"FORMULATION DEVELOPMENT OF EXTENDED RELEASE CAPSULE FOR THE TREATMENT OF PARKINSON'S DISEASE"

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in Partial Fulfillment for the Award of the Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

BY

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Under the guidance of

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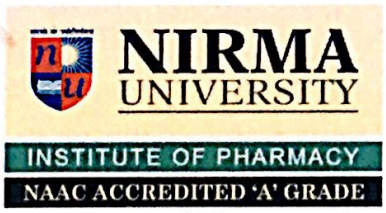

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May 2019

CERTIFICATE

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TO WHOEVER IT MAY CONCERN

This is to officially certify that Ms. Prajakta Shah has interned in Cipla R&D from 1st June 2018 to 28th Feb 2019. In these 9 months, she has been a part of the Formulation R&D function where she has performed the project - Formulation Development of an Extended Release Capsule for the treatment of Parkinson's Disease.

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With Warm Regards,

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DECLARATION

*I hereby declare that the dissertation entitled "**Formulation development of extended release capsule for the treatment of parkinson's disease**", is based on the original work carried out by me under the guidance of Dr. Mayur Patel, Associate Professor, Department of Pharmaceutics, Institute of Pharmacy, Nirma University. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.*

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PRAJAKTA H. SHAH

CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATION

SR.NO.	SHORT FORM	ABBREVIATION
1.	MUPS	Multi-Unit Pellet System
2.	MR	Modified Release
3.	ER	Extended Release
4.	API	Active Pharmaceutical Ingredient
5.	FBP	Fluidized Bed Processor
6.	XRD	X-Ray Diffraction
7.	SEM	Scanning Electron Microscopy
8.	HPMC	Hydroxy Propyl Methyl Cellulose
9.	EC	Ethyl Cellulose
10.	MCC	Micro Crystalline Cellulose
11.	MCT	Medium Chain Triglycerides
12.	IPA	Isopropyl Alcohol
13.	RH	Relative Humidity
14.	NLT	Not Less Than
15.	NMT	Not More Than
16.	HPLC	High Performance Liquid Chromatography
17.	BCS	Biological Classification System
18.	IP	Indian Pharmacopoeia
19.	BP	British Pharmacopoeia
20.	USP	United State Pharmacopoeia

FORMULATION AND DEVELOPMENT OF EXTENDED RELEASE CAPSULE FOR THE TREATMENT OF PARKINSON'S DISEASE

ABSTRACT:

Extended release formulations are gaining high importance in the field of solid oral dosage form as they are extending the effect of drug release. The marketed immediate release product showed many side effects and was not able to achieve a proper plasma concentration profile and hence there was a need of developing a multiparticulate system which can provide a uniform dosing which can reduce the intra-subject variability. The multi-unit particulate system including the pellets, minitablets are preferred where the drug-excipient or the physicochemical interaction interferes with the drug release. The present work aims in developing an extended release dosage form which can decrease the dosage frequency and help in achieving peak plasma concentration. The concentration of the pore former like povidone k-90 and the plasticizer medium chain triglyceride were optimized in order to sustain the release of the drug. Various polymers like ethyl cellulose and surelease have been optimized to achieve a prolong effect of drug. The batch is processed in fluidized bed processor by maintaining various process parameters and the final optimized batch has been filled in to capsules and various parameters like assay, water content, dissolution, particle size distribution, % yield have been evaluated. So, it can be concluded that the optimized batch shows no major change in the dissolution profile as of the reference product and hence multiparticulate system can be considered as a valuable approach for the development of extended release delivery of the drug.

1. AIM AND OBJECTIVE:

The oral drug delivery is thought to be one of the furthermost drug deliveries which can easily be administered and provides quite higher advantages compared to the other route of delivery. Amongst the oral dosage form, multiparticulate is considered to be a promising target for achieving the desired drug release profile and can also provide sustained or controlled drug release. The multiparticulates are providing better therapeutic effects with minimal side effects. They are having advantages like flexibility in different release patterns, avoids dose dumping and have short gastric residence time.

The field of the invention was development of extended release capsules for the curing the Parkinson's disease. The Drug A is used for various conditions which can be treated by NMDA receptor antagonists including the treatment of symptomatic parkinsonism, idiopathic Parkinson disease and postencephalitic parkinsonism which can cause the damage to the nervous system by intoxication of carbon monoxide. The drug is also having some activity against viral M2 channel inhibitor and can also be used in curing the infection caused by various viral diseases specifically the influenza A virus.

There are many immediate released marketed formulations of the Drug A available in the market which are to be administered two to three times a day. There are some dose related CNS side effects which are accompanying with the drug including the confusion, dizziness, insomnia, hallucinations and nightmares and are exacerbated when the drug is administered at night. It is observed that the immediate release formulations are acting as stimulant causing insomnia and sleep disturbances. So, to avoid that the last dose is to be administered no later than 4 pm in order to minimize the side effects. This kind of dosing can achieve the peak plasma concentration in the evening or night and very low plasma concentration in the morning and hence to avoid such problems the extended release formulation is developed.

The need of the investigation was to develop a formulation which can result in patient having higher plasma concentration upon waking in the morning without adversely affecting the sleep. There was a need in the art of the method of administering the drug shortly before they wish to sleep without causing any of the sleep disturbance or insomnia. It was also necessary to develop such kind of formulation which can achieve a suitable peak plasma concentration in the morning after the patient wakes up. In addition, the patients

face difficulty in swallowing the multiple medications so a formulation is to be developed which can be administered once daily and is oral dosage form which is small in size and do do not cause pill burden.

There are basically three aspects of developing the formulation which includes:

(i) To develop an extended release formulation comprising of drug or salt thereof, for use in a method of administering less than 3 hours before the patient wishes to sleep.

(ii) The other need of the formulation was to provide such extended release formulation which can reduce the sleep disturbances even after taking the drug prior to 3 hours before bedtime.

(iii) The other aim of invention was to develop and extended release formulation used to treat levodopa induced dyskinesia, dementia, fatigue or any other symptom related with the parkinson's disease.

The objective of developing extended release capsule is to provide a formulation having the bioequivalence with the reference product in which there is no difference amongst the rate and extent of absorption of the active pharmaceutical ingredient.

2. INTRODUCTION

There have been many recent advances in the period of novel drug delivery system and the area of extended release formulation have expanded much by means of providing targeted drug delivery to specific organ and controlling the rate of drug release to that specific sites. (1)

The oral drug delivery is the most favoured route of administration for the drug molecules because of the affluence of administration and hence oral extended route is considered to be a promising target for the drug delivery. (2) It is essential to develop control release formulations because of the problems faced in the safety, biopharmaceutical development and patient compliance issues related with the treatment.

For an Extended Release formulation, the therapeutic level is to be maintained over a protracted period of time and the design and technological construction is completed in manner that the effect is produced. With the development of this formulation there is also rein that the drug should have targeted delivery. The matrix type delivery of oral extended release delivery is considered to be more prominent because of the complete explanation about the pharmacokinetic and the biopharmaceutical advantages over the conventional delivery. (1)

The objective of the extended drug delivery is that the proper amount of the drug is reaching the targeted site and the concentration is achieved. (3) There are some drugs which can achieve the level easily like simple solutions or immediate release formulations but for some of the drugs the modification is done in order to accomplish the release. (4) Two types of drug delivery are considered which includes:

- ✓ Spatial Placement: This delivery is considered to be targeting and drug is delivered to specific target tissue.
- ✓ Temporal Delivery: This type of delivery helps in controlling the release rate of the drug to the specific target tissue. (3)

The modified release delivery refers to dosage form in which the drug release properties are based on the time course or specific location to provide a therapeutic objective which is not obtained from the conventional dosage forms. The modified release dosage form is classified as:

- Delayed Release Formulation
- Extended Release Formulation (5)

The extended release dosage form has high degree of absorption but the release of the drug is considered to be a rate limiting step. The absorption phase (Ka) is unimportant as compared to the release phase (Kr).

2.1 EXTENDED RELEASE FORMULATION:

Many of the drug delivery systems are available in market but the most preferred one is the oral route of drug delivery as it is patient compliant. The oral extended release formulation is considered to be most effective amongst other immediate release formulations. In immediate release dosage form the peak plasma concentration is achieved easily but it cannot remain same for a longer period of time and hence some drugs need an extended release effect and for such kind of drugs this route is considered appropriate.

Some patients need to take the drug twice or thrice daily and for them extended release formulation is developed. In extended release formulation the drug can achieve the peak plasma concentration slowly but it remains stable for a larger period of time and hence the patient does not need to take many doses in a day. Only once a day the dose is given and the effect remains for a prolonged time period. (6)(7)

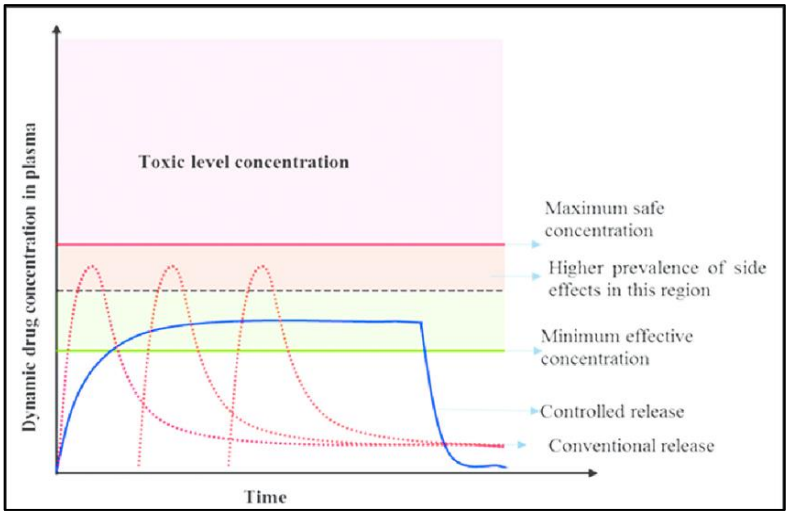


Figure 1 Drug Release in Different Formulation

The clinical effects of the drug can be correlated with the amount of the drug in the blood plasma. The clinical effect of the drug can be observed above the minimum effective concentration (MEC). The effects above the maximum safe concentration (MSC) can lead to harmful side effects. The area between the minimum effective concentration and the maximum safe concentration is considered to be the therapeutic effective window.

The extended release formulation provides a continuous release above the minimum effective concentration for a longer period of time and the release of the drug is related to the concentration of drug present in the blood plasma.

2.1.1. ADVANTAGES OF EXTENDED RELEASE FORMULATION:

- ✓ Reducing the dose of administration of drug.
- ✓ Less side effects compared to other dosage forms.
- ✓ Improved patient compliance.
- ✓ Less irritation is observed in the gastrointestinal tract.
- ✓ They are maintaining the therapeutic concentration and in order can decrease the toxicity by slowing down the absorption of dug.
- ✓ They are having the ability of minimizing systemic and local side effects of the drug.
- ✓ When there is chronic dosing the extended release formulation can also minimize the accumulation of the drug.
- ✓ The extended release formulation can maintain the stability of the drug when the product undergoes any of the degradation stages including the oxidation or hydrolysis.
- ✓ The total use of the drug becomes less when used in extended release dosage form which results in increasing the bioavailability of the drugs.
- ✓ The treatment efficiency also increases by using such kind of dosage form and helps in providing special kind of effects.

2.1.2. DISADVANATGES OF EXTENDED RELEASE FORMULATION:

- ✓ They are having less transit time which can cause a problem.
- ✓ There are chances of dose dumping.
- ✓ Inter subject variability because of the different physiological behaviours of the patients.
- ✓ Complications with the stability of the drug during the passage of GIT.
- ✓ As extended release dosage form can have a high amount of drug in it so there are chances that the release of the drug may change and it can cause an alteration in the drug release profile.
- ✓ When the extended release pellets are large in size then it may cause irritation while transit through GIT.
- ✓ The preparation cost of extended dosage forms is high and the release rate from each dose can be different.
- ✓ When the extended release formulation is prepared, they may get release in the intestine but sometimes it gets affected by the food or other parameters.

2.2 INTRODUCTION TO PARKINSON'S DISEASE:

There are many of the age-related disorders which are seen amongst people and parkinson's disease is considered to be one of them. Around 2-3% of the population is affected by parkinson's disease. There is deterioration of substantia niagra (SN) and there is occurrence of lewy bodies which are formed due to the aggregation of the various proteins mainly the α-synuclein. It is considered to be a part of family disorders which is collectively known as synucleinopathies including the PD, dementia with the lewy bodies (DLB) and multiple system atrophy (MSA).

The pathogenic process starts early before the diagnosis of the disease and based on the symptoms, it is categorized as preclinical PD, prodromal PD, and the clinical PD.

In the preclinical phase of PD, the neurodegeneration starts but there are no symptoms observed at that time. The prodromal stage is when the symptoms start to appear but the PD cannot be diagnosed. Lastly, when the motor symptoms appear it is considered to be

clinical PD. It is considered that the clinical PD occurs when the dopaminergic neurons are degenerated or died and the motor symptoms arise. The challenge in PD is to identify the predormal stage as the neuroprotective therapy is available at that stage and if early diagnosis is not done the it becomes difficult to identify degenerative process.

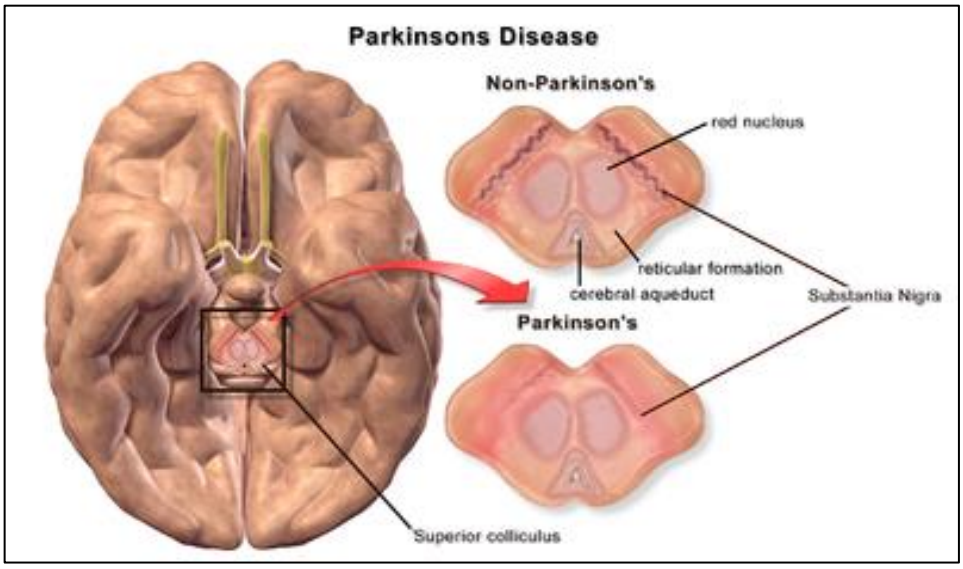


Figure 2 Effect of Parkinson in Brain

The most common non-motor features include insomnia, sleep related disorders, excessive daytime sleepiness. During the phase of prodromal the disorders like sleep disturbance, rapid eye movement, restless legs syndrome is observed. If all such disorders are observed during early phase of PD then it would become easy to treat them.

In the recent decades, it was observed that quick development of various genetic methods has led to genetic information which showed mutation in genes like SNCA, VPS35, GBA, PINK1, SMPD1 and LRRK2.

3. MULTI-UNIT PARTICULATE DRUG DELIVERY SYSTEM:

Multi-unit particulate system is oral dosage form consisting of small particles exhibiting specific characteristics. The particles are spherical in shape having the diameter of 0.05-2.0 mm. (9) They are distinct particles that are combined into one single unit in order to provide a multi-unit system. The formulations included in this delivery includes:

- Granules
- Sugar seed
- Powders
- Crystals
- Mini-tablets
- Ion exchange resin particles
- Pellets

They are compressed into tablets or either filled in capsule shells. They are having many of the beneficial characteristics compared to the single unit systems. The multi particulate system have better in vivo performance than the single unit system due to the less irritation caused in the intestine by providing a slow transit from the colon and achieving better drug release. In multi-unit system the drug is divided into many sub units and even if there is failure in few of the units it is not as major failure as observed in the single unit system.

The advantage of dividing the dose into multi units is that if the drug is incompatible in single unit then it can be given in form of multiparticulates, if there are drugs having different drug release profile they all can be combined into multiparticulate to obtain the overall release profile, different strength of the drugs are available which can be changed by multiparticulates. (10)

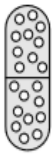
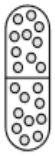
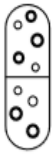
Examples of different multiple-unit systems		
Multiple-unit system	Description	Examples
	Capsule filled with minitablets	Macrobid® Dilacor® XR
	Capsule filled with powder and granules	Cardene® SR
	Capsule filled with coated pellets	Inderal® LA Prilosec® Losec®
	Capsule filled with pellets of different coating levels	Cardizem® CD Compazine® Spansule
	Tablet comprising pellets or micropellets	Toprol® XL Naprelan

Figure 3 Types of Various Multiparticulate System

3.1. FACTORS AFFECTING DESIGN OF MUPS:

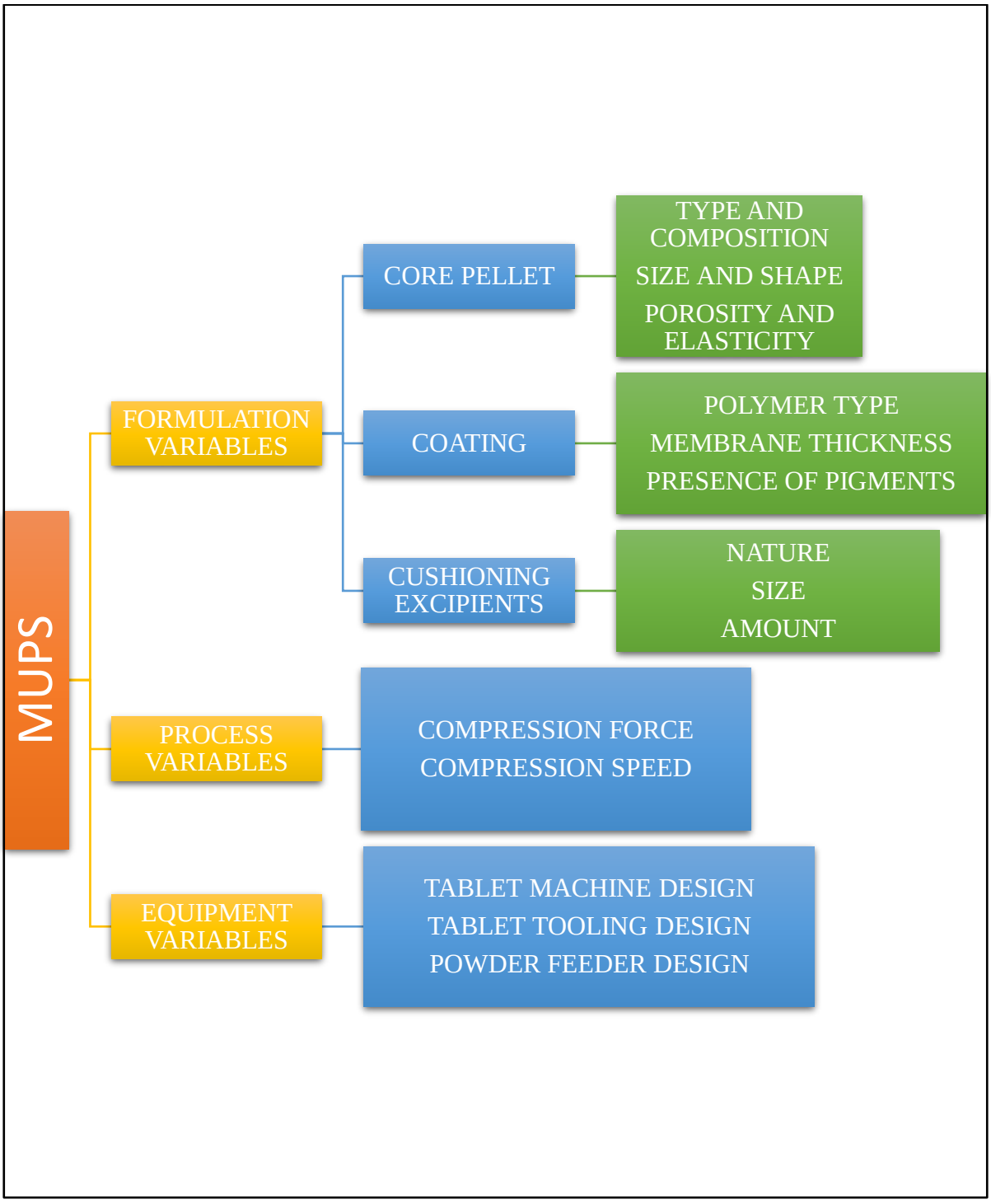


Figure 3: Factors affecting MUPS

3.2. NOVEL TECHNIQUES OF MUPS:

Table 1 Techniques of MUPS

TECHNOLOGY	DESCRIPTION
CODAS Elan	Verelan which is a chronotherapeutic oral drug absorption system shows release action after 4-5 hrs.
COLAL® By Alizyme therapeutics Ltd.	The drug pellets, capsules or tablets are coated with ethyl cellulose and form of starch called glassy amylose.
Diffucaps® Eurand	The inner core which is made of sugar or MCC spheres which is then coated with ethyl cellulose like polymer and the drug gets released after 4-5 hrs.
Diffutab	There are small beads which are further composed of many layers.
Eurand's minitabs	They are tiny cylindrical tablets of 2 mm diameter with sophisticated drug release membranes.
Eurand's pulsatile and chrono release system	The pellets are filled into capsules which are administered at bed time and the release of the drug occurs at predetermined rate achieving the maximum plasma concentration in the morning.
Flashtab	It is oro dispersible tablets having drug and rate controlling membranes.
Innoherb	They are micropellets having herbal compounds I them.
IPDAS	It is intestinalprotective drug absorption system which rapidly disintegrates tablet having controlled release pellets.
KV/24	They are neutral cores having controlling polymers which can attain a drug release in predetermined manner.
Macrocap®	It is having the presence of immediate release pellets which are prepared by extrusion-spheronization or layering techniques using the nonpareil seeds.
Multipart®	Multiparticulate drug dispersing shuttle- tablet which are acting as carrier for the controlled release pellets.

Pelletized delivery system	The pellets having specific release which are filled into capsules.
PRODAS	Programmable oral drug absorption system which has minitabs that are filled into capsules.
Stabilized pellet delivery sytem	Diffucaps or the minitablets which are filled into capsules.
TMDS	It is actually the Time multiple action delivery system which is having controlled release rate of the pellets that can be compressed into single tablet.

