It should produce rapid disintegration(hydrophilic) when tablet meets saliva in the mouth
- It should be **compactable** enough to produce less-friable tablets.
- It can able to produce good mouth feel to the patient. Thus, small **particle size** are preferred to achieve patient compliance.
- It should has good flow since it improve the **flowability** of the total blend.
- **Super disintegrants:** Crosspovidone, Microcrystalline cellulose, sodium starch glycollate, sodium carboxy methyl cellulose, pregelatinzed starch, calcium carboxy methyl cellulose, and modified corn starch. Sodium starch glycollate has good flowability than crosscarmellose sodium. Cross povidone is fibrous nature and highly compactable.
- **Flavors:** Peppermint flavor, cooling flavor, flavor oils and flavoring aromatic oil, peppermint oil, clove oil, bay oil, anise oil, eucalyptus oil thyme oil, oil of bitter almonds. Flavoring agents include, vanilla, citrus oils, fruit essences
- **Sweeteners:** Aspartame, Sugars derivatives
- **Fillers:** Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, calcium sulfate, pregelatinized starch, magnesium trisilicate, aluminum hydroxide.

- **Surface active agents:** sodiumdoecylsulfate, sodiumlaurylsulfate, polyoxyethylene sorbitan fatty acid esters (Tweens), sorbitan fatty acid esters (Spans), polyoxyethylene stearates.
- **Lubricants:** Stearic acid, Magnesium stearate, Zinc state, calcium state, talc, polyethylene glycol, liquid paraffin, magnesium laury sulfate, colloidal silicon dioxide.

(b) Sugar Based Excipients:

This is another approach to manufacture MDT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel. Mizumito et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate.

Type 1 saccharides (lactose and mannitol) exhibit low mould ability but high dissolution rate.

Type 2 saccharides (maltose and maltilol) exhibit high mould ability and low dissolution rate.

6. Cotton Candy Process: [18]

The cotton candy process is also known as the “candy floss” process and forms on the basis of the technologies such as Flash Dose30 (Fuisz Technology). An MDT is formed using a candy floss or shear form matrix; the matrix is formed from saccharides or polysaccharides processed into amorphous floss by a simultaneous action of flash melting and centrifugal force. The matrix is then cured or partially recrystallised to provide a compound with good flow properties and compressibility. The candy floss can then be milled and blended with active ingredients and other excipients and subsequently compressed into MDT.

However, the high processing temperature limits the use of this technology to thermo-stable compounds only.

7. Mass-Extrusion: [19, 20]

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

PATENTED TECHNOLOGIES FOR MOUTH DISSOLVING TABLET:[21 -25]

1) Zydis Technology.
2) Durasolve Technology.
3) Orasolve Technology.
4) Flash Dose Technology.
5) Wow Tab Technology.
6) Flash Tab Technology.
7) Oraquick Technology.
8) Quick –Dis Technology.
9) Nanocrystal Technology.

1) Zydis Technology:

Zydis, the best known of the mouth-dissolving/disintegrating tablet preparations, was the first marketed new technology tablet. A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile, and must be dispensed in a special blister pack. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds. A major claim of the Zydis product is increased bioavailability compared to traditional tablets. Because of its dispersion and dissolution in saliva while still in the oral cavity, there can be a substantial amount of pre-gastric absorption from this formulation. Any pre-gastric absorption avoids first-pass metabolism and can be an advantage in drugs that undergo a great deal of hepatic metabolism. There are some disadvantages to the Zydis technology. As mentioned earlier, the Zydis formulation is very lightweight and fragile, and therefore should not be stored in backpacks or the bottom of purses. Finally, the Zydis formulation has poor

stability at higher temperatures and humidities. It readily absorbs water, and is very sensitive to degradation at humidities greater than 65%.

2) Orasolv Technology:

OraSolv was Cima's first mouth-dissolving/disintegrating dosage form. The OraSolv technology, unlike Zydis, disperses in the saliva with the aid of almost imperceptible effervescence. The OraSolv technology is best described as a mouth disintegrating tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The major disadvantage of the OraSolv formulations is its mechanical strength. The OraSolv tablet has the appearance of a traditional compressed tablet. However, the OraSolv tablets are only lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets. For that reason, Cima developed a special handling and packaging system for OraSolv. An advantage that goes along with the low degree of compaction of OraSolv is that the particle coating used for taste masking is not compromised by fracture during processing. These formulations can accommodate single or multiple active ingredients and tablets containing more that 1.0 g of drug have been developed. Their disintegration time is less than 30 seconds. The OraSolv formulations are not very hygroscopic.

3) Durasolv Technology:

DuraSolv is Cima's second-generation mouth-dissolving/disintegrating tablet formulation. Produced in a fashion similar to OraSolv, DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. DuraSolv tablets are prepared by using conventional tabletting equipment and have good rigidity (friability less than that 2%). The DuraSolv product is thus produced in a mouther and more cost-effective manner. DuraSolv is so durable that it can be packaged in traditional blister packaging, pouches or vials. One disadvantage of DuraSolv is that the technology

is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction.

4) Flash Dose Technology:

The FlashDose technology utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. This procedure has been patented by Fuisz and is known as Shear form. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue. Flash dose tablets consist of self–binding shear form matrix termed as “floss”. Shear form matrices are prepared by flash heat processing and are of two types.

5) Wowtab Technology

The Wowtab mouth-dissolving/disintegrating tablet formulation has been on the Japanese market for a number of years. The WOW in Wowtab signifies the tablet is to be given “With Out Water”. The Wowtab technology utilizes sugar and sugar-like (e.g., mannitol) excipients. This process uses a combination of low mouldability saccharides (rapid dissolution) and high mouldability saccharide (good binding property).The two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and mouth dissolution rate. Due to its significant hardness, the Wowtab formulation is a bit more stable to the environment than the Zydis or OraSolv. It is suitable for both conventional bottle and blister packaging. The Wowtab product dissolves quickly in 15 seconds or less.

6) Flashtab Technology

Prographarm laboratories have patented the Flashtab technology. This technology involves the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, extrusion-spheronization, simple pan coating methods and microencapsulation. The microcrystals of microgranules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation, and compressed into tablets. All the processing utilized the conventional tabletting technology, and the tablets produced are reported to have good mechanical strength and disintegration time less than one minute.

7) Oraquick Technology

The Oraquick mouth-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. The taste masking process does not utilize solvents of any kind, and therefore leads to mouther and more efficient production. Also, lower heat of production than alternative mouth-dissolving/disintegrating technologies makes Oraquick appropriate for heat-sensitive drugs. KV Pharmaceutical claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking. Oraquick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the Oraquick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives.

8) Quick –Dis Technology

Lavipharm has invented an ideal intra-oral mouth dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intra-oral drug delivery system, trademarked Quick-Dis™, is Lavipharm's proprietary patented technology and is a thin, flexible, and quick-dissolving film. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. The typical disintegration time is only 5 to 10 seconds for the Quick-Dis™ film with a thickness of 2 mm. The dissolving time is around 30 seconds for Quick Dis™ film with a thickness of 2 mm.

9) Nanocrystal Technology

For MOUTH DISSOLVING TABLETs, Elan's proprietary NanoCrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using NanoCrystal technology. NanoCrystal particles are small particles of drug substance, typically less than 1000 nm in diameter, which are produced by milling the drug substance using a proprietary wet milling technique. NanoCrystal colloidal dispersions of drug substance are combined with water-soluble ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds.

2. SUPERDISINTEGRANTS:

To achieve rapid disintegration, direct-compression MDT formulations typically contain high levels of a superdisintegrant. Depending on the level and characteristics of the active pharmaceutical ingredient (API) and the desired release profile, the levels of superdisintegrant used can be 8–10 wt % of the formulation, and it can be higher or lower in some cases. Thus, in developing an MDT formulation for direct compression, choosing the optimal superdisintegrant is critical.

SELECTING THE SUPERDISINTEGRANTS[26,27]**:**

Although the superdisintegrant primarily affects the rate of disintegration, when used at high levels it can also affect mouth feel, tablet hardness, and friability. Thus, several factors must be considered when selecting a superdisintegrant.

- ***Disintegration*:** The disintegrant must quickly wick saliva into the tablet to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration in the mouth.

- ***Compactability*:** When manufacturing an ODT, it is desirable to have tablets with acceptable hardness at a given compression force to produce robust tablets that avoid the need to use specialized packaging while maximizing production speed. Thus, a more compactable disintegrant will produce stronger, less-friable tablets.

- ***Mouth feel:*** To achieve patient compliance, ODTs must provide a palatable experience to the patient. Large particles can result in a gritty feeling in the

mouth. Thus, small particles are preferred. If the tablet forms a gel-like consistency on contact with water, however, it produces a gummy texture that many consumers find objectionable.

- ***Flow:*** As with all direct-compression tablet formulations, attaining good flow and content uniformity is important to achieving the required dosage per unit. In typical tablet formulations, superdisintegrants are used at 2–5 wt % of the tablet formulation. With ODT formulations, disintegrant levels can be significantly higher. At these higher use levels, the flow properties of the disintegrant are more important because it makes a greater contribution to the flow characteristics of the total blend.

MECHANISM OF SUPERDISINTEGRANTS [28,29,30]

The tablet breaks to primary particles by one or more of the mechanisms listed below

1. Because of heat of wetting (air expansion)

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and can not describe the action of most modern disintegrating agents.

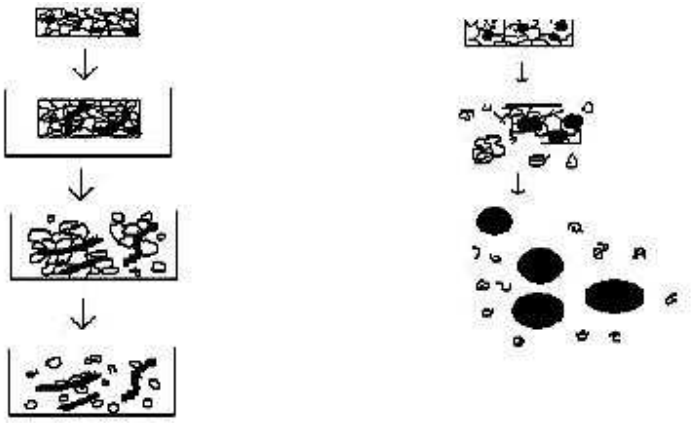
2. Swelling:

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

3. Porosity and capillary action (Wicking):

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

WICKING **SWELLING**



Water is pulled into pores by disintegrant and reduced the physical bonding force between particles.

