EMERGING TRENDS IN DEVELOPMENT OF MULTIVARIATE MODELS IN SOLID DOSAGE FORMS - A REVIEW

Thesis submitted to the Institute of Pharmacy, Nirma University, partial fulfilment of the requirements for the Degree of

BACHELOR OF PHARMACY

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Semester VIII

(PROJECT WORK BP812PW)

UNDER THE GUIDANCE OF

Dr. Shital Butani

INSTITUTE OF PHARMACY
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List of Abbreviations

ACE	Angiotensin Converting Enzyme
AIDS	Acquired Immune Deficiency Syndrome
API	Active Pharmaceutical Ingredient
BBD	Box-Behnken-design
CCT	Compression Coated Tablets
CR	Controlled Release
FC-TABLET	Film-coating Tablet
GI TRACT	Gastrointestinal Tract
HIV	Human Immunodeficiency Virus
HME	Hot Melt extrusion

HPMC	Hydroxypropyl Methylcellulose
HPMCP	Hydroxypropyl Methyl Cellulose Phthalate
IR	Immediate Release
MUPS	Multiple Unit Pellet Systems
NSAID	Nonsteroidal Anti-inflammatory Medication
OSDRC	One step Dry Coated
PVAP	Polyvinyl Acetate Phthalate
PVP	Polyvinylpyrrolidone
SC-TABLET	Sugar Coated Tablet
US	United State

ABSTRACT

In the formulation and manufacture of pharmaceuticals, the creation is pursued in the application of multivariate modelling methods designed with the creation of these intricate solid dosage forms in mind. The paper investigates a range of multivariate modelling techniques for predicting dissolution profiles and optimising formulation compositions, such as factorial and mixed designs. It also looks at more contemporary developments, such as the incorporation of artificial intelligence to improve predictive modelling and optimise production procedures. It demonstrates the usefulness and practical use of these strategies through case studies. In the end, the review emphasises how important multivariate modelling is for improving pharmaceutical production methods and handling formulation difficulties. Multi-layer tablets—especially bi- and tri-layer tablets—presents special potential and challenges. This review delves into the new directions being.

Keywords: OSDrC, MUPS, Hot melt Extrusion, Inlay tablet, Pelletization.

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Chapter 1: - Introduction to Multivariate Modelling

1.1 Introduction

The Indian Pharmacopoeia defines pharmaceutical tablets as solid, flat, or biconvex dishes that are made by compressing an active pharmaceutical component or mixture of medications. A compacted solid dosage form containing medication, either with or without excipients, is called a pharmaceutical tablet. Size, weight, and form vary depending on the quantity of medicinal substances and the planned mode of administration. The tablet is the most often used dosage form and offers several advantages, including cheap cost, precise dosing, great chemical and physical stability, and effective production. It has been suggested that tablets are the preferred dosage form in the worldwide pharmaceutical business, with sales of tablets predicted to surpass US$500 billion by the end of 2027. Thus, for the multivariate models in solid dose form, we outline the universal characteristics, introduction, categorization, and general considerations in this paper. Granulation, granule drying, specialist die cavity filling control, tablet coating, and a few more unit operations and evaluation tests like the disintegration and dissolving tests are used in the preparation of these kinds of multivariate tablets. These are the areas where the quality of the tablet is most affected. To increase the uniformity and efficiency of the unit operations—which indirectly impact the quality of the product—it is imperative to critically examine the impacts of factors impacting the unit activities, such as temperature, velocity, flow pattern, and other fluid parameters. This review covers the roles of the most popular multivariate modelling techniques in the tablet manufacturing process. The study concentrates on using multivariate modelling approaches to process understanding, optimization, process monitoring, and process control within multiple unit activities to develop and improve these multivariate models to decrease mistakes in the modelling process. Furthermore, the status of continuous tablet production is examined, along with the application of multivariate modelling techniques in this procedure. Drug combinations, which are composed of two or more drugs in a single dose form, were developed for a variety of purposes, including emergency circumstances and common

conditions like parkinsonism and allergic rhinitis. These kinds of formulations were first intended to consolidate many APIs into a single dosage for patients who, for assorted reasons, were unable to take their prescriptions regularly. Nowadays, however, physicians usually prescribe two or more medications in isolation for patients with a single ailment. People, however, demand relief from a single dosage, quick site therapeutic concentration, and dosing maintenance at the same level for a minimum of 12 hours in today's challenging environment.

1.2 History and Patents

I. The notion originated in 1896 when a British patent for a rotating compression machine that could operate tablet in tablet was awarded. Three hoppers make up this rotary compression machine: the first two supply the granules for the top and bottom layers, while the third hopper feeds the already compressed core tablet into the die using a reciprocating finger. Additionally, the main tablet might be expertly centred using this machine.

II. A tablet compression machine that could insert previously compressed core tablets onto a die using a toothed disc was also awarded a 1917 US patent. This patent identifies his compression device as a layer press, but if the core was smaller than the die's diameter, it might also create tablets.

III. Edward Alexander Hotko, Scotch Plains, and Leon Lachman obtained a US Patent (3325365) in 1967 for creating a method of compressing enteric coating into core tablets. (Edward Alexander Hotko 1967)

IV. Groenendaal and Sijbrands obtained a European patent (0181650) in 1985 for their compression-coated dispersible tablet technology. (Sijbrands 1985)

V. Grenier et al. were granted a US patent (US 8980363 B2) in 2015 for their invention of a process and device that creates tablets with a centred compression coating. (al 2015)

VI. In 2016, Kawano et al. received a US patent (US 9433632 B2) for their innovation that included a tablet within a tablet. A patent consists of a dry-coated tablet with an outer layer of enteric-coated micro granules containing proton pump inhibitor and an inner core of enteric-coated acetylsalicylic acid. (K. e. al. 2016)

VII. Application filed by Pharmacia LLC European Patent no. EP1399309A1 for A method is disclosed for producing coated compressed tablets, using at least one upper punch. The upper punch can be a single punch with a hollow shaft (1) containing a movable rod (3) with a tip (4) that is extended or retracted as the rod moves within the shaft. (LLC 2018)

1.3 Introduction to polymers (Salawi 14)

Polymer (Greek, poly-many, mers-unit, or part) Polymer has influenced our lifestyle in such a way that it would not be wrong to say that we are in polymer age. For example, house-hold utensils, clothes, furniture, automobiles, space aircraft etc. These are so frequently used by people that an ordinary person calls them by names like plastics, fibres, rubber resins etc.

Choosing the right polymer involves considering factors like drug solubility, release profile, stability, and manufacturability. Common polymers include hydroxypropyl methylcellulose (HPMC), ethyl cellulose, polyvinylpyrrolidone (PVP), and various grades of methylcellulose.

Each polymer has unique properties that affect drug release kinetics, such as swelling behaviour, erosion rate, and permeability. For instance, HPMC is often used for controlled release formulations due to its ability to form gel layers and control drug diffusion.