3.3. PELLETS:

The pellets were first introduced in market in the 1950s by research scientists SmitKline and French which were filled into capsules. They have gained much importance in the field of research as they provided much better benefits compared to the other oral solid dosage form. Pelletization is a process where the granules, powders or excipients are converted into spherical free flowing units which are specified as pellets. The pellets are ranging from size 0.5-1.5 mm and can be prepared using different techniques amongst which the drug layering and compaction are the most widely used ones. (11)

These pellets are used orally by filling into hard gelatin capsules or tablets which can easily disperse in stomach and pass through the gastrointestinal tract without the loss of depot.

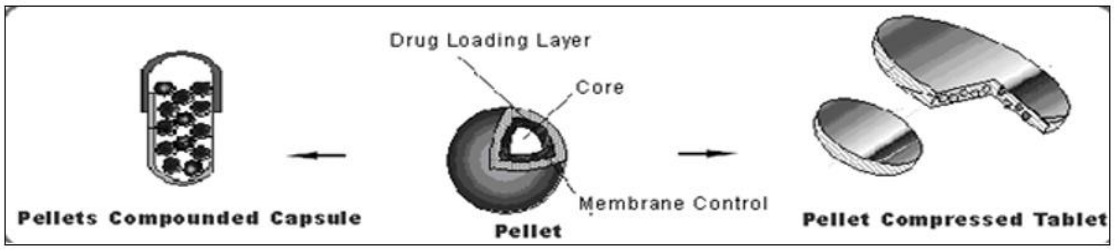


Figure 4 Pellets Compressed into Tablets and Capsules

3.3.1. IDEAL CHRACTERISTICS OF PELLETS:

- For a proper film coating the pellet should be spherical and should have a flat surface.
- Generally, the particle size should range between 600-1000 µm i.e. as narrow as possible.
- They should have the active ingredient in large amount so that final dosage form is small in size between the limits.
- They should have specific flow characteristics which includes low friability, proper physical strength and integrity, should prevent segregation while compression and capsule filling.
- The pellets should have high bulk density so that weight and content uniformity is achieved. (12) (13)

3.3.2. ADVANATGES OF PELLETS:

Pellets are considered to be more competent drug delivery system compared to the single unit system and it plays a role in each step of development which includes:

(a) PROCESS ADVANTAGE: As the pellets are spherical in shape having low surface area to volume ratio so are considered appropriate for the uniform and flexible drug delivery. (14)

(b) THERAPEUTIC ADVANTAGE: When the pellets are administered they can easily pass through the GIT which helps in increasing the absorption of the drug; show less dose dumping; improve the drug bioavailability by reducing the fluctuations in the peak plasma and reducing the side effects; reduce the irritation in gastrointestinal by providing a slight quantity of drug in single pellet; improve the safety and efficacy of the drug; decreases the intra and inter patient variability; useful for the acid sensitive drugs. Based on such therapeutic advantages, many of the industries have started their development towards the palletization technology and the equipment which are necessary are also being provided. (15)(16)

(c) FORMULATION ADVANTAGES: The pellets provide a better advantage by compressing into either a tablet or being filled in capsules or in developing suspension. These pellets are coated in the fluidised bed coater which coats each pellet with the active ingredient and the drug release is uniform. (17)

Sustained release, controlled release, gastro resistant drug delivery can be achieved by coating the pellets as they can be classified into different strengths deprived of the changes made in the process of the formulation. Even the bio incompatible agents can be delivered through the pellets having diverse release profiles at the same site in the gastrointestinal tract. The safety and efficacy with this formulation exceed the other dosage forms. (14)

The pellets are having certain characteristics which includes the:

- **IMPROVED FLOW CHARACTERISTICS:** they are spherical in shape due to which they can flow easily and can be used in the process where the precise dose is required. Eg: capsule filling, packaging, tableting, moulding.

- **PACKING OF BEDS AND COLUMNS:** The spherical units ameliorate the reproduction of beds having similar surface area, permeability and the void volumes as these beds are used as chemical reactors. The calculations and the predictions become easy as most of the equations are based on the symmetrical bodies and hence pellet approach is considered to be very appropriate.

- **COATING:** The coating is done in order to stabilize the active ingredient and to manage the release of active ingredients. For such coating the spherical shape is considered to be the most suitable one as there are no surface edges which makes it economical and no surplus coating material is mandatory for the same.

- **DENSITY:** The packaging and processing can be improved by spheronising the granules. The spheronisation increases the true and bulk density of the granules.

- **FRIABILITY AND HARDNESS:** Spheronisation decreases the friability and helps in improving the hardness which decreases the generation of fines. These both parameters depend on the surface characteristics and the internal cohesive forces. During the transportation the generation of fines also decreases by reducing the friability and increasing the hardness.

- **MARKETING:** Sometimes the spheronisation is done in which improves the appearance of the product and some of the marketing reasons. (18)(19)

3.3.3. DISADVANTAGES OF PELLETS:

- The size of the pellet changes from each formulation but usually lies within 1 -2 mm.
- Compared to the single unit, the dose is high because of its high bulk density.
- The pellets are to be filled in capsules which can increase the cost or are compressed in to tablets which can destroy the film coating on the pellets.
- Processing is complicated and time consuming and a lot of process variables are involved.
- The excipients are needed in large quantity.
- Skilled or trained personal required and advanced technology becomes a major requirement.
- There are large number of manufacturing steps and sometimes there is lack of efficacy and reproducibility.

3.3.4. FORMATION AND GROWTH OF PELLET:

The pellets have a particular characteristic of withstanding the force while manufacturing and coating. It is necessary to have that mechanical strength because if it fails it would break down easily and they may disintegrate. They are in constant motion in the fluid bed equipment where they are constantly rub against the wall and there is attrition amongst the pellets itself and hence it becomes necessary to have that precise strength to overcome the abrasion while the development. There are many of the mathematical and theoretical equations used for evaluating the strength of the pellets, the growth and formation of pellets and the bonding forces acting between them.

BONDING FORCES: There are some of the physical forces which bind the units together and help in determining the strength of the pellets. Some of the mechanical forces are also needed which brings the particles together like tumbling, kneading, agitation, extrusion and compression.

- Attraction of the solid particles:

  There are some attraction forces which bring the particles together. They are some short-range forces but the effectiveness decreases as the distance between the individual particles increases and hence can lead to decrease the size of the particle. They are holding the particle initially and then bind the final product for longer period of time.

- Interfacial force and capillary pressure in liquid surface:

  The liquid phase is responsible for generating the cohesive forces internally amongst the particles. The strength of the pellet depends on the type of the solvent and the addition time. It is necessary to add the solvent before or at time of agglomeration. When the solvent is added prior to the agglomeration the liquid fills the void space and agglomerates are formed. When the solvent is added during the agglomeration phase and at the same time the ratio of the solvent with respect to its void volume is less than the stage can be known as pendular state.

  There is attraction of particles by the negative pressure generated at liquid bridges and surface tension of the liquid. Thus, the void space gets filled and the capillary state is achieved. There is strong bond created between the capillary pressure and the interfacial forces. There also exists a state between these two phases which is known as funicular state.

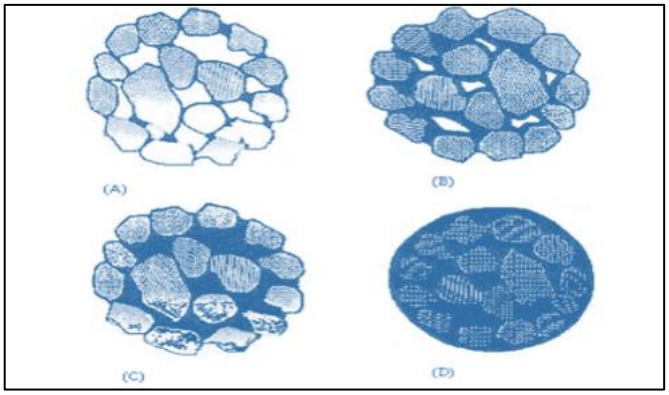


Figure 5 Types of State involved in growth of pellets

The funicular state is consisting of the liquid bridges which has presence of gas and can be filled with liquid same as in pendular state. The cohesive forces are responsible for agglomeration of the particles. The other state is the droplet state where the liquid envelops the agglomerates and these particles are apprehended by the surface tension of the droplet. This state does not possess any of the interparticle capillary bonding where the concave surfaces gets replaced with the convex surfaces of the liquid droplets. The strength of the droplet is depending on the surface tension.

- **ADDHESIVE AND COHESIVE FORCES:**

There are some binders which form solid bridges and harden during the agglomeration process. The thin adsorption layers can also form strong bonds between the particles by increasing the contact between the interparticle. The contact increases when any high-pressure compression or bonding forces are applied.

- **SOLID BRIDGES:**

The solid bridges are defining the strength of the final product after the primary methods have been applied for the initial bonding of the particles by different mechanisms which includes:

1. **MELTING:** The melting is a process in which the substances tend to melt and then solidify when cooled by forming strong solid bridges. The composition of the molten material and agglomeration determines the size of the bridge either small or large.

2. **HARDENING:** The binders get harden after the process of curing and form solid bridges which provide the strength to the finished product. The agglomerates are formed by the adhesion forces of the particles.

3. C**RYSTALLISATION OF SOLUTES:** The solvent evaporates and the dissolved substance gets bind by forming the solid component of the liquid.

4. **CHEMICAL REACTION:** This method is generally not used in the pharmaceutical industry. The above-mentioned techniques are the most commonly used ones for the manufacturing of pellets. The cooling process occurs during the compression, spray congealing or extrusion.

- **MECHANICAL INTERLOCKING:** This process occurs when the compression or agitation of the bulky particles takes place. They can provide good mechanical strength to the pellets. (20)

GROWTH MECHNAISM:

The mechanism of pellet formation plays a major role in the optimization of pelletization process. There are various theories and techniques included in the growth of pellets. It includes the nucleation, coalescence, abrasion transfer and the layering process which are affecting the process of pelletization either directly or indirectly.

1. **NUCLEATION:** this is a process where the particles are held together in a manner that it forms three phase which includes air-solid nuclei and water. They are forming the liquid bridges appearing pendular in nature. The solvent is either sprayed slowly on to the dry powder forming the moist solid nuclei or the solvent is added all at once to the main elements in a very controlled manner. As the function of the time changes there is also change in the nature and mass of the nuclei.

2. **COALESCENCE:** It is a process where the large sized particles collide with each other. The proper collisions are observed only if the nuclei have presence of additional surface moisture and if not than the deformation of the nuclei is

not observed unless there is some mechanical pressure applied. In this process the number of the nuclei gets reduced but there is no change in the total mass of the system.

3. **ABRASION TRANSFER:** This stage involves the transferring of one particle from one direction to the other direction without any specific preference in any of the particular direction. In this process, there should not be any change in the quantity of the particles. The particles are observed to be changing their size continuously till there is transfer of the material ongoing.

4. **LAYERING:** The layering process involves the deposition of the materials on the already formed nuclei. It is not necessary that the material which is deposited is moist or dry but, in this process, there is no change in the number of nuclei. Only the size of the nuclei increases with the time and hence the mass of the system gets increased.

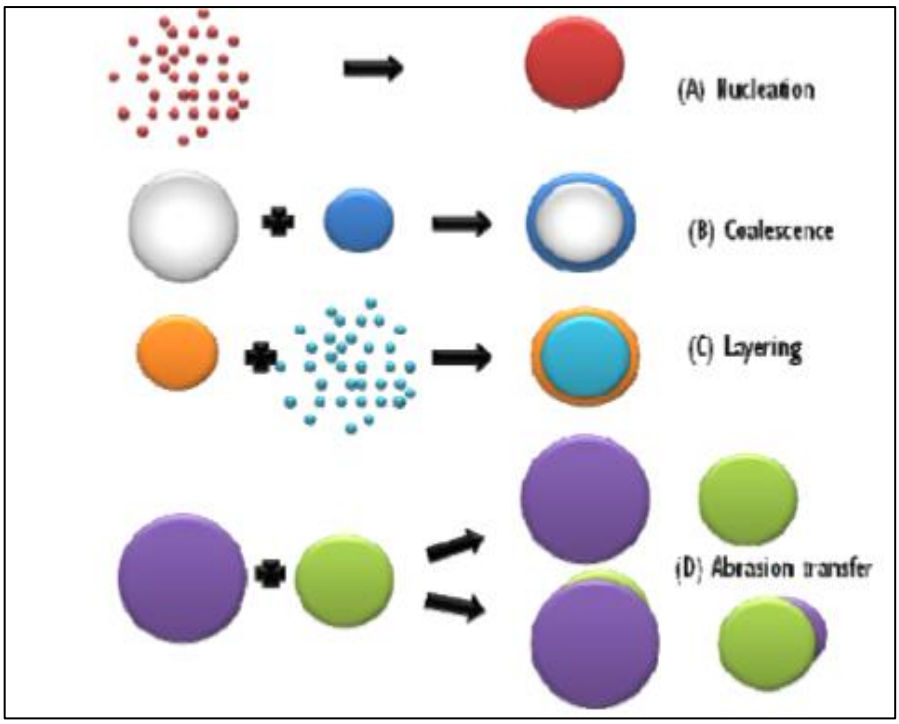
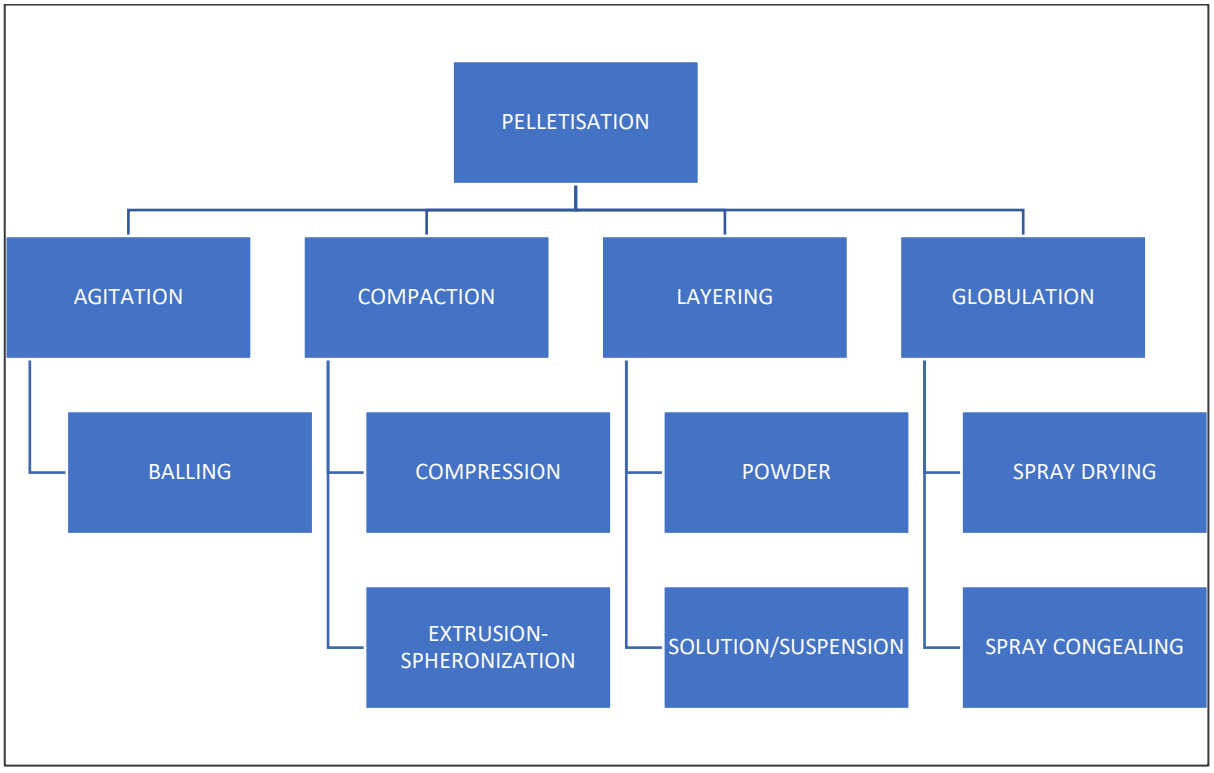


Figure 6 Growth Mechanism of Pellets

5. **REDUCTION OF SIZE:** Basically, there are three different mechanism for the size reduction which is involved in the growth of the pellets. The particles are reducing their size because of the breakage, attrition or the shatter of the pellets. Those particles having proper plasticity may coalesce forming the large particles on the collision. (12)

3.3.5. PELLETIZATION TECHNIQUES:



3.3.5.1. AGITATION:

- BALLING: Due to the problems faced in the content uniformity and particle size distribution the balling method is not widely preferred in the pharmaceutical industry. The various phases in growth of pellets is observed by using equipment like pan, disc pelletizer or drum.

The first phase is nucleation phase which includes the collision of particles and coalescence so that the particles form a nuclei. There are numerous factors which are accountable for the size of the particles which includes the viscosity of the solvent, the moisture content present in them, the wettability of the substances.

The second phase is the transition phase where the particles collide or the small particles are crushed so that they can be layered on the large particles. This phase is totally size dependent where the large particles carry the fines which are produced by crushing or attrition. The formation of fines continues until a stage is reached where the collision of particles decreases thus leading to the growth of the pellets.

At this stage the balling stage is achieved and surface abrasion is observed. As a result the layering becomes necessary for the growth of pellets which includes spherical agglomeration or emulsion solvent diffusion. There is tumbling action observed which form dense pellets of good strength. (21) (22)

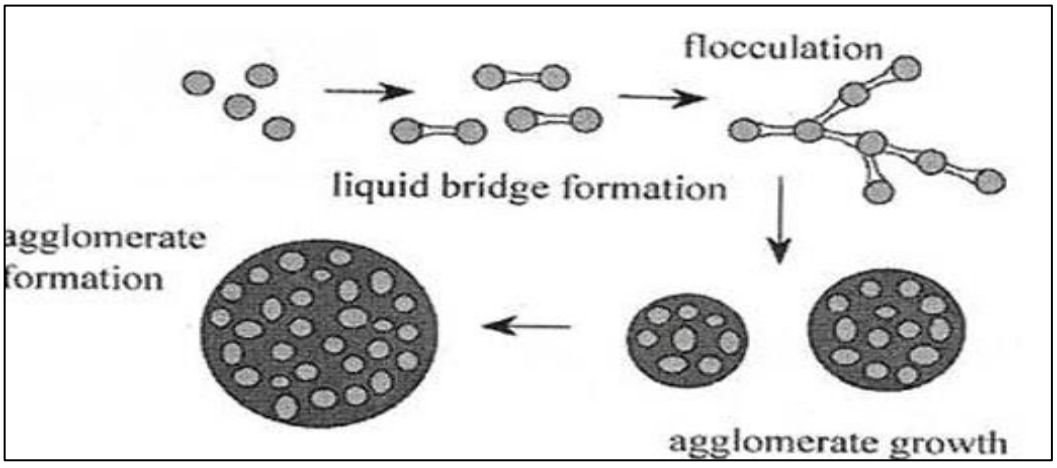


Figure 7 Spherical Agglomeration of Pellets

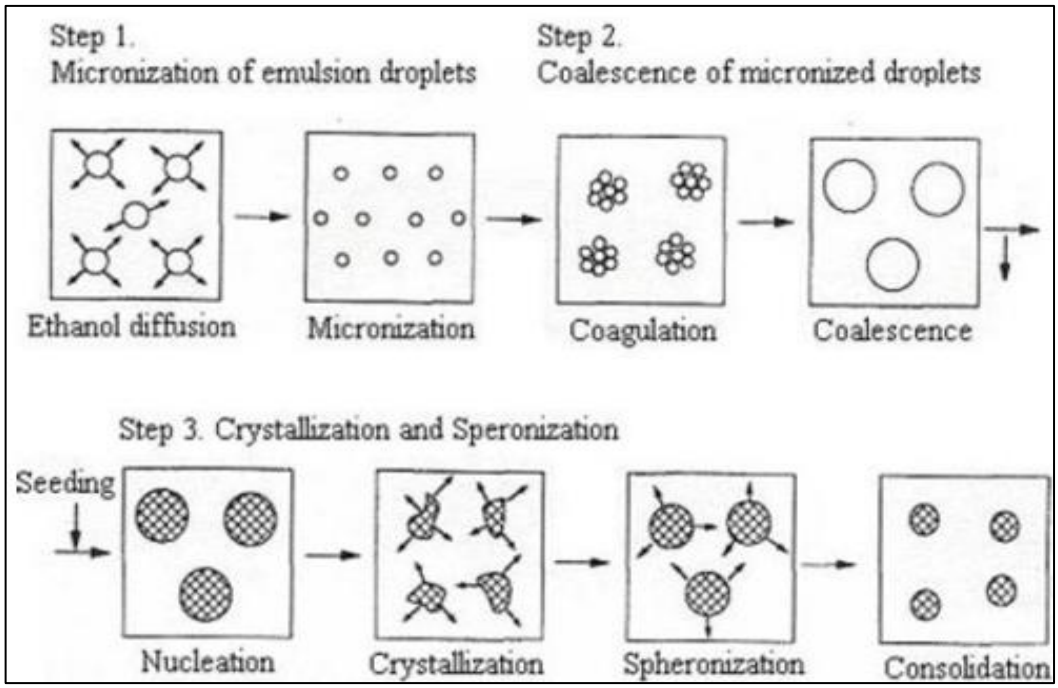


Figure 8 Emulsion Solvent Diffusion Technique

3.3.5.2. COMPACTION:

- COMPRESSION: The compression is a process where the pressure is applied to the mixture of active ingredients and excipients for the preparation of pellets having particular size and shape. The pellets are then filled into capsules. (23) (24)

- EXTRUSION-SPHERONIZATION: The actual concept of multiparticulate was introduces in the 1950s which created interest in developing such kind of dosage form for various drug delivery.

  The method which gained much importance for the development of pellets was extrusion-spheronization. It is considered to be a multi-step procedure involving dry mixing, granulation, extrusion and spheronization, later on drying and screening of the powder. The initial step is the dry mixing where the excipients and the drug is mixed then wet granulation is done. In the granulation process the powder gets converted into mass which can be easily extruded. The prepared extrudes are then transferred to the spheronizer where the spherical rods are prepared by the breakage

of the extrudes due to the friction of the wall and the centrifugal force is involved in it. (25)

Due to the gravitational force the particles fall on the friction plate and the cycle keeps on going until the sphericity is achieved. The extrusion spheronization involves the use of many unit operations but the critical equipment is considered to be the one where the proper pellets are formed.