Particles swell and break up the matrix form within; swelling setup; localized stress spreads throughout the matrix.

Fig. 2: Disintegration of Tablet by Wicking and Swelling

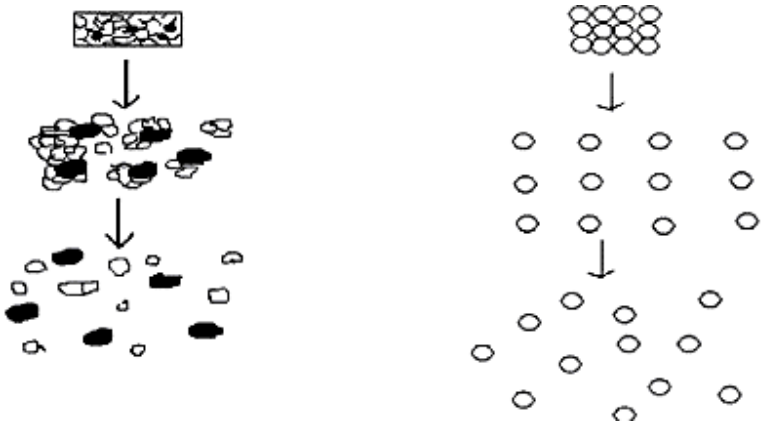
4. Due to disintegrating particle/particle repulsive forces:

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

5. Due to deformation.

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a break up of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

DEFORMATION **REPULSION**



Particles swell to precompression size and break up the matrix

Water is drawn into pores and particles repel each other because of the resulting electrical force

Fig. 3: Disintegration of Tablet by Deformation and Repulsion

6. Due to release of gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

***Table 1*: List of Superdisintegrants**

Superdisintegrants	Example	Mechanism of action	Special comment
Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose® Solutab® Vivasol® L-HPC	Crosslinked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation -Starch free
Crosspovidone Crosspovidon M® Kollidon® Polyplasdone®	Crosslinked PVP	-Swells very little and returns to original size after compression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab® Primogel®	Crosslinked starch	-Swells 7-12 folds in < 30 seconds	-Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine®	Crosslinked alginic acid	-Rapid swelling in aqueous medium or wicking action	-Promote disintegration in both dry or wet granulation
Soy polysaccharides Emcosoy®	Natural super disintegrant		-Does not contain any starch or sugar. Used in nutritional products.

Table 2: *Commercially Available MOUTH DISSOLVING TABLETs*[30]

TECHNOLOGIES	***TRADE NAME***	***ACTIVE INGREDIENT***	***MANUFACTURER***
Freeze Drying	Feldene Fast Melt	Piroxicam	Pfizer, USA
	Claritin Redi Tab	Loratidine	Schering plough, USA
	Maxalt MLT	Rizatriptan	Merck, USA
	Zyprexia	Olanzepine	Eli Lilly, USA
	Pepcid RPD	Famotidine	Merck, USA
	Zofran ODT	Ondansetron	Glaxo, UK
	Zooming ZMT	Zolmitriptan	AstraZeneca, USA
	Zelapar TM	Selegilline	Amarin,UK
Disintegrant Addition	Tempra Quicklets	Acetaminophen	Bristol Myers, USA
	Febrectol	Paracetamol	Prographarma, France
	Nimulid MDT	Nimesulide	Panacea Biotech, India
	Torrox MT	Rofecoxib	Torrent pharma, India
	Olanex Instab	Olanzapine	Ranbaxy, India
	Romilast	Montelukast	Ranbaxy, India
Sugar Based Excipient	Benadryl Fastmelt	Diphenhydramine & Pseudoephedrine	WarnerLambert, USA

- ***Evaluating physical characteristics of commercial superdisintegrants***[26,32,33]

  Currently available disintegrants were evaluated for particle size, particle-size distribution, flowability, compactability, particle shape, and morphology.

The following superdisintegrants were studied:

- **Crosspovidone A1** (standard particle-size grade) (Polyplasdone XL, International Specialty Products, Wayne, NJ);
- **Crosspovidone A2** (fine particle-size grade) (Polyplasdone XL-10, ISP);
- **Crosspovidone B** (Kollidon CL, BASF, Ludwigshafen, Germany);
- **sodium starch glycolate** (Explotab, JRS Pharma, Patterson, NY);
- **Crosscarmellose sodium**(Ac-Di-Sol, FMC, Philadelphia, PA).

- Crospovidone is an insoluble, neutral cross-linked homopolymer of N-vinyl-2-pyrrolidone. It is available in various particle sizes.
- The *US Pharmacopeia* defines sodium starch glycolate as the sodium salt of a carboxymethyl ether of starch or of a cross-linked carboxymethyl ether of starch, and crosscarmellose sodium is defined as the sodium salt of a cross-linked, partly O-(carboxymethylated) cellulose.

The selection of the optimal disintegrant for a formulation depends on a consideration of the combined effects of all of these factors:

(a) Particle size and distribution. A comparison of particle sizes of various disintegrants is shown in Table I and Figure 1.

Table I: Particle size and flowability index.

Superdisintegrant	Typical average particle size (μm)	Flowability index
Crospovidone A1	115	50
Crospovidone A2	30	47
Crospovidone B	110	44
Croscarmellose sodium	50	31
Sodium starch glycolate	50	58

Table: Particle size and flowability index.

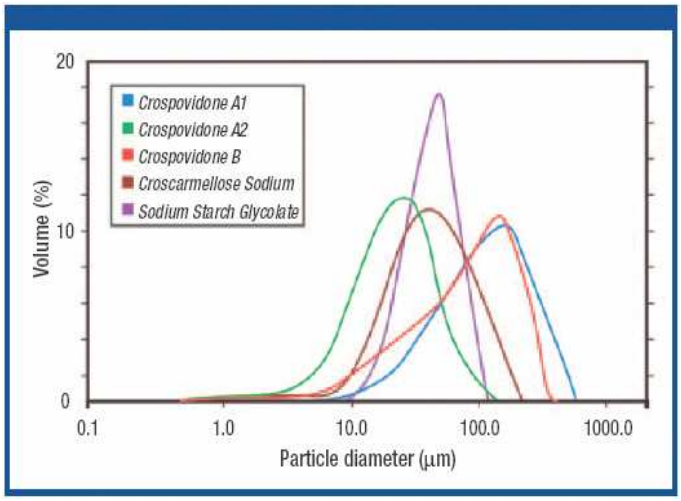


Figure I

Sodium starch glycolate and crosscarmellose sodium show similar average particle sizes; however, sodium starch glycolate has a narrower distribution, which contributes to the good flow properties. The particle size differences between the various types of crospovidone are shown. Because crospovidone

A2 offers the smallest average particle size (~30 μm), it is often preferred because small particles result in a smoother mouth feel.

(b) Flowability. Flowability index results are shown in Table I. Sodium starch glycolate provides the best flow as a result of its spherical particle morphology and narrow particle size distribution.

(c) Particle shape and morphology. When examined under a scanning electron microscope, sodium starch glycolate particles are spherical (Figure 2). Crospovidone particles appear granular and highly porous, although crospovidone B particles appear less porous. This porous particle morphology facilitates rapid wicking of liquid into both particle and tablet and contributes to the compactability of the material. Crosscarmellose sodium particles have a fibrous structure.

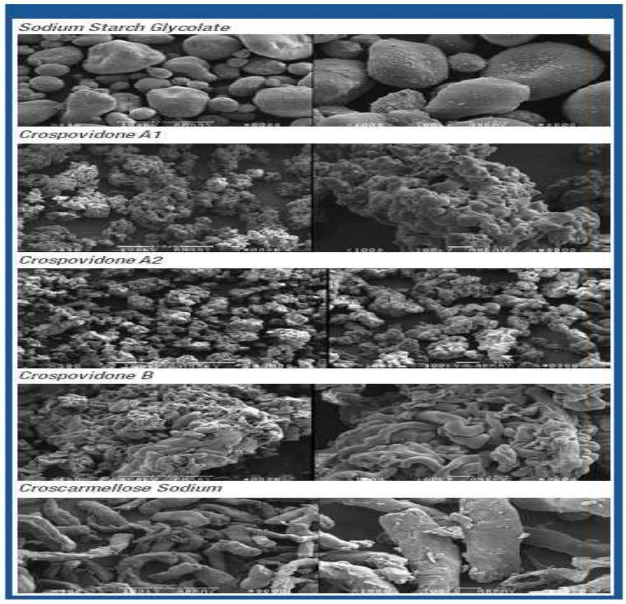


Figure II

(d) Compactability. The compactability of each of the disintegrants was evaluated by comparing the breaking force, at various compression forces, of pure compacts of each disintegrant with small amounts of lubricant and glidant added (see Figure 3). Results indicate that crospovidone is the most highly compactable disintegrate tested, thus producing the highest tablet-breaking force at a given compression force.

