"EXPLORING THE EFFECT OF PROCESS VARIABLE IN PELLETS COATING BY WURSTER FLUID BED COATER"

A Thesis Submitted to

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in Partial Fulfillment for the Award of the Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

BY

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Under the guidance of

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May 2018

CERTIFICATE

This is to certify that the dissertation work entitled "EXPLORING THE EFFECT OF PROCESS VARIABLE IN PELLETS COATING BY WURSTER FLUID BED COATER" submitted by Mr. NIDHISH PATEL with Regn. No. (16MPH109) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutics" 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 **Mr. Nidhish Patel,** from **Nirma University, Institute of Pharmacy, Ahmedabad** has undergone 9 months training **(19th Jun 2017 to 12th March 2018)** in **Formulation Development at** Cadila Healthcare Limited, Ahmedabad. During this Period he has done a project entitled **"Exploring the Effect of Process Variable In Pallets Coating by Wurster Fluid Bed Coater"** successfully under the Guidance of Mr. Ritesh Kapoor (Deputy General Manager).

We wish him better achievements in his future endeavors.

Thanking You.

Yours faithfully,

For Cadila Healthcare Ltd

Niral Bhatt
Senior Manager
Human Resources

DECLARATION

I hereby declare that the dissertation entitled "Exploring The Effect of process variable in pellets coating by using Wurster Fluid Bed Coater ", is based on the original work carried out by me under the guidance of Dr. Dhaivat C. 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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DEDICATED TO MY FAMILY AND NEPHEWS, DEVANSH AND VIVAN

Acknowledgment:

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14th may 2018 *Mr. Nidhish.Babubhai.Patel*

INDEX

LIST OF ABBREVIATIONS

SR NO	SHORT FORMS	ABBREVIATIONS
1	MUPS	Multi Unit Particulate System
2	FBP	Fluid Bed Processor
3	ADP	Air Distribution Plates
4	HPMC	Hydroxypropyl Methylcellulose
5	HPC	Hydroxypropylcellulose
6	PEG	Polyethylene Glycol
7	IPA	Iso Propyl Alcohol
8	RS	Releted Substances
9	LOD	Loss on Drying

A.LIST OF FIGURES

B.LIST OF TABLES

Exploring the effect of process variable in pellets coating by wurster fluid bed coater

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Abstract:

The aim of the present investigation was to study the effect of various process parameters for enteric coating of pellets by fluid bed processor in wurster coating process, as well as the optimization of such parameters during scale-up process. Bottom spray technique is one of the most preferred approaches for coating of multi-unit pellets and mini-tablets. Several process related factors influence the performance of formulation; and thorough knowledge about these factors and their control during process scale-up helps smooth technology transfer as well as promotes reduction of batch failure. Preliminary, several batches were formulated by varying different factors like seal coating thickness, percentage of enteric coating, ratio of coating solution, spray rate, humidity, temperature, etc. to understand the effect of such factors at a glance. Later on, critical factors like inlet humidity, chamber temperature and spray rate were identified as significant parameters affecting the coating process. Critical factors were further optimized by applying 2^3 full factorial design, whereby these factors were studied at two levels and other factors were fixed at single level as per preliminary batches. Result indicated that all the independent parameters have positive effect and interaction of the parameters have not significant effect or negative effect on the T10, T15, T20 and impurity. Study revealed that spray rate and temperature have positive effect on the dissolution and RH has positive effect on the total impurity (RS). Optimized batch was obtained scientifically by overlay plot by response surface methodology for various factors. Scale-up batch was also formulated as per optimized batch, and no significant difference in product performance was observed, which indicates that appropriate selection of critical factors and their control helps in smooth process scale-up.

CHAPTER-1

INTRODUCTION

1.1 MULTI UNIT PARTICULATE SYSTEM:

Conversion of the granules and fine powder of drug as well as excipient into the small, spherical, free flowing by agglomeration is known as the pelletization techniques. Range of the pellet is between the 0.5 to 1.5 mm, but other size can also be prepared. By using many method pellets can be prepared but mostly drug layering and compactions used widely. Irrespective to the manufacturing process which is used, pellets must have the following criteria.

(A) It should have spherical and having a smooth surface, this both are considered as important characteristics for the film coat.

(B) Size of the particle should as much as narrow. But the 600 and 1000µm is consider as the optimal for the pharmaceutical uses.

(C) To maintain the size of the final formulation form in the limit pellets must have contain the possible amount of the active ingredients.

Pellets are generally used for the oral controlled release formulations with the gastro retentive otherwise it should have sustained release properties or it must have the site specifics delivery. For that pellet with coating are given in the hard gelatin capsules otherwise it can also be used as disintegrated tablets which releases the drug in the acid from the pellets.

Development and design of the formulation depends on the role pellets and the role is based on the novel technique of manufacturing used for the delivery systems. For the targeted delivery property which offers the flexibility for that formulation must be in multi unit form like coated and filled capsules otherwise can be in compressed tablet form. Compare to the other formulation safety and efficacy is much higher. While the oral formulation higher degree of flexibility provide by the pellets.

Without the formulations, pellets can be separated into proper desired strength; meanwhile incompatible agents which are bioactive can be blended for the delivery or those with the different release rate at the different or else at the same site in the gestrointestinal path.

There are some advantages of the pellets over the single unit like tablet and powders fill into the capsule. Pellets disperse smoothly in the gastrointestinal path when taken orally, it also boost the absorption of drug and reduce the irritation of the mucosa with some of the irritable drug due to less quantity of the drug into the individual pellet, it also reduces the intrapatient and interpatient variables.[36][37]

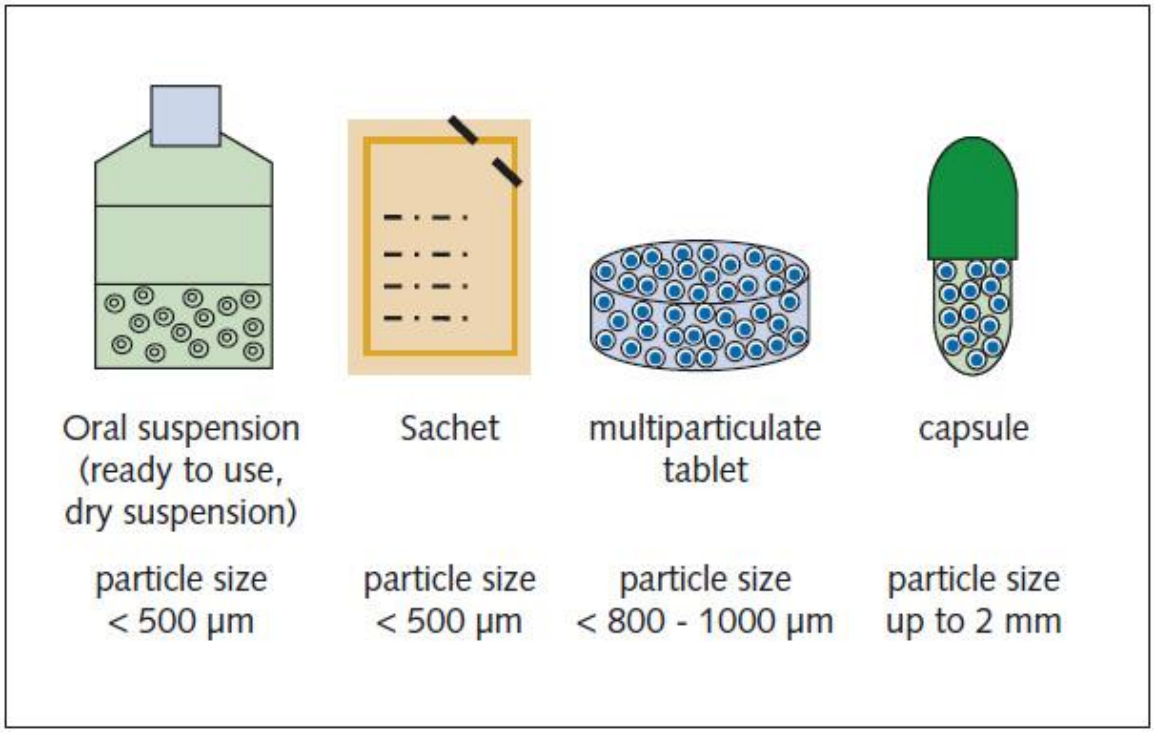

Fig:1.1 Size of particle

1.1.1ADVANTAGE OF THE PELLETS:

- Without changing in the processes or the change in the dosage form this can be divided in the expected dosage forms strengths.
- Significant benefit over the single unit forms can be obtain when active ingredient with pellets are in the formulation of capsule, suspension otherwise it can be in disintegrating tablet.
- It can be also used for the delivering the incompatible bioactive agent.For the delivery in the gastrointestinal path as well as in the different or the same site pellets can be used for the proper release rate.

- It also helps in the reduction of the irritation in mucosa because of the irritable drug , it also dissolve freely into the gastro intestianal tracts.
- Coating: Generally coating is done for the stabilizing the active ingredient in granules and it can also provide the controlled release rate of the drug. Easy way of the coating is on the sphere shape because of the not presence of the edge. It is easy to fill the irregularities on the surface because it is economical to coat extra coat on of the material.

Density increase: by the spheronization bulk as well tap density can be increased this helps to increase the process of packaging.

Improved the flow properties: In which the perfect dose is required or in which automated process can used in that excellent flow properties is required for that spheres are used like in tablet, moulding operation, filling of capsule and its packaging.

Hardness and friability: surface characteristics and internal cohesive force decide on the basis of friability and hardness. Friability of granules can be decrease and hardness can be increased by the spheronization. This helps to decrease in the fines while the handling and transport.

1.1.2DISADVANTAGES OF THE PELLETS:

- Dosing is separated by the volume other than the number and sepreted single dose is important.
- Changes are observed in formulation to formulation leads to change in the pellet size but it is in between the 1 to 2 mm.
- Cost increases because of the capsule filling or sometimes tableting destroys the coat of the pellet.[36]

1.2 PROPERTIES OF THE PELLETS:[17][41]

1.2.1 COATED PELLET:

- It should have proper drug release properties

1.2.2 UNCOATED PELLET:

- Uniform sizes and shapes
- Flow properties must be good
- Packing must be reproducible
- Higher strengths
- Surface must be smooth
- Coating should be easy
- Less friability

1.3 STAGE OF THE PELLETS GROWTH:

Various steps involves in the pellet formation:

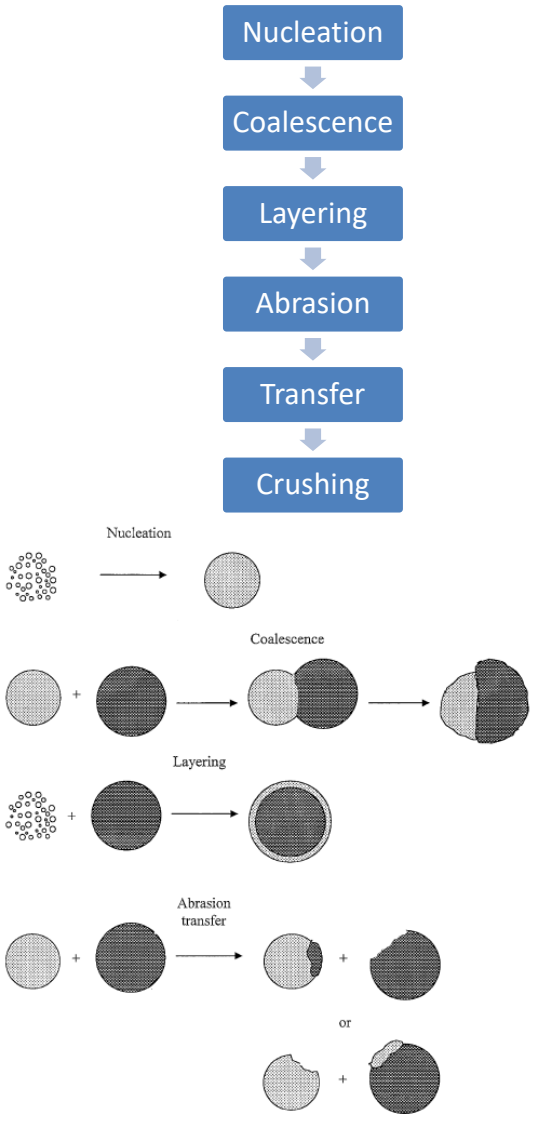

Fig 1.2 Stage of pellets growth

1.4 METHODS OF PREPARATION:[24]

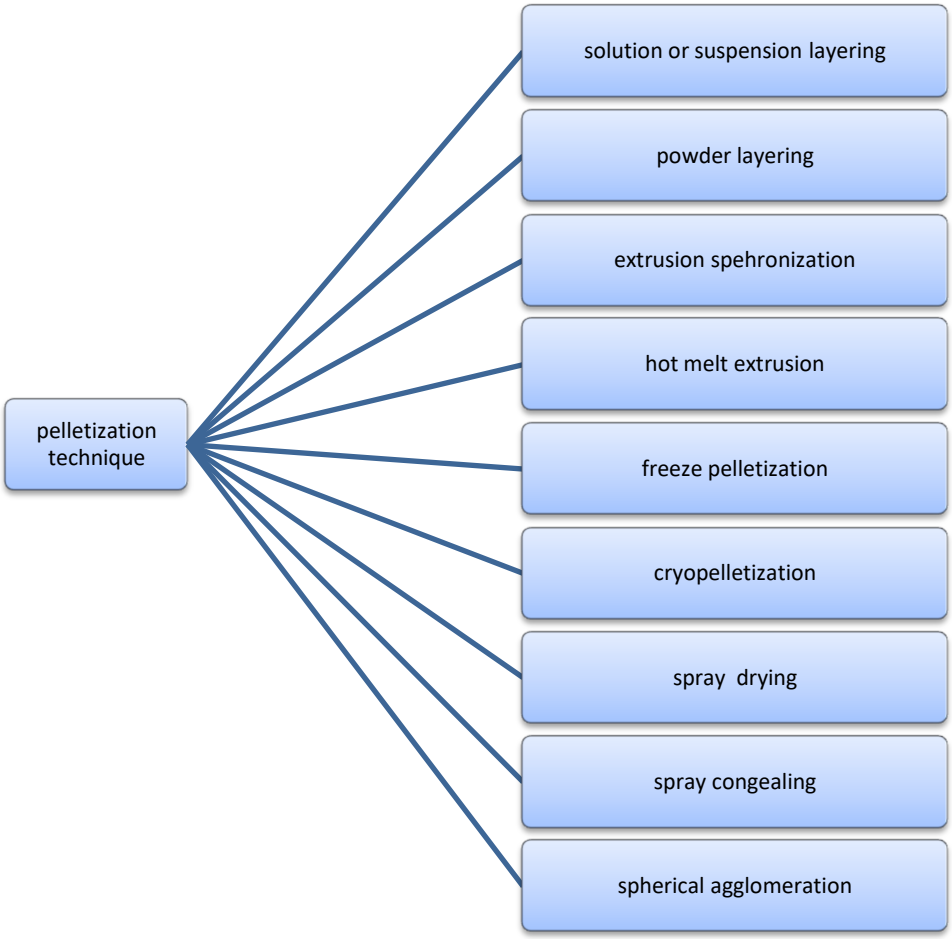

Table 1.1 Pellatization technique

1.4.1 SOLUTION OR SUSPENSION LAYERING:

This process involves coalescence of the either suspension or solution which is made up of the drug substance and binding solution on the seeds this might be inert or granule type materials. Procedure involves that dissolve the entire component in the perfect quantity to make the desired viscosity then after it is used for the sparing. The sprayed droplet coalescence with the pellets and form uniform coat on the surface for this it requires the

proper conditions of drying. This can be done by the drying phase in which material dissolves and forms the solid bridge this helps to keep the material together on the pellets.