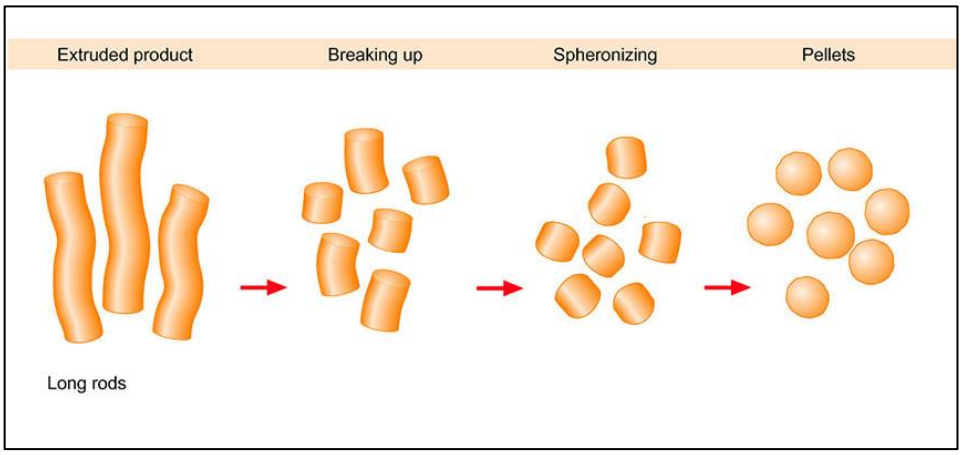


Figure 9 Extrusion Spheronization Technique

The advantage of this technique is that it has the capacity of incorporating more amount of the active ingredients without increase in the size of the pellets. It can also have the amalgamation of two or more of the active ingredients in any of the ration in the same unit. The physical properties of the excipients and the drug can be improvised and the particles having narrow particle size, high bulk density, dust free and with the smoother surface can be produced. (26) (27)

3.3.5.3. LAYERING:

The layering is considered to be a pelletization technique where the drug is layered on the started material which can be either a nonpareil or coarse material in the powder, suspension or solution with the use of binders. This layer is considered to be the inner coat and further with the use other excipients the outer layer is formed.

The starting material should have an even surface, globular shape, uniform particle size and hence there occurs uniform coating. (28) (29)

- DIRECT PELLETIZATION: This is kind of layering where the homogeneous pellets are achieved without the detectable core. The whole process is carried out in fluidized bed processor or high shear mixers. (15)

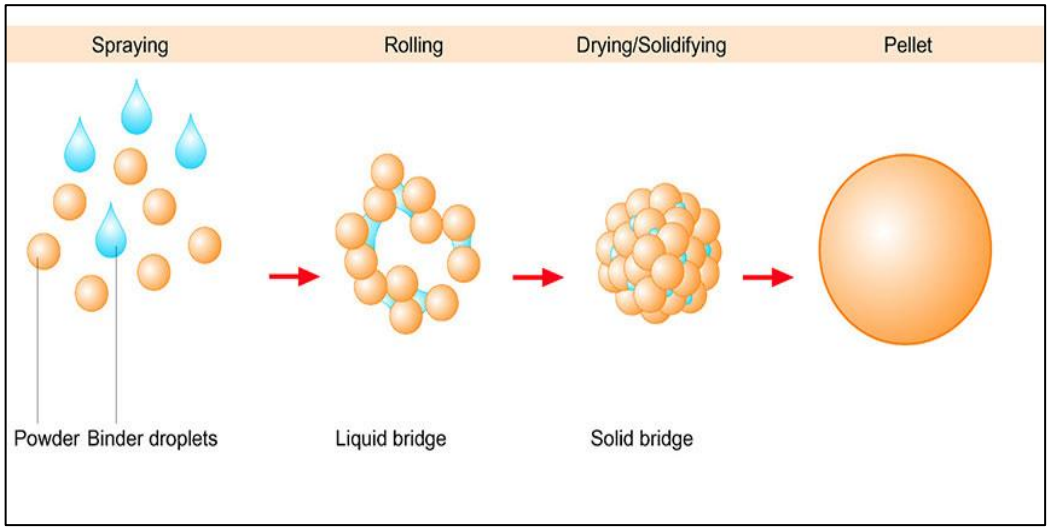


Figure 10 Direct Pelletization

- POWDER LAYERING: There are various equipment available for the powder layering and the advantage of this process is that the layering of the drug can be done with the use of less amount of the liquid due to which it is considered to be more efficient.

The binders which are used in this process incudes the gelatin, carboxymethylcellulose, povidone, hydrxypropyl methyl cellulose. There is use of rotatry fluid bed having a tangential nozzle. The nonpareil seeds are loaded in this rotar and the active ingredient is fed into the machine using the feeder. The binder solution helps in binding the active ingredient to the nonpareil seeds and thus the coating layer is formed. The magnitude of the starting material depends on the amount of the drug which is to be loaded. If we want to achieve higher dug loading then the size of the starting material should be small but that can also create problems of agglomeration.

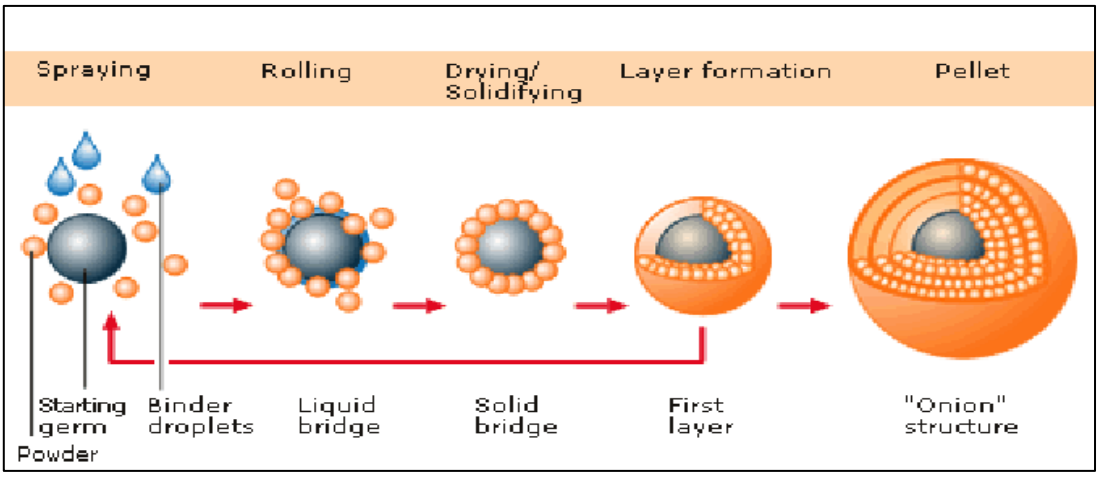


Figure 11 Powder Layering

Due to such problems the other parameters like slit air, spray rate and inlet temperature should be controlled. The critical factors are considered to be the powder feed rate, the flow of inlet air and the binder spray rate. The drug which is not involve din coating is removed through the exhaust air which is later on affecting the potency and the product yield. The other important factor which should be considered is the size of the active ingredient and the flow property because it may affect the powder layering. Normally it is said that the unit size of the API should be minimum which is less than 30 microns. (30)

- SOLUTION/SUSPENSION LAYERING: The fluid layering is used for the intermediates or the active agents which are dispersed in the liquid. In this process the mass increases as there is increase in the particle size but the total number of the particles remain the same. The rotary fluid bed is generally used in solution layering on the nonpareil seed and then coating is done in order to provide a modified release of the active ingredient. The adhesion of the liquid on the substrate is very necessary and based on it the drug coating of the pellets is identified.

Materials which can be used as starting material are sugar spheres having presence of saccharides and its derivatives including oligosaccharides, polysaccharides and other polymers such as plastic resins, silica glass, some of the organic substances like fumaric, tartaric acid, citric acid etc. (31) (32)

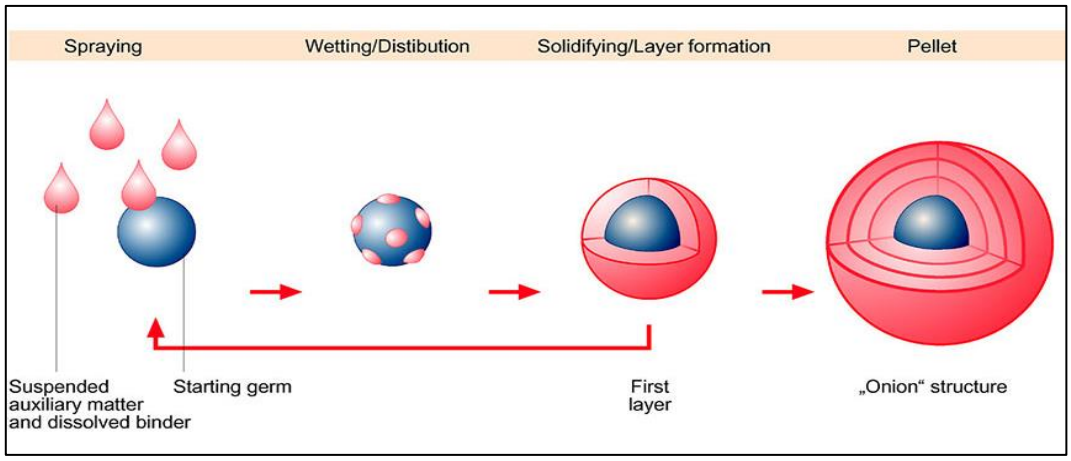


Figure 12 Solution Suspension Layering

3.3.5.4. GLOBULATION:

This is a process where the pellets are generated by atomizing the solutions, suspensions, hot melts. The solid particles are produced form the liquid phase by evaporation or through cooling of the liquid phase.

- SPRAY DRYING: In the spray drying process, the hot gas steam comes in contact with the atomized droplets and thus the evaporation of the liquid starts where there is transfer of mass and heat depending on the temperature, the humidity and the properties which are surrounding the droplet. The more the evaporation of the liquid the more solidification begins. These particles are held by some of the capillary forces and later on the solid bridges are formed. The continuous process forms a porous layer on the outward of the droplets and hence the crust width increases by evaporation and crystallization of the active material, any binder or excipients. The rate controlling step is considered to be the diffusion of the liquid across the crust and expansion of the crust. The polymer gets rigidized through the crosslinking of the aldehydes, calcium chlorides.

- SPRAY CONGEALING: In this process the droplets are cooled down underneath the melting point of the solvent. The solid bonds are formed which hold the particles from the congealed melts. The particles remain nonporous, strong and intact upon

addition as there is absence of solvent evaporation in the method. The initial step of the pelletization is the binding of the primary particles by the physical forces. The strength and the physicochemical properties are actually responsible for the physical forces and hence are considered important for the development of the pellet drug delivery.

3.4. FLUIDIZED BED PROCESSOR:

Fluidized bed processing includes the cooling, agglomeration, drying, coating of particles and granulation. This technique can be used equally for the heat resistant and heat sensitive materials. The air is passed through the product layer and the velocity conditions are controlled so as to create the fluidized state. The heat is passed through tubes or panels in the fluidized layer. The cold air is also used to remove the heat. In this process there is coating done over the substances present in the fluidized bed in order to protect the substances or to modify that substances.

In the process, the solution is sprayed on the solid particles and hence the coating is achieved. The fluidizing gas is also used to dry the coat on the slid particles. Nowadays, modified fluidized bed processors are used as they have more mass transfer and high energy. Based on the development, there are few machines which includes:

- Double walled centrifugal fluid bed granulator
- Tangential spray or centrifugal bed granulator
- Wurster coating process equipment (33)

1. **DOUBLE-WALLED CENTRIFUGAL GRANULATOR:**

   The granulator is double walled having the inner wall in open or closed position. The powder layering is carried out when the inner partition is closed so that the liquid can be applied simultaneously so that the multiparticulates can attain the desired particle size. After the application of liquid, the particles enter the drying zone. The air is continuously passed through it till the moisture level gets achieved.

2. **TANGENTIAL SPRAY GRANULATOR:**

   This type of granulator was actually developed for the granulation but after which it was used to perform various unit operations which includes the manufacturing, coating of multiparticulates that are preferred in the solution/suspension layering or powder layering for the pelletization technique. The principle is related with the

fluidization air velocity, centrifugal force, and the gravitational force. These forces generate a motion which help the particles to move in the bed.

The equipment is having the rotating disc with the centrifugal force pushing the particle towards the vertical wall of the chamber. The force is generated which carry the article along with it towards the vertical wall along with product in the expansion chamber. The particles here lose their cascade and momentum towards the centre of the disc. Along with this there is another feature of this which includes the spray method. After the drug layering gets completed, the liquid is to be sprayed tangentially. The degree of the mixing is dependent on the velocity, fluidization air volume, size and width. The yield and the quality of the pellets depend on the above parameters.

3. **WURSTER COATING EQUIPMENT:**

Generally, the wurster coating is used in pharmaceutical industry for the pellet and powder coating. The dimensions of the wurster container is 100-500g till 800 kg. They are generally used for coating of particles having size less than 100µm. The equipment is conical having air distribution plate (ADP) at the bottom region which is known as the orifice plate. There is open zone of the plate which allows more air to permeate. The air accelerated upwards due to which particle pass through the spray nozzle which is adjusted in the centre of air distribution plate. The one part of the nozzle is used for the liquid and the other for the atomization of air at predecided volume and pressure. The spray angle is approximately 30-50° also known as coating zone. There is down bed region which is external to the partition. The air distribution plate is selected on the source of the size of the material and the density of the material.

The air flows from the bottom region so that the particle remain in suspended form. The height of the column is controlling the rate of the substrate. As the coating is done the load in the column increases and hence the height of the column is

increased in order to achieve the desired pellet flow. There is expansion are above the product container for decreasing the particle velocity and the air.

The fluidized bed techniques are regularly known for the mass transfer and the heat transfer and even the process is considered to be very real. For the highly soluble materials the droplets are used on the surface forming a film and then the drying takes place. After applying the initial coat, the rate of the spraying is increased. The organic solvents when sprayed form a quality film as it has the minimum potential for the spray drying of the film.

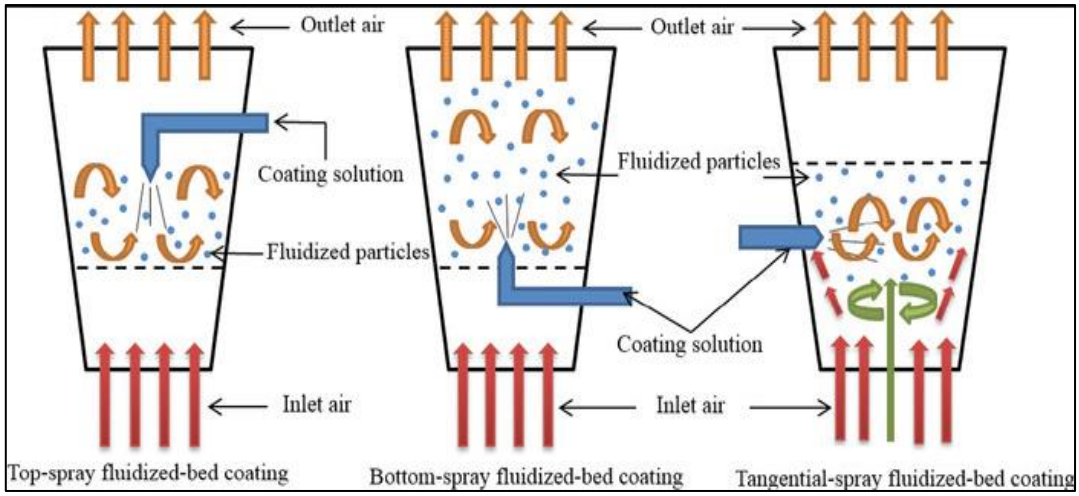
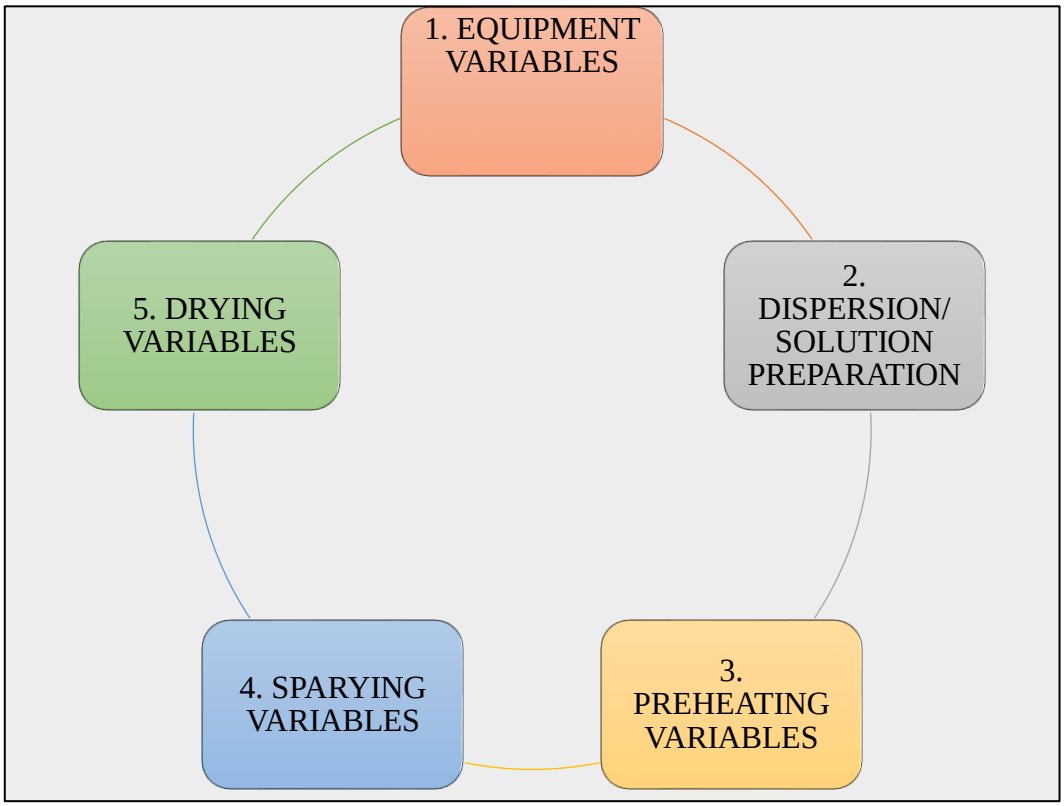


Figure 13 Fluidized Bed Processor

3.4.1. PROCESS VARIABLES OF WURSTER COATING:



The wurster process is having five process variables which affect the quality of pellets. It includes equipment variables, preheating of variables, spraying variables, solution preparations and drying variables.

AIR DISTRIBUTION PLATE: (ADP)

There should be minimum attrition during fluidisation and hence proper ADP has to be selected. The fluidization volume is affecting the particle velocity in which the smaller particles require less air volume to achieve specific height compared to the larger particles. The differential pressure and the air velocity should be almost same in the air distribution plate. Hence when there are small particles the plate which is used should have lesser opening so that the resistance is created and there is better distribution of air. Based on the size of the pellets there are some recommendations for the selection of plate. (34)

Table 2 Properties of Air Distribution Plate

EQUIPMENT	PELLET SIZE	PLATE COMBINATION
6" Wurster	<500 micron	A
	250<<1200 micron	B
	600<<1800 micron	C
	>1200 micron and tablets	D
For commercial models	<300 micron	A-I
	150<<800 micron	B-I
	500<<1200 micron	B-H
	700<<1400 micron	C-H
	800<<1800 micron	C-G
	>1500 micron and tablets	D-G

COLUMN HEIGHT:

The column height should be properly adjusted so that the substrate can easily circulate throughout the spraying zone. The height of the column is changed by keeping in mind various properties like flow, shape, size and bulk density

The column height is considered to be a significant factor in coating the substrates and in the release of the drug of the coated pellets. The reason behind it was that the pellets are flowing in the column and are getting the exposure of the coating droplets in that spraying zone. When the gap between the column is too much then the particles tend to agglomerate and when the gap is too less then there are chances of over wetting of the particles. The height should be adjusted in a manner that maximum pellets can enter the column. Care is taken that the height is not changed frequently. The column gap generally used for 6" wurster is 15-25 mm and for 18" wurster is 40-50 mm. (35)

FILTER BAGS:

The filter bag is preferred to avoid the material loss and allow the air to permit through it. If the porosity of the bag is high then there is much loss of the material and if the porosity is less then there would be clogging which will interrupt the

process and it would affect the yield. The filter bag should be selected on the basis of the size of the particle and the previous experiences.

COATING SOLUTION/SUSPENSION:

The care is taken that the coating solution and suspension should contain that amount f the solid content which can be sprayed. If the viscosity of the solution is very high then it can affect the size of the pellets and there would be change in the surface are of the pellets. The viscosity of the coating solution should not exceed 25 mPas.

NOZZLE TIP DIAMETER:

The smaller the nozzle the consistent spraying is observed but the smaller nozzle can choke easily. In order to avoid agglomeration of the particles, the coating fluid should be atomized. The nozzle which is in use should be such that it atomizes the coating fluid even if the coating fluid delivery rate is high. The larger droplets of the coating fluid do not spread evenly and they take time to dry compared to the smaller particles. The very minute droplets can dry very easily. Some of the droplets get in connection with the pellets and get dried before spreading which can lead to irregular surface of the pellet. The multiple nozzles are used to avoid the formation of agglomerates with the large droplets of the coating fluid.

INLET TEMPERATURE AND PRODUCT TEMPERATURE:

The inlet air is to be heated previously and should then enter the coating chamber so as to improve the evaporation of the coating material sprayed on the core. The air temperature needs to be controlled as it may affect the quality of the coat. The dry environment can lead to spray drying effect while the over wetting can lead to agglomeration. The optimal temperature is the one where there is slow evaporation of the solvent in a manner that there is no agglomeration of the substrates and coalescence of the polymer particles. When the air temperature is kept very high then it can lead to the rough coat which will not provide a proper drug release.

When the temperature is too low then long time is required for the drying of the coating material which can migrate the drug to the coat layer. The drug which is dissolved can reduce the surface tension of the liquid layer which is responsible for lowering the capillary forces and hence avoiding the distortion and coalescence of the spray droplets. (36)

AIR VOLUME:

It is used for circulating and drying of the substrates in the coating process. If the air flow is not proper then there is no sufficient drying of the substrates and they are not able to remove moisture from the sprayed droplets which can lead to agglomeration of the particulates.

When excessive air flow is provided it can lead to the attrition conditions which may erode the coating and the stress cracks are observed on the particulates. This can decrease the drug release profile of the drug. There are different criteria for different equipment coating which generally depends on the dimensions, particle density and the shape of the product. A bubbling kind of fluidization is preferred for the organic type of coating as to minimize the static charge and similarly for the aqueous type of coating rigorous type of fluidization is more preferred. (37)

DEW POINT:

Along with the temperature the humidity is also playing an important role in the drying of the coated pellets. The psychometric charts are preferred for finding the interaction between the humidity and the temperature. The humidity of the air changes every day from season to season.