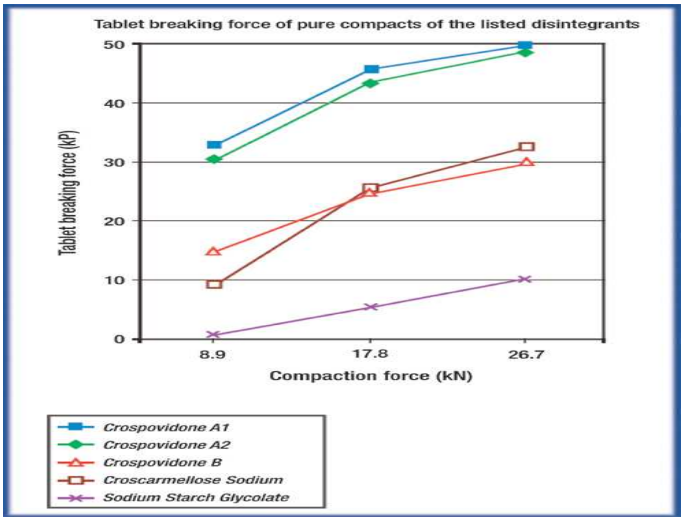
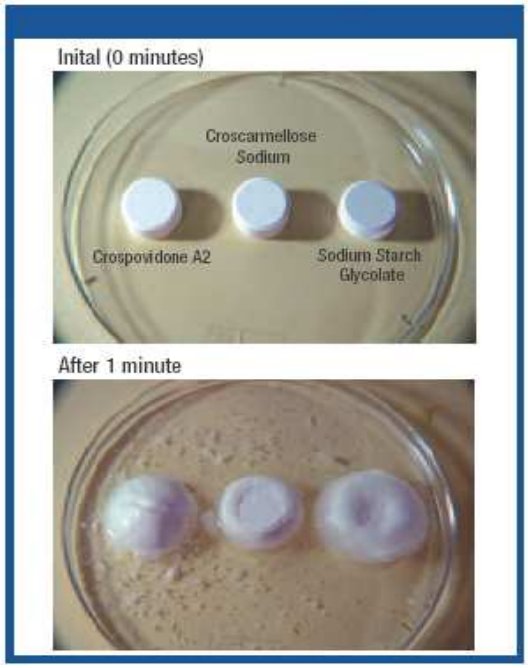


Figure III

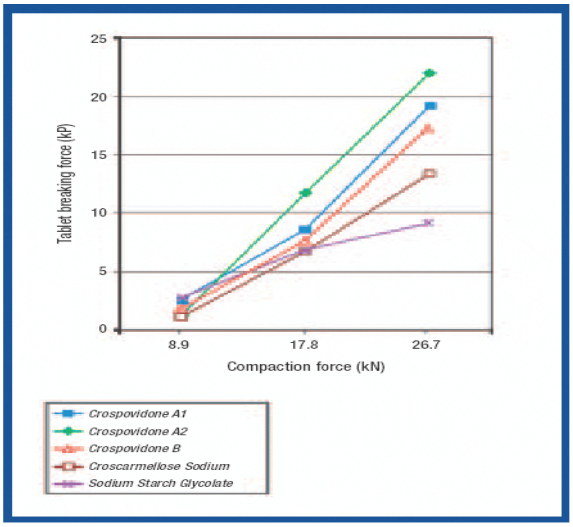
Nonetheless, the results also show that crospovidone A1 and B, with similar particle size, perform significantly differently. Crospovidone A1 is more compactable than crospovidone B.



When representative placebo tablets with crospovidone A2, sodium starch glycolate, and croscarmellose sodium were placed in a Petri dish with a small amount of water, the relative ability of the various disintegrants to wick water into the tablet was observed. One minute after contact with water, the tablet containing crospovidone A2 was fully hydrated and soft throughout because crospovidone quickly wicks water into the tablet. Meanwhile, the centers of the tablets made with sodium starch glycolate and croscarmellose sodium remained dry and hard. Although the tablet with sodium starch glycolate swelled, the outer edge appeared gel-like.

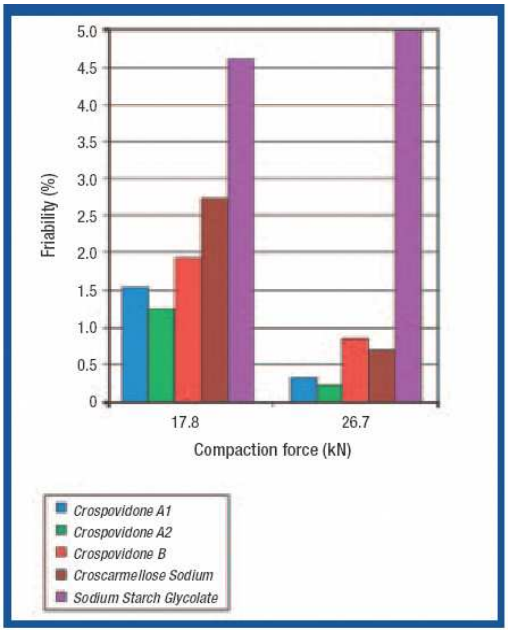
Relation between different pharmaceutical properties[26,34,35]*:*

(1) Relation between compaction force & tablet breaking force:



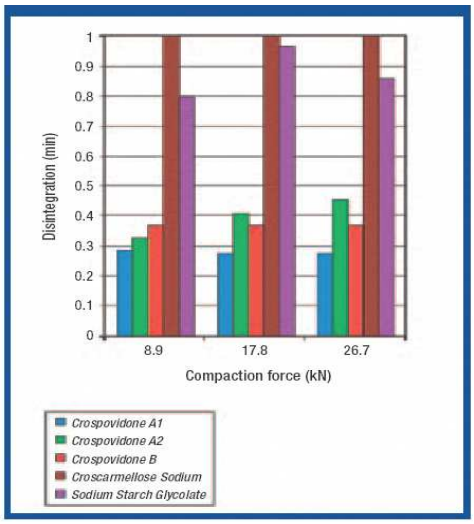
As per graph, it is concluded that, as compaction force increases tablet breaking force also increases. Crosspovidone has highest linearity between compaction force & tablet breaking force

(2) Relation between compaction force & friability:



As per graph, as compaction force increases, friability decreases. Minimum friability is of Crosspovidone A2 at compaction force 26.7 kN.

(3) Relation between compaction force & Disintegration:



As compaction force increases, disintegration time increases.

3. AMLODIPINE BESYLATE:

Drug Profile:

1. Drug class: Antihypertensive

2. Category: second generation dihydropyridamol Ca++ channel blocker

3. CAS number[36]: 88150-42-9

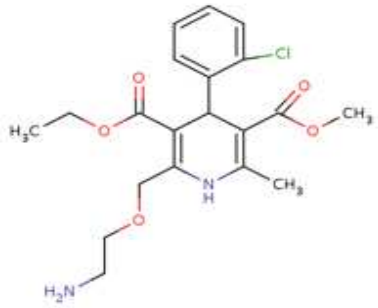
4. Official status: Drug is official in USP, IP, BP and EP.

5. Chemical name[36]***:*** 3-Ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate.

6. Molecular formula[36]: $C_{20}H_{25}ClN_2O_5$

7. Molecular weight[36]: 408.879 g/mol

8. Structural formula[36]***:***



9. Physicochemical properties:

a) Description and Solubility[3]: a white powder. It is slightly soluble in water and isopropanol; freely soluble in methanol; and sparingly soluble in dehydrated alcohol.

b) Melting point: 178-179^{o}C

c) Experimental Water Solubility- 75.3 mg/L

d) Predicted Water Solubility- 7.40e-03 mg/mL

e) Experimental LogP/Hydrophobicity- 1.9

f) Predicted LogP- 2.22

g) Optical rotation4: Between -0.10° & +0.10° at 20°C (solution 10mg/ml in methanol).

h) Dissociation constant (Pka)5: 8.6

i) Partition coefficient (log p)5: (o/w) 3.0

10. Storage condition[39]:

Preserve in tight container, protected from light, store at room temperature.

11. Pharmacological action and clinical pharmacology:

a) Mechanism of action[37]:

- Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle.
- Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites.

- Amlodipine had a strong blocking action on both the L-type and N-type Ca2+ channels expressed in the oocyte. The potency of the amlodipine block on the N-type Ca2+ channel was comparable to that on the L-type Ca2+ channel.
- The blocking action of amlodipine on the N-type Ca2+ channel was dependent on holding potential and extracellular pH, as has been observed with amlodipine block on the L-type Ca2+ channel. A depolarized holding potential and high pH enhanced the blocking action of amlodipine,
- Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa = 8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.
- The time course of block development by amlodipine was similar for L-type and N-type Ca2+ channels. However, it was slower than the time course of block development by nifedipine for the L-type Ca2+ channel.
- Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.
- The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

    - ✓ *Exertional Angina*: In patients with exertional angina, amlodipine reduces the total peripheral resistance (after load) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

- ✓ *Vasospastic Angina*: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A_2 analog in experimental animal models and in human coronary vessels *in vitro*. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in vasospastic (Prinzmetal's or variant) angina.

b) Pharmacokinetics and Metabolism:

- After oral administration of therapeutic doses of amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%.
- The bioavailability of amlodipine is not altered by the presence of food.
- Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.
- *Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients.
- Elimination from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours.
- Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.
- The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.
- Elderly patients and patients with hepatic insufficiency have decreased clearance of Amlodipine with a resulting increase in AUC of approximately 40 to 60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

c) Pharmacodynamics:

- *Hemodynamic*[36]*:*

  - Following administration of therapeutic doses to patients with hypertension, Amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.
  - Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.
  - With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients.
  - The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105 to 114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90 to 104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/–2 mmHg).
  - In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

- As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co administered with beta blockers to man. Similar findings, however, have been observed in normals or well compensated patients with heart failure with agents possessing significant negative inotropic effects.

➢ *Electro physiologic Effects*[37]:

- Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing.
- Similar results were obtained in patients receiving amlodipine and concomitant beta blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

❖ *Clinical Studies*

➢ Effects in Hypertension:

✓ *Adult Patients*:

- The antihypertensive efficacy of amlodipine has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on Amlodipine and 538 on placebo. Once daily administration produced statistically significant placebo corrected reductions in supine and standing blood pressures at 24 hours post dose, averaging about 12/6 mmHg in the standing position and 13/7 mmHg in the supine position in patients with mild to moderate hypertension. Maintenance of the blood pressure effect over the 24-hour dosing interval was observed, with little difference in peak and trough effect. Tolerance was not demonstrated in patients studied for up to 1 year.
- The 3 parallel, fixed dose, dose response studies showed that the reduction in supine and standing blood pressures was dose-related within the recommended dosing range.
- Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure. Effects were similar in black patients and in white patients.

✓ *Pediatric Patients:*

Two-hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to amlodipine besylate 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 5 mg at the end of 8 weeks had lower blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5-mg dose. Adverse events were similar to those seen in adults.

➢ **Effects in Chronic Stable Angina:**

- The effectiveness of 5 to 10 mg/day of amlodipine in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind clinical trials of up to 6 weeks duration involving 1038 patients (684 amlodipine, 354 placebo) with chronic stable angina. In 5 of the 8 studies significant increases in exercise time (bicycle or treadmill) were seen with the 10 mg dose.
- Increases in symptom-limited exercise time averaged 12.8% (63 sec) for amlodipine 10 mg, and averaged 7.9% (38 sec) for amlodipine 5 mg. Amlodipine 10 mg also increased time to 1 mm ST segment deviation in several studies and decreased angina attack rate.
- The sustained efficacy of amlodipine in angina patients has been demonstrated over long-term dosing. In patients with angina there were no clinically significant reductions in blood pressures (4/1 mmHg) or changes in heart rate (+0.3 bpm).

