1 INTRODUCTION

1.1 PREAMBLE

For controlled release drug delivery system, oral route drug delivery system is more acceptable. In recent years, pharmaceutical scientist have more interest in oral modified release dosage forms. Conventional technologies, including multiparticulate drug delivery system has great importance, due to easily adjustable drug release profile and control drug release. These systems released drug at variable or constant release rates to achieve drug concentration in the therapeutic window. The desired drug release profile gives uniform drug absorption in the body to get good therapeutic activity which leads to reduces side effects (Dey N S et al., 2008). Multiparticulate drug delivery systems comprises more numbers of small particles of excipients and active ingredient where each unit demonstrating desirable features for whole dosage form. Multiparticulate drug delivery systems are prepared by methods including pelletization, extrusion spheronization, spray congealing, spray drying and granulation.

1.1.1 Multiunit particulate system (MUPS) : A drug delivery system

Multiunit particulate systems (MUPS) are one of the novel multiparticulate drug delivery systems technique for controlled and/ or modified drug delivery. However, MUPS offers various advantages over conventional delivery systems. Multiparticulate systems shows less inter- and intra-subject variability than conventional oral formulations and more reproducible pharmacokinetic behavior. Pellets-in-Tablet reduces the tablet's esophageal residence time and also improved stability than suspensions and capsules (Abdul A S et al., 2010).

MUPS concept can be used to develop delayed release formulations, taste masking, modified release, controlled release and orodispersible formulations for pediatric and geriatric patients. This MUPS technology used to achieve desired objectives from the dosage form.

1.1.2 Advantages of MUPS tablets

Below are the advantages of MUPS tablets formulation over pellets filled in capsules and modified release formulations.

I. Pharmacokinetic advantages :
Pellets from MUPS tablets rapidly and uniformly transit from stomach to small intestine. Hence localized irritation reduces significantly, so more uniform drug absorption and hence improved bioavailability.

Pellets more uniformly emptying from stomach to small intestine which gives faster dissolution of coated pellets and hence Tmax and Cmax achieved in enteric coated formulations. While in sustained release MUPS tablets, uniform drug release and dose dumping reduced hence reduced the inter-subject variations (Reddy S et al., 2012).

II. Pharmacodynamic advantages:

✓ Small pellets size has large surface pellets from MUPS tablets uniformly emptying and uniform drug release in GIT which leads to uniform absorption of drug which facilitated consistent and desire therapeutic action of drug.

✓ Each pellets from MUPS tablets acts as individual unit hence there are many units compared to single unit in conventional dosage form which reduces the inter- and intra-subject variability in absorption and helps to reduce dose dumping and reduced incomplete drug release (Reddy S et al., 2012).

III. Patient friendly dosage form better patient compliance:

✓ Mouth dissolving MUPS tablet dosage form disintegrate on tongue and palatable in taste as per geriatric and pediatric patients those cannot administer tablets comfortably.

e.g. Prevacid SoluTab

✓ For administration of mouth dissolving MUPS tablet, no need of water. So it help during travelling. Such tablets also contains sweeteners and flavours so more accepted from geriatric and pediatric patients.

✓ MUPS tablet can be divisible without changing the dosage form characteristics which not possible in case of pellets in capsules.

✓ The MUPS have less ability to adhere to gastrointestinal tract during administration.

✓ MUPS tablets has less volume/size leads to more acceptance from patient (Reddy S et al., 2011).

1.1.3 Challenges in designing of MUPS tablet formulation

There are many additional challenges in MUPS tablet manufacturing compared to pellets in capsules and conventional tablets.
✓ Pellets has more electrostatic charge which leads to flow issues during compression which can be solve using talc however strength of tablet reduced.

✓ In blend of pellets and additive, there is always difference in size, shape and density issue. The pellets are more spherical than excipients and higher density. The blending of such materials always critical for blend uniformity. The pellets segregated during loading and unloading of blend. The issues can be resolved by using similar shape, size and density additives and proper blending parameters.

✓ The ratio of pellets to excipients is important for uniform mixing. The pellets concentration more than 50% leads to de-mixing.

✓ High percentage of pellets in tablets leads to damaging of pellets coat.

✓ Due to compression, pellets coat cracked or made structural changes leads to changes the drug release. This is more critical in delayed release dosage form. The cracking of film can be overcome by using optimized plasticizer quantity, cushion coat, cushioning agent in extragranular part (Hedstrand A G et al., 2002).

✓ MUPS tablets have more weight variation, low hardness and friability issues.

1.1.4 Pelletizing techniques

Pelletization process is an agglomeration process which converts powders of drug and additives into spherical, small and free flowing units defined as pellets (Ghebre-Sellassie I, 1989). The coating technique type more affects the film structure and, hence the resultant drug release and release rate from polymer coated pellets (Lecomte F et al., 2004). There are various manufacturing techniques for production of spherical pellets.

The techniques are categories based on different techniques of production, equipment type. Recently famous widely accepted pelletization method is centrifugal granulation where pellet formation, drying and pellets coating process performed in single pot (closed system). In this process, yield is high compared to other techniques. The other techniques are direct pelletization, solution/suspension layering, extrusion/spheronization and powder layering.

Pelletization processes are expensive and lengthy. Single batch may takes several hour or days to completed. Other rarely used pelletization processes has limited application and less industrial applications are melt spheronization, cryopelletization,
congealing/drying and spherical agglomeration. In powder layering technology, drug added in powder form on the pellets along with continuous binder spraying where powder addition rate, binder spray rate, atomization air pressure and pellets speed are process variables (Kleinebudde and Knop, 2007).

1.1.4.1 Extrusion-spheronization
This technology has multistep process involved, dry mixing of active and additives, wet granulation using binder, extrusion of wet mass, spheronization of extrudes to get spherical pellets, drying of pellets and screening the required particle size pellets for next step. The process parameters involves granulation parameters, water uptake, extrude rpm, screen aperture, plate rpm spheronizer, plate type and spheronization time.

1.1.4.2 Solution/suspension layering
This technology involves the continuous deposition coat of suspension or solution of drug substance along with or without binders on starter seeds. Such process to be carried out in fluidized centrifugal granulators, conventional coating pan and Wurster coaters. The process efficiency and pellets quality of pellets produced related to the type of the equipment used (Ghebre-Sellassie I et al., 2002). Generally, sugar spheres preferred as starter core which contains sucrose and starch however due to less friability, microcrystalline cellulose pellets also used those has good strength. The bottom spray coating called as the Wurster system. The tangentially sprayed or solution or suspension spraying achieved by Hüettlin technology. This technology improves the product yield and reduces process time significantly.