This process won't finish until the desired weight gain or yield obtained. for this process size of drug plays versatile role because as the size increases higher quantity of the binder is used. Because of this viscosity of the solution incenses hence constant stirring required to prevent the settling of the particles. This may also creates problems like blocking of the gun settling in the tube. For this technique size of the API must be less than 10-50µm.for this technique fluid bed centrifugal granulator, conventional pan coat or wurster can be used.

1.4.2 POWDER LAYRING:

In this technique on the nuclei excipient as well as drug or both of them can be deposited by using the solution. Specialized liquid is used because in this binding solution as well as the dry powder required for the coating. The primary requirement of the powder layering method which is the used apparatus must have solid wall for preventing the loss of the powders before the powder is taken which is wet used for the layering process.

In the initial stage binding liquid and milled powder is added together in the controlled manner. At the staring stage particle bound themselves and forms the seed after that it start the forming pellet by using the liquid bridge comes from the spray solution. With the help of solid bridge this liquid bridge can be replaced by using the binder. Layering wont finished until the desired size of the pellets achieve. It is most important that powder is delivered accurately during the whole process as well as it is also important that addition of the binder liquid rate is must be maintained.[24][44]

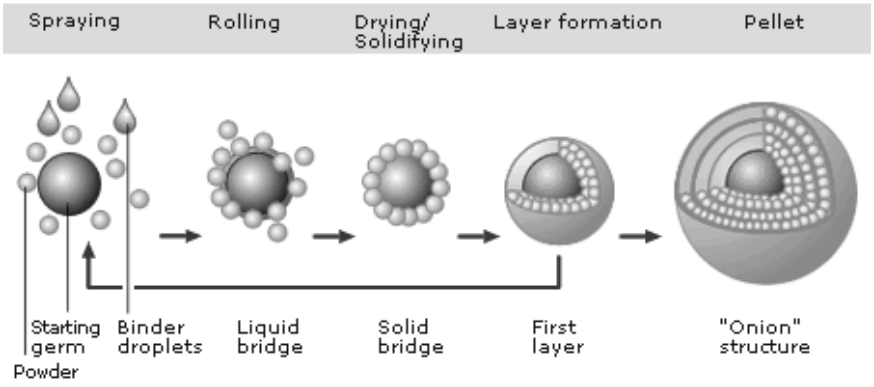

Fig 1.3 Drug layering

If the rate of the powder is high than it may increase the generation of the dust and if the ratio of addition is higher than the chances of the wetting will be higher it may affect the quality as well as the yield. Coating pan centrifugal fluid and tangential spray can be used for the drug layering.

1.4.3 EXTRUSION SPHERONIZATION:

For producing the proper size of the pellets in industry mostly this process used. The main advantage of this process is used to formulate the high capacity loaded drug pellets. There are various steps involves like:

(A) Dry mixing

(B) Wet granulation

(C) Extrusion

(D) spheronization drying

(E) Drying

(F) Screening

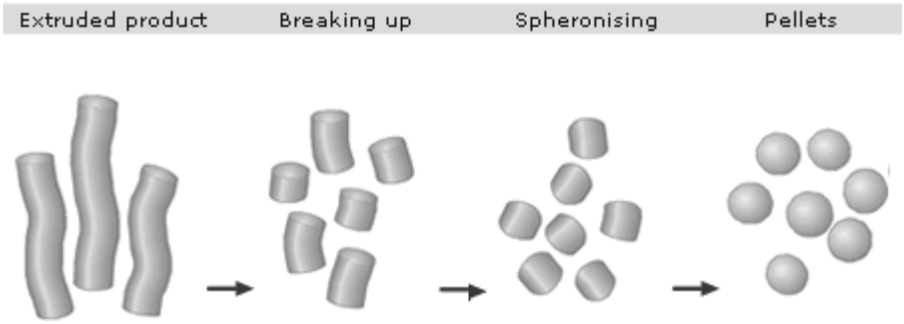

Fig 1.4 Extrusion spheronization

Dry mixing is the first step in which drug and excipient are mixed together by using the wet granulation process in this plastic type of mass generated for the ease of the extrusion. The mass is then is passed from the cylindrical dies having diameter of the 0.5 to 2.0 mm in the diameter for the cylindrical shape. By cutting and drying cylindrical shape pellets can be formed. Then these extruders are shift into the spheronizer in which they are immediately converted by braking to the cylindrical shape because they are pushed outside as well as at the up side also because of the centrifugal force by the rotating frictions.

After that they dried at the room temperature or desired temperature to set the size, hardness and density. For various process screw fed, high sphere mixture, ram, spheronizer, fluid bed dryer, gravity extruder and oven can be used.[41][47]

1.4.4 CRYOPELLETIZATION:

This is the process in which liquid dosage form are converted into the solid sphere shape. After this pellets are lyophilized or freeze dried for the removal of the oraganic solvent or water. Amount Liquid nitrogen is selected on the bases of the solid content and the temperature of liquid dosage forms. This is used for the formulation of the controlled as well the immediate release dosage forms. In this droplet formation is the most difficult step for the technique this is based on the viscosity, surface tension, solid content or equipment design.

1.4.5 SPHERICAL AGGLOMERATION:

This is also known as the balling in which powder by mixing with the proper quantity of the liquid or higher temperature converts particles in spherical by rolling, drums and mixers.

1.4.6 HOT MELT EXTRUSION:

This technique is now a day use for the manufacturing of the spherical shape pellet without using the solvents or water. This helps to remove the instability variable crates while the on going process because of the water. Drug release is based on the diffusion coat hence further coating is not required. It is generally used for the transdermal, controlled release and for the sustain release formulations.

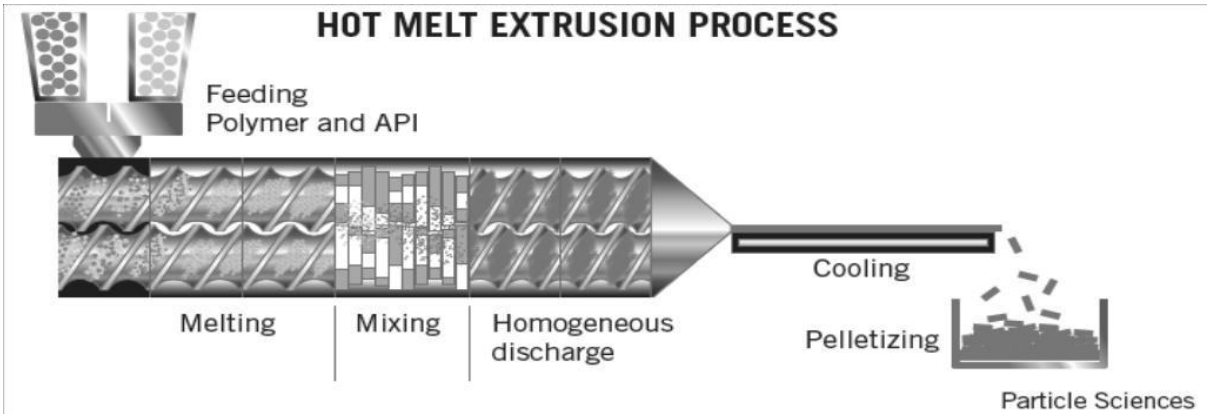

Fig 1.5 Hot melt extrusion

This method consist the following process:

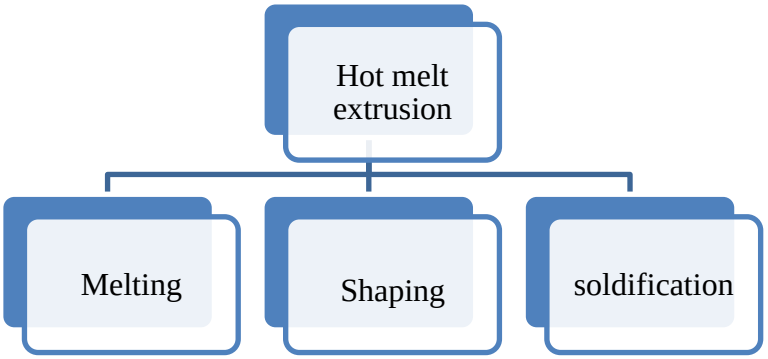

Table 1.2 Hot melt extrusion process

1.4.7 SPRAY DRYING AND SPRAY CONGEALING:

This is also known as the globulation process, which involves solution, hot melt atomization and suspension formations. Spray drying is the process in which the solution or suspension is being sprayed along with the drug entities; it may have presence or absence of the excipients, in the hot air steam generation to dry quickly with spherical shape.

This is mostly used for the increasing the dissolution rate. This is the process in which drug melts and dissolves in the gum, waxes or fatty acids, then after is being sprayed in the chamber in that temperature is under the melting points of the ingredients for the manufacturing of the spherical shape.

1.4.8 FREEZE PELLETIZATION:

This is the new technique for the manufacturing of the spherical shaped pellet having the API. This method involves, solid carrier and API are being molten and then introduced into the immiscible and inert column of the solutions. They can be moved only either upward or the downward this is also happen on the bases of the liquid density inside the column. In this method less variables are affecting which have many advantages over the many techniques like quality and cost of the product. It give the product with the narrow distribution size. This method do not require the drying because pellets solidifies at the room temperature.[24]

1.4.9 COMPRESSION:

It is the one type of manufacturing process for pellet. Different size of the pellets can be prepared using compacting mixture or he API under the pressure. Process variable controlling and formulation are same as the tablet preparations.

1.5 INTRODUCTION

1.5.1 FLUIDIZED BED COATER:

FBD is widely used since last few decade because it provides the higher energy and mass transfers. This process involves drying, agglomeration, cooling, coating, and granulations this can be used for both heat resistant as well as heat sensitive. This is the process in which coating occur inside the FBP, in that coating is being done for the desired release or to change the behaviours. There are three basic machines involved for the fluid bed technology.[19][20]

(A) Top spray

(B) Bottom spray

(C) Tangential spray

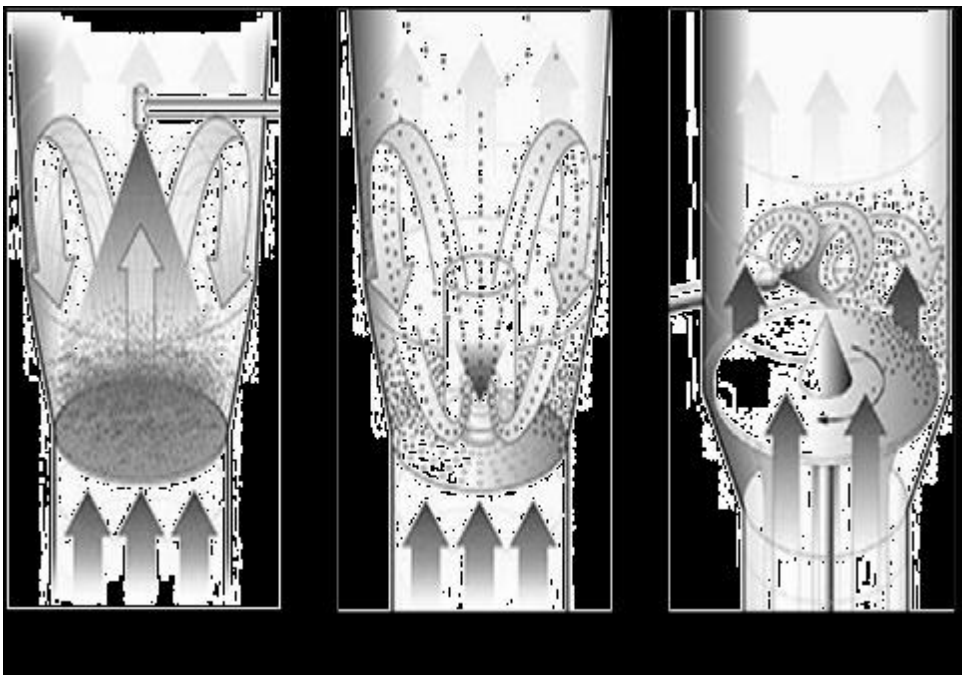

Fig 1.6 Types of spray

(A) TOP SPRAY:

Lengthened chamber allow the pellet to stay in the fluidization for long time that travels with the higher velocity it helps to reduce the agglomeration. Conical shape allows the decelerations of streamed air uniformly. Larger filter housing is present in it. 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. Nozzle is kept lower into the expansion chambers it helps to coat the materials coalescence on the surface of the pellet particle from the short distances; it also provides longer drying of the coated pallets

This is used for organic as well as aqueous film coating, hot melt small particle and granules, and control release coat.

(B) BOTTOM SPRAY:

This method contains cylindrical container with plate which is perforated. In this the second cylinder is present which is fitted above the perforated plates. For the dispensing of the coating liquid the nozzle is fitted in the middle of the plate. The design of the plate consist larger holes in the area below the coating panel. This method is widely used for the sustain release pellets because it give arranged flow of the particle and highly reproducible films. By using this method aqueous, oraganic, suspension, solvents, emulation, hot melts and films can be operated. It mostly used for the mini tablets, pellets, and small particles having the size of the 100 to 600 kg.

