"FORMULATION OPTIMIZATION OF EXTENDED RELEASE PELLETS PREPARED BY WURSTER TECHNOLOGY FOR AN ANTIEPILEPTIC DRUG"

A Thesis Submitted to

NIRMA UNIVERSITY

In Partial Fulfillment for the Award of the Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

BY

GRIVA ACHARYA (17MPH103), B. PHARM.

Under the guidance of

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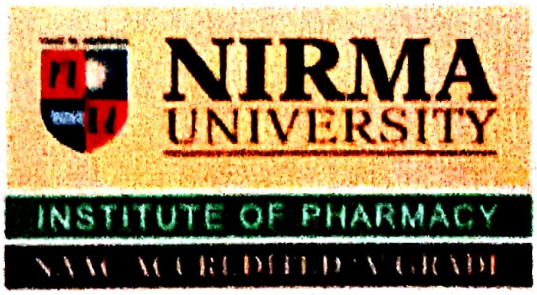

Department of Pharmaceutics

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Ahmedabad-382481

Gujarat, India.

May 2019

CERTIFICATE

This is to certify that the dissertation work entitled "Formulation Optimization Of Extended Release Pellets Prepared By Wurster Technology For An Antiepileptic Drug" submitted by Ms. GRIVA ACHARYA with Regn. No. (17MPH103) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutics Department" is a bonafide research work carried out by the candidate at the Department of Pharmaceutics, Institute of Pharmacy, Nirma University under my/our guidance. 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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This is to certify that **Ms. Griva Acharya,** from **Nirma University, Ahmedabad** has undergone training from **03.07.2018 to 28.02.2019** in **Formulation Development Department** at Cadila Healthcare Limited, Ahmedabad. During this Period she has done a project entitled **"FORMULATION OPTIMIZATION OF ER PELLETS PREPARED BY WURSTER TECHNOLOGY FOR AN ANTIEPILEPTIC DRUG"** successfully under the Guidance of **Mr. Vimal Kaneria** (Deputy General Manager).

We wish her better achievements in her future endeavors

Thanking You.

Yours faithfully,

For, Cadila Healthcare Ltd.

Niral Bhatt
Deputy General Manager
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CERTIFICATE OF ORIGINALITY OF WORK

This is to undertake that the dissertation work entitled "Formulation Optimization Of Extended Release Pellets Prepared By Wurster Technology For An Antiepileptic Drug" Submitted by Ms. GRIVA ACHARYA with Regn. No. (17MPH103) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutics Department" is a bonafide research work carried out by me at the "Pharmaceutics Department", Institute of Pharmacy, Nirma University under the guidance of "Dr. Dhaivat parikh". I am aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad. According to that, this work is original and not reported anywhere as per best of my Knowledge.

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DECLARATION

I hereby declare that the dissertation entitled "Formulation Optimization Of Extended Release Pellets Prepared By Wurster Technology For An Antiepileptic Drug", is based on the original work carried out by me under the guidance of Dr. Dhiavat parikh, Assistant 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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LIST OF ABBREVIATION

SR NO.	SHORT FORMS	ABBREVATIONS
1	MUPS	Multi-unit particulate system
2	FBP	Fluid bed processor
3	ADP	Air distribution plate
4	IPA	Iso-propyl alcohol
5	RS	Relative substance
6	EC	Ethyl cellulose
7	TEC	Tri-ethyl citrate
8	DCM	di-chloromethane

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ABSTRACT:

The objective this research is to develop extended release multiunit particulate system for an antiepileptic drug by using fluid bed processor equipped with bottom spray technology which is also known as wurster technology. This formulation comprises of an extended release component which retards the release of drug coated on the core pellets. The extent of extended release coat and concentration of extended release component is optimized to achieve predetermined dissolution profile. Formulating modified release drug delivery system for highly soluble drug is difficult. Present research comprises of ethyl cellulose acts as rate controlling hydrophobic barrier while povidone k-30 acts as pore former component which helps in release of drug in which attributes affecting the quality target product profile was identified by using initial risk assessment and batches were planned accordingly. Reservoir technology by using wurster coating process was used to develop extended release pellets where, subsequent coating is applied on core pellets. In drug layering stage, drug solution prepared was dispersion solution. Therefor viscosity played an important role in drug layering as low viscosity of dispersion solution lead to decreased coating efficiency as loss of amorphous drug during the process occurs. Viscosity of the dispersion depends upon the quantity and type of binder used. However, higher viscosity may lead to the agglomeration of pellets. Thus, optimized concentration of PVP k-90 were used during drug layering process. 3% barrier coating using Opadry clear was done to smoothen the drug layered pellets for the ease of subsequent coating process. Extended release coat applied on the barrier layer coated pellets, determines the release of the drug from the formulation. Thus, in present research ratio of EC: PVP K-30: Triethyl citrate: talc was optimized to 68:32:10:10 to obtain desired drug release profile.

1. INTRODUCTION:

1.1 Epilepsy:

A group of neurological disorders is characterized as epilepsy. These epileptic seizures can be described as vigorous shaking which can be transitory to unpredictably long episodes.(Penfield & Jasper, 1954) Epileptic seizure may lead to physically injured patient and sometimes breaking of bones may also occur. The reason of epilepsy in most of the patient is not known. Brain tumor or shock or sometimes injury and brain infection may result in epilepsy. (Kumar, Das, & Raju, 2012)In brain cerebral cortex, impaired activity of neurons causes epileptic seizure. Diagnosis of epileptic seizure is done by brain imaging and ensured by electro encephalogram. Epileptic seizures can be treated with medications in 75% of cases. Epilepsy can be classified as:

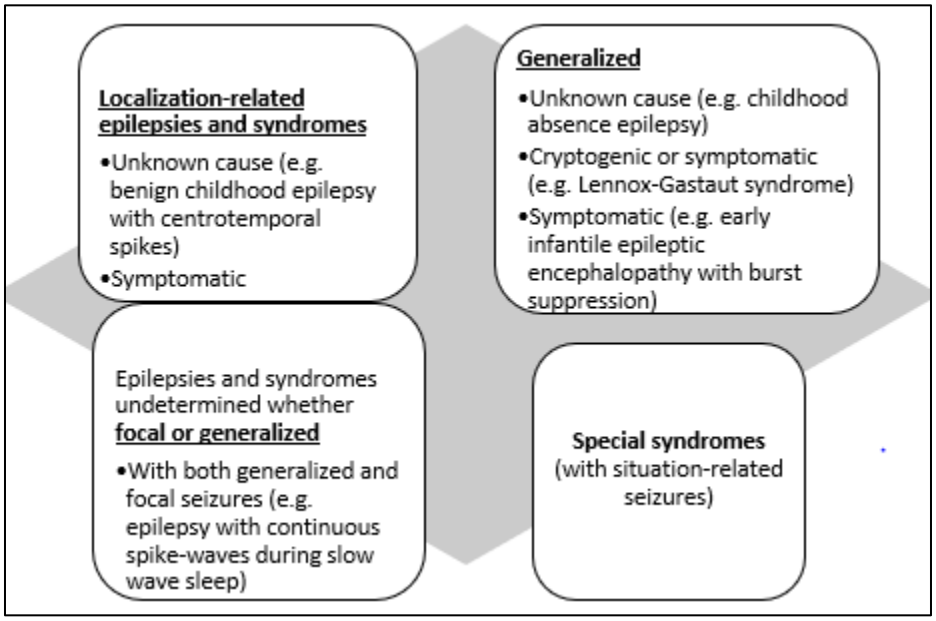


Figure 1 types of epileptic seizures

(Fisher et al., 2005)Anticonvulsant drug used for the treatment of epilepsy is given on the bases of type of seizure by which patient is suffering of as well as considering the other health issues, medication is chosen. Medications used for the treatment of epilepsy includes carbamazepine, valproic acid, phenytoin, lamotrigine and topiramate. (Hauser & Hesdorffer, 1990)For focal and generalized epileptic seizure, carbamazepine and valproic acid can be prescribed. While ethosuximide is used for the absence seizure. In present research, the antiepileptic drug used for the treatment of epileptic seizure is acts by blocking the action potentials caused by a sustained depolarization of the neurons and blocks the action of sodium channels.(Fisher et al., 2005) It also increases the action of the neurotransmitter gamma-aminobutyrate (GABA) at $GABA_A$ receptor. This drug is BSC class 3 drug having high solubility in aqueous media. Immediate release formulation for this drug is available in market. But this drug is having some severe adverse effect which include somnolence, speech disorder, ataxia.(Penfield & Erickson, 1941) Abnormal vision, problem associated with memory, diplopia, paresthesia and acute myopia can also be take place. Thus, nevertheless drug is having long biological half-life of 19-21 hours, it is generally not prescribed as once a daily dose as fluctuation in plasma drug concentration after administering single high dose lead to precipitation of side effect.(Galanopoulou et al., 2012) For this reason, drug is prescribed in twice daily dose but after taking each dose there is increase in plasma drug concentration followed by decrease concentration which again rise after administration of second dose, which results in to peak and valleys plasma concentration vs time profile which is very harm full for the patient. Thus, it was required to formulate once daily dose for this drug. (Rosenow & Lüders, 2001)Therefore, there is a need for a formulation of topiramate, which reduces or eliminates the side effects associated with peaking and fluctuating plasma levels of the drug and preferably may be administered in a once-daily regimen.s New, highly soluble and bioavailable forms of topiramate are also needed in order to increase the safety and effective ness of the drug. For this purpose, extended release formulation of this drug is formulated. Multiunit particulate system is advantageous over tablet is that, as it is made up of several micro sized pellets, each of them release the drug independently to other pellet results in very rare chances of dose dumping. Moreover, particle size of pellets is in microns results in higher surface area which helps in controlling the release in more efficient way from the formulation.

Multi particulate system:

Multi particulate system can be defined as "converting granules or fine powder of drug and excipient into small, spherical and free flowing form by using agglomeration process is known as palletization." Size range of multiunit particulate system is generally in 0.5-1.5 mm. pellets can be prepared by using various methods. i.e., drug layering of pellets or extrusion spheronization method. Ideal characteristics of pellets should be:

- For the ease and efficient film coating process, surface of pellets should be smooth and shape should be spherical.
- Narrow particle size distribution, considering 600-100 µm as optimal size for pharmaceutical applications.
- Pellets should contain sufficient amount of excipient to maintain size of the final formulation.

Use of Multi particulate system is advantageous in developing the modified release dosage forms with or without gastro retentive characteristics. They are also used to achieve extended release drug dissolution profile and sometimes for site specific delivery usually in colon targeted drug delivery system multiunit particulate system is used. (Ratul & Baquee, 2013b)

For specific drug delivery system that defines the specific action of formulation. Depending on that, formulation development, design and component as well as method of preparation of formulation is selected. Modified release dosage form or targeted drug delivery can be formulated in solid orals are generally formulated as multiunit system or a single unit system. Multiunit system includes pellets or micro particles filled in capsule and single unit system includes tablet formulated by matrix or reservoir technology.(N. & A., 2016) Pellets provides greater flexibility in formulation and also prevents the chances of dose dumping as compare to tablet and thus, efficiency and safety point of view pellets are highly preferable. Moreover, in multiunit particulate system, two different strength of drug or two incompatible drugs can be incorporated in to one formulation. Acid labile drug can be efficiently delivered by subsequent coating on core pellets this is generally used in case of colon targeted drug delivery. Over single

unit dosage form it is also advantageous pharmacokinetically. Due to the smaller particle size and increased surface area, pellets can be uniformly dispersed in GIT which enhances the absorption characteristic of drug and decreases the local side effect caused by the long retention at the mucosal membrane. Interpatient as well as intervariable variability can be prevented by using multiunit particulate system. Size of the pellets for different formulations is shown in following figure:

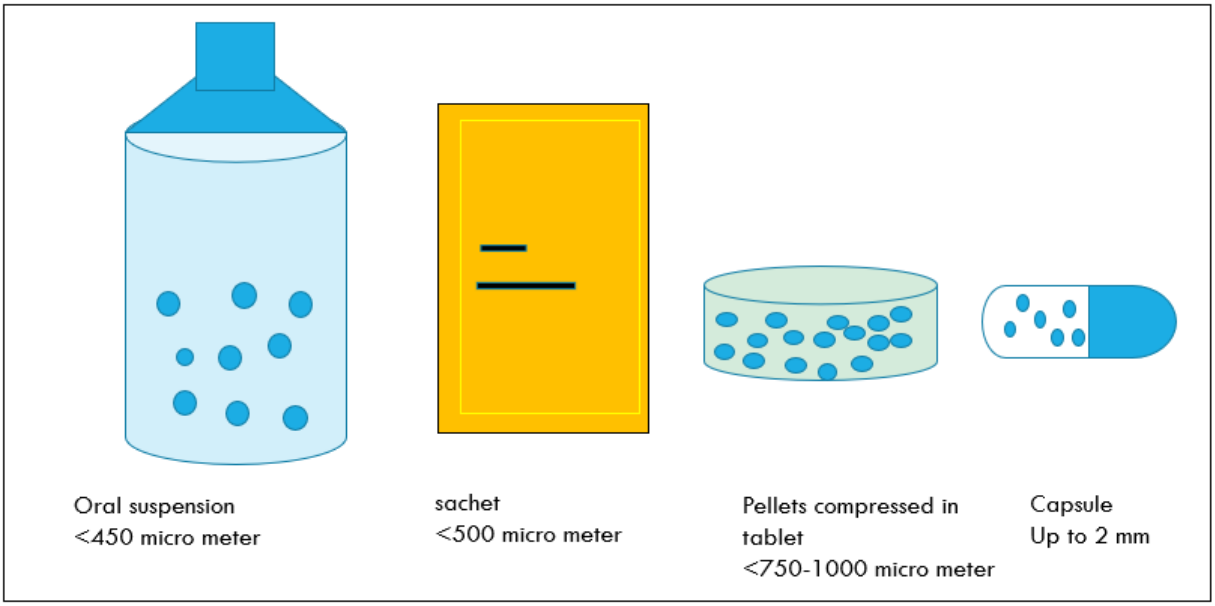


Figure 2 size of pellets for different formulation

Advantages of the multiunit particulate system:

1. Two or more different strength can be incorporated into one single dosage form without changing process
2. Delivery of biologically active component become easy by coating it with acid resistant polymer and it can be delivered as targeted site with desired release rate.
3. Chances of dose dumping are very less as compared to single unit dosage form.
4. Delivery of muco irritant agent which cause local irritation after administration, i.e., NSAIDs, can be prevented as smaller particle size lead to uniform distribution in gastric mucosa and efficient absorption resultant less or no damage to the mucosal membrane.

5. Ease of coating in case of stabilization of drug granule by the coating or rate controlling membrane coating process. As it provides smooth spherical shape for the coating. Moreover, irregularities of the coating membrane caused by amorphous drug can be overcome by coating extra coat to achieve smooth surface of the pellets.
6. An excellent flow property can be achieved by using pellet system as it increases the bulk and tap density, Carr's index increases. This improved flow property helps in capsule filling and packaging process of the pellet system.
7. By using the spheronization process for manufacturing pellets, granule with low friability and high hardness can be achieved which reduces the number of fines generated and that helps in process handling and packaging of the pellets.