➢ **Effects in Vasospastic Angina:**

In a double-blind, placebo-controlled clinical trial of 4 weeks duration in 50 patients, Amlodipine therapy decreased attacks by approximately 4/week compared with a placebo decrease of approximately 1/week ($p<0.01$). Two (2) of 23 amlodipine and 7 of 27 placebo patients discontinued from the study due to lack of clinical improvement.

❖ ***INDICATIONS AND USAGE[40]:***

1. Hypertension:

Amlodipine Orally Disintegrating Tablets is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

2. Coronary Artery Disease:

- *Chronic Stable Angina:*

Amlodipine Orally Disintegrating tablets are indicated for the symptomatic treatment of chronic stable angina. Amlodipine Orally Disintegrating Tablets may be used alone or in combination with other antianginal agents.

- *Vasospastic Angina (Prinzmetal's or Variant Angina):*

Amlodipine Orally Disintegrating Tablets are indicated for the treatment of confirmed or suspected vasospastic angina. It may be used as monotherapy or in combination with other antianginal drugs.

❖ *CONTRAINDICATIONS*[41]

Amlodipine Orally Disintegrating Tablets is contraindicated in patients with known sensitivity to amlodipine.

❖ *WARNINGS:*

➢ **Increased Angina and/or Myocardial Infarction:**

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

❖ *PRECAUTIONS*[37]

➢ General:

Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, caution, as with any other peripheral vasodilator, should be exercised when administering amlodipine, particularly in patients with severe aortic stenosis.

❖ *DRUG INTERACTIONS:*

In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

➢ Effect of other agents on amlodipine[37]:

- *CIMETIDINE:* Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.
- *GRAPEFRUIT JUICE*: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.
- *MAALOX (antacid):* Co-administration of the antacid Maalox with a single dose of Amlodipine had no significant effect on the pharmacokinetics of amlodipine.
- *SILDENAFIL:* A single 100 mg dose of sildenafil (Viagra®) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When Amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

➢ Effect of amlodipine on other agents[37]:

- *ATORVASTATIN:* Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.
- *DIGOXIN:* Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.
- *ETHANOL (alcohol*): Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.
- *WARFARIN:* Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time. In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

➢ Pediatric Use:

The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

➢ Geriatric Use:

- Clinical studies of amlodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.
- In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40 to 60%, and a lower initial dose may be required.

❖ *ADVERSE REACTIONS[38]:*

- **Cardiovascular:**

arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.

- **Central and Peripheral Nervous System:**

hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.

- **Gastrointestinal:**

anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

- **General:**

allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

- **Musculoskeletal System:**

arthralgia, arthrosis, muscle cramps, myalgia.

- **Psychiatric:**

sexual dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

- **Respiratory System:**

dyspnea, epistaxis.

- **Skin and Appendages:**

angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular..

- **Special Senses:**

abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

- **Urinary System:**

micturition frequency, micturition disorder, nocturia.

❖ OVERDOSAGE[39]

- Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral Amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more time times the maximum recommended human dose on a mg/m^2 basis) caused a marked peripheral vasodilation and hypotension.

- Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited.

❖ DOSAGE AND ADMINISTRATION[39]

- **Adults:**

  The usual initial antihypertensive oral dose of Amlodipine Orally Disintegrating Tablets is 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly individuals, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding Amlodipine Orally Disintegrating tablets to other antihypertensive therapy. The recommended dose for chronic stable or vasospastic angina is 5 to 10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency.

- **Children:**

  The effective antihypertensive oral dose in pediatric patients ages 6 to17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients.

Mannitol

1. Nonproprietary Names

- BP: Mannitol
- JP: D-Mannitol
- PhEur: Mannitolum
- USP: Mannitol

2. Synonyms

Cordycepic acid; E421; manna sugar; D-mannite; mannite;

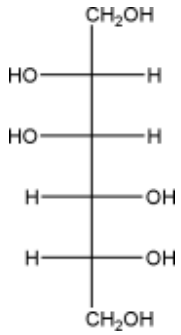
3. Chemical Name and CAS Registry Number

D-Mannitol [69-65-8]

4. Empirical Formula and Molecular Weight

$C_6H_{14}O_6$ 182.17

5. Structural Formula



6. Functional Category

Diluent; diluent for lyphilized preparations; sweetening agent; tablet and capsule diluent; tonicity agent.

7. Applications in Pharmaceutical Formulation or Technology

Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients.

Mannitol may be used in direct-compression tablet applications, for which the granular and spray-dried forms are available, or in wet granulations. Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel'.

Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (<7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations, and as a carrier in dry powder inhalers. It is also used as a diluent in rapidly dispersing oral dosage forms. It is used in food applications as a bulking agent.

8. Description

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol.

Mannitol occurs as a white, odorless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism.

9. Pharmacopeial Specifications

Table: Pharmacopeial specifications for mannitol.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	—	+	—
Solution appearance	+	+	—
Melting range	166–169°C	165–170°C	164–169°C
Loss on drying	≤0.3%	≤0.5%	≤0.3%
Chloride	≤0.007%	—	≤0.007%
Sulfate	≤0.01%	—	≤0.01%
Arsenic	≤1.3 ppm	—	≤1 ppm
Microbial contamination	—	≤100/g	—
Assay (dried basis)	≥ 98.0%	98.0–102.0%	96.0–101.5%

10. Typical Properties

- ✓ *Density (bulk):*

  0.430 g/cm^3 for powder;

- ✓ *Density (tapped):*

  0.734 g/cm^3 for powder;

- ✓ *Density (true):*

  1.514 g/cm^3

- ✓ *Flowability:*

  powder is cohesive, granules are free flowing.

- ✓ *Melting point:*

  166–168°C

11. Stability and Storage Conditions

Mannitol is stable in the dry state and in aqueous solutions. Solutions may be sterilized by filtration or by autoclaving and if necessary may be autoclaved repeatedly with no adverse physical or chemical effects. The bulk material should be stored in a well-closed container in a cool, dry place.

12. Incompatibilities

Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride. Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic. Sodium cephapirin at 2 mg/mL and 30 mg/mL concentration is incompatible with 20% w/v aqueous mannitol solution.

13. Method of Manufacture

Mannitol may be extracted from the dried sap of manna and other natural sources by means of hot alcohol or other selective solvents. It is commercially produced by the catalytic or electrolytic reduction of monosaccharides such as mannose and glucose.

14. Safety

Mannitol is a naturally occurring sugar alcohol found in animals and plants; it is present in small quantities in almost all vegetables. Laxative effects may occur if mannitol is consumed orally in large quantities. If it is used in foods as a bodying agent and daily ingestion of over 20 g is foreseeable, the product label should bear the statement ‘excessive consumption may have a laxative effect’. After intravenous injection, mannitol

is not metabolized to any appreciable extent and is minimally reabsorbed by the renal tubule, about 80% of a dose being excreted in the urine in 3 hours.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Mannitol may be irritant to the eyes; eye protection is recommended

Aspartame

1. Nonproprietary Names

- BP: Aspartame
- USPNF: Aspartame

2. Synonyms

3-Amino-*N*-(α-carboxyphenethyl)succinamic acid *N*-methyl ester;

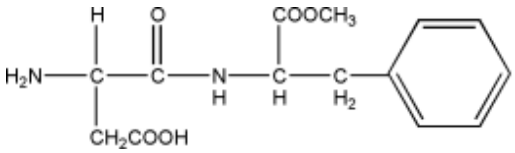
3. Chemical Name and CAS Registry Number

N-α-L-Aspartyl-L-phenylalanine 1-methyl ester [22839-47-0]

4. Empirical Formula and Molecular Weight

$C_{14}H_{18}N_2O_5$ 294.31

5. Structural Formula



6. Functional Category

Sweetening agent.

7. Applications in Pharmaceutical Formulation or Technology

Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations. It enhances flavor systems and can be used to mask

some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose.

8. Description

Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.

9. Pharmacopeial Specifications

Table: Pharmacopeial specifications for aspartame.

Test	PhEur 2005	USPNF 23
Characters	+	—
Identification	+	+
Heavy metals	≤10 ppm	≤0.001%
Loss on drying	≤4.5%	≤4.5%
Assay	98.0–102.0%	98.0–102.0%

10. Typical Properties

- ✓ *Acidity/alkalinity:*

  pH = 4.5–6.0 (0.8% w/v aqueous solution).

- ✓ Flowability:

  44% (Carr compressibility index)

- ✓ Density (bulk):

  0.5–0.7 g/cm^3 for granular grade;

- ✓ Density (tapped):

  0.29 g/cm^3 (Spectrum Quality Products)

- ✓ Melting point:

  246–247°C

- ✓ Solubility:

  slightly soluble in ethanol (95%); sparingly soluble in water. At 20°C the solubility is 1% w/v at the isoelectric point (pH 5.2). Solubility increases at higher temperature and at more acidic pH, e.g., at pH 2 and 20°C solubility is 10% w/v.

11. Stability and Storage Conditions

Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form the degradation products L-aspartyl-L-phenylalanine and 3-benzyl-6-carboxymethyl-2,5-diketopiperazine. The bulk material should be stored in a well-closed container, in a cool, dry place.

12. Incompatibilities

Differential scanning calorimetry experiments with some directly compressible tablet excipients suggests that aspartame is incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate. Reactions between aspartame and sugar alcohols are also known.

13. Method of Manufacture

Aspartame is produced by coupling together L-phenylalanine (or L-phenylalanine methyl ester) and L-aspartic acid, either chemically or enzymatically. The former procedure yields both the sweet α-aspartame and nonsweet β-aspartame from which the α-aspartame has to be separated and purified. The enzymatic process yields only α-aspartame.

14. Safety

Aspartame is widely used in oral pharmaceutical formulations, beverages, and food products as an intense sweetener and is generally regarded as a nontoxic material. However, the use of aspartame has been of some concern owing to the formation of the potentially toxic metabolites methanol, aspartic acid, and phenylalanine.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Measures should be taken to minimize the potential for dust explosion. Eye protection is recommended.