The selection process typically involves formulation studies and testing to determine the polymer's compatibility with the drug, its ability to achieve desired release profiles, and its stability over time. Additionally, considerations such as regulatory approval, cost, and availability also play a role in the selection process.

1.3.1 Selecting the appropriate polymer.

I. **Controlled Release:** The degree of control over medication release rates varies amongst polymers. Formulators can produce a desired release profile, such as delayed, sustained, or instantaneous release, by using the right polymer or combination of polymers.

II. **Drug Stability:** Polymers can shield pharmaceuticals against deterioration brought on by light, air, and moisture in the environment. They can serve as barriers, preventing outside influences from affecting the medication and preserving its potency for the duration of the tablet's shelf life.

III. **Physical Properties:** The polymers utilized influence the physical characteristics of tablets, including their hardness, friability, and disintegration time. By selecting the best polymer, the mechanical strength and disintegration properties of the tablet can be ensured for patient use, packaging, and production.

IV. **Compatibility with Excipients and Active Pharmaceutical Ingredients (APIs):** Polymers need to work well with the other excipients and APIs that are included in the formulation. Problems with compatibility might result in unpleasant responses, decreased therapeutic effectiveness, or unstable formulations. Therefore, the success of the formulation depends on the choice of polymers that work well with other ingredients.

V. **Manufacturability:** Some polymers are easier to make than others because of their unique qualities. Certain polymers, for instance, increase tablet consistency, lessen adhering to punches and dies during compression, or improve flow characteristics. Selecting polymers with low processing resistance helps expedite production and provide a constant level of tablet quality.

Table 1 : Different Grades of Polymer with their Uses

POLYMER	GRADES	USES	EXAMPLE	REFERENCE
ETHYL CELLULOSE	-	Coating, extended release, matrix.	Amphetamine Diltiazem, Rabeprazole	(Zaid 4613)
HPMC	HPMC E15 HPMC K1000M	Sustained Released	Ketoprofen Lornoxicam Formulate	(Ahmed, Mota and Shahba 33)
HPC	-	Binder, film forming, Thickening agent	-	(D, S and Shivprasad 12)
HPMCP	-	Enteric Coated, Modified Released-Viscosity enhanced. Taste Masking	-	
PVAP	-	Enteric Coated Sustained Released	-	(D, S and Shivprasad 18)
EUDRAGIT	EUDRAGIT RS 30D EUDRAGIT NE 30D EUDRAGIT NM 30D EUDRAGIT L 30D55 EUDRAGIT FS 30D	Sustained Released Enteric Coated	-	(Ahmed, Mota and Shahba), (Gupta, Beckert and Deusch 207), (Augsburger 22)
CROSCARMELLOSE SODIUM	-	Table Disintegration Improved Bioavailability	-	(D, S and Shivprasad 15)

		Compatibility With Various API		
CROSPOVIDONE	-	Table Disintegration Fast Dissolving Tablet	-	

1.4 Multivariate Models

Reducing the frequency of dose administration enhances patient compliance. This formulation enables the separate administration of two incompatible substances. In tablets designed for drugs with short half-lives, each layer contains both a loading dose and a maintenance dose, thereby improving the bioavailability of the drug. The tablet, consisting of two separate drug layers, facilitates its use in combination therapy. By dividing medications that may interact adversely or providing a protective barrier against stomach irritation or degradation, multilayer tablets can minimise unwanted side effects.

1.4.1 Drug Release Profiles with Multivariate Models of Tablets

Compressed polymeric coat coating has been developed and explored for use on tablets for modified or regulated drug delivery systems to improve medication performance, increase pharmacological efficacy, and decrease side effects. based on the simplest matrix device, where the drug is dispersed uniformly across the network of polymers. On the surface of cores, different polymer properties can be partially coated to provide a variety of controlled or modified releases. Using this concept, preparations that adequately enhance or modify the release of medications can be created. A tablet with a compression coating is one where the coat completely encloses the surface of the core within it. These coats prevent medications from dissolving, evaporating, or breaking down altogether until the polymeric coat is gone entirely.

Various drug release patterns could be achieved based on the makeup of the core and coating layers.

I. Controlled release (Kanwar and Gautam 101): - A compression-coated tablet has a solid barrier coated over a fast disintegrating or modified release core (Kanwar and Gautam 22). Polymeric substances, diluent (as a release modifier), and medication (for longer release) could all be included in the barrier. This concept suggests that the possible modified drug releases for gastrointestinal tract areas include prolonged release and delayed release (time, pH, and microbiological control).

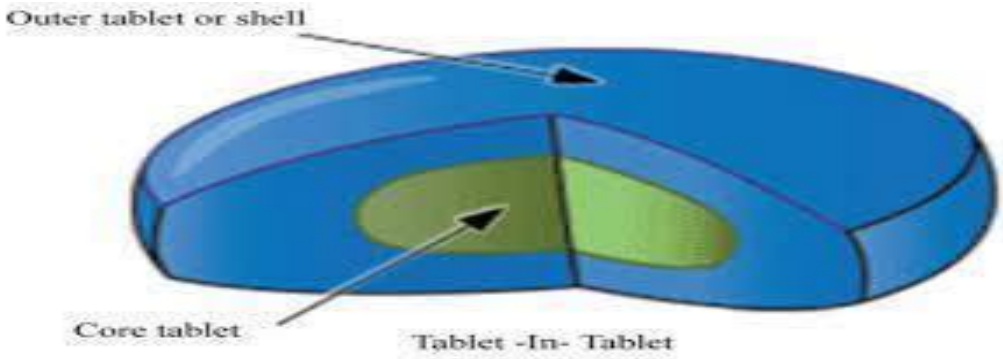


Figure 1 : Tablet-in-tablet technology

(Gaikwad 15.16)

II. Delayed release (Shi, Lin, and Liu 8323): - All the core's surface must be compression coated to achieve delayed release, which is described by a lag phase and a release phase. Within this group, pulsatile release—which is characterized by rapid drug release following a predetermined lag time (Shi, Lin, and Liu 8325)—may also be included. The lag time for drug release may be managed by applying several polymeric coatings that were distinguished with triggering features, as was explored in the colonic drug delivery system.

III. Multi-phasic release (Gaikwad and Kshirsagar 33): - When it comes to treating illnesses with distinct daily cycles, multiphasic release is a delivery method that works best; continuous medication release falls short of ideal therapeutic efficacy. Drug concentrations for these conditions must change throughout the day. When symptoms are at their worst, drug dosages should be at their maximum. Because the drug is presented by the system as a non-uniform drug distribution matrix in the coat and core, biphasic drug release is generated. When therapeutic drugs are mixed into a single tablet, different drug releases, such as sequential or multi-phasic, can be accomplished. Several layers of compression coating can be produced on tablets to provide the intended therapeutic effects. Impax Pharmaceuticals Inc. is the patent holder for multiple- layer compression-coated tablets with instant release (outer coat), prolonged release (middle coat), and immediate release (core). By modifying the drug loading and polymer type in each layer, distinct drug release patterns may be achieved.