Disadvantages of multiunit particulate system:

1. In multiunit system dosing is differentiate by the volume of pellets and not by the number of pellets. While separation of single dose is required.
2. Minor change in size of pellets is observed in batch to batch formulation development process
3. Capsule filling coast is added in case of pellets system. As compression of pellets into the tablet may lead to damage of controlled release film of the pellets.("Pelletization Technology : Methods and Applications-A Review," 2015)

1.3 Stages involved in palletization:

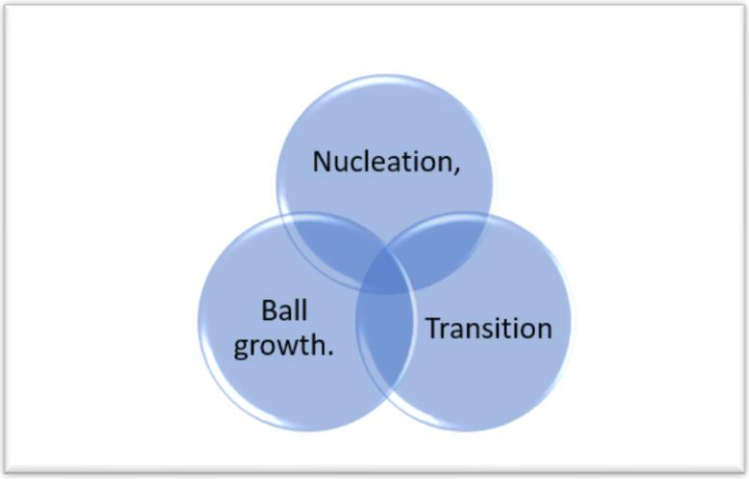


Figure 3 Process of palletization involves three sequential regions

But, based on the experiments, formation of pellets was described in following stages:

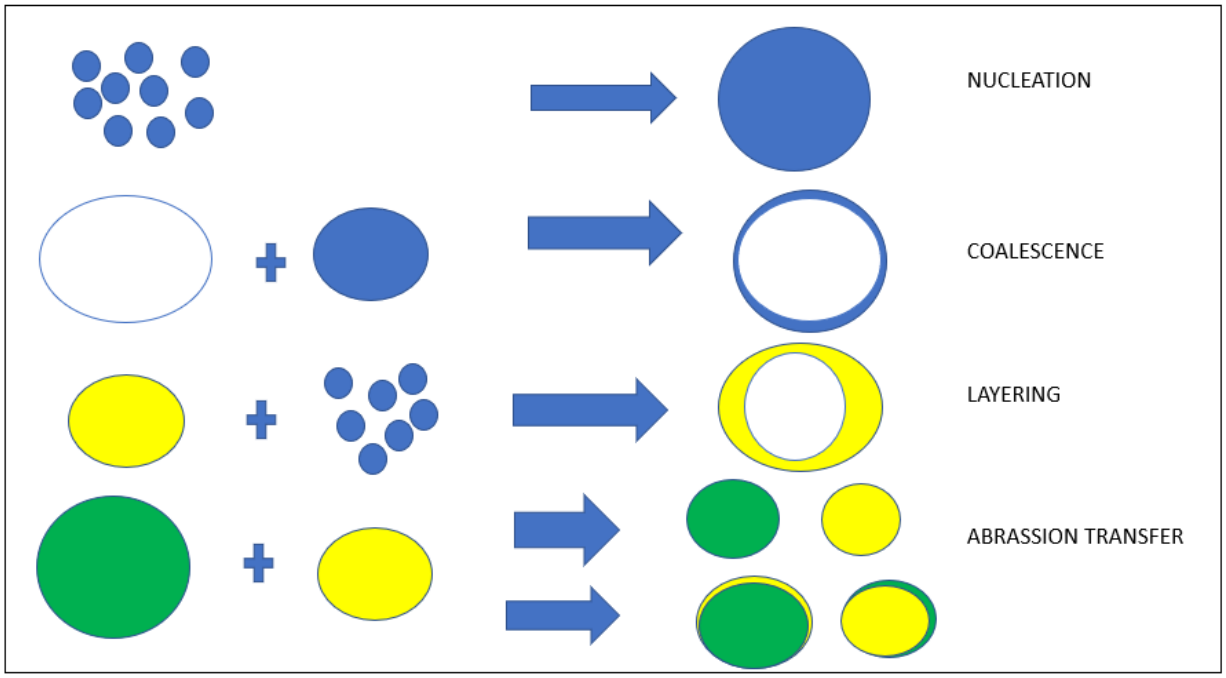


Figure 4 formation of pellets

1. Nucleation process:

It is an initial stage of palletization. In this stage, palletization occurs by the wet powder. The dry particle upon contact with water converts into the three phasic system which is air-water-liquid system. The hydrogen bonds formed during this stage provides the strength of bonding the particles resultant decreased particle size of powder takes place. nuclear formation rate highly depends upon the particle size of the particle in powder, imbibed water inside the particle, rheological property of the powder particle as well as the process parameters. i.e., rate of drying.(Bhairy et al., 2015; Khan, Malviya, & Sharma, 2014)

2. Transition stage:

Transition phase involves mechanism of particle coalescence and coating. coalescence can be defined as, “the formation of large particle by collision of well-formed nuclei”. Mechanism of coalescence need moisture nuclei. While layering process involves coating of particles on existing nuclei. Fine production, coalescence followed by drug layering takes place till collisions of particle decreases. And further rate of pellet growth declines.

3. Ball growth phase:

This phase involves abrasion transfer which is material transfer between the granules. Mass of particle does not change during this phase but size of particle continuously changes throughout this stage.(Rahman et al., 2009)(Yadav & Verma, 2016)

1.4 Palletization methods:

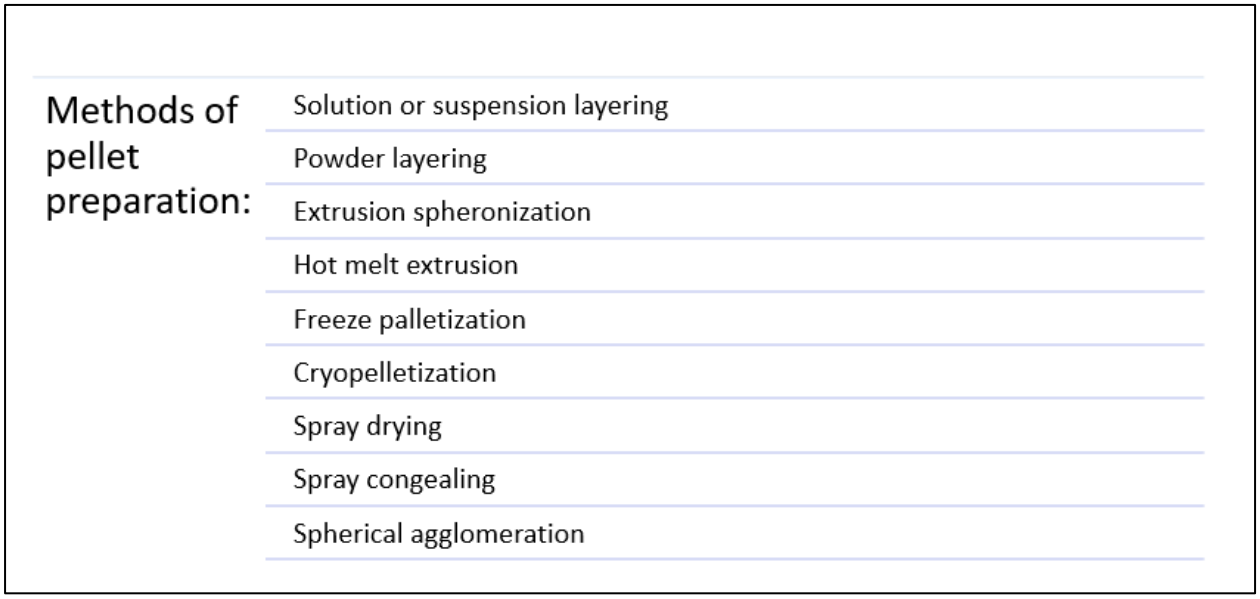


Figure 5 methods for pellet preparation

1.4.1 Solution and suspension coating:

Coating of the suspension ore solution process is coalescence of solution on the core pellets. Solution or suspension is composed of pharmaceutical API and binder which helps to form uniform layer on the pellets. For this purpose, drug and excipient are dissolved in aqueous or non-aqueous solvent system to prepare solution of required viscosity. This solution is further sprayed on to the core pellets, coalescence takes place between the droplet sprayed and the core pellets followed by uniform coating on the surface of pellets. Followed by spraying, there is drying phase in which solid bonds between the sprayed material takes place. In this process, weight gain is continuously monitored. Process is considered as complete, only after desired weight gain is achieved. Particle size of the pharmaceutically active ingredient plays an important role for this technique. As for coating larger sized particle amount of binder used will be more resultant increase in viscosity which lead to problem in process parameters like, blockage of spraying nozzle and accumulation of particles in spraying tube. To prevent this, 10-15 µm is considered as standard particle size for this process.(Chen, Li, Chen, Sun, & Zheng, 2017)(Tripathi, Reddy, & Reddy, 2012)

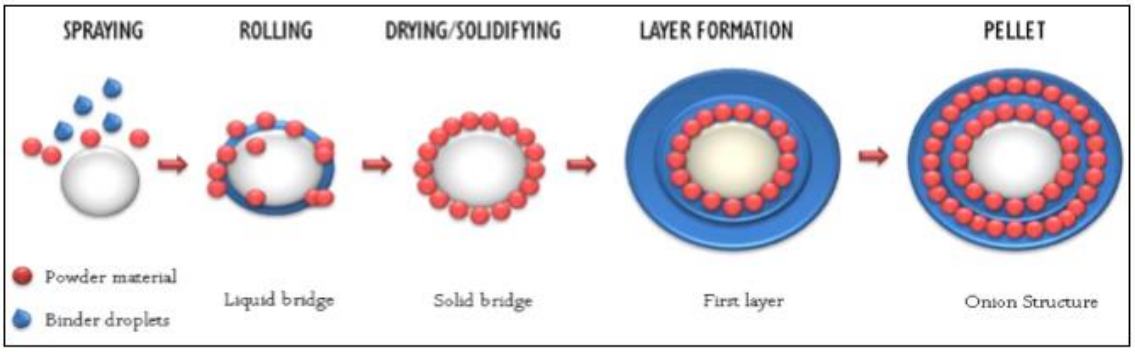


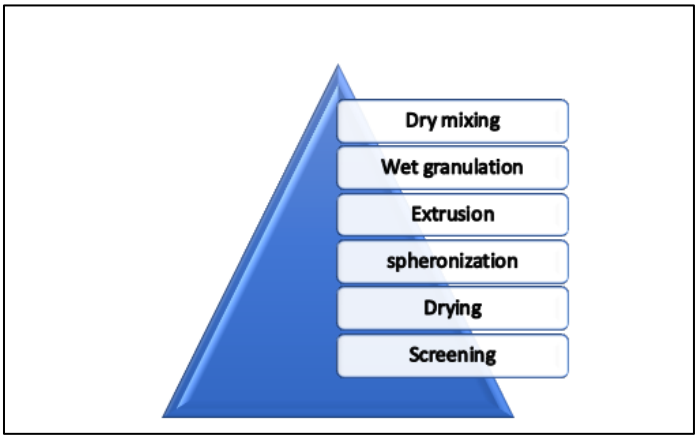
Figure 6 coating process on core pellets

1.4.2 Coating of powder on the core pellets:

This technique utilizes the solution in which excipient for nuclei formation and pharmaceutical drug both are dissolved or dispersed. Initially, binder solution and drug are added. During the stirring, drug particle binds with each other and seed formation takes place which results into the pellets by utilizing the hydrogen bridging provided by sprayed solution. These hydrogen bonds are further replaced with the solid bridge provided by the binder. Rate of drug addition and binder liquid addition is important parameters.(Rashid, 2001)

1.4.3 Pellets by using extrusion spheronization technique:

To formulate specific sized pellets, this technique is widely used. Major advantage of this method is that high strength of drug can be easily incorporated in to the pellet system. Process of extrusion spheronization involves following stages:



Extrusion spheronization starts with preparing wet mass of drug and excipient. Which is initiated with mixing dry powdered drug and excipient followed by addition on binder solution characterized as wet granulation process.(Kristó et al., 2016) At the end of this stage plastic mass is generated. This prepared mass is further passed from the extruder. This extruder is composed of cylinder-shaped dies which have 0.5-2 mm diameter. Extrudes that come out from the extruder are subjected to spheronizer which cut down the extrudes in cylindrical shape.(Shah, Mehta, & Gohel, 2016) This is done because of pushing extrudes to the surrounding wall as well as pull down motion developed by centrifugal action developed by the rotating fractions. Followed by this stage, spheronization pellets are dried at room temperature or at maintained temperature. Drying stage is responsible for the hardness and density of the pellets.(Gandhi, Kaul, & Panchagnula, 1999)

1.4.4. Cryopelletization:

Cryopelletization process involves conversion of liquid to solid sphere. Non-aqueous solvent containing drug forming suspension system, is drop by drop added to liquid nitrogen. Which freezes the particles. These freeze particles are subjected to lyophilization procedure during which organic solvent entrapped is removed. Critical step involved in this method is method is drop formation which depends upon the viscosity of the suspension and the surface tension as well as the solid content.(Sirisha, Suresh, Vijayasree, Devanna, & Murthy, 2014; Supriya, Rajni, A.C, & Rana, 2012; Veena, Senthil Kumar, & Parthiban, 2012; Vikash et al., 2011)(Knoch, 2013; Ratul & Baquee, 2013a)

1.4.5 Spherical agglomeration:

Spherical agglomeration process involves powder mixing by using specific quantity of solvent. This balling process can also be done under high temperature at which particle are converted in to spherical pellets in rolling drum or in mixers.

1.4.6 Hot melt extrusion method:

This method is solvent free method. Pharmaceutically active component which is facing stability problems due to water can be formulated by using this method. Matrix type pellets

formulation is prepared by this method thus, further coating of rate controlling membrane is not required. (Cheboyina & Wyandt, 2008)

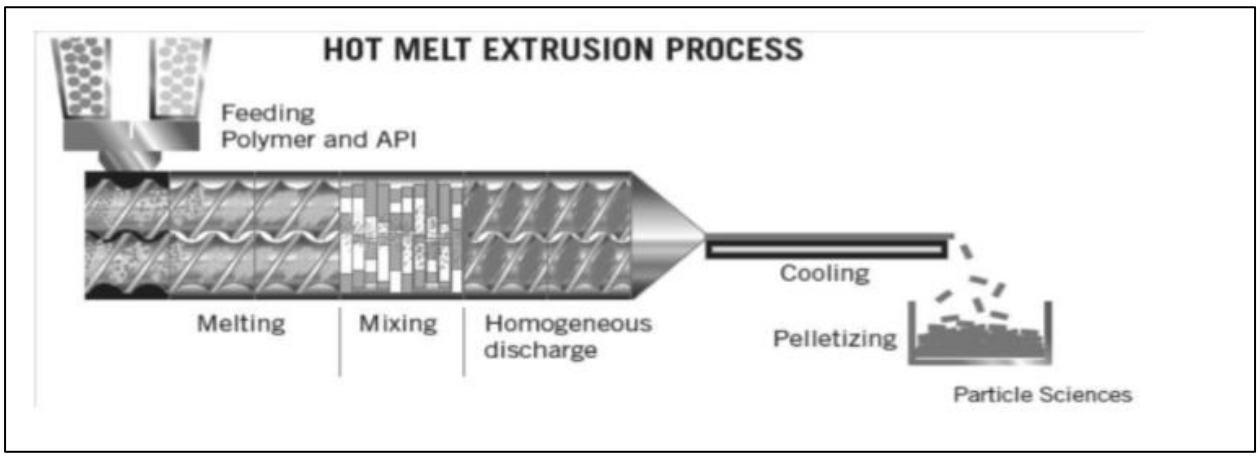


Figure 7 hot melt extrusion process

1.4.7 Spray drying and spray congealing method:

This method is called as globalization. It comprises of solution preparation, hot melt atomization followed by formation of suspension. Spray drying process involves spraying of suspension containing drug into hot air which rapidly dries the droplet. This method is used for poorly soluble drug to increase dissolution rate. Drug is melted and incorporated in to waxy material with known melting point. Which is subjected to high temperature at which waxy material melt down to formulate spherical sized pellets.

1.4.8 Freeze palletization technique:

It is newly discovered method of palletization. In freeze palletization, drug and excipients are melted and added to immiscible solvent system. Due to density difference phase separation takes place and solidification of pellets takes place at the bottom of the column at the room temperature.(Kandukuri, Allenki, Eaga, Keshetty, & Jannu, 2009)

1.5 Fluidized bed processor (FBP)

This technology is most widely used because it offers high processing energy and efficient mass transfer. FBP offers usage of both heat resistant as heat sensitive drug operations. All stages involving coating, granulation and drying occurs in single process. In FBP coating and drying can be done simultaneously. Three types of FBP machines are industrially used:

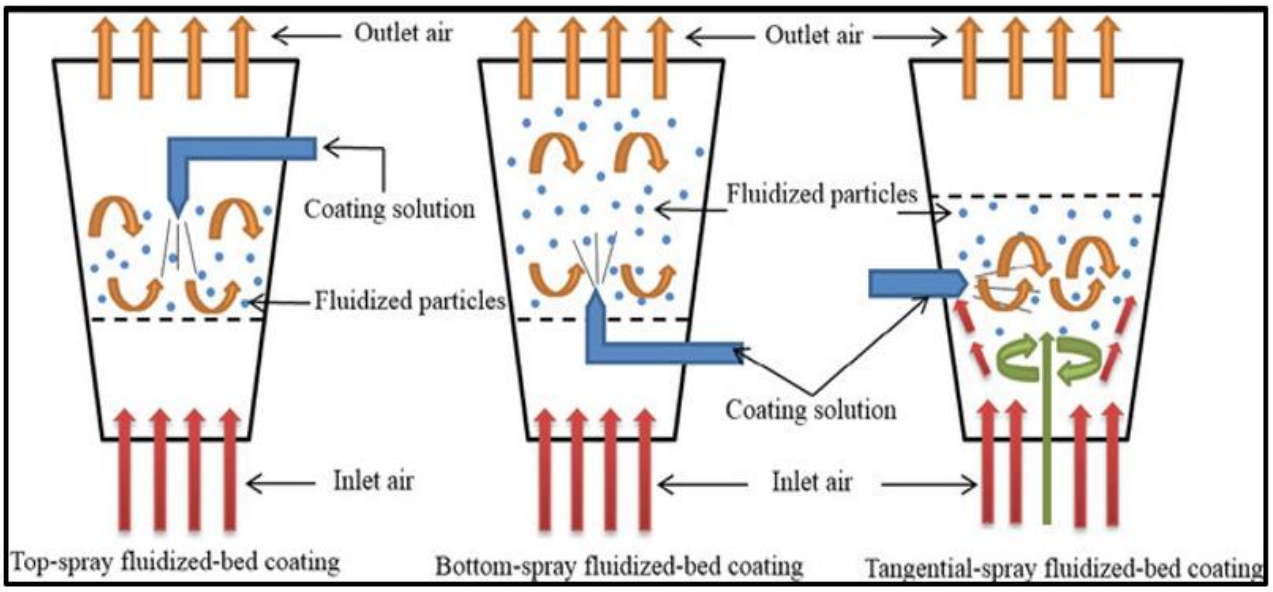


Figure 8 fluid bed processor

1. Top spray:

Process chamber having sufficient length allows pellet to be fluidized with velocity to reduce risk of agglomeration of pellets. Shape of process chamber is conical which helps in distributing hot air throughout the chamber uniformly. The arrangement provides proper shaking that help the fines to come back into the bed without the fluidization interruption this helps to reduce the agglomerations. Spray nozzle is there at the top of the process chamber which is associated with the coalescence of pellets with coating solution from very short distance providing longer drying path for the coated pellets.

2. Bottom spray:

Bottom spray technology is widely used for the coating of the pellets. It is also known as wurster technology. Bottom spray FBP is equipped with cylindrical shaped process chamber having perforated plate at the bottom above which cylinder shape fitting is there which is known as column. Coating solution is sprayed on the pellets through spraying nozzle fitted at the bottom, at the middle of perforated plate. This perforated plate has large size pore at the middle area and smaller sized pore at the periphery of the plate. Number of pores present at the periphery area determines the type of plate used. This technology is preferably used in developing modified release dosage forms as it provides continuous, uniform and reproducible coating procedure.