(C) TANGENTIAL SPRAY:

This is the wet granulated based method used since last 19080s. In this the nozzle is presented in the side of the container. The basic function is spinning the variable disk. While the ongoing process three main forces are involved mechanical force which helps in the particles moment, granulation and mixings (A) spinning disk which creates the centrifugal forces. (B) The lifting forces created by the air which is travels from the disk. (C) Gravitational force because of that particles fall on the disks. This create the spiralling kind of the helical structure give the best mixing chance and give proper granules having the content uniformity.[20]

1.6 WURSTER COATING

It is the technology which is used for the formation of proper film on the powder, and pellets. It is also used for drying and coating.

Film formation process required volatilization of aqueous or non aqueous solvent for the file formation on pellets. File formation occur based on the drying of the pellets. This system have more drying temperature than the other system.

1.7 MECHANISM OF COATING IN WURSTER.

Wurster apparatus generally use in the industry for powder and pellet coating. The size of the container is 100 to 500 gm to 800 kg can be used. Mainly this is used for coating 100 micron size tablets. The chamber of wurster apparatus is conical & cylindrical partition is having half the diameter at the bottom at the coating site. In the bottom site orifice plate which is known as the air distribution plate (ADP). This plate divided into two region . one area which is open it is under the wurster apparatus column is highly permeable to pass more air volume and velocity. Inlet air as pass upside pellets or particles passes from nozzle which is in the between the air distribution plate. Nozzle which mounted between the Air distribution plates having two type of properties (A) one part of it is for the passing of the solution and one part of nozzle is for the atomized air in fixed pressure and volume. The pattern of the spry is droplet which is like solid cone, the angle of spray is around the 30-50 which is known as the zone of coating. one region is known as down bed part that is in the outer part of the division. Selection of the ADP (air distribution plate) is depending on the density as well as the size of used material.

Role of the down bed part or region is to keep the materials into the suspended type and strained horizontal to site which is in base of the partition. Role of the columns height helps to maintain the flow of the solution parallel into the zone of the coating. While coating process was continuous size of the batch was increased meanwhile so at the same time height need to be adjusted for achieving the flow of the pellet. Expansion region is up site part of the products container the role of this is to maintain and to reduce the air as well as the velocity of the particles.

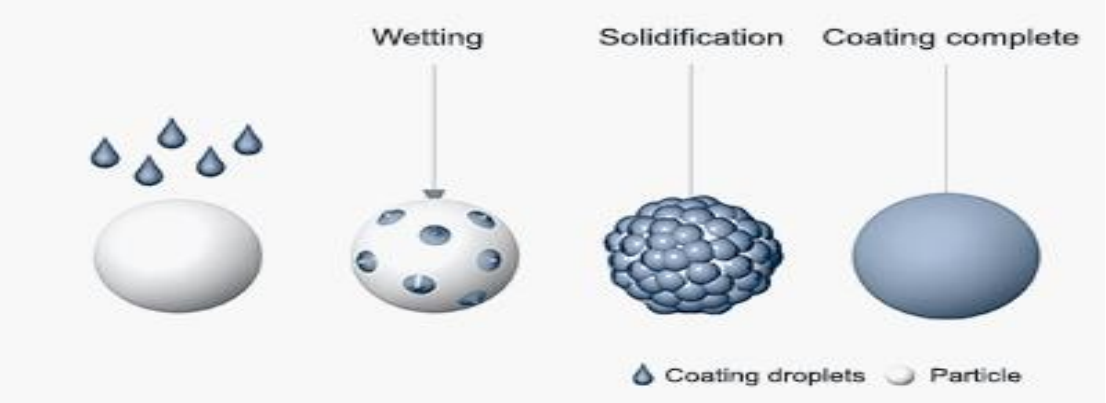

Fig 1.7 Mechanism of coating

Each and15 every technique of the fluidized bed coating is known as the higher rates of mass as well heat transfers but in all this wurster is much effective techniques. Material having higher water solubility that is coated by using wurster without any kind of problem of penetration of core. Droplets which are applied on the outer layer of the core that will spared and it generate film that is continuous and constant drying was also simultaneously carried out. As the initially coat applied then after spray rate can be increased. The high quality of the films are generated by using the organic solvents, in this generated droplet that impose on the core fast to decreases the potential of drying of film.[20][36]

1.8 VARIABLES OF WURSTER COATING

There are main five mostly affecting process factors which affects the quality. (a) equipment variables (b) solution (c) preheating (d) spraying and (f) drying.

Table 1.3 Variables of wurster coating

1.9 AIR DISTRIBUTION PLATES (ADP)

To reduce the attrition and to obtain the perfect consistency fluidization proper air distribution plate need to be selected. The rate of the fluidization affect the velocities of the particles as the smaller the particles it require the less the air volume than the bigger particle. the velocity of air as well as the pressure difference must be same at the ADP. Hence while using small particles, having lesser opening are plates used for generating resistances at plate for the good distribution of air. There are different types of the plates used depending on the pellet size.[19]

1.10 TYPES OF PLATE BASED ON THE SIZE

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

Table 1.4 Types of air distribution plate

1.11 COLUMN HEIGHTS:

Proper circulation of the pellets can be obtained by the adjusting the gap of partition from the spray zones and up bed partitions columns. On the basis of the flow, shape, density and size column height is being adjusted. This is also considered as the critical parameters for coating of the small subtract and it was found that it changes the drug releasing of pellet. this problem was generated because of the pellet flow in the columns and exposures of the subtract to coating solution droplet into the spraying zone.

The slugged like form and slow flows of the pellets from the columns creats the agglomerations in which gap of column is more and in that less pressures of generated to take particles into the column. If the column's gap is too less than very less amount of pellets comes in column because of that loss of material may be happened and over wetted pellets may also be generated. So proper height of the columns need to be adjusted so that proper amount of pellets comes into columns. Frequent changes of the column are not required. The column gap for wurster is about to 6'' and in wurster of 40 to 50mm about to 18'' is recommended.[20][36]

1.12 FILTER BAG:

Filter begs use to prevent the defeat of the materials and to permit air to passes through. If the porosity is higher it leads to higher loss. And if the lower will be the porosity than the optimal it leads to the filter stuck and the process will be interrupted which leads to affect the product's yield. Selection of the is on the bases of the past experiences and size of the materials. With the help of differential pressure porosity of filter begs can be examine while the coating.[19][20][32]

1.13 NOZZLE TIP SIZE OR DIAMETER:

Selection is carried out on the basis of the size of the nozzle, as the smaller nozzle is inserted more the spray will be but nozzle choking is also observed mostly with the smaller nozzle. To prevent the agglomeration in pellet coating more atomization fluid need to be generated as compare to the pan coater. It is most important that used nozzle is enough able to atomized the solution which is used for the coating it should also work as at the high spray rate also. Sometimes larger droplet of the coating solution was also generated because of the poor performances of the used nozzle this problem occur nozzle cannot distribute properly droplets on the core pellets which are going to be coated and it also causes that it may not dry quickly as compare to the smaller droplet. Small droplet quickly dries. Some of the droplets might be dried before they come in contact with pellets or tablet that may leads to inappropriate coating on the pellet surface. For proper and uniform atomization, in which spray rate increases above the capacities of nozzle larger spray droplets have seen with the smaller droplet, as the larger droplet generated leads to agglomerates. To prevent agglomeration multi unit nozzle can be used.[19][20]

1.14 COATING SOLUTIONS OR NATURE OF SUSPENSIONS:

it must have sufficient solid contents for the ease of spraying. As the viscosity is higher the droplet size of the coating solutions is affected and this may leads to the change in the surface of pellets. If the solution is more viscous and tacky in nature then spray rate need to be reduced. Mostly with the higher solid contents will increase the process time. Meanwhile in HPMC and ethyl cellulose it is completely opposite specially they are in the solution form.[20][36]

1.15 DEW POINT:

Drying of the coated pellets is also affected by the temperature and humidity inlet air. With the help of psychometric charts the relationship can be determine between temperature and humidity. Humidity changes as the season changes or it also changes day today. Evaporating capacity of air changes with the change in the dew points of the air. Though the temperature is low but drying capacity of the air can be increased by the lower humidity but that will create higher static charge in products.fir the removal of this variable at the initial level specific and absolute level need to be same compulsorily at the starting stage of the developments.

Higher humidity (absolute) will create depression in the air temperature below the dew point, this will causes the condensations of the water either in the machine or on the products surfaces. At the initial stage for the water soluble drug higher moisture content is not suitable. Once the initial coat is generated than after humidity can increased as the static charge generated once on the pellet are coated by the polymers. To create similar environment in the wurster chambers while the coating lab scale or the pilot scale batch, it is required to be run the process at the dew point value. This factor is scale independent.[19][20]

1.16 INLET AND PRODUCTS TEMPERATURE:

To increase evaporation of the coating solutions sprayed on the pellets the inlet air must be heated. Air temperature controlling is very important because it affects qualities of the coat formation. Mostly higher temperature produces dry environments generate spray dried powder and over wetting leads to agglomeration while attrition. The proper temperature produced proper evaporation of the coating liquids which produced slowly and proper sprayed film of coating solution on the pellets by coalescence of polymeric particle and it also avoid agglomerations and drug migrations in the layer of liquid. Higher temperature leads to the drying of the droplets quickly and don’t coalesces when come in contact with the core particle. This will create discontinuous coat which is porous and uneven and this will not give desired release of drug.

Higher temperature may also lead to the spray drying of the atomized droplet of the coating material before impinged on the pellets this will leads to the loss of coating material and leads to thinner coat. Spray drying of droplet produces embedded into the film coats and it disturb the continuity.

On the other side if the temperature less then comparatively longer time requires for the coating this will leads to the migration of the soluble drug from the core to the moistened coat layers. Soluble drug reduce the surface tensions of liquid's layer it also lower the capillary forces which is important to produce the deformations and the coalescence of the sprayed droplets. Drug embedded in final coat might be dissolves on come in contact with the dissolutions media leads to porous as well as permeable coats.

If temperature is too much lower than the minimum film formation temperatures it will also create problem that coalescence not occur it will leads to discontinue and inappropriate film.[20]

1.17 SPRAY RATE:

Binary nozzles are used in the wurster apparatus. During the process spreading, formation, coalescences and evaporations happen almost simultaneously while the process. The spray rate is depended on the core particle and the solution's properties. The evaporation happen by the atomization air which us used for the development of the sprat mist that helps to increase the viscosity of the droplet. In solvent based coating, excessive atomization pressure leads to spray drying effect of the spray.

Based on the drying efficiency and tackiness nature of the solution spray rate is being adjusted. For the coating of the smaller particles the droplet size is being kept as small by increasing atomization or by decreasing the spray rate to prevent the formation of the agglomerations. At the starting of the coating spray rate required to be kept less to prevent the solubilisation of the core. After the formation of the initial coat spray rate can be increase afterwards.

It is shown that as the size of the particle is too big it should take the more droplet without any agglomeration. As the particle enlargement become higher it is important to increase

the spray rate at specific time interval. As the spray rate is higher it increases the possibility of the agglomeration and leads to the less proper coating, whereas lesser the spray rate produces the small droplet and it avoid the agglomerations, specially at that time when smaller core pellets used.

Though the spray rate is less and faster drying of the droplet avoid the colescence of the polymers leads to the poor formation of the coat.[34]

1.18 AIR VOLUME:

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 produces 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.

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.[20][34]

1.19 ATOMIZATION AIR PRESSURE:

Pneumatic nozzle is used for generally for the spraying of the coating solution. Thish nozzle use air pressure used to convert coating materials in the droplet forms. Higher the atomization of generates small spray droplet and it is important to avoid agglomeration, specially at that time when coating is carried out on the smaller pellets.

If the atomization pressure is higher than droplet of spray may propelled away quickly this will not help in droplet and core contact. High atomizations also crats the attriation of the core and leads to fines.

If the atomization is low it will creates coarse droplet, this are dried slowly and support in the formation of the liquid bridge between the core, leads to agglomeration of the pellets. In larger capacity equipment the is one consideration is that it may have sufficient drying capacity, and rate limiting factor is the incapability of the nozzle to atomize the liquid at the speed at which process air removes the generated water vapours. The only option for taking advantage of higher drying capacity is to increase the nozzle that is use the more compress air at the same pressures.

A process in which drying capacity is too high with limited droplets size will generate unnecessarily delayed productivity. Change the nozzle to the HS nozzle, it uses the higher compressed air with the similar atomization of air pressure, this will leads to the sudden change in the drying capacity uses.[34]

1.20 DRYING/CURING TIME:

Solution viscosity increased as the polymer dissolves in the organic solvents. While the film form at that time gel like phase generate by solvent evaporation and polymeric film formed. Meanwhile for aqueous dispersion film generation is much difficult.

Anti tacking agents and surfactant are used in the aqueous dispersions for the formation of good film and process coating. Plasticizer can be used for the reduction in the minimum film formation temperature of the polymer with the higher glass TG(transition temperature). Coating which is based on the aqueous dispersion in which when polymer and particle comes in contact with each other that will generate coalescence while the drying.[19][34]

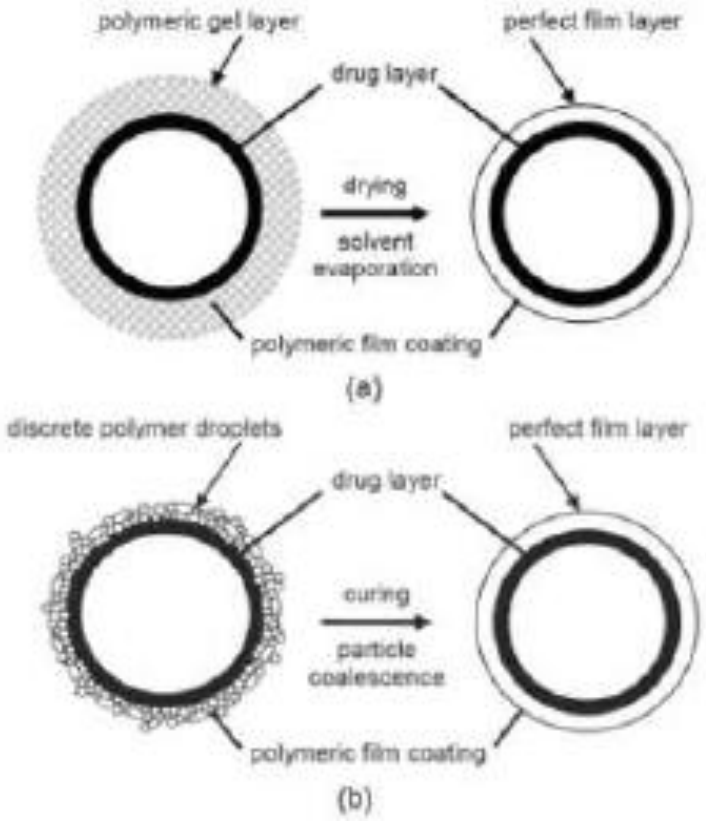

Fig 1.8 Mechanism of film formation

(a) Image shows film formation of organic solution. (b) Image shows the film formation of aqueous polymeric dispersion

1.21 SCALE UP PROCESS:

Process parameter in the fluid bed process can be controllable, which give easy optimizations and reproducible product. There is relation between spray rate, process time and spray rate spraying time increasingly at different interval in each scale over 5 various sized chamber with two multiple and single nozzle. Coating which is applied that also shows that time of process also increases in the multiplication of 5 and 3.1 for two of the various products from small scale to higher scale.