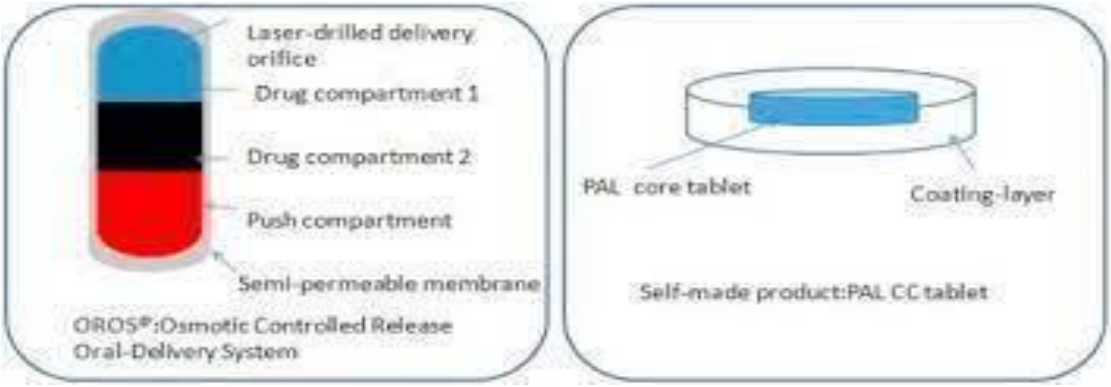


Figure 2 Osmotic controlled release oral-delivery system

(Jaimini 3,4)

IV. pH-controlled release (Gaikwad and Kshirsagar 34): - Site-specific medication delivery, particularly for the colon, can be achieved via a delayed-release approach that uses enteric polymers as a coating. This system has generated considerable interest in the local treatment of various gastrointestinal diseases and systemic absorption enhancement of therapeutic agents that are susceptible to enzyme digestion within the upper GI tract, although time-controlled release is not feasible due to significant

changes in gastric emptying times. Fukui et al.,2001a, with the intention of colon targeting, produced Diltiazem hydrochloride compression coated tablets.

V. Microbial controlled release (Patil, Marathe, and Bobade 16): - One use for a delayed release method is colon medication targeting. This technique relies on certain enzymes generated by entero-bacteria in the colon breaking down the polymeric compression coat.

Alginates, amylase, arabinoxylan, cellulose, chitosan, chondroitin sulfate, dextran, galactomannan (guar gum, locust bean gum), inulin, karaya gum, laminarin, pectin, starch, tragacanth gum, xanthan gum, and Xylan are examples of microbiologically degradable polysaccharides with glycosidic bonds that can be used as a coat. High methoxy pectin was one of the studied polysaccharides utilized for colonic-specific medication administration that might be utilized in compression-coated tablets. The combination of bacterially regulated systems and time (pH) with spray-dried chitosan acetate and ethyl cellulose is being investigated.

1.5 Aim

The manufacturing of tablets involves many unit operations that possess multivariate and complex characteristics. The interactions between the material characteristics and process related variation are presently not comprehensively analysed due to univariate detection methods. The aim is to reach an optimised model for the compression of the solid dosage form.

1.6 Objective

Pharmaceutical companies are beginning to invest in innovative processes capable of producing solid dosage forms that better meet the needs of the patient while providing efficient manufacturing operations. This review discusses emerging solid dosage form manufacturing technologies, namely hot-melt extrusion and fluidized hot-melt granulation, DUREDA Technology, OSDRC Technology, MUPS, Inlay Tablets etc,

for the tailor-made and different dosage regimens to be followed. The review stated the multivariate models for the optimization of the manufacturing techniques for the solid oral dosage forms.

The thesis includes the reviewed articles having the manufacturing technology involving the development and optimization of the technology for the solid oral dosage forms.

Chapter 2: - Literature Review

2.1 Bi-Layer Tablet

A sustained release tablet can be created with an immediate release for the first dose and a progressive release for the maintenance dose over time. Alternatively, two incompatible chemicals can be separated using a bi-layer tablet, or two drugs can be released sequentially simultaneously. Bilayer tablets are used to treat a variety of medical disorders by combining two medications, either the same or different, in a single dose. These tablets are used in many different formulations, such as multilayered matrices and partially coated monolithic formulations. Modified release is achieved by encapsulating the API layer between one or two inactive layers to provide swellable/erodible barriers and change the total surface area available for the API layer.

Bilayer tablets have a unique construction in which the medicine is released quickly from the first layer and gradually released over time in the form of an extended-release dose from the second layer. To lessen interlayer interaction, distinct layers of each medicine are crushed when two incompatible medications are mixed into bilayer tablets. An intermediate layer of inert material can also be added. Ensuring the production of a workable tablet formulation requires meeting several requirements, such as having a strong enough mechanical structure and the desired drug release profile. Formulators may find this job difficult due to the inherent poor flow and compatibility properties of some drugs, particularly when creating bilayer tablet formulations employing double compression techniques.

One of the key issues is inadequate adhesion and bonding at the contact between compacted layers. Interfacial cracks resulting from residual strains within the tablet are the main cause of this issue. Layer separation or delamination results from these fissures, which propagate across a small region. These instances might not become apparent immediately upon compaction; rather, they might appear only subsequently during procedures like packing, shipping, or storage.

A trio of drugs that are commonly used together to treat HIV infections. The first anti-HIV pharmaceutical approved for clinical use, zidovudine (AZT), is widely used to treat AIDS, either on its own or in combination with other antiviral drugs. For zidovudine, sustained release tablets are a better mode of administration than typical dose forms because the drug is soluble in water, soluble in all pH ranges, and absorbed throughout the gastrointestinal tract. AIDS is treated with lamivudine, a potent antiviral drug. Lamivudine is a potent reverse transcriptase inhibitor derived from nucleoside analogues. Lamivudine is rapidly absorbed and has a bioavailability of more than 80% when taken orally. Lamivudine is administered multiple times daily due to its moderate half-life of five to seven hours.

Ibuprofen with Famotidine Tablets in a Bilayer Form: While famotidine is a histamine-2 receptor antagonist used to lower stomach acid, ibuprofen is a nonsteroidal anti-inflammatory medication (NSAID) used for pain management. This combination lowers the risk of gastrointestinal irritation while treating diseases like rheumatoid arthritis and osteoarthritis.

Omeprazole and aspirin bilayer tablets: Aspirin is a nonsteroidal anti-inflammatory medication used to treat pain, lessen inflammation, and stop blood clots from forming. Proton pump inhibitors like omeprazole lessen the formation of stomach acid. By using this combination, the risk of gastrointestinal bleeding connected to aspirin medication is decreased (Akhtar, Jamshaid and Zaman 34). (Cappuccio, Markandu and Singer)

2.2 Trilayer Tablets

Tri layer tablets are designed so that the first layer releases the medication right away, while the second and third layers are engineered to release the medication gradually, acting as an extended-release medication or as a second dose. Pharmaceutical agents can be released in an ordered fashion thanks to Tri layer tablets, which enable the controlled release of several medications in a preset order. This is especially helpful for combination therapies that call for the use of medications with various release profiles or modes of action.