Microcrystalline Cellulose

1. Nonproprietary Names

- BP: Microcrystalline cellulose
- USPNF: Microcrystalline cellulose

2. Synonyms

Avicel PH; *Celex*; cellulose gel; *Celphere*; *Ceolus KG*; crystalline cellulose; E460;

3. Chemical Name and CAS Registry Number

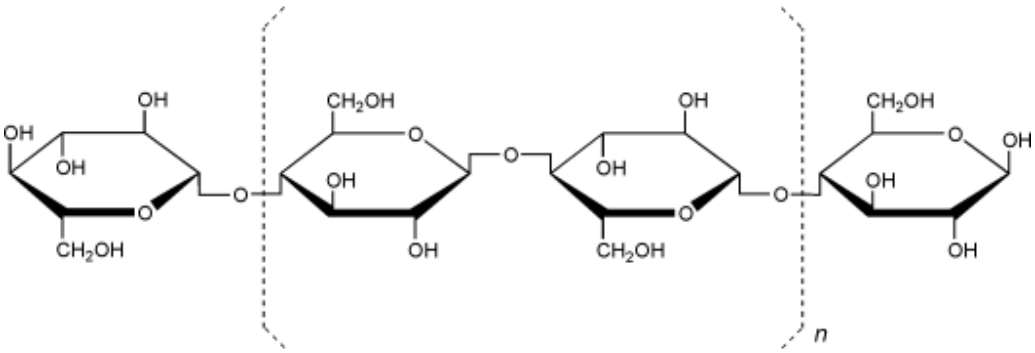
Cellulose [9004-34-6]

4. Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ ≈36 000

where $n \approx 220$.

5. Structural Formula



6. Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

7. Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.[1–7] In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant[8] and disintegrant properties that make it useful in tableting.

Microcrystalline cellulose is also used in cosmetics and food products;

Table I: Uses of microcrystalline cellulose.

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluent	20–90
Tablet disintegrant	5–15
Tablet binder/diluent	20–90

8. Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

9. Pharmacopeial Specifications

Table : Pharmacopeial specifications for microcrystalline cellulose.

Test	JP 2001	PhEur 2005 (Suppl 5.1)	USPNF 23
Identification	+	+	+
Characters	+	+	—
pH	5.0–7.0	5.0–7.5	5.0–7.5
Bulk density	+	—	+
Loss on drying	≤7.0%	≤7.0%	≤7.0%
Residue on ignition	≤0.05%	—	≤0.1%

10. Typical Properties

- ✓ Angle of repose:

  49° for *Ceolus KG*;

- ✓ Density (bulk):

  0.337 g/cm^3;

- ✓ Density (tapped):

  0.478 g/cm^3;

- ✓ Melting point:

  chars at 260–270°C.

- ✓ Solubility:

  slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

11. Stability and Storage Conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

12. Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

13. Method of Manufacture

Microcrystalline cellulose is manufactured by controlled hydrolysis with dilute mineral acid solutions of α-cellulose, obtained as a pulp from fibrous plant materials. Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spray-dried to form dry, porous particles of a broad size distribution.

14. Safety

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

Silicified Microcrystalline

1. Nonproprietary Names

None adopted.

2. Synonyms

ProSolv.

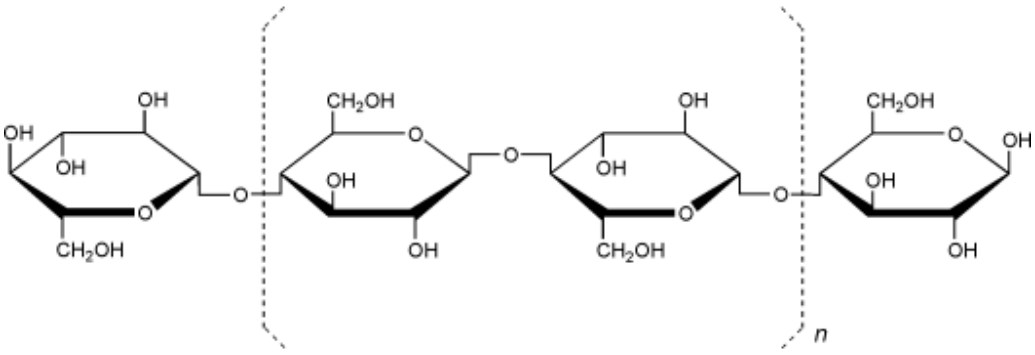
3. Chemical Name and CAS Registry Number

Section 8.

4. Empirical Formula and Molecular Weight

Section 8.

5. Structural Formula



6. Functional Category

Tablet and capsule diluent.

7. Applications in Pharmaceutical Formulation or Technology

Silicified microcrystalline cellulose is used as a filler in the formulation of capsules and tablets. It has improved compaction properties in both wet granulation and direct compression compared to conventional microcrystalline cellulose. Silicified microcrystalline cellulose was specifically developed to address the loss of compaction that occurs with microcrystalline cellulose after wet granulation.

8. Description

Silicified microcrystalline cellulose is a synergistic, intimate physical mixture of two components: microcrystalline cellulose and colloidal silicon dioxide (for further information *see* Cellulose, Microcrystalline and Colloidal Silicon Dioxide). Silicified microcrystalline cellulose contains 2% w/w colloidal silicon dioxide.

9. Pharmacopeial Specifications

-

10. Typical properties

- ✓ Acidity/alkalinity:
  pH = 5.0–7.5 (10% w/v suspension)
- ✓ Density:
  1.58 g/cm^3
- ✓ Density (bulk):
  0.31 g/cm3
- ✓ Density (tapped):
  0.39 g/cm^3

- ✓ Moisture content:

  typically less than 6% w/w.

- ✓ Solubility:

  Practically insoluble in water, dilute acids, and most organic solvents. The microcrystalline cellulose component is slightly soluble in 5% w/w sodium hydroxide solution.

11. Stability and Storage Conditions

Silicified microcrystalline cellulose is stable when stored in a well-closed container in a cool,dry place.

12. Method of Manufacture

- Silicified microcrystalline cellulose is manufactured by co-drying a suspension of microcrystalline cellulose particles and colloidal silicon dioxide so that the dried finished product contains 2% w/w colloidal silicon dioxide.
- The colloidal silicon dioxide appears physically bound onto the surface and inside the silicified microcrystalline cellulose particles. Extensive studies using different spectroscopic methods have failed to show any form of chemical interaction.4,6,7

13. Safety

See Cellulose, Microcrystalline and Colloidal Silicon Dioxide.

Hydroxy propyl Cellulose

1. Nonproprietary Names:

- BP: Hydroxy propyl cellulose
- USPNF: Hydroxy propyl cellulose

2. Synonyms:

Cellulose, hydroxy propyl ether; E463; hyprolose; *Klucel*; *Methocel*; *Nisso HPC*;

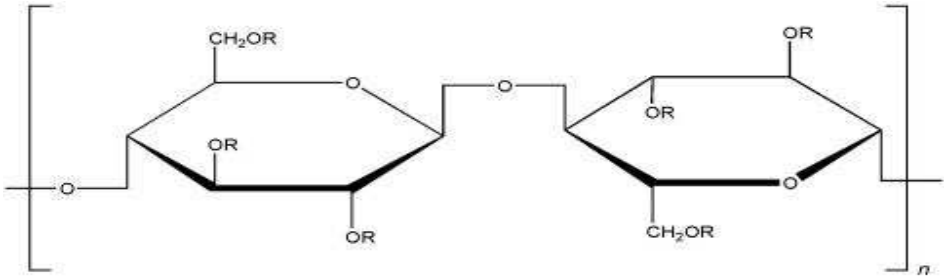
3. Chemical Name and CAS Registry Number:

Cellulose, 2-hydroxy propyl ether [9004-64-2]

4. Empirical Formula and Molecular Weight:

The PhEur 2005 and USPNF 23 describe hydroxy propyl cellulose as a partially substituted poly(hydroxy propyl) ether of cellulose. It may contain not more than 0.6% of silica or another suitable anticaking agent. Hydroxy propyl cellulose is commercially available in a number of different grades that have various solution viscosities. Molecular weight has a range of 50 000–1 250 000;

5. Structural Formula:



R is H or $[CH_2CH(CH_3)O]_mH$

6. Functional Category:

Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology:

Hydroxy propyl cellulose is widely used in oral and topical pharmaceutical formulations;

Uses of hydroxy propyl cellulose.

Use	Concentrations(%)
Extended release-matrix former	15–35
Tablet binder	2–6
Tablet film coating	5

- In oral products, hydroxy propyl cellulose is primarily used in tableting as a binder, filmcoating, and extended-release-matrix former. Concentrations of hydroxy propyl cellulose of 2–6% w/w may be used as a binder in either wet-granulation or dry, direct-compression tableting processes. Concentrations of 15–35% w/w of hydroxy propyl cellulose may be used to produce tablets with an extended drug release. Typically, a 5% w/w solution of hydroxy propyl cellulose may be used to filmcoat tablets.

8. Description:

Hydroxy propyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder.

9. Pharmacopeial Specifications:

Table II: Pharmacopeial specifications for hydroxy propyl cellulose.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Apparent viscosity	+	+	+
Appearance of solution	+	+	—
pH (1 in 100)	5.0–7.5	5.0–8.5	5.0–8.0
Loss on drying	5.0%	7.0%	5.0%
Residue on ignition	0.5%	—	0.2%

10. Typical Properties

- ✓ Acidity/alkalinity:

  pH = 5.0–8.5 for a 1% w/v aqueous solution.

- ✓ Density (bulk):

  0.5 g/cm3

- ✓ Melting point:

  softens at 130°C; chars at 260–275°C.

- ✓ Solubility:

  Soluble 1 in 10 parts dichloromethane; 1 in 2.5 parts ethanol (95%); 1 in 2 parts methanol; 1 in 5 parts propan-2-ol; 1 in 5 parts propylene glycol; and 1 in 2 parts water. Practically insoluble in aliphatic hydrocarbons; aromatic hydrocarbons; carbon tetrachloride; petroleum distillates; glycerin; and oils.

11. Stability and Storage Conditions:

Hydroxy propyl cellulose powder is a stable material, although it is hygroscopic after drying. Aqueous solutions of hydroxy propyl cellulose are stable at pH 6.0–8.0, with the viscosity of solutions being relatively unaffected.