Mechanism of wurster coating process
The Wurster process has wide application in pharmaceutical industry for powder coating and pellets coating. The Wurster containers are available in the size that 100-500g to 800 Kg batch size can run. The Wurster process is preferred for particles coating from less than 100µm to tablets. The coating chamber of Wurster is typically slightly conical, and houses a cylindrical partition that is about half the diameter of the bottom of the coating region. At the bottom region, air distribution plate (ADP) also know as orifice plate accommodated. ADP divided in two regions. The open area of the plate that is under the Wurster column, is more permeable to allow more air
volume and air velocity transport parallel to air flow. As inlet air accelerate upward, particles pass a spray nozzle that is mounted in the center of this up bed ADP. The nozzle is a binary type - one port of nozzle for liquid while other for atomized air at predefined volume and pressure. The spray pattern is in a solid cone of droplets, with a spray angle approximately 30–50° called as coating zone. Down bed is the region outside the partition. The ADP selected based on size and density of material used. The air flow in the down bed region keeps material in suspended form and drawn horizontally into the gap at the base of the partition. The height of column controls the rate of substrate flow horizontally into the coating zone. During coating in progress, mass increased gradually so height of column increased to achieve desire pellets flow. Above the product container is the expansion area, which is typically conical to allow for decreasing air and particle velocity.

![Figure 1.1 Wurster mechanism](image)

The technology is applied to produce enteric coated pantoprazole pellets suggesting to improve pantoprazole stability in acidic media, due to the enhancement of the polymer film formation on the surface of the pellet. Enteric coating ensures the immediate release in alkaline media at the site of the action.
1.1.4.3 Powder layering

In this technology involves the deposition of layers of dry formed of drug along with excipients on cores with the help of a binder (Ghebre-Sellassie I and Knoch A, 2002). Equipment which revolutionized powder-layering process as a pelletization technique is tangential spray of centrifugal fluidized bed granulator/rotary fluidized bed granulator.

![Figure 1.2 Principle of the powder layering process](image)

Powder layering process can be chosen instead of the solution/suspension layering process in cases when the solution or suspension is too thick, or has a low potency, but the high pellets potency is required, when the process is too long, when the drug is not stable in the solution or comparatively low pellets density is desired (for rapid disintegration) (Jones D M, 2005).

1.1.4.4 Direct pelletization

![Figure 1.3 Principle of the direct pelletization process](image)

Direct pelletization process leads to formation of homogeneous pellets which have
microscopically uniform structure and no core can be detected. The pelletization of powdered starting materials is facilitated by the addition of binder liquid and a suitable movement of wetted powders. Direct pelletization processes are mainly performed in high shear mixers and fluidized bed equipment (Kleinebudde P and Knop K, 2007).

1.1.5 Types of pellets
Pellets can be coated with a polymer directly i.e. in matrix coated pellets drug solution or dispersion coating or other approach is the drug layering technique and those coated with a polymeric dispersion or solution (reservoir coated pellets) (Figure 1.4).

Figure 1.4 Schematic presentation of - a) matrix coated pellet and b) reservoir coated

1.1.5.1 Matrix coated systems
In this system, drug solution or dispersion is sprayed on the pellets controlled drug release. The drug uniformly distributed in the polymer either dispersed or dissolved form. This system have many advantages for easy manufacturing and low cost due to single step process, lower risk of dose dumping. Interaction of polymer-drug can occur which bring benefits for mechanical properties such plasticizing effect (Glaessl B et al., 2009; Jenquin M R and McGinity J W, 1994).

The disadvantages is the burst release (Huang X and Brazel C S, 2001) and incomplete release in a desired time. The ratio of polymer to drug where drug concentrated in layers of matrix and increased diffusion pathway (Rahman N U and Yuen K H, 2005; Rahman N U et al., 2006).
1.1.5.2 Reservoir coated systems

In this system contains drug layered core coated with the polymer. There are some advantages of reservoir coated system such as high drug loading can be done compared to matrix coated system and release profile of drug can be achieved by varying the type of polymer and/or its concentration.

Aqueous coating and organic coating

The pellets can be coated with an aqueous polymer dispersion or organic solutions to achieve desire controlled release profile. The organic coating has many disadvantages like viscosity of solution dependent on the polymer concentration used and molecular weight of polymer (Wheatley T A and Steuernagel C R, 1997). Organic solutions has some disadvantages like the residual solvents remains in the coating which changes the film properties explosion hazards and environmental pollution.

Aqueous polymeric dispersion is more users friendly so more preferred in pharmaceutical industries. Mechanism of film formation i.e. organic and aqueous are different (Lehmann K, 1994). In organic polymeric solution, polymer dissolved in solvent and during drying solvent evaporated and gel like structured formed. After complete solvent evaporation, intact polymeric film is formed (Figure 1.5). In aqueous dispersion, film formation mechanism is very complex (Fukumori Y, 1994). Aqueous dispersions also contain additives like surfactants which acts as stabilizers during the production process. Additives like anti-taking agents and plasticizers enhance coating properties of film and process. The plasticizers reduce minimum film formation temperature (MFT) (Wheatley C.R et al, 1997). Film formation is related to
minimum film formation of the aqueous dispersion and glass transition temperature of
the polymer. Water also acts as plasticizer which reduced the Tg of the some selected
polymers. Lippold and Monells Pages showed a linear relationship between the Tg
and MFT for different polymer/plasticizer concentrations (Lippold and Monells
Pages, 2001).

Figure 1.6 Film forming mechanism of aqueous polymer dispersions coat

1.1.6 Evaluation of pellets
1.1.6.1 Size distribution
Pellets size has significant impact on release profile hence pellets sizing is important
test. Pellets length and mean particle size determine pellets size. Generally, simple
sieving and scanning electron microscopy tests are performed.

1.1.6.2 Pellets shape
The sphericity of the pellets is one of the pellet parameters. Roundness index/shape
factor must be 1.0-1.2. The visual inspection of pellets by microscope is another
method to determine the pellet shape (Lian-Dong H et al., 2006).

1.1.6.3 Surface morphology
Scanning electron microscopy is used to study the surface morphology and cross
section of pellets. Sood A et al. in 2004 concluded the use of optical microscopy to
examine the microstructure of pellet surface (Sood A et al., 2004).
1.1.6.4 Specific surface area
The surface area of pellets is directly related with shape and size of the pellets. In film coating and uncoated pellets calculation, surface area is required because drug release directly related to surface area.

1.1.6.5 Friability
Friability of the pellets is one of the important parameters need to consider. Pellets having high friability generate fines and rough surface pellets. Friability of pellets are determined by using special designed Erkew. Friability of pellets can be determine by different method using fluid bed with Wurster insert by using stream of air (Steckel H. and Mindermann-Nogly F, 2004).

1.1.7 Pelletization equipment
The production of spheroid pellets process does not differ a lot from the wet granulation process, in which moistening liquid is required. This also means that the equipment involved in the wet granulation can be used for production of pellets like fluidized bed granulator and high-shear mixer. Different types of spherical pellets require different type of equipment. Extruder and spherizer is the usually used for homogenous pellets mixing also high-shear mixer and rotary fluidized bed used while the production of heterogeneous pellets is carried out in top spraying or different types of bottom spraying fluidized bed equipment.