Pharmacokinetics: A Tri layer tablet's individual layers can be made to release their respective drug components at different rates, allowing for the customization of pharmacokinetics to attain the best possible therapeutic results.

Disease Management: Tri layer pills are helpful for treating multiple parts of a disorder at once or for conditions needing intricate treatment plans. This is particularly useful in multiple-disease conditions like lifestyle disease.

Layer Segregation: The Tri layer tablet's layers are made to be chemically and physically separate from one another. This makes it possible to separate incompatible excipients or APIs and to incorporate various medication combinations or release methods.

Drug Compatibility: Tri layer tablets' architecture facilitates the mixing of several medications, each of which may have unique physicochemical characteristics or compatibility problems. Drugs that are incompatible can be separated into different layers to maintain their stability and effectiveness.

Tri layer tablets containing phenylephrine, dextromethorphan, and paracetamol: The symptoms of the flu and cold are frequently relieved with this combination. As an analgesic and antipyretic, paracetamol lowers fever and pain. Phenylephrine is a nasal decongestant, and dextromethorphan suppresses coughing. When combined, they offer relief from a variety of cold and flu symptoms. Tri layer tablets containing hydrochlorothiazide, amlodipine, and lisinopril: The purpose of this combination is to treat hypertension. Amlodipine blocks calcium channels, lisinopril inhibits the angiotensin-converting enzyme (ACE), and hydrochlorothiazide is a thiazide diuretic. By using various methods, the combination of these medications lowers blood pressure and effectively manages hypertension (Cappuccio, Markandu and Singer 19).

Tri layer tablets containing folic acid, iron, and vitamin B12: This combination is used to treat anaemia, especially in people who are deficient in any of these three nutrients Iron, vitamin B12, and folic acid are the three vital components required for red blood cell formation and function. This Tri layer tablet formulation aids in the simultaneous treatment of several nutrient deficiencies, encouraging the production of red blood cells and easing anaemia symptoms (Zec, Roja and Matovinović 23).

2.2.1 Technology Used for Multivariate Bi/ Tri Layer Tablets

I. DUREDA (Akhtar, Jamshaid and Zaman 20) Technology: DUREDAS technology works with a variety of APIs and excipients, it can be used in bilayer tablets that contain different medication combinations. Through manufacturing, storage, and usage, this compatibility guarantees the formulation's stability and integrity.

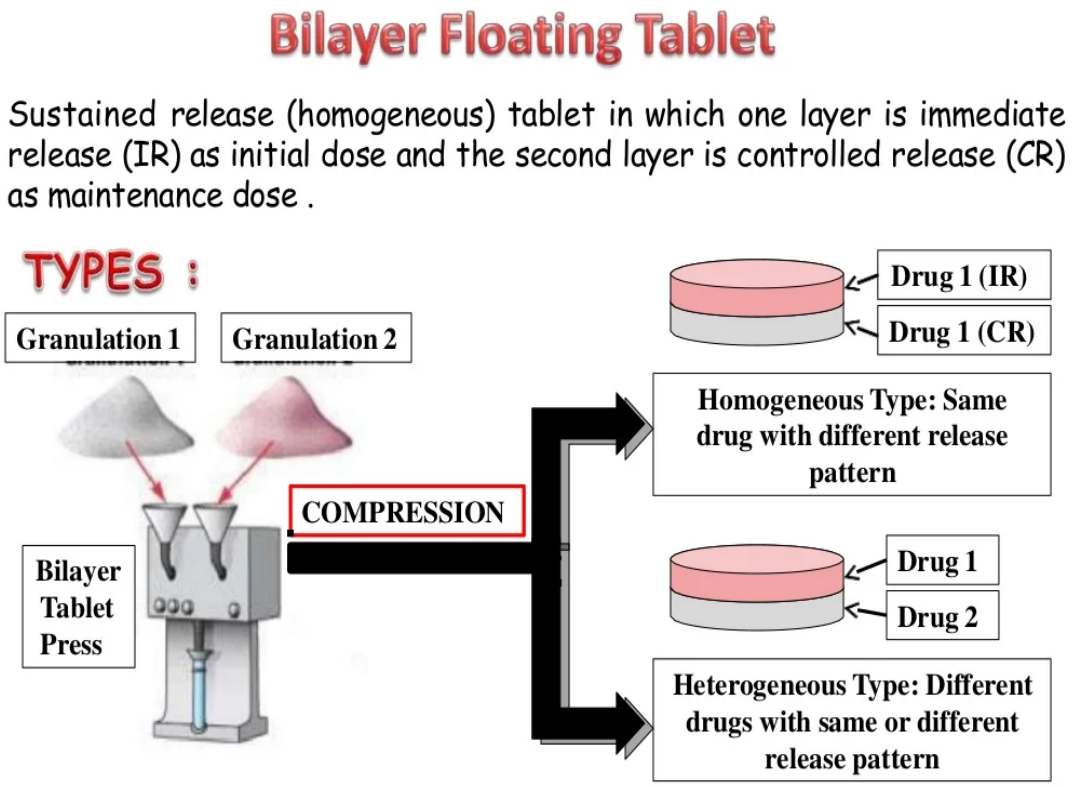


Figure 3: Bilayer Floating tablet

(Reddy, Rao. V and Kumar.K. 13).

II. Compression-coating (Kanwar and Gautam 16): It is also used for bilayer tablet formulation. A tablet press loads the first layer into the die cavity, and the second layer formulation is put on top. The first bilayer tablet is formed by compression force using a tablet press. The first bilayer tablet is then covered

with the third layer formulation, and a second compression step is used to create the Tri layer tablet, which ensures that the layers stick together.

III. Hot Melt Extrusion (HME): This technique is used to make Tri layer tablets and other solid oral dosage forms. Polymers and APIs are melted and mixed, then extruded to create a homogenous mixture that can be compacted into tablets.

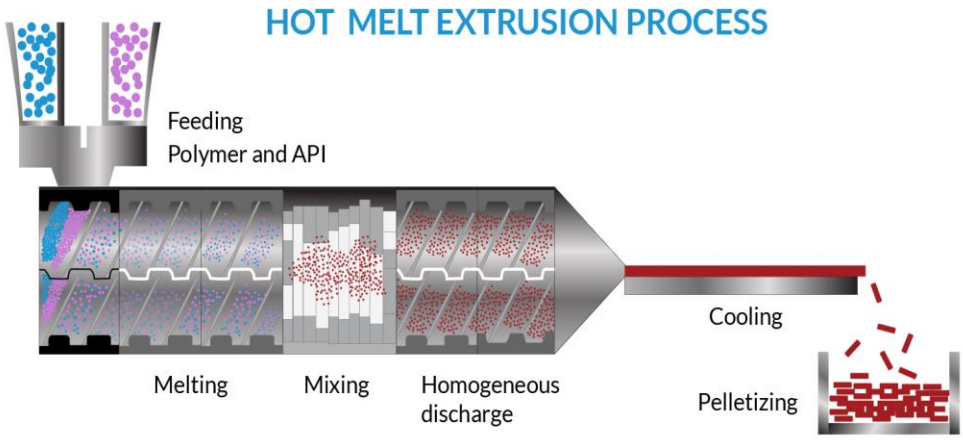


Figure 4: Hot melt extrusion process

(Reddy 12)

Table 2 Manufacturer's Name, Drug Formulated by Them and Category to Which Drug Belongs.