Crospovidone

1. Nonproprietary Names

- BP: Crospovidone
- USPNF: Crospovidone

2. Synonyms

Crosslinked povidone; E1202; *Kollidon CL*; *Kollidon CL-M*; *Polyplasdone XL*; *Polyplasdone XL-10*;

3. Chemical Name and CAS Registry Number

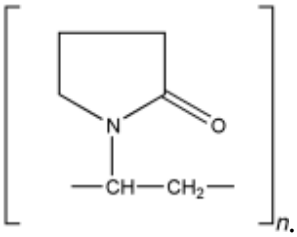
1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4. Empirical Formula and Molecular Weight

$(C_6H_9NO)_n$ >1 000 000

The USPNF 23 describes crospovidone as a water-insoluble synthetic crosslinked homopolymer of *N*-vinyl-2-pyrrolidinone. An exact determination of the molecular weight has not been established because of the insolubility of the material.

5. Structural Formula



6. Functional Category

Tablet disintegrant.

7. Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels.

8. Description

Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

See SEM 1.

9. Pharmacopeial Specifications

Table I

Table I: Pharmacopeial specifications for crospovidone.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
pH (1% suspension)	—	5.0–8.0
Water	—	≤5.0%
Residue on ignition	≤0.1%	≤0.4%

10. Typical Properties

- ✓ Acidity/alkalinity:

  pH = 5.0–8.0 (1% w/v aqueous slurry)

- ✓ Moisture content**:**

  maximum moisture sorption is approximately 60%.

- ✓ Solubility:

  practically insoluble in water and most common organic solvents.

11. Stability and Storage Conditions

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

12. Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials

13. Method of Manufacture

Acetylene and formaldehyde are reacted in the presence of a highly active catalyst to form butynediol, which is hydrogenated to butanediol and then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reaction in which pyrrolidone and acetylene are reacted under pressure. The monomer vinylpyrrolidone is then polymerized in solution, using a catalyst. Crospovidone is prepared by a ‘popcorn polymerization’ process.

14. Safety

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. Short-term animal toxicity studies have shown no adverse effects associated with crospovidone. However, owing to the lack of available data, an acceptable daily intake in humans has not been specified by the WHO.

Vanillin

1. Nonproprietary Names

- BP: Vanillin
- USPNF: Vanillin

2. Synonyms

4-Hydroxy-*m*-anisaldehyde; *p*-hydroxy-*m*-methoxybenzaldehyde

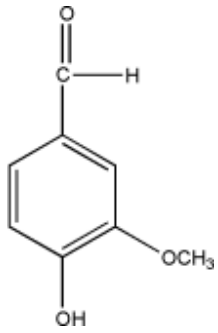
3. Chemical Name and CAS Registry Number

4-Hydroxy-3-methoxybenzaldehyde [121-33-5]

4. Empirical Formula and Molecular Weight

$C_8H_8O_3$ 152.15

5. Structural Formula



6. Functional Category

Flavoring agent.

7. Applications in Pharmaceutical Formulation or Technology

Vanillin is widely used as a flavor in pharmaceuticals, foods, beverages, and confectionery products, to which it imparts a characteristic taste and odor of natural

vanilla. It is also used in perfumes, as an analytical reagent and as an intermediate in the synthesis of a number of pharmaceuticals, particularly methyldopa. Additionally, it has been investigated as a potential therapeutic agent in sickle cell anemia and is claimed to have some antifungal properties.

8. Description

White or cream, crystalline needles or powder with characteristic vanilla odor and sweet taste.

9. Pharmacopeial Specifications

Table

Table I: Pharmacopeial specifications for vanillin.

Test	PhEur 2005	USPNF 23
Identification	+	+
Characters	+	—
Loss on drying	≤1.0%	≤1.0%
Sulfated ash	≤0.05%	—
Residue on ignition	—	≤0.05%

10. Typical Properties

- ✓ Acidity/alkalinity:

  aqueous solutions are acid to litmus.

- ✓ Density (bulk):

  0.6 g/cm^3

11. Stability and Storage Conditions

Vanillin oxidizes slowly in moist air and is affected by light.The bulk material should be stored in a well-closed container, protected from light, in a cool, dry place.

12. Incompatibilities

Incompatible with acetone, forming a brightly colored compound.[7] A compound practically insoluble in ethanol is formed with glycerin.

13. Method of Manufacture

Vanillin occurs naturally in many essential oils and particularly in the pods of Vanilla planifolia and Vanilla tahitensis. Industrially, vanillin is prepared from lignin, which is obtained from the sulfite wastes produced during paper manufacture. Lignin is treated with alkali at elevated temperature and pressure, in the presence of a catalyst, to form a complex mixture of products from which vanillin is isolated. Vanillin is then purified by successive recrystallizations.

14. Safety

There have been few reports of adverse reactions to vanillin, although it has been speculated that cross-sensitization with other structurally similar molecules, such as benzoic acid, may occur.

Magnesium Stearate

1. Nonproprietary Names

- BP: Magnesium stearate
- USPNF: Magnesium stearate

2. Synonyms

Magnesium octadecanoate; octadecanoic acid,

3. Chemical Name and CAS Registry Number

Octadecanoic acid magnesium salt [557-04-0]

4. Empirical Formula and Molecular Weight

$C_{36}H_{70}MgO_4$ 591.34

The USPNF 23 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$)..

5. Structural Formula

$[CH_3(CH_2)_{16}COO]_2Mg$

6. Functional Category

Tablet and capsule lubricant.

7. Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams. *See also* Section 18.

8. Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

See SEM: 1, SEM: 2.

9. Pharmacopeial Specifications

Table: Pharmacopeial specifications for magnesium stearate.

Test	JP 2001	PhEur 2005	USPNF 23
Identification	+	+	+
Characters	—	+	—
Microbial limits	+	+	+
Aerobic microbes	≤1000/g	$\leq 10^3$/g	$\leq 10^3$/g
Assay (dried, as Mg)	4.0–5.0%	4.0–5.0%	4.0–5.0%

10. Typical Properties

- ✓ Crystalline forms:

  high-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.

- ✓ Density (bulk):

  0.159 g/cm^3

- ✓ Density (tapped):

  0.286 g/cm^3

- ✓ Density (true):

  1.092 g/cm^3

11. Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

12. Incompatibilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

13. Method of Manufacture

Magnesium stearate is prepared either by the interaction of aqueous solutions of magnesium chloride with sodium stearate or by the interaction of magnesium oxide, hydroxide, or carbonate with stearic acid at elevated temperatures.

14. Safety

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.

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4. LITERATURE REVIEW

4.1 Mouth Dissolving Tablets

- Gohel[42] et al (2004) prepared the mouth dissolved tablets of Nimesulide using vaccum drying technique. Granules containing Nimesulide, camphor, crorospovidone and lactose were prepared by wet granulation technique. Camphor was sublimed from the dried granules by exposure to vacuum. The tablets were evaluated for % friability, wetting time and disintegration time. In the present investigation a 3^2 full factorial design was used to investigate combined effect of two formulation variables: amount of camphor and amount of superdisintegrant. The results of multiple linear regression analysis revealed that for obtaining a rapidly disintegrating dosage form, tablets should be prepared using optimum concentration of camphor and higher percentage of crospovidone.

- Ahmed S. Zidan[43] et al (2006) formulated and optimized mouth dissolving tablets containing Rofecoxib using solid dispersion. The purpose of the present investigation was to increase the solubility and dissolution rate of Rofecoxib by the preparation of its solid dispersion with polyvinyl pyrrolidone K30 (PVP K30) using solvent evaporation method. For the preparation of Rofecoxib mouth dissolve tablets, its 1: 9 solid dispersion with PVP K30 was used with various disintegrants and sublimable materials. The obtained results showed that dispersion of the drug in the polymer considerably enhanced the dissolution rate. The drug-to-carrier ratio was the controlling factor for dissolution improvement.

- Keith J. Simons[44] et al (2006) prepared fast-disintegrating sublingual tablets. Four tablet formulations, A, B, C, and D, containing 0%, 6%, 12%, and 24% of Epinephrine bitartrate, respectively, and microcrystalline cellulose: low-substituted hydroxypropyl cellulose (9:1), were prepared by direct compression,

at a range of compression forces. Tablet weight variation, content uniformity, hardness, disintegration time, wetting time, and friability were measured for each formulation at each compression force. All 4 tablet formulations at each compression force were within the USP limits for weight variation and content uniformity. At a mean ± SD hardness of ≤ 2.3 ± 0.2 kg, all tablet formulations passed the USP friability test. At a mean ± SD hardness of ≥ 3.1 ± 0.2 kg, all tablet formulations resulted in disintegration and wetting times of <10 seconds and <30 seconds, respectively.

- Abdelbary[45] et al (2004) prepared orally disintegrating tablets using a hydrophilic waxy binder. The incorporation of Superpolystate® in the formulation of RDT was realised by means of two different granulation methods: wet granulation by using an emulsion of this waxy binder as granulating liquid and melt granulation where the molten form of the binder was used. The potential of the intragranular addition of croscarmellose sodium as a disintegrating agent was also evaluated. An improvement in tablet hardness and friability was observed with both granulation methods where we were able to obtain RDT with a disintegration time of 40 ± 2 seconds and a hardness of 47.9 ± 2.5N.

- Koizumi[46] et al (1997) presented an invention, which related to rapidly saliva tablets using sublimation technique. Compressed tablets of Mannitol did not dissolve in water due to the low porosity. To increase the porosity of tablets sublimation was done. Tablets were prepared by direct compression containing mannitol and camphor. A high porosity was achieved due to formation of many pores due to camphor sublimation. The compressed tablets have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva.

- Shawn A. Mitchell[47] et al studied a compaction process to enhance dissolution of poorly water soluble drugs using low-viscosity HPMC. The purpose of this study was to develop a technique to enhance the dissolution rate of poorly water-soluble drugs with low-viscosity HPMC without the use of solvent or heat addition. The

compaction processes enhanced drug dissolution relative to drug alone and also relative to corresponding loosely mixed physical mixtures. The roller compaction and slugging method produced comparable dissolution enhancement. The mechanism for dissolution enhancement is believed to be a microenvironment HPMC surfactant effect facilitated by keeping the HPMC and drug particles in close proximity during drug dissolution.