1.1.7.1 Fluidized bed equipment

Figure 1.7 Schematic of a fluidized bed apparatus - (A) bottom spray with Wurster column insert; (B) top spray technique; (C) tangential spray technique
The introduction of an expansion space between the product container and the filter chamber, and the inclusion of a liquid-spray nozzle in that space, gave rise to fluid bed agglomeration and in more recent years, unique processes for the coating of granulates, pellets and powders have expanded the use of granulation manufacturing equipment. In general, the main processing option can be characterized by spray nozzle position and orientation and by design principle of fluidization gas distribution into the processing chamber. Different processing options were created in order to manufacture different products in fluid bed equipment.

There are three basic configurations in fluidized bed processing:

- bottom-spray processing and Wurster processing (Figure 1.7A)
- top-spray processing (Figure 1.7B)
- rotor processing (tangential spray) (Figure 1.7C)

The last two configurations are used for pelletizing and coating in laboratory, pilot and commercial scale equipment. The type of process used may significantly influence finished dosage form properties.

### 1.1.7.2 Conventional fluidized bed granulator

First powder, later granules or pellets are fluidized in the cylindrical product container by an air stream. The inlet air passes a screen or a perforated plate, fluidizes the particles and leaves the product container through a filter. This exhaust air filter prevents product losses and air pollution. The fluidizing air can be heated to the

![Figure 1.8 Schematic representation of the Wurster product chamber and process: (A) product chamber; (B) partition, (C) orifice plate; (D) nozzle and (E) expansion chamber.](image-url)
desired temperature to dry or melt the fluidized product. The molten binder or binder solution is sprayed onto the fluidized particles through a nozzle which has to be heated in case of molten binder. The spray nozzle is usually an air-atomizing nozzle which uses pressurized air to produce droplets from a liquid. Droplet size of coating fluid can be controlled through atomizing air pressure. Position of the nozzle is above the fluidized product in most cases (Kleinebudde P and Knop K, 2007).

1.1.7.3 Rotary fluidized bed processor
Since conventional fluidized bed granulator was not the method of choice for production of pellets, there was a need to modify the equipment in order to achieve highly spherical and high density pellets (Gu et al., 2004).

![Figure 1.9 Schematic representation of centrifugal fluid-bed equipment](image)

This movement is described in different literature in different terms like of rope-like tumbling, twisted rope, spiral, spiral helix and others. The achievement of ideal product movement is of a high importance. In the beginning of the process this type of the movement is difficult to achieve because of the dry or moderate wet powder, but at the end of the process, in the spheronization phase, the movement is of a critical importance. If the movement does not occur in the spheronization phase, no spherical pellets will be obtained. The nozzle or the nozzles in the rotary processor are often positioned tangentially in the wall of the container in the height of the fluidized product (Kleinebudde P and Knop K, 2007).

1.1.8 Coating of pellets
Polymer used in coating either in solution or dispersion form. Some time additives like plasticizers, anti-tacking agent, binder, wetting etc required as per polymer nature
to prepare coating solution or dispersion and for ease processing. Solvent evaporated after drying and polymeric film form. So polymers required additional drying at elevated temperature for continuous film. There are various film forming mechanisms.

1.1.8.1 Mechanism of film formation

Figure 1.10 Film formation mechanism for water based polymeric dispersion - A) Droplets of polymeric dispersion, B) polymeric dispersion deposition, C) Closed-pack of polymer particles, D) Formation of flexible polymer film

1.1.8.2 Glass transition temperature

Glass transition temperature (Tg) is important to understand flexibility of film. Flexibility of film changes as per Tg increased or decreased. Tg is the minimum
temperature at which film changes from glassy/brittle to flexible/elastic.

1.1.8.3 Minimum film - forming temperature
Minimum film formation temperature (MFT) is the temperature above polymeric film formed. Product temperature maintained at least more 10°C than MFT. Polymers like ethylcellulose when used in aqueous dispersion form required additional drying at high temperature to form continuous film formation after coating due to high Tg.

1.1.9 Compression of coated pellets
Compressibility and compactability are the two concepts has slight difference. In compressibility, powder volume decrease under pressure while in compactability, powder becomes tablet which has sufficient strength. Under one theory, in compaction particles rearranged, deform either plastic or elastic mechanism (Sun C and Grant DJW, 2001).

Maintain the pellets property after compaction is the major in compaction process. Polymer coating not withstand the compression force during compression thus alter the drug release, mostly faster release profile. During designing of MUPS tablet, formulator optimize compaction process crucially. The main compression process variables are compression force and turret speed. With respective formulation variables, elasticity of coated pellets and cushioning nature of extragranular excipients are important to control cleavage of pellets during compaction.

1.1.10 MUPS tablet design
The variables to be consider during designing of MUPS tablet are presented in Figure 1.11.
a. Pellet composition

Many scientists studied the impact of pellets composition on pellets quality and hence compression behavior. Material used in manufacturing of pellets is an important to maintain desire release profile. Core pellets are classified in soft and hard pellets. Soft pellets contains soft ingredients which has chances to fill intergranular pores due to the primary particles can move within the core while harder pellets failed at compression pressure.

Nicklasson studied the behavior of alone microcrystalline cellulose (MCC) and combination with dicalcium phosphate and polyethylene glycol pellets at the time of compression and after compression process and concluded that pellets deformation was depend on their mode of, capacity and resistance to deformation. He used polyethylene glycol as a cushioning agent to study compression behavior of pellets. He used MCC-based beads of theophylline, those are hard, and comparative softer beads which prepared with glycercyl monostearate (Nicklasson F and Alderborn G,1999).

Iloanusi and Schwartz used wax to the MCC pellets to study crucial role in plastic deformation during compression. Wax used as a cushioning agent and pellets with wax coating had more compressibility than pellets without wax as a compression modifier (Iloanusi N O and Schwartz J B, 1998).
b. Size and shape
After compression, pellets deformed hence size of pellets has significant impact on compaction properties and drug release from pellets. Larger pellets are more susceptible for compression than small pellets. Small pellets are comparative more stronger and withstand more compression pressure at lesser deformation (Haslam J L et al., 1998). The strength of core pellets affects the final strength of tablet and which helps ensures the desired release rate.
Johansson studied the relation of deformation of individual pellets with their size. Deformation was more for larger pellets than small pellets. Due to increase pellets size, force-transmission decreased (Johansson B et al., 1998). Beckert revealed that harder pellets were withstand more for compression forces and coated pellets were susceptible to rupture (Beckert T E et al., 1996).

c. Density and porosity
Pellet density and its porosity has an important role to achieve content and weight uniformity. Modification of intra-granular porosity can densify and deform pellets during compression (Nicklasson F and Alderborn G, 2000, Habib Y S et al., 2002). Binder quantity and amount used in pelletization decide the compaction has directly related to porosity.
Tuton concluded that high porosity pellets densely packed and these pellets not affected the drug release. However low porosity pellets were slightly densified in compression which alter the drug release (Tuton A et al., 2003).

d. Nature of polymer
Polymers are the main component which decide the drug release in modified- or controlled-release dosage form. The ideal polymer has sufficient elasticity and plasticity to withstand compaction and compression. There are various polymers used to modify the drug release either cellulose base like ethylcellulose or synthetic like methacrylic acid polymer. Generally, for extended release formulations, ethyl cellulose and ammonio methacrylate copolymers are used for water insoluble drugs (Hogan J, 2002).

e. Amount of polymer coating
Thicker polymeric coat to pellets has good elasticity hence damage of coated pellets minimize during compression than thin coat. Thickness of coat has directly related to resistance to cracking.