3. Tangential spray:

Tangential spray method is used for the wet granulation process. In this method spraying nozzle is fitted at the side of process chamber. Principle function involved in is spinning the variable disk. during the coating process following three forces helps in moment of particle, granulation process and mixing:

- Centrifugal force created by the spinning dish
- Uplifting force due to air
- Gravitational force of falling particle (Korakianiti, Rekkas, Dallas, & Choulis, 2000)

WURSTER COATING:

Wurster technology is used for the coating of powder or pellets as well as drying of the granules. for the efficient coating, solvent whether it be aqueous or non-aqueous, it should be evaporated as coating depends on the drying process.(Nikowitz, Jr, Pintye-hódi, & Jr, 2011)

Mechanism involve in wurster coating process:

Wurster coating technology is used for the pellet and powder coating purpose where, it utilizes the 100gm to 800 gm capacity process chamber to coat submicron sized pellets. Process chamber of wurster process is conical in shape having cylindrical column in the centre.at the bottom of the process chamber plate with different sized orifice is present which is known as "Air Distribution Plate (ADP)". ADP plate is sub divided in to two different regions. First part is having larger sized orifice an placed under the column of the process chamber which is highly permeable for the hot air travelling from the bottom to fluidized pellets present in chamber. while second part having small sized orifice distributed at the periphery of the plate. Spraying nozzle present at the bottom to spay the coating solution have two major characteristics: one is, nozzle with bifunctional property of spraying coating solution as well as atomization of the droplets of the sprayed solution.

Spraying angle of the spraying solution around 25-45 creates cone shape which is called as "zone of coating". Bottom plate is used by considering the particle size and the density of pellets. Column height determines the flow of pellets parallel to zone of coating. During coating process, column height should be increased with respect to increased size of column to maintain the flow of pellets throughout the process. In this process rate of heat as well as mass transfer high and which results to an efficient coating process. API having high aqueous solubility are coated with least core penetration problem. Droplets of spraying solution uniformly spread over the surface of pellet and creates continuous film followed by drying.(Solanki, Basuri, Thakkar, & Patel, 2010)

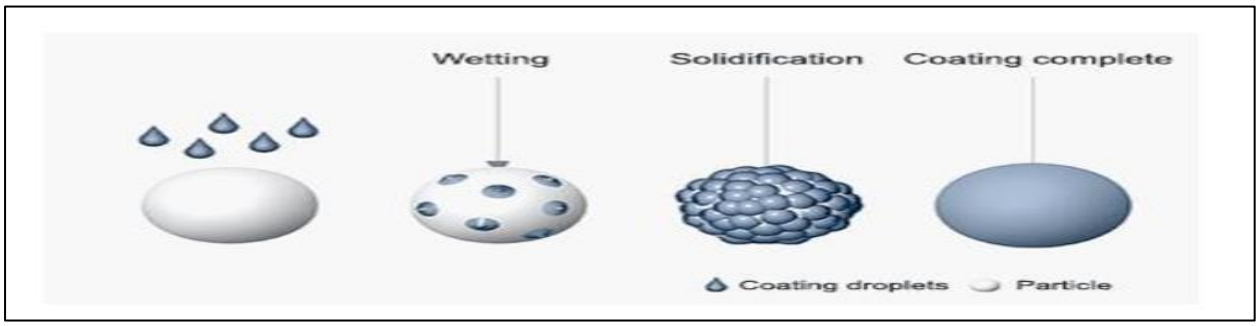
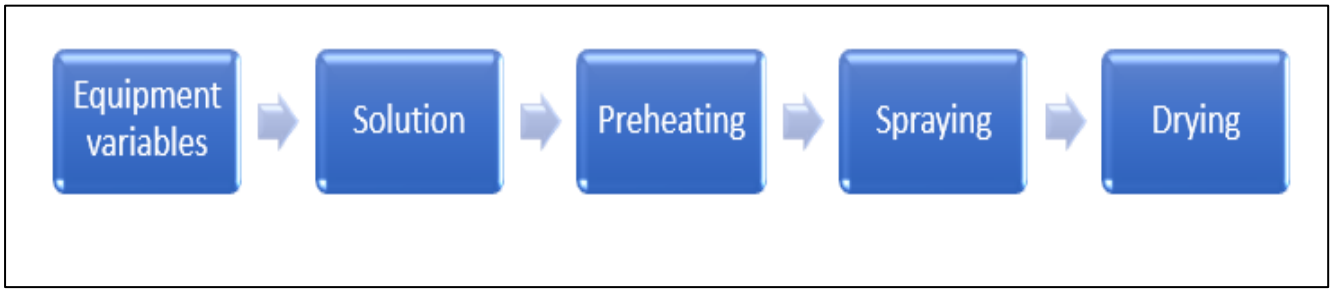


Figure 9 pellet coating

Process variable involved in pellet coating by wurster technology:



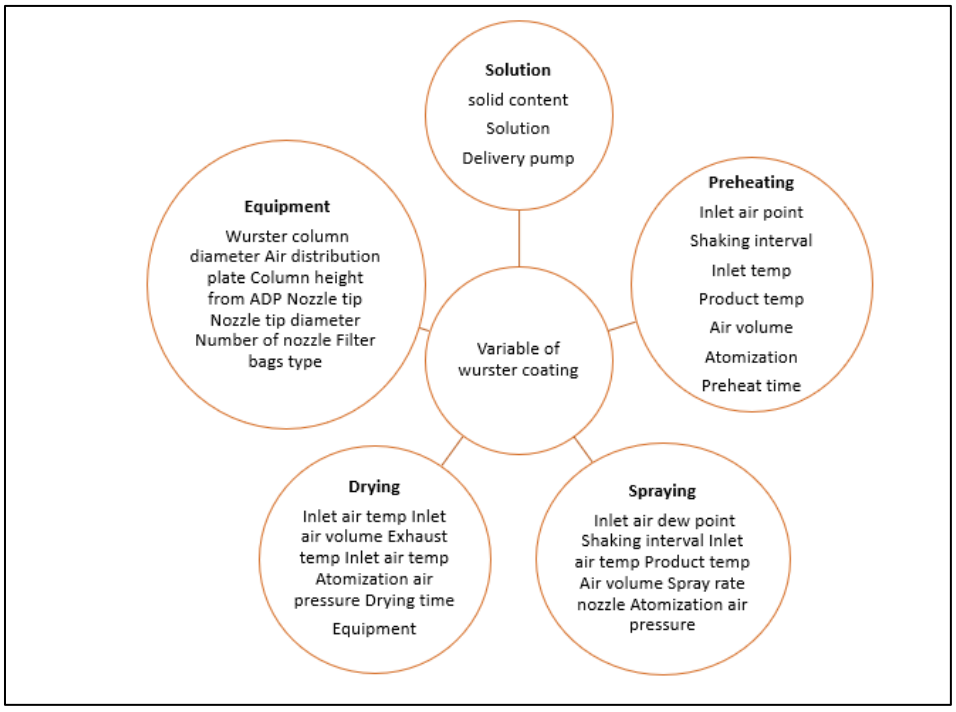


Figure 10 process variable for coating process

1. Air Distribution Plate (ADP):

During the coating process, air distribution plate is needed to decrease attrition and to get consistent fluidization by proper air distribution and efficient flow of pellets. Velocity of fluidized pellets is affected by size of pellets and volume of air required to fluidized it. At the air distribution plate, velocity of fluidization air and pressure difference should be identical. Thus, when smaller sized pellets are used plates having lesser number of orifices are used to generate resistance for efficient distribution of air. Types of air distribution plate used in wurster process.(Kumar et al., 2012)

equipment	Pellet size in micron	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

2. Column height:

Circulation of pellets is important variable as inefficient circulation may lead to accumulation and followed by agglomeration. (Patel, Patel, & Joshi, 2018)This can be prevented by adjusting distance of column from the zone of coating and up bad partition of column. Column height is set by considering the size of pellets and density as well as flow required for the pellets coating. Column height is critical process parameter specifically for the small sized pellets as exposure of pellets to sprayed solution in coating zone determines the level of coating which affects the rate of dissolution from the formulation. If gap between bed of pellets and column is high, agglomeration of pellets occurs due to excess spraying due poor flow and if it is too low, then very less quantity of pellets will enter in column resultant over wetted pellet generation. Thus,

height of column plays an important role in pellet coating process.(Mikulski, Celej, Jankowski, Majewska, & Mikulska, 2011)

3. Nozzle diameter:

Nozzle diameter of spraying nozzle is selected depending on the quantity of solution to be sprayed as well as viscosity of the spraying solution. During coating process of pellets, higher atomization pressure is required to convert large droplet into smaller once to prevent agglomeration of the pellets. For the nozzle, it is important to note that it should be able to atomize spraying solution and should also provide high spray rate during the process. Inefficiency of nozzle may lead to generation of larger sized droplets. (Srivastava & Mishra, 2010)

4. Coating solution:

Coating solution should contain adequate amount solid contain which helps in ease of coating process. Viscosity of spraying solution determines the quality of spraying as highly viscous solution than spray rate is to be reduced and solution with solid content lead to prolonged process time.(Xu, Khan, & Burgess, 2012)(Osei-yeboah, Lan, & Calvin, 2017)

5. Dew point:

Dew point can be defined as," the atmospheric temperature below which water droplets begin to condense and dew can form". During the pellet coating process, coating is followed by drying process which is highly dependent on inlet temperature and humidity of the process chamber. (Patel et al., 2018)Psychometric chart is used to understand relationship between humidity and inlet air temperature. Drying is process of evaporation of solvent from the surface of the pellets which changes with the change in dew point of process chamber air. By maintaining lower humidity efficient drying can be carried out in lower temperature but that also increases the chance of static charge generation. While, in highly humid condition, depression in air temperature lower the dew point results in condensation of water at the surface

of process chamber or on the surface of pellets. For the coating of water-soluble drug, at the starting of the process high moisture is not recommended but as the process proceeds humidity can be increase as development of static charge on the surface of pellet will take place.(Article, 2011)

6. Inlet temperature and product temperature:

Quality of coating depends upon the product temperature which is controlled by maintaining balance between inlet temperature and exhaust temperature. Drug migration and agglomeration of pellets can be controlled by constantly monitoring the product temperature.(Mikulski et al., 2011) Porous and nonuniform coating occurs in high temperature as spraying droplets are rapidly evaporates before reaching to the surface of pellets. While in low temperature process time increases as coated particle of drug migrates toward the moist surface of the pellets which affect the rate of dissolution.(Palugan, Cerea, Zema, Gazzaniga, & Maroni, 2015)

Thus, optimum product temperature is requiring. Preferable when aqueous system is used it is kept as 40°C while in case of non-aqueous system it is kept as 29-31 °C.

7. Spray rate:

In wurster coating process, binary spraying nozzle is used for the spraying of coating solution. During coating, number of process takes place simultaneously including spraying of solution, coalescences between droplet and pellets and evaporation of solvent. Spray rate for the coating highly depends on the properties of particle dissolved in coating solution as well as properties of coating solution which include the drying capabilities and stickiness of the solution. For the coating of small sized pellets or particles, droplet size of coating solution is kept very smaller to prevent agglomeration. Core solubilization occurs at the beginning of the process, thus, at this stage spray rate kept is very low and further, as process occurs spray rate is increased slowly. (Wang et al., 2015)

8. Volume of Air:

It is important for the proper fluidization and proper drying of the pellets while the coating. Less air flows might not provide proper drying to the air in the circulations of pellets and might not remove the moisture from the settled droplets while the coating and it leads to the more agglomerations.

Though higher airflow can produce the higher attrition and it creates erosion of the core or cracks and may also augments spray drying. This also creates the loss of the release property of the functional coating. ("Recent Techniques For Oral Time Controlled Pulsatile Technology Recent Techniques For Oral Time Controlled Pulsatile Technology," 2009)

Rate of air flow is different for the all equipment and it also depend on the characteristics of the products such as particle size, density and shape. Bubbling type of fluidization used for the non-aqueous coating because it reduces the generation of the static charge and friction between particle, but in aqueous coating process more precise fluidization is required for more drying capacity.

9. Drying time:

Higher viscosity solution due to polymer dissolved in it need to be evaporated in order to form continuous film over the surface of pellets. As film formation occurs after formation of gel state on evaporation of solvent. due to high glass transition temperature of polymer dissolved in solution, high drying temperature required to form a film, to reduce it plasticizers is added to it.(Srivastava & Mishra, 2010)

2. AIM AND OBJECTIVE OF RESEARCH

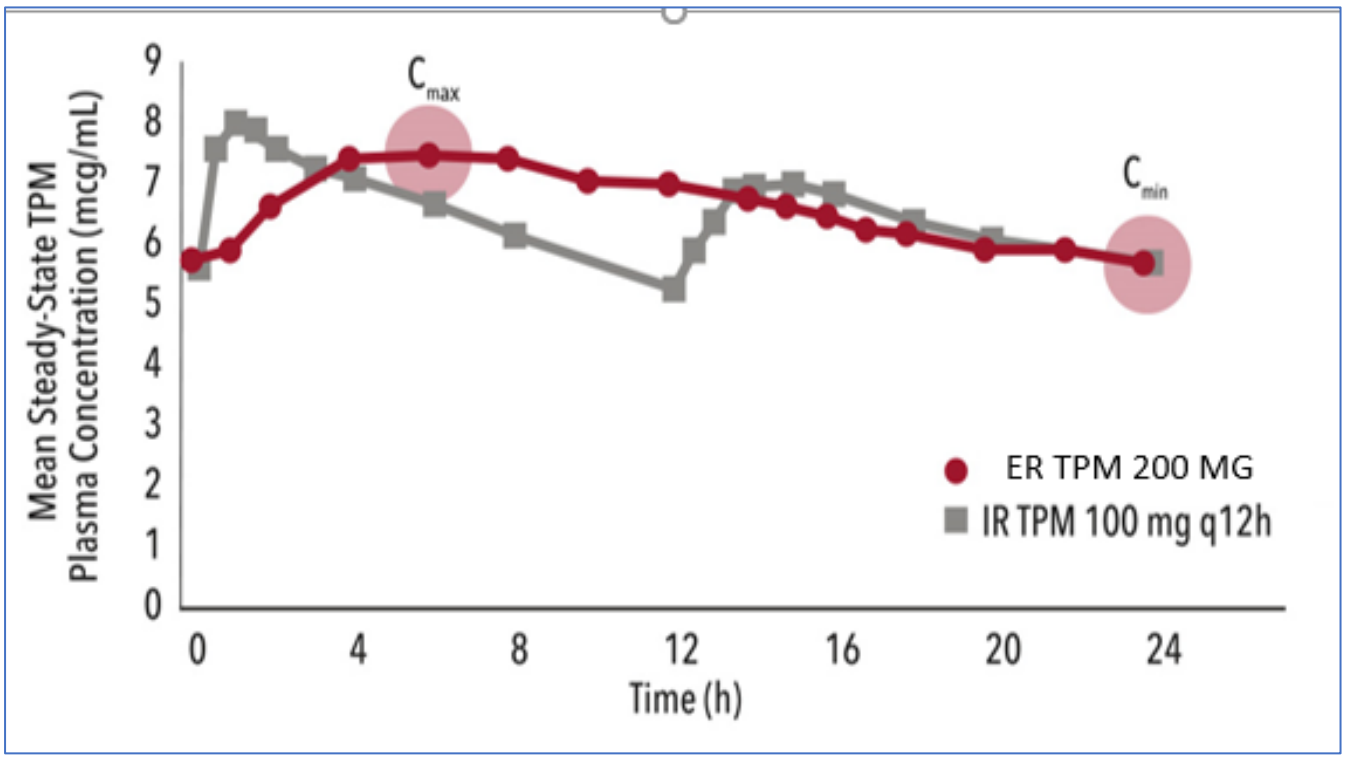
2.1 AIM:

Multi-unit particulate system is prepared by using many techniques among which wurster coating process is widely used method. Aim of this research is to formulate extended release multiunit particulate system for an antiepileptic drug and establish the bioequivalence with the innovator's drug product. To formulate this system, drug layering technique using reservoir technique was used in which subsequent layering on drug followed by barrier layer coating and extended release coat as applied. To retard the release of drug ratio of ethyl cellulose and hydroxy propyl cellulose was optimized. Process parameters were also evaluated to obtain high efficiency of the process.

2.2RATIONALE:

Extended release multiunit particulate system for an antiepileptic drug is prepared to provide drug release for 8 hours suggesting twice daily dose in treatment of epileptic seizure. Immediate release formulation for this drug is available in market. But this drug is having some severe adverse effect which include somnolence, speech disorder, ataxia. Abnormal vision, problem associated with memory, diplopia, paresthesia and acute myopia can also be take place. Thus, nevertheless drug is having long biological half-life of 19-21 hours, it is generally not prescribed as once a daily dose as fluctuation in plasma drug concentration after administering single high dose lead to precipitation of side effect. For this reason, drug is prescribed in twice daily dose but after taking each dose there is increase in plasma drug concentration followed by decrease concentration which again rise after administration of second dose, which results in to peak and valleys plasma concentration vs time profile which is very harm full for the patient. Therefore, there is a need for a formulation of topiramate, which reduces or eliminates the side effects associated with peaking and fluctuating plasma levels of the drug. For this purpose, extended release formulation of this drug is formulated. Multiunit particulate system is advantageous over tablet is that, as it is made up of several

micro sized pellets, each of them release the drug independently to other pellet results in very rare chances of dose dumping.



