CHAPTER 1: PREAMBLE

1.1 Introduction:

Multiparticulate drug delivery system (MDDS), were widely used for administering via oral route, it includes number of smaller discrete subunits which has different properties. It’s mainly based on subunits like microspheres, granules, pellets, beads, minitab and spheroids. Such type of subunits gives various advantage as compare to monolithic type devices. In MDDS, active pharmaceutical materials are get divides into number of subunits, typically which has number of spherical units which have diameter of about 0.052 mm to 1.98 mm. To utilize or to administer total dose these subunits to be compacted in tablets or get filled into a optimistic packs or properly encapsulated 1.

The composition consisting of multicomponent MDDS is feasible because it reveals various mode of action, it shows synergistic or additive effect, minimizes individual’s doses and minimize the side effects. Though it is more costly as compare to single therapies in the short term, it minimizes treatment failure ratio, reduce rate of case fatality and drop in development of resistance for designing of new units in long term type therapy 2.

Multiple unit dosage units are pharmaceutical compositions in that the active substance is available as a variety of smaller independent multiple units. To provide the recommended daily dose, these type of small units are get properly filled into a typical sachet and compressed or encapsulated into a solid dosage form. Multiple units are discrete small particles which provide the multiple unit type system. They also show number of benefits over single-unit type systems due to of their very smaller size. Multiple units are less depending on gastric emptying, which results in minimum intra and inter -subject type variation in gastro-intestinal transit type. They also uniformly distributed and very minimum suppose to cause local type irritation.

Recently more efforts is given on the designing of multiple unit dosage type units as compare to single unit type systems due to their various advantages like improved bioavailability, minimum risk of systemic type toxicity, decreased risk of local type irritation and calculated gastric type emptying.
There are multiple justifications for designing a active substance as a multiple unit system for e.g., to improve disintegration type in the stomach, or to show give a comfortable, rapid disintegrating type tablet which get dissolve in aqueous medium early to swallowing which can also aid compliance with elder volunteers and small Childs. Multiple unit system provides well reproducible pharmacokinetic pattern than monolithically or conventional formulations. After process of disintegration which observes within a very less minutes even in seconds, the individual subunits get pass immediately through a GI tract. If these particles or units have diameter not more than 1.99 mm, they have ability to left the stomach in continuous manner, even though the pylorus is being closed. These results in less inter and intra subject variations in bioavailability and plasma levels.

Safety of active substance may be improved by utilizing multiple dosage units, especially for modified type release patterns. For e.g., if film type coat of a single-unit (monolithic) enteric coating type tablet is get break, the total dose will get release in the stomach where it might be cause ulceration or pain or minimizes efficacy, based on the justification for selecting the prevention of the enteric type spraying. On other hand, if there is any break to the film type coating stage of a single unit tablet with a extended release type composition, this may results into “dumping of dose” and shows major adverse effects. In contrast, in multiple unit composition, the typical release properties are provided into each single type subunit and any type of breakage impact the release pattern of the small unit included, it shows a less portion of the overall dose, minimizing the safety concerns.
VARIOUS APPROACHES OF MULTIPLE UNIT FORMULATION

A multiple unit floating and pulsatile type drug delivery pattern was designed by utilizing sodium alginate and porous type calcium silicate, for site and time specific releasing of drug.

An oral type extended and modified onset of extended pattern releases the dosage units leads to appropriate the chronological biota’s of arthritis (rheumatoid type arthritis) was recommended to the colon targeted type drug design.

The multiple unit type system comprising of drug coated of cores of cellulose acetate were encapsulated in pH dependant eudragit S-100 type microcaps were developed for chronotherapeutic type drug delivery. The targeted delivery of meloxicam to the organ like colon have implementation in multiple therapeutic type areas, which also involve topical type treatment of disorders of colon like ulcerative-colicis, crohn disease, constipation, spastic colon and the irritable type syndrome of bowel.

Techniques of multiparticulates implemented for colon targeted delivery which includes formulations in typical form or pellets type, micro particles, granular particles, and the nano size particles. They are easily moving through the GI tract due to tiny particle size in comparison to particle size of single unit type dosage forms, which leads to very low intra and inter subject variation. However, multiple unit systems are very uniformly distributed in GI tract and confirm highly similar absorption of drug. A multiparticulate type system of beads of hydrogel of chitosan has been evaluated for the colon-targeted delivery of macro-molecules by utilizing fluorescein’s is othio-cyanate type labeled type bovine serum of albumin as a protein type model.

Multiple units can be formulated by various approaches. Various conditions of developing needed for different methods to manufacture multiparticulates of specific characteristics. Some of typical techniques broadly classified like spray drying, granule formation, pelletization and spray congealing. Drug particles may be layered around them or entrapped within the multiple units. To achieve desired release profile of drug, the multiple unit system can be well modified in multiple ways.

One approach to modify release profile of drug in multiple unit system is to properly coat the small units. Multiple justification to coat the multiparticulates are to provide chemical type
stability, to enhance physical properties, to obtain functional coats, and also to improve acceptance of patient. Coats were formed over the surface using different polymeric coating agents which are classified as water loving or aqueous dispersion of polymer, molten polymers, polymers solution and dried type powders. The controlled release like as targeted release, sustained type release, pulsatile type release and delayed type release can be achieved based on type of coating material utilized during coating. Air suspension coating technique was most commonly used method for the application of coating over multiple units. Various other techniques involve coating, coacervation, compression, evaporation of solvent, and the complexation of interfacial surface. Formation of multiple unit systems by spray congealing and spray drying method is also possible.

A composition of multiparticulates may also allow controlled or modified release pattern of the active substance for a long range rates of release and to allow the rate of drug release to be set at a previous determined interval, such type of composition may be prepared utilizing a melt-congeal technique which keeps the crystalline nature of active substance during the melt-congealing stage. Drug delivery system by osmotic type system could be achieved by a multiple unit type system by various/different level of coating over pellets has been developed, this coating consist of semi permeable type membrane of cellulose polymer, followed by injecting water which penetrate into core type and produces a saturating type solution of the components which are water soluble. Inducing of purified water influx due to osmotic pressure results in a fast expansion of a membrane which leads to pores formation. The osmotic component and the active substance distributed from such pores follows zero order model. Addition of osmotically active agent in formulation results in a different drug release pattern. Dissolution rate and lag time were depending on level of coating and the osmotic characteristics of the dissolution media.
**Techniques of pelletization**\(^{15,16}\):

Based on process and class of apparatus chosen, formation of sphere and development may occur in multiple directions. A most commonly used pelletization processes are described in Figure 1.

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**Figure 1: Techniques of pelletization**

**A. Balling:**

Balling is process of pelletization in which after adding approx. amount of liquid, powders changes there form to spherical size particles by a regular tumbling or rolling process.

**B. Drug layering:**

In this process deposition of drug substance from various layers of suspension, solution or dried powders on sugar seeds or starting material. The initial particles needed for the manufacturing of pellets by the coating technique are the sugar beads upon which a powdery drugs are layered and the required coating was utilized.