- Abdelbary[48] et al (2005) determined the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration. In the present study, they evaluated the disintegration profile of RDT manufactured by main commercialised technologies, using the texture analyzer. In order to simulate as much as possible the oral disintegration of these dosage forms, a new operating structure was developed. This structure mimics the situation in the patient's mouth and provides a gradual elimination of the detached particles during the disintegration process. Moreover, the oral disintegration time of the same products was evaluated by 14 healthy volunteers. Results obtained when artificial saliva at 37^{o}C was employed as disintegration medium were used to correlate the in vitro and oral disintegration times. Excellent correlation was found and in addition, we were able to achieve a qualitative measure of the mouth feel by comparing the thickness of the tablets and the penetration distance obtained from the disintegration profile.

- Fukami[49] et al (2006) formulated a rapidly disintegration tablet in the oral cavity using a Glycine as a disintegrant. Wetting time prepared from carboxymethylcellulose (NS-300) having the hardness of 4kg was 3 seconds. Tablets containing NS-300 showed fastest disintegration compared to other formulations. These results suggest that NS-300 possessed excellent wetting nature and resulted in the rapid disintegration of tablet. Ethenzamide and ascorbic acid were added to the formulation, and their disintegration behaviors were evaluated. Ethenzamide did not affect the disintegration property; however, ascorbic acid prolonged disintegration time. It was suggested that the tablet

formulation containing NS-300 and Glycine was highly applicable to water-insoluble drug, such as Ethenzamide.

- Shirwaiker[50] et al (2004) prepared fast disintegrating tablets of Atenolol. The preparation contained an active ingredient, sugar (mannitol), superdisintegrant and dicalcium phosphate. Required quantities of each ingredient were weighed, mixed and prepared the tablets by dry granulation. All the formulation had disintegration time of less than 70 seconds. Among the three superdisintegrant Ac-Di-Sol showed the highest efficacy. Formulation containing 10 % Ac-Di-Sol showed the least disintegration time of 30 ± 2 seconds compare to Explotab and Polyplasdone XL.

- Mishra [51] et al (2005) prepared rapidly disintegrating tablets of Valdecoxib. The poor aqueous solubility of the drug results in variable dissolution rate and poor bioavailability. In the present, invention tablets were prepared using various superdisintegrant following direct compression. All formulation showed disintegration time of less than 60 seconds along with rapid *in vitro* dissolution. All the formulation showed more than 70 % dissolution in 30 min.

- Amin[52] et al (2005) presented an invention, which relates to fast disintegration tablets for oral administration. Taste masked adsorbents of Ofloxacin were prepared using cationic exchange resins. Taste evaluation of tablets showed complete masking of the bitterness of Ofloxacin. The taste-masked complex of the Ofloxacin was further incorporated into mouth dissolve tablets in combination with Metronidazole benzoate. All the formulation exhibited an in vitro dispersion time less than 50 seconds.

- Remon[53] et al (1997) prepared the rapidly disintegrating tablets by lyophillization. Tablets contained hydrochlorothiazide, Maltrodextrin, hydroxyethylcellulose and gelatin. The solutions were poured into blisters and freeze dried. Maltrodextrin

could be a filler of choice for the production of lyophilized tablets as freeze-drying due to amorphous network, which dissolved in the water with seconds. They evaluated gelatin, xanthan gum and hydroxyethylcellulose a binding agents in the formulation of freeze dried tablets with Maltrodextrin as filling agents.

- Chaudhari[54] et al (2005) prepared fast dissolving tablets of Famotidine. In this study the bitter taste of Famotidine was masked using drug: Eudragit E 100 in different ratios (1:1 to 1:10). For taste masking the ratio was optimized to 1:4 by time intensity. The different superdisintegrant (Ac-Di-Sol, Polyplasdone) with their varying concentration were used for disintegration of tablets in mouth. The formulation containing 2 % of Ac-Di-Sol and Polyplasdone showed 91.89 % and 101.07 % release respectively in 12 min.

- Vijaya[55] et al (2006) prepared Meloxicam rapidly disintegrating tablets by direct compression. The tablets were prepared with three superdisintegrant like SSG, Ac-Di-Sol and L-HPMC. The hardness of tablets was found to be less than 10% and disintegration time of tablets was found to be less than 1 minute, except L-HPMC. In-vitro drug release study showed enhance dissolution rate compared to pure Meloxicam.

- Sreenivas[56] et al (2006) prepared mouth dissolve tablets of Ondansetron by direct compression. In this study a varity of disintergrant like crospovidone, croscarmelose, pregelatinized starch, sodium starch glycolate and L-HPC were selected at 5 % and 10 % concentration. The friability of all the formulation between 0.16 to 0.36 %. The in vitro disintegration time for all formulation varied from 10 to 15 seconds. In all the formulation the drug release was almost up to 80-100% after 15 min.

- Shirwaikar A[57] et al (2006) formulated and evaluated fast dissolving tablets of Granisetron hydrochloride by direct compression method using superdisintegrants. A combination of mannitol and silicified microcrystalline

cellulose (SMCC) in the ration 70:30 was used in the study. Study concluded that crospovidone and croscarmellose sodium are better disintegrants for formulation of fast dissolving tablets of Granisetron HCl.

- Halakatti P.K.[58] et al (2006) formulated rapidly disintegrating tablets of Domperidone by applying two methods. Sodium starch glycolate and treated agar used as superdisintegrants in mass extrusion technique and treated agar method respectively.

- Mahajan H.S.[59] et al (2004) formulated mouth dissolving tablets of Salbutamol sulphate by direct compression method. SSG, croscarmellose sodium, treated agar were used as superdisintegrants while microcrystalline cellulose used as diluents. Formulation containing SSG along with other superdisintegrants showed rapid in-vitro and in-vivo dispersion time, as compared to other formulation.

- Nayak S.M.[60] et al (2004) prepared fast dissolving tablets of Promethazine theoclate using effervescent melt, super disintegration addition and melt technologies. Tablets from effervescent melt and super disintegration addition technique released 92 % and 89 % of the drug at the end of 10 min.

- Kaushik D.[61] et al (2004) prepared mouth dissolving tablets of Olanzepine by effervescent approach. Sodium bicarbonate and citric acid were used as effervescent agent and their ratio was optimized. The study revealed that 10:8 ratio of sodium bicarbonate and citric acid in the Olanzepine mouth dissolving tablets gave a soothing fizz, excellent mouth feel, good palatability and quick dissolution profile.

- Devi V. K.[62] et al (2006) prepared orodispersible tablets of Fluconazole with two different volatilizable compounds viz. ammonium chloride and camphor by wet granulation method. The best formulations were compared with marketed conventional tablets.

- Mahajan H.S.[63] et al (2004) studied on mouth dissolving tablets of Sumatriptan succinate. Tablets were prepared by using disintegrants like sodium starch glycolate, carboxymethyl cellulose sodium and treated agar by direct compression method. The tablets were evaluated for various tests. The study showed that formulation containing sodium starch glycolate and carboxymethyl cellulose was found to give the best results.

- Patel D.M.[64] et al (2004) formulated orodispersible tablets of Rofecoxib by granulation method that carried out by solid deposition method using three superdisintegrants namely SSG, crospovidone, croscarmellose sodium. From that crospovidone giving lowest disintegration time and wetting time as compared to remain superdisintegrants.

- Kuchekar B. S.[65] et al (2006) prepared orodissolving tablets of Promethazine hydrochloride by direct compression method using superdisintegrants, sodium starch glycolate, croscarmellose sodium. Study revealed that formulation containing 4% of SSG and 1-3 % of croscarmellose sodium were found to give the best results.

- Patel D. M.[66] et al (2006) prepared fast dissolving tablets containing solid dispersion of Valdecoxib. They were prepared solid dispersion with mannitol polyethylene glycol 4000, and PVP K12. Valdecoxib solid dispersion with PVP K12 showed maximum drug release hence, the tablet formulation containing Valdecoxib PVP K12 solid dispersion was prepared with a view to improve its water solubility.

- Poornima D. Amin [67] et al (2004) formulated patient compliant dosage form for Roxithromycin. The present study deals with various techniques utilized for taste masking of roxithromycin viz granulation with udragit E100 and complexation with ion exchange resins. Of these, complexation with ion exchange resin yielded complete test masking. The test masked complex was then formulated in to palatable mouth dissolve tablet.

- Amin Purnima[68] et al studied that Indion 414 as superdisintegrant in formulation of mouth dissolve tablets. The present research paper introduces Indion 414, an ion exchange resin, as a new superdisintegrant for pharmaceutical dosage forms. Model drugs belonging to various classes were taste masked and formulated into palatable mouth dissolve tablets. Experiments were carried out to evaluate the disintegrant property of Indion 414 by incorporating Indion 414 in fast disintegrating dosage form like mouth dissolve tablets.

- Mane Avinash[69] et al (2003) formulated highly porous, mouth dissolving tablets of Domperidone using meltable binder polyethylene glycol-4000, a diluent-mannitol and sublimable material like camphor and ammonium bicarbonate. The amounts of volatilizable material were varied from 10% to 60% w/w to obtain various formulations. Two of the formulations having 40% w/w of ammonium bicarbonate and 20% w/w of camphor exhibiting least disintegration time.

- Shishu[70] et al (2006) prepared rapidly disintegrating Diazepam tablets by using microcrystalline cellulose as directly compressible filler and sodium starch glycolate as super disintegrants.

- Gordan[71] et al found that aging decrease the dissolution efficiency of superdisintegrant in wet granulated tablets. The formulation that initially exhibited faster dissolution showed decrease in dissolution after storage. So out of sodium starch glycolate, croscarmellose and crospovidone, croscarmellose is most affected.

4.3 AMLODIPINE BESYLATE

- D.M. McDaid[78] were prepared Amlodipine base from its besylate salt and various physicochemical properties relevant to transdermal delivery determined. Permeation of the drug from a range of hydrophilic and hydrophobic bases through hairless mouse skin was studied and the influence of the penetration enhancers sodium lauryl sulphate 1% and propylene glycol 20% in a sodium carboxymethylcellulose 3% gel base was examined. The flux of drug could be further enhanced using variable percentage of ethanol in the donor phase. The influence of various rate controlling membranes and a contact adhesive on drug permeation was examined. In vivo studies using rabbits were performed to assess the suitability of a reservoir-type device. Employing data obtained from in vitro studies involving human abdominal skin, it was possible to predict the plasma profile resulting from the application of a similar device onto human skin over a period of 1 week and was found to be inadequate for clinical use. No adverse local effects in the animal model arising from the application of the transdermal device were observed by them.