Before the manufacturing of the scale up batch important variables and their outcome on the yield should be known while the manufacturing of the lab scale. While the

formulation is the scale up activities starts than it is for the scale up and scale out the manufacturing. Many of them are very easy to set up like batch size, spray solution viscosity, batch size, base plate, batch size, concentration, apparatus assembly, dew point, and column height.

There are various parameter can be set by taking trials those are known as dependent variables such as air pressure, air volume, atomization, spray rate and products temperature. These are very to recognize at the small scales formulations it needs lesser time and costs. Than after DOE(design of experiments) for the settle the most critical parameter as per the regulatory guidelines. To decrease the trial for that different software used like design expert.

Based on the statistical results range can be set for the parameters and based on that process validation carried out for the freezing the parameters. After the variable is fixed only one may be remain but mass effect because of increasing the weight of in the commercial scale. After studying all he parameters it is easy for the compensates the mass effects by small changes in the approximate parameters of the pilot scale and the scale up batch. After the fixing the parameters at the lab scale further step is to predict the parameters for the scale up batch.

After the three successful reproducible batches manufacturing further step is to generate the parameters for the pilot scale batch having single wurster. The formulation of products is generally carried in 6'' wurster having the batch load of the 0.5 to 2 kg. Spray nozzle and wurster column are small. 18'' wurster is appropriate for the pilot batch in which base plate and wurster column are too large.

Single spray nozzle used in lab to pilot batches but size of the nozzle is larger and allow higher spray rates. Density of mass flow and batch depth increases. From the lab to pilot scale batches coating zone increase. In pilot and commercial batches coating zone will remain the same only change observed is that wurster column.

That’s why role of the wurster column base area is important in uniform coating. Every parameter must be proportional to the wurster column base area in comparison with the lab scale batch. In scale up batch it was found that all the process variable are important

after understanding the process variables at the scale down model it will be much easier to analyze.[20]

Same controlled process will apply, all the variables remain same in the pilot scale batch. The mass effect will be only affected by the unknown factor. Stepwise approach needs to be followed to adjust the parameter for scale up.

From the lab to pilot scale occupancy must be same and meanwhile the distribution plate needs to be same geometrically in each part of the apparatus. Ratio of the air volume to the plate areas and spray rates to the air volumes must be maintained. The factor for the scale up from the GPCG 1.1to the FBE 125C is normally 9 time depended on the supplier. Scale up factors is applicable to the spray rate, atomization air pressures and air volume.

Some of the variables are discussed below.[19][32]

1.22 AIR VOLUME:

Fluidization is based on the air volume during the process. This can be decided based on the scale up batch optimization from the small to large scale the velocity kept same. To same velocity can be obtained by the base plates which are below the columns of lab as well the pilot equipments. This is also known as the fluidization air volumes.

Below equation can applied for the calculation of the airflow.

V2=V1*A2/A1

V1= Air flow at lab scale model

V2= Air flow in the scale up trial

A1= Base area of the column for lab scale

A2= Base area of column in pilot model[19][20]

1.23 BATCH SIZE:

“Batch size means first of all generates the pilot scale up and after that decide the equipment” The parameters changes a little based on the size of the batch because of the mass effects. First of all fix and process validation is carried out for the batch size change. It is important to kept the batch size in the appropriate occupancy.

Example: in pam glatt GPCG 1.1, the working capcity(volume) is 2.4 lit, meanwhile in the Pam FBE 125 is 84 lit, means PAM 125 is 35 times more bigger than the GPCG 1.1. It means if the batch planned for the PAM 125 than it must be 35 times higher than the GPCG 1.1. For the non functional coating working volume can be 20-100 % and for the non functional 20-80% can be set.[19][20]

1.24 SPRAY RATE AND ATOMIZATION AIR PRESSURE:

Spray rate can be increases by increasing the drying efficiency it is not based on the batch size. Sometime it also becomes the critical variable for various perspectives. First of all it is economically time consuming process leads to increasing the cost. Longer the process, it will create the many problems while the on going process like clogging of the nozzle. As the inlet increases in relation to that only spray rate can be increase.

During the scale up trials drying capacity is considered as the critical parameter. There are various rate limiting steps like batch size, capacity of drying, and droplets size of the coating solution into the coating area and core materials. Temperature and humidity remain constant in the scale up batch, only on the bases of air volumes the drying capacity can be can be increase.

With respect to inlet air volume only the spray rate can increase. Over the conventional coating gun spray nozzle with the HS wurster have several advantages. Agglomeration generates near to the spray gun because bigger the droplets are generated there whereas hs wurstercompliant, in that coating gun and martial do not come in contact with each other and that’s why spray rate can be also increased higher.

Below equation shows calculation for the spray rate for the pilot scale batches.

$S2=S1*V2/V1$

V1= air flow of lab trial

V2= air flow of scale up trial

S1= spray rates of the lab trial

S2=spray rate in the pilot trial

To maintain the droplets size, increasing in air atomization and spray rate must equal than only process can be maintain. For same droplet size for the lab trial and pilot trial air atomization air volumes and spray rate must be same.

Maximum 4 to 5 bar range pressure can be used for the atomization air volumes. Mechanical stress on the core is higher because of high velocity this occur because of the higher atomization air pressures. Though at the lab scale if high pressure was used then also in scale up trial either spray gun having the bigger capacity used such as HS guns or spray rate must be slow.

By any how spray rate need to be maintained by reducing or increasing inlet air temperature.[19][20]

1.25 MASS EFFECT:

Based on the lab scale equipment's batches performance mass effect cannot be predicted. 6''is considered as best for the lab sale models and 18'' is considered as the best for the large scale models. Fluidization of material adjusted 125 cm or lesser height, and height of bed 200 mm, it should not be more than that, for the 6'' wurster this need to be set. For the 18'' wurster approximately 600mm heoght of bed and 2 meter height for fluidization is being set.[19][20]

CHAPTER-2

AIM

EXPLORING THE EFFECT OF PROCESS VARIABLE IN PELLETS COATING BY WURSTER FLUID BED COATER

AIM:

There are many method used for the manufacturing of the multiunit particulate system wurster coating is one of them and widely used. The aim the present investigation was to check the effect of the parameters, how to control them and to fix the range at scale down batch to get the good results. These limits were used to get the similar result in scale up batch. Enteric coated pellets were formulated by changing the various parameters like percentage of seal coat, percentage of enteric coat, ratio of coating solution, temperature, spray rate and RH and subjected to evaluation parameters like related substance, %yield and drug release at 10, 15 and 20 min. design was applied on the critical parameters by using the design expert.

RATIONAL

During the wurster process many parameters affects, measurable parameters can be controllable whereas fixed parameters are not changeable. To obtain the good result critical parameters are required to be controlled it can be done by fixing them or by limit, those can be controlled this helps in smooth process and to achieve desired result.

In many cases it was seen that batch failed in scale up this occurred because of the parameters. So at the scale down batches limits of the parameters can be set so in scale up the effect of them can be prevented. Range will helps to give idea that between the range processes will continue without any problem and result of the scale down as well as scale up batch can obtain similarly. By understanding and controlling the effect of parameters, it helps to reduces the chances of the batch failure in scale up.

OBJECTIVE

- To check the effect of parameters.
- To set the range of parameters.
- To check the effect of parameters on results and how to control them.
- To get the similar result of scale down and scale up by fixing and controlling the parameters.

CHAPTER-3

LITERATURE REVIEW

LITERATURE SURVEY:

LITERATURE SURVEY OF MPUS:

Bharkatiya M. et al 2012:

Reported that the importance of the Multi unit particulate system over the conventional system and the advantages over the single unit formulation. Manufacturing of the pellets by using various techniques known as the pelletization like suspension or solution layering, extrusion spheronization, powder layerings, freeze pelletization spray drying, cryopelletization, spray agglomeration, and spray congalings. [48]

Khan A. et al 2014

Reported that multi unit particulate system provides good therapeutic actions and helps to achieve controlled as well as delayed release pellets without the risk of dose dumping blending flexibility, for the various pattern release, it also provides the little gastric residence times and reproducibility. Pellatization is the method for manufacturing of the pellets, this also helps to manufacture beads as well. [49]

Ramu S. et al 2013

Study show that the advantages of the multi unit particulate system, pellets over the conventional or single unit forms the manufacturing techniques shows how to manufacture pellets from the fines. Studies show the advantages and disadvantages along with the applications of the manufacturing technique also show the evaluation and factor.[50]

FLUIDIZED BED COATER:

Chauhan J. et al 2011

Study shows that description about the coating process on the pellets in fluidized bed coating. It gives the idea about the coating of the pellet by using the solution droplets. It show that the drying granulation agglomeration coating and drying are involved in the process of fluidization. It is mostly used for the products like heat resistance and heat

sensitive products. this study shows the different types of the coating like top spray, bottom spray and tangential spray and the factors involves in the coating process.

Shrevastava S. et al 2010

Study shows that importance of the fluid bed coating 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. Study also reviewed that the novel technologies used for the pelletization techniques like MicroPx, Procell, and CPS and shows the applications advantage and disadvantage. [52]

Puspati R et al 2014

Study show that the importance of the fluid bed process for the development of the new dosage forms. Study reviewed the principle involve in the process that is material which is to be coated is in the suspension form with help of the air stream. This 3 principle those are top sprays, bottom sprays and tangential sprays are discussed in detailed. Study show the advantage disadvantage and new technologies used in the FBP. It also shows the problem solutions of the parameters observed during the process.[53]

Sonar G.et al 2015

Study show that importance of the wurster coating over the other pelletization techniques and it also provides many advantages in the single process. It shows that wurster is the constantly working continuous, less interruption as well as provides the high degrees of the reproducibility are main benefits of this technique. It shows that the many factors affect the process during the process they are called as the process variables. Basically, five types which affects the process like coating liquid variables, equipment variables, spraying variable, drying and preheating variables which affect the coating process. Study shows the detailed description of the all the variables and there sub parts. It also shows that many of them are having the medium or low risk. All the risk are required to study at the small scale batch while the developing the qulity by designs as well experimental designs by various software. Study shows that how to control the variable at the lab scale

to prevent their effect at the scale up batch. Wurster based methods scale up is totally on the bases of the optimization of the all process variable as well identify the risk of the variables and carrying out in the scale up factor which is provided by the vendors are required to be calculated. Lab scale as well as the commercial batch of the wurster must be liner and almost similar while the manufacturing this is the important key for the proper carrying out of the scale up factors.

Asija R. et al 2012

Study shows the development of the wurstercoating. It also show the applicability of the wurster apparatus like it can be used for the non aqueous as well as aqueous solution based coating. It reviewed that the high quality of the film can be developed by using this method it shows that this can be used for the suspension, solvent, aqueous, emulations films. This can be used for the coating of the tablets, pellets and capsules having batch size from the 100g to 600kg. This can be used for the controlled as well as the extended release or enteric coating pellet. Study shows the detailed description of the all parameters as well.

Pulgamwar G. et al 2015

Study show that the fluid bed is important for the manufacturing of the novel formulation with the higher therapeutic efficiency. Study reviewed that it is used for the improvement of the powder properties for tablet compression. High quality granules can be obtain by the controlling the process parameter by well measured. It shows that it is used for the granulations, coating or layering of the various range of the particle size. It is also used for drying process based on the location of the nozzle that is spray, bottom and tangential detail description shown in the study. Study reviewed that advance pelletization method efor the manufacturing of the new dosage form which are based on the “Multiunit particulate system” having good therapeutic efficacy discussed in details.

EXCIPIENTS

Singh S. et al

Study shows that the ideal property for the drug delivery system (A) it must be in single dosage form in all while the entire treatment. (B It must have fewer side effects. (C) It

must release the active ingredient the specific site. This can be achieved by the specific polymer. This study shows that the importance of the eudragit and their details. It also shows that use of the eudragit for the different drug delivery system and give detail description of the physicochemical properties.[54]

Sonje A. et al. 2013

Study shows that polymer selection based on the release of the drug. Polymer has basically two types of the properties (A) stability of the polymer in the acidic pH (B) it must dissolve slowly to for the proper release rate. The study shows the role of eudragit in different drug delivery mechanism and their physicochemical properties.[55]

Phadtare D. et al. 2014

Study shows that importance of the hypromellose in drug release in effective manner. This review shows that the details of the HPMC and use. It shows the thermal, chemical as well as mechanical properties, hydration from the matrix, and mechanism of the drug release from the polymeric matrix of HPMC. This also shows the maximum value used for the different type of dosage forms.

Huichao W. et al 2014

Study shows the details about the application of the HPMC in pharmaceutical formulations. Based on the induction application of liquid, solid, controlled gel and capsule preparation. The review shows the role of HPMC in pharmaceutical preparations.[56]

CHAPTER-4

EXPERIMENTAL WORK

4.1 GENERAL PROCEDURE:

In pellet prapration, there were 3 basic steps involved (A) drug layering (B) seal coating (C) entric coating.optimization of coating solution was done for that different concentration of IPA/WATER mixture was prepared and used for drug layered pellets. In drug layering solution was prepared and sprayed on the sugar spheres and drying was carried out for 30 min and after that pellets were passsed through the 30 mesh sieve.

Required quntity was taken for the further process on pellet.before that otimization of seal coating was carried out and then seal coating was done. Coating solution was prepraed and sprayed on the drug layered pellets after that 30 min drying was done.

Entric coating was done on the seal coated pellets which is the last step. In enatric coating different parameter were observed which are criticle and design was applied on those paramter and after that sacle up batch was taken by fixing the parameters and using factors provided by the vendor to obtain the same result as scale down.