Placebo seeds has mostly utilized as first substrates in pellets manufacturing by the layering stage like sucrose and recently microcrystalline cellulose seeds also used as a starting material for drug layering.
Layering techniques are the more commonly controlled and easy pelletization process. The layering technique consist of the adding constant layers of active moieties from liquid or dried powders on unit with can be crystal shape or granular shape of the similar material or initial starter type beads. They are divided into 2 categories: powder layering and suspension or solution layering.

In suspension or solution type layering active substance powders and other individuals are suspended or dissolved in media. A drops available on initial beads or initiated cores and coated uniformly as suspension or solution is coated over cores. Drying stage allowed, substance which is dissolved to get crystallize and / or develop solid linkage in between core substance and starting layers of active and / or over the subsequent layering of active or polymer. Perform such stages till the achievable coats of active substance or excipients manufactured.

Layering of drug on pellets is very important and critical stage in pelletization because efficiency of release controlling polymer coating is based on drug loaded on pellets. In powder layering, binder solution cooperates to create subsequent coats of dried powder of active substance and any individuals on initial cores. In such process a active materials are attached to initial beads and sequentially for preparing spheres by using liquid linkages initiated from the coated binder solution. These liquid linkages are subsequently changed by solid linkages produced either from any material or a binder in the solution media. Subsequent layering of the active substance with binder material continues till the targeted pellet size is achieved. Successive layers may or may not contain same composition.

The most useful instruments for spraying process are the conventional or standard coatings pan and fluidizing type bed coaters (bottom, top and tangential type spraying pattern).

Conventional pans are commonly utilized for pelletization process. From the financial angle, utilization of conventional pans is not much recommended due to the more labor costs and period management, and minimum yield. Main limitation of pan coater is the minimum processing control parameters. Currently modified forms of pans has designed, it minimizes disadvantages as of previous system.
**Fluidized bed processor**

This is a machine which may manage various processes like pelletizing, spraying, granulating and drying. It has a more effective drying process and homogenous type material spraying reached. Advantageous for a multiple scale of stage apps like drying, spraying, agglomeration, drying and granulation. Prevents material from light, humidity, air. Applicable for sustain release coating, granule formation of pellet and hot melt type coating. It is used for selective manipulation of surface properties of the particle.

With liquid bed based spraying, materials are much fluidized and the material of coating was coated on and properly dries. Tiny droplet size and minimum viscosity of the spraying material confirms an uniform product coating. Various number of fluidized bed coaters like top, bottoms spray type (wurster process) and rotor pellet coating (tangential pattern).

**Top spray coating**

Such technique is useful for spraying binder preparation for powdery granule formation. Spheres are get moved in the flowing pattern of warm air stream, that is reflected in product column through base plate. The binding preparation is coated onto the fluidizing bed from above opposite the air pattern (counter current) by utilizing different size of nozzles. Volume of air is managing the middle of stream of particle near to nozzles. Drying carried out as materials to transfer above direction in flow of air. It is advisable, at a coating with taste mask is used, in addition it is useful for applying hot melt type spraying. Continuous spraying coater is advisable for protective or color spraying. Top spray spraying is generally used for light granulation. The granulation carried out by using top spray coating process is not heavy in nature and it is useful for rapid release system because in rapid release system the drug should deliver from formulation as soon as possible after administration.

**Bottom spray coating**

The technique is useful for pellets solution type or sugar/film type layering, specifically required for a modified release substances. In such type of technique, a complete surface covering may be targeted with minimum utilization of layering material. When warm air
passes via bottom plates of column and particular coating container, it creates the siphonage like mechanism.

Convection is generated via more pressure from bottom to top. The spheres will fall downward and returned into column of coating repeatedly; on other hand the bottom spray will flow towards above to reach purpose of coating. As the material moves upward, they dried and downward over the wurster column returning to the base plate.

Useful for applying modified release type spraying to a large variety of multiple units and also applicable for layering of active substance when the dosage of drug is in minimum to normal scale.

**Tangential spray coating (Rotor pellet coating)**

It is useful for powder layering, solution type layering or sugar/film type layering. In such system the core material are kept on turntables and warm air is passed above between turntables and granule formation specific area. A air passage creates the core material to move on turntables. At similar time, solution of layering is sprayed toward moving cores via spray gun with pumps.

The technique includes parallel layering and drying of core, layering over layering, till the continued actions reaches a achievable thickness of layering or desired size of granules. It is useful for applying extended release type film sprayings to a wide range of multiple unit materials, useful for active coating if dose type is minimum to maximum and is applicable as a spheronization stage for preparing pellets from fines.

**Formulation**

Optimizing variables of process is very difficult for useful designing of product in pellets form. In stage of development formulation properties are carefully noted and selected both quantitatively and qualitatively. Layering of solution is generally applied when the potential of the required pellets is minimum, since manufacturing of pellets having high potential is
not easy financially by utilizing layering of solvent from a formulation containing minimum solid content.

Active substance particle size is very useful factor during solution type layering. Since micron size materials prepare smooth type pellets and it permits sequential type film layering generally for modified releasing uses. If size of particle is more, maximum binder amount needed moving the particles over the core; on other hand pellets of minimum potential and not smooth surface are manufactured. The yield is generally very low.

Solution of binding generally enhances density of spheres. They should neglect growth in viscosity of formulations and shouldn’t improve the release spherical properties. Generally less molecular wt. polymers are more susceptible with the active pharmaceutical ingredients.

At time of powder layering it is special that delivery rate of powdery mixture to be optimistic as the solution application rate to avoid under or over-wetting. The powdery mixture should have very good flow characteristics, not to be adhere to feeding screw and sides, and also not forming holes like rat within the upper stage of equipment. Anti-adherence may improve the flow properties.

In coating composition role of each ingredient is very important some plays role of plasticizer or binder or glidant to avoid gun blocking during process. Many times anti-oxidants are also used in formulation which are susceptible to oxidative degradation. In extended release or delayed release formulation different grades of eudragit is used as a main coating component.

C. Powder layering:

In powder layering, binding solution is initially applied over the non-pareils after that the adding of powdery mixture till the required spheres size is produced. After drying, the disperse material get crystallize which forms solid linkages. Figure 2 provides the mechanism of powdery mixture layering.
D. Solution and suspension layering:
Mechanism of such layering process: This coating includes addition of different coats of suspensions and solutions of active moieties, sequentially, on non pareils which contain active substances. In suspension or solution coating, the ingredients of composition get dispersed or suspended in media and check viscosity of liquid sprayed. As the liquid or
suspensions are moved over the material bed, the drops spread evenly over surface after that the drying which converts dispersed materials to crystalline and form solid linkages. The process is on going till the targeted layers of active are achieved to achieve optimum release pattern. Figure 3 reveals mechanism of liquid or suspension layering.

E. **Spray drying and spray congealing:**

It is a globule formation process, it includes atomizing of liquid or suspensions to provide sphere shape units or spheres. At spray drying, active substance in liquid or suspension is coated into a warm stream of air to create more sphere shape and dry substances. At stage of spray congealing, an active moiety is permitted to disperse or dissociates and sprayed to chamber of air at which temperature is less than melting figure of composition parts and give sphere shape granules.

Spray-drying shows another type process with short type application in the designing of medicinal type pelletize formulations, based on globule formation. During spray-drying, a drug suspension or solution is sprayed, with use or without use of ingredients, in a warm stream of air, generating highly dried and sphere shape particles.

Although this technique is useful for developing modified release spheres, it is very usually provided to enhance dissolution rate and, bioavailability of minimum solubilized active substance. To achieve *In vitro* and *In vivo* co relationship during the same process is really very difficult task.

Also, this method is utilized for processing heat sensitive pharmaceuticals, like: ascorbic acid, amino acids, liver extracts, pepsin, antibiotics and similar enzymes, thiamine and protein hydrolysate. The spray-dried powder particles are very homogenous, almost spherical, nearly uniform in size. The operation and design of the spray drier can also improve various number of the characteristics of the final product, like size of particle and its distribution, bulk density, moisture content, porosity, friability and flow ability.

Spray-chilling is a process identical to spray-drying. Spray-chilling is technique at which active substance is permitted to dissolve or disperse, melt in warm melting of waxes, gums,
fat acids or other melting solid materials. The dispersion is then coated into a air stream and 
other gases with a temp. less than melting stage of the composition variables.
In specific processing conditions, sphere shape cingulated spheres are formed. The resultant 
material could be utilized for manufacturing of prolonged-release type dosage units.

**F. Compaction:**

In this process, active materials or granular particles are pressured along composition aids 
through a mechanical pressure to create spheres of predefined sizes and shapes. It can be sub 
grouped in extrusion and compression.
Currently, pellets formation by melting process is utilized commonly for preparation of 
spherical particles utilizing a various class of instrument, example a high-shearing blender. 
Other Pellet formation techniques, like globule formation, compression and balling were 
utilized.

**G. Compression:**

At initial steps of compressed formation, materials which are previously treated using dried 
mixing or by wet granule formation followed by dry formation, resequence them to create a 
small compact blend. At larger forces, the materials undergo elastic and plastic 
deformation, 
which leads to increase inter particle contact. The half tablet dissolution is the main milestone 
during compression of small multiple units.

**H. Extrusion**:  

Extrusion process involves three unit operation. At stage of wet granule formation, dried mix 
is segregated using binder solution. The wet mass is then transfer to the extrudizer to 
manufacture highly dense extrudes.
Such extrudes are arrange using capillary pressures, the solid linkages produced as a result of 
decrease in humidity and mechanically interlocking, Such extrudes are get transformed to 
spherical particle after spheronizing stage.
Extrusion consist of application of force to a wetted material till this passes via calibration type openings of a screens or dies plate of the extrudizer and then reshape into tiny segment of extrudes. As the mass moves through the extruder screen, the form extrudates usually crack under its inner type weight.

Generally the extrudes has the similar length. The extrudes has lot of plastic intensity in respect of deformation, but a high plastic intensity can result into extrudes which stuck to one another during process as they are collected and further processed in the spheronizer. The segments diameter and final size of the spheroids based on the opening diameter in the extruder screen. In response to produce reproductible results, it is advisable to monitor extrusion parameters like: feed rate, die temperature, air pressure, powder consumption and compression chamber pressure.

The extruder screen to be used to generate capillary force is depend on the required fraction of spheres required in coating

Operation of extruder is also important for getting uniform spheres after processing. If the water content is wet mass which is going to process is more then extruder speed should be kept low otherwise it will form lumps due to lack of capillary forces and if the wet mass content optimized water content then speed can be increase to get uniform extrudes.

I. **Spheronization**²¹,²²:

Spheronization develop with extruded material having cylinder sized units that are break in uniform lengths and were sequentially converted into spherical sizes. The speed of plate, air pressure and spheronization time gives major role during spheronization technique.

Such process refers to the forming of spherical shaped units from the smaller rods which produced by extruding process.
The essential part of the spheronizer is a friction plate. The indentation pattern on the plate can have multiple designs, which correspond to selective purposes. The most common design is the cross-hatch type pattern with grooves intersecting each other at a 90° angles. In order to form spheres, the extrudates are bring onto the rotating type friction plate of the spheronizer, which may gives a rolling motion to the material.

In addition, in order to get high yield of spherical type pellets, it is important that the extrudates are non-friable and have suitable plastic properties which allow them to take a suitable spherical shape.

The process of spheroid formation by extrusion / spheronization is almost similar to the wet granulation process, having the presence of a moistening liquid. However, there are two important differences in the granulation steps: the quantity of granulation liquid required to obtain pellets with homogenous sphericity along with size which is nearly to be higher compare to for a uniform dispersion of the granulation fluid, similar wet granulation leads to a product with a high quality.

Extrusion/spheronization is a useful process for preparing pellets with needful properties. However, this process is very labor-intensive and high expensive than the conventional wet-granulation technique, as its use should be specific only for production of spherical shape pellets for controlled type release of drugs. Technological advances now permit the production of spherical pellets by various new processes, like fluid-bed and rotary type granulation.

In these cases, specialized equipments permits the whole cycle of wet spheronization, coating and drying of the pellets to be done in one closed system.

**Benefits of spheronization**

• The flowing properties of spherical particles made it accessible for movement by multiple unit searched in formulation factory, inclusive of transfer of vacuum.

• The sealing of tiny spherical particles into tiny collectors, like hard gelatin type caps, or higher collectors is highly suitable than other type dried forms like powdery mixtures or
granular materials. Remove standard issues with different dose because of sealing issues with powdery mixture.

- Spherical particles are hard substances and have minimum ratio of surface area to volume, hence medicinal formulations may be sprayed with a less of spraying solution. Useful for targeted delivery of active material.

- Spraying may give modified, site specific delivery at various sites in body. Needful for targeted delivery of active material.

- Sphere shape materials were very rapidly blended. Smoother spherical particles are optimum based on which to target a spraying material. Less spraying interval and spraying component are utilized.
  - It avoids step of drug loading which helps to avoid process variables during drug loading.

- Spherical particles may minimize fines manufacturing and dusty material while export, transport and sealing.

- Based on uncohesive pressures along surface properties sphere formation maximizes the tensile strength and minimizes tensile strength of granular particles.

Extruding spheronizing is a multiple stage technique consisting of below stages.

1) Dry mixing

Dried blending of many substances is carried out to collect uniform powdery mixture type dispersed state or mixture by utilizing various classes of mixers as high shear mixer, twins shell mixer, planetary blender and tumblers blender.

During dry mixing the process parameters needs to be study because it will change during wet massing due to resistance to flow will increase the torque value during wet massing and the difference between dry mixing parameters and wet massing parameters will be optimize.
2) Wet massing

Wetting of powdery disperse formation is carried to prepare a enough rubbery compact for extrude formation process. Such granule formation process is identical to a normal wet granule formation except endpoint of granulation process. A granule formation ending point found via pattern of the wetting compact at extrude formation process. The more widely utilized granule forming equipment is sigma blade blender or planetary blender or Hobart mixer and more shearing blender. Mainly, planetary blender is utilized generally for many granulation and blending process. More shearing blender shows a maximum quantity of energy into the wetted compact which is get converted in heat also produces evaporating of granule formation liquid. It converts the extrude formation pattern of the wetted compact. With chilling the container of granulation can stop such kind of issues.

3) Extrusion

This step comes after wet granulation step. This technique may be referred as confirmative test for formation of wet granules and an inert confirmation for total sphere formation process.

Extrusion is a process of application of force to a wet mixture till it pass via opening is a mechanism which finds dimensional properties of particles of segregation. Due to different geometrical parameters which are well explained by the openings, extrudes length is generally the single dimensive type variable. This process is the main considering type point in the finalize size of particles of spheres. A diameter of the opening screen of extraditing assembly proportionally limits the diameter of the extrudes.

In such technique the wetting type material is transfered via a extraditing equipement to generate rod like sized materials of optimum diameter. The extrudes should have sufficient plastic intensity to change the form but no widely so the particles of extrudates stick to remaining materials when moved while sphere formation technique. The granule formation liquid plays as the binder solution to generate the specific granular particles and a lubrication stage while extrude formation process.
4) Spheronization

Spheronization process was initially shown by Nakaharas in 1964. Spheres or pellets formation during the spheronizing stage is based on the formation of extrudes. The extrudates type granule formation should have the common properties of firmness, cohesively and plastic intensity.

Such process has categories in three different parts like splitting of extrudates or cylindrically segmentation, segregation of the breakage type materials and smooth forming surface of materials.

Breakage of cylindrically shape components are observes due to the interactive reaction between extrudes and rounding plate, station type wall and other type extrudes. Segregation observe when the tiny segments prepared while breakage steps are catch by the more size granular particles at smoothing stage. Sphere shaped parts are formed at smooth forming stage by creating the rotational type movement of every granule or particle at its axial in consistently varying type plates.

Extruder and Spheronizer

The extraditing equipment for the extrude formation type technique has distinguished generally as sieves and baskets, screw, rolling and ramming type extraditing equipment. Screw extraditing equipment were strictly only continuous type extrude formation machines, as material could be exited in a continuous and smooth flow. The procedure of the extrude formation type equipments prepare mass of particles. Depending on feed class principle utilized to pass the material near the die wall, this are widely classes as screwing, gravitational type or and piston-like extruders.

Screwing like extruders also has screws which moves through the horizontally which moves the mass by horizontal axis, it may be axially or radially. Dies plate placed axial manner in axial type extrude machine.
In radial type extrude machine the movement zone is very small; the mass is then extrudized radial manner via screens placed over the horizontal surface of the specific screw. Gravity fed type extrude machine involves the rotarizing type cylinder and rotarizing type gear extrude machine, this differentiated specifically in drawing multiple different counter rotational parts.

In the rotational part type extruder one among two counter type rotational cylinders is hollow shape and perforative type, where remaining type cylinder behaves as a forcing roller. Rotarization gearing type extrude machine have two orifice type counter rotational gearing cylinders with the holes countered bored.

In ram type extrude machine a piston which may get changes places and pressurises the different mass via a die at last. Ram type extrude machine are preferably utilized in designing stage as it can also be utilized to determine the rheometrical characteristics of the compositions.

A spheronizing equipment is called as merumerizing equipment which includes vertical orifice type container with a horizontal type rounding or frictionary plates where the extrudes are breaks into tiny parts by the connecting with frictionary plate or another material or with stainless steel compartment. The frictionary plate is very important for generating energy which is required to provide spheres and for limiting the extent duration of pellets and is served along with interparticulate friction type.

The frictionary type plate, a rounding type disk along a specific prophetically grooving surface to improve the frictional pressures which is the very necessary part of instrument. Two different rheological concepts are commonly utilized. A cross hatching type pattern with grooves moving at the right direction to other and the radially type pattern with grooves moving radial manner from the center point of the plate.

In air forcing type spheronizing equipment the less quantity of dried air permits the granular particles to move through each other much comfortably and allows the mechanically induce fluidizing process. The frictionary plate which behaves identical to a plates a optimum type merumerizer, exceptional which looks as propellting type part which is kept up. The base is perforateive to distribute aeronautical system along the product.
More currently, various classes of fluidizing type bed coaters has designed very neatly for preparation of compressed spheres like extraditing spheronizing step in a single process. Such typical process resolve multiple issues near to multiple sprocess extraditing process as well as spheronizing process; it utilizes minimum interval, needs less labor costing and short area.

4) Drying

To get needed inlet RH in spheroids at warming step is required. The spheroids were warm at a normal temp. and at rising type temp. in a oveny /triad dryer or in a fluidizing equipment. D.1. Wilsons et.al, 2006 studied effect of type of drying on physical-chemical characteristics and compact forming properties of the extruding–spheronizing unit type of a avicel grade/PEG type/liquid portion. Depend on its research cold-warming kept size and shape of granular units, while ovens-warming gives no smoothy spherical particles due to the not even shrinking of the wetted unit.

Forming of compacts of single fraction gives that the granular density converts marginally, along ovens type-warm particles manufacturing tablet form of small voids for supplying compression force. It gives detailed relationship in tablet tensile strength and voids. Major difference were seen in tablet release rate of drug, with the cold warm type mass containing multiple-regimen type behavior along initial drug releasing rate consistent in response of magnitude more in comparison to the ovens-warm form.

5) Screening

It is important to reach specific sizing range, and for such reason sieving stand were utilized. In scannerio, spheres produced by extruding spheronizing process, screening is necessarily needed after production, in response to neglect spheres which have more size poly-dispersion index.
J. Hot Melt Extrusion spheronization\textsuperscript{23}:

Melting sphere formation is a technique in which a active moiety and ingredients are changes in a molted or partially molted state and sized utilizing proper instrument to serve spherical units or granular units. The technique needs different instrument like blending equipment, extruding equipment, cutting equipment and spheronizing equipment.

Industrial related uses of the extruding step are known from 1930’s. Wetted material type extruding process was very widely utilized process of preparing sphere shaped granules. Hot-melt type extruding step is most commonly utilized manufacturing techniques in rubber, plastics and foodland industries.

Recently, maximum than one half plastically materials, adding sheets, plastically bags and rods are prepared by such technique. Now melt extruding process is searched his location in era of the medicinal preparation process.

This technique is recently applicable in medicinal for preparation of multiple range of dosage units and composition to improve release of active substance like sustained and rapid release pellets, tablets and granular material, transdermal patch of the active substance and improving drug release rates for sparingly soluble active substances.

\textbf{Benefits:}

- No any liquid or aqueous solution utilized in such technique. Less manufacturing stages required hence time taking warming stages removed. Fine particles dispersion is observe uniform in nature.
- There is no requirement of compression ability of drug substance and whole process is efficient, simple and continuous. It is also useful for different multivitamins which are occupied in single composition
• Stable at varying moisture levels and pH, no need of extra coating as active substance release is limited by diffusion. Safety usage in individuals due to its water insoluble and no swelling property.

Disadvantages:

• Needs very more input of energy. This technique is which the processing step could not applicable to particles which are sensitive to heat which leads to extended temp. contained.
• Minimum melting-point type binding solution risks conditions in which softening or melting of binding agent observes at storage and handling of the agglomerated particles.
• Binders having maximum melting-point needs more melting temp. and will plays role to un stability issues mainly for materials which are heat-sensitive.

Uses:

In pharmaceutical type factory the melt extruding process has utilized for different reasons, like
• Enhancing the drug release criteria and biological availability of the active substance by preparing a solid solution or dispersion.
• Modifying or limiting drug release by manufacturing various release pattern spheres and granular particles. Applicable for masking the bitter type taste of drug substance, improving drug release rates for sparingly soluble active substance.
**Extrusion Technique:**

Pharmaceutical materials prepared utilizing melt extruding process has permitted in Europe, America and Asian countries. Melt extruding technique includes 3 main steps: plasticizing or melting a typical solidified mass, fine tuning of the molted mass also solidification of the desired mass in targeted shape.

A warm melting extruding type contains a mass feeding type hopper, extruder inside a type of heating rod, having 3 changing type parts, and sphere former. The hopper keeps the specific mass and regularly kept it in extruding equipment, which have a heating type barrel having the rotary screw. Sphere formation may be performed in one set of instrument, like a jacketing type, higher shear rate blender where some parts of a composition are get melting to create spherical shape type materials. The technique is very matching to wet granule formation, except the binding agent is in molted form and it do not need aqueous material or another solutions to liquidity it. The active material is initially mixed with the proper medicinal ingredients, like waxes and polymers, and it extrudized at a retargeted temp. condition. The temp. during spheronization must be more sufficient so it partly smoothen the extrudes to allow its deforming and parallel type sphere formation. The extrudes break in homogenous cylindrical type parts along the pelletizing equipment. The components are well sphere forming in jacketing type sphere former to create very equal pellets size.

The one screw type extruding machine is the very necessary class of extruding machine utilized due to its benefits of comparatively cheap value, reliability and ruggedness. The designing of the extruding type die is supported by multiple parts like components of extrudates and processing factors of extruding equipment.

Much of the raw components utilized in such process has been used in traditional process. The mass in which the active substance is in dispersion form is known as heating carrier. At this stage the carrier is generally transfer into a molted form. The carrier material is generally
A typical excipients or very minimum melting point waxy material such as poly-oxamer 188 (micro), polyethylene glycol, bees wax, gelucire 50/13, carnaubas wax, microcrystalline waxy material and paraffin waxy material.

In 1994, Follonir and his colleagues searched warm-melt extrude formation technique to manufacture extended-release type spheres of diltiazem HCl; a comparatively very stability, easily soluble active substance which was added in typical polymer-dependant spheres for extended-release type caps. Four specific polymeric forms are evaluated for extruded type process, such as CAB (cellulosic acetate butyrate), ethylcellulose, (EVAC) poly (ethylene co-vinyl acetate) and a poly-methacrylate excipients (Eudragit® RSPM). The plasticizing agent involved diethyl phthalate or triacetin. A spheres manufactured, having soft like surface with minimum porous nature. The drug release pattern of active substance was diphasic, along EVAC and CAB spheres showing minimum rate of release.

The utilization of plasticizer in medicinal grade polymers alters active substance release characteristics and enhances appearance of surface typical dosage units. Plastic former enhance polymers flexibility by minimizing hardness and glass transition temp. of typical mass and lower degradation of warm sensitive type material.

A detailed uses of warm-melting extrude formation was explained by Sato, miygawa, and his colleagues in 1996-97. The evaluated the modified release pattern and type of pattern of diclofenac sodium. These scientist used a twinning-screw type compound type extrude former, carnaubas wax, the ideal active ingredient, and another rate limiting substance to produce spheres. Initially research proves a waxy matrix along very more mechanically strong may be resulted at temp. less than wax melting point. Drug release patter of diclo sodium from typical waxy granules were motivated by the composition of the granule type particles. The pattern of limiting type excipients which were changes in composition includes methacrylate copolymer (Eudragit S/L-100), hydroxypropyl cellulose, and NaCl.

The researcher forces benefits of utilizing twinning-screw type extrude former for waxy matrix dosage forms, like more shaking and dispersion capacity, minimum temperatures and minimum retention time of the mass in typical extrude former.
Pauly Wany Siai Hengi. et.al. were also observe the limitations of melting type pellet forming process in 8-l more rate shear blending by using typical energy use by motor impelling. They also utilized supertab grade of lactose as bulky material along with PEG 3000 grade as a melting binder. He evaluated the impacts of binder concentration, average particle size distribution of bulky material and after-melt type impelling rotations on co-relation with specific energy utilization and pellets growth.

Use of typical energy was found as a useful channel for keeping the melty type pellet forming technique, and particular energy uses is better correlating with growth of spheres. The average size of spheres produced becomes relatively maximum with enhancing typical energy type utilization.
K. Cryopelletization24:

In this process, drops of a solvent composition are transferred in solid sphere shape units or spheres by utilizing liquid nitrogen as optimum media.

Such technique is typically designed for a nutritional factory for lyophilizing the viscosity based bacterial suspending form, could be utilized to generate active substance loaded spheres. In cryo-pelletization process the spheres could be manufactured by permitting drops of solvent composition like emulsion, suspension, or solution, which came in touch with the liquidities nitrogen at -159.9°C at this temp. liquidities nitrogen is utilized as solidification media. A process allows instant and uniform cooling of product which processed due to faster transfer of heat which observes between liquid nitrogen and droplets. The needed quantity of liquidities nitrogen for producing a mentioned quantity based on concentration of solids and temp. of solvent medium or suspending medium which is processed. The spheres are easily warmed in traditional type freeze dryers to discard organic solvents or water.

The instrument consisting container which having perforated plate down to which a liquid nitrogen reservoir which having conveyers belts along transporting type baffles get immersed. The changing rate of conveyers belts gives the needed time of residence which needed for the pellets freezing. The freeze pellets are moved in storing container at -60.0°C early warming in typical freezing dryers. Instruments of various scale like production size and laboratory scale are available. Forming of droplet is important stage in cryo-pelletization process and its forced by composition relative some variables, instrument design and related various technical changes. Composition type changes involve surface tension, viscosity and availability of solid.

Solid content and viscosity of the solvent composition should be more high and does not cross a optimum limit which is based on composition. Surface active tension of the solvent
composition enhances drops creation and the size. Adding surfactant minimizes the surface tension also prepares particle of small size.

The design and diameter of shearing edges of typical holes in perforating plate enhances the shape and size of spheres.
As diameter of nozzle is small, the tiny the spheres prepared. The gap between the reservoir of liquid nitrogen and the perforated plate should be such that it permits the drops to become spherical shape before come in contact to liquid nitrogen, due to typical pellets shape highly based on the gap but it couldn’t be much that it tends to deforming of the spheres. When its expectable to have spheres below 2.0 mm diameter. the liquid nitrogen needs to be stir in continuous manner to avoid segregation.

This process must be utilized to prepare active substance loaded spheres or granules for controlled and immediate release composition.
L. FREEZE PELLETIZATION

This is a very easy and recent modified process for preparing spherically matrix type spheres having drug substances. In such process a molted type solids carrying material along a distributed drug substance is subjected as typical drops in immiscible and inert liquid column.

It involves minimum processing variables and shows many benefits towards pellet formation techniques, By considering spheres quality and processing value. The spheres prepared by such method are very spherical along very micro sizing distribution. Since a spheres are solid in nature at normal temp., it does not need any warming.

Molted type solid channels are involved as specific drops into the liquid compartment in which such molted mass is not miscible. Such drops may travel either downward or upward movement based on its density in response to the type of solvent in column and it get solidified in sphere shaped granules. Carriers may be hydrophobic or hydrophilic which get melted at a temp. 5 - 10°C more as compare to melting point of carrier solid material.

Two different class of instruments are utilized and the equipment priority based on the dense property of the molted type solid material. The compartment of two different instruments are subdivided in two different portion, first part through which the molted type solidified channel is subjected and well kept in 25-100°C, second cooling part where solidifying of droplets observes and well kept at 0 to -40°C utilizing cooling mix of dry ice along acetone.

The active material and other typical ingredients were mixed along molted type channel to produce dispersion or solution. Such dispersion or solution is subjected as different drops utilizing nozzles or needles in inlet compartment of solvent and dropping from a specific distance, so the drops will kept intact as it come down in solvent compartment. Needle type gauge from 15-30 based on desired pellets size. In case of cold pelletizing type I a molted
type solidified channel are subjected from very upper part of compartment due to dense solid channels is higher as compare to density of solvents utilized in columns and channels get solidified at bottom part, in cold pelletizing type II case the molted solidifying channel were subjected from bottom of the compartment due to dense solid carriers are less in proportion to the solution utilized in column and channel get solidified at the upper portion.

Adjustable channel for cold pelletizing process is such, have solid in nature at normal temp. with having melting point less than 100°C in respect to decrease degraded nature of the drug substance. For cold pelletizing type I, hydrophilic channel like polyethylene glycol, poly-vinyl alcohol and minimum melting range sugars (maltose, dextrose) were utilized. Useful solvents for specific compartment are very minimum dense oil like vegetable oil, mineral oil and silicone oil.

For cold pelletizing type, hydrophobic type channels of very minimum dense like glyceril behenate, glyceril palmito-stearate, and glyceril mono-stearate are utilized as typical solid channels. Useful solvents for compartment are very more dense hydrophilic type solvents like ethyl alcohol, solvent PEG, water and glycerine. For modified release type spheres having mixture of hydrophobic and hydrophilic liquids, solids which were not miscible with hydrophobic and hydrophilic type molted solid states which are utilized as freezing solvent in the specific compartment.

Chrysty M. Wyandlt, et al, evaluated pattern of active substance release from waxy-based extended release type matrixing spheres produced by a recent and modified freeze pelletizing type technique II. They find the release of active substance significantly based on waxy type utilized and aqueous type solubility of drug substance. The release of drug substance minimized as hydrophobicity of waxy mass maximized and the release of drug improved as aqueous type active substance solubility improved. In (GMS) glyceril mono-stearate spheres, rate of active substance release minimized as loading of theophylline type improved.

On other hand, the rate of release maximized as active substance loading of diltiazem HCl maximized in Preceerol type spheres. Theophylline at very minimum active substance loads having in dissolving manner in GMS spheres and release follows’ mechanism of desorption. At high loading, theophylline type present in a crystalline manner and release follows controlled dissolution-consistant release for all waxy materials which are evaluated.
Granulex is very recent technology for pelletization. Previously every formulator commonly use extrusion spheronization process to prepare spheres which is good technique but Granulex has slightly different mechanism as compare to extruder Spheronizer.

In extrusion spheronization it is necessary to prepare wet mass by using granulation process and if batch size is more then granulation needs to perform in multiple lots which may cause variation in chemical and physical properties of wet mass. After granulation, wet mass needs to extrudized. In extrusion technique if batch size is more then formulator needs to optimize quantity of wet mass to be extrude in specific time period. It is observed that in first cycle water content in wet mass is more but if formulator needs to perform multiple cycles then at last cycle the wet mass gets air dried and it has less water content as compare to first cycle. Due to variation in water content lot to lot, it will impact on sphericity and size of spheres form. As the sphericity is different lot to lot and variation in sphere size it is difficult to reproduce drug release pattern batch to batch.

In granulex technique, there is no need of performing granulation using rapid mixer granulator and no need to extrude the wet mass followed by spheronization.

In this technique, feeding rate of dry mix and spray rate of coating or binding material needs to optimize. Initially feeding rate of dry mix per minute was check and then efforts were taken to match spray rate of coating solution with feeding rate of dry mix. If formulator could not able to balance both rates then it is difficult to form uniform granules but if formulator can optimize the feeding rate of dry mix and spray rate of coating material then it is the best technique for formation of spheres and it is easy to reproduce batches using granulex technique.
Slit air and slit air temperature are main process parameters in granulex technique. Slit air should be optimum enough so that it will maintain the air flow inside the chamber and keep the product temperature within required range. Slit air keeps the spheres moving and avoid formation of doublets during process. Slit air will be optimize by physical observation of spheres. If spheres are getting more wetly in nature then formulator needs to increase slit air flow and slit air temperature. In this technique coating solution and dry mix get deposited on sugar spheres simultaneously and forms the spherical granules. Sphericity of the granules observe is much better than spheres produce by extrusion and spheronization process.

It is very less time consuming and advance technique for formation of drug loaded granules which further coated with release controlling polymer using wurster process.
FILM COATING:

There are different types of coating which have a characteristic function (such as eudragit coating to extend the drug release until it reaches the respective site), but here the simple case will be examined.

Coating process is used for number of reasons like,

1. To coat a substance which having bitter taste in the mouth and having an unpleasant odour.
2. To improve stability of substance which are light sensitive and subject to atmospheric oxidation.
3. To improve release profile of drug, e.g. controlled release coating, osmotic pumps, etc.
4. To distinguish non-compatible materials from each other.

Film-coating compositions usually have below components:

A. Polymer.
B. Plasticizer.
C. Pigment/opacifying agent.
D. Vehicle.

A. Polymers:

The polymers generally utilized in coating of film are a cellulose derivatives, like the cellulosic ethers, or acrylic polymer and co-polymers. Other polymers like more molecular weight poly-ethylene glycols, poly-vinyl pyrrolidone, poly-vinyl alcohol and waxy substances are also utilized for film coating.

1. Polymers Used for Conventional Film Coating –
Methylcellulose (MC), Hydroxypropyl cellulose (HPC), Hydroxy propyl methylcellulose (HPMC), Hydroxy ethyl cellulose (HEC).

2. Polymers Used for Modified Release Application –
   Methacrylate ester copolymers, Methacrylic acid copolymers, Ethyl cellulose (EC),

B. Plasticizers:

Plasticizers are less molecular weight substances having impact on physical properties of a polymer to improve its utilization as film-coating material. A principle of action for a plasticizing agent is to intercept them in single polymerizing strands hence cracking below to high extension excipient-excipient interactions. They are also useful to minimize the glass transition temperature.

B.1 Classification:

The mostly utilized plasticizing agent are divided into 3 parts:

a. Polyols

1. Propylene glycol;
2. Polyethylene glycols PEG (generally the 200–6000 grades);

b. Organic esters

1. Dibutyl sebacete;
2. Phthalate esters (diethyl, dibutyl);
3. Citrate esters (tri-ethyl, acetyl tri-ethyl, acetyl tri-butyl);
4. Triacetin.
c. Oils / glycerides

1. Acetylated monoglycerides;
2. Castor oil.

C. Colorants/ Opacifiers:

They are useful due to following reasons,
1. Colorants are useful for identifying individual materials to patients, mainly those takes number of medicines.
2. They are useful for imaging of brand by preparation to lower the risk of counterfeiting.
3. Colorants are useful to protect light sensitive products by applying film coating to the tablets.

C.1. Classification:

1. Organic dyes and their lakes: Sunset Yellow, Quinoline Yellow, Patent Blue V, etc.
2. Inorganic colours: It having needful opacifying potential, e.g. titanium dioxide.
3. Natural colours: e. g. Carmine, Riboflavine, Anthocyanins.

D. Solvents/Vehicles:

These materials provide coating parts to surface of the particle or tablet. Different types of solvents having capacity of being utilized are:

1. Water
2. Alcohols
3. Esters
4. Ketones
5. Chlorinated hydro-carbons.
FLUIDIZED BED COATING \textsuperscript{26}:

In 1940’s the fluidization technique was introduced on large rate in petrochemical factory to initiate reaction between the warm vapors and catalyst in breaking of high hydrocarbons to oil of fuel but technique was initially implanted for medicinal use in year 1959 by wurster. Tablet coating by forcing the solution of coating over tablet bed kept in hot air stream was investigated by wurster who filled his initial patent in 1953. Wurster performs formation of granules from powder in FBP out in 1960.

Fluidization is unit operation in which tiny solid forms are converted in a fluidy state after coming in touch with gas. At some gas accelerations, solvent will boost the spheres, gives freedom of movement without addition.

**Equipment description:** A GPCG (Glatt-Powder-Coater-Granulator) of Glatt are mainly utilized for techniques which are very uniform, reproducing and clean on product by utilizing fluidized bed processes. Size of batch varies from 4 kg to 1.45 t/batch.

**It gives benefits like:**

**All-in-one:**

As required from coating of powders to very easy drying. Whether granule formation or agglomerate formation, coating of particle or the pellet formation. Where layering from up (Top Spray), or bottom (Bottom Spray) or any side (Tangential Spray): it means everything is easy with Glatt. It is very flexible type equipment.

**Unique technology:**
Glatt provides an optimum ratio of volume of air flow to amount of material utilized. The conical type force relieves zone and results minimized flowing speed permit although tiny materials to be activated. At centre of granule formation is GPCG single pipe nozzle placed. Which joins continuous spray pattern with optimum type medium delivery and very simple cleaning.

**Simple handling:**

Both vertical and horizontal flow of material may be understood with different size. Contained feed type process by utilizing gravitational force or suction which may be introduced. The container is get nil by moving it in movement carriage (up to some level of batch size). Dusting-free feeding and tipping in collector on single lifted column. Emptying may stepwise be done from sides by meaning of gravity or by suction or as the rapid and very efficient technique of all vertically with single glatt moving type bottom.

**Innovative ABC-technology:**

The single ABC-technology (Anti Bearding Cap) permits coating without any bearding. The ideal supplements to ABC technology: The single micro-coating to nozzles which avoids the deposition of coat former on the cap of nozzle.

No any procedure downtime which is due to nozzle washing.

No blocking of liquid material

No any disturbance of spraying like fashion.

**Pharmaceutical Uses**

The technique of FBP is utilized to prepare different stages of controlled, limited or modified release active substances. These type of solid unit forms are mainly in the form of tablets or capsules having maximum limits of an drug substance Product properties include:

Pellets with high density

Smooth and soft coating type pellets
Narrow type distributions of particle size, and
Maximum mass and flowing ability.

**Main medicinal uses involve:**

Extended and modified release of pellets for capsule filling.
Delayed release or sustained release enteric targeted pellets
Multiple unit approach
Multiple unit erode formation matrix pellets
Pellets for highly specific tableting uses
Rapid drug release pellets for typical sachets

**Principle of fluidization**

The principle of operating fluidization process are depend on condition that, if gas is permitted to move through a material of particular solid at velocity higher than particles velocity of settling and minimum than terminal velocity and equivalent to lesser velocity of fluid formation \( V_{mf} \). In technique of fluid formation, inherent mixing between gas or solids occurs which results in optimum temperature condition and uniform size distribution of particle through a bed.

**Theory of fluidization:**

Stages of fluidization: The steps of fluidizing are mainly depend on velocity of fluid moving through bed of particle. The stages of fluidization are described as below.

1. Static bed
2. Expansion bed
3. Mobile bed
4. Bubble forming technique
5. Pneumatic transportation

**Role of fluidization velocity:**

A bulk of lastly spread solid material is transfer in fluidizing bed by moving action of gas moving through it. 3 different steps could be evaluated in fluidization stage based on gas velocity transfer from it. Which involve,

1. **Fixed or static Bed:**

   When liquid is pumping in up direction through bed of tiny particles of solid at minimum flow rate, the solvent percolating via void pore without interrupting bed. It is called as a fixed bed procedure.

2. **Expanded bed or particulate fluidization:**

   At initial rate of flow the bed gets expand. It’s called as an expanded bed.

3. **Mobilized bed:**

   If the up-directional flowing rate is maximum a bed get moves pneumatically and might be easily sweep out of procedure vessel. It is called a mobilizing bed procedure.

4. **Bubble formation:**

   If the velocity get increased after mobilized bed formation, the bed get expands marginally withrise in voidage which results in formation of bubbles.
5. **Pneumatic transport:**

Pneumatic transport occurs when up movement force of moving air blows particle outside the bed.

In fixing bed, the substances are in touch with one another and backing everyone’s weight. In expanding bed the substances has a specific distance in particle to particle and drag forces of solvent motivate them. The expanding bed is also known as fluidizing bed. As mention in figure 4, the fluid velocity via bed in direction opposite to gravity find out whether the bed is fix or expanding or left out.

![Diagram of fixed, fluidized and mobilized beds](image)

(a) Slow rate of flow  (b) Intermediate rate of flow  
(c) Fixed bed, Fluidized bed, Mobilized bed

**Figure 4:** Fixed, fluidized and mobilized beds.
FLUIDIZED BED PROCESSOR (FBP)

Advantages of FBP

1. Rapid mixing, uniform temperature.
2. Process is easy to control
3. Avoid sudden change in temperature, hence response slowly to variations in operating process.
4. Applicable for small and large scale operations.
5. Rate of mass and heat transport are more, needing minimum surfaces.
6. Continuous process.
7. Control of process is easy due to stable processing conditions.
8. Coating and drying take place in single machine.
9. Useful for modified drug delivery system by applying different coating.

Disadvantages of FBP

1. Bubble forming beds of tiny substances are critical to judge and are have minimum efficiency.
2. Substance break up may occur.
3. Sizing and class of particles, which may be handled by such process, are restricted.
4. Due to the multiple coatings during fluidization process, there is some challenges in going to scaling-up from small range to new parameters.
Applications

1. Fluidizing bed processors are utilized in warming of multiple substances like powder, granules, tablet dosage forms etc.
2. This procedure is commonly utilized in granule formation of medicinal powders (Top spray granulation technique).
3. Fluidizing bed coating instruments are utilized for coat forming of granular particles, tablets, powders, spheres etc.
4. The three classes (Top, Bottom and Tangential) spray are commonly utilized for non organic or organic solution based polymers filmy coat formings.
5. Top-sprays fluidizing bed coat forming is utilized to mask taste, granulation, controlled release on substances/tablet dosage forms. Coating with bottom spray is developed for controlled or enteric release and tangential spraying is utilized for sustained release and enteric coated substances.

An Overview of fluid bed coating process 27, 28, 29

Principle of operation
In fluidizing bed process, substances are fluidized and the coat forming material sprayed over it and dried. Smaller drops and minimum spraying viscosity results in optimum coating of product.

Glatt also gives batch fluidizing bed process in various batch sizes with:
1. Top-spray coat forming,
2. Bottom-spray coat forming (wurster process),
3. Tangential-spray coat forming (rotor pellet process)
Figure 5: Fluidized bed processor (FBP) mini glatt

A. TOP SPRAY COATING

Figure 6: Top spray fluidizing bed coating

B. BOTTOM SPRAY COATING (WURSTER COATING)

Figure 7: Bottom spray fluid bed coat forming (wurster type coating)

C. TANGENTIAL SPRAY COATING (ROTOR-PELLET PROCESS)
Top spray technique is used for different types of coating. In top spray coating, particles are fluidized through heating air flow, which is provided in container of product through a B plate at bottom. The solvent of coating is sprayed in the fluidizing bed counter currently using various size of nozzle. Drying takes place by continuous movement of particles in the airstream. Fine droplet size and minimum viscosity of coating solution confirm the uniform distribution.

The figure 6 shows the top spray coating of fluidized bed processor.

Bottom spray process is recommended for a modified release delivery pattern. In wurster technique, a complete coating over surface of particle may be done with a minimum utilization of coat forming unit. The spraying nozzle is placed at below plate reflects in a spraying technique which is not parallel with air pattern. By using a column and down disc of various perforations, units which are be coat are enhance inner side a wurster column and move through spray cone parallaxly. As materials are generally moves in up direction, they dried and get down out of the wurster column back in direction to base plate. They again transport from outer periphery of column to the inner periphery of the column where it again accelerated by a spray, such technique is known as air suspension technique which gives an good even film due to which units of multiple sizes are coats uniformly.

The figure 7 shows the bottom spray coating of fluidized bed processor, this process known as Wurster process.

Tangential spray coating is preferred with maximum content of solid, the material is fit in a spiral motion using moving down disc, which have slit air in a bed of powder at side edges. A
nozzle of spray is positioned in tangential manner to rotary disc and spray continuously in bed of powders. The target in following a useful coat forming procedure is to confirm that spraying coat forming substance comes to substances to be coat without over wet forming.

**Parameters affecting fluidization bed coating**

1. **Feeding particle size:**

   Pellets particle size should be optimum for coating and fluidization. If particle size is much large, fluidization problem will occurs. If having smaller size, twinning and agglomerates will form.

2. **Spraying gun parameters:**

   Atomized air of the coating solution provides a alternative to the problem of providing solution to the mass. The location of spraying tip in fluidization bed based on equipment build up and a variety of nozzle positions and nozzle size. The nozzles may be fitted above bed, inside of bed or at bottom above the base plate. The bottom spray is design to move substances via spraying zone as fast as possible. Recent designs permits the utilization of multiple nozzles spraying from bottom. During top coating, excessive spraying of coating solution was perform to wet the surface of particles Diameter of nozzle also plays main role in coating, if the rise in load in FBP, we need to use nozzle with more diameter and for high viscous solutions, larger diameter of nozzle is used.

3. **Coating solution:**

   While handling of fluidizing bed and pan coating technique, solvents of organic nature were mostly utilized in making of coating solutions. It is better to provide fast coating at less fluidizing gas ratio and at minimum temp., but its uses has lowered due to strict documents
on factory hygiene and safety factors needed during its utilization. Due to such reason, there has more utilization of aqueous units to substitute the organic medium, and these needs more fluidizing air capability and also heating units. The concentration coating solution should be such that it kept spray running. A specific coating material is having a plasticizing agent, polymer and liquid, in pigments.

4. **Coating thickness and uniformity:**

An effort to continuously check the thickening and uniform coating within substances and between single substance is necessary in assuring feasibility of such bunch of stages. Uniformity of particles plays major role to improve the coating efficiency.

5. **Particle circulation:**

Wurster process has an internal cylinder (also called as column) to accelerate flow of particles within a bed. The spraying nozzle is situated at bottom next to base plate, so that flow of particles which are coated is in same movement as a fluidizing gas. Other designs like a rotor-tangential spraying, it provides changing speed plate and slit rather than traditional distributor disc to accelerate movement of substance.

6. **Temperature and humidity distributions:**

In fluidization process, both mass and heat transport should took place for substances which coated. The temp. and humidity measures are signs of these transfers. The maximum fluidization temp. results in small or no growth of particle, while too less fluidization temp. course defluidization by wet quenching. When the humidity and temp. patterns are developed for specific bed process, it’s easy to measure bed size without moving chance of wets quenching. Humidity control during wurster process can be done by using dehumidifier if the
material is hygroscopic in nature. Humidity also plays major role to avoid static charges during coating.

The inlet RH is very important parameters during pelletization as the spray rate increased by keeping inlet temperature constant then inlet RH start increasing and it will avoid formation of static charge during pelletization which generally occurs due to over drying.

7. **Water evaporation rate and moisture effect:**

Water evaporation rate is most important factor during aqueous film coating. The energy needs for evaporating aqueous medium are much higher than that for organic solvents. The film formation can occur by different mechanisms, based on whether the polymer is dispersed or solvated in an aqueous media. The rate of water loss may have impact on the product performance and efficiency of the coating process. Moisture may have effect on properties of polymeric coatings. An aqueous film-coating stage have effects of water, due to the possible entrapment of water in the micro domains of the film. Moisture in a film coating reflects effect of plastisizer on the polymer\(^\text{31-33}\).

**Process Parameters:**

A. **In drying process:**

Below inlet air stages are delicate & useful at all stages of granulation, drying and coat forming.

1. **Temperature:**

As inlet air temperature rises, rate of drying also rises. Such process to maximize drying rate may not used always due to few substances are sensitive to more temp. e.g. Ibuprofen get liquefy next to 59°C temp. of inlet air which could be optimize without harming quality of
substance. If temp. is higher, it leads to blister forming. If temp. is minimum, soft spots may be formed. Temperature also plays important role to improve coating efficiency.

2. **Humidity:**

Humidity in inlet-air must be minimum and dehumidifying air must be utilized for higher rate of drying due to rate of drying increases as humidity of inlet air decreases.

3. **Air flow rate:**

The rate of air flowing must be limited optimally in place