- Dong-Jin Janga[79] had improve the bioavailability and photostability of poorly water-soluble and photosensitive amlodipine, dry emulsion (DE) which was prepared by spray-drying the oil-in-water emulsion of amlodipine. Labrafil M 1944 CS and dextrin were employed as oil phase and matrix material, respectively. Dispersing DE in distilled water formed an emulsion with a mean droplet size 1.4-fold larger than that of the homogenized amlodipine emulsion before spray-drying (0.24±0.30 _m versus 0.17±0.02 _m). The mean droplet size of DE remained unchanged during 6-month storage at room temperature. 94.4% versus 33.1% of amlodipine remained intact after 24-h UV irradiation of amlodipine as DE formulation or as powder. These data suggest that DE formulation greatly improved the photostability of amlodipine, as well as

increasing the physical stability of emulsion systems. *In vitro* release of DE was higher than that of amlodipine powder (66% versus 48% release at 60 min). Consequently, DE formulation resulted in 2.6- and 2.9-fold higher *C*max and AUC0–24h of amlodipine compared after oral administration of amlodipine powder in rats. Their data suggest that the DE may be a potential oral dosage form for amlodipine to improve its bioavailability.

- Yinghua Suna[80] had developed and evaluated a drug-in-adhesive transdermal patch for S-amlodipine (S-AM) free base. Initial in vitro experiments were conducted to optimize the formulation parameters before transdermal delivery in rats. The effects of the type of adhesive and the content of permeation enhancers on S-AM free base transport across excised rat skin were evaluated. For in vivo studies, patches were administered transdermally to rats while orally administered S-AM in suspension and intravenously administered S-AM solution were used as controls. The plasma level of SAM following transdermal application could be maintained for 72 h. After transdermal administration to rats, the absolute bioavailability was 88.8% for S-AM free base. After dose normalization, the areas under the plasma concentration–time curve (AUC) and mean residence times (MRT) were evidently increased and extended, respectively. This suggests that the transdermal application of S-AM in a drug-in-adhesive transdermal patch may be used for the treatment for hypertension.

- Atram SC[81] had developed an optimized bilayer tablet for antihypertension patients using Metoprolol succinate and Amlodipine besylate as a model drug candidate by optimization technique. A 3^2 factorial design was employed in formulating bilayer tablet with individual release layer i.e. sustained release layer and immediate release layer. The independent variables selected both cases HPMC(X1), Starch 1500 (X2) and SSG (X1), MCC (X2), respectively. Two dependent variables were considered: t50 (Y1), Q12 (Y2) and t50 (Y1), Q2 (Y2),

respectively. The main effect and interaction terms were quantitatively evaluated using mathematical model. Bilayer tablets were evaluated for thickness, hardness, friability, drug content and in vitro dissolution studies. The drug release of Amlodipine besylate and Metoprolol succinate depicted non-fickian diffusion and Super Case II transport mechanism, respectively.

- Menger Chung[82] had studied bioequivalence of combination tablets containing amlodipine besylate/atorvastatin calcium with coadministered matching doses of amlodipine besylate and atorvastatin. calcium tablets was investigated in randomized, 2-way crossover studies in healthy volunteers (N = 126). Subjects received a single dose of the amlodipine/atorvastatin tablet or coadministered matching doses of amlodipine and atorvastatin at the highest (10/80 mg; n = 62) and lowest (5/10 mg; n = 64) dose strengths. Atorvastatin geometric mean ratios for maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve (AUC) for the highest and lowest dose strengths were 94.1 and 98.8, and 104.5 and 103.8, respectively. Amlodipine geometric mean ratios for C_{max} and AUC for the highest and lowest dose strengths were 100.8 and 103.4, and 100 and 102.7, respectively. The 90% confidence intervals for all comparisons were within 80% to 125%, demonstrating bioequivalence for amlodipine and atorvastatin at both dose strengths. Use of amlodipine/atorvastatin combination tablets may provide a more integrated approach to treatment of cardiovascular risk.

- Abdoh[83] studied the compatibility of amlodipine besylate in its solid formulations with various drug excipients. The various factors affecting amlodipine besylate stability were studied using high-performance liquid chromatography (HPLC). It has been found that binary 1:1 mixtures of amlodipine besylate and an excipient are stable at 65°C and 40°C/75% RH. Further investigations were conducted to

study the stability of amlodipine besylate in multicomponent mixtures, including mixtures with actual formulations. The study reveals that mixtures of lactose, magnesium stearate, and water induce some instability on amlodipine besylate. The major degradation product confirmed by HPLC-mass spectrometry is amlodipine besylate glycosyl. This is in conformity with the well-known Maillard reaction between primary amines and lactose. Thus, lactose-free amlodipine formulations were recommended by them from the safety, quality, efficacy, and process cost points of view.

- Nahata MC[84] had determined the stability of amlodipine besylate in two liquid dosage forms under refrigeration and at room temperature. Commercially available amlodipine tablets (Norvasc-Pfizer) were used to prepare two suspensions: one in extemporaneously prepared 1% methylcellulose in syrup (1:1), and another in equal volumes of commercially available OraPlus/OraSweet. Each suspension containing amlodipine 1 mg/mL was stored in 10 plastic prescription bottles; 5 were stored at 4 degrees C and 5 at 25 degrees C. Samples were collected immediately after preparation (day 0) and on days 7, 14, 28, 42, 56, 70, and 91. Amlodipine concentration was measured by stability-indicating HPLC method. Physical and chemical stability (> 90% of the initial concentration) of amlodipine in the two extemporaneously prepared suspensions during storage in plastic prescription bottles at 4 degrees C and 25 degrees C. Observed mean concentrations exceeded 90% of the initial concentrations in both suspensions for 91 days at 4 degrees C and 56 days at 25 degrees C. No noticeable change in physical appearance or odor was observed; pH changed slightly in the methylcellulose-containing formulation stored at 25 degrees C. So Amlodipine was stable in two suspensions when stored in plastic prescription bottles for 91 days at 4 degrees C or 56 days at 25 degrees C. These formulations may be considered for pediatric or elderly patients who are unable to swallow tablets. The liquid dosage form would also permit accurate administration of amlodipine doses to infants and young children based on their body weight.

- Fiorenzo Mignini[85] has investigated open, randomized, two-period crossover trial in 24 healthy volunteers over a 144 h period the bioequivalence of amlodipine maleate tablets 10 mg versus amlodipine besylate tablets (Norvasc® 10 mg). Plasma amlodipine concentrations were assessed by ultra performance liquid chromatography interfaced with a double quadrupole mass spectrometer. The area under the curve total (AUC_t) and the area under the curve to infinity (AUC_{inf}) values, peak plasma concentration (C_{max}), and time to attain peak (t_{max}) were not statistically different between the two drugs. AUC_t and AUC_{inf} values were higher ($p < 0.05$) in females than in males. The tolerability profile was comparable for the two salts of amlodipine. These findings indicate that amlodipine maleate and besylate are bioequivalent and were well tolerated, which suggests that the plasma kinetics of amlodipine depend on the properties of the molecule itself. Hence, the two salts investigated could be used interchangeably in clinical practice.

SUMMARY

Many patients, especially elderly find it difficult in swallowing tablets, capsules, fluids and thus do not comply with prescription, which results in high incidence of non-compliance oriented research has resulted in bringing out many safer and newer drug delivery systems. Rapidly disintegrating/dissolving tablet is one of such example, for the reason of rapid disintegration or even with saliva. Significance of this drug delivery system includes administration without water, accuracy of dosage, ease of portability, alternative to liquid dosage forms, ideal for pediatric and geriatric patients and rapid onset of action

Identification of amlodipine was carried out by using melting point estimation, by UV spectrophotometrically, and by IR spectroscopy & drug was identified as pure amlodipine besylate. Estimation of amlodipine was carried out by standard curve in 0.01 N HCL media.

A direct compression technique was used to prepare MDT as it is economical, simple, less time consuming. The formulations were evaluated for % friability, wetting time, disintegration time, & in-vitro drug release study

MDT were initially formulated with mannitol, considering its advantages in terms of easy availability, cost-effectiveness, negative heat of dissolution and relative rapid dissolution, but poor weight uniformity due to poor flowability & diverse sticking to die cavity limits its alone application in MDT. SO combination of Mannitol SD 200 & MCC in 50 : 30 ratio was used which is investigated by formulation trials. SMCC was selected in formulation instead of MCC because of presence of 2 % Silicon dioxide which decreases friability & also decrease wetting & disintegration time. As crospovidone XL 10 was costlier than crospovidone XL & it was not added any advantage to formulation so, crospovidone XL was selected. By varying amount of crospovidone, 8% was

optimized as optimum concentration as higher amount leads to higher friability & lesser amount results in low wetting & disintegration time. HPC & HPC-EXF were used in formulation trials but HPC-EXF (4%) was selected in final formulation development as HPC being higher binding effect decreases wetting & disintegration time. Tablets were compressed by varying compression force to obtain tablets with different hardness. 4-5 kp hardness was selected as best hardness as lower hardness (2 kp) results in higher friability & higher hardness (6 kp) leads to lower wetting & disintegration time.

Thus present work was aimed to formulate MDT of amlodipine besylate using super disintegrants which provide better dissolution.

3^2 full factorial design was employed to study the effect of independent variables, concentration of crospovidone & HPC-EXF on disintegration time & friability by using contour plot & 3 D surface plot.

Amlodipine besylate MDT was compared with Amlodipine besylate IR tablet. By experiments, it was estimated that Amlodipine besylate MDT was dissolved more rapidly than Amlodipine besylate IR tablets.

The accelerated stability study was conducted as per ICH guideline & the formulations were found to be stable, with insignificant changes in physical characteristic, drug content, disintegration time & drug release property.

An attempt was made to prepare MDT of Amlodipine besylate with appropriate mechanical strength which would disintegrate in oral cavity in less than 30 secs & provide immediate control over hypertension due to faster release of amlodipine in to GI tract & total drug would be released in with in 5 mins.

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