Sr.no.	**Manufacturer or research**	**Drug formulated**	**Category**
I.	Alka-Seltzer plus day cold	Paracetamol, Dextromethorphan, Phenylephrine	Tri layer tablet
II.	Zestoretic	Lisinopril, Hydrochlorothiazide	Bilayer tablet
III.	Blexten	Bilatine	Bilayer
IV.	Nature's bounty	l-Theanine, Chamomile, Lavender	Tri layer

2.3 Compression Coated Tablets

Controlled or modified-release formulations are one type of tablet formulation that has become increasingly significant in pharmacological therapies because of its many advantages. Tablet-in-tablet technology, while still less common, has drawn more attention recently as a means of producing products that have been altered after being issued. It entails employing specifically made tableting equipment to condense granular materials around a prefabricated tablet core (Gaikwad and Kshirsagar 9). The process of compression coating is dry. The internal core and outer coat of this kind of tablet, known as a compression-coated tablet, are separate components. One turret is used to prepare the core, which is a tiny porous tablet. Following the manufacturing process, the tablet core is moved (centred) to a slightly bigger die that has coating powder partially poured into it. A tablet within a tablet is created by filling the top of the core with more coating powder and compressing it once more.

Transferring the tablet to the second die chamber is a complex mechanical process due to the possibility of tilting. To achieve a rapid-release product, the coat is primarily water soluble and readily dissolves after ingestion. Because the inner core releases the medicine later, and the outer layer provides the initial dose, this tablet lends itself easily to being a repeat action tablet. However, when the chemical is released quickly from the core, a completely different blood level is obtained with the possibility of overdose toxicity. To prevent medication release in the stomach when the first dosage is added to the exterior sugar coating, the core tablet is coated with enteric polymer, which also prevents the simultaneous release of both layers. However, while producing and delaying the manufacturing process, interpretation of the coating operation is required. In other instances, the inner core could be a liquid composition intended to release the core immediately upon dissolving the coat.

2.3.1 Technologies Used in the Development of the Formulations

It has been said that the compression coating technique involves employing specifically created techniques to compress a coat around a core. The procedure entails the core is first compressed before being moved to a sizable die that already has some (half) of the coating material in it. To create the compression-coated tablets, more coating material is applied to the centralized core, and the mixture is squeezed. There are two main categories of machinery used to prepare press-coated tablets: compression of the core and coating into a single, continuous circle; core previously prepared on several machines.

I. OSDRC (Kanwar and Gautam 11): -The OSDRC system, a unique one-step dry-coated tablet manufacturing process, was unveiled. The technology does not require prior core tablet preparation to produce compression-coated tablets in a single step. According to the OSDRC process schematic, the core and coat were prepared.

Initially, precompression from the upper-centre punch created the lower-outer layer. The punches in the higher and lower centres were then pushed up and slid down, respectively. The powder for the core was filled and pre-compressed using the punch in the upper middle. Once the lower outer punch was eventually lowered downward, the upper and lower punches loaded and crushed the powder for the second outer layer, uniting the centre and outside punches. This technology, which can generate a dry-coated tablet in a single turn, may be installed on the turn table of a rotary tableting machine.

The OSDRC (Patil, Marathe and Bobade 5,6,7) method may be used to produce compression-coated tablets with a side outer coat thickness of either 0.5 or 1 mm.

Figure 5 : Punches used in OSRDC Technology

(Jaimini 5)

II. Dividable compression coated (Jaimini, Chauhan, and Sharma. 6,7): - It has two prepared cores in the controlled-release coat. The creation of dividable compression-coated tablets aimed to alter the dosage to suit each patient's unique medication kinetics. The feasibility of this dividable control-released compression-coated tablet has been proven by comparable drug release from dividable and non-dividable tablets. Partially compression-coated layer tablets, or doughnut-shaped tablets, were created using a specially designed punch set.

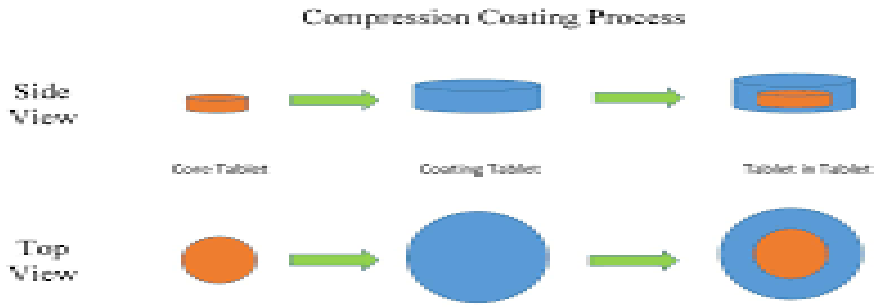


Figure 6 : Process of compression coating. (Jaimini 7)

III. Inlay tableting process (Jaimini, Chauhan, and Sharma. 8): - This kind of multilayer tablet has the top surface entirely covered with a coating, yet the core tablet is still totally encircled by revealed. Tablets were crushed using core rod tooling, which only exposes a single surface of the core to the outside and inserts more medication into the cup area. During preparation, the coating