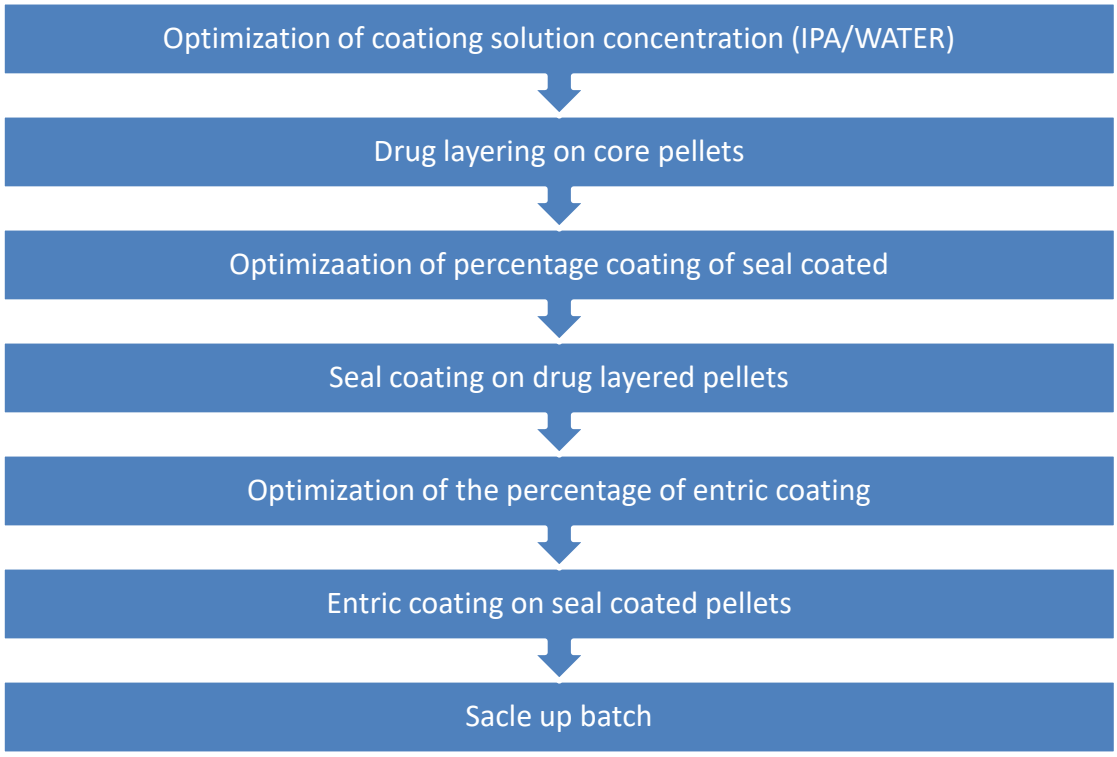

Table 4.1 Procedure steps

4.2 LIST OF MATERIAL AND EQUIPMENT USED:

Table 4.2 Material and supplier

Material name	Supplier
SUGAR SPHERE	Signet chemical
HPMC E5 LV	Colorcon, dow chemical
HPC LF	International speciality
TALC LUZINAC	Signet chemical
PEG 400	Monochem
IPA	Phener
EUDRAGIT L 100	Evonic
TEC	s.javari
FERRIC OXIDE RED	Signet chemical

Table 4.3 Equipment

Equipment	Company
Weighing machine Model- DS-862 (10gm-6kg)	Essae teraoka ltd
Weighing machine Model- MS 2045 01(0.1mg-220gm)	Metter toledo Switzerland
GPCG 1.1	Pam glatt
Stirrer	REMI lab

4.3 MATERIALS DETAILS:

Table 4.4 Material details

Sugar sphere	
Category	Capsule/tablet diluents
Description	It is genrally used as the inert core for the tablet as well as the capsule mainly for the malty particulates sustained release dosage forms. They are generally generated based on the drug

	coat mostly done with the help of the polymeric coat. Meanwhile drug as well as the matrix coat is applied on the core pellets. The API released from the coat via diffusion process otherwise it may release from the polymer by controlled erosions. Various mixture of the drug in the one single formulation can be formulated by the coating process of the drug and different polymer on the core pellets. They are available in various sizes. They are differentiated on the bases of the diameter.

HPMC E5	
Category	Polymer
Description	It solubilises into both organic as well as aqueous media and it is used for the fill coating. There are two grade used for the formulations. (a) Lower viscosity: This can be used for aqueous film coating liquids. (b) Higher viscosity: This can be used for the oraganic solvents. The main function the HPMC E5, it is also used for the thicknig agent and helps to increase the tensile strength as well as flexural strength. It slso helps for increasing the surface coat.

HPC	
category	Polymer/binder
Description	It solubilises into both water as well as alcohol the film of HPC is tacky and leads to restraints on the coats. It is used in the combination which provides adhesion to pellets. Mixture of HPC(non ionic polymer) and HPMC helps to form stronger gel of the final matrix, it also helps to decreases the diffusion as well as erosion rates. Molecular weight of the HPC is generally in between 100000 to 7000000 Da for faster water

	dissolving polymer. This mixture is generally used for the slow drug release mechanism.

Talc	
Category	Antiadhering agent
Description	It is generally used in the range between 1-5% as anti adhering agent. Tackiness is considered as the important parameter while the coating process this may become tacky based on the glasss transition temperature. So to avoid this problem anti adhering agent is added. Generally talc is widely used to avoid this problem. But it was found that use of talc leads to sedimentation of the material while the spraying of the solution, clogging of the spraying nozzles as well as leads to incompatibility sometimes with the solution. Sphericirty and agglomeration capacity are considered as the critical parameters when the talc is used for the inert core for the layering of the drug. For decreasing the poor strength problems and for giving the sphericity to granule the used talc must be Wet Spherical Agglomeration(WSA) was used for the pellet coating. Talc have good agglomerating and micrometric is excellent properties and it is good as compare to the sugar sphere. Combination of the talc and sugar sphere used in pan coating which shows good drug layering as well as coating efficiency and good drug release path in in vitro studies, that's why talc is used for the coating. It also have deformable like properties which helps to generate disintegration matrix it also have benefits of the pellet. Talc particles avoid fracture while the compressions.

	As comparing to the sugar sphere talc having less strength.

PEG	
Category	Plasticizer
Description	Solid grades of the PEG used for the film coatings as well as the hydrophilic polishing materials. For the plasticizer solid grades are used. These grades are also used for the film forming polymers. Liquid grade generally used for the film coating. It also helps to increase water permeability and also helps for the protection against lower pH of the enteric coating. It is generally used for the microencapsulated product in that it helps as plasticizer in that it also helps to prevent the destruction of the film coat while the compression in the capsule. For improving the mechanical strength for the coating in the formulations plasticizer are added in the dosage forms. For the good and continuous film Plasticizer and film forming are compatible with each other. Plasticizers are mandatory to be mixed with the polymer having less film formation capability and for coalescence of the particles. It helps to reduce the glass transition temperature and reduces the minimum film forming temperature for the coating process. Plasticizer generate channel for the drug to diffuse for coated pellet through insoluble film. For good solubility less molecular weight glycol is added. Molecular weight up to 600 PEG is selected for easy solubilisation in water.

TEC	
Category	Plasticizer
Description	Some ester like TEC, tributyl citrate acetyl tributyl and

	acetyltriethyl are genrally used as the plasticizer. It is generally used for the coating of the capsule, tablets, granules and beads used for immerdate release, eantric coating, taste masking and sustained release.

Eudragit L 100	
Category	Polymer
Description	Various types of eudargit used for the film formation on the pellets it is based on the pH value like at pH >6 eudragit L is used, at pH>7 eudragit S & FS. This is amorphous polymers having the 9 to > 150°c glass transition temperature. This polymer is nontoxic, biodegradable nonabsorbable, and biodegradable. Anionic eudragit L genrally dissolves at the ph grter than 6 that is mostly used for the enatric coating, whereas for colon target drug delivery eudargit S is used which is soluble at above pH 7. Eudragit L 100 55 used for release into duodenum whereas eudragit L 30D 55 aqueous dispersion used for the pH 5.5. For release into jejunum or ileum at pH 6 eudragit L 100. And the mixture of the eudragit S 100 and L 100 used for the release into pH 6.0-6.5. Eudragit L as well as S are the anionic polymer they are differnciate on the basis of the methacrylic acid ester the formed film is insoluble less under pH 5 this helps to produce resistance in gastric fluid.in intestine at pH 5.5 based on the several mechanism like salt generation in netural or alkaline medium helps to dissolve the films step by steps.

IPA	
Category	Solvent or vehicle
Description	It is generally used for the film coating of both tablet as well as for pellets. It can be removed by the evaporation. Sometime to avoid static charge and for reducing the cost some time along with IPA water is used.

4.4 EVALUATION PARAMETERS:

DISSOLUTION:

Dissolution was checked by using Paddle apparatus at 100 RPM in two media buffer 6.8 and in acidic pH 1.2 (0.1N HCL).

In acidic pH release must be less than 1% to prevent the drug release enteric coating was done. In intestine at 20 min 85 % and at 30 min more than 95% drug released must be required to pass the test.

TOTAL IMPURITY:

"Some part of the novel drug molecules which is not chemical part is known as the new drug substance"

There are three typed of the impurities.

(A) Organic: Intermediates, staring material, by products, reagents and degraded products

(B) Inorganic: heavy metal, reagents, inorganic salt

(C) Residual solvents: inorganic or oraganic liquid used as the solvents for the preparation of the coating solution.

Total impurity must be less than 1 % to pass the test.

STABILITY CONDITION:

The rationale behind this test is to give information about the quality of the API as well as how the different environment affect to the product that leads to the degradation like light temperature and humidity. It helps to create the storage condition of the formulations.

There are 4 climatic zones for the stability test.

Zone 1: Temperature

Zone 2: Subtropical and may be high humidity

Zone 3: dry and hot

Zone 4: humid and hot

Accelerated stability testing: it helps for the identification of the shelf life of the formulation by increasing the decomposition rate for that temperature of the reaction need to be increased. Self life can be identified in month with the help of the accelerated stability.

Stability condition for formulation: 40ºc/75% RH ±2ºc ±5% RH for 3months.

LOSS ON DRYING:

It can be expressed as the loss of the mass in percentage (% w/w) because of the loss of the volatile and water based solvents that can remove by the special conditions. This method helps to measure the amount of the water or volatile substance in the formulations.

Limit for the LOD: Not more than 3%.

% YIELD:

This can be calculated based on the ratio of the theoretical total amount used for the formulation and practical yield that is obtain after the trial.

%yield= theoretical yield *100/ practical yield.

4.5 GENERAL PROCEDURE FOR DRUG LAYERING ON CORE PELLETS:

All the ingredients were weighed accurately. IPA and water mixture were prepared in one beaker. Mixture was divided into two halves in separate beaker then drug was added in beaker (A) and mix them till API is completely soluble.

The solution of HPMC (Hydroxypropyl MethylCellulose), HPC(Hydroxypropyl cellulose) and PEG(polyethylene glycol) was prepared in other beaker (B) mix them properly. The prepared solution of beaker B was transferred into beaker A. Talc was added in the beaker and continues stirring was carried out for 45 min.

Sugar sphere was loaded into the FBP and the prepared solution was sprayed on the sugar spheres by using bottom spray method.

All the parameters were noted and maintained. The coated pellet sifted from the 40 mesh sieve for removing the aggregates. % yield was calculated.

PROCEDURE FOR THE SEAL COATING ON THE DRUG LAYERED PELLETS:

All the ingredients were weighed accurately. HPMC and HPC were added in water and IPA mixture mix it for 30 min. TEC and talc were mixed in the above mixture. Continuous stirring was carried out for 45min.

The prepared solution was sprayed on the drug coated pellets. All the parameters were maintained and recorded. The coated pellets were passed through 40 mesh sieve. %yield was calculated.

PROCEDURE FOR ENTERIC COATING SEAL COATED PELLETS:

All the ingredients were weighed properly and Eudragit L 100 was dissolved in acetone completely. Talc, TEC and ferric oxide red were dissolved in IPA/water and mix the prepared solution with the eudragit solution.

Sprayed the above solution on the seal coated pellets and passed through the 30 mesh sieve maintained and record all the parameter. Calculate the % yield.

4.6 compositions (mg/capsule):

Table 4.5.1 Drug coating

Composition	Category	Weight
Sugar sphere	core pellets	100 mg
API	API	20 mg
HPMC E5	Binder	9.90 mg
HPC-LF	Binder	9.90 mg
TALC LUGINAC	Anti tacking	5.90 mg
PEG 400	Plasticizer	3.89 mg
IPA/WATER(70:30)	Coating solution	Q.S

Table 4.5.2 Seal coating

Composition	Category	Weight
Drug layered pellets	Core pellets	149.59 mg
HPMC E5	Binder	4.9 mg
HPC –LF	Binder	4.9 mg
TEC	Plasticizer	2.0 mg
TALC LUGINAC	Anti tacking	3.0 mg
IPA/WATER	Coating solution	q.s

Table 4.5.3 Enteric coating

Composition	Category	Weight
Seal coated pellets		165 mg
Eudragit L100	Polymer	12 mg
TEC	Plasticizer	2.5 mg
TALC LUGINAC	Anti tacking agent	5.4 mg
IPA/WATER/ACETONE	Coating solution	Q.S

4.7 Preliminary Batches

4.7.1 Effect of enteric coating on drug layering:

Table 4.6 (Batch-P1)

Composition	Batch P1(enteric coating)
Weight of drug coated pellets(gm)	818.19
%yield (gm)	932.85 (99.2%)

Note: trial one was carried out to check the effect of enteric coating on the drug layering.

PROCEDURE:

Same as above.

RESULT AND CONCLUSION

Results show that Batch (trial 1) was failed in RS (related substance) in trial 1 and it was found that the dissolution was near to the criteria.

The batch was failed in trial 1 in which direct enteric coating was applied. The drug was found to be incompatible with the enteric coating material. Results show that seal coating is compulsorily required between the drug layering and enteric coating. Result also shows that dissolution was not much affected by direct enteric coating. So in trial 2 different percentage of the seal coating was carried out.

4.7.2 Seal coating

Table 4.7 (Batch-P2, P 3, P 4)

Composition	Batch P2	Batch P3	Batch P4
Percentage of seal coating	**8%**	**10%**	**12%**
Initial weight of pellets	818.25	818.20	818.15

%yield(gm)	880.56(99.5%)	894.3(99.3%)	910.44(99.3%)

RESULTS AND CONCLUSION

Results show that all the batches were passed in RS.

In trial 2, 3, and 4, different percentage of seal coating was carried out but the batch with 10% was selected for further process. 8% coating was carried out in trial 2 in which coat was thin but the results show the dissolution near to the criteria but RS was comparatively higher so in next batch 4% of coat was decided to increase hence in next trial 10% coat was applied. Result of batch 3 with 10% coat was found to be desired so batch was passed the test. Batch 4 was taken with further with 4%, hence in next batch was taken with 12%. The results of batch 4 show that the batch was passed.