When there is change in the dew point, there is change in the air efficiency. The lower the humidity in the inlet air enhances the capacity of drying the air even if the temperature is low but the high static charge could be observed in the product. The care should be taken from the initial stage development so as to avoid the static charge.

When the humidity level is too high it can result in the depression of the air temperature under the dew point which causes the condensation of water either on the product or on the machine. For water soluble substrate it is necessary to avoid the high moisture content at the initial level. The humidity should be amplified after the preliminary coating of the pellets with the polymer and the static charge can be avoided. The process should be carried out in same environment in the wurster chamber at the dew point mode and this dew point is independent factor. (38) (39)

SPRAY RATE:

Generally, for the wurster apparatus two nozzles are used. The spreading, coalescence, the formation of droplet and the evaporation happens simultaneously. The spray rate rest on on the properties of the solution and the core particles. There is increase in the droplet viscosity when the evaporation occurs by atomising air which is sprayed in the form of mist. According to the viscosity of the solution and the drying efficiency, the spray rate needs to be adjusted.

When the particles are small, the droplet size needs to be maintained low to avoid the agglomeration which can be done by increasing the pressure of atomization or decreasing the rate of the spray. At the early stage the spray rate is kept low so as to avoid the solubilisation of the core pellet or to avoid the interaction of the core pellet with the solution. Once the layer is formed then the spray rate can be increased but specifically up to a certain level. It is observed that once the particle size increases it can have large number of droplet size without any agglomeration. And when the particle size increases it is necessary to increase the spray rate at regular intervals. (40)(41)

ATOMIZATION AIR PRESSURE:

When the atomization pressure is kept high, the mist proportions would be low and the probabilities of forming aggregates would also decrease but excess pressure can also lead to particle shooting in the filter bag. Mostly, the pressure atomized is kept between 2-4 bar. The pressure also depends on the variety of binder which is used, the rate of evaporation of the solvent and the viscosity of the solvent. While

optimising the spray rate the droplet size should be kept small because higher the pressure smaller will be the droplet. (42)

DRYING/CURING TIME:

The viscosity of the solution depends mostly on the type of binder used. The film formation occurs by forming a gel like phase and then the evaporation takes place. The film formation is complicated in the aqueous phase. Some of the agents like surfactants, anti-tacking agents or some of the plasticizers are used for improving the film formation. The polymers which are having high glass temperatures form film very quickly and for such substrates some of the plasticizers are used to decrease the minimum film forming temperature. The polymer particles interact with the core particles forming coalescence during the drying in aqueous dispersions. (43)

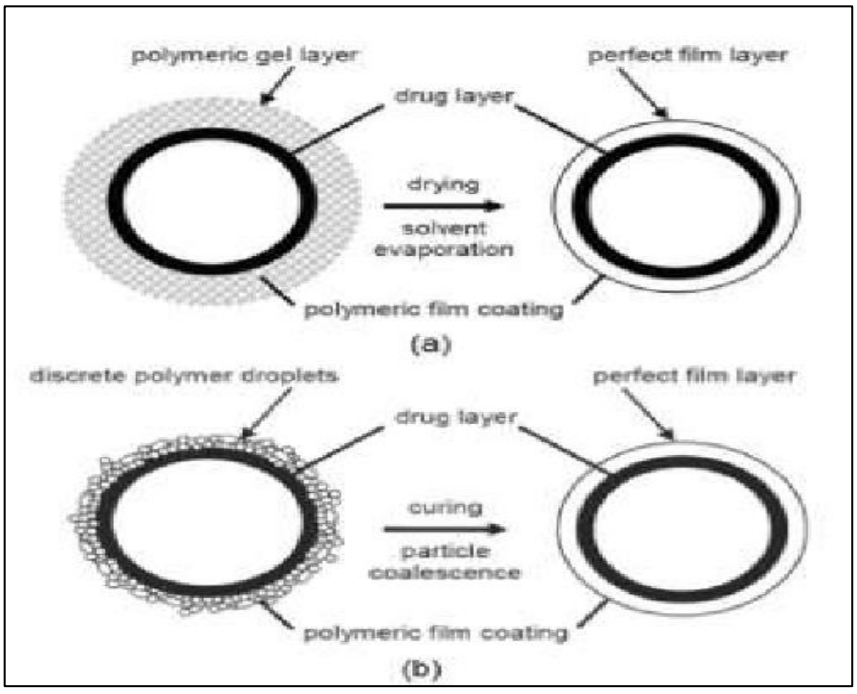


Figure 14 Effect of Drying and Curing on Pellets

3.5. MECHNAISM OF RELEASING DRUG FROM PELLETS:

Basically, the drug release occurs in three ways:

1. **EROSION:**

   The coating gets eroded with time and the drug gets released from the pellets.

2. **OSMOSIS:**

   The osmotic pressure is created inside the particle by water imbibing in it and then the drug is forced out in the exterior environment through the coating.

3. **DIFFUSION:**

   When the aqueous fluids present in the gastrointestinal tract come in contact with the particle, the water gets diffused in the interior of particle and hence the dissolution takes place releasing the drug through the coat of the pellet.

3.6. EVALUATION OF PELLETS:

The pellets are evaluated on the basis of various measures which includes the endurance of the material and the suitability of the material. The basic characteristics of pellets includes:

- SHAPE: The shape of the pellet has influence on coating, filling of the pellets into capsules and dies. The analysis of shape can be done through the ring gap analyser, scanning electron microscopy (SEM) for both the quantitative and qualitative analysis. The shape can also be identified through the microscope or the stereomicroscope. The other method which can be applied is taking the optimum size of the pellets, staining in the dye solution and then drying in hot air oven.

The pellet is recorded by measuring the length and width and the calculation is done on basis of following equation:

S= P2/ (12.56 *A)
Where,
A= Area which is in cm^2
P= It is the Perimeter of the circular tracing

Other equation to calculate the shape is:
4Πa/P2
Where,
A= projection area
P= projection perimeter

- PARTICLE SIZE DISTRIBUTION: This can be done using sieve analysis which is considered to be economical and simple. Even microscopy methods like SEM and laser diffraction can be carried out. The features of the pellets affect the drug release and coating. The other method of determining the size is through the fret diameter which is obtained from different angles. The size data was selected on the basis of normal distribution curve.

- SURFACE AREA: The surface area is considered to be a major factor in the drug release and can change from batch to batch. The surface area needs to be analysed through the gas adsorption, air adsorption and particle size distribution. The surface roughness can affect the packaging and flow of the pellets. (44)

- BULK AND TAP DENSITY: The potency is affected by the bulk density and tap density of the finished product. It can cause segregation and thus leading to batch to batch variation. This kind of density can be measured using the pycnometer. It can also be calculated by using the ratio of the weight to the engaged volume of the pellets.

- HARDNESS AND FRIABILITY: They are measured in order to withstand the coating when high attrition is generated during the transportation or packaging. There are various equipments through which friability can be measured. It includes the Roche friabilator, pharma test friabilator, Erweka friabilator. It is considered that the friability should be less than 0.08%. The hardness can be measured using the Kaul pellet hardness tester.

- POROSITY: The porosity is affecting the action of the drug dissolved which influences the drug release of the pellets. It is quantified by SEM and quantitatively by mercury porosimeter. Initially the sample is introduced in the chamber which is then degassed and then covered completely with mercury. The pressure is applied and the amount of the mercury which enters the pores is measured. The pore radius can be calculated using the following formula:

  $R = 2\ g\ [\cos q] / P$

  Where,

  $g = 480$ ergs/cm^3

  $q = 140°$

  r = It is the pore Radius

  p = It is the mercury-intrusion pressure

- FLOWABILITY: The flowability of the pellets can be calculated using the angle of repose. It is said that if the angle ɵ is <30 ° then the flow is excellent and if the ɵ is >40 ° then the flow is poor.

- TENSILE STRENGTH: This can be measured by using the tensile apparatus which is 5kg load cell. The radius of the pellets is calculated and strained till the failure occurs. The strength can be calculated by using the failure load value (F) and the area of the pellets (R). The equation used for the following is:

  $\sigma f(s) = 0.4F / \pi R2$

- DISSOLUTION: The dissolution is related with the parameters such as hardness, drug loading, the film coating, physical structure changes of the matrix, the surface properties, the pellet shape and the release profiles of the drug. Usually USP apparatus I and II are used for carrying out the release of the drug of pellet. (45)

3.7. MARKETED FORMULATION OF PELLETS: (13)

Table 3 Marketed Products of Pellets

PRODUCT NAME	DRUG	CATEGORY	FORMULATION	COMPANY
Esomeprazole	Esomeprazole magnesium	Anti-ulcer	Delayed release	Astra Zeneca
Prevacid solu tab	Lansoprazole	Anti-ulcer	Delayed release	Takeda
Iosec MUPS	Omeprazole magnesium	Anti-ulcer	Delayed release	Astra Zeneca
Theodur	Theophylline	Anti-asthmatic	Extended release	Key

4. LITERATURE REVIEW:

Sunil b Jaiswal et al. have discussed about the problems which are faced during compacting the pellets into tablet. There are many oral modified release multiunit dosage forms that are having better therapeutic effect compared to the single unit dosage form. The multiparticulates are filled into capsules or can be compressed into tablets but there are some mechanisms which are involved in the compaction of multiparticulate system. There are some process related parameters which are affecting the compaction of the pellets into tablet. The aim of the innovation was to develop a multi-unit pellet system which can disintegrate easily and provide a proper drug release compared to the uncoated pellets.

They identified the challenges which are faced during tabletting the pellets into tablets. The compaction study of the pellets was done which is quite different from the compaction of powders. There are various process related parameters and excipients which are affecting and hence are to be optimized providing a proper drug release. The type of polymer is the most important variable which can affect the drug release. The polymer which is used should be having a proper thickness to withstand the forces, strength, ductility so that during the compaction they do not get rupture. Earlier the polymers which were used were not having that strength that they can with stand the forces and hence are avoided in the preparation of the multi-unit pellet system. The mechanical properties of the film are investigated in response to the stress and based on it the polymer is finalized. The excipients should be compatible with the pellets and hence are choose wisely. The compression forces and the pellet excipient ratio are studied properly. The size of the excipients, porosity also have an impact on the compaction of pellets. Thus, the polymers, excipients should be selected in a manner that they do not affect the compaction of pellets into tablets. (46)

Abdrei deshavsky et al. studied about the preparation and evaluation of pulsative multiparticulate drug delivery which was having a coat of aqueous dispersion Aquacoat® ECD. The pulsative delivery is consisting of three layers. (i) A core having drug in it. (ii) A swelling layer having the presence of binder and superdisintegrant and (iii) A water permeable polymer coating which is insoluble.

As the water penetrates inside, the swellable layer gets expanded and breaking of the outer membrane starts which results in drug release. The lag time was quicker when theophyliine 10%w/w was coated on the sugarsphere compared to the theophylline 100%w/w. The release after the lag time was observed to be quick and complete as the swelling agent like carboxymethyl cellulose (AcDiSol®) was used. To achieve a sustained release effect swelling agents like the low substituted hydroxypropyl cellulose (L-HPC) and sodium starch glycolate (Explotab®) were used. The actual concentration of AcDiSol® was identified to be 26%w/w for very less soluble theophylline and 48%w/w for soluble propranolol HCL.

The lag time can be regulated by increasing the coating of the outer membrane. The outer membrane when coated with aqueous dispersion Aquacoat® showed quite faster rupturing of the membrane and the drug was easily release from it compared to the outer membrane coating of ethyl cellulose formed using the organic solvent. Even the addition of talc showed brittleness increasing the drug release and can reducing the sensitivity of the lag time by varying the coating levels. The microscopical observation showed that the drug release started after rupturing of the outer membrane. (47)

Karim amighi et al studied the melt pelletization for the prolonged release of the matrix pellets by using the high shear mixer in the laboratory The pellets of phenylephrine hydrochloride were studied by using binder mixture of compritol® 888 and precirol® ATO 5. The binder concentration of the pellets was increased from 18 to 80%w/w and the effects of the impeller speed, jacketed temperature, massing time were studied. The results showed that the pills with narrow size distribution can be achieved by maintain the chopper speed 4000 rpm, impeller speed of 800 rpm and the massing time of 8 mins. The particle size analysis was done and the size of the pellets ranged from 700µm- 1500µm.

The drug release profiles can be studied in various solvents including the phosphate buffer at pH 7 for all controlled release pellets and at pH 1.5 for ciprofloxacin pellets as it is having low solubility in pH 7. The drug release totally depends on the physico-chemical properties of the drug and mainly on the solubility of the drug in the aqueous medium. The faster drug release was obtained from ketoprofen pellets compared to the other pellets at pH 7 and highest drug release at pH 1.5 was observed of ciprofloxacin pellets. (48)

Vinod gaikwad et al. studied the quality by design approach for the development of pellet based multicore tablets which can be sued for the controlled release of the drug Metoprolol succinate. The important aspect was to develop the multicore tablets for the treatment of cardiovascular disease. The multi-core does not show much effective results and hence the pellet based multicore tablets were prepared to improve the characteristics.

The pellets based multicore tablet showed extended release effect of the drug for a maximum time period of 543.2 min and followed the zero-order drug release mechanism. The drug content was quite high in pellets based multi core tablet compared to the granules based multi core tablet. The multi core tablets can be used for the pulsative drug delivery by keeping the core at programmed distance within the coat layer. The multicore tablets are used for the combination therapy in which one drug can be placed in the core and the other in the coat so as to avoid the incompatibilities. The optimization can be done by developing once daily kind of formulation by increasing the number of the core layer.

The developed pellets based multicore tablet have shown hardness of 4 kg/cm, friability <1% and the drug content up to 98.6±0.6% which is in the range. The optimized batch showed controlled release for long period of time and hence this type of study is considered as promising target for the development of controlled release formulation. (49)

Kramar et al. studied the evaluation parameters for the sustained release multiparticulate of diclofenac sodium. The study was based on evaluating the polymethacrylic film prepared with aqueous dispersion. The film coatig of the pellets was done in fluidized bed apparatus. The independent variables for the evaluation were (i) quantity of coating dispersion (ii) the concentration of plasticizer (triethylcitrate) and (iii) methacrylate polymer ratio (Eudragit RS: Eudragit RL). The 3^3 Box-Behnken design was applied. The dependent variables were the dissolution of diclofenac sodium at 3,4 and 6 hrs.

After carrying out the experiments, the drug release profiles of diclofenac were obtained. The response surface plots were plotted using some of the independent and dependent variables. Based on the results it was found that the optimized procedure showed 40% release of the drug in 3 hr. the quantity of coating solution, different polymer ratio and

concentration of plasticizer was 400g, 3:1 and 25%w/w respectively. The optimized batch showed release which was quite near to the predicted values. The surface and thermal characteristics of the polymethacrylic films were also studied to identify the influence of the plasticizer which changes the release of the diclofenac sodium.

To identify the quantitative effect of the different levels of the factors on the drug release were predicted by using the polynomial equations. It was also observed that there was good film forming when the concentration of the plasticizer triethyl citrate was increased above 20%. (50)

Eva roblegg et al. used vegetable calcium stearate (CaSt) as thermoplastic excipient for the development of the sustained release pellets. The matrix is extruded which is then pelletized using the one step continuous process with the hot strand. The vegetable CaSt is extruded between the temperature of 100-130°C. the drug release of 20% coated paracetamol was 11.54 % after the 8 hr of densification and hence was stated that the drug release gets affected by the drug loading and the size of the pellets. The functional additives can be added to increase the release of the drug.

Two plasticizers were used for increasing the in vitro drug release. The glyceryl monostearate increased the drug release by creating pores outward and showed no impact on the process parameters. The addition of tributyl citrate also increased the release of the drug up to certain extent. As per the results, CaSt pellets can be prepared by above method and it was observed that paracetamol did not melt and behaved as solid suspension. The addition of plasticizers also helped in modifying the release of the drug.

The controlled release pellets can be prepared using HME having a hot strand cutter with two rotating knives. The DSC curve was investigated for CaSt and four peaks were obtained in first heating cycle which can be reversible as cooling takes place. The plasticizers decreased the process temperature and provided an appropriate melt viscosity. The tackiness of the TBC increased by increasing the aspect ratio. The pellets having no plasticizer showed less release rates and great densification of pellets was also observed. (51)

Prakash Thapa et al. conducted a study investigating the influence of the ethyl cellulose and curing conditions on the pellets by using the quality be design approach. Drug methimazole which is freely soluble was studied by carrying out the test parameters like the mechanical strength, drug release and true density of coated pellets. The spectroscopic and thermal studies were also carried out by carrying out the differential scanning calorimetry (DSC), Raman spectroscopy, Fourier transform infrared spectroscopy (FT-IR), Atomic force microscopy (AFM) and scanning electron microscopy (SEM).

The process of drug loading and ethyl cellulose coating was carried out in the fluidized bed processor. The analytical results show that there is no interaction between the ethyl cellulose and the drug. The regression model was used for the prediction of the dependent variables (hardness of the pellet, true density and the release rate at 1,4,8 and 12 hr). It was observed that curing and degree of coating had the highest impact on all the response variables. The monte carlo simulations were used to build the design space. The accuracy and the control variables were also optimized.

By carrying out the different degree of coating the observation was that by increasing the coating thickness, the drug release can be reduced from the pellets and the zero-order release was obtained. Curing had an important role in aqueous dispersion as the primary drug release was controlled by diffusion. By carrying out curing at higher temperature, the homogeneous film was formed which can be studied by using AFM and SEM. (52)

Leopold et al. studied about shellac for the enteric coating. The shellac is used as coating material in many of the food products. As shellac is having high dissolution pH, it is used with some additives for the enteric coating. This has led to the usage of shellac in many of the sustained and controlled release formulations. In the present study, the immediate release theophylline pellets are coated with sub coats like citric acid, Eudragit® E and calcium chloride having the coating of shellac. The drug release from each coating were evaluated.

The interaction of the different sub coating and the shellac was studied using FT-IR. All the formulation showed a prolong release effect. The calcium chloride some ionic interaction with the shellac. The citric acid showed reduction in degree of dissociation and

the effect of Eudragit® was studied by solubility characteristics of the basic polymer. Using the proper substance and adjusting the concentration can help in achieving a sustained release effect.

All the sub coats except the Eudragit® E was approved for the pellet formulation with shellac. The combination of calcium chloride and citric acid with shellac are used for the formulation of many of the dietary supplements and sustained release vitamin formulations.

4.1. LITERUTURE SURVEY OF PARKINSON'S DISEASE:

Fanny Faivre et al stated that the parkinson's disease is a neurodegenerative disease having motor symptoms like loss of dopamine but there are some non-motor symptoms which includes the psychiatric disorders like depression and anxiety. They appear at the early stage where the motor symptoms are not even visible and have a major influence on the patient's life. There were many of the research work done on the motor symptoms of the disease but the scientists were not able to identify the actual changes which arise in the disease. So, after this the research was done on the animal models on the non-motor symptoms.

The present article represented the mechanistic aspects which have symptoms for the preclinical testing for the new medical approaches. The preclinical testing also needs more of the standardization and the robustness for the outputs. The variability which is present in the animal models can be considered as the change in the individual and hence are contributing towards the heterogeneity in the experimental studies. The aspects which are considered needs to be tested in non-human and rodent models as well. (53)

Hao Deng et al stated that 15 % of the Parkinson's patient are having the family history and other 10% of the population are having the mendelian inheritance. This review is based on the overview about the neuropathology, clinical and genetic forms. They have also performed the screening of the risk factors associated with PD and their impact on the genes. In the past years, there has been a great progress in the identification of the genetic risks of PD. There are many studies which are based on the understanding of the mechanism of the disorder.

The interactions which are caused between the protein products of the causing gene has revealed the actual pathogenic mechanism which lead to the development of PD. The interactions can be the mitochondrial dysfunction, the impairment in the dopamine release, accumulation of the alpha-synuclein, activated microglia.

There are various methods including the transcriptomics, immunomics, genomics, lipidomic which utilize various animal models and help in identifying the genetic contributors for the PD. The levodopa is considered to be the most efficient therapy for the treatment of the motor and non-motor symptoms by understanding the pathway. The therapies are tried in order to improve the quality of life of patient. (54)

4.2. LITERATURE SURVEY OF FLUIDIZED BED ROCESSOR:

Okoronkwo C.A. et al studied the drying characteristics of the fluidized bed fryer. The parameters included the heater, air blower, drying chamber and the materials used were maize, yam etc. The evaluation for the drying was done by measuring the drying time, moisture content and based on the data available it was observed that it took 150 minutes at temperature of 60°C for reducing the moisture content of yam from 75.4 % to 11% while keeping it in storage conditions maintaining the external conditions. Similarly, other temperature effects were also tried on the maize which includes the 300°C.

When the products are dried below their optimum temperature it was observed that there was more moisture present in it due to which there was increase in the mass of the substances. And if the drying was carried out above the optimum temperature then thermal degradation was observed. The effect of this could be cracking, non-uniform drying, shrinking. From the results, it was concluded that fluidized bed dryer can be considered as an alternative approach for the preparation of cohesive solids which preserve the quality of the dry solids. (55)

Wnukowski P. et al discussed about the humidity and temperature as an vital feature for the processing of the coating particles in the fluidized bed processor. The top spray was carried out using the non-submerged spray nozzle. The high humidity and low temperature are formed inside the bed deep inside during the process. The topmost part of the bed is

having the lowest gas temperature. The area below the high temperature is considered to be stable and having constant gas temperature. Based on this, four different zones have been identified which are used in coating.