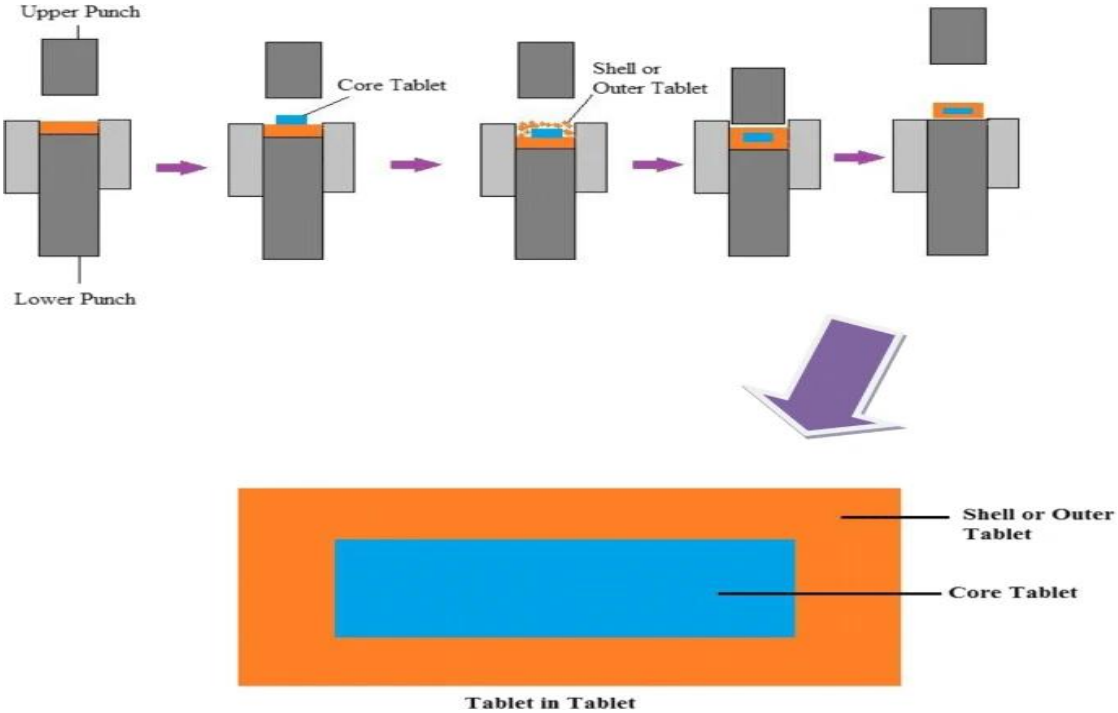


Figure 7 : Preparation of INLAY tablets.

(Jaimini 8)

material is only added to the bottom of the die cavity, and the core is then positioned on top of it. The major body component might consist of an uncoated granulation that is compressed around the enteric-coated inlay region. With this change, the enteric coating shields the inlay section of the tablet for a predefined amount of time, allowing time for the inlay portion to be released and digested in the gastrointestinal system[16].

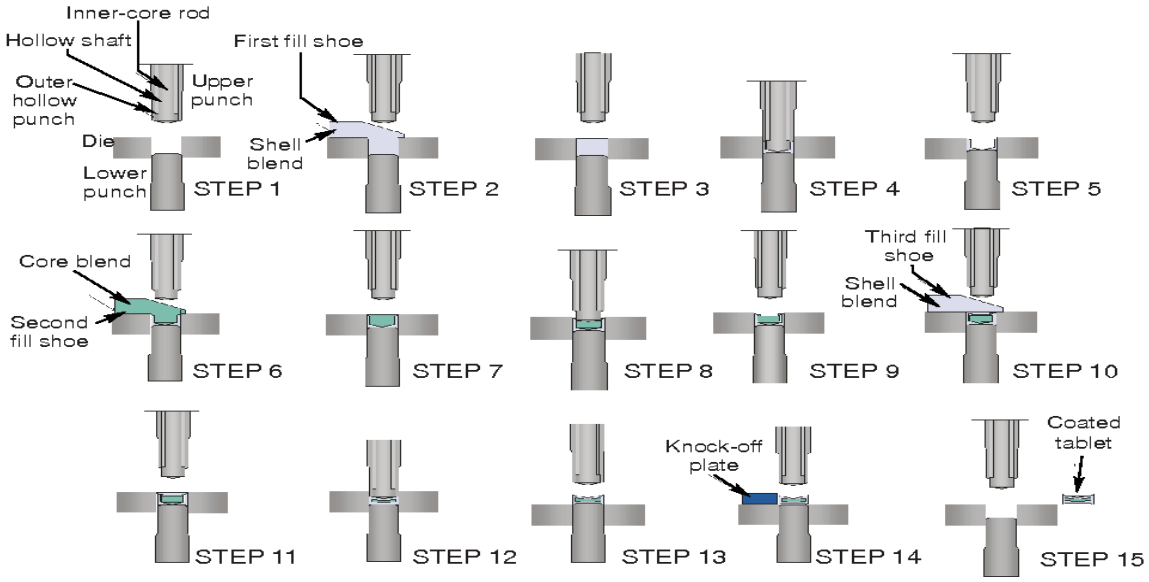


Figure 8 : Preparation of INLAY tablets

(Gaikwad 18)

Table 3 : Manufacturer's name, drug formulated by them and the category to which drug belongs.

Sr no	Manufacturer/ research	Drug formulated	Category	Ref.
1	Roche Palo	Naproxen	Enteric-coated tablet	(Patil, Marathe, and Bobade 7)
2	Wyeth Ltd.	Conjugated oestrogen	SC-tablet(sugar-coated)	
3	Novartis P'ceuticals	Diclofenac	FC-tablet(film-coating)	
4	Mylan	Mebeverine hydrochloride	SC-tablet(sugar-coated)	
5	Pfizer Medical Information—the US	Misoprostol	Enteric coated	
6	Highnoon	Rabeprazole	Enteric coated	
7	People's Hospital of Wuxi Xishan	Zopiclone	Box–Behnken-design (BBD), compression coated tablets (CCTs)	(Zhou, Li and Liu 57)
8	Department of Pharmaceutics, C.L. Baid Metha College of Pharmacy, Thoraipakkam, Chennai, Tamil Nadu, India	Mesalamine and Prednisolone	colon delivery	(Rathnam and Bhadane. 11)

2.4 MUPS (Multiple Unit Pellet Systems)

Oral drug delivery is the most widely used and convenient method of administration. Nowadays, the design of solid dosage forms frequently makes use of Multiple Unit Pellet Systems (MUPS) tablets (Jain and Vishwavidyalaya) (Waston, Lucas and Hoy 20). MUPS offers better pharmacokinetic advantages over monolithic dose formulations (Khar, Vyas and Ahmad). Typically, pellets are created with the goal of producing sustained-release, gastrointestinal-resistant oral modified release forms with the ability to operate as pulsatile drug delivery systems. To accomplish these goals, coated pellets are supplied in the form of hard gelatine capsules or dissolving tablets that dissolve quickly in the stomach. Compared to other dosage forms, the formulation has greater levels of safety and efficacy. A wide range of versatility is offered by pellets when creating oral dose forms. They can be coupled to deliver incompatible drugs or particles with various release characteristics to the same or different areas in the gastrointestinal system. Additionally, they can be divided into the required dose without altering the recipe or procedure. When taken orally, oral pellets usually spread out easily throughout the digestive system, increasing drug absorption while reducing local mucosal irritation from some irritating medications (Oliver and Sherrington 209). MUPS are conveniently supplied as disintegrable tablets that disperse throughout the stomach and small intestine into their constituent subunits, resulting in a consistent oral transition and continuous bioavailability. A few hundred coated pellets containing active medicinal components are present in each MUPS pill, delivering the medication at a predefined rate and facilitating absorption to maintain a steady blood profile (Bhad, Abdul and Jaiswal 10) (Prabhakaran, Prushothaman and Sriganesan 7) (Gaware and Panday 7).

Objectives for the preparation of MUPS Tablets (Gaware and Panday 9):

I. For a medication delivery device with regulated release.
II. Regarding enteric release and colon-targeted drug delivery methods.
III. Creating a taste-masked, mouth-melting dosage form.
IV. Blending medications in the same dose form that have distinct release patterns.

V. Controlled release forms allow for higher medication doses than capsules do.
VI. Greater pharmaceutical dosage than achievable when using capsules while using controlled release form.