But batch 3 with 10% coating show desired result, it was selected because if 2% percentage more or less coat applied in further trials still there were not significant changes observed.

Table 4.7.1 result table

Results	Batch P2	Batch P3	Batch P4
Related substance %	0.87	0.54	0.52

4.7.3 Effect of temperature RH and spray rate

Table 4.8 (Batch P5, P6)

	Batch P5	Batch P6
product temperature (°c)	28-33	
temperature(°c)	30	35
Exhaust temp (°c)	26-30	
Atomization (bar)	1.2	

Column height (mm)	17	
Spray pump RPM	8	8
Blower %	50	
Inlet RH(%)	25	20

Note: effect of spray rate was checked while enteric coating process.

PROCEDURE: same as enteric coating.

RESULT AND CONCLUSION OF Batch P5:

Results show that batch 5 was failed in because of agglomeration and batch was failed in RS also.

In batch 5 effect of higher temperature and RH were checked but batch was failed because of agglomeration reason behind this was found that higher temperature leads to sticking and this produced lumps of the pellets and higher RS increases the degradation and leads to increase in total impurity So in batch 6 it was decided to take with higher the temperature and lower RH

RESULT AND CONCLUSION OF Batch P6:

Result shows that the batch was passed

Batch 6 was carried out with the high spray rate and higher temperature so higher temperature prevent sticking and it was found the inlet RH was less helps to prevent degradation.

Conclusion: As the temperature increases RH decreases higher temperature helps to prevent sticking and lower RH helps to prevent the degradation of the product.

4.7.4 OPTIMIZATION OF COATING SOLUTION:

Table 4.9 (Batch-P7, P8, P9)

Batch 7	Batch P8	Batch P9
100% IPA	50:50 (IPA/water)	70:30(IPA/water)

RESULT AND CONCLUSION:

Result shows that batch 9 was passed and used for further batches.

It was found that in batch 7 with 100% IPA highly static charged was observed during the process. Because of higher static charge flow pattern was not proper and good surface morphology was not achieved. So based on result of trial 7 water was used in next trial to prevent static charge.

Batch 8 was taken by using 50:50 (IPA:water). It was found that there was not static charge observed because of water, but during the process higher temperature was required because of water. Less yield was obtained. Hence further trial was taken with less amount water decreased.

Batch 9 was carried out with 70:30(IPA:water). It was found that comparatively less temperature required. Results show that % yield was higher and loss was also less. So for further trial 70:30 was used.

4.7.5 OPTIMIZATION OF THE ENTERIC COATING

Table 4.10 (Batch P10, P11, P12)

Enteric coating percentage	**BATCH P10 8%**	**BATCH P11 12%**	**BATCH P12 16%**
Initial weight (gm)	894.7	894.5	894.6
yield (gm)	961.4	997.2	1032.8

Table 4.10.1 parameters

Parameters		Range during process
Temperature	Set temperature	31-33
	Actual	29-32
Product Temperature (°c)		29-31
Exhaust Temperature(°c)		26-30
Atomization (bar)		1.2
Column height(mm)		17
Spray pump RPM		2-5
Inlet RH (%)		20-25

RESULTS AND CONCLUSION:

Results show that batch 11 gave good dissolution than other trial.

Result of batch10 show that it was failed in dissolution it was found that thin coat was formed on the seal coated pallet and dissolution in acid was found higher and batch was failed so in next batch it was decided to take batch with 4% extra coat.

In batch 11 and 12 it was observed that both give good yield and good dissolution but it was found that batch 10 with 12% gave good dissolution compare to the batch 11. It was observed that batch having 16% enteric coating forms thick coat due to which slow dissolution was obtained compare to the batch 12 so for further batch 12% enteric coating was used.

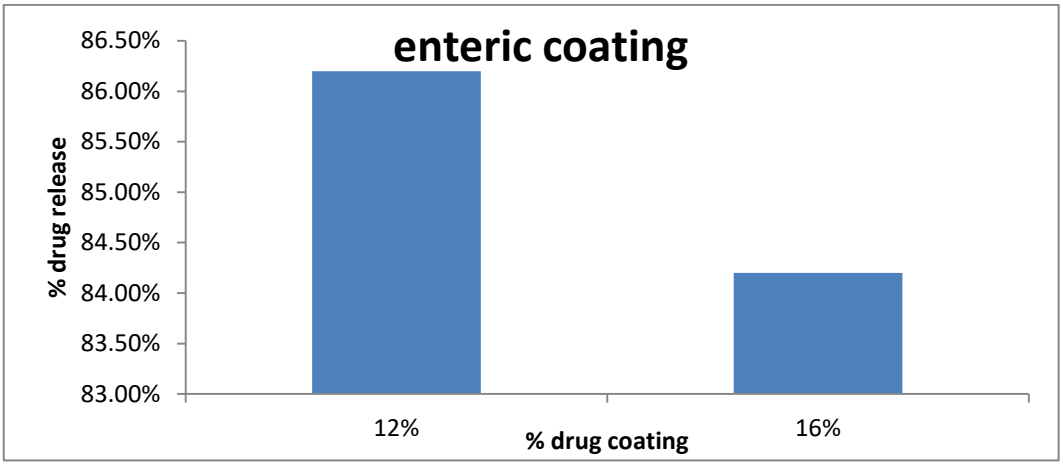

Fig 4.1 Graph of enteric coating

4.7.6 DESIGN EXPERT BATCHES

2^3 full factorial Design was applied by using design expert on the most critical parameters (A) inlet RH (B) Temperature (C) spray rate

Table 4.11

BATCH (D13 to D24)	Run	Factor 1 Inlet RH %	Factor 2 Temperature °C	Factor 3 Spray rate gm/ml
D 13	1	35	34	2
D 14	2	25	30	5
D 15	3	25	30	5
D 16	4	35	26	8
D 17	5	15	26	2
D 18	6	15	34	8
D 19	7	15	34	2
D 20	8	15	26	8
D 21	9	35	26	2
D 22	10	25	30	5
D 23	11	25	30	5
D 24	12	35	34	8

TABLE 4.12 RESULT OF BATCH D13 to D24

Trial	Run	Dissolution at 10 min	Dissolution at 15 min	Dissolution at 20 min	Total impurity
D 13	1	35.5	57.1	80.2	0.78
D 14	2	34.7	66.1	87.8	0.73
D 15	3	38.2	66.4	88.1	0.72
D 16	4	43.3	70.1	92.2	0.81
D 17	5	37.1	59.3	82.9	0.61
D 18	6	41.2	68.3	90.8	0.54
D 19	7	36.4	57.3	80.4	0.63
D 20	8	44.2	70.2	92.4	0.64
D 21	9	36.5	59.4	83.0	0.80
D 22	10	37.7	65.9	86.5	0.74
D 23	11	35.2	66.7	87.6	0.70
D 24	12	41.6	68.4	89.9	0.81

Those batches are consider as passed in which more than or equal to 85% drug release was obtain.

Effect of slow spray rate, temperature and RH

Trial	RH	Temperature	Spray rate	Dissolution 10 min	Dissolution 15 min	Dissolution 20min	RS
1	35	34	2	35.5	57.1	80.2	0.78
5	15	26	2	37.1	59.3	82.9	0.61
7	15	34	2	36.2	57.3	80.4	0.63
9	35	26	2	36.9	59.4	83.0	0.80

It can be seen that at the slow spray rate and high temperature causes to decrease in the dissolution. It was found that higher spray rate form spray drying effect and reduces the yield and it forms uneven coat on the surface of the pellets so it decreased the dissolution.

It was found that as the RH increases, total impurity also increases because of the higher water content in the air so it may causes degradation by hydrolysis or oxidation whereas at lower RH this was not observed and RS was less though it was within the criteria.

Medium spray rate, temperature and RH

Trial	RH	Temperature	Spray rate	Dissolution 10 min	Dissolution 15 min	Dissolution 20min	RS
2	25	30	5	34.7	66.1	87.8	0.73
3	25	30	5	38.2	66.4	88.1	0.72
10	25	30	5	37.7	65.9	86.5	0.74
11	25	30	5	35.2	66.7	87.6	0.70

It can be seen that batch show good result. It was found that all the parameters not affected much on the result. Dissolution was also within the criteria. RS was also less because of the less water content in the air helps to prevent the degradation.

High spray rate, temperature and RH

Trial	RH	Temperature	Spray rate	Dissolution 10 min	Dissolution 15 min	Dissolution 20min	RS
4	35	26	8	43.3	70.1	92.2	0.81
6	15	34	8	41.2	68.3	90.8	0.54
8	15	26	8	44.2	70.2	92.4	0.57
12	35	34	8	41.6	68.4	89.9	0.79

It was found that at the higher temperature dissolution decreases and it also produced the spray drying effect and also decreased the %yield it was observed that at higher temperature proper film was not formed. At lower temperature dissolution was higher because in that film was properly formed.

It was found that as the RH increases total impurity also increases because of the higher water content in the air so it may causes degradation by hydrolysis or oxidation whereas at lower RH this was not observed and RS was less though it was within the criteria.

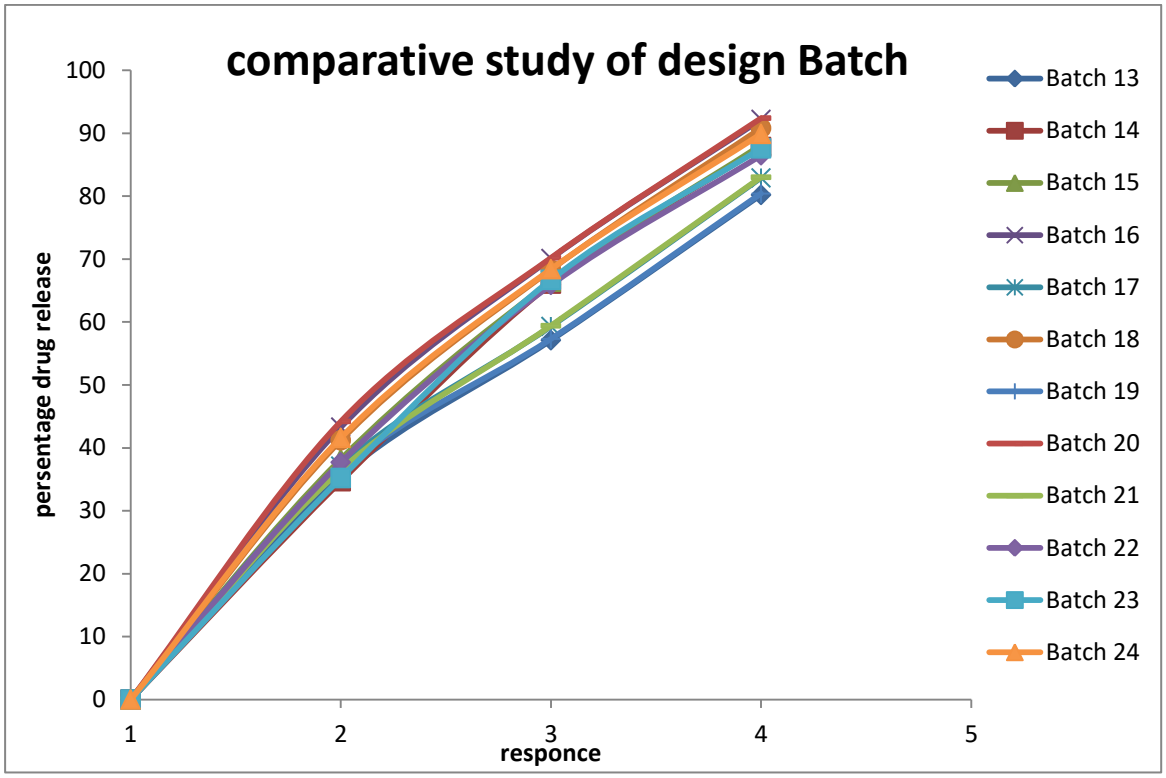

Fig 4.2 Comparative chart of Batches (Response 2-10min, 3-15min,4-20min)

DRUG RELEASE AT t10 MIN:

Drug release of the all the batches were separately taken as shown in above table. Value was obtained in the range of 34 to 47%. On the basis of that polynomial equation was generated.

Based on the polynomal equation it can be identified that the individual parameter(X2,X3) have positive efffect on the dependent variable and it was observed that intrection of paramter have negligible effct on the dependent varible. So it was concluded that as the value of independent variable increases the value of Y3 increases.

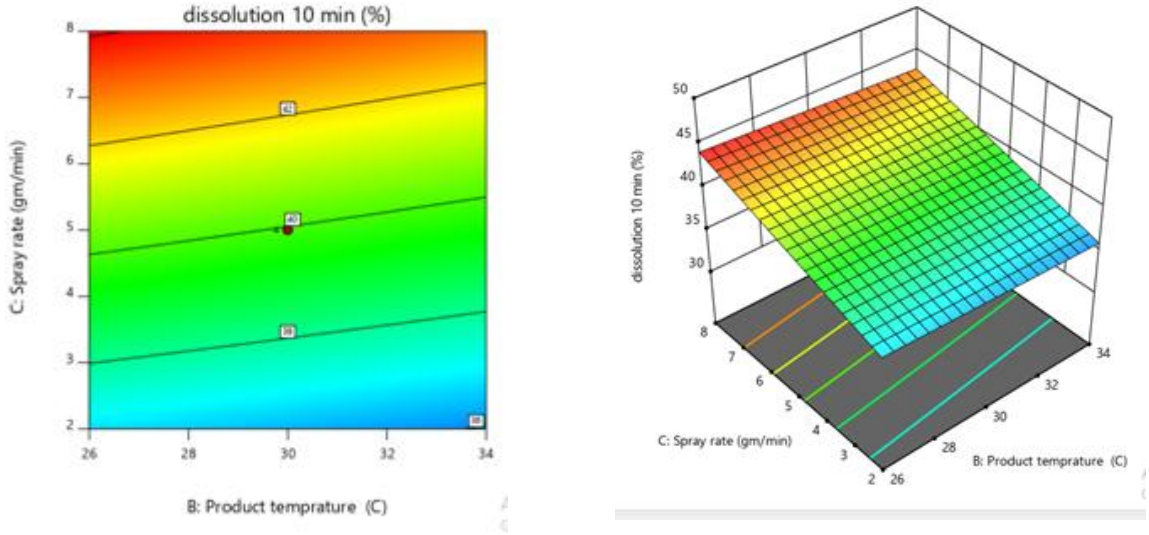

Fig 4.3 3d-graph of t10 min

The above figure show that the relation between the product temperature, spray rate and dissolution.

Based on the response following approaches can be used.