**f. Plasticizer**

Plasticizers are used in polymer dispersions mostly in water dispersions to reduce the glass transition temperature which helps in coalescence of dispersion. Polymer coalescence depend on the product temperature and coating time. Onions revealed two-stage theory in the process of coalescence of polymeric dispersions. First stage involves evaporation of the aqueous layer and formation of transparent continuous film of coated material. Coalescence of some polymers is completed in second stage. In actual process, water between inter spaces evaporates slowly and bring separate particles close to each others. At the end, particles fused and form strong film which is continuous. Amount of plasticizer not affect the drug release from reservoir pellets (Heinamaki J T *et al*., 1995). Felton concluded that as plasticizer content increase, tensile strength of film increased. Increased plasticizer made film more elastic and withstand deformation during compression (Felton L A *et al*., 1997).

**g. Tabletting excipients**

Cushioning excipient has significant role in MUPS tablet formulations. Cushioning excipients helps to prevent damage of cracking of pellets during compression process. Cushioning excipients rearrange between pellets and themselves and reduce void space to avoid direct contact of pellets after compression pressure. Tabletting excipients selected based on the size and density similar to pellets to avoid weight variation and segregation issues (Aulton M E *et al*., 1994). Polyethylene glycol and MCC are good excipients due to plastic deformation for compaction (Beckert T E *et al*., 1996, Haubitz H *et al*., 1996). Lactose undergo fragmentation which protect gives better protection than MCC (Stubberud L *et al*., 1998). Particle size of excipient smaller than 20 µm can prevent coating damage while particles bigger more 20 µm alter the dissolution rate (Dwibhasyam V S N M, 2008; Yao T *et al*., 1998). Waxes are good cushioning agent those facilitate good protection to pellets from compression (Vergote G J *et al*., 2002).
h. Compression process variables

Compression force is important process variables in MUPS compression which need to optimize during process optimization. From several studies it was revealed that, compression force 15kN was sufficient to form smooth tablet surfaces. Flament studied impact of compression force on theophylline-loaded pellets coated with acrylic polymer. It was observed that 6 kN force was enough for deformation while compression force increased upto 20 kN did not alter the dissolution profile considerably (Flament M P et al., 1994). Salako prepared pellets with MCC based those deformed which are hard while glycercyl monostearate used to prepare soft pellets (Salako M et al., 1998).

1.1.11 Excipients for ideal MUPS of reservoir pellets

1.1.11.1 Methacrylic acid polymer

Polymethacrylates are synthetic polymers available in anionic and cationic form of methacrylic acid and other clusters in various ratios. These are available in aqueous, organic dispersions and dry form used for modified release formulations. Methacrylic acid copolymer, Eudragit L30D-55 is the polymeric dispersion has copolymers in 1:1 ratio. It contains sodium lauryl sulphate or teen 80 as surfactant. This polymer start dissolving from pH 5.5.

1.1.11.2 PlasACRYL HTP20

Eudragit L30D-55 required additives like plasticizers and anti tacking agent to run process smoothly and efficiently. Talc is traditionally used as anti-tacking agent however it has disadvantage of like nozzle clogging and sedimentation. Glycerol monostearate (GMS) is newly used as anti-tacking agent which is hydrophobic in nature and used with tween 80. Preparation of GMS dispersion is critical. PlasACRYL HTP20 is special designed additives contained GMS, triethyl citrate (TEC) and polysorbate 80 in defined percentages. It has 20% solid content. If required more TEC in polymeric coating then it can add in polymeric dispersion along with PlasACRYL HTP20 (Levine S, 2012; Bodinge S et al., 2012).

1.1.11.3 Microcrystalline cellulose

Total three types of microcrystalline cellulose (MCC) used for the development of MUPS. Celpheres CP-203 prepared from MCC granulation used as starter core those
are more strong and less brittle than sugar spheres also have low elastic deformation characteristic than sugar spheres which beneficial for MUPS formulation. Avicel PH 200 has 180 µm mean particle size and 0.35 g/ml of bulk density (Rowe R C et al., 2009). Due to larger particle size, enhances flow also maintains the high levels of compressibility with minimum weight variation and content uniformity in pellets compression. Ceolus KG-1000 having the lowest bulk density i.e. 0.12 g/cm³ among MCC grades. Ceolus KG-1000 puts impact on blend flow at higher percentage in formulation. It has superior compatibility compared with PH-101 and other standard MCC grades. Ceolus KG-1000 particles have extremely large L/D value. The particles easily arrange perpendicularly to the applied force upon compaction; therefore the contact area of the MCC particles is increased. Entanglement of particles also easily occurred under compression force which provides additional compactability (Honda Y et al., 2010; Kucera S U et al., 2012; DiNunzio J C et al., 2012).

1.1.12 Process variables involved in Wurster-based coating process

The Wurster process have five sets of process variables affecting the quality of pellets - Equipment variables, solution preparation variables, preheating variables, spraying variables and drying variable those are discussed in detail below.

1.1.12.1 Air distribution plate (ADP)

Suitable ADP need to select for constant fluidization and with minimum attrition. The fluidization volume affects velocity of particle while smaller particle requires lesser air volume to attain certain height than the bigger particles. The air velocity and differential pressure at the air distribution plate must be almost same. Therefore, when deal with the smaller particle, use plate with lesser opening area to create the resistance at the ADP to have better distribution of the air (Shetty, 2010; Qiu Y et al., 2009). There are some recommendation for plate selection based on size of pellets or power (Table 1.1).
Table 1.1 Guideline for plate selection with respect to the final particle size

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Pellet size in micron</th>
<th>Plate combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>6” Wurster</td>
<td>&lt; 500 Micron</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>250 &lt;&lt; 1200 Micron</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>600 &lt;&lt; 1800 Micron</td>
<td>C</td>
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<td></td>
<td>&gt; 1200 Micron and Tablets</td>
<td>D</td>
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<tr>
<td>For commercial models</td>
<td>&lt; 300 Micron</td>
<td>A – I</td>
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<td>150 &lt;&lt; 800 Micron</td>
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<td>500 &lt;&lt; 1200 Micron</td>
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<td></td>
<td>&gt; 1500 Micron and Tablets</td>
<td>D - G</td>
</tr>
</tbody>
</table>

1.1.12.2 Column height

Appropriate adjustment of the partition gap ensures proper substrate circulation through the spray zone and up the partition column. The height of column changed based on the particle properties like size, shape, flow and bulk density (Porter and Ghebre-Sellassie, 1994). This was due to the pellets flow in column and pellets exposure to coating droplets in spraying zone (Fitzpatrick et al., 2003; Shelukar et al., 2000).