The shape and the size of the particle depends on the high humidity and low temperatures. Basically, the two shapes are formed which includes the bell and funnel shape. The pockets of low temperature and high humidity are formed exclusively inside the bed using the lactose- water system or the glassbeads- water system. The pockets show fluctuations in the humidity as well as in gas temperature. (56)

5. DRUG AND EXCIPIENT PROFILE:

5.1. DRUG PROFILE:

Table 4 Parameters of Drug

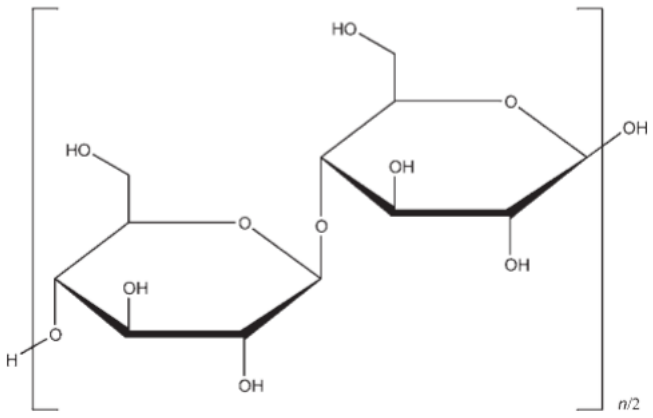
PARAMETERS	DESCRIPTION
APPEARANCE	It is stable, white or nearly white crystalline powder
MELTING POINT	180-192°C
pH	3.0-5.5
MOLECULAR WEIGHT	187.71g/ml
LOG P (octanol/water partition)	2.44
pKa (Dissociation constant)	10.45
DRUG CATEGORY	Anti-viral and Anti-Parkinson
BCS CLASS	Class III (High solubility and Low permeability)
STABILITY	Stable in light, heat and air
ASSAY	NLT 98.5 NMT 101.0

Table 5 Pharmacokinetic Parameters of Drug

PHARMACOKINETIC PARAMETERS	DESCRIPTION
ABSORPTION SITE	It is well absorbed from gastrointestinal tract.
PLASMA PROTEIN BINDING	Approximately 67% bound to plasma proteins over a concentration range of 0.1 to 2.0 µg/mL.
METABOLISM	No appreciable metabolism, although negligible amounts of an acetyl metabolite have been identified.
DISTRIBUTION	Vd is 3 to 8 L/kg, suggesting extravascular distribution.
ROUTE OF ELIMINATION	It is primarily excreted unchanged in the urine by glomerular filtration and tubular secretion.
Tmax	9-15 hrs
Cmax	1.1-2.6 ng/ml per mg of amantadine
HALF-LIFE (t1/2)	Mean half-lives ranged from 10 to 14 hours, however renal function impairment causes a severe increase in half-life to 7 to 10 days.
AUC_{0-T} (mg*h/ml)	44-83 ng*h/ml per mg of amantadine

5.2. EXCIPIENT PROFILE:

5.2.1. MICROCRYSTALLINE CELLULOSE:

PROPERTY	DESCRIPTION
NONPROPRIETARY NAMES	BP: Microcrystalline Cellulose JP: Microcrystalline Cellulose PhEur: Cellulose, Microcrystalline USP: Microcrystalline Cellulose
SYNONYMS	Cellets, cellulose gel, avicel, crystalline cellulose, emcocel, fibrocel, MCC sanaq, vivapur, tabulose, pharmacel, ceolus KG, E460
CHEMICAL NAME	Cellulose
MOLECULAR WEIGHT	36000
STRUCTURAL FORMULA	
FUNCTIONAL CATEGORY	Tablet disintegrant, diluent, adsorbent, suspending agent
APPLICATIONS IN PHARMACEUTICAL TECHNOLOGY	They are widely used in pharmaceuticals mainly as diluent in capsule and tablet formulation, also as binder in both dry and wet granulation. It also possesses some properties of lubricant and disintegrant which makes it useful in tabletting. They are also used in cosmetics and food industries.

DESCRIPTION	They are purified depolymerized cellulose which are white odourless crystalline powder having porous particles. They are available in different grades which have different properties and applications.
DENSITY	0.337g/cm³
MELTING POINT	260–270°C
MOISTURE CONTENT	They are having moisture content less than 5%. There are different grades having various amount of water. It is hygroscopic material.
SOLUBILITY	They are slightly soluble in 5% w/v of sodium hydroxide solution, insoluble in water, acids and other organic solvents.
STABILITY AND STORAGE CONDITIONS	They are stable though they are hygroscopic material. They should be placed in closed container in cool, dry place.
RELATED SUBSTANCES	The related substances include the microcrystalline cellulose and carboxymethyl cellulose sodium, microcrystalline cellulose and guar gum, microcrystalline cellulose and carrageenan, powdered cellulose, silicified microcrystalline cellulose.
INCOMPATIBILITIES	They are incompatible with strong oxidizing agents.

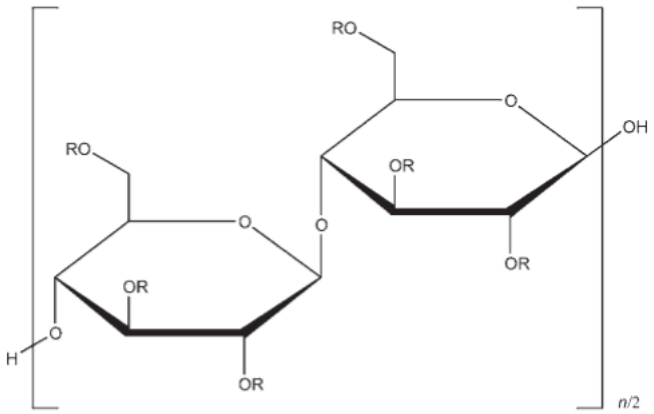
Table 6 Different Concentration of MCC

Use of microcrystalline cellulose	Concentration (%)
Adsorbent	20-90
Anti-adherent	5-20
Capsule binder/diluent	20-90
Tablet disintegrant	5-15
Tablet binder or diluent	20-90

Table 7 Commercially Available Grades of MCC

Grade	Particle size (µm)	Supplier
Avicel pH 101	50	FMC Biopolymer
Avicel pH 102	100	FMC Biopolymer
Avicel pH 103	50	FMC Biopolymer
Avicel pH 105	20	FMC Biopolymer
Avicel pH 112	100	FMC Biopolymer
Avicel pH 113	50	FMC Biopolymer
Avicel pH 200	180	FMC Biopolymer
Avicel pH 301	50	FMC Biopolymer
Avicel pH 302	100	FMC Biopolymer
Celex 101	75	International Specialty Products
Ceolus KG-802	50	Asahi Kasei Corporation
Emcocel 50M	50	JRS Pharm
Emcocel 90M	91	JRS Pharm
MCC Sanaq 101	50	Pharmatrans Sanaq Ag
MCC Sanaq 102	100	Pharmatrans Sanaq Ag
Vivapur 101	50	JRS Pharm
Vivapur 102	90	JRS Pharm
Vivapur 12	160	JRS Pharm

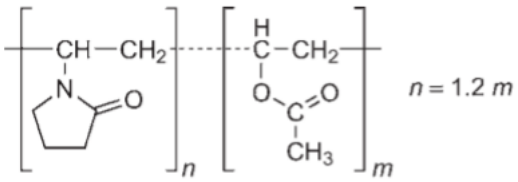
5.2.2. HYPROMELLOSE:

PROPERTY	DESCRIPTION
NONPROPRIETARY NAMES	BP: Hypromellose JP: Hypromellose PhEur: Hypromellose USP: Hypromellose
SYNONYMS	HPMC, Hypromellosum, Methylcellulose propylene glycol ether, Methocel, Methyl hydroxypropylcellulose, Pharmacoat, Tylopur
CHEMICAL NAME	Cellulose hyroxypropyl methyl ether
MOLECULAR WEIGHT	It is approximately 10,000-1500000
STRUCTURAL FORMULA	 where R is H, CH_3, or $CH_3CH(OH)CH_2$
FUNCTIONAL CATEGORY	Controlled release agent, dissolution enhancer, coating agent, emulsifying agent, bio adhesive material, dispersing agent, modified release agent, solubilizing agent, sustained release agent, thickening agent, tablet binder, stabilizing agent, emulsion stabilizer, viscosity increasing agent, granulation aid
APPLICATIONS IN PHARMACEUTICAL TECHNOLOGY	It is widely used in ophthalmic, topical, oral pharmaceutical formulations. In oral formulations, it is used as film forming agent, binder, as a matrix in extended release formulations.

	The concentration between 2-5% can be used as binder in wet or dry granulation. The high viscosity grades are used to provide a modified release formulation at level of 10-80% in tablets and capsules. Based on the viscosity grades, the concentration of 2-20% w/w are used as film forming agent to coat the tablets. The lower viscosity grades are generally used for aqueous film coating whereas high viscosity grades are used for the organic solvents. It is also used as suspending and thickening agent for topical formulations. The concentration between 0.45-1.0% can be used as thickening agent in eye drops and for nasal formulations the concentration is 0.1%. Additionally, it is used in the manufacturing of capsules, as wetting agent in hard contact lenses, as adhesive in plastic bandages and in cosmetics.
DESCRIPTION	It is tasteless, odourless, white or creamy white fibrous or granular powder.
DENSITY	0.341 g/cm³
MELTING POINT	190-200°C
MOISTURE CONTENT	It absorbs moisture from atmosphere. The amount of the water absorbed depends on the initial moisture content.
SOLUBILITY	It is soluble in cold water, insoluble in hot water, chloroform, ether. Certain grades of Hypromellose are soluble in acetone solutions, propan-2-ol, dichloromethane and other organic solvents.
STABILITY AND STORAGE CONDITIONS	It is stable material although it is hygroscopic in nature. It undergoes reversible sol-gel transformation upon heating and cooling. The aqueous solution should be preserved using antimicrobial agents and

	can be sterilized by autoclaving. It should be stored in well closed container and cool dry place.
RELATED SUBSTANCES	Hydroxyethyl cellulose, hydroxypropyl cellulose, ethyl cellulose, methyl cellulose
pH	5.0-8.0 in 2% aqueous solution

5.2.3. COPOVIDONE:

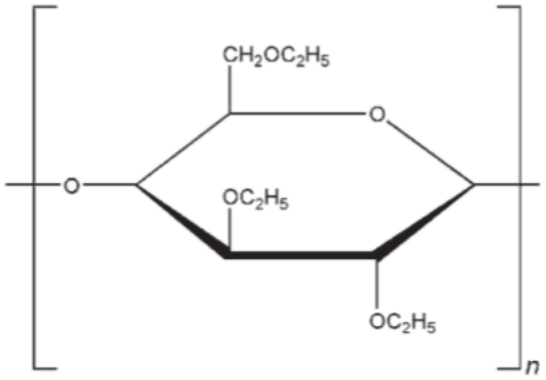
PROPERTY	DESCRIPTION
NONPROPRIETARY NAMES	BP: Copovidone PhEur: Copovidone USP: Copovidone
SYNONYMS	Polymer with 1-vinyl-2-pyrrolidinone, acetic acid vinyl ester, copolyvidone, copovidonum, plasdone S-630, kollidon VA64 polyvinylpyrrolidone-vinyl acetate copolymer
CHEMICAL NAME	Acetic acid ethenyl ester, polymer with 1-ethenyl-2-pyrrolidinone
MOLECULAR WEIGHT	The molecular weight of kollidon VA64 is identified to be 45000-70000. The average molecular weight of copovidone is expressed in K-value.
STRUCTURAL FORMULA	
FUNCTIONAL CATEGORY	Tablet binder, film forming agent, granulation aid
APPLICATIONS IN PHARMACEUTICAL TECHNOLOGY	It can be used as film former, tablet binder, and as matrix material in controlled release formulations. It can also be used as binder in direct compression and wet granulation. It is usually added to the coating solution to form a film. It has good adhesion hardness, elasticity and has good moisture barrier.
DESCRIPTION	It is white to yellowish white amorphous powder. It is usually spray dried having fine

	particle size. It is having slight odour and faint taste.
DENSITY	0.24-0.28 g/cm³
MELTING POINT	140°C
SOLUBILITY	More than 10% solubility is observed in 1,4-butanediol, glycerol, chloroform, dichloromethane, ethanol, methanol, polyethylene glycol 400, propylene glycol. Less than 1% solubility is observed in liquid paraffin, pentane, cyclohexane.
STABILITY AND STORAGE CONDITIONS	It is stable and should be stored in well closed containers in cool and dry place.
RELATED SUBSTANCES	Crospovidone, povidone
INCOMPATABILITIES	It is incompatible with most of the organic and inorganic ingredients. If they are exposed to high water levels then they form molecular adducts with some of the materials.
k-VALUE	25.4-34.2 for plasdone S-630

Table 8 Different Concentration of Copovidone

USES OF COPOVIDONE	
USE	CONCENTRATION (%)
Film-forming agent	0.5-5.0
Tablet binder for direct compression	2.0-5.0
Tablet binder for wet granulation	2.0-5.0

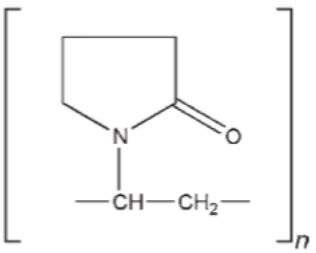
5.2.4. ETHYL CELLULOSE:

PROPERTY	DESCRIPTION
NONPROPRIETARY NAMES	BP: Ethyl cellulose PhEur: Ethyl cellulose USP-NF: Ethyl cellulose
SYNONYMS	Aqualon, Aqua coat ECD, Ethocel, Surelease, Ethylcellulosum
CHEMICAL NAME	Cellulose ethyl ether
MOLECULAR WEIGHT	It has wide range of molecular weights based on the value of n
STRUCTURAL FORMULA	
FUNCTIONAL CATEGORY	Flavouring agent, tablet filler, tablet binder, coating agent, viscosity increasing agent
APPLICATIONS IN PHARMACEUTICAL TECHNOLOGY	It is widely used in topical and oral formulations. For oral formulations, it can be used as hydrophobic coating agent in tablets and granules. The coatings of ethyl cellulose are used in modifying the release of the drug, to improve the stability of formulation, to mask an unpleasant taste and in order to avoid the oxidation. The modified release formulations can be produced using the matrix former.

	Ethyl cellulose when dissolved in solvent mixture or any organic solvent then it can be used to make water insoluble films. Higher viscosity grades of ethyl cellulose can form strong and durable film. The solubility of the ethyl cellulose films can be modified by the addition of any plasticizer or Hypromellose. The aqueous ethyl cellulose films can be made using either surelease or aqua coat ECD. The drug release can be controlled by diffusion through the film coating. The ethyl cellulose coated beds and granules have the ability to absorb pressure and protect the coating during compression. Mostly high viscosity grades are used in microencapsulation. In topical formulations, ethyl cellulose can be used as thickening agent in creams, lotions and gels. It has been used as stabilizer for the preparation of emulsions. They are also used in foods and cosmetics.
DESCRIPTION	It is free-flowing tasteless powder having white to light tan coloured shade.
DENSITY	0.4 g/cm³
GLASS TRANSITION TEMPERATURE	129-133°C
SOLUBILITY	It is practically insoluble in propylene glycol, glycerine and water. It contains less than 46.5 % of the ethoxy groups which makes it freely soluble in chloroform, tetrahydrofuran and in other aromatic hydrocarbons.

STABILITY AND STORAGE CONDITIONS	It is stable slightly hygroscopic material. It is resistant to both diluted and concentrated alkali. It is more sensitive to acidic materials than the cellulose esters. It undergoes oxidative degradation when exposed to sunlight at high temperatures. This can be avoided by using some of the anti-oxidants.
RELATED SUBSTANCES	Hydroxyethyl methyl cellulose, methyl cellulose, hydroxyethyl cellulose
INCOMPATABILITIES	It is incompatible with the microcrystalline wax and paraffin wax.

5.2.5. POVIDONE:

<table>
<tr><th>PROPERTY</th><th>DESCRIPTION</th></tr>
<tr><td>NONPROPRIETARY NAMES</td><td>BP: Povidone
PhEur: Povidone
USP-NF: Povidone
JP: Povidone</td></tr>
<tr><td>SYNONYMS</td><td>Kollidon, plasdone, poly[1-(2-oxo-1-pyrrolidinyl) ethylene], polyvinylpyrrolidone, polyvidone, povidonum</td></tr>
<tr><td>CHEMICAL NAME</td><td>1-Ethenyl-2-pyrrolidinone homopolymer</td></tr>
<tr><td>MOLECULAR WEIGHT</td><td>
<table>
<tr><th>K-VALUE</th><th>MOLECUULAR WEIGHT</th></tr>
<tr><td>12</td><td>2500</td></tr>
<tr><td>15</td><td>8000</td></tr>
<tr><td>17</td><td>10000</td></tr>
<tr><td>25</td><td>30000</td></tr>
<tr><td>30</td><td>50000</td></tr>
<tr><td>60</td><td>400000</td></tr>
<tr><td>90</td><td>1000000</td></tr>
<tr><td>120</td><td>3000000</td></tr>
</table>
</td></tr>
<tr><td>STRUCTURAL FORMULA</td><td> 
</td></tr>
<tr><td>FUNCTIONAL CATEGORY</td><td>Dissolution enhancer, suspending agent, disintegrant, tablet binder</td></tr>
</table>

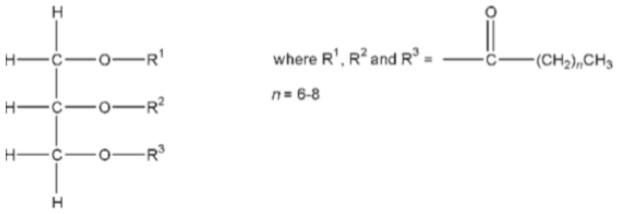
APPLICATIONS IN PHARMACEUTICAL TECHNOLOGY	It is primarily used in solid-oral dosage forms. In tablets, they are used as binders for the wet granulation process. They are also added in the powder blend as dry binder with the addition of alcohol, water or hydroalcoholic solutions. They are also used as coating agents when the active pharmaceutical ingredient is to be coated on the sugar bead or MCC spheres. They are also used as viscosity increasing agent, suspending agent and stabilizing agent.
DESCRIPTION	It is fine, white to creamy white coloured, odourless powder. The povidones with the k-value equal or lower than 30 are manufactured by spray drying and occur as spheres. The povidone k-90 and higher k-value are manufactured by drum drying and occur as plates.
DENSITY	0.29-0.39 g/cm³
MELTING POINT	Softens at 150°C
SOLUBILITY	It is freely soluble in ethanol, chloroform, methanol. It is practically insoluble in mineral oil, hydrocarbons and ether.
STABILITY AND STORAGE CONDITIONS	It darkens on heating at 150°C by reducing its aqueous solubility. It may be stored under normal conditions without any degradation

	and decomposition. As the powder is hygroscopic it should be stored under airtight containers.
RELATED SUBSTANCES	Crospovidone
INCOMPATABILITIES	It is incompatible with wide range of inorganic salts either natural or synthetic chemicals. It can form molecular adducts in the solution of tannin, phenobarbital, salicylic acid.

Table 9 Different Concentration of Povidone

USES OF POVIDONE	
USE	CONCENTRATION (%)
Carrier for drugs	10-25
Dispersing agent	Up to 5
Eye drops	2-10
Suspending agent	Up to 5
Tablet binder, diluent or as coating agent	0.5-5

5.2.6. MEDIUM CHAIN TRIGLYCERIDES:

PROPERTY	DESCRIPTION
NONPROPRIETARY NAMES	BP: Medium-chain triglycerides PhEur: Triglycerides, medium-chain USP-NF: Medium-chain triglycerides
SYNONYMS	Captex 300, captex 355, crodamol, MCT oil, Miglyol 810, Miglyol 812, Myritol, Nesatol, Waglinol 3/9280
CHEMICAL NAME	Medium-chain Triglycerides
STRUCTURAL FORMULA	
FUNCTIONAL CATEGORY	Solvent, emulsifying agent, therapeutic agent, suspending agent
APPLICATIONS IN PHARMACEUTICAL TECHNOLOGY	They are used in parenteral, oral and topical preparations. In oral formulations they are used for the preparation of microemulsions, oral emulsions, solutions and suspensions of drugs. They are also considered as absorption enhancers which are used in capsules as fillers or as lubricant and antiadhesion agent in tablets. The medium chain triglycerides are used as nutritional agent. They are included in the diet which are associated with the malabsorption of fat like cystic fibrosis. They are digested more than the long chain triglycerides. They are having better advantages in the pharmaceutical formulations which includes better

	spreading on the skin, good penetration properties, good compatibility, stable against oxidation.
DESCRIPTION	It is colourless to slightly yellowish oily liquid which is practically tasteless and odourless. They solidify at 0°C.The oil is free from products of cracking.
SOLUBILITY	They are soluble in all proportions at 20°C in benzene, chloroform, ethanol, methanol, ether, propan-2-ol. They are miscible with the long chain hydrocarbons and triglycerides which are practically insoluble in water.
STABILITY AND STORAGE CONDITIONS	They are stable over wide range of the storage temperatures which are experienced in temperate and tropical climates. They should be stored at temperature not exceeding 25°C and not exposed to the temperature above 40°C for longer period of time. When the temperature is low the samples of medium chain triglycerides become viscous or solidify. During the preparation of various microemulsions, self-emulsifying systems the microbial contamination should be avoided because they become active in the presence of moisture and cause hydrolysis. They can be sterilized by maintaining the temperature 170°C for 1 hour. They are protected from light and kept in well closed container as they remain stable for longer period of time.
RELATED SUBSTANCES	Suppository bases, hard fat, coconut oil, vegetable oil.

INCOMPATABILITIES	Care is taken that they do not come in contact with polystyrene containers or packaging as plastic becomes brittle rapidly. The low-density polystyrene should not be used in packaging as they may penetrate the plastic at high temperatures. The materials which are recommended for the medium chain triglycerides include the low-density polyethylene, glass, polypropylene and metal.

6. EXPERIMENTAL WORK:

EQUIPMENTS AND MATERIALS:

Table 10 Equipment Used in Research Work

NAME OF EQUIPMENT	COMPANY	MODEL
Fluid Bed Processor (GLATT)	ACG	GPCG 1.1
Fluid Bed Processor (GLATT)	Glatt pharma	GPCG 1.1
Automatic capsule filling machine	Dott-Bonapace	IN-CAP
Maula capsule filling machine	PAM	F30
Analytical sieve shaker	Retsch GmBH	AS200 digit
Binocular microscope	Labomed	Vision 2000
Tap density tester	Electrolab	ETD-2
Halogen moisture analyzer	Mettler Toledo	HG63-P
Balance(precision)	Sartorius	
Balance(precision)	Mettler Toledo	
Dissoultion test appartaus	Electrolab	TDT-08T
Vernier calliper	Electrolab	VDT-08L
HPLC system	Shimazdu	
Laboratory stirrer	Remi	RQ-124/A
Laboratory stirrer	IKA	RH basic KT/C

Table 11 Materials Used in Research Work

INGREDIENTS	SUPPLIER	CATEGORY
Drug A	Zhejiang apeloa kangyu pharma	Active ingredient
MCC spheres	Asahi KASAEI	Core seeds
HPMC 3cps	Dow	Binder
Copovidone	BASF	Binder
Talc USP	Imerys	Anti-tack
Isopropyl alcohol	-	Solvent
Ethyl cellulose	Colorcon	Coating polymer
Povidone	BASF	Pore former
Medium chain triglycerides	Cremer	Plasticizer
Magnesium stearate	Avantor	Lubricant

6.1. PRE-FORMULATION STUDIES:

The preformulaion study is the preliminary step for the development of any dosage form. This study helps in determining the important parameters which can affect the final formulation of the dosage form. They are categorized as the study of physical and chemical properties of drug alone and along with the other excipients.

This preformulation studies can help in identifying the effect of the drug or other excipients on the method of manufacture, formulation design, the pharmacokinetic properties of the product. Various tests are carried out in the preformulation studies which includes:

1. Organoleptic properties
2. Micromeritics properties
3. Drug-excipient compatibility studies

6.1.1. ORGANOLEPTIC PROPERTIES:

The appearance, odour and colour are identified and the results are evaluated.