- To obtain the desired drug release proper spray rate must be maintained for higher spray rate higher the temperature required for proper drying of the film.
- Less temperature and less spray rate it also helps to causes the above condition.

DISSOLUTION AT t15 MIN:

Drug release of the all the batches were separately taken as shown in above table. Value was obtained in the range of 56 to 71 %. On the basis of that polynomial equation was generated.

Y2=+61.79+0.052X1+0.23X2+1.83X3-0.0018X1X2-00.0089X1X3-0.000521X2X3+0.000312X1X2X3

Here X1=Inlet RH

X2=Product temperature

X3=spray rate

Based on the polynomal equation it can be identified that the individual parameter(X2,X3) affect on the depedent variable, it was observed that all the independent factors have positive effect. It was found that interacation of the independent varible have negligible effect. So it was concluded that as the value of independent (X2, X3) variable increases the value of Y2 increases.

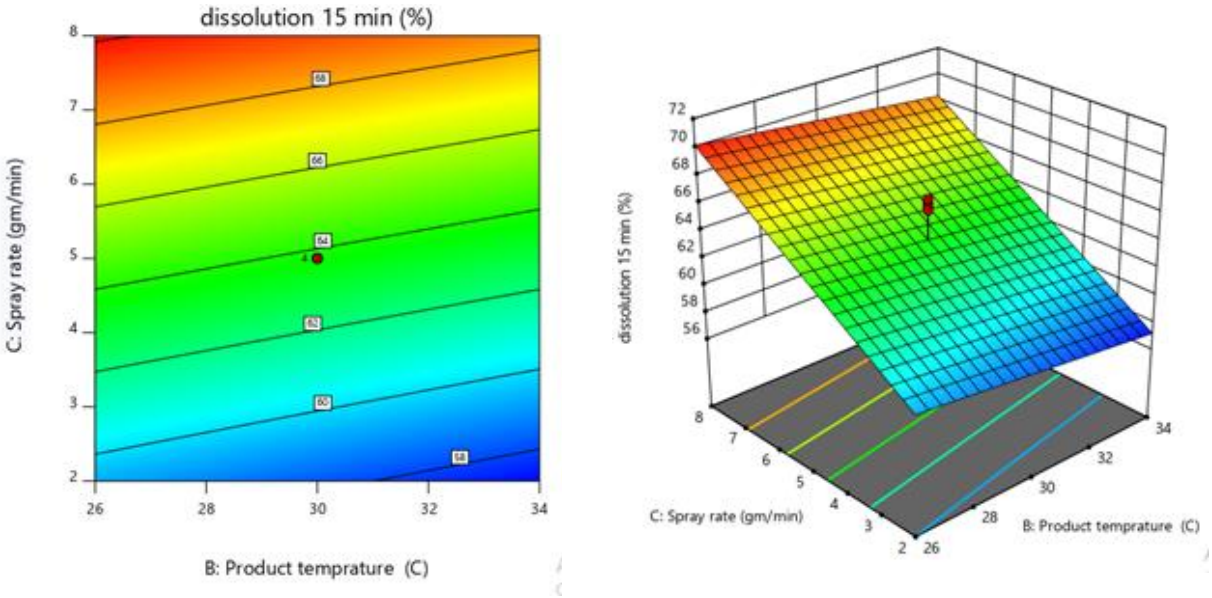

Fig 4.4 3d-graph of t15 min

The above figure show that the relation between the product temperature and spray rate.

It was observed that dissolution increases as the spray rate increase with respect to the temperature. From the above graph it was observed that for desired release, spray rate must be low and temperature should be sufficient for proper drying.

FOR t20 MIN:

Drug release of the all the batches were separately taken as shown in above table. Value was obtained in the range of 81 to 93%. On the basis of that polynomial equation was generated.

Y3=+74.21+0.59X1+0.13X2+3.78X3-0.019X1X2-0.0104X1X3-
0.068X2X3+0.0033X1X2X3

Here X1=Inlet RH

X2=Product temperature

X3=spray rate

Based on the polynomal equation it can be identified that the individual parameter affect on the depedent variable, it was observed that all the independent factors have positive effect. It was found that interacation of the independent varible have negligible effect. So it was concluded that as the value of independent variable increases the value of Y3 increases.

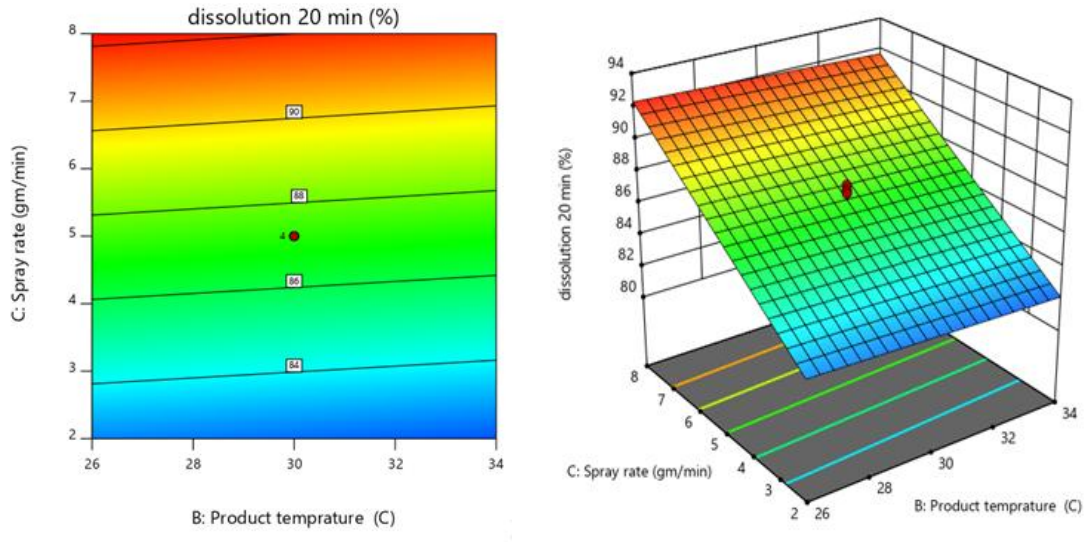

Fig 4.5 3d-graph of t20 min

The above figure show that the relation between the product temperature and spray rate.

It was observed that dissolution increases as the spray rate increase with respect to the temperature. From the above graph it was observed that for desired release spray rate must be low and temperature should be sufficient for proper drying.

EFFECT ON IMPURITY:

Total impurity was checked for the individual trial the above table shown the results of the total impurities. The range of the impurity was found between 5 and 8.this shows that total impurity was affected by the product temperature and RH. Based on that polynomial equation was generated.

Y4=-0.066+0.29X1+0.019X2+0.14X3-0.00070X1X2-0.0046X1X3-
0.0052X2X3+0.00016X1X2X3

Where X1=Inlet RH

X2=Product temperature

X3=Spray rate

The polynomial equation shows that independent variable(X1) has positive effect on the dependent variable. So it was concluded that as the value of independent variable(X) increases the value of Y4 increases.

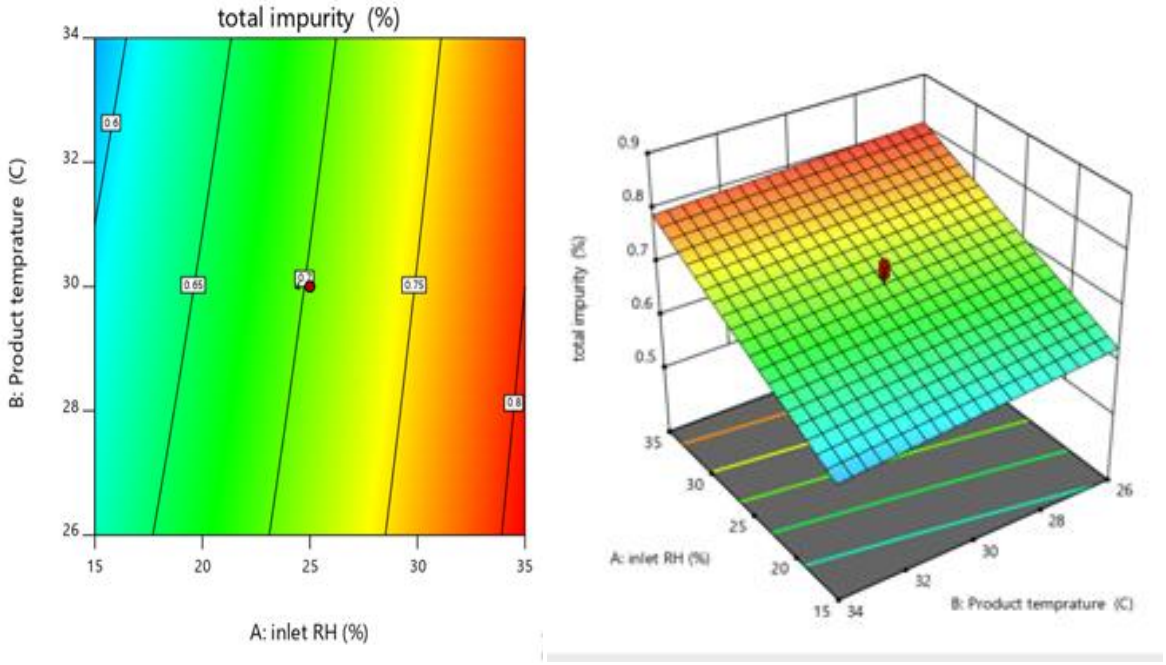

Fig: 4.6 3d-graph of impurity

It was observed that total impurity increases as the RH increases. It was found that as the increases in RH leads to degradation of the product because of the hydrolysis or oxidation this happened because it contained more water.

4.8 CONFORMATIONAL (BATCH 25)

Table 4.13

Condition	RH	Product temperature	Spray rate	Dissolution at 20 min	Impurity
Design condition And result	**15**	**30**	**8**	**92**	**0.605**
Trial condition And result	**15-17**	**29-31**	**8**	**91.73**	**0.584**

Result and conclusion:

At 20 min similar result was observed as shown in the software and impurity was also similar. At 20min 91.73 % drug release was obtained and impurity was 0.584 %. Hence the trial passed.

Formulation of Optimized batch:

On the basis of the preliminary trial and based on the factorial design, range of the RH was decided and product temperature was fixed. Based on the design expert software following area was obtain which shows the optimized batch.

Overlay plot

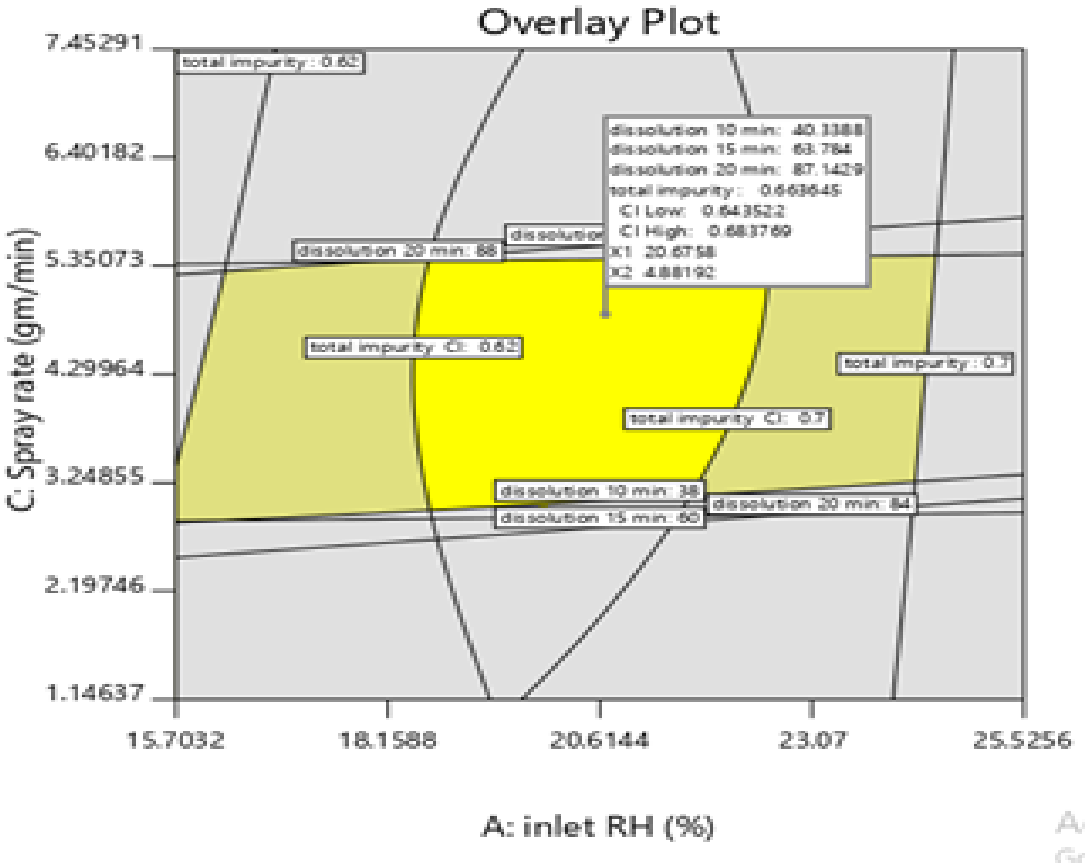

Fig 4.7 Overlay plot

4.9 OPTIMIZED BATCH (BATCH- O26)

Table 4.14.1 Drug layering

Composition	Category	For 5500 capsule
Sugar sphere	core pellets	550 gm
API	API	110 gm
HPMC E5	Binder	54.45 gm
HPC-LF	Binder	54.45 gm
TALC LUGINAC	Anti tacking	32.59 gm
PEG 400	Plasticizer	21.39 gm
IPA/WATER(70:30)	Coating solution	Q.S

Table 4.14.2 Seal coating

Composition	Category	For 5500 caps
Drug layered pellets	Core pellets	818.25gm
HPMC E5	Binder	26.95 gm
HPC –LF	Binder	26.95 gm
TEC	Plasticizer	11 gm
TALC LUGINAC	Anti tacking	16.5 gm
IPA/WATER	Coating solution	Q.S

Table 4.14.3 Film coating

Composition	Category	For 5500 capsule
Seal coated pellets	Core pellets	894.70 gm
Eudragit L100	Polymer	66 gm
TEC	Plasticizer	19.7 gm
Talc Luginac	Anti tacking agent	29.7 gm
IPA/Water/Acetone	Coating solution	Q.S

TABLE 4.14.3.1 PARAMETERS

Parameters		Range during process
Temperature	Set temperature	31-35
	Actual	30-33
Product Temperature (°c)		29-32
Exhaust Temperature(°c)		26-30
Atomization (bar)		1.2
Column height(mm)		17
Spray pump RPM		2-8
Inlet RH (%)		18-25

RESULT AND CONCLUSION:

The prepared batch of the optimized batch was passed.