The slow and slugged form flow of particles through column leads to increased in agglomerates which column gap is too more and insufficient pressure differential created to draw particles in column. While, when gap is too small, less pellets draw in the column and coating material loss and chances of over wetting. Adjust the column height such a that maximum pellets comes in column. Frequently change in column height is not recommended. The recommended gap for 6” Wurster is 15-25 mm and for 18” Wurster is 40-50 mm.

1.1.12.3 Nozzle tip diameter

With smaller the nozzle insert more consistent will be the spray. Smaller nozzle insert also have disadvantages like nozzle choking. The agglomeration in Wurster controlled by optimizing more atomization air pressure than tablet coating in pan coater. Nozzle should have capability to atomize the coating fluid even at coating fluid dosing
increased. Larger droplets of coating material produced low performance of nozzle and not even dry faster like smaller droplets. In contrast, very small droplets dried quickly. Faster drying cause rough surface of core. Agglomeration tendency can be avoid using multiple unit nozzles.

1.1.12.4 Filter bags
In case, the porosity is higher than optimum, the loss of material will be high. If the porosity is lower than optimal, the filter will clog and processing will be interrupted which impact on the product yield. A filter bag is selected based on particle size of material and previous experience. The porosity of filter bag during coating can examine by monitoring differential pressure.

1.1.12.5 Coating solution/suspension nature
Coating solution/suspension should have enough solid content to easy spraying. If the viscosity of coating liquid is more it will affect on droplet size and change the pellets surface. The ideal coating liquid velocity should not be more than 250 mPa.s.

1.1.12.6 Inlet and Product temperature
The inlet drying air is usually heated before passing into the coating chamber to enhance the evaporation of coating material sprayed onto the cores. Control of the air temperature is important as it affects the quality of coats formed. Generally, excessively dry environment showed spray drying while agglomeration due to overwetting. The optimal temperature allows the evaporation of solvent to take place at a rate that is sufficiently slow for adequate spreading of spray droplets and coalescence of polymer particles, and fast enough to avoid agglomeration and drug migration into the liquid layer. When the temperature of the air is too high, sprayed droplets dry quickly and do not coalesce when impinged on the core particles. This forms discontinuous coats which are rough and porous and will not impart the desired controlled release properties of a functional coat (Fukumori Y, 1994). Spray dried coating materials can disturb the film integrity.

In methacrylic acid based coating, at higher temperature spray gun choked frequently due to film formation of low glass transition coating dispersion. So it recommended that run the methacrylic acid based coating below 30°C product temperature. While in
aqueous ethylcellulose based coating required minimum 45°C product temperature required due to its high Tg.

1.1.12.7 Air volume
Air volume is responsible for the circulation and drying of substrates during coating. Insufficient airflow may not provide sufficient drying air to circulate the substrates and remove the moisture from the deposited sprayed droplets during coating and consequently result in a high degree of agglomeration. For functional coats, this can result in loss of the desired release properties (Qiu Y et al., 2009). The airflow rate should be unique for each coating equipment and also depends on product characteristics such as particle density, size, and shape. For non-aqueous coating a bubbling type of fluidization in down bed is suggested to minimize the generation of static charge and particle friction, whereas in aqueous based coating fluidization required rigorous to have more drying efficiency.

1.1.12.8 Dew point
Temperature, inlet air and humidity have effect on drying of coated particles. The relationship between temperature and relative humidity or moisture content of air at different atmospheric pressures may be derived from psychometric charts (Shallcross, 1997). The humidity of air varies from season to season and even day to day also. Evaporating efficiency of air changes because of dew point. Drying capacity increase with lower the humidity however it will increase the static charge. To eliminate the static charge, air with sufficient amount of humidity required in inlet air. Humidity required to increase only after the initial coating. Static charge develops once the pellets are coated with polymers. The dew point is scale independent factor.

1.1.12.9 Spray rate
In Wurster binary nozzle are used. The spray rate of coating solution depends on the solution properties and core particles. In case of solvent coating, sometime excessive atomization pressure leads to spray drying of spray portion. Spray rate to be optimize for controlling tackiness of solution and drying efficiency. Coating of smaller particle required small size droplets which achieved by decreasing the spray rate and or increasing the atomization air pressure.
At the beginning of coating the spray rate must be kept low to avoid solubilizing the core, seepage of the drug or coating polymer in to other layer. Spray rate can be increased after initial barrier coating. Droplet size can be increased, once particle size becomes bigger without agglomeration and increase of spray rate is needed at regular intervals (Swarbrick J and Boylan J C, 1992).

High spray rates leads to formation of agglomeration while low spray rates increase the coat uniformity. Low spray rates also enable smaller spray droplets to be formed which would reduce agglomeration, especially when coating smaller substrates. However, if the spray rate is too low, fast drying of the droplets could prevent coalescence of polymer particles, resulting in poorly formed coats.

1.1.12.10 Atomization air pressure

![Figure 1.12 HS spray gun design](image-url)
To achieve smaller droplet size, high atomization pressure required. At low atomization pressure, agglomerates formed while at high atomization pressure, disturb the pellets to droplet contact (Heng et al., 1999).

High speed (HS) gun used to spray coating solution at more speed than normal gun. HS can bear more compress air hence achieve high spray rate.

1.1.12.11 Drying/curing time

The polymers dissolved in organic solvent increased the solution viscosity. During film formation, gel like phase create during solvent evaporation and polymer film formed (Fig. 1.13) (Muschert S, 2008). In aqueous dispersions, film formation is more complicated (Fukumori Y, 1994). Surfactants, anti tacking agent and plasticizers are used aqueous dispersion to improve film nature and coating process. Plasticizers used to reduce film formation temp of polymers having high glass transition temperature (Tg) (Wheatley T A and Steuernagel C R, 1997). In aqueous dispersions base coating, polymer particles come into contact with each other and form coalescence during drying (Paeratakul O, 1993).

![Figure 1.13 Schematic diagram](image)

Figure 1.13 Schematic diagram a) film forming mechanism from organic polymer solution b) film forming mechanism from aqueous polymer dispersion
1.1.13 Scale up process

The process parameters in the fluid beds are controllable precisely, which ensures easier optimization and reproducibility of the product quality. There are some wrong concepts related to Wurster based scale up process. Lots of scientific publications are available on Wurster processing, optimization and scale up. Still question arises - “What would be the scaling up factor and consideration for reproducibility of the product quality in Wurster coating?”. The industry needed proper designing for scaling up factor.