OBJECTIVE OF RESEARCH:

- To select core pellets
- To optimize process parameters for coating using lab scale mini GLATT process
- Drug layering on core pellets.
- Establishment of equivalence by dissolution profile of developed product and innovator's product.

3. LITERATURE SURVEY

3.1 Literature survey for Multi-Unit Particulate System (MUPS):

Magdalena M.et al. 2017 studied the polymer effect on taste masking using different type of eudragit polymer Grade and MUPS formulated by different techniques. from all the grades, Eudragit® E PO was used for the taste masking polymer. MUPS were formulated by extrusion technique and spray-drying approach utilizing the drug, Eudragit® E PO as well as lipid for enhancing the taste masking effect. Among these, ground extrudes were efficiently delayed the release of drug in salivary pH and found more stable in at after storage as compared to spray dried pellets.(Gittings, Turnbull, Roberts, & Gershkovich, 2014)(Münster, Schoch, Schmidt, & Breitkreutz, 2017)

Chen K. et al. 2017 studied the effect of enteric coating polymer for the development of duloxetine hydrochloride pellets. For the development, core pellets were coated with drug layer coat followed by barrier layer coat and enteric coat. For optimization of enteric coat three type of polymer were investigated, Aqoat® AS-LF, Eudragit® L30D55 and HPMCP-HP55 for coating weight gain of 35,26 and 24 % respectively. Study concluded that the pellets prepared with Eudragit® L30D55 and Aqoat® AS-LF was optimized on the basis of dissolution profile and stability studies.(Kuang et al., 2017)(Abdul, Chandewar, & Jaiswal, 2010)

Tongkai C. et al. 2017 formulated a tablet from controlled release MUPS and discussed about the parameter that are important for production of TMUPS. It also discusses about the drug properties, effect of cushioning agents and techniques to prevent damage caused to pellets during process.(Chen et al., 2017)(I. M. El-Mahdi, P. B. Deasy, 2002)

Saurabh S. et al. 2010 review the palletization technique for formulation of MUPS. Technologies discussed in this article is CPS™, MicroPx™, ProCell™. Applications as well as pros and cons are discussed associated with these technologies.(Fang, 2013; Ghebre-Sellassie & Knoch, 1996; Hirjau, Nicoara, Hirjau, & Lupuleasa, 2011; Kandukuri et al., 2009; Supriya et al., 2012; Thakkar et al., 2012)

Literature survey for wurster technology:

Shrevastava S. et al 2010 Studied importance of wurster technology for the formulation of the novel dosage forms with the high therapeutically efficiency. It shows the application of the fluid bed coating for coating, agglomeration, drug layering and granulation of the verity of the pellets. It is also used for the drying process as well. It shows that the types of the spray used for the coating and they are mainly different on the basis of the nozzle locations. (Avalle et al., 2014; Guignon, Duquenoy, & Dumoulin, 2002; Luštrik et al., 2013; Shelukar et al., 2000)

Table 1 Literature survey for epilepsy

Sr no.	Title of article	Description
1	Identification of new epilepsy treatments: Issues in preclinical methodology by Galanopoulos AS et.al.	Provide a framework that will help define future guidelines that improve and standardize the design, reporting, and validation of data across preclinical anti-epilepsy therapy development studies targeting drug-resistant seizures, electrogenesis, and comorbidities.(Engel & International League Against Epilepsy (ILAE), 2001; Fisher et al., 2014, 2005; Monteiro, Aroca, Margarit, & Herán, 2019; Shorvon, 2011)
2	Epilepsy and anatomy of human brain by Penfield W. et.al.	Structure-function coupling in 45 seizures from 9 drug-resistant localization-related epilepsy patients undergoing routine evaluation for epilepsy surgery.(Feindel, 1982)
3	Epilepsy fact sheet	"Epilepsy Fact sheet". WHO. February 2016. Archived from the original on 11 March 2016. Retrieved 4 March 2016. (World Health Organisation, 2016)

Table 2 Patents

Patent no.	Patent name	Description
US 8298580	Sustained-release formulations of antiepileptic drug	The formulations comprise a Sustained-release component and an optional immediate release component, the compositions of which can be selectively adjusted, respectively, to release the active ingredient along a pre-determined release profile.(Liang & Bhatt, 2014; Wagenaar & Den, 2009)
US 2009/0022794	Anti-epileptic drug tablet formulation	The invention provides pharmaceutical compositions, which are suitable for manufacturing tablet formulations by direct compression. The compositions preferably comprise spray-dried granulated mannitol and provide tablets of desired friability and hardness.(Bhatt & Vieira, 1993; Vieira, 2012)

4. EXPERIMENTAL WORK:

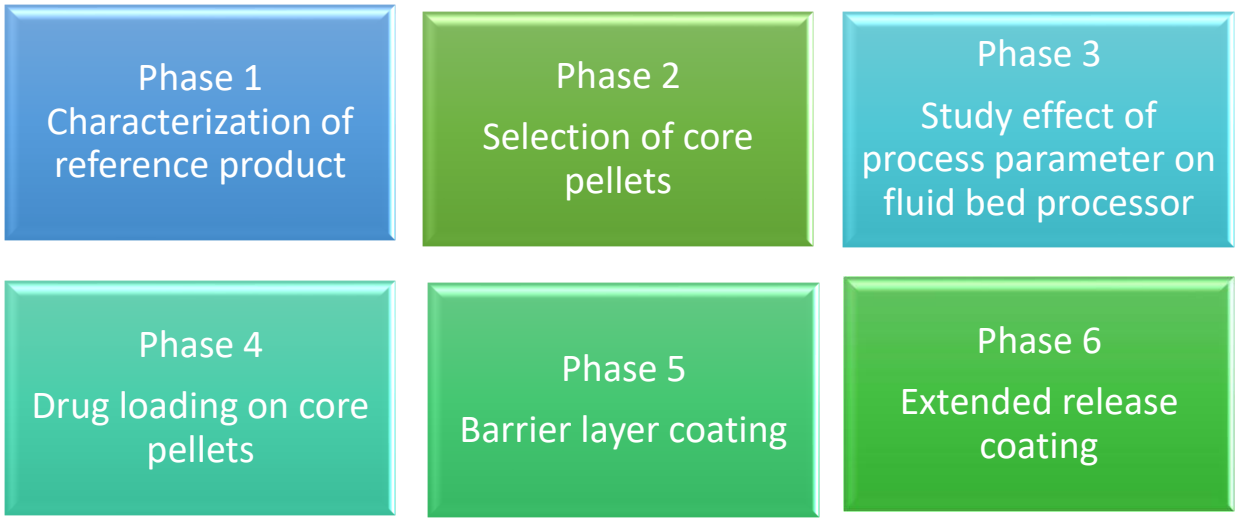


Table 1 Equipment

NAME OF EQUIPMENT	COMPANY
Fluid Bed Processor (GLATT)	Glatt pharma
Fluid Bed Processor (GLATT)	chronnimach
Extruder	chronnimach
Spheronizer	chronnimach
Tap density tester	Electrolab
Halogen moisture analyzer	Mettler Toledo
Dissoultion test appartaus	Electrolab

Table 2 Material used:

Test product	Function
Antiepileptic drug	Active pharmaceutical ingredient
Microcrystalline cellulose(sphere)	Core substance
Povidone (K-90)	Binder
Polyethylene glycol	plasticizer
Hypromellose 6cps	Barrier coating
Polyethylene glycol	Film forming agent
Sodium carbonate anhydrous	Alkalizer
Talc	Anti-tacking agent and lubricant
Ethyl cellulose 20cps	Rate controlling agent
Povidone (k-30)	Pore former
Triethyl citrate	plasticizer
Purified water	Vehicle
Methylene chloride	Dispersion media
Isopropyl alcohol	Dispersion media

4.1 PHASE: 1 CHARACTERIZATION OF REFERENCE PRODUCT:

4.1.1 Drug release of reference product:

Dissolution:

The drug release of Reference Listed Drug (RLD) (antiepileptic drug) extended release capsules 200 mg were characterized using Office of Generic Drugs (OGD) recommended dissolution media and in-house developed dissolution media.

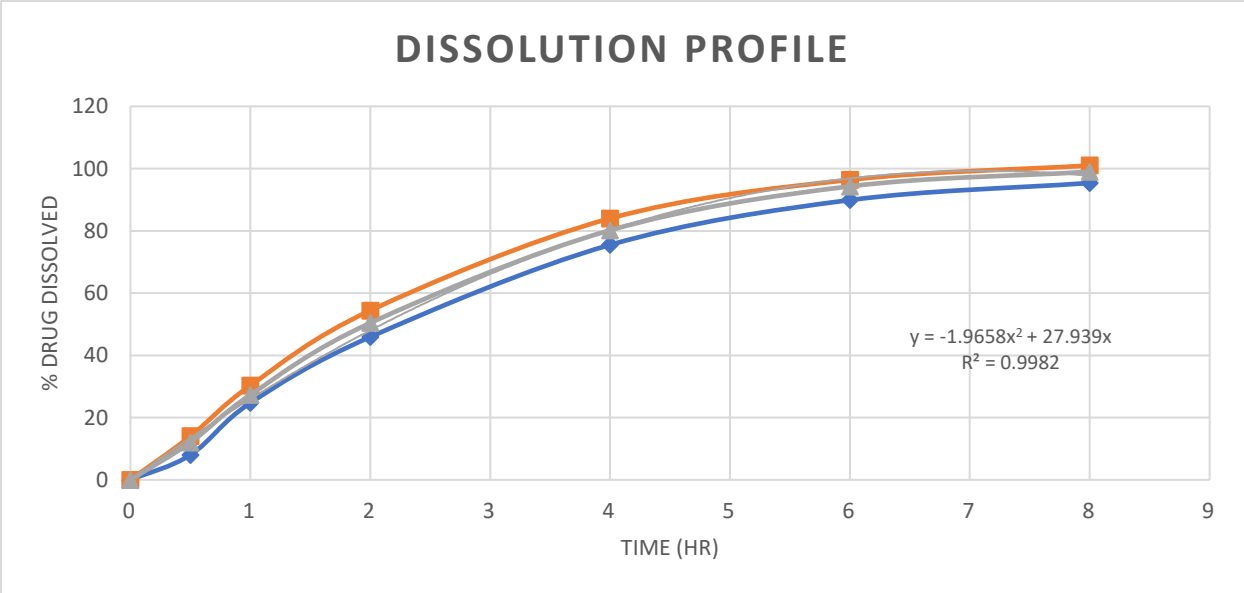
Table 3 selection of dissolution media

OGD recommended dissolution media				
USP apparatus	Speed (RPM)	media	Volume(ml)	Time point (hour)
Paddle (2)	50	0.05M phosphate buffer, pH 7.5	750	1,2,3,4,5,6 and 8
Basket (1)	100	50mM TRIS buffer, pH 7.2 TRIS: TRIS (hydroxy methyl amino methane)	900	0.5,1,2,4,6 and 8

It is observed that OGD has two dissolution method recommendations for API extended release capsule. These methods are acceptable for the development process. 50mM TRIS buffer at pH 7.2 was used as dissolution media. 900 ml dissolution media were taken in USP-1 (Basket) apparatus at 100 RPM. Samples were collected at 0.5 hr, 1 hr,2 hr,4 hr,6 hr and 8 hr. samples were analyzed by using HPLC method. for detection of the concentration of API, refractive index detector was used.

Table 4 dissolution profile for reference product

900 ml, 50mM TRIS buffer pH 7.2, USP-1(basket), 100 RPM (200mg)							
Time point (hr)	0	0.5	1	2	4	6	8
Min	0	8	24.7	45.9	75.5	89.9	95.4
Max	0	14	30.3	54.4	84	96.4	101
Mean	0	12	27.3	50.4	80.2	94.3	99
RSD	0	18.4	7.5	6.1	4.4	2.8	2



CONCLUSION:

RLD XR (API) extended release capsule 200mg shows complete dissolution in OGD recommended method hence OGD recommended dissolution method i.e., 900 ml of 50mM TRIS buffer pH 2.2 USP-1 at 100 rpm at 0.5 hr, 1 hr,2 hr,4 hr,6 hr and 8 hr has been considered for development.

4.1.2 Physicochemical Characterization of Reference Product:

The formulation development started with thorough physicochemical characterization of reference product. The attributes of proposed generic product are decided on the basis of reference listed drug (RLD) characterization.

Table 5 physical characterization of reference product:

RLD XR (API) EXTENDED RELEASE CAPSULE					
STRENGTH	25 mg	50 mg	100 mg	150 mg	200 mg
Average capsule weight(mg)	99.2	168.2	312	448.8	591
Avg filled weight (mg)	60.5	119.4	241.6	359.6	487.8
Capsule size	Size 4	Size 3	Size 1	Size 0	Size 0EL
Capsule volume (cc)	0.21	0.30	0.50	0.68	0.78

4.1.3 Composition Of Reference Product:

Based on the reference product labelling, excipient used in the reference product are provided in table below. The functions of each excipient are also provided based on literature and prior knowledge of excipient's functions.

Table 6 list of components of reference product

Reference drug product component	Functions
API	Antiepileptic drug
Microcrystalline cellulose	Diluent
Hypromellose	Binder and release controlling agent
Ethyl cellulose	release controlling agent
Diethyl phthalate	plasticizer
Components of capsule shell	
Hypromellose	Capsule shell former
Titanium dioxide	Opacifier
Black iron oxide	Coloring agent
Red iron oxide	Coloring agent
Yellow iron oxide	Coloring agent
Black pharmaceutical ink	Printing ink
White pharmaceutical ink	Printing ink

Dissolution method development/selection:

Development of a dissolution method that can act as the suitable predictor of equivalent pharmacokinetics to the RLD was pursued to allow assessment of API extended release capsule manufactured during development.

OGD recommended dissolution method:

FDA has been recommended two dissolution methods for API extended release capsule which are as follow:

Table 7 OGD recommended dissolution methods

USP apparatus	Speed (RPM)	media	Volume(ml)	Time point (hour)
Paddle (2)	50	0.05M phosphate buffer, pH 7.5	750	1,2,3,4,5,6 and 8
Basket (1)	100	50mM TRIS buffer, pH 7.2 TRIS: TRIS (hydroxy methyl amino methane)	900	0.5,1,2,4,6 and 8

Dissolution media:

API exhibit pH independent solubility across the pH from 1 to 7.5 solubility of the API is given below:

Table 8 Solubility of API

Medium	Solubility (mg/ml)
0.1 N HCl	7.7
pH 4.5 Acetate buffer	8.19
pH 6.8 potassium phosphate buffer	7.57
Water	8.02
pH 7.2 TRIS buffer	8.22
pH 7.5 phosphate buffet	7.66

Though API has good solubility across the pH range, it is not stable in acidic dissolution media hence dissolution media is preferably to be selected from alkaline buffer. Selection of development product uses Hypromellose capsule shell as that of RLD XR traces present in capsule shell interact with large group cation such as potassium and induce gelation. This gelation retards the dissolution of Hypromellose capsule. TRIS buffer does not carry any cation which may induce the gelation hence TRIS buffer and alkaline pH 7.2 is suitable as dissolution media.

Table 9 Dissolution of API

900 ml, 50mM TRIS buffer pH 7.2, USP-1(basket), 100 RPM (200mg)							
Time point (hr)	0	0.5	1	2	4	6	8
Min	0	8	24.7	45.9	75.5	89.9	95.4
Max	0	14	30.3	54.4	84	96.4	101
Mean	0	12	27.3	50.4	80.2	94.3	99
RSD	0	18.4	7.5	6.1	4.4	2.8	2

It was observed that first time point 0.5 hr shows significantly higher %RSD. High %RSD may be attribute of the Hypromellose capsule shell which takes higher time than gelatin shell to disintegrate and shows variation in first time points.

CONCLUSION: OGD recommended dissolution method has been found to be suitable for the development and QC purpose, from the dissolution profile, three time points have been selected for the QC purpose.

Dissolution specification for 200 mg strength is:

1 hr: not more than 35%

2 hr: 37-67%

6 hr: not less than 75%

Composition Of Drug Product:

4.1.4 Drug substance

Physical and chemical properties:

Table 10 Summary of physicochemical properties of API:

Characteristic	Observation	
Physical description	White to off white crystalline powder	
Aqueous solubility (solubility at different pH)	**Buffer at different pH**	**Solubility(mg/ml)**
	0.1 N HCL	7.7
	pH 4.5 acetate buffer	8.19
	pH 6.8 potassium phosphate buffer	7.57
	water	8.02
	pH 7.2 TRIS buffer	8.22
	pH 7.5 phosphate buffer	7.66
From the above data, it can be concluded that API has good solubility throughout pH range. The calculated dose solubility volume is as follows: 200/7.57 (highest strength/lowest solubility) = 26.42 < 250 ml.		

Dissociation constant	11.09 (strong acidic)- 3.7 (strong base)
Melting range	123℃ to 127 ℃
Partition coefficient	-0.7
Hygroscopicity	Non-hygroscopic
Therapeutic category	Anticonvulsant

Characterization of drug substance:

API drug substance is thoroughly evaluated for its physical and chemical properties which may affect the final quality of drug product. The following drug substance attributes are taken into consideration for the drug product development.

1. Aqueous solubility at various pH
2. Particle size
3. Micromeritic properties
4. Chemical stability

The drug substance's solubility at various pH: One representative batch of API was selected to study solubility in aqueous media as a function of pH as per method for BCS and solubility results are presented in table below:

Table 11 Solubility of drug substance

Medium	Solubility (mg/ml)	Solubility (mg/ 250 ml)
0.1 N HCl	7.7	1925
pH 4.5 Acetate buffer	8.19	2048
pH 6.8 potassium phosphate buffer	7.57	1893
Water	8.02	2005
pH 7.2 TRIS buffer	8.22	2055
pH 7.5 phosphate buffet	7.66	1915

The aqueous solubility of API is high (~7 to 8 mg/ml)

Calculated dose solubility volume:

Maximum strength for API is 200 mg

Strength to solubility ratio 9 for (0.1 N HCl) = 200/7.70= 25.97 ml (which is less than 250 ml)

Therefore, API is considered as highly soluble drug substance according to BCS classification.