6.1.2. MICROMERITICS PROPERTIES:

6.1.2.1.PARTICLE SIZE DISTRIBUTION: This process is conducted using the Malvern Master Sizer.

6.1.2.2.DERIVED PROPERTIES:

- BULK DENSITY: A known amount of the powder is taken in a cylinder and the volume is noted. It can be calculated using the formula:

  Bulk density= Mass (m)/ Initial volume of the powder (Vo)
  Here, the mass is in gm and the volume is in ml.

- TAPPED DENSITY: This test is carried out in the tester and according to the USP method the amount of the taps is set. The cylinder distance is kept 14±2 mm and there occurs 80 drops/min. After that the tap density can be calculated by:

  Tapped density= Mass (m)/ Final volume of the powder (Vo)
  Here, the mass is in gm and the volume is in ml.

- ANGLE OF REPOSE: the flow property of the powder can be calculated using the angle of repose. The sample is dispersed through the walls of the funnel maintaining a fixed position in such a manner that the height of 2 cm is kept above the hard surface. The sample is added till the lower tip of the funnel touches the upper part of the powder. It is calculated by:

  $\Theta = \tan^{-1}(h/r)$

  Where,
  Θ= It is the angle of repose
  h= The height of the pile
  r= Radius of the base of pile

  The interpretation of the angle of repose can be considered as:

Table 12 Angle of Repose

Angle of repose (ɵ)	Type of flow
<20	Excellent
20-30	Good
30-34	Passable
>40	Very poor

- CARR'S INDEX: The carr's index is considered to be one of the most imperative parameters in identifying the characteristics of powders and granules. The formula for it is:

  Carr's index = Tapped density – Bulk density/ Tapped density * 100

  The interpretation for the carr's index can be done as follows:

Table 13 Compressibility Index

% Compressibility	Flowability
5-15	Excellent
12-16	Good
18-21	Fair passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

- HAUSNER'S RATIO: It is also calculated to identify the flowability of the powder. It can be calculated using following formula:

  Hausner's ratio = Tapped density/ Bulk density

  The interpretation of the hausner's ratio can be done as follows:

Table 14 Hausner's Ratio

Hausner's ratio	Flowability
<1.25	Good flow
1.25-1.5	Passable
>1.5	Poor flow

6.1.3. SOLUBILITY ANALYSIS:

The solubility is identified by dissolving a particular amount of the substance in a definite volume using some conditions like temperature. It depends on various parameters which finally affects the bioavailability of the drug. The solvents which are generally used includes the water, 0.1 N HCL, acetate buffer pH 4.5, phosphate buffer pH 6.8.

- **PREPARATION OF 0.1 N HCL:**
  For this the concentrated HCL (85ml) was added in 1L of volumetric flask and then diluted to 1L using water.

- **PREPARATION OF ACETATE BUFFER pH 4.5:**
  Around 2.99g of sodium acetate and 1.66 ml of glacial acetic acid in water. Dilute with some water to make 1000ml and mix. Adjust the pH to 4.5 with glacial acetic acid or sodium hydroxide if necessary.

- **PREPARATION OF PHOSPHATE BUFFER pH 6.8:**
  Add around 20.209 g of sodium phosphate dibasic heptahydrate and around 3.394 g of sodium phosphate monobasic monohydrate to 800 ml of distilled water. The pH is adjusted using HCL or NaOH if required.

6.1.4. DRUG EXCIPEINT COMPATABILITY STUDIES:

The compatibility study of drug with various other excipients was studied by carrying out the physical observation.

PROCEDURE:

The drug was mixed with different excipients in different ratios. They were filled in vials of 10 ml and were covered using the rubber stoppers. Finally, they were sealed with the aluminium stoppers the vials were exposed at different temperature

including 121°C for moist heat sterilization, 105°C for dry heat sterilization and at 25°C/ 60%RH, 40°C/ 75% RH, 60°C. They were evaluated at initial stage and after 4 weeks.

Table 15 Ratio of Drug Excipient Compatibility

NO.	EXCIPIENTS	RATIO
1.	Drug A	1:0
2.	Microcrystalline Cellulose	1:1
3.	Hydroxypropyl methyl cellulose	1:1
4.	Copovidone	1:1
5.	Talc	1:0.5
6.	Ethyl cellulose	1:1
7.	Magnesium stearate	1:0.5
8.	Medium Chain Triglycerides	1:1
9.	Povidone k-90	1:0.5

6.1.5. FORCED DEGRADATION OF API:

The forced degradation is a process in which additional stress is provided to the natural degradation process. These studies are carried out to identify the changes that occur due to the additional stress. They are carried out before the final formulation and some of the external stresses are given to it.

The long-term storage tests are also carried out due to the stringent FDA regulations. The tests are very expensive as many of the factors are also involved in it which includes:

- pH
- Light
- Temperature
- Oxidation

6.1.6. PHOTOSTABILITY TESTING:

The intrinsic photostability testing is done in order to evaluate whether the light exposure does not result in unacceptable change of the product. The related substances are identified by keeping the samples in photo-controlled and photo-exposed conditions. After the photostability is done the samples are analysed for assay and impurities.

6.2. REFERENCE PRODUCT CHARACTERIZATION:

The prepared formulation is compared to that of the reference product in order to observe that the prepared product complies all the parameters according to the actual one. There are many factors which are to be considered while preparing the formulation and there are some excipients or process variables which are to be kept same.

6.2.1. PHYSICAL OBSERVATION OF CAPSULE:

The capsules and the pellets were observed physically by selecting randomly some of the capsules from the packed container.

6.2.2. WEIGHT:

The weight of filled capsule, empty capsule, the total no of pellets in capsule were identified. Even the length and the thickness of the capsule was measured.

6.2.3. ASSAY:

The assay is an analytical procedure which involves the quantitative and qualitative measurement of the presence of the active material. The active material can be a drug or biochemical substance.

6.2.4. IN VITRO DISSOLUTION METHOD:

The dissolution study was carried out in USP apparatus II using degassed purified water as medium at speed of 50 RPM. The capsule was loaded in the dissolution apparatus in paddle using cage sinker. The temperature was maintained at 37±0.5°C and the aliquots were collected at different time points like 2,4,6,8,10 and 12 hours by replacing the same dissolution media at each time point. The collected samples were analysed for the amount of the drug release from each time point.

Table 16 In-Vitro Dissolution

Name of sample	USP Apparatus	Speed (RPM)	Medium	Volume/ temperature	Sample time points
Drug A	II (Paddle)	50	Degassed purified water	900 ml for the 170 mg strength at 37±0.5°C	2,4,6,8,10,12 hours

6.3. OPTIMIZATION TRIALS:

(A). COMPOSITION TABLE FOR EXTENDED RELEASE PELLETS AS PER LITERATURE:

Table 17 Composition Table

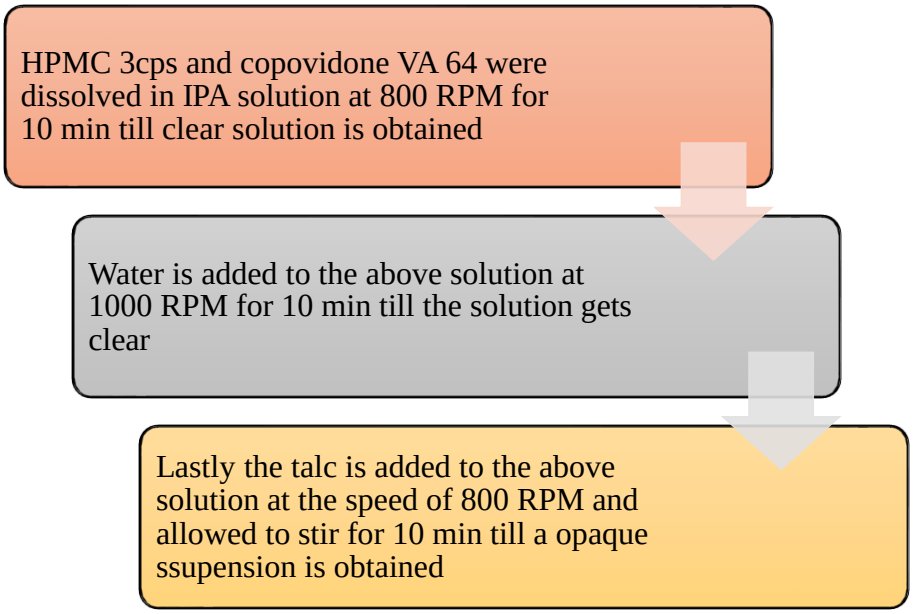
COMPOSITION	COMBINED %W/W OF CAPSULE	FUNCTION
Drug loading		
Drug A	40-50%	Active moiety
Microcrystalline cellulose spheres (Celephere®)	10-15%	Core seeds
Hydroxy propyl methyl cellulose (HPMC-3cps)	10-15%	Binder
Copovidone (Kollidon VA64)	1-5%	Binder
Talc	1-5%	Anti-tack
Isopropyl Alcohol	q.s.	Solvent
Purified water	q.s.	Solvent
Seal coating		
Hydroxy propyl methyl cellulose (HPMC-3cps)	5-10%	Coating polymer
Talc	0.5%	Anti-tack
Isopropyl Alcohol	q.s.	Solvent
Purified water	q.s.	Solvent
Polymer coating		
Ethyl cellulose	10-20%	Coating polymer
Povidone	1-5%	Pore former
Medium chain triglycerides	1-5%	Plasticizer
Isopropyl Alcohol	q.s.	Solvent
Purified water	q.s.	Solvent
Magnesium stearate	0-1%	Lubricant

(B). GENERAL PROCEDURE FOR PELLETS:

I. DISPENSING:

The materials are which are necessary for the development of the formulation are dispensed from the store where all the materials are kept. The materials were dispensed by considering 10% overages in order to avoid the further loss and to avoid the effect on the % yield.

II. DRUG SOLUTION PREPARATION:



The water:IPA ratio was kept 80:20

SOLUTION/SUSPENSION DETAILS:

Table 18 Characteristics of Drug Loading Solution

Characteristics	Description
% Of solid material	25.00% w/w
Appearance	White to off white coloured suspension

III. DRUG LOADING

Table 19 Process Parameters of Drug Loading

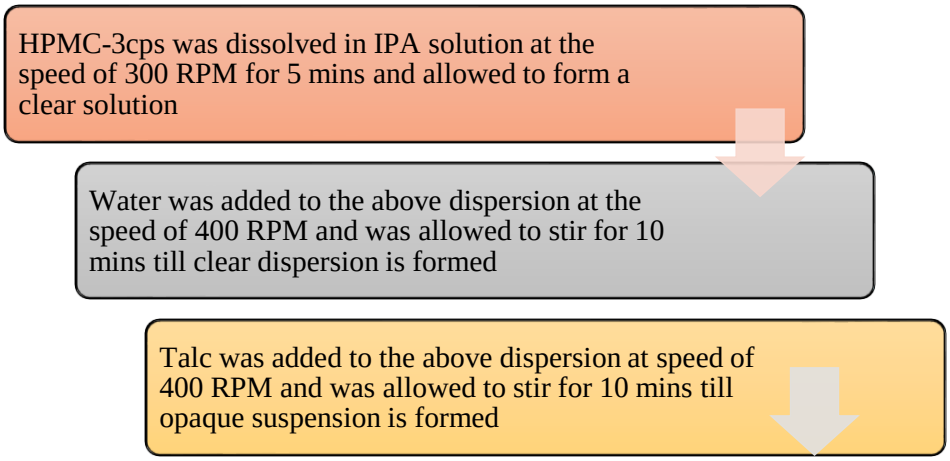
Process parameters	Description
Type of spray	Bottom spray
Cylinder height	10-20 mm
Spray gun nozzle diameter	0.8 mm
Type of plate	Plate B

Table 20 Processing Variables of Drug Loading

Inlet temperature	45°C
Product temperature	39°C
Exhaust temperature	39°C
Spray rate	5 gm/min
Air flow velocity	69 m/s
Drive speed	65
Inlet air RH	10%
Atomization	1.0 bar

After the solution of drug loading is sprayed on the pellets then drying is carried out for 10 mins. After the completion of process some of the drug loaded pellets are reserved for stability purpose.

IV. SEAL COATING SOLUTION PREPARATION:



The water:IPA ratio was kept 80:20

SOLUTION/ SUSPENSION DETAILS:

Table 21 Characteristics of Seal Coating

Characteristics	Description
% of solid material	10%w/w
Appearance	White to off white coloured suspension

V. SEAL COATING:

Table 22 Process Parameters of Seal Coating

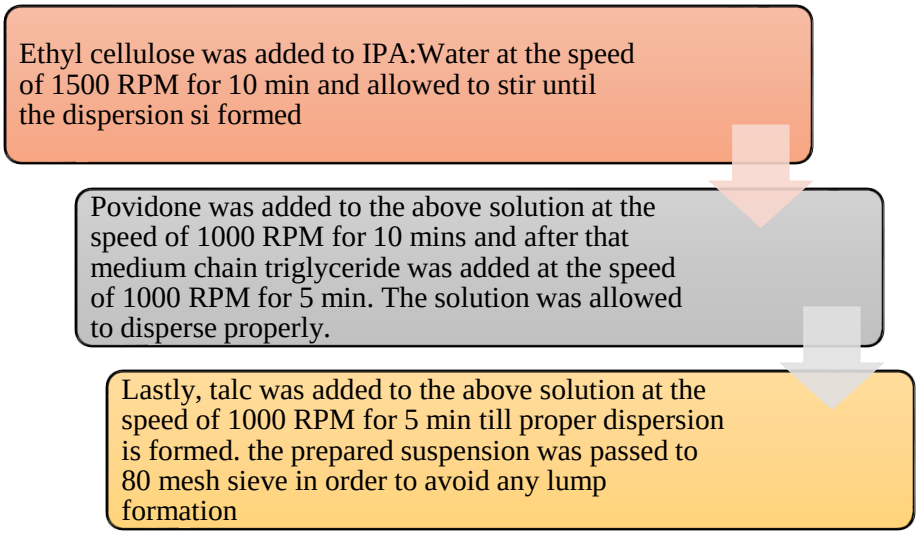
Process parameters	Description
Type of spray	Bottom spray
Cylinder height	10-20 mm
Spray gun nozzle diameter	0.8 mm
Type of plate	Plate B

Table 23 Processing Variables of Seal Coating

Inlet temperature	46°C
Product temperature	38°C
Exhaust temperature	38°C
Spray rate	3 gm/min
Air flow velocity	105 m/s
Drive speed	75
Inlet air RH	11%
Atomization	1.0 bar

After the seal coating is done there is drying time provided for 5 mins. After the completion of process, the sample was removed for stability purpose. The coating efficiency and other parameters are also calculated at this stage.

VI. POLYMER COATING SOLUTION PREPARATION:



The water:IPA ratio was kept 10:90

SOLUTION/ SUSPENSION DETAILS:

Table 24 Characteristics of Polymer Coating

Characteristics	Description
% of solid material	10%w/w
Appearance	Translucent clear dispersion

VII. POLYMER COATING:

The polymer coating was done using such properties:

Table 25 Process Parameters of Polymer Coating

Process parameters	Description
Type of spray	Bottom spray
Cylinder height	15 mm
Spray gun nozzle diameter	1.2 mm
Type of plate	Plate B/plate C (depending on the type of load)

Table 26 Processing Variables of Polymer Coating

Inlet temperature	40°C
Product temperature	35°C
Exhaust temperature	35°C
Spray rate	5 gm/min
Air flow velocity	118 m/s
Drive speed	87
Inlet air RH	23%
Atomization	1.2 bar

After the polymer coating is done there is curing time provided or the proper hardening of the pellets occur by completely removing the moisture from it. There are some conditions which are followed during curing process.

Table 27 Curing Variables

Inlet temperature	38°C
Product temperature	35°C
Exhaust temperature	35°C
Air flow velocity	35 m/s
Drive speed	38
Inlet air RH	23%

VIII. BLENDING WITH MAGNESIUM STEARTE:

After the coating process gets completed there is blending done by magnesium stearate in order to avoid the static charge between the pellets.

Table 28 Blending Parameters

Inlet temperature	38°C
Product temperature	35°C
Exhaust temperature	35°C
Air flow velocity	35 m/s
Drive speed	38
Inlet air RH	22%

IX. CAPSULE FILLING:

The capsule filling can be done using automatic capsule filling machine or either manually.

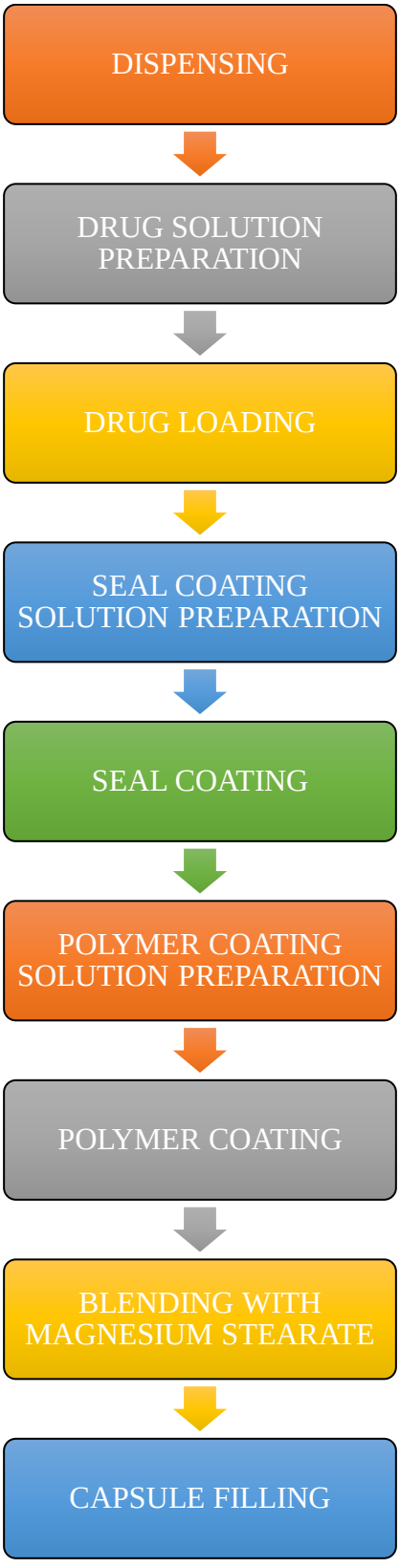
Table 29 Parameters of Capsule Filling

Size of capsule	00
Cap colour	Light blue opaque
Body colour	Light blue opaque
Average weight of cap	37 mg
Average weight of body	59 mg
Average weight of capsule	96 mg

X. PACKAGING:

The prepared capsules were packed in HDPE container, Alu-Alu blister pack.

FLOW CHART OF THE BRIEF MANUFACTURING PROCESS OF THE FORMULATION:



(C). QUALITY BASED DESIGN PARAMETERS:

- **QUALITY TARGET PRODUCT PROFILE (QTPP) AND CRITICAL QUALITY ATTRIBUTES (CQAs):**

  Some of the parameters like dissolution, content uniformity, assay, water content and degradation products are considered as critical parameters in this formulation.

- **QUALITY TARGET PRODUCT PROFILE (QTPP) FOR PACKAGING:**

  The reference product is filled in HDPE container while the prepared formulation will be kept for both HDPE container as well as blister pack.

- **RISK ASSESSMENT ATTRIBUTES OF DRUG SUBSTANCE:**

  Based on initial risk assessment, the particle size is considered as critical quality attributes.

- **RISK ASSESSMENT OF EXCIPIENTS:**

  The critical excipients identified are substrate (MCC sphere), copovidone, povidone, ethyl cellulose and medium chain triglycerides. The size of the substrate is also considered to be a critical parameter.

- **CRITICAL PROCESS PARAMETERS:**

  The process variables like spray rate, drive speed, atomization pressure, air flow velocity of the drug loading and polymer coating are considered to be critical.

6.3.1. FORMULATION TRIALS FROM TRIAL 1 TO TRAIL 7:

The strength of the Drug A is 170 mg per capsule. The formulation trials are taken on the basis of literature available. The important excipients which are studied includes the concentration of ethyl cellulose, the quantity of pore former, quantity of plasticizer and the concentration of HPMC.

The main parameter which is important in the formulation is the dissolution. The dissolution is considered as critical aspect which needs to be achieved in the prepared formulation.

TRIAL 1: To take a trial batch by using the excipients disclosed in literature and achieve the dissolution as per the reference listed product.

TRIAL 2: To take a trial batch by increasing the concentration of ethyl cellulose and addition of talc in polymer coating.

TRIAL 3: To take a trial batch by decreasing the quantity of pore former (Povidone) by 3% in the polymer coating.

TRIAL 4: To take a trial batch by increasing the quantity of pore former (Povidone) by 3% in the polymer coating.

TRIAL 5: To take a trial batch by increasing the quantity of plasticizer (Medium Chain Triglycerides) by 5% in the polymer coating.

TRIAL 6: To take a trail batch by decreasing the quantity of plasticizer (Medium Chain Triglycerides) by 5% in the polymer coating.

TRIAL 7: To take a trial batch by increasing the quantity of HPMC and Talc in seal coating.

FORMULATION TRIALS							
INGREDIENTS	TRIAL 1	TRIAL 2	TRIAL 3	TRIAL 4	TRIAL 5	TRIAL 6	TRIAL 7
DRUG LOADING	Quantity(mg)	Quantity(mg)	Quantity(mg)	Quantity(mg)	Quantity(mg)	Quantity(mg)	Quantity(mg)
Drug A	170	170	170	170	170	170	170
MCC pellets	48.6	48.6	48.6	48.6	48.6	48.6	48.6
Hypromellose (3 cps)	20	20	20	20	20	20	20
Co-povidone (Kollidon VA 64)	11.4	11.4	11.4	11.4	11.4	11.4	11.4
Talc	6	6	6	6	6	6	6
IPA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Weight of drug loaded pellets	**256**	**256**	**256**	**256**	**256**	**256**	**256**
SEAL COATING							
Hypromellose (3cps)	11	11	11	11	11	11	31.6
Talc	5	5	5	5	5	5	14
IPA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Weight of seal coated pellets	**272**	**272**	**272**	**272**	**272**	**272**	**301.6**

POLYMER COATING	TRIAL 1	TRIAL 2	TRIAL 3	TRIAL 4	TRIAL 5	TRIAL 6	TRIAL 7
Ethyl cellulose	62.1	82.1	82.1	82.1	62.1	62.1	62.1
Povidone k-90	8.4	8.4	5.75	11.06	8.4	8.4	8.4
Medium chain triglycerides	7.5	7.5	7.5	7.5	10.7	4	7.5
Talc	-	20	22.25	16.94	16.4	23.1	-
IPA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Magnesium stearate	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Weight of polymer coated pellets	**350.4**	**390.4**	**390**	**390**	**370**	**370**	**380**

Table 30 Composition Table for Trial 1 to Trial 7

6.3.2. SURELEASE®:

This is a polymer which is used for taste masking and modified release formulations. They help in developing many of the extended release formulations. They are having the presence of ammonia in it. There are some specific characteristics of surelease which includes:

(i) They are aqueous dispersions.
(ii) They are environment friendly and are easy to use.
(iii) They are complete kind of formulation which can be directly used.
(iv) They are accepted n many of the countries.
(v) They are reproducible and hence provide proper drug release in each formulation.