Currently FDA is focusing on the Quality by Design (QbD) concept where in one has to build the finished product quality attributes in the design itself. Nowadays USFDA also demanding for scientific approach for scale activity based on development batches. In one of the USFDA’s guide to inspections report pre/post approval issues explained the expectations of regulatory authority on scale up activity said - it is important that the development and scale-up of the process be well documented so that there should be link between the bio/clinical batches and the commercial process can be established (USFDA, 1994).

Before attempt for successful scale up, key variables and their effect on the output should be identified during lab scale. If scientist design scale up activity during development stage itself then it will be very easy to scale up and scale out the formulation. Wurster process has ‘n’ number of variables. Some of them are easy to establish e.g. batch size, spray liquid viscosity, concentration, spray assembly setting, base plate, column height and dew point etc. Perform some trials to fix some dependent variables like air volume, atomization air pressure, spray rate, product temperature etc. It is easy to understand the variables in small scale and it requires less time and cost. Finally apply design of experiments (DoE) to fix up most critical parameters as per regulatory requirement. To minimize the number of trials further one can use statistical software like Design-Expert software (Stat-Ease, Inc., Minneapolis, MN). Base on the statistical analysis freeze the ranges for the parameter and validate the process to check the reproducibility and freeze the parameter. Once these variables are frozen, "mass effect" is the one factor left which need to consider as batch weight increase from lab scale to commercial scale. After completion of parameters studies then it will be simple to compensate mass effect by doing minor changes in the predicted parameter in pilot and commercial level. After freezing the parameters at lab model next step is predicting the parameter for scale up.
Since, at least 3 successful reproducible development batches done then next step is to set up parameters for pilot batch also have single Wurster. The development of the product is normally done 6” wurster with the batch size 0.5 to 2 kg. The Wurster column and spray nozzle is small means total coating zone is small. The recommended pilot model is 18” wurster where the wurster column and base plate are much larger. From the lab to pilot although there is single spray nozzle but the nozzle is comparative bigger and can carry higher spray rate. Batch depth and mass flow density increases. Overall, the coating zone increases from lab to pilot scale. The overall coating zone will remain same in pilot and commercial scale except the height of the wurster column. Therefore, base area of wurster column plays important role in efficient coating. All process parameters should be proportional to the base area of wurster column compared with lab model column.

All the process variables have significance in scale up models. Once the effect of variables are studied and understood the impact in lab model equipment then it will make the prediction of process parameters easier. Same process controls need to apply in pilot batches. Mass effect is the unknown factor. Like the lab scale, follow the sequential approach to set the parameter for the scale up.

Linear scale up from lab scale to pilot scale assumed that the occupancy are the same and the distribution plate in each piece of equipment is geometrically similar. Additionally, ratios of air volume to plate area and spray rate to air volume maintained. The scale up factor from Pam GPCG 1.1 to Pam FBE 125C is approximately 9-fold based on vendor recommendation. This scale up factor is applicable for air volume; spray rate and atomization air pressure. The variables considered during successful scale up batch in Wurster are discussed below.

1.1.13.1 Batch size

First step to design pilot scale up after deciding equipment is defining the batch size. The process parameter may change slightly depending on the batch size due to mass effect. Set and validate the process for any change in the batch size is important. Batch size should be within the recommended occupancy. e.g. For Pam GPCG 1.1, the working volume is 2.4 liter, where as Pam FBE 125 it is 84 liter, i.e. 35 times. If pilot scale up planned in FBE 125C then batch size should be 35 times of batch size taken in GPCG 1.1 (Table 2). Working volume of batch at initial and final stage
should be in 20 to 100% for non functional coating and 20 to 80% for functional coating limit.

1.1.13.2 Air volume
Fluidization pattern during processing is depending on air volume. The air volume of scale up batch decided based on optimized lab scale batch. From lab to pilot scale the face velocity must be kept same. To maintain the same velocity one must know the base plate area under column of lab and pilot equipment. It is expressed in the term of fluidization air volume. Following equation can be used to calculate the Airflow.

\[ V_2 = V_1 \times \frac{A_2}{A_1} \]
Where, \( V_1 \) = Air flow at Lab model,
\( V_2 \) = Air flow for scale up model,
\( A_1 \) = Base area of wurster column for lab model,
\( A_2 \) = Base area of wurster column for pilot model.

1.1.13.3 Spray rate and atomization air pressure
The spray rate shall be increase always in proportional to increase in the drying capacity and not considering the batch size. The spray rate is one of the important process parameters. The process time is depend on the spray rate delivered. The drying capacity, batch size, core material and droplet size of coating liquid in coating zone are the rate limiting factors. Inlet air humidity and temperature should remain same for the scale up batches, the drying efficiency is increased only it terms of air volume. The spray rate can be increased in the same fold increase in the inlet air volume. Spray nozzle with HS Wurster has benefits over conventional coating gun. The droplet size is larger near the tip of spray gun which formed agglomerated while by accommodating HS Wurster, material not comes in contact with coating gun and spray rate can increase. Following equation is used to calculate to predict the spray rate in pilot model.

\[ S_2 = S_1 \times \frac{V_2}{V_1} \]
We can also say that \( S_2 = S_1 \times \frac{A_2}{A_1} \)
Where, \( V_1 \) = Air flow at lab model
\( V_2 \) = Air flow for scale up model,
S₁ = Spray rate in Lab model,
S₂ = Spray rate in pilot model

The increase in spray rate should be compensated with the increase in the atomization air pressure to maintain the droplet size of the spray mist. Always keep the droplet size same both in lab as well as pilot model one has to keep the spray rate to atomization air volume same.

Normally atomization air volume should restrict them maximum pressure up to 4 to 5 bar. Higher the atomization air pressure the mechanical stress on the core will be high due to higher velocity. If higher air pressure used in lab model then in scale up use either spray rate needs to be reduced or use HS gun which is higher capacity gun. Any change in the spray rate from the scale up factor of airflow shall be compensated by either increasing or reducing the inlet air temperature.

1.1.13.4 Mass effects
Mass effect can't predict based on batch performance in small scale equipment. The best scale up of Wurster process is from 6” lab model to 18” industrial scale model. In 6” Wurster, bed height not more than 200 mm and material fluidized up to 125 cm or less height. In the 18” Wurster, bed height is up to 600 mm, and fluidization up to 2 meters height. The scale up from 18” to 32” or more capacity Wurster is more simple due to bed height is almost same.

1.1.13.5 Theoretical parameters
Since product temperature and dew point are most critical factors that have an impact on the product movement as well as release profile, during scaling up these parameters should be kept constant.