Particle size of the drug substance:

As inferred from solubility data, API is high soluble compound where drug solubility does not govern and controlled by extended release coating. Hence, particle size control from formulation point of view is not of importance.

However, process involves spraying where bigger particles or its lumps may block the spray nozzle or may show poor efficiency. For the process suitability particle size control has been kept as a part of specification.

In order to assure consistent product quality, three representative batches were selected for characterization of particle size distribution. Dry dispersion method using Malvern Mastersizer was used for characterization.

Table 12 particle size of drug substance

Batch no. Particle size	Batch-1	Batch-2	Batch-3
D (50)	4	3	3
D (90)	9	7	9

Conclusion:

Particle size does not show lot to lot variation. In order to achieve process ease, two tier particle size, as given below, has been considered.

- D (90): Not more than 15 microns
- D (50): Not more than 8 microns

Micromeritics properties of drug substance:

In addition to solubility and particle size distribution, micromeritics like bulk density and tapped density has also measured in same three batches.

Table 13 micromeritic properties of drug

Batch no.	Batch-1	Batch-2	Batch-3
Bulk density (g/cc)	0.44	0.33	0.32
Tapped density (g/cc)	0.54	0.42	0.41

Conclusion:

Bulk density and tapped density for representative batches have been close and reproducible. Additionally, process of API drug loading does not depend upon flow properties of API hence these parameters have not been kept as a part of specification.

Solid state chemical stability studies:

API stress testing was done to investigate impurity profile of an API. To study pathway of degradation and to enable development of stability-indicating process. The specified stress condition was intended to achieve 5-20% degradation of API or to represent a typical stress condition.

The stressed samples were compared to the unstressed sample (control). Stress conditions and results are listed in table below:

Table 14 solid state chemical stability studies

IMPURITY	AS SUCH CONDITION	ROOM TEMP TREATMENT	THERMAL TREATMENT
API	99.97	99.98	99.98
Impurity-1	Not detected (ND)	ND	ND
Impurity-2	Below limit of quantification (BLQ)	BLQ	BLQ
mx. Unknown impurity	0.006	0.004	0.003
Total impurity	0.006	0.004	0.003

IMPURITY	Acid treatment			Alkali treatment		
	0.1N*	0.1N**	0.01**	0.1*	0.1**	0.001**
API	92.12	99.36	97.24	91.93	99.82	97.1
Impurity-1	ND	ND	ND	ND	ND	ND
Impurity-2	BLQ	BLQ	BLQ	BLQ	BLQ	0.0019
Max unknown	0.403	0.103	0.011	0.325	0.018	0.007
total	0.446	0.103	0.011	0.344	0.018	0.026

*(with neutralization) **(without neutralization)

Samples were analyzed by HPLC equipped with refractive index detector. Degradation peaks can be easily differentiated from the peak of API. Purity index of API is more than 0.990. indicating no significant interference of degrades with the main peak.

Impurity-1 was not detected in any of the forced degradation pathway. Impurity-2 was also stable and were below BLW. Only significand degradation was observed in acid and alkali degradation routes producing maximum unknown impurity up to 0.4% in acid degradation with 0.1N HCL with neutralization. Based on forced degradation study, API can be considered as a stable molecule. Forced degradation study suggested to avoid direct contact of any acidic or alkali with API. However, these findings to be verified during compatibility study.

4.1.5 **Excipient Compatibility Study:**

Excipient drug substance compatibility was assessed and analysis of binary mixtures of excipient and drug substance in the solid state was carried out. Sample were stored at 40℃/75% RH in glass vials for 1 month (open condition). common excipients, functioning as diluent, binder, rate controlling agent, antitacking agent, dispersion media.

The excipient to drug substance ratio selected based on intended function and maximum quantity that can be used in final formulation for API ER capsule.

Table 15 excipient compatibility study- chemical analysis

Sr no.	ingredient	Ratio		Initial			40℃/75% RH (1 month)		
		API:	Excipient	Imp 2	unknown	total	Imp 2	unknown	Total
1	API	1	-	ND	ND	0	ND	ND	0
2	API + sugar sphere	1	5	ND	ND	0	ND	ND	0
3	API+ mcc sphere	1	5	ND	ND	0	ND	ND	0
4	API+ HPMC	1	2	ND	ND	0	ND	ND	0
5	API + EC	1	2	ND	ND	0	ND	ND	0
6	API + WATER	1	-	ND	ND	0	ND	ND	0
7	API+ PVP	1	1	ND	ND	0	ND	ND	0
8	API + TEC	1	0.5	ND	ND	0	ND	ND	0
9	API + TALC	1	0.5	ND	ND	0	ND	ND	0
10	API + PEG	1	0.5	ND	ND	0	ND	ND	0
11	API + SODIUM CARBONATE	1	0.5	ND	ND	0	ND	ND	0

4.1.6 **Drug Product**

4.1.6.1 QUALITY TARGET PRODUCT PROFILE (QTPP)

QTPP can be defined as," a set of elements that defines the drug product." It is established as target for drug product. Drug release and assay were specified as CQAs.

Table 16 QTPP for drug product

QTPP ELEMENTS	IDEAL CHARACTERISTIC	CRITICAL QUALITY ATTRIBUTE	EXPLANATION
Administration	Oral route	N	Formulation is prepared to be administered through oral route
Formulation	pellets	N	Equal distribution in gastro intestinal track
Strength	200 mg	N	Pharmaceutically active dose
Release profile of product	For 1 hour it should not be more than 35% For 2 hour it should be in range of 37-67% Up to 6 hour it should not be less than 75%	Y	specification given in pharmacopoeia
Assay	90 to 110%	Y	Requirement given by regulatory authorities

*N= no and Y= yes

Risk valuation by Failure Mode and Effect Analysis (FMEA)

FMEA tool was used for initial risk assessment. FMEA tool can identify the failure modes having effect on product and which can cause failure of product. i.e., QTPP requirements. The sternness of failure effect (S), possibility of accurance (O) and prior detection (D) for cause of failure was rented. Which can be given as,

Risk Priority Number = S *O *D

The risk nature is stated as high-red colored if of RPN number is between 285-990, medium - yellow colored for number between 90-280 and low-green colored for 1-95. Attributes that impact the quality attributes are further evaluated.

4.2PHASE 2 : CORE PELLETS SELECTION:

Inert Core pellets acts as the substrates on layering of drug as well as barrier layer coating and release controlling coating is done. Tartaric acid sphere microcrystalline cellulose (MCC) sphere and sugar sphere are used as core pellets in pharmaceutical industries. MCC sphere also known as celphere are made up of 100 % MCC while sugar spheres are made up of sucrose and starch.

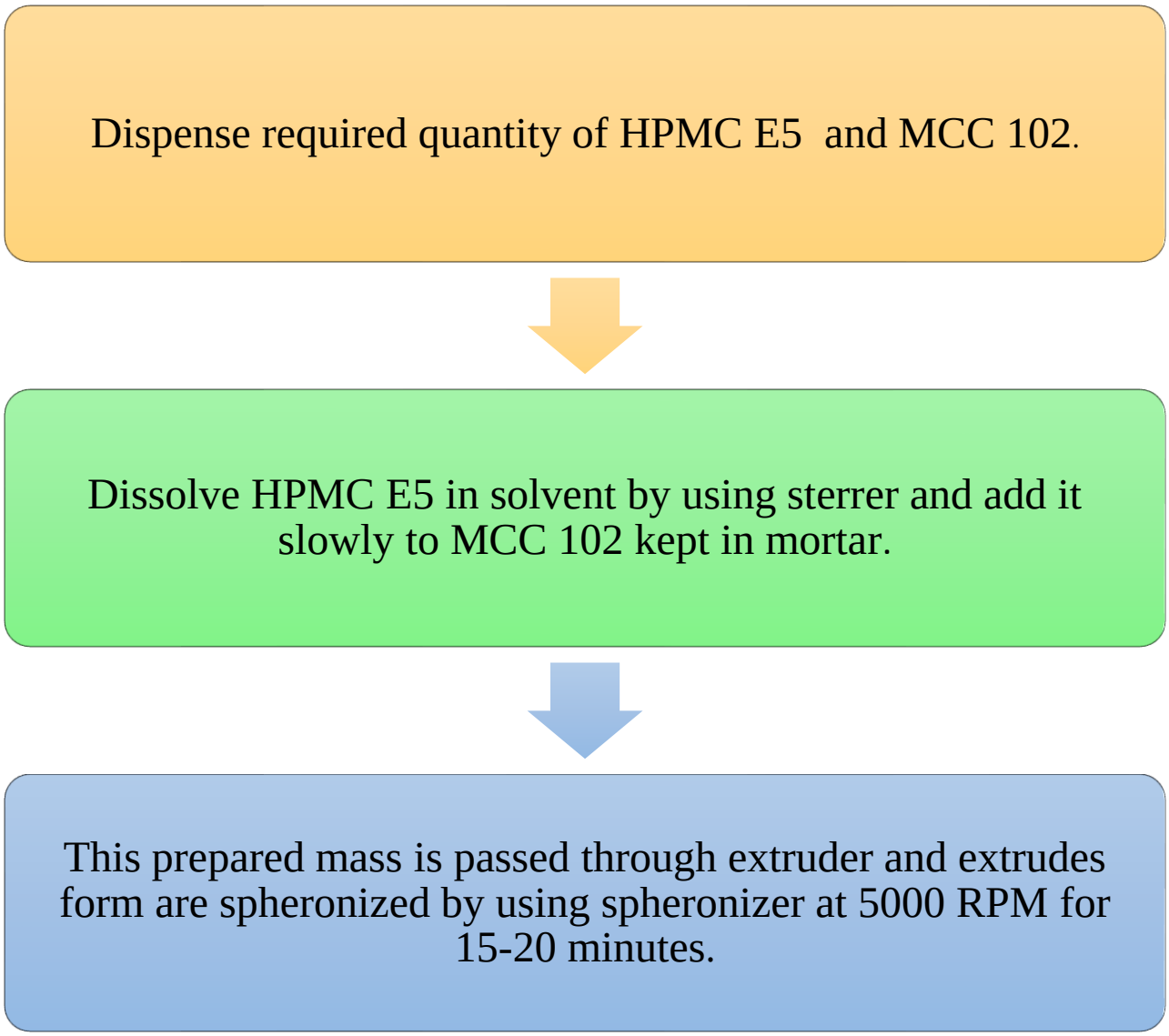
Sugar sphere intake in several disease like diabetes and hypertension is not desirable. Moreover, sugar sphere was found more hydrophilic in nature and having effect on the drug release profile of the formulation. Tartaric acid spheres used soluble in aqueous media in addition desired use is for ER purpose. Thus, celphere are utilized as inert core pellets. Celphere are highly spherical and have narrow particle size distribution providing consistent drug layering and accurate coating. Moreover, celphere have low friability and high mechanical strength which allows them to tolerate the shear developed in Wuster coating. For the given reasons, MCC sphere was used as inert core material for the further process development.

Selection of core pellets from pellets prepared by extrusion spheronization technique using lab scale extruder and spheronizer and ready-made readymade pellets was studied.

Core pellets prepared by extrusion spheronization technique, involve four stage process:

- Granulation
- Extrusion
- Spheronization
- drying

Method of preparation:



To formulate pellets with desired flow properties and size, trials were taken for the optimization of formulation:

Table 17 Optimization of binder concentration:

Batch	A1	A2	A3	A4	A5
HPMC E-5	5%	10%	5%	10%	7%
PVP K-30	-	-	3gms	-	-
Binder usage (IPA: water) (75:25)	12ml	10ml	10ml	15ml	15ml
MCC-102	20 g				

CONCLUSION:

By performing this experiment it was observed that, 10% w/v HPMC E-5 solution in 15 ml of IPA: water (75:25) can be used for the granulation process to formulate pellets.

Ratio of IPA : water was optimized by performing following trials. Where, 10% w/v HPMC E-5 as binder solution was used.

Quantity of binder solution prepared was 15 ml for all the following batches.

Batch	A6	A7	A8	A9	A10	**A11**	A12
IPA	30%	70%	50%	80%	60%	**75%**	75%
Water	70%	30%	50%	20%	40%	**25%**	25%

CONCLUSION: IPA : water in ratio of 75:25 was able to formulate sphere. Thus, it was selected for the further development process

Table 18 Result of optimized batch:

Parameters	Batch A11
Bulk Density	0.7
Tap Density	0.734
Hausner's ratio	1.05
Carr's index	4.63
%Yield	80.8%

Conclusion:

As per the results obtained, pellets formulated by extrusion spheronization technique showed good flow properties. But, it was having wide size distribution range suggesting non-uniform particle size. Moreover, they were highly friable as compared to ready made pellets. Thus, for the further development, readymade ready made pellets were used.

4.3PHASE: 3 STUDY THE EFFECT OF PROCESS PARAMETERS ON COATING PROCESS:

To study the effect of process parameters on coating process, mini GLATT machine was used. Inert MCC pellets were coated by 5% w/w solution of HPMMC E5.

HPMC E5 is a semisynthetic, inert, viscoelastic polymer used in eye drops, as well as an excipient and controlled-delivery component in oral medicaments, found in a variety of commercial products. It is water soluble polymer. But for the ease of process, selection of solvent is required. As temperature, spray rate and atomization play an important role in evaporation of solvent and formation of continuous film on the pellets.

Table 19 selection of dispersion media:

For the selection of dispersion media, trials were taken by using 50 gm of MCC CP 507 pellets as inert core material. And 10%w/v HPMC E5 as coating solution. Coating was performed up to 10% weight gain on core pellets.

Sr no.	Ingredients	Composition (mg/capsule)			
		Batch A1 IPA: WATER (100:00)	Batch A2 IPA: WATER (80:20)	Batch A3 IPA: WATER (70:30)	Batch A4 IPA: WATER (60:40)
1	IPA	95	76	66.5	57
	WATER	00	19	28.5	38

Table 20 Process parameters

PARAMETERS	OBSERVED RANGE
Inlet temperature	55
Product temperature	40
Blower drive (%)	65-72
Spray rate(gm/min)	20
%RH	-
Atomized air	1
Coating level (%)	Up to 10%

Conclusion:

In development of coated pellets using lab scale wuster coating machine, it was observed that control over temperature, spray rate and atomization were limited. Thus, only in batch A1, 10% pellet coating was observed. While in other batches agglomerates were formed suggesting that, due to higher spray rate particles are failed to flow and agglomerates were formed.

Effect of product temperature:

55 gm of 10% HPMC E5 coated pellets were taken to study the effect of product temperature on process of ER coating. For ER coating process, EC 10cps: L-HPC (7:3) in IPA: DCM (5:95) as dispersion media was taken.

Though being non-aqueous coating process, product temperature requirement target is 28-32°C, impact of product temperature may cause damage to process efficiency and ultimately assay. Three target product temperature ranges were studied in final composition and evaluated for its impact on dissolution.

Table 21 study the effect of temperature:

Batch No.	**T1**	**T2**	**T3**
Product tem level	low	medium	High
temperature	25	30	35
Equipment and process parameters			
Distribution plate	c	c	c
Nozzle tip diameter (mm)	1	1	1
Spray rate	20-23 g/ml	20 g/ml	21-24 g/ml
Atomization air pressure	1	1	1
Blower speed (%)	40-44	41	40-44

Conclusion:

At low product temperature, inefficient solvent evaporation lead to agglomeration of pellets. While at high temperature coating efficiency is reduced to 76% as compared to batch T2 (86%). Thus, for alcoholic dispersion system 30°C is considered as optimized temperature for coating process

.

4.4PHASE: 4 DRUG LAYERING ON CORE PELLETS:

Drug solution preparation:

PVP K-90 and PEG 400 were dissolved in water solution at 800 RPM for 10 min till clear solution is obtained

Drug is added slowly to the solution and this dispersion is than filtered through 100 µ filter to remove lumps from the dispersion.

Optimization of dispersion media:

Experiment 1: to study effect of semi-aqueous media in varying size of MCC sphere:

For optimization of dispersion media, two trials were taken.

1. By using IPA: water in ratio of 80:20
2. By using water

15%w/v was the solid content of the drug layering solution. In which, API and Povidone K-90 as binder and PEG 400 was used as film former in ratio of 2:1 was added. MCC sphere CP 507 were taken as inert core pellets.