They are preferred in coating of pellets, granules and many of the drug particles. Surelease is considered to be a starting formulation for many of the actives. It is prepared by blending ethyl cellulose with plasticizer which is then melted and extruded. It is then blended in ammoniated water under high shear mixing. Lastly, the water addition is done to the final solid contents.

There are some trials which are taken by changing the polymer from ethyl cellulose to surelease and the dissolution studies are studied for the same.

TRIAL 8: To take a trial batch by changing the polymer from ethyl cellulose to Surelease in polymer coating.

TRIAL 9: To take a trail batch by coating 50 % additional surelease in the polymer coating.

OPTIMIZATION WITH SURELEASE:

Table 31 Composition Table of Trial 8 and Trial 9

COMPOSITION TABLE		
INGREDIENTS	TRIAL 8	TRIAL 9
DRUG LOADING	QUANTITY (mg)	QUANTITY (mg)
Drug A	170	170
MCC pellets	48.6	48.6
Hypromellose (3 cps)	20	20
Co-povidone (Kollidon VA 64)	11.4	11.4
Talc	6	6
IPA	q.s.	q.s.
Water	q.s.	q.s.
Weight of drug loaded pellets	**256**	**256**
SEAL COATING		
Hypromellose (3cps)	31.6	31.6
Talc	14	14
IPA	q.s.	q.s.
Water	q.s.	q.s.
Weight of seal coated pellets	**301.6**	**301.6**
POLYMER COATING		
Ethyl cellulose	69.6	104.4
Povidone k-90	8.4	8.4
Medium chain triglycerides	-	-
IPA	-	-
Water	q.s.	q.s.
Magnesium stearate	0.4	0.4
Weight of polymer coated pellets	**380**	**414.8**

6.3.3. OPTIMIZATION OF CONCENTRATION OF ETHYL CELLULOSE:

Table 32 Composition Table for Trial 10 to Trial 12

INGREDIENTS	TRIAL 10	TRIAL 11	TRIAL 12
DRUG LOADING	QUANTITY (mg)	QUANTITY (mg)	QUANTITY (mg)
Drug A	170	170	170
MCC pellets	48.6	48.6	48.6
Hypromellose (3 cps)	20	26	26
Co-povidone (Kollidon VA 64)	11.4	11.4	11.4
Talc	6	6	6
IPA	q.s.	q.s.	q.s.
Water	q.s.	q.s.	q.s.
Weight of drug loaded pellets	**256**	**262**	**262**
SEAL COATING			
Hypromellose (3cps)	31.6	11	11
Talc	14	5	5
IPA	q.s.	q.s.	q.s.
Water	q.s.	q.s.	q.s.
Weight of seal coated pellets	**301.6**	**278**	**278**
POLYMER COATING			
Ethyl cellulose	72	82	90
Povidone k-90	8.4	11	8
Medium chain triglycerides	7.5	10	6.5
Talc	10.5	5	5
IPA	q.s.	q.s.	q.s.
Water	q.s.	q.s.	q.s.
Magnesium stearate	0.4	0.4	0.4
Weight of polymer coated pellets	**400.4**	**386.4**	**387.9**

After finalizing the concentration of plasticizer and pore former, the concentration of ethyl cellulose was optimized. There are two types of extended release coating excipients including pH dependent and non pH dependent. Ethyl cellulose is considered to be a non pH dependent polymer. The samples are collected after the pellets are coated as 62mg/capsule, 72mg/capsule, 82mg/capsule, 92mg/capsule.

All the samples are analysed after coating and the dissolution is checked for each of the sample. The aim is to coat the pellets with ethyl cellulose of the same concentration as that of the reference product.

TRIAL 10: To take a trail batch by changing the concentration of ethyl cellulose from 62 mg/ capsule to 72 mg/capsule.

TRIAL 11: To take a trail batch by increasing the concentration of HPMC in drug loading and changing the concentration of ethyl cellulose to 82 mg/capsule along with increasing the concentration of pore former and plasticizer.

TRIAL 12: To take a trail batch by increasing the concentration of ethyl cellulose to 90 mg/capsule and slightly decreasing the concentration of pore former and plasticizer.

6.3.4. OPTIMIZED TRIAL AND ITS REPRODUCIBILITY:

Table 33 Composition Table of Trial 13 and Trail 14

INGREDIENTS	TRIAL 13	TRIAL 14
DRUG LOADING	QUANTITY (mg)	QUANTITY (mg)
Drug A	170	170
MCC pellets	48.6	48.6
Hypromellose (3 cps)	23	23
Co-povidone (Kollidon VA 64)	11.4	11.4
Talc	9	9
IPA	q.s.	q.s.
Water	q.s.	q.s.
Weight of drug loaded pellets	**262**	**262**
SEAL COATING		
Hypromellose (3cps)	11	11
Talc	5	5
IPA	q.s.	q.s.
Water	q.s.	q.s.
Weight of seal coated pellets	**278**	**278**
POLYMER COATING		
Ethyl cellulose	85	85
Povidone k-90	8.4	8.4
Medium chain triglycerides	7.5	7.5
Talc	11	11
IPA	q.s.	q.s.
Water	q.s.	q.s.
Magnesium stearate	0.4	0.4
Weight of polymer coated pellets	**390.3**	**390.3**

After the optimization of ethyl cellulose, it was found that the dissolution between 82 mg/capsule and 92 mg/capsule was quite near to the reference product and based on it the further batch of ethyl cellulose was taken at around 85mg/capsule. The dissolution and other parameters like assay, water content, impurities and particle size distribution were verified for the same. Based on the above data available, the reproducibility batch was further taken.

TRIAL 13: To take a trail batch by changing the concentration of ethyl cellulose to 85 mg/capsule and keeping the quantity of pore former and plasticizer as per literature.

TRIAL 14: To take a reproducibility batch as per the previous batch.

6.3.5. PACKAGING AND STABILITY:

The extended release capsules are packed in 60 count opaque HDPE bottles with induction, sealed and in aluminium blister strips.

The stability studies are carried out to observe that if any of the environmental factors like humidity, temperature and light. The effect of various factors like the dosage form, the composition, the excipients, the nature of the container closure system, packaging environment is measured. The degradation of the product is tested. The stability is checked at 25°C/60% RH, 30°/75% RH and at 40°C/75% RH. The long term, intermediate and accelerated stability studies are carried out for a product.

7. RESULT AND DISCUSSION:

7.1. PREFORMULATION STUDIES OF DRUG:

7.1.1. ORGANOLEPTIC PRPERTIES OF DRUG:

Table 34 Characteristics of Drug

CHARACTERISTICS	DRUG
Appearance	Crystalline powder
Colour	White
Odour	Characteristic
Taste	Metallic

7.1.2. MICROMERITIC PROPERTIES:

7.1.2.1. PARTICLE SIZE DISTRIBUTION:

This parameter is done using microscope and the size of the API was found to be 250.5µm to 1866.8µm.

7.1.2.2. DERIVED PROPERTIES:

Table 35 Micromeritics of Drug

PROPERTIES	RESULT
Bulk density	0.66 gm/cm³
Tapped density	0.77 gm/cm³
Angle of repose	21
Carr's index	18.75%
Hausner's ratio	1.23

7.1.3. SOLUBILITY ANALYSIS:

Table 36 Solubility Analysis of Drug

MEDIA	SATURATION SOLUBILITY (mg/ml)
0.1 N HCL	382.8
Acetate buffer pH 4.5	408.5
Phosphate buffer pH 6.8	403.9
Water	413.0

The supreme solubility of the drug can be observed in the distilled water and hence the solvent water is selected to be the best medium for dissolution studies.

7.1.4. DRUG EXCIPIENT COMPATABILITY STUDY:

Sr no.	Excipients /API	Ratio	Qty (g)	Parameters	CONDITIONS INTERVAL						
					Initial	121° c- 30 min MHS	105°c-6hrs(open) DHS	25°c/60 % rh-4w (open)	25°c/60 %rh-4w(closed)	40°c/75 % rh-4w (open)	40°c/75 % rh-4w (closed)	60°c-4w (open)
1.	Drug X	NA	1.70	Appearance	White to off white crystalline powder	No change	No change	No change	No change	No change	No change	No change
				SMI		BDL	BDL	BDL	BDL	BDL	BDL	BDL
				Total IMP		BDL	BDL	BDL	BDL	BDL	BDL	BDL
2.	Microcrystalline cellulose	1:1	3.40	Appearance	White to off white powder	No change	No change	No change	No change	No change	No change	No change
				SMI		BDL	BDL	BDL	BDL	BDL	BDL	BDL
				Total IMP		BDL	BDL	BDL	BDL	BDL	BDL	BDL

3.	HPMC 3cps	1:1	3.40	Appearance	White to off white powder	No change	No change	No change	No change	No change	No change	No change
				SMI		BDL	BDL	BDL	BDL	BDL	BDL	BDL
				Total IMP		BDL	BDL	BDL	BDL	BDL	BDL	BDL
4.	Copovidone	1:1	3.40	Appearance	White to off white powder	No change	No change	No change	No change	No change	No change	No change
				SMI		BDL	BDL	BDL	BDL	BDL	BDL	BDL
				Total IMP		BDL	BDL	BDL	BDL	BDL	BDL	BDL
5.	Talc	1:0.5	2.55	Appearance	White to off white crystalline powder	No change	No change	No change	No change	No change	No change	No change
				SMI		BDL	BDL	BDL	BDL	BDL	BDL	BDL
				Total IMP		BDL	BDL	BDL	BDL	BDL	BDL	BDL
6.	Ethyl cellulose	1:1	3.40	Appearance	White to off white powder	No change	No change	No change	No change	No change	No change	No change
				SMI								
				Total IMP		BDL	BDL	BDL	BDL	BDL	BDL	BDL
						BDL	BDL	BDL	BDL	BDL	BDL	BDL

7.	Magnesium stearate	1:0.5	2.55	Appearance	White to off white powder	No change	No change	No change	No change	No change	No change	No change
				SMI		BDL	BDL	BDL	BDL	BDL	BDL	BDL
				Total IMP		BDL	BDL	BDL	BDL	BDL	BDL	BDL
8.	Medium chain triglycerides (miglyol 812)	1:1	3.40	Appearance	White to off white powder	No change	No change	No change	No change	No change	No change	No change
				SMI		BDL	BDL	BDL	BDL	BDL	BDL	BDL
				Total IMP		BDL	BDL	BDL	BDL	BDL	BDL	BDL
9.	Povidone k90	1:0.5	2.55	Appearance	White to off white powder	No change	No change	No change	No change	No change	No change	No change
				SMI		BDL	BDL	BDL	BDL	BDL	BDL	BDL
				Total IMP		BDL	BDL	BDL	BDL	BDL	BDL	BDL

Table 37 Drug Excipient Compatibility

7.1.5. FORCED DEGRADATION OF API:

Table 38 Forced Degradation Study

Sequence No. of impurities		**1**	**2**	**3**	**4**
Unstressed sample	Retention time (min)	15.64	15.79	16.54	16.86
	Assay (%)	0.05	0.07	0.12	0.06
Sample stressed under acid condition	Retention time (min)	15.64	15.79	16.54	16.86
	Assay (%)	0.05	0.07	0.11	0.07
Sample stressed under basic condition	Retention time (min)	15.63	15.79	16.54	16.86
	Assay (%)	0.06	0.07	0.11	0.07
Sample stressed under oxidation condition	Retention time (min)	15.63	15.79	16.54	16.86
	Assay (%)	0.06	0.09	0.11	0.07
Sample stressed under light	Retention time (min)	15.69	15.79	16.54	16.86
	Assay (%)	0.22	0.11	0.10	0.49
Sample stressed under high temperature	Retention time (min)	15.61	-	16.54	16.86
	Assay (%)	0.07	-	0.11	0.07

After the forced degradation study under the above-mentioned conditions, there is no degradation impurity having assay more than 0.05%. hence the drug was found to be stable under various stress condition.

7.1.6. PHOTOSTABILITY OF API:

Table 39 Photostability study

CONDITION	RELATED SUBSTANCE (%)		
	ASSAY	SMI	TOTAL
Photo-controlled sample	100.1	BDL (<0.1%)	BDL (<0.1%)
Photo-exposed sample	100.4	BDL (<0.1%)	BDL (<0.1%)

SMI- Single max impurity

BDL- Below detection limit

After carrying out the photostability testing, it was identified that the Drug is not photosensitive as the impurities are less than 0.1 %.

7.2. REFERENCE PRODUCT CHARACTERIZATION:

7.2.1. PHYSICAL OBSERVATION:

APPEARANCE	The 137 mg capsule is light blue opaque size #0 capsule.

7.2.2. WEIGHT:

Table 40 Description of Innovator Capsule

PROPERTY	DESCRIPTION
Weight of filled capsule	497 mg
Weight of unfilled (empty) capsule	98 mg
Total no. of pellets	956 pellets (checked manually from 1 capsule)
Weight of pellets	404 mg
Weight of 10 pellets	2 mg
Weight of 20 pellets	10 mg
Weight of 30 pellets	12, 14, 17 mg
Weight of 50 pellets	23, 24 mg
Weight of 100 pellets	45 mg
Length of capsule	21.3 mm
Thickness of capsule	7.3 mm

7.2.3. ASSAY:

The Assay was done in HPLC system and the assay value of the reference product was found to be 96.0%.

7.2.4. IN VITRO DISSOLUTION:

Table 41 In-Vitro dissolution of Innovator

Apparatus: USP II (Paddle); Media: Degassed purified water; Speed: 50 RPM	
Time (hr)	**% Drug Dissolved**
2	2
4	10
6	33
8	62
10	81
12	93

7.3. FORMULATION TRIALS:

7.3.1. RESULTS OF TRIAL 1 TO TRIAL 7:

Table 42 Dissolution Release of Trial 1 to Trial 7

DISSOLUTION RELEASE								
TIME	**INNOVATOR**	**TRIAL 1**	**TRIAL 2**	**TRIAL 3**	**TRIAL 4**	**TRIAL 5**	**TRIAL 6**	**TRIAL 7**
0	0	0	0	0	0	0	0	0
2	2	7	2	6	10	3	7	8
4	10	35	12	27	37	14	25	26
6	33	56	24	53	65	33	44	46
8	62	75	47	73	79	54	67	64
10	81	87	57	85	91	70	78	76
12	93	102	74	93	98	80	94	84

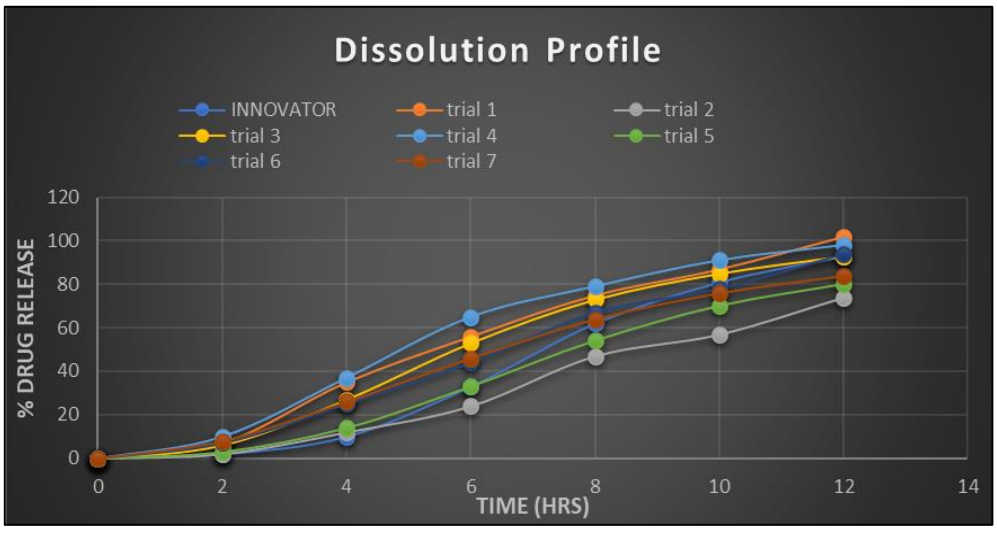


Figure 15 Drug Release of Trial 1 to 7 vs Innovator product

Table 43 Characteristics of Trial 1 to Trial 7

CHARACTERISTICS	DESCRIPTION							
	Innovator	**Trial 1**	**Trial 2**	**Trial 3**	**Trial 4**	**Trial 5**	**Trial 6**	**Trial 7**
Assay	96	97.4	98.3	97.8	97.6	98.2	98.4	97.5
Water content	2.1	2.4	2.4	2.3	2.2	2.1	2.2	2.1
% yield	99.87	99.55	98.78	98.67	99.56	97.43	97.86	99.85
LOD	1.54	1.65	1.32	1.77	1.68	1.65	1.79	1.85
Bulk Density	0.66	0.69	0.65	0.62	0.65	0.67	0.66	0.61

INFERENCE:

TRIAL 1: The batch was taken according to the literature available and the results showed that the dissolution was faster compared to the innovator. High static charge was also observed during the polymer coating as no lubricant was added in the batch. So, the further batch is taken with use of talc and by accelerating the concentration of ethyl cellulose.

TRIAL 2: The batch was taken by increasing the concentration of ethyl cellulose by 5% and the dissolution showed better release compared to the earlier batch but still could not match the reference product dissolution. The talc was also added during this batch and hence less static charge was observed during the batch.

TRIAL 3: The concentration of pore former has a great impact in the release of the drug. By decreasing the concentration of the pore former by 3 % the drug release was fast and there was no change in the dissolution. No change was observed by decreasing the rate of drug release so it was concluded that by decreasing the concentration of pore former the drug release is not delayed.

TRIAL 4: The batch was also taken by increasing the concentration of pore former by 3% but the drug release was quite fast as the pores were formed easily and the drug release became fast. So, by rising the concentration of the pore former, the drug release was quite high and could not meet the release as shown by the reference product.

TRIAL 5: The quantity of plasticizer was increased in this batch which was responsible for forming a good film having the proper strength which helped in decreasing the drug release. Initially the drug release was quite same to the reference product but later on after 8 hrs the drug release decreased highly which concluded that by changing the increasing the concentration of plasticizer by 5 % there is not much improvement in the dissolution profile.

TRIAL 6: In this batch, the quantity of plasticizer was decreased and by decreasing the plasticizer the film forming strength also reduced due to which the release of the drug increased significantly. The dissolution profile also showed higher release of the drug and was detected that by changing the concentration of plasticizer by 5% the sustained release effect of the drug could not be seen.

TRIAL 7: In this batch the quantity of HPMC and talc were increased in the seal coating. The need of increasing the concentration was to have a quite extended effect as it can form a proper thick coating around the drug loading layer by delaying the release of the drug. But according to the results by increasing the concentration by 5% the seal coating layer showed no result on the drug release. Hence, the conclusion was that by making any changes in the seal coating layer, there won't be any modification in the drug release profile so the concentration of HPMC and talc were kept the same as in all the other batches.

7.3.2. RESULTS OF TRIAL 8 AND TRIAL 9:

Table 44 Dissolution Release of Trial 8 and Trial 9

DISSOLUTION RELEASE			
TIME	**INNOVATOR**	**TRIAL 8**	**TRIAL 9**
0	0	0	0
2	2	90	60
4	10	101	90
6	33	103	102
8	62	105	104
10	81	106	106
12	93	105	109

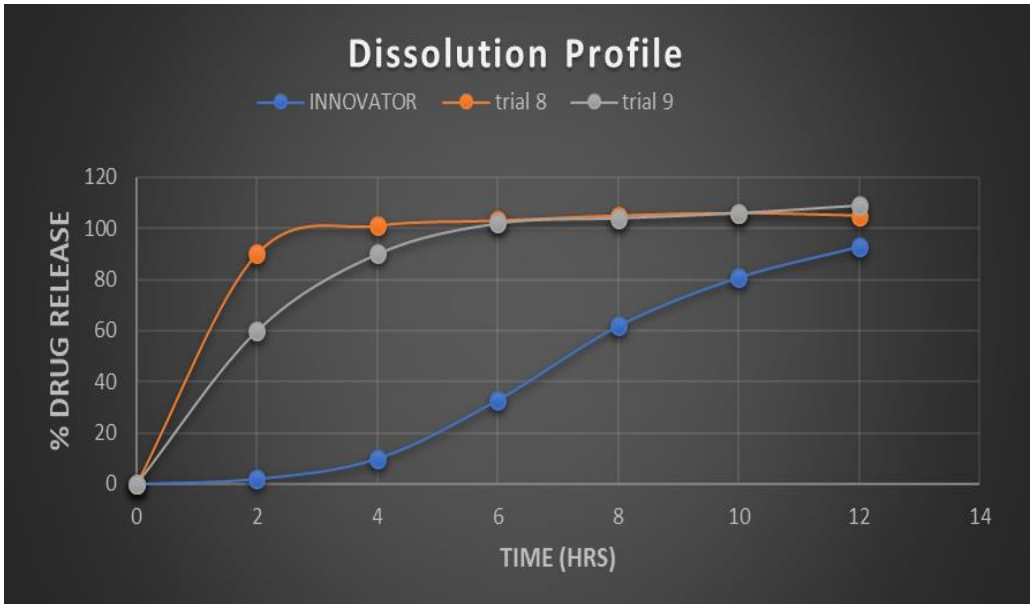


Figure 16 Drug Release of Trial 8 and 9 vs Innovator Product

Table 45 Characteristics of Trial 8 and Trial 9

CHARACTERISTICS	DESCRIPTION		
	Innovator	**Trial 8**	**Trial 9**
Assay	96	94	96.2
Water content	2.1	2.6	2.2
% yield	99.87	95.3	92.6
LOD	1.54	1.78	1.65
Bulk Density	0.66	0.85	0.82

INFERENCE:

TRIAL 8: After trying the polymers like ethyl cellulose the polymer was changed to surelease which is an aqueous dispersion. The results displayed that the drug release was not sustained but there was increase in the release of the drug. After 2 hrs only the drug release was 90% which showed that this polymer did not help in extending the rate of drug release. The assay was also quite low in this batch and the % yield was also less as compared to the other batches.