There may be some deviation in the results from lab scale even after maintaining the parameters as per the scale up calculations based on mass effect. Any one or more parameter may have to be changed marginally to achieve desired release profile. Scale up activity starts with preliminary trials with predicted parameter, analyze the results, and take action if required to match the profile. If all the parameter and their effect on the release were studied in the lab scale then it will be easier to predict the analytical results and vary the parameters to get desired profile. Process validation is recommended to check the robustness of the process before filing the parameters or planning the scale out activity.
1.1.14 Biorelevant dissolution

Physiological conditions vary wildly along the gastrointestinal (GI) tract. Not to mention inter-subject variability, various factors within an individual, such as disease states, physical activity level, stress level and food ingestion, considerably influence the GI conditions (Dressman J B et al., 1998). The effects of this variability on the performance of MR systems are even more pronounced given that the dosage forms are designed to remain in the GI tract for the substantially longer period of time and transit through various conditions compared with IR systems. Inhomogeneous distribution of fluid in the small and large intestine (Schiller C et al., 2005) is one of many factors that potentially contributes to the variability of drug release and absorption. Physiological properties in various GI compartments with and without effect of food are presented in Table 1.2 and Table 1.3.

Table 1.2 Physiology of the GI tract of healthy humans in fasted state

<table>
<thead>
<tr>
<th>Location</th>
<th>Fluid volume (ml)</th>
<th>Transit time (h)</th>
<th>pH</th>
<th>Osmolality (mOsm/kg)</th>
<th>Buffer capacity (mmol/L·∆pH)</th>
<th>Surface tension (mN/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>45</td>
<td>1-2</td>
<td>1.5-1.9</td>
<td>98-140</td>
<td>7-18</td>
<td>42-46</td>
</tr>
<tr>
<td>Duodenum</td>
<td>105</td>
<td>3.6</td>
<td>6.5</td>
<td>178</td>
<td>5.6</td>
<td>32.3</td>
</tr>
<tr>
<td>Jejunum</td>
<td></td>
<td></td>
<td>6.8</td>
<td>271</td>
<td>2.4</td>
<td>28</td>
</tr>
<tr>
<td>Ileum</td>
<td></td>
<td></td>
<td>7.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Colon</td>
<td>13</td>
<td>7-20</td>
<td>6.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 1.3 Physiology of the GI tract of healthy humans in fed state

<table>
<thead>
<tr>
<th>Location</th>
<th>Fluid volume (ml)</th>
<th>Transit time (h)</th>
<th>pH</th>
<th>Osmolality (mOsm/kg)</th>
<th>Buffer capacity (mmol/L·∆pH)</th>
<th>Surface tension (mN/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>800-900</td>
<td>1.4-4.0</td>
<td>3-7</td>
<td>217-559</td>
<td>14-28</td>
<td>30-31</td>
</tr>
<tr>
<td>Duodenum</td>
<td>900-1000</td>
<td>3.8</td>
<td>5.1-5.4</td>
<td>390</td>
<td>18-30</td>
<td>28.1-28.8</td>
</tr>
<tr>
<td>Jejunum</td>
<td></td>
<td></td>
<td>5.2-</td>
<td>-</td>
<td>14.6</td>
<td>27</td>
</tr>
</tbody>
</table>
Biorelevant media is the media which mimic the biological conditions and select the media based on the physico-chemical properties of drug substance and target of dosage form.

The biorelevant dissolution test for oral dosage forms is developed to simulate the physiological conditions in the gastrointestinal (GI) tract that can affect drug dissolution; these include the properties of GI fluids (composition, volume, pH), gastric emptying (especially for non-disintegrating systems), intestinal transit, GI motility and hydrodynamic patterns, GI enzymes, and the presence or absence of food. Biorelevant dissolution testing is valuable in the generation of successful in vitro–in vivo correlations (IVIVC) or in vitro–in vivo relationship (IVIVR). The in vitro dissolution study in biorelevant dissolution medium was carried out using same method described for Nabumetone and Nicorandil respectively with replacement of dissolution medium. There are four major biorelevant dissolution medias used. Those are Fasted-State Simulated Gastric Fluid (FaSSGF), Fed-State Simulated Gastric Fluid (FeSSGF), Fasted-State Simulated Intestinal Fluid (FaSSIF) and Fed-State Simulated Intestinal Fluid (FeSSIF) and pH of each is 1.6, 5.0, 6.5 and 5.8 respectively.

### Table 1.4 Composition of Fasted-State Simulated Gastric Fluid (FaSSGF) and Fed-State Simulated Gastric Fluid (FeSSGF)

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>FaSSGF</th>
<th>FeSSGF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium taurocholate (µM)</td>
<td>80</td>
<td>-</td>
</tr>
<tr>
<td>Lecithin (µM)</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Pepsin (mg/mL)</td>
<td>0.1</td>
<td>-</td>
</tr>
<tr>
<td>Sodium chloride (mM)</td>
<td>34</td>
<td>237</td>
</tr>
<tr>
<td>Acetic acid (mM)</td>
<td>-</td>
<td>17</td>
</tr>
<tr>
<td>Sodium acetate (mM)</td>
<td>-</td>
<td>29</td>
</tr>
<tr>
<td>Ortho phosphoric acid (mM)</td>
<td>-</td>
<td>5.5</td>
</tr>
<tr>
<td>Sodium dihydrogen phosphate (mM)</td>
<td>-</td>
<td>32</td>
</tr>
</tbody>
</table>
Purified water | q.s. 500ml | q.s. 1000 ml
Hydrochloric acid q.s. | pH 1.6 | pH 5.0

Table 1.5 Composition of Fasted-State Simulated Intestinal Fluid (FaSSIF) and Fed-State Simulated Intestinal Fluid (FeSSIF)

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>FaSSIF</th>
<th>FeSSIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium taurocholate (mM)</td>
<td>3.0</td>
<td>15</td>
</tr>
<tr>
<td>Lecithin (mM)</td>
<td>0.75</td>
<td>3.75</td>
</tr>
<tr>
<td>Sodium hydroxide pellets (g)</td>
<td>0.174</td>
<td>4.04</td>
</tr>
<tr>
<td>NaH$_2$PO$_4$.H$_2$O</td>
<td>1.977</td>
<td>17</td>
</tr>
<tr>
<td>Sodium chloride (g)</td>
<td>3.093</td>
<td>12</td>
</tr>
<tr>
<td>Glacial acetic acid (g)</td>
<td>-</td>
<td>8.7</td>
</tr>
<tr>
<td>Purified water</td>
<td>q.s. 500ml</td>
<td>q.s. 1000 ml</td>
</tr>
<tr>
<td>Hydrochloric acid q.s.</td>
<td>pH 6.5</td>
<td>pH 5.0</td>
</tr>
</tbody>
</table>

1.1.15 Quality by Design (QbD)

The last decade has seen a significant transformation in pharmaceutical quality regulation from an empirical process to a more science and risk-based approach. There are two approaches for pharmaceutical development, the empirical and systematic (pharmaceutical quality by design, QbD) approaches. QbD is a systematic risk-based, proactive approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control based on sound science and quality risk management\(^1\). Thus, QbD is concerned with the achievement of certain predictable quality with desired and predetermined specifications through relating the critical material attributes (CMA) and critical process parameters (CPP) to the critical quality attributes (CQAs) of drug product. It uses multivariate experiments to understand product and process and to establish a design space through design of experiments (DOE). In the QbD context, for a product to be of consistent quality the process must be very well understood. Therefore, all its sources of variability must be indentified and explained; afterwards, that at the end, consistent product quality is ensured (ICH Q8, ICH Q9, ICH Q10). Building from the QbD scheme, methods can be used upstream at the beginning
stages of research, development and design phases, meanwhile the product quality should be proactively controlled in the manufacturing process. The application of QbD scheme in pharmaceutical development is presented graphically in Figure 1.14.