Results:

Batch	B1 (IPA: water)	B2 (water)
assay	102.8%	99.5%

Solution stability in semi aqueous media:

Time (hr)	Description	Assay		Total impurity
		B1	B2	
Initial	Clear solution	99.7	99.1	BQL
24	Clear solution	100.5	100	BQL
36	Clear solution	101.6	100.1	BQL
48	Clear solution	101.9	100	BQL
72	Clear solution	100.8	99.1	BQL

CONCLUSION:

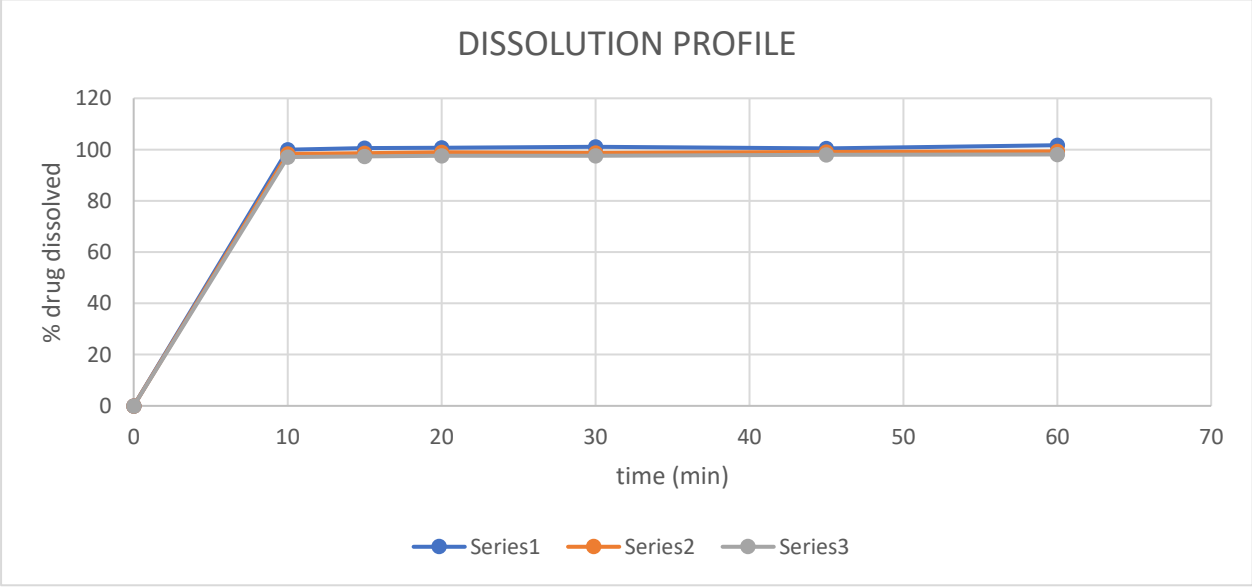
After performing the studies, it was noticed that there was no major change in assay of the two dispersions. Moreover, in case of hydroalcoholic dispersion media, considering the environmental hazard and risk of residual solvent at end of the coating process, water was selected as dispersion media for the development process.

AIM: optimization of coating weight gain(percentage)

Ingredients	Composition (mg/ capsule)		
	C1	C2	C3
MCC sphere CP 507	397.037	335.6	289.730
API	200	200	200
Povidone K 90	12	12	12
PEG 400 NF	2.400	2.4	2.4
Purified water	QS	QS	QS
Total	611.437	550	504.13
Percentage drug loading weight gain	**54**	**64**	**74**

Results:

Batch	**C1**	**C2**	**C3**
assay	100.3%	100.4%	99.5%
Time(min)	**Dissolution media: 50mM TRIS buffer pH 7.2, USP-1 (Basket),100 RPM**		
	Batch C1	Batch C2	Batch C3
0	0	0	0
10	99.9	98.3	97.1
15	100.6	98.6	97.3
20	100.7	98.9	97.6
30	101.1	98.7	97.6
45	100.5	99.1	98.0
60	101.7	99.3	98.1



Conclusion:

10% difference in percentage weight gain during drug loading process does not have any impact on dissolution. Thus, 64% weight gain in drug loading is considered as optimize level for the further development process.

AIM: optimization of binder (povidone K 90 level):

Prototype development of drug loading system was based on experience and has been discussed above showing suitability for the process. However, this was further challenged for the level of binder. Batch D2 has optimum binder quantity (12 mg/capsule) and change in binder povidone quantity to 9mg, i.e.-25% in batch D1 and 15 mg i.e., +25% in batch D3 has been evaluated. Control of said binder level has been checked for the possible impact on assay and dissolution.

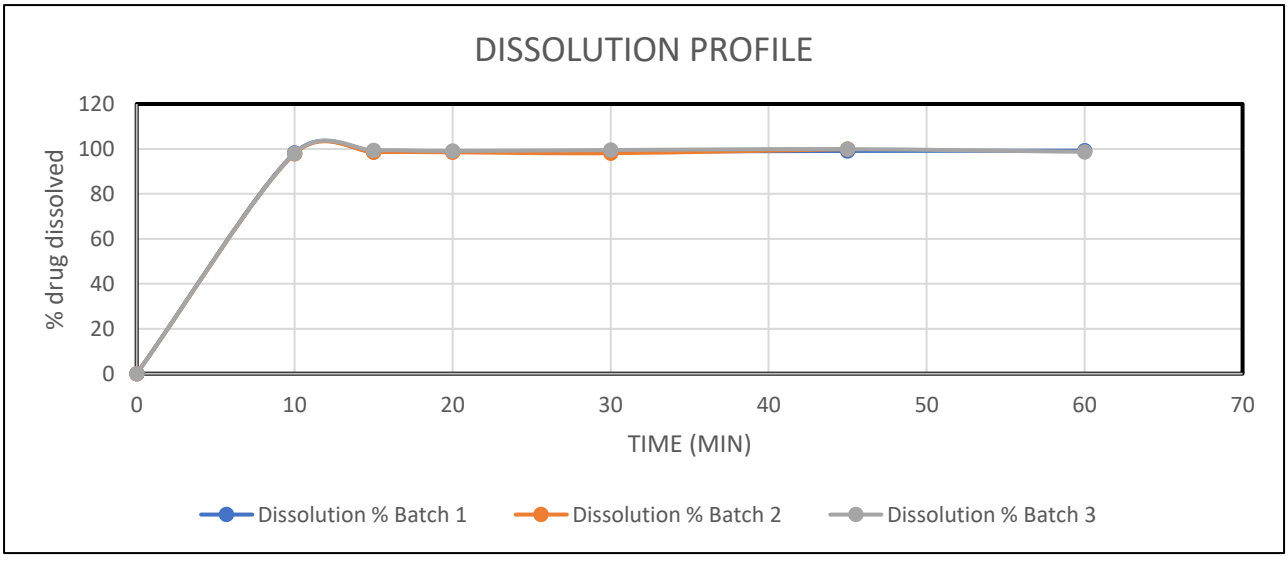
All other parameters were kept constant during trials.

Table 22 optimization of binder concentration

Sr no.	**Ingredients**	**Composition (mg/capsule)**		
		Batch D1	Batch D2	Batch D3
1	MCC SPHERE CP507	335.6	335.6	335.6
2	API	200	200	200
3	**POVIDONE K 90**	**9**	**12**	**15**
4	PEG 400	2.4	2.4	2.4
5	WATER	QS	QS	QS
Total		547.	550	553

Results:

Batch	D1	D2	D3
assay	99.1	99.4%	100.2%
Time(min)	**Dissolution %**		
	Batch D1	Batch D2	Batch D3
0	0	0	0
10	98.2	97.9	98
15	98.7	98.6	99.4
20	98.8	98.5	99.1
30	98.8	98.1	99.5
45	99.1	99.9	99.9
60	99.2	99.9	98.7



Conclusion: After performing the studies, it was noticed that there was no major change in assay of the two dispersions and hence 12mg povidone K-90 was selected as film forming agent.

Table 23 Final formulation up to drug loading stage:

Sr no.	ingredients	Composition (mg/capsule)
		Batch D2
1	MCC SPHERE CP507	335.6
3	API	200
4	POVIDONE K 90	12
5	PEG 400	2.4
7	WATER	QS

4.5 PHASE: 5 BARRIER LAYER COATING:

Barrier layer coating is applied to smoothen the surface of pellets. Smooth surface of pellets is beneficial for obtaining uniform coating of extended release coat. In Barrier layer coating, coating agent used are generally Hypromellose, hydroxypropyl cellulose and povidone. Further, plasticizer is added to provide flexibility to this film.

1. Selection of barrier coating agent:

Water soluble polymer has been used as the barrier coating agent. These classes of materials include, Hypromellose, povidone, gums and hydroxypropyl cellulose. Further, addition of plasticizer is required for the flexibility of the film. Given formulation uses opadry as a coating agent which is ready to use polymer-plasticizer premix for coating. Opadry clear is manufactured by colorcon. It contains Hypromellose 6 cps and PEG (3350) in ratio of 10:1.

4% aqueous solution of opadry clear is prepared and used for the barrier layer coating.

2. Selection of alkalizer:

API is sensitive to acidic environment of stomach and slowly reacts with acid. API can be degraded by acid present in stomach. however, the process is very slow. Requirement of alkalizer is evaluated and titrated. Alkalizer selection was based up on avaibility and prior knowledge. For solid oral formulation, sodium carbonated and sodium bicarbonate are widely used alkalizer. Sodium carbonate is advantageous over sodium bicarbonate as it one molecule of sodium carbonate can react with two molecules of acid. Thus, sodium carbonate was selected which is having better neutralizing capacity.

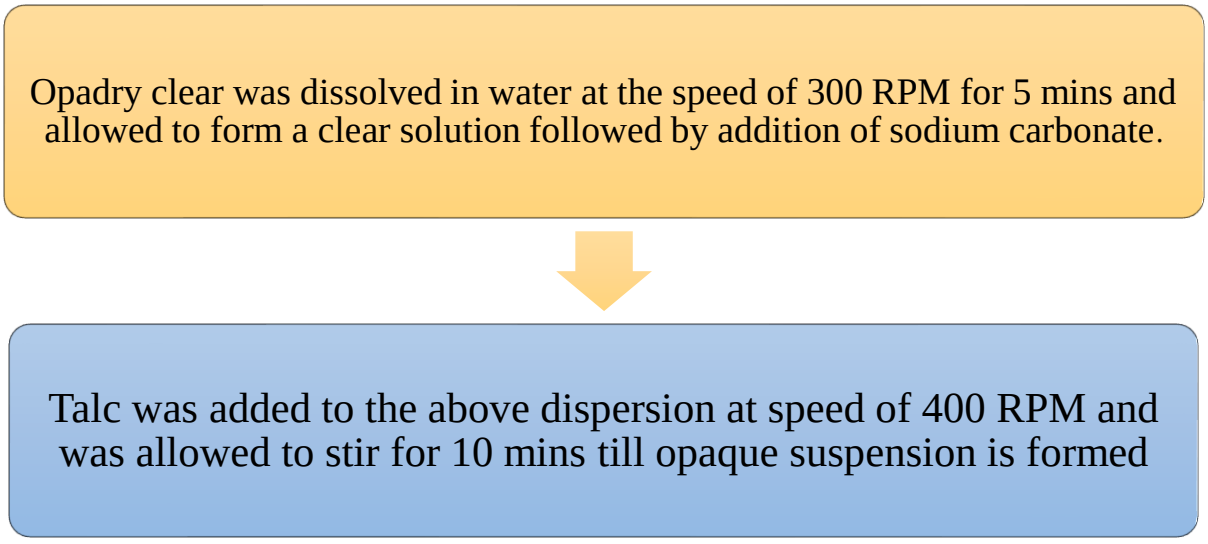
3. Selection of anti-tacking agent:

most widely used antitacking agent is talc. It provides the process smoothening and reduces the static charge developing during the process. Micronized talc was used in process in 20% fraction of total solid in barrier coating layer.

4. Manufacturing process selection:

For the barrier coating of the pellets, Glatt particle coater and granulator (G.P.C.G) fluid bed processor having bottom spray assembly was used. 3% weight gain was considered as optimum based on surface required of the pellets.

Preparation of barrier coating solution:



Optimization of formulation:

Depending upon the initial risk assessment, trial was designed and performed.

Table 24 Final formulation up to drug loading stage:

CQA	FORMULATION COMPONENTS		
	BARRIER COATING AGENT	SODIUM CARBONATE	TALC
ASSAY	LOW	LOW	LOW
DISSOLUTION	MEDIUM	MEDIUM	LOW
CONTENT UNIFORMITY	LOW	LOW	LOW

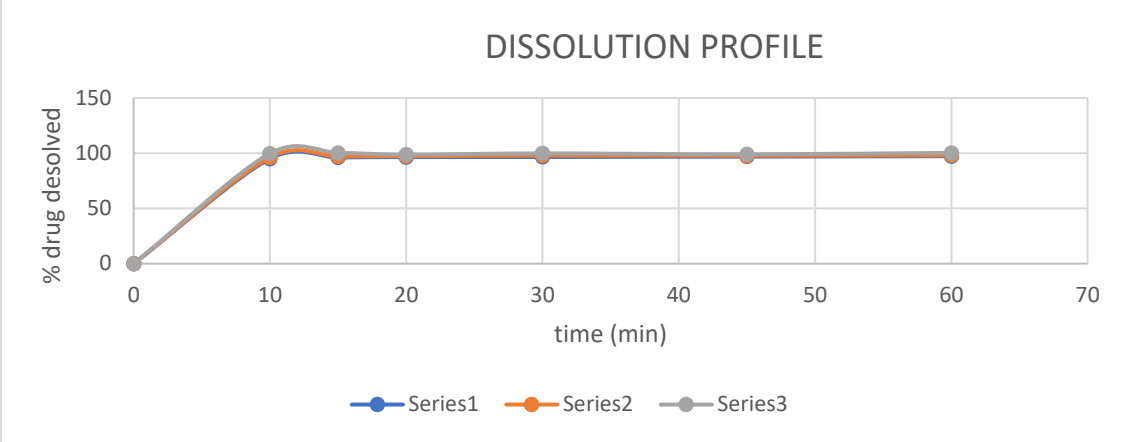
MATERIAL LEVEL (QUALITATIVE/ QUANTITATIVE)	MATERIAL IMPACT ON DRUG PRODUCT CQA	CATEGORIZATION	JUSTIFICATION
Barrier coating agent	Assay	Low	Barrier coating agent does not have any impact on assay.
	Dissolution	Medium	Dissolution may be independent on the coating agent hence risk is medium
	Content uniformity	Low	Small weight gain by barrier coating does not have impact on the uniformity
Sodium carbonate	Assay	Low	Addition of small amount of any component does not reduce the binding efficiency of opadry
	Dissolution	Medium	API is acid labile, a small amount of alkalizer may add benefit on acid prevention. Being alkalizer, dissolution of barrier coated pellets to be evaluated.
Talc	Assay	Low	A fraction of coating was consisted of antitacking agent for process smoothening. This talc does not have any role in assay, uniformity in content and dissolution.
	Dissolution	low	
	Content uniformity	low	

Table 25 AIM: optimization of Opadry layer

Ingredients	**Composition (mg/capsule)**		
	Batch E1	Batch E2	Batch E3
	Barrier coating level:2%	**3%**	**4%**
Drug loaded pellets	550	550	550
Opadry clear	**7.467**	**11.2**	**14.933**
Sodium carbonate	1.333	2.0	2.667
talc	2.2	3.3	4.4
Purified water	QS	QS	QS
TOTAL	561	566.5	572

RESULTS:

Batch no.	**D1**	**D2**	**D3**
assay	99.8	100.4	100.2
Dissolution media: 900 ml, pH 7.2 tris-(hydroxyethyl)aminomethane(TRIS) (50mM), USP-1 (basket), 100RPM			
TIME (min)	E1	E2	E3
0	0	0	0
10	95.0	96.2	99.7
15	96.1	97.1	100.3
20	96.5	97.3	98.7
30	96.6	97.9	99.8
45	96.9	97.7	99
60	97.3	98.1	100.3



Observation: It was observed that opadry clear has been an easy to use and easy to process barrier coating agent with aqueous application. It was also seen that it does not provide any impact on dissolution at even 10 minutes.

Conclusion: - Based on above observation barrier coating in range of 2-4% w/w can be used for development. Hence optimum quantity i.e., 11.2mg/ capsule (3%) has been finalized.

Table 26 AIM: optimization of alkalizer

Ingredients	**Composition (mg/capsule)**		
	Sodium carbonate: NIL F1	Sodium carbonate: 2mg/ ml F2	Sodium carbonate: 5 mg/ capsule F3
Drug loaded pellets	550	550	550
Opadry clear	11.2	11.2	11.2
Sodium carbonate	**Nil**	**2**	**5**
talc	3.3	3.3	3.3
Purified water	QS	QS	QS
total	566.5	566.5	566.5

Results:

Dissolution media: 900 ml, 0.1 HCL, USP-1, 100 rpm, TIME POINT: 2hrs. Followed by 900 ml, pH 7.2 tris-(hydroxymethly) aminomethane(TRIS) (50mM), USP-1 (basket), 100 RPM, time point :4,6,8 hrs.				
Time (Hr)	Reference product	Batch F1 Sodium carbonate level: NIL	Batch F2 Sodium carbonate level: 2mg/ capsule	Batch F3 Sodium carbonate level: 5 mg/capsule
0	0	0	0	0
2hr in 0.1N HCL	39.60	51.88	39.85	51.88
4 hr in pH 7.2	88.10	93.78	89.95	89.18
6 hr in pH 7.2	95.20	94.88	94.65	91.68
8 hr in pH 7.2	96.80	94.98	95.75	92.18

Observation: Since aim of experiments were to compare end release difference by proving pellets a biomimicking condition where they pass from the acid where it may degrade API. It is observed that end release is not significantly different in vitro conditions of change over dissolution. All batches show complete end release representing no or comparable minimum degradation by acid.

Conclusion: Based on earlier experience and concept of acid prevention due to technologically differences in reference product and development product, a 2mg/capsule quantity of sodium carbonate has been considered for further development.

Table 27 Barrier layer coating: final formulation

INGREDIENT	COMPOSITION	
Drug loading	Mg/capsule	%w/w
MCC NF Sphere (Celephere CP507)	335.600	59.24
API	200	35.30
Povidone K90	12	2.12
Polyethylene 400 NF	2.400	0.42
Purified water	QS	-
Subtotal weight drug loaded pellets	550	97.08
Barrier coating		
Opadry clear	11.200	1.98
Sodium carbonate	2.00	0.35
talc	3.300	0.58
Purified water	QS	
Subtotal weight of barrier coated pellets	566.500	100

Table 28 Updated risk assessment of formulation variable with justification:

MATERIAL LEVEL (QUALITATIVE/ QUANTITATIVE)	MATERIAL IMPACT ON DRUG PRODUCT CQA	CATEGORIZATION	JUSTIFICATION
Barrier coating agent	Dissolution	low	Dissolution has been evaluated and no adverse impact on dissolution is identified hence risk is reduced to low
Alkalizer	dissolution	low	amount of alkalizer has been optimized and 2 mg quantity has been found to be acceptable in dissolution.