2.4.1. Multi-Unit Pellet Technology

2.4.1.1 Pellitization

Pelletization is the agglomeration process that creates free-flowing, spherical or non-spherical units by converting fine material into pellets (A, MS and VK 3282,3283,3284,3285,3286). These are the number of tiny, distinct units that exhibit desired attributes (HP, JK and RR 1,2,3,4,5). Granulation and pelletization are similar terms with different ranges of size (N. Jawahar and Anilbhai. 1915,1916). These techniques are used to develop pellet whose size ranges from 0.5 to 1.5 and granules whose size is between 1.0 to 2.0 mm and 20 to 50% porosity (N, H and A 176).

2.4.1.2 Cryopelletization

These are produced by lyophilizing a thick bacterial solution. Liquid nitrogen can be used as a fixing medium to transform the liquid medium into solid spherical particles, which can then be used to create pellets or spherical particles. This makes it easier for the liquid medium to freeze instantly or breaks down materials that allow heat to be transferred from droplets to liquid nitrogen quickly. Equipment includes a conveyer belt with transit baffles and a storage container with a perforated plate and reservoir. Spraying from the top, the liquid substance travels through the perforated plate, comes into touch with the liquid nitrogen, and freezes as a result. These pellets are kept frozen at -600°C (Sruthi and Reddy. 10).

2.4.1.3 Freeze pelletization

This method produces pellets with a high or desired quality while using fewer process variables. The active chemicals are dissolved into the molten solid carrier mass and then injected as droplets into an immiscible and inert column. This eliminates the

requirement for drying, and the resulting pellets will have a limited size distribution. Depending on the material's density, the substance will travel both upward and downward in this. The melting point of the solid carriers that are utilized should be less than 100 since this will reduce the degradation of the active components (Sruthi and Reddy. 12,13).

2.4.1.4 CPS (Complex Prefect Spheres) pelletization

In the year 2000, the Glatt gm blt in Binzen, Germany, devised this technology. Using an innovative fluid bed rotor and the direct pelletization technology, they can generate both matrix type and micro pellets. The altered bed rotor has extra components for direct particle movement in addition to a conical-shaped revolving disk. This kind of drug layering is done on an inert core and on dry powder using liquids that come in various forms, such as emulsions and solution suspensions, both of which exhibit drug layer quality. This type of drug layering is conducted on dry powder and an inert core utilizing a variety of liquids that display drug layer quality, including emulsions, solutions, and suspensions. The CPS rotor determines the pelletization's end point. Pellets can be made to have the appropriate density by rolling them and applying various forces, such as centrifugal force and rotating disc speed. In this technique, the drug loading ranges from 0.1% to 90%, the particle size distribution is >90% between 0.7 and 0.9 mm, the surfaces are smooth, the attrition and friability are low, the porosity is low, and the particle size ranges from 0.1 to 1.5 mm (Sruthi and Reddy. 23,24).

2.4.1.5 Pro-cell methodology (Sruthi and Reddy. 25)

It's an expressed kind of continuous grouping together technology in which vertical air flow fluidizes the particles in the spouted bed. The air enters the processing chamber via the side, not the bottom plate or inlet distribution plate, as opposed to a traditional fluid bed processor. The shape of the fluid bed processor is larger at the top and narrows at the bottom, which might result in a significant fall in the fluidized velocity of process air. This result demonstrates a regulated flow pattern and particle circulation within the chamber. It is a straightforward technique of pelletization and

granulation. In this method, as well as other methods, inert beads are not utilized. Agglomeration and spray solidification are the processes that result in the formation of pellets or granules. It is employed in the production of high density, low porosity spherical pellets, which yield micro-pellets or granules of the matrix type with a size range of 0.05–1.5 mm. This kind of hot melt granulation technique achieves a 100% drug loading without the requirement for excipients or the evaporation of organic or water-based solvents due to the process chamber's design and processing features.

Table 4 : Manufacturer's Name, Drug Formulated by Them And The Category To Which Drug Belongs (Mazumder, Mahanti and Pal 263,272).

Sr.no.	**Manufacturer or research**	**Drug formulated**	**Category**
1.	Key pharmaceuticals	Theophylline	Extended release
2.	Astra Zeneca	Omeprazole magnesium	Delayed release
3.	Takeda	Lansoprazole	Delayed release Oro-dispersible tablet
4.	Astra Zeneca	Metoprolol tartrate	Extended release
5.	Middlebrook pharmaceuticals, lnc	Amoxicillin	Prolonged release pulsatile delivery technology
6.	AstraZeneca	Metoprolol tartrate	Zero order kinetics
7.	Key Pharmaceuticals	Potassium	Sustained release

2.4.2 Pelletization Techniques:

2.4.2.1 Drug Layering Technique:

In pelletization processes, layering techniques (powder layering and layering from solution/suspension) are often applied. Because layering procedures skip the crucial step of nucleating the centre nuclei, which is the basis for granule agglomeration while ensuring spherical form, the use of starting cores promotes the pelletization process (Kállai-Szabó, Farkas and Lengyel 1299).

By using a solution, suspension, or dry powder layering technique, pellets containing active ingredients can be created from the inert core. There are benefits and drawbacks to each method (Kállai-Szabó, Lengyel and Farkas 194).

2.4.2.2 Powder Layering (K.Srinivasarao* 141):

Whether the drug is soluble in the binding liquid or not, full dissolution does not happen in powder layering liquid because of low liquid saturation. Usually, the nuclei are sprayed with a binder solution first, and then powder is added. Through capillary forces created in the liquid phase, the majority of the nuclei fall into the revolving pan of the disc, pick up the powder particles, and form layers of tiny particles that stick to the nuclei and each other. Until the required particle sizes are reached, more powder is layered on the nuclei as more bonding occurs from the liquid spraying. Solid bridges partially replace liquid ones as the binder and other dissolved materials crystallize out during drying. Fines may absorb moisture upon binder spraying and enter a nucleate phase.

2.4.2.3 Solution/Suspension Layering: (K.Srinivasarao* 145)

In the process of solution/suspension layering, the application medium is used to dissolve or suspend drug particles and other components. Droplets of the solution or suspension are sprayed onto the cores, where they impinge on the starting seed or cores and disseminate uniformly. Allowing the dissolved material to crystallize and create

solid bridges between the drug substance's core and first layer as well as between subsequent layers of the drug substance or polymer is made possible by the drying process that follows. Until the required drug or polymer layers develop, keep going through this process. Using the started seeds which could be inert materials or drug crystals or granules this technique includes depositing multiple layers of solution or suspensions of drugs and binders. (Sanjay and Patel 133,134,135)

2.4.3 Through Globulation:

2.4.3.1 Spray Drying: (K.Srinivasarao* 146)

Spray drying produces dry, very spherical particles by spraying a drug solution or suspension with or without excipients into a heated air stream. This technique is typically used to increase the dissolution rates and, thus, the bioavailability of poorly soluble medicines, even though it is appropriate to produce controlled-release pellets. The spray-dried powder particles have a nearly uniform size, are almost spherical, and are homogenous. Many aspects of the product, including bulk density, porosity, moisture content, flowability, friability, and particle size and distribution, can be affected by the design and operation (Sanjay and Patel 145,146) of the spray drier.