TRIAL 9: As per the results of the above batch, the further batch was taken by additionally coating 50% of the surelease to the already coated batch just to observe that there is any alteration in the drug release. But the results showed that even after coating 150% of the surelease there is no change observed in extending the release of the drug. And after all the observations, it was concluded that by changing the polymer from ethyl cellulose to surelease, there is no alteration in the drug release and hence ethyl cellulose was finalized as polymer for the polymer coating.

7.3.3. RESULTS OF TRIAL 10 TO TRIAL 12:

Table 46 Dissolution Release of Trial 10 to Trial 12

DISSOLUTION RELEASE				
TIME	**INNOVATOR**	**TRIAL 10**	**TRIAL 11**	**TRIAL 12**
0	0	0	0	0
2	2	4	4	4
4	10	26	16	15
6	33	53	31	31
8	62	75	46	47
10	81	87	60	62
12	93	93	70	73

Figure 17 Drug Release of Trail 10 to 12 vs Innovator Product

Table 47 Characteristics of Trial 10 to Trial 12

CHARACTERISTICS	DESCRIPTION			
	Innovator	**Trial 10**	**Trial 11**	**Trial 12**
Assay	96	97.9	98.6	97.2
Water content	2.1	2.6	2.2	2.8
% yield	99.87	98.79	99.56	98.98
LOD	1.54	1.76	1.25	1.28
Bulk Density	0.66	0.68	0.67	0.68

INFERENCE:

TRIAL 10: The batch was taken by accelerating the concentration to 72mg/ capsule and the concentration of HPMC and talc was kept high and the dissolution was studied. The results showed that the release of the drug increased compared to the concentration of ethyl cellulose as 62mg/ capsule. So, it was concluded that the other excipients can also affect the drug release and hence the further batch would be taken by changing the other excipients along with the ethyl cellulose.

TRAIL 11: In this batch they tried to rise the concentration of ethyl cellulose to 82 mg/ capsule and even the pore former and plasticizer were increased slightly. The concentration of HPMC was also increased in drug loading stage. From the obtained data, it was seen that the drug release was decreased compared to the further batch but pore former and plasticizer did not play any role in decreasing the drug release. So, from the above observations, it was concluded that the quantity of pore former and plasticizer were kept same as that of the literature while there is only change made in the concentration of ethyl cellulose which is affecting the drug release.

TRIAL 12: The concentration of ethyl cellulose was accelerated to 90 mg/ capsule and the results exhibited that the drug release was quite sustained but they sustained more compared to the reference product. Based on the above observations it was seen that the concentration of ethyl cellulose of 82 mg/capsule and 90 mg/capsule were quite neared to the dissolution obtained in the reference product and hence the further batch was taken between the concentration range of 80-90 mg/ capsule.

7.3.4. RESULTS OF TRIAL 13 AND TRIAL 14:

Table 48 Dissolution Release of Trail 13 and Trial 14

DISSOLUTION RELEASE			
TIME	**INNOVATOR**	**TRIAL 13**	**TRIAL 14**
0	0	0	0
2	2	1	1
4	10	11	9
6	33	36	34
8	62	68	65
10	81	83	85
12	93	94	95

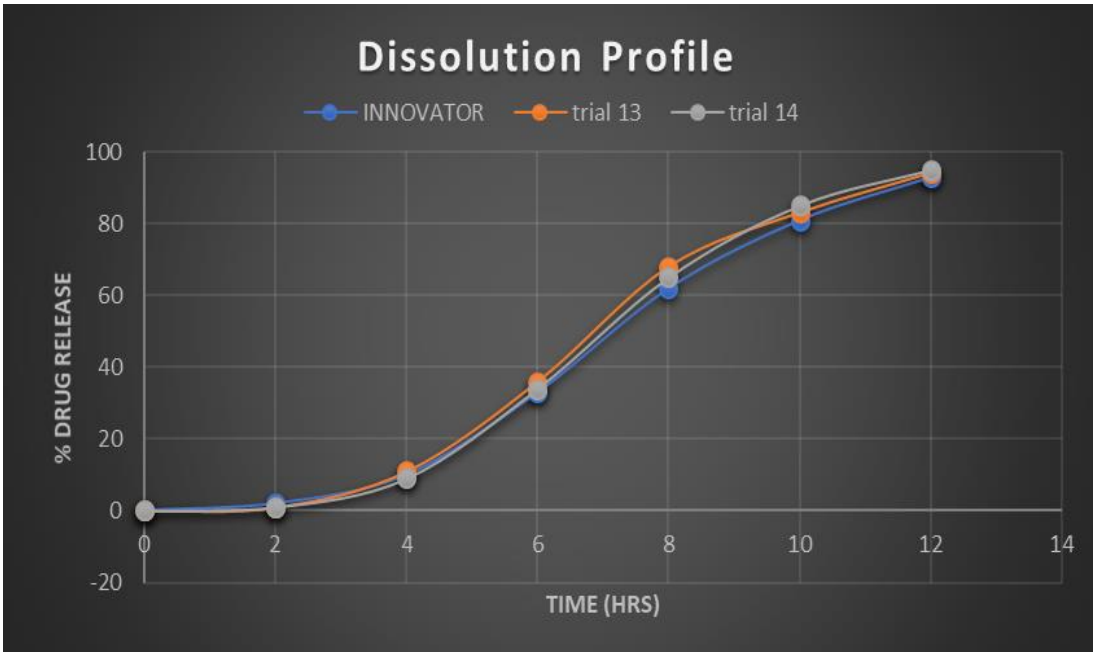


Figure 18 Drug Release of Trial 13 and 14 vs Innovator Product

Table 49 Characteristics of Trial 13 and Trial 14

CHARACTERISTICS	DESCRIPTION		
	Innovator	**Trial 13**	**Trial 14**
Assay	96	98.5	98.8
Water content	2.1	2.4	2.6
% yield	99.87	99.85	99.82
LOD	1.54	1.50	1.59
Bulk Density	0.66	0.67	0.65

PARTICLE SIZE DISTRIBUTION:

Table 50 Particle Size Analysis

	TRIAL 13		**TRIAL 14**	
SIEVE MESH (#)	**Ret %**	**Cum % retention**	**Ret %**	**Cum % retention**
20	39.37	39.37	33	33
40	60.32	99.69	63	96
60	0.248	99.938	1.89	97.89
80	0.049	99.987	0.62	98.51
100	0	99.987	0	98.51

INFERENCE:

TRIAL 13: The concentration of ethyl cellulose was kept at 85 mg/capsule and the experimental data disclosed that the dissolution was very much similar to that of the reference product. The concentration of HPMC was also changed in the drug loading stage which showed good drug loading efficiency. So, this batch was finalised and the other parameters like assay, water content, % yield, LOD were similar to that of reference.

TRIAL 14: A reproducibility batch was taken on the basis of the earlier batch and the reproducibility for all the parameters was observed. This batch was considered as an optimized batch and based on it the scale-up batch would be taken.

7.3.5. STABILITY STUDIES:

The stability studies are carried out of the initial trails including trail 1 and trial 2. The stability is checked for 1-month sample by carrying out at initial, 30°C/ 75% RH and 40°C/ 75% RH

RESULTS OF TRIAL 1: (ALU-ALU Blister)

Table 51 Stability Studies of Trial 1

PARAMETERS	**LIMITS**	**INITIAL**	**30°C/ 75% RH**	**40°C/ 75% RH**
			1 M	**1 M**
DESCRIPTION	The 170 mg capsule is an opaque size #0 capsule	The 170 mg capsule is an opaque size #0 capsule	Complies	Complies
ASSAY (%)	90.0-110.0%	97.2	95.3	96.9
RELATED SUBSTANCES (%)				
ANY UNSPECIFIED IMPURITY	NMT 0.5%	BDL (0.1%)	BDL (0.1%)	BDL (0.1%)
TOTAL IMPURITIES	NMT 0.2%	BDL (0.1%)	BDL (0.1%)	BDL (0.1%)
DISSOLUTION				
2 Hrs	NMT 20%	3	5	3
8 Hrs	45-70%	67	65	68
12 Hrs	NLT 75%	88	82	85
WATER CONTENT	NMT 6.0%	1.89	1.85	1.78

INFERENCE: The above results comply within the provided limits and hence the product is considered to be stable for 1- month period.

RESULTS OF TRIAL 2: (ALU-ALU Blister)

Table 52 Stability of Trial 2

PARAMETERS	LIMITS	INITIAL	30°C/ 75% RH	40°C/ 75% RH
			1 M	1 M
DESCRIPTION	The 170 mg capsule is an opaque size #0 capsule	The 170 mg capsule is an opaque size #0 capsule	Complies	Complies
ASSAY (%)	90.0-110.0%	96.2	94.8	95.7
RELATED SUBSTANCES (%)				
ANY UNSPECIFIED IMPURITY	NMT 0.5%	BDL (0.1%)	BDL (0.1%)	BDL (0.1%)
TOTAL IMPURITIES	NMT 0.2%	BDL (0.1%)	BDL (0.1%)	BDL (0.1%)
DISSOLUTION				
2 Hrs	NMT 20%	2	1	1
8 Hrs	45-70%	58	61	63
12 Hrs	NLT 75%	85	87	88
WATER CONTENT	NMT 6.0%	1.63	1.98	1.48

INFERENCE: The above results comply within the provided limits and hence the product is considered to be stable for 1- month period.

- **SIMILARITY FACTOR:** The similarity factor (f2) was measured by comparing the dissolution of innovator and the optimized batch. The equation for measuring f2 is

$$f_2 = 50 \times \log 10 \times \frac{1}{1 + 1/n \times \sum (Rt - Tt)^2} \times 100$$

- The f2 value was found 77, which is greater than 50, so it was concluded that there is no significant difference between the dissolution profiles of innovator and batch 13. Thus, it can be concluded that developed extended release multiparticulate drug delivery system can give similar site-specific release as that of the reference product.

8. CONCLUSION:

The current work was done to formulate extended release capsules which are used in curing the parkinson's disease. The pellets were filled in capsules and the coating of the pellets was done using the equipment fluidized bed processor using wurster technique. The pellets were coated firstly with the drug and the process parameters were optimized during the drug loading stage. The pellets were further seal coated using HPMC and Talc and the optimization of the excipients was done to provide an extended release effect of the drug. Lastly, the polymer coating was done using the seal coated pellets and the evaluation characteristics were performed.

The preformulation studies were carried out which stated that the drug was crystalline having good particle size with proper sphericity of the pellets. The evaluation parameters of capsules were also performed by investigating the cap and body size, the number of the pellets filled in the capsule, the lock strength of the capsule. Based on the characteristics of the drug and its side effects, it was decided to prepare an extended release formulation for the same.

The earlier batches from Trail 1 to Trial 7, the optimization of the pore former povidone k-90 and plasticizer medium chain triglycerides was done. Based on the obtained results the quantity of pore former and plasticizer was finalized. The optimization of the amount of HPMC and Talc was also carried out for investigating the effect of the release of the drug in the formulation.

The further batches were taken by changing the polymer from ethyl cellulose to surelease in order to observe that if there is any sustained released obtained or not. Trial 8 and Trial 9 was carried out for the same.

Then the process was optimized using some of the parameters like spray rate, product temperature, drive speed, air distribution plate along with the optimization of the quantity of ethyl cellulose. The results were quite near to the reference product and finally the optimized batch was taken.

The optimized batch exhibited good dissolution profile when compared to the reference product and along with that other evaluation parameters were comparable to the reference product. The evaluation parameters like assay, water content, related substances, were studied. Optimized pellets showed good sphericity, dissolution profile and appropriate flow property.

The dissolution profile showed extended release up to 12 hrs and the actual objective of the formulation was fulfilled.

The stability studies were carried out which showed valuable results with no change in the formulation which proved it to be stable after the particular period of time. Thus, it was concluded that the research work fulfilled the aim in preparing a formulation which is bioequivalent to the reference product and hence this work would help further researches to prepare a formulation which can help in curing the parkinson's disease.

1. Howard C A, Loyd V A. Modified release solid dosage forms and drug delivery systems, Pharmaceutical dosage forms and drug delivery systems, 8th edition, Lippincot Williams and Wikins. 2004; 648.
2. Sachdeva V, Alam MS, Kumar R, Kataria MK. Oral multiunit pellet extended release dosage form: A review. International Current Pharmaceutical Journal. 2013 Sep 14;2(10):177-84.
3. Zierenberg B. The contribution of pharmaceutics to the improvement in drug therapy, modern drug research, Paths to better and safer drugs, Yvonne C M, Volkhard A. Volume 12, Marcel Dekker, New York, Basel. 401-412.
4. Malinowski H. J. , Marroum P. J., Encyclopedia of Controlled Drug Delivery vols. 1 and 2, Food and Drug Administration Requirements for Controlled Release Products . John Wiley & Sons New York. 1999. I (1):P. 381-395.
5. Aulton M. E. Pharmaceutics: The Science of Dosage Form Design, Churchill Livingstone, Hartcourt Publisher, Edinburgh. 2002.
6. Li V H K, Lee V H L. Controlled drug delivery: Fundamentals and applications, (Robinson J R, Lee V H L, eds.) 2nd Ed., Marcel Dekker Inc., New York. 1987; 4 – 36. 4.
7. Lachman L, Liberman H A, Kaing J L. Theory and Practice of Industrial Pharmacy, 3 rd Ed ., Varghese Publishing House, Bombay. 1987; 430 – 453.
8. Speers M., and Bonnano C., Economic aspects of controlled drug delivery, Encyclopedia of Controlled Drug Delivery. New York, Acta. Pharm. Suecica. 1999. P. 341-347
9. Dey, N. S., Majumdar, S., & Rao, M. E. B. (2008). Multiparticulate drug delivery systems for controlled release. *Tropical Journal of Pharmaceutical Research*, *7*(3), 1067-1075.
10. Tang, E. S., Chan, L. W., & Heng, P. W. (2005). Coating of multiparticulates for sustained release. *American Journal of Drug Delivery*, *3*(1), 17-28.
11. Ghebre-Sellassie, I., Pellets: A general overview. In GhebreSellassie, I (ed.), Pharmaceutical Pelletization Technology. Marcel Dekker, Inc., New York, USA, Vol. 37, 1989, pp. 1-13.

12. Jawahar, N., & Anilbhai, P. H. (2012). Multi unit particulates systems (MUPS): a novel pellets for oral dosage forms. *Journal of Pharmaceutical Sciences and Research*, *4*(9), 1915.
13. Sirisha, V. R. K., Sri, K. V., Suresh, K., Reddy, G. K., & Devanna, N. (2013). A review of pellets and pelletization process-a multiparticulate drug delivery system. *International Journal of Pharmaceutical Sciences and Research*, *4*(6), 2145.
14. Bechgaard, H., & Nielsen, G. H. (1978). Controlled-release multiple-units and single-unit doses a literature review. *Drug Development and Industrial Pharmacy*, *4*(1), 53-67.
15. Ghebre-Sellassie I and Knoch A: Pelletization techniques. Encyclopedia of Pharmaceutical Technology, Informa Healthcare, Edition 3, 2002.
16. Digenis, G. A. (1994). The invivo behavior of multiparticulate versus single unit dosage formulations. Ghebre-Sellassie, I., Ed. Multipaticulate Oral Drug Delivery.
17. Eskilson, C. (1985). Controlled release by microencapsulation. *Manufacturing Chemist*, *56*(3), 33-39.
18. Harris, M. R., & Sellassie, G. (1989). Pharmaceutical pelletization technology. *Drug and The Pharmaceutical Sciences*, *37*, 217-239
19. Govender, T., & Dangor, C. M. (1997). Formulation and preparation of controlled release pellets of salbutamol by the air suspension technique. *Journal of microencapsulation*, *14*(4), 445-455.
20. Ghebre-Sellassie, I; Mechanism of pellet formation and growth, in Ghebre-Sellassie, I. (ed.) Pharmaceutical pelletization technology, Marcel Dekker, Inc., New York and Basel, (1989a), 123 – 143.
21. Sherrington, P. J., & Oliver, R. (1981). Compaction and other granulation methods. *Granulation, Heyden, London, Philadelphia*, 141-152.
22. Lavanya, K., Senthil, V., & Rathi, V. (2011). Pelletization technology: a quick review. *International Journal of Pharmaceutical Sciences and Research*, *2*(6), 1337.
23. Conine, J. W., & Hadley, H. R. (1970). Preparation of small solid pharmaceutical spheres. *Drug & Cosmetic Industry*, *106*(4), 38.

24. Kader, A., & Jalil, R. (1998). In vitro release of theophylline from poly (lactic acid) sustained-release pellets prepared by direct compression. *Drug development and industrial pharmacy*, *24*(6), 527-534.
25. Erkoboni D.F: Extrusion-Spheronization as a Granulation Technique. In Parikh, D.M. (ed), Handbook of Pharmaceutical Granulation Technology, Marcel Dekker, Inc. New York, Edition 81, 1997: 333-365.
26. Galland, S., Ruiz, T., & Delalonde, M. (2007). Twin product/process approach for pellet preparation by extrusion/spheronisation: Part I: Hydro-textural aspects. *International journal of pharmaceutics*, *337*(1-2), 239-245.
27. Muley, S., Nandgude, T., & Poddar, S. (2016). Extrusion-spheronization a promising pelletization technique: in-depth. *microscopy*, *502*, 503.
28. Gamlen, M. J. (1985). Pellet manufacture for controlled release. *Manufacturing Chemist*, *56*, 55.
29. Nastruzzi, C., Cortesi, R., Esposito, E., Genovesi, A., Spadoni, A., Vecchio, C., & Menegatti, E. (2000). Influence of formulation and process parameters on pellet production by powder layering technique. *AAPS PharmSciTech*, *1*(2), 14-25.
30. Kovacevic J, Mladenovic A, Djuris J, et al. Evaluation of powder, solution and 736
    suspension layering for the preparation of enteric coated pellets. Eur J Pharm Sci 2016; 737 85:84–93
31. Parikh D.M. "Layering in rotary fluid bed a unique process for the production of spherical pellets for controlled release" Presented at Interphex-USA, New York, NY. May 18, 1991.
32. Hileman G.A., Sarabia R.E. "Manufacture of immediate and controlled release spheres in a single unit using fluid bed rotor insert" Presented at the Annual Meeting of the American Association of Pharmaceutical Scientists (AAPS), Poster PT 6167, 1992.
33. Saini, V. (2009). Fluidized bed processing for multiparticulates. *J. Chem*, *2*(2), 447-450.
34. Shetty, V. (2010). Wurster Coating-Scale up and Scale out. *Pharma Times*, *42*(11), 33-37.

35. Christensen, F. N., & Bertelsen, P. (1997). Qualitative description of the Wurster-based fluid-bed coating process. *Drug development and industrial pharmacy*, *23*(5), 451-463.
36. Maronga, S. J., & Wnukowski, P. (1998). The use of humidity and temperature profiles in optimizing the size of fluidized bed in a coating process. *Chemical Engineering and Processing: Process Intensification*, *37*(5), 423-432.
37. Cole, G. C. (1995). Coating pans and coating columns. In: Cole, G. C. (Ed.), Pharmaceutical Coating Technology. London: Taylor and Francis. p. 205-239.
38. Frisbee, S. E., Mehta, K., & McGinity, J. (2002). Processing factors that influence the in vitro and in vivo performance of film-coated drug delivery systems. *Drug Deliv*, *2*(1), 72-76.
39. Shallcross, D. C. (1997). Handbook of psychrometric charts. *Chapman & Hill, London*.
40. Mehta, A. M. (1988). Scale-up considerations in the fluid-bed process for controlled-release products. *Pharmaceutical Technology*, *12*(2), 46-52.
41. Adjei, A., Doyle, R., Reiland, T., Swarbrick, J., & Boylan, J. C. (1992). Encyclopedia of Pharmaceutical Technology, Vol. 6.
42. Wan, L. S., Heng, P. W., & Liew, C. V. (1995). The influence of liquid spray rate and atomizing pressure on the size of spray droplets and spheroids. *International Journal of Pharmaceutics*, *118*(2), 213-219.
43. Wheatley, T. A., & Steuernagel, C. R. (1997). Latex emulsions for controlled drug delivery. *Drugs and the pharmaceutical sciences*, *79*, 1-54.
44. Mehta, M.A: Evaluation and characterization of pellets. In: GhebreSellassie, I.(ed.) Pharmaceutical Pelletization Technology Marcel Dekker, 1989: 241-265.
45. Bianchini R, Bruni G, Gazzaniga A and Vecchio C: Influence of extrusion-spheronization processing on the physical properties of dindobufen pellets containing pH adjusters. Drug Development and Industrial Pharmacy 1992; 18: 1485-1503.
46. Abdul, S., Chandewar, A. V., & Jaiswal, S. B. (2010). A flexible technology for modified-release drugs: multiple-unit pellet system (MUPS). *Journal of controlled release*, *147*(1), 2-16.

47. Dashevsky, A., & Mohamad, A. (2006). Development of pulsatile multiparticulate drug delivery system coated with aqueous dispersion Aquacoat® ECD. *International journal of pharmaceutics*, *318*(1-2), 124-131.
48. Hamdani, J., Moës, A. J., & Amighi, K. (2002). Development and evaluation of prolonged release pellets obtained by the melt pelletization process. *International journal of pharmaceutics*, *245*(1-2), 167-177.
49. Gaikwad, V. L., Sharma, S. N., Bhatia, M. S., & Mahadik, K. R. (2018). Development of controlled release cellulose-pellets based multicore tablets. *European Polymer Journal*, *105*, 389-397.
50. Kramar, A., Turk, S., & Vrečer, F. (2003). Statistical optimisation of diclofenac sustained release pellets coated with polymethacrylic films. *International journal of pharmaceutics*, *256*(1-2), 43-52.
51. Roblegg, E., Jäger, E., Hodzic, A., Koscher, G., Mohr, S., Zimmer, A., & Khinast, J. (2011). Development of sustained-release lipophilic calcium stearate pellets via hot melt extrusion. *European Journal of Pharmaceutics and Biopharmaceutics*, *79*(3), 635-645.
52. Thapa, P., Thapa, R., Choi, D. H., & Jeong, S. H. (2018). Effects of pharmaceutical processes on the quality of ethylcellulose coated pellets: Quality by design approach. *Powder technology*, *339*, 25-38.
53. Farag, Y., & Leopold, C. S. (2011). Development of shellac-coated sustained release pellet formulations. *European journal of pharmaceutical sciences*, *42*(4), 400-405.
54. Faivre, F., Joshi, A., Bezard, E., & Barrot, M. (2018). The hidden side of Parkinson's disease: studying pain, anxiety and depression in animal models. *Neuroscience & Biobehavioral Reviews*.
55. Deng, H., Wang, P., & Jankovic, J. (2018). The genetics of Parkinson disease. *Ageing research reviews*, *42*, 72-85.
56. Maronga, S. J., & Wnukowski, P. (1998). The use of humidity and temperature profiles in optimizing the size of fluidized bed in a coating process. *Chemical Engineering and Processing: Process Intensification*, *37*(5), 423-432.

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