CQA	FORMULATION COMPONENTS		
	BARRIER COATING AGENT	SODIUM CARBONATE	TALC
ASSAY	low	low	low
DISSOLUTION	low	low	low
CONTENT UNIFORMITY	low	low	low

4.6PHASE 6 : EXTENDED RELEASE COATING:

Barrier coated pellets are to be further coated with ER coating polymer. This polymer coating is the major drug release governing factor and responsible for product's long acting performance. An in house developed ER coating dispersion consists of water insoluble polymer as rate controlling polymer, water soluble polymer as pore former, triethyl citrate as plasticizer and talc as antitacking agent was used.

Table 29 Initial risk assessment:

CQA	FORMULATION COMPONETS- ER COATED PELLETS						
	Polymer coating level	Polymer aging	Polymer lot to lot variability	Additional pore former level	Plasticizer level	Antitacking agent level	Viscosity of the coating dispersion
Dissolution	High	Medium	Medium	High	Medium	Medium	Medium
Alcohol induced dose dumping	high	medium	medium	high	low	low	low

MATERIAL LEVEL (QUALITATIVE/ QUANTITATIVE)	MATERIAL IMPACT ON DRUG PRODUCT CQA	CATEGORIZATION	JUSTIFICATION
Polymer coating level	dissolution	high	ER coating level is most important factor determining the dissolution which is the ultimate goal of the extended release formulation. The risk of the polymer coating level to impact drug release from the ER coated beads is high.
	Alcohol induced dose dumping	high	ER coating polymers are insoluble in water and soluble in alcohol. Risk exists on dose dumping it is on high risk and to be checked for corresponding dissolution pattern.
Polymer aging	dissolution	medium	Selected ER coating polymer are stable under the accelerated and normal condition of storage. However change in product is to be verified. Risk is medium.
	Alcohol induced dose dumping	medium	

Polymer lot to lot variability	Dissolution	Medium	Lot to lot variability could affect the drug release profile under both normal and alcohol stress condition. However, the polymer will be sourced from a single supplier and, if necessary, controlled by tighter internal specifications beyond that of the USP. Therefore, the risk of polymer variability to impact drug release is medium
	Alcohol induced dose dumping	medium	
Additional pore former level	dissolution	high	Pore former are water soluble components responsible for drug release acceleration. The concentration of PVP may impact drug release under the both normal and alcohol stressed conditions. The risk is high.
	Alcohol induced dose dumping	high	
Plasticizer level	Dissolution	Medium	Plasticizers play a limited role in controlling dissolution and, therefore, the drug

			release profile. The risk of TEC concentration to impact drug release from the ER coated beads is medium.
	Alcohol induced dose dumping	low	Plasticizers composites a small fraction of ER coating and hence irrespective to its solubility, significant role in dose dumping is not expected.
Antitacking agent level	dissolution	medium	An anti-tacking agent is used to minimize static charge during coating. It has a tendency to change the drug release properties if used in proportional level.
Viscosity of coating dispersion	Dissolution	Medium	If coating dispersion is highly viscous, then the dispersion cannot be effectively atomized and the quality of ER polymer film may be adversely affected. This could affect process as well.

SELECTION OF ER COATING COMPONENTS:

1. Selection of coating polymer and pore former:

Ethyl cellulose is used as ER coating polymer in reference product. Ethyl cellulose is made up of non-ionic ethyl ether of cellulose. It is soluble in organic solvents and widely used in pellet formulations. For the ease of process non-aqueous solvent was used for the formulation development.

As ethyl cellulose is semisynthetic polymer, it is having variation of critical attributes. For this reason, USP-NF recommends strict justification for EC on viscosity grade. Ethoxy content and viscosity are the important attributes in case of ethyl cellulose.

Attributes	**USP/NF justification**	**Aqualon's justification**
Ethoxy content (% assay)	444-51	48-49.5
Viscosity (cps)	8-12	8-11

Accurate specification results in reduced batch to batch variability.

Ethyl cellulose is recommended to use with water soluble pore former. It includes polymer like, povidone, hydroxypropyl cellulose and Hypromellose. Povidone is used and ratio of EC and povidone was optimized based on its dissolution profile.

2. Selection of plasticizer:

As EC is water insoluble polymer, plasticizer should be miscible with it. Triethyl Citrate (TEC) is widely used plasticizer. As per the vendor recommendation and literature survey, 10-2-% weight of EC was used for the prototype formulation in ER coating process.

3. Selection of antitacking agent:

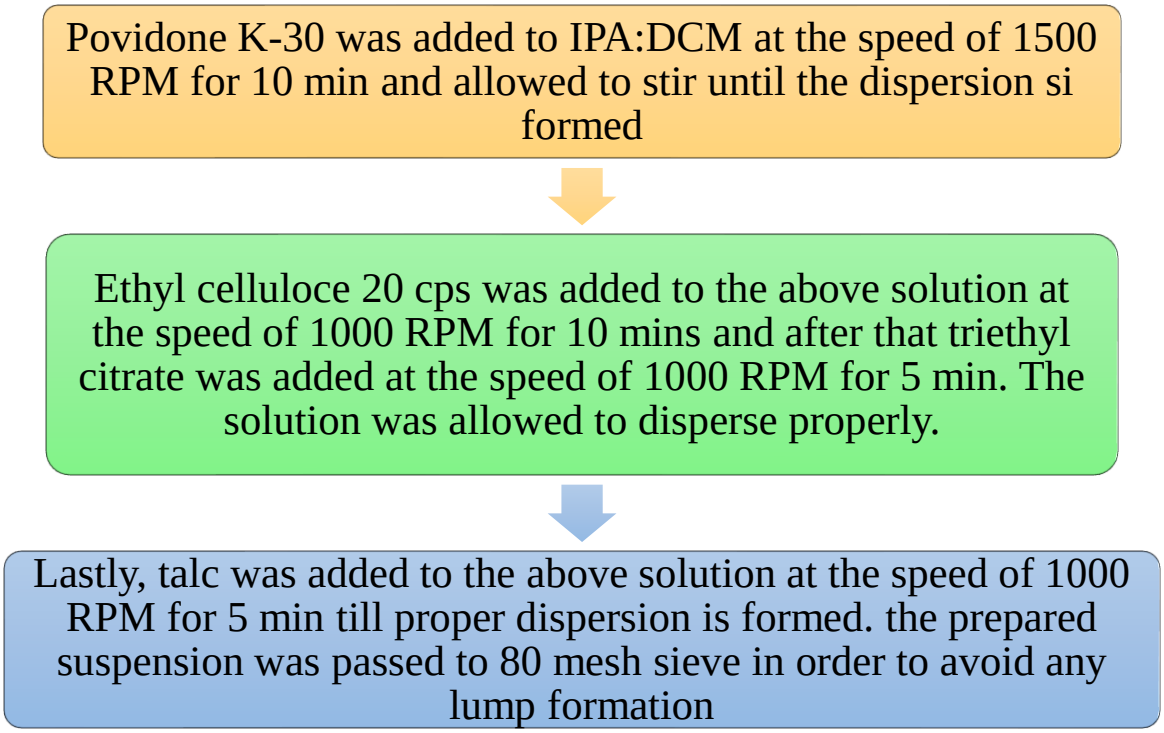
Antitacking agent is used to decrease sticking caused by high viscosity of polymer or the static charge developed because of non-aqueous solvent system. Requirement of antitacking agent

depends upon the amount of static charge developed during the process. Micronized talc is used for this purpose as it is uniformly dispersed in the solution

4. Selection of dispersion media:

Depending on literature survey of pellets formulation, methylene dichloride with isopropyl alcohol in ratio of 1:1 used to prepare 5% w/w solution.

Preparation of ER coating solution:



Process selection and prototype development for ER coating:

For developing extended release multi particulate system, drug loading and barrier coating was done and detailed above. For extended release pellets, ethyl cellulose as hydrophobic polymer, povidone as pore former and TEC is used as plasticize. considering the dissolution of reference product, target dissolution of extended release pellets was set to 50-6-% release in 2 hours. For

the preliminary trial 70:30:10:10 of EC: povidone: TEC: talc was selected. Based on the result of dissolution, further, formulation was optimized.

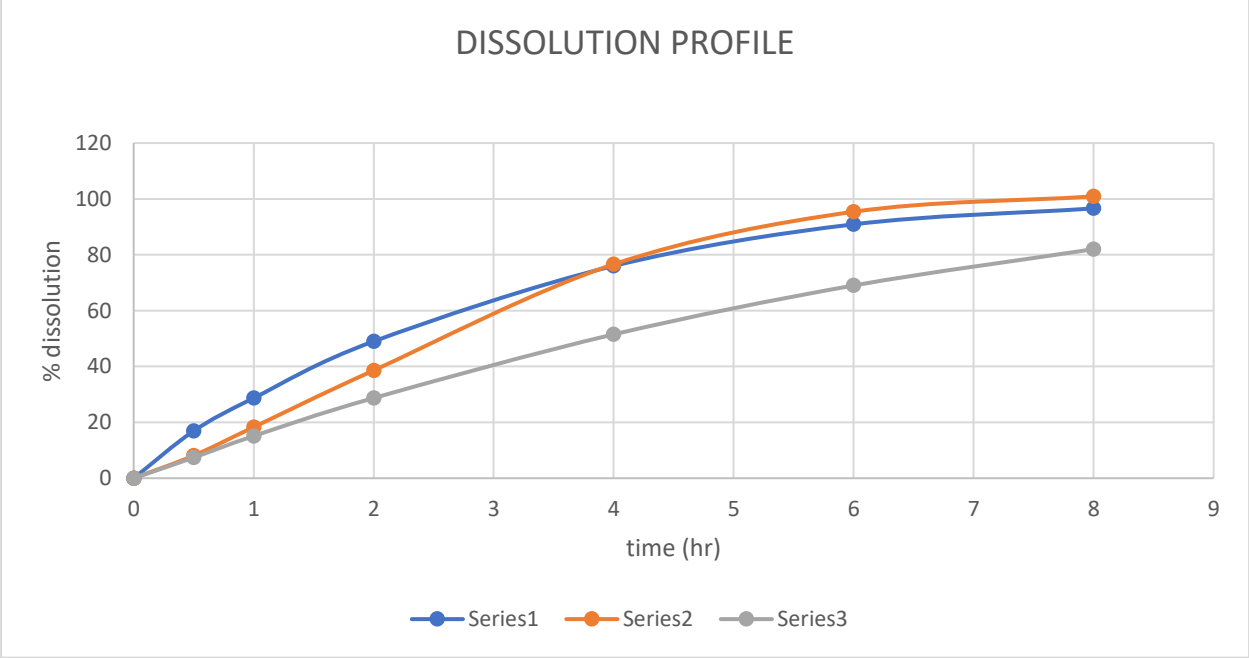
Table 30 Process selection and prototype development for ER coating:

Batch number	**objective**	**Ratio of EC: PVP: TEC: Talc**
G1	Initial ER coating evaluation	70:30:10:10
G2	Optimizing ER polymer ratio	66:34:10:10
G3	Optimizing ER polymer ratio	68:32:10:10
G4	Verification of polymer ratio and coating target	68:32:10:10

Ingredients	**Composition (mg/capsule)**			
	Batch G1	Batch G2	Batch G3	Batch G4
API barrier coated pellets	556	566.5	566.500	566.500
Ethyl cellulose 10 CPS	**32.562**	**46.736**	**32.102**	**32.102**
Povidone k-30	**13.955**	**24.076**	**15.107**	**15.107**
Triethyl citrate	4.651	7.081	4.721	4.721
Talc	4.651	7.081	4.721	4.721
Methylene dichloride	QS	QS	QS	QS
Isopropyl alcohol	QS	QS	QS	QS
Final weight of pellets	611.821(8% Weight gain)	651.474(15%)	623.161(10%)	623.161

RESULTS FOR BATCH G1: for the given formulation, sample was collected at 5% and 10% coating level to check effect of percentage coating on dissolution:

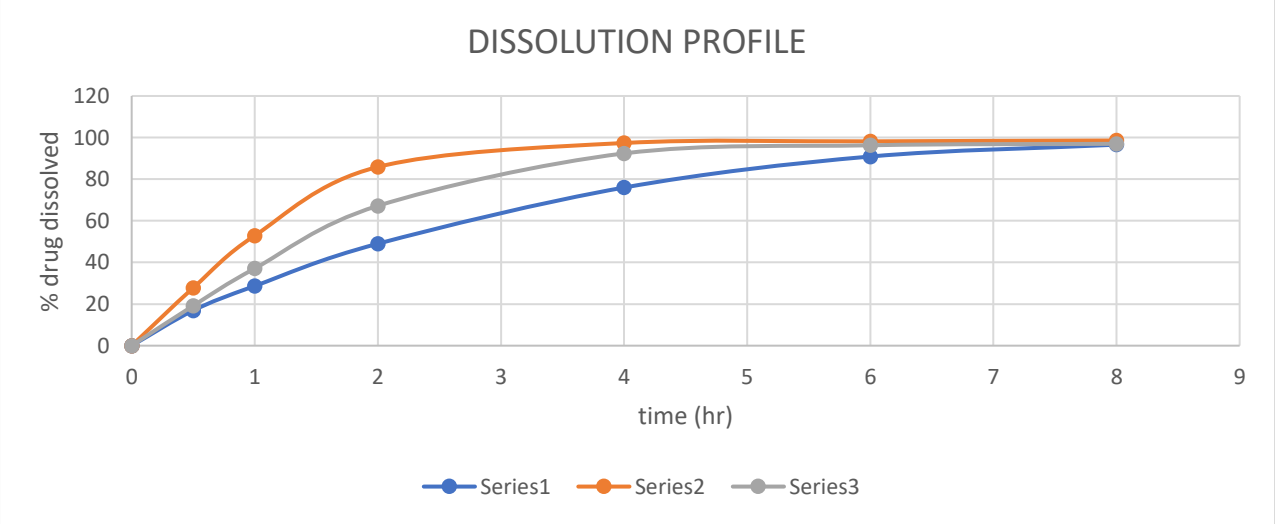
Dissolution media: 900 ml, pH 7.2 tris-(hydroxymethyl) aminomethane(TRIS) (50mM), USP-1 (basket), 100 RPM			
Time(hr)	Reference product	5% coating	8% coating
0	0	0	0
0.5	16.9	8.1	7.4
1	28.7	18.3	15.1
2	49	38.6	28.7
4	76	76.6	51.5
6	90.9	95.4	69
8	96.6	100.9	82



RESULTS FOR BATCH G2:

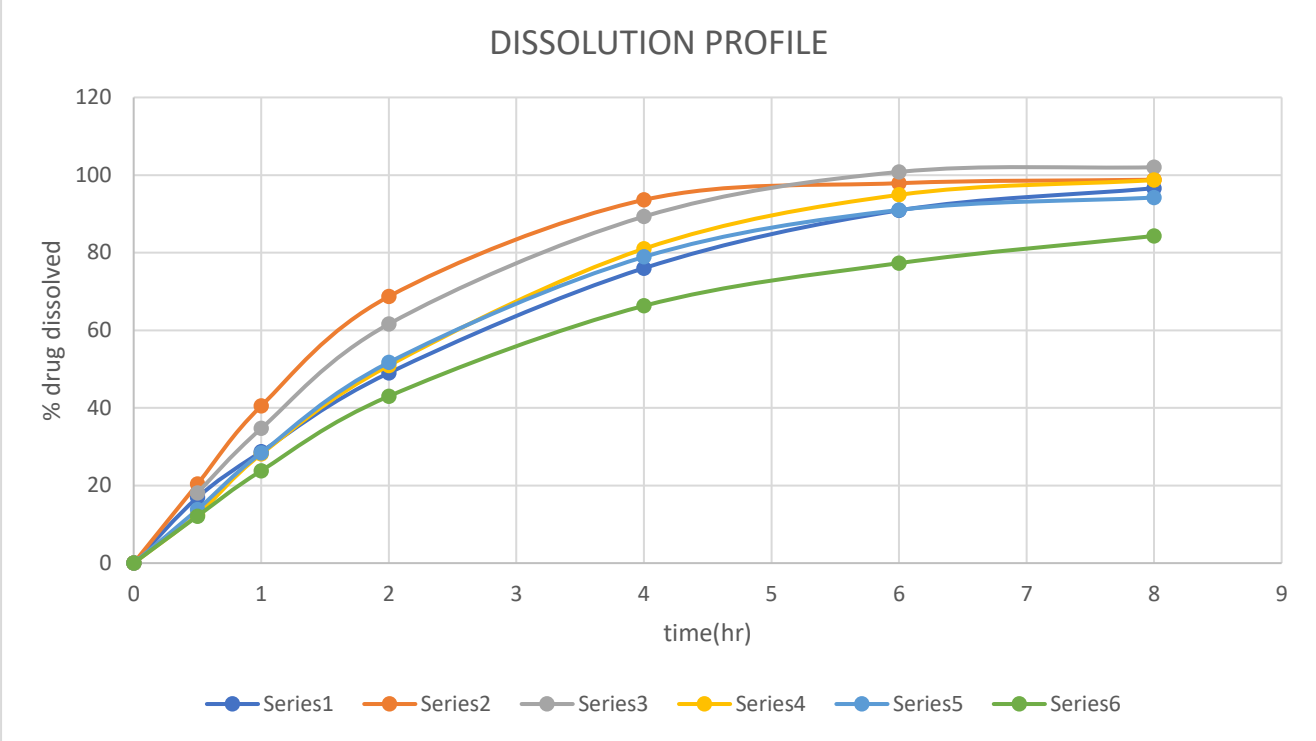
for the given formulation, sample was collected at 10% and 12% coating level to check effect of percentage coating on dissolution:

Dissolution media: 900 ml, pH 7.2 tris-(hydroxymethyl) aminomethane(TRIS) (50mM), USP-1 (basket), 100 RPM			
Time(hr)	Reference product	10% coating	15% coating
0	0	0	0
0.5	16.9	27.8	19.2
1	28.7	52.9	37.1
2	49	85.9	67.2
4	76	97.4	92.4
6	90.9	98.2	96.3
8	96.6	98.6	97



RESULTS FOR BATCH G3: for the given formulation, sample was collected at 7.5 %, 8%, 8.5%, 9.25 % and 10% coating level to check effect of percentage coating on dissolution:

Dissolution media: 900 ml, 50 mM TRIS buffer pH 7.2, USP-1 (basket), 100 RPM						
Time(hr)	Reference product	7.5% coating	8% coating	8.5% coating	9.25% coating	10% coating
0	0	0	0	0	0	0
0.5	16.9	20.4	18.1	17.4	13.8	12.1
1	28.7	40.5	34.7	33.1	28.4	23.8
2	49	68.7	61.6	59.0	51.7	43
4	76	93.6	89.3	87.1	78.9	66.3
6	90.9	97.9	100.8	96.3	91	77.3
8	96.6	98.8	102	97.9	94.2	84.3
	F2	48.58	54.925	61.33	82.75	54.64



Series 1: reference drug

Series 2:7.5% ER coated pellets

Series 3: 8% ER coated pellets

Series 4: 8.5% ER coated pellets

Series 5: 9.25% ER coated pellets

Series 6: 10% ER coated pellets

Conclusion:

From above experiments, it was observed that dissolution profile of batch G3 of 8% to 9.25% coating found acceptable and close to target dissolution as 2 hr dissolution between 50-60% and 8.5 % to be considered as target ER coat.