2.4.3.2 Spray Congealing: (K.Srinivasarao* 147)

It is a method that is identical to spray drying. The technique known as "spray congealing" involves allowing the drug to melt, spread, or dissolve in hot melts of fatty acids, gums, waxes, or other substances that melt. Following that, the dispersion is sprayed into the airstream and other gases that have a temperature lower than the melting point of the constituents of the formulation. Pellets that have congealed into spheres are produced with proper processing conditions.

2.4.4 Through Agitation:

2.4.4.1 Balling: (K.Srinivasarao* 147)

This method of pelletization involves continuously rolling and thumbing mixes in pans, discs, drums, or other containers to generate pellets. Finely divided particles transform into spherical particles with the addition of suitable volumes of liquid.

Chapter 3 :Methodology:-

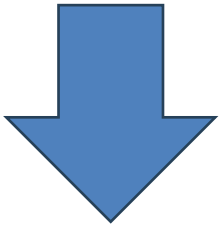
3.1 Introduction

An enormous number of international journals are accessible. for instance, International Journal of Educational Research, International Research Journal of Basic and Clinical Studies, International Research Journal of Biochemistry and Bioinformatics, International Research Journal of Biotechnology, International Research Journal of Engineering Science, Technology and Innovation International Research Journal of Microbiology, International Research Journal of Pharmacy and Pharmacology.

3.2 Method

About 150 articles and reviews from international journals were found through our search, and research materials were gathered and carefully examined for the models from industry and research showing the advancement in the solid dosage form. The articles and research papers consisted of the modelling techniques for multivariate drug release patterns and form multi-purpose medicines for the patient compliance.

Additionally, we discovered 100 articles that were specifically relevant to our review topic through the screening process. The parameter for the screening were from the potential newer technologies used in modelling, the keywords for relevant articles were mostly multivariate models, MUPS, Compression coated, DUREDA etc. , the model articles were also screened for their optimization of the conventional models in the solid dosage form, the screening parameter was also for the blending medications which would have variate release patterns.



We selected about 40 articles for our thesis work consisted of the review articles which are constructive of the multivariate sophisticated modelling techniques. The screened articles also consisted of commercial products selling with the technology used to manufactured them. The screened articles consisted of papers investigating a range of multivariate modelling techniques for predicting dissolution profiles and optimising formulation compositions, such as factorial and mixed designs as well as multivariate modelling is for improving pharmaceutical production methods and handling formulation difficulties.

Chapter 4 :- Results And Discussion

Currently, the pharmaceutical and healthcare industries are moving through a period of unparalleled change. Major multinational pharmaceutical companies are restructuring, consolidating, merging and more importantly critically assessing their competitiveness to ensure constant growth in an ever-more demanding market where the cost of developing novel products is continuously increasing. The pharmaceutical manufacturing processes currently in existence for the production of solid oral dosage forms are associated with significant disadvantages and in many instances provide many processing problems. Therefore, it is well accepted that there is an increasing need for alternative processes to dramatically improve powder processing, and more importantly to ensure that acceptable, reproducible solid dosage forms can be manufactured. Consequently, pharmaceutical companies are beginning to invest in innovative processes capable of producing solid dosage forms that better meet the needs of the patient while providing efficient manufacturing operations. This article discusses two emerging solid dosage form manufacturing technologies, namely hot-melt extrusion and fluidized hot-melt granulation.

Numerous advances have been introduced to improve material attributes, engineering of manufacturing equipment and development of efficient analytical techniques. Quality by design-based formulation development approaches have been applied to reduce the variability in the processes to develop robust tablet dosage forms. In addition, new raw materials have been deployed to improve manufacturability and functionality of tablet formulations. These include the modification of existing excipients with enhanced purity or physical properties (e.g. particle size) and co-processing with other materials to improve their performance in manufacturing processes. Moreover, development and use of multi-functional materials provide lean manufacturing opportunities with significant economic impact.

The last few years have seen the development of novel tabletting technologies which improve machine performance. These advances in machine design aim to overcome limitations associated with conventional manufacturing approaches such as the

denaturation of thermolabile active ingredients, material wastage, multiple processing steps and elevated costs due to protracted processing time, labour and maintenance of equipment. In addition, lean and continuous manufacturing concepts have been employed to ensure rapid, safe and efficient manufacturing operations.

Tablet manufacturing routines involving advanced granulation approaches, hot melt extrusion, extrusion / spheronization, injection molding, spray drying, spray congealing, coprecipitation and nanotechnology-based approaches have been developed over several years to produce robust tablet formulations with improved performance characteristics.

According to a report regarding novel drug approvals, published by FDA's Centre for Drug Evaluation and Research, in 2018, tablet dosage forms were the first choice, in ~ 39% cases, when developing medicines from drugs, due to the convenience and ease of use. Despite various advancements (in terms of novel excipients, equipment manufacturing methods, tableting technologies and analysis approaches), pharmaceutical manufacturers are facing a variety of challenges associated with incompatibility between the drug and excipients .

The terms 'unique', 'high-quality', 'reasonable' and 'innovative' are the keywords of this technology. OSDRC technology employs a double punch action that enables dry-coated tablets to be assembled in a single run. This makes possible a completely new type of formulation process and new types of pharmaceutical products never before seen. No doubt, it is a revolution in tableting technology.

Chapter 5 : Conclusion

In conclusion, the polymer age has firmly established polymers as indispensable materials in various aspects of daily life, spanning from household essentials to innovative aerospace technologies. Their role in pharmaceutical formulations is pivotal, as selecting the appropriate polymer involves meticulous consideration of factors such as drug release kinetics, stability, and manufacturability. The ongoing advancements in polymer science continue to drive innovations in drug delivery systems, shaping the future of medicine.

Multilayer tablets stand out as innovative solutions in enhancing drug delivery, offering a spectrum of benefits from controlled release profiles to targeted therapies. Bilayer and Tri layer tablets cater to diverse medical needs, enabling combination therapies and tailored pharmacokinetics. Their versatility revolutionizes medication administration, promoting efficacy and patient comfort.

Furthermore, controlled or modified-release formulations, complemented by tablet-in-tablet technology, represent significant strides in pharmacological therapies. Innovations like compression coating and dividable compression-coated tablets enhance drug delivery precision and patient adherence. The emergence of technologies such as OSDRC streamlines manufacturing processes, bolstering efficiency and product consistency. Additionally, the utilization of Multiple Unit Pellet Systems (MUPS) and various pelletization methods underscores a commitment to tailored medication delivery, ensuring optimal therapeutic outcomes.

As pharmaceutical formulation continues to evolve, these diverse technologies hold the promise of revolutionizing drug development, providing safer and more effective treatments for patients worldwide. The integration of advanced polymer science into pharmaceutical research and development will continue to drive progress, opening new avenues for personalized medicine and improved patient outcomes. Thus, the

future of medicine is shaped by the ongoing advancements in polymer science and its applications in drug delivery systems.

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