In first stage, define Quality Target Product Profile (QTPP), identify CQAs and the potential risk factors are determined by risk assessment in the initial design during product development. In second stage, carry out the development batches with multivariate to improve process knowledge using DoE wherever needed and reduce the risk based on the experiment results. In last stage, define design space, use quality management tools to manage the risk and finalize control strategy.

To improve process knowledge, statistical DoE is valuable tool to establish in mathematical form the relationships between CMAs, CPPs and CQAs (ICH Q8, ICH Q9, ICH Q10). A range for each process parameter and their combinations can be defined, in which the desired CQAs values are achieved. Also, a range for the quality of combinations of raw material attributes and process parameters that need to be realized by the process, to ensure that the CQAs stay within the Design Space.

Figure 1.14 Systematic QbD flow in product development
1.2 PROBLEM ON HAND
Proton pump inhibitors (PPIs) used to maintain longer duration of gastric acid suppression in more degree, have good degree of capacity and better healing capacity in gastric acid-related disorders than H2 receptor antagonists (Cheer S M et al., 2003).

![Figure 1.15 Mechanism action of proton pump inhibitors](image)

PPIs are used to manage gastric diseases like peptic ulcer disease, Zollinger–Ellison syndrome and gastro-oesophageal reflux disease. PPIs are used in triple therapy i.e. with clarithromycin, metronidazole or amoxicillin are two antibiotics, in peptic ulcer disease (Welage L S et al., 2000) and also used in the NSAID-induced PUD and prophylaxis of stress- and (Lanza F L et al., 1998, Singh G et al, 2005). These disorders always require long-term treatment (Hanlon J T et al., 1997, Lazarou J et al, 1998) and receiving PPIs (Ramirez F C et al., 2000).

Pantoprazole belongs to the proton pump inhibitors (PPI) drug category, which inhibits gastric acid secretion of primary stimulus and also used in the therapy of gastric and duodenal ulcerative disease in the treatment of the heartburn and other symptoms associated with Gastroesophageal Reflux Disease (GERD), for the treatment of erosive esophagitis and long term treatment of pathological hyper
secretary conditions, including Zollinger-Ellison syndrome. The mechanism action of the PPI’s is inhibition of H+/K+-adenosine triphosphate widely known as proton pump or acid pump due to an enzyme present in the gastric parietal cells (Figure 1.13) (Jai Moo Shin et al., 2013, Haitham F et al., 2011, Ralph-Steven Wedemeyer et al., 2014).

All PPIs are acid labile and heat sensitive. Hence development of dosage form is critical to protect drug in acidic environment. As a traditional way, PPIs are available in tablet form those are enteric coated. Enteric coating is functional coating and any minor change in critical process parameters leads to failure of whole dosage form and drug degraded in stomach only. Many times, patients not aware about precautions related to such enteric coated formulations like do break or crush the tablets. Pantoprazole is more prescribed PPI for long term regimen. Patients are reluctant to take tablet(s) daily once or twice up to several months. To develop a stable and patient friendly dosage form of PPIs is a challenging work.

1.3 OBJECTIVE OF RESEARCH

The objective of this research was to develop Pantoprazole Multiple-Unit Pellet System (MUPS) tablets which has oro-dispersible properties. There are number of brands available of Pantoprazole delayed release tablets has monolithic conventional enteric coated tablets but geriatric and pediatric patients are reluctant to administer the tablets due to long dosage regimen. The MUPS tablets are suitable dosage form in multiparticulate system and more superior than conventional and modified drug delivery. Compression of pellets coated with functional coat and has additional disintegrating property are more suitable for patients like for administration, easily divisible etc.

Pantoprazole is more critical molecule which is unstable in acidic environment, at high humidity and high temperature. At these conditions, Pantoprazole colour change to light to dark brown. It was more challenge to control crushing of pellets during compression and drug release in acidic media without compromising physical characteristics of tablet.

MUPS tablets contained coated or uncoated pellets compressed blended with suitable extragranular excipients and compressed at suitable compression force at compaction machine.

The objectives of the research are enlisted below:
1. To develop MUPS tablets of proton pump inhibitor drug will have sufficient oro-dispersibility suitable for pediatric and geriatric patients
2. To maintain minimum tablet weight suitable for administration
3. To systematic development of MUPS tablets based Quality by design (QbD) principle
4. To develop chemically and physically stable MUPS tablet
5. To develop simple and solvent free manufacturing process
6. To develop divisible tablets without altering the drug release.

1.4 SCOPE OF RESEARCH WORK
Nowadays, number of patients having gastric diseases like peptic ulcer, Zollinger–Ellison syndrome and gastro-oesophageal reflux disease etc are increased due to change in lifestyle. Mostly, adults whose age is more than 40 years are the victims of such diseases. In addition to gastric diseases most of the adults also suffered with hypertension and/or diabetes. Many of the adults take tablets twice a day till death. So through this research, it has been tried to develop patient compliant dosage form. The enteric coating is bitter in taste hence patients reluctant to take such a medicines. While oro-dispersible MUPS tablets contains small pellets, sweetener, flavouring agent and cooling agent like conventional dispersible tablets. Such tablets could be developed in the favour of patient’s ease of administration and most widely accepted in society.

1.5 ORGANIZATION
In this portion, the information is provided about the project work. Initially the information contains the detail information on the products which were formulated during the work. The pages also have detail information on various processes which were used during formulation of the pellets. Some advance industrial processes is also added. Lastly very short profile on medicaments is given which contains information about the nature and properties of medicament.

1.5.1 PRODUCTS
In current piece of research work attempts have been done to formulate the MUPS tablet from enteric coated Pantoprazole pellets so as to release the medicaments with delayed form used in gastric diseases.
The finished product tablet made up of pellets and extragranular excipients.

Pellets: Pellets made up of non-pareil seeds, non-functional and functional coat. Sugar spheres and MCC pellets were evaluated as non-pareil seeds. Seal coating and cushion coating were the non-functional coating and enteric coating was the functional coating.

Extragranular excipients: Extragranular excipients contain fillers, cushioning agent sweetener, flavouring agent, glidant and lubricant.

1.5.2 PROCESSES

There are several pelletization processes available, out of few are practically possible for industrial scale like extrusion-spheronization, suspension/solution layering, powder layering.

The development start with selection of pellets manufacturing process. Initially, pellets developed using all three pelletization technique while suspension/solution layering pelletization technique was the more reproducible and had more product yield.