It was found that Weight of final pellets was 1004.2gm after all process and % yield was 99.37%. Result shows that %assay was within the limit 97-110%. LOD was found 1.8%. The results shows that Dissolution F2 (similarity index) was more than 50 and the % drug release was obtain same as the innovator's results. The trial was also passed in RS and was 0.64 % (limit less than 1).

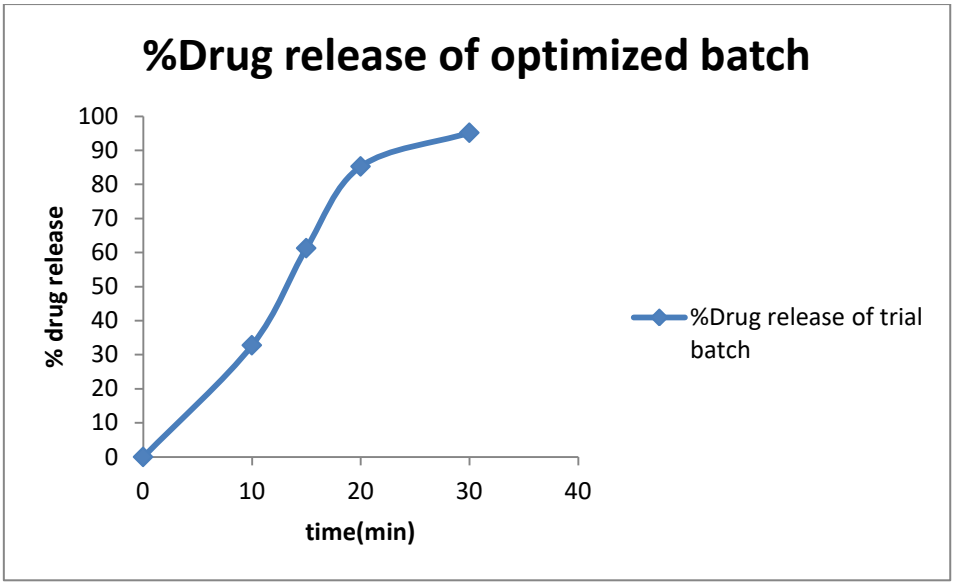

Fig 4.8 Comparative dissolution graph of optimized batch

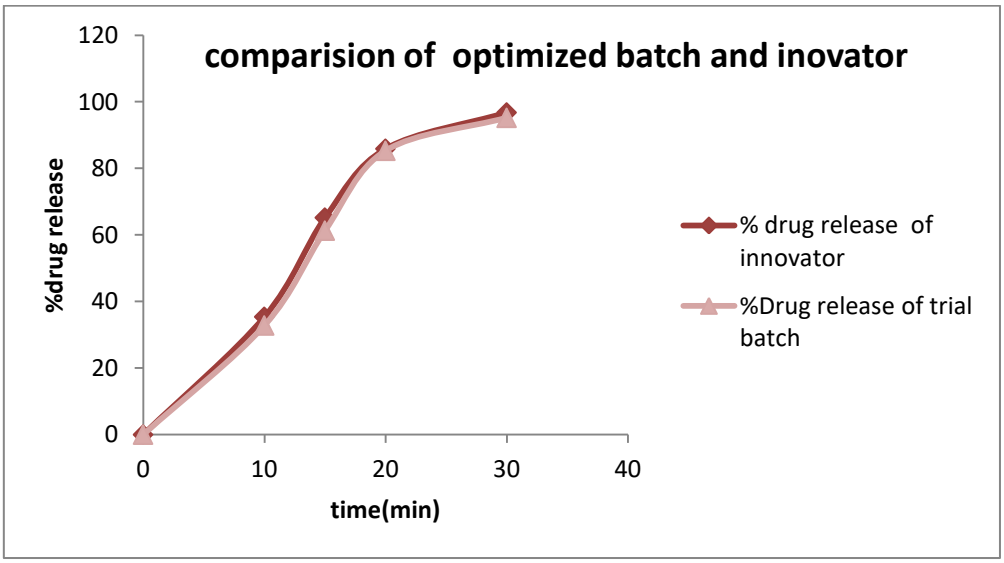

Fig 4.9 Comparative dissolution profile of optimized batch and innovator

4.10 SCALE UP BATCH (BATCH S27):

Table 4.15.1 Drug coating

Composition	Category	Weight
SUGAR SPHERE	core pellets	19.25 kg
API	API	3.85 kg
HPMC E5	Binder	1.925 kg
HPC-LF	Binder	1.925 kg
TALC LUGINAC	Anti tacking	1.55 kg
PEG 400	Plasticizer	0.77 kg
IPA/WATER(70:30)	Coating solution	Q.S

Table 4.15.2 seal coating

Composition	Category	Weight
DRUG LAYERED PELLETS	Core pellets	29.08 kg
HPMC E5	Binder	0.9625 kg
HPC –LF	Binder	0.9625 kg
TEC	Plasticizer	0.385 kg
TALC LUGINAC	Anti tacking	0.5775 kg
IPA/WATER	Coating solution	Q.s

Table 4.15.3 enteric coating

Composition	Category	Weight
SEAL COATED PELLETS	Core pellets	31.710 kg
Eudragit L100	Polymer	2.31 kg
TEC	Plasticizer	0.479 kg
TALC LUGINAC	Anti tacking agent	1.039 kg
IPA/WATER/ACETONE	Coating solution	Q.S

Note: In scale up batch factor was used which was provided by the vendor.

RESULT AND CONCLUSION:

Results show that batch was passed in dissolution as well as RS it was found that results were obtain same as the scale down.

- Total weight of the final pellets was 35.29 kg was obtained.
- %yield=99.33% was obtained
- LOD = 1.87%

Factor 35 was used for scale up, and it was observed that the occupancy was similar to scale down batch. Factor 10 was used for spray rate study in the scale up batch and the spray rate was found that the process worked smoothly without the formation of agglomerates and sticking of pellets was avoided. Factor 10 demonstrates that working within the limit of 18-85 will give good results. Also, when the limit was crossed beyond 85, sticking was observed.

TABLE 4.15.3.1 PARAMETERS

Parameters		**Range during process**
Temperature	Set temperature	31-35
	Actual	36-30
Product Temperature (°c)		29-33
Exhaust Temperature(°c)		26-30
Atomization (bar)		2.5
Column height(mm)		40-45
Spray pump RPM		18-72(80)
Inlet RH(%)		18-25

4.11 STABILITY STUDY:

Description:

White opaque body and white opaque cap, size "2" hard gelatin capsule filled pellets.

Table 4.16 Stability data

description	Standard	Initial	1 M	3 M
Net content	1846 mg (±3)	1850 mg	1846 mg	1844 mg
LOD	NMT 3.0%	1.8%	1.7%	1.9%
Related substance	NMT 1 %	0.53 %	0.61%	0.66%
Dissolution	Acid – NMT 10% at 60 min	1.2	1.4	1.2
	Buffer- NLT 95% at 30 min	95.2	95.4	96.2
Stability criteria : 40°C/75% RH, ±2°C/±5% RH UPTO 3 MONTHS				
PACK : 30 Count in normal HDPE bottle 100 cc				

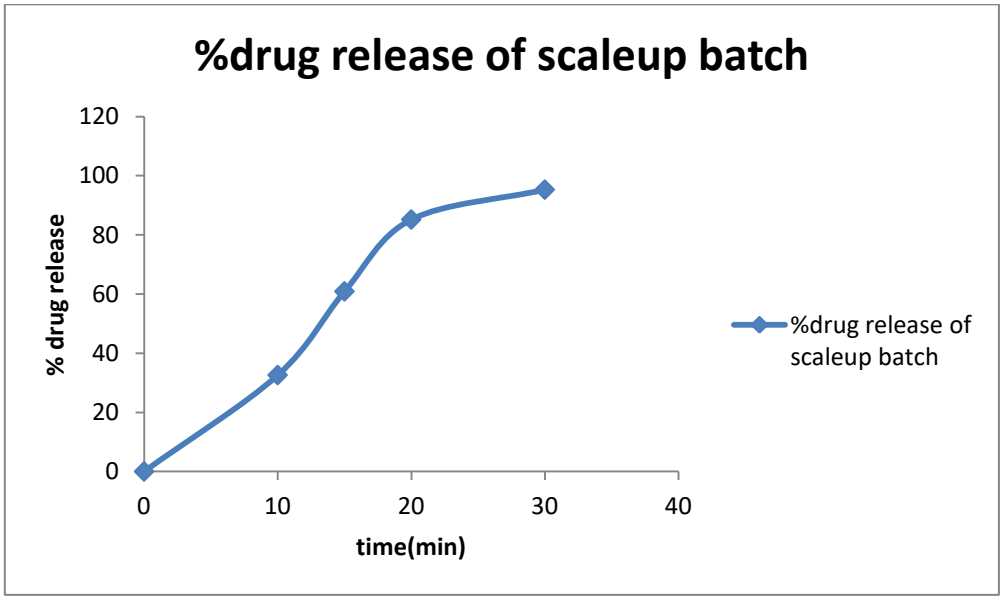

Fig 4.10 Comparative dissolution profile of scale up batch

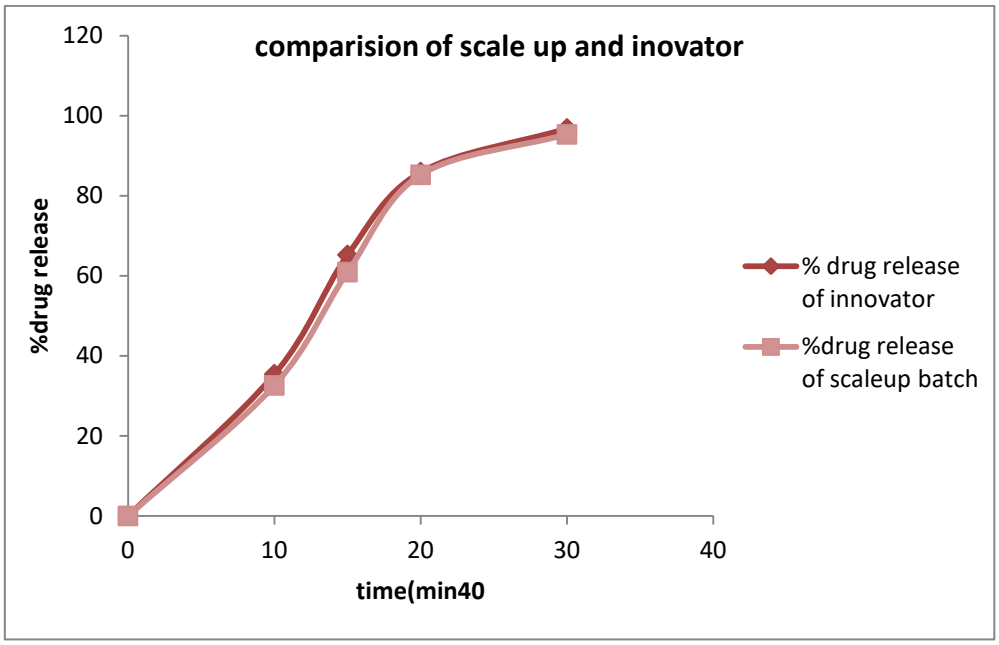

Fig 4.11 Comparative dissolution profile of scale up batch and innovator

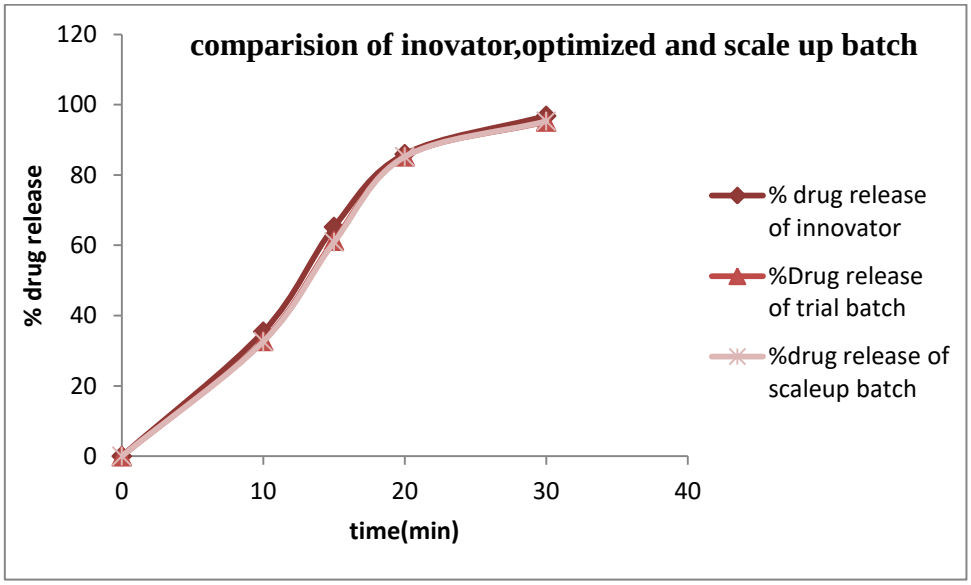

Fig 4.12 Comparative dissolution profile of optimized batch, scale up batch and innovator

CHAPTER-5

SUMMARY

Wurster fluid bed coater is widely used for the pellet coating. It is the one of the pelletization technique 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. Wurster based coating process mostly involved air volume, product temperature, spray rate, and ait atomization pressure are high risk process variables that can be reduce by systematic optimization study where as the column height and filter beg, dew point and drying time are medium risk factors which can be fixed during the lab scale batches. Various scale up problems reported can be traced for improving the correlation of these factors or poor equipment design.

Preliminary batches were prepared to study the effect the various parameters on the pellets and their response. For that various trial were taken like effect of enteric coating, optimization of seal coating, effect of spray rate, coating solution than 2^3 full factorial design was applied on the critical parameters to check the RS, %yield and LOD and % drug release at t10min, %drug release at t15min and %drug release at t20min. After that conformational trial was taken to check the selected model's result.

Based on that batch 25 was taken as optimized batch which shows the desired result. Based on that scale up batch was taken, for that factors were used for %occupancy and spray rate to obtain the similar result like lab scale batch.

Over all it can be concluded that proper release of the drug can be obtain by controlling the spray rate as well as the temperature and related substance can be reduced by humidity.

It can be concluded from the above work that experimental design may be useful for researcher in achieving the desired characteristics of the dosage forms within the optimum time in systemic circulations.

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