AIM: To check alcohol induced dose dumping in batch G3 and comparison with reference product

Dissolution media: 900 ml, pH 7.2 tris-(hydroxymethyl) aminomethane(TRIS) (50mM), USP-1 (basket), 100 RPM				
Time(min)	Reference product		Test product (G3)	
	0.1N HCL	0.1N HCL+40% Alcohol	0.1N HCL	0.1N HCL+40% Alcohol
0	0	0	0	0
15	0.4	0	0.0	0.4
30	2.2	0.3	1.5	2.9
45	4.5	2.0	4.6	6.2
60	6.5	5.2	7.6	11.1
75	8.7	8.2	11	15.4
90	10.8	11.3	14.3	19.2
102	13.0	14.5	18.7	22.4
120	15.1	17.4	22.6	25.4

Observation and conclusion:

- Process was satisfactory
- Alcohol induced dose dumping is also checked in pellets of batch G3 filled in Hypromellose capsule in media without and with 40% alcohol.
- Test passes the requirement of similarity with reference product in 40% alcohol.
- It is also observed that test and reference both are having significant unit to unit variability in dose dumping study.

Optimization of formulation:

Product quality can be affected by critical raw material. Considering this, trials were taken. Basically, two experiments were designed based on the risk assessment,

1.optimizationof TEC content:

As per the development batch ratio of EC: Povidone was fixed to 68:32. this polymer ratio is to be checked for sensitivity of triethyl citrate as inadequate triethyl citrate can affect the drug release of ER coating. Quantity of triethyl citrate was considered against parts of polymer used. A sum of 100 parts of polymer is taken in ER coat where TEC is 10% of total polymer as 10 parts.

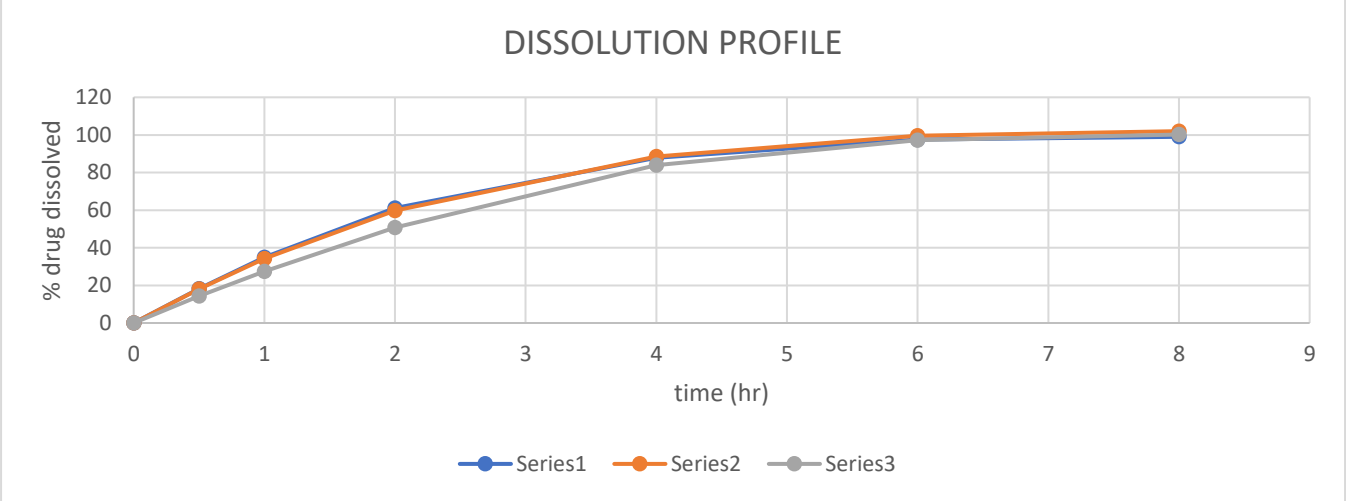
Ingredients	Batch H1 8 parts TEC	Batch H2 10 parts TEC	Batch H3 12 parts TEC
API barrier coated pellets	566.500	566.500	566.500
Ethyl cellulose	27.749	27.287	26.839
Povidone k-30	13.058	12.841	12.630
Triethyl citrate	**3.265**	**4.013**	**4.736**
Talc	4.081	4.013	3.947
Methylene dichloride	QS	QS	QS
Isopropyl alcohol	QS	QS	QS
Sub total amount of ER coated pellets	614.653	614.654	614.653

*QS to get solid content of 5% with 1:1 of DCM: IPA

ER coating represents 8.5% weight gain

Results:

Dissolution media: 900 ml, pH 7.2 tris-(hydroxymethly) aminomethane(TRIS) (50mM), USP-1 (basket), 100 RPM			
Time(hr)	Batch H1	Batch H2	Batch H3
0	0	0	0
0.5	18.2	18.1	14.3
1	35.0	34.2	27.5
2	61.2	59.8	50.8
4	87.9	88.5	83.9
6	97.5	99.5	97.2
8	99.0	102.0	100.2
	94	reference	59



Observation: No significant change in dissolution observed on ranging TEC from 8 to 10 parts however further increase in TEC shows marginal change in dissolution

Conclusion: The result represents that TEC quantity can be fixed from 8 to 10 parts of total polymer content (EC and povidone). A 10 parts has been finalizing for further product optimization.

2. optimization of ER coating level

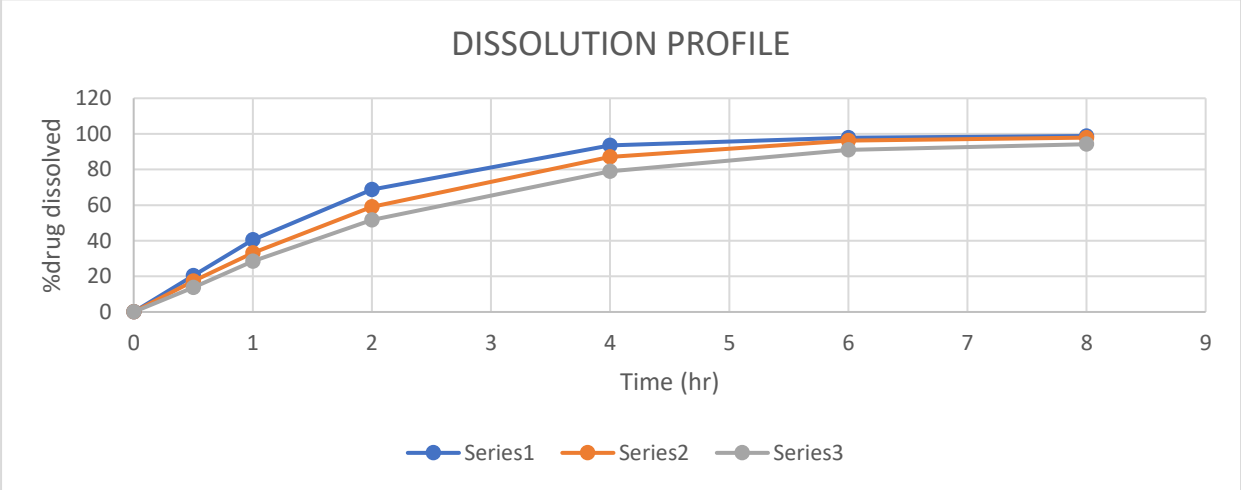
After performing the previous trials, the optimized ration obtained for EC: povidone: TEC: talc was 68:32:10:10. Change in this ratio can lead to change in dissolution profile. thus, ratio cannot be changed and impact of percentage coating can be evaluated. 8.5% of target ER coating was compared with 7.5% and 9.25% coating, and change in dissolution was evaluated.

Composition:

Ingredients	Batch I1 7.5%	Batch I2 8.5%	Batch I3 9.25%
API barrier coated pellets	566.500	566.500	566.500
Ethyl cellulose	24.076	27.287	29.694
Povidone k-30	11.330	12.841	13.974
Triethyl citrate	3.541	4.013	4.367
Talc	3.541	4.013	4.367
Methylene dichloride	QS	QS	QS
Isopropyl alcohol	QS	QS	QS
Sub total amount of ER coated pellets	608.988	614.654	618.901

As solvent in ratio 1:1 to get solid content of 5%

Dissolution media: 900 ml, pH 7.2 tris-(hydroxymethyl) aminomethane(TRIS) (50mM), USP-1 (basket), 100 RPM			
Time(hr)	Batch I1	Batch I2	Batch I3
0	0	0	0
0.5	20.4	17.4	13.8
1	40.5	33.1	28.4
2	68.7	59.0	51.7
4	93.6	87.1	78.9
6	97.9	96.3	91.0
8	98.8	97.9	94.2
	57	reference	61



Observation:

Similarity factor obtained after change in percentage coating from 8.5 to 7.5 and 9.25%, minor change was observed but F2 values were above 50 which was comparable.

Conclusion: ER coating level of 7.5 to 9.25% was considered as optimized level for laboratory scale development.

Summary of final qualitative and quantitative attributes:

	Formulation	**Excipient range selected**	**Quantity for final desired formulation**
Formulation optimization	Triethyl citrate	8-12%	10%
	ER coating level	8-10%	8-9.25%
	ER coating ratio	70:30:10:10 68:32:10:10 64:34:10:10	68:32:10:10

Table 31 Updated risk assessment of formulation variable with justification:

s

CQA	**FORMULATION COMPONETS- ER COATED PELLETS**						
	Polymer coating level	Polymer aging	Polymer lot to lot variability	Additional pore former level	Plasticizer level	Antitacking agent level	Viscosity of the coating dispersion
Dissolution	low	low	low	low	low	low	low
Alcohol induced dose dumping	low	low	low	low	low	low	low

MATERIAL LEVEL (QUALITATIVE/ QUANTITATIVE)	MATERIAL IMPACT ON DRUG PRODUCT CQA	CATEGORIZATION	JUSTIFICATION
Polymer coating level	dissolution	Low	Polymer coating level has been optimized for fix ratio of coating components. A range of 7.5-9.25 % coating shows similarity and since it is optimized, risk is reducing
	Alcohol induced dose dumping	low	
Polymer aging	dissolution	Low	Selected ER coating polymer are stable under the accelerated and normal condition of storage. Risk is reduced to low
	Alcohol induced dose dumping	low	
Polymer lot to lot variability	Dissolution	Low	Ethyl cellulose has been selected from a vendor with specification are set in a narrow therapeutic range, further variation is not expected
	Alcohol induced dose dumping	low	
	Alcohol induced dose dumping	low	

Table 32 Final formulation

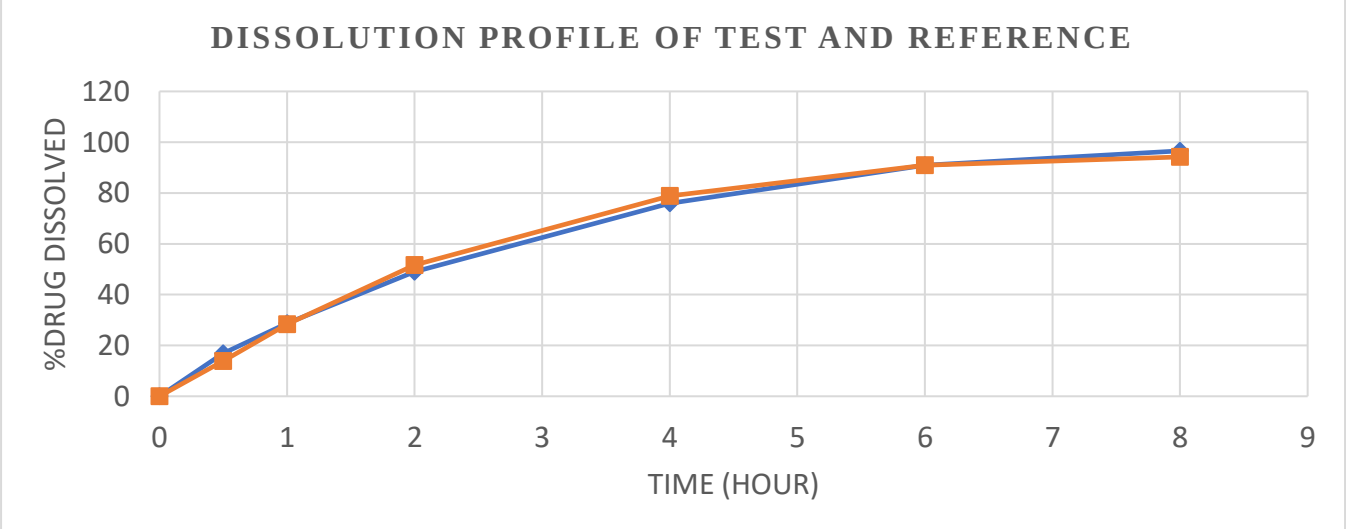
INGREDIENT	COMPOSITION	
Drug loading	Mg/capsule	%w/w
Celephere CP50)	335.600	59.24
API	200	35.30
Povidone K90	12	2.12
Polyethylene 400 NF	2.400	0.42
Purified water	QS	-
Subtotal weight drug loaded pellets	550	97.08
Opadry clear	11.200	1.98
Sodium carbonate	2.00	0.35
talc	3.300	0.58
Purified water	QS	
Subtotal weight of barrier coated pellets	566.500	100
Ethyl cellulose	27.286	4.42
Povidone K-30	12.841	2.08
Tri ethyl citrate	4.013	0.65
Talc	4.013	0.65
Subtotal of ER coated pellets	614.653	99.46

4.7 Result and Conclusion:

From the Comparison of drug release from reference product and test product (batch F3 for 9.25% coating), **similarity factor obtained (*f2*) is 82.75 and dissimilarity factor(*f1*) is 27.92.**

Table 33 Comparison of dissolution profile of test and reference product

900 ml, 50mM TRIS buffer pH 7.2, USP-1(Basket), 100 RPM (200mg)				
Time point (Hr)	Reference product	Test product	(Rt-Tt)	$(Rt-Tt)^2$
0	0	0	0	0
0.5	16.9	13.8	3.1	9.61
1	28.7	28.4	0.3	0.09
2	49	51.7	-2.7	7.29
4	76	78.9	-2.9	8.41
6	90.9	91	-0.1	0.01
8	96.6	94.2	2.4	5.76



5. SUMMARY:

Wurster fluid bed coater is widely used for the pellet coating. It is the one of the palletization techniques for the manufacturing of the pellets. Wurster technique was selected for understanding the effect all the process parameters and their effect to increase the film coat as well as to minimize the effect of them for best results. During the initial stage of the research, reference product was characterized to decide the quality target product profile. Which helps to develop product having desired standard of quality and efficacy. Followed by this stage, selection of core pellets among the pellets prepared using extrusion spheronizer and readymade pellets. By developing the method to prepare MCC pellets, it was observed that pellets prepared by extrusion spheronization process, friable pellets were made. Thus, with the objective of withstanding the rigors developed during the fluid bed process, non-friable readymade pellets were used. Further, effect of process parameters including product temperature, atomization and spray rate on coating process were studied using fluid bed processor.

Product development by using wurster technology where, core pellets were coated with subsequent layers of coating on drug layer having highest effect on assay of drug product followed by barrier layer coating to smoothen the surface of drug layered pellets. During this stage, alkalizer was added to minimize drug degradation rate in stomach pH. However, it was observed that drug is slow reactor representing no significant difference in dissolution profile suggesting. At the final stage of coating process pellets were coated with extended release coat having high impact on drug release profile of the drug. Various trials were taken optimizing the extent of coating and ratio of hydrophobic ethyl cellulose to hydrophilic pore former povidone k-30. At the ratio of EC:Povidone k-30 of 68:28 and extent of coating 9.25% highest similarity was observed with reference product. From the Comparison of drug release from reference product and test product (batch F3 for 9.25% coating), similarity factor obtained (*f2*) is 82.75 and dissimilarity factor(*f1*) is 27.92. Suggesting optimized formulation for ER antiepileptic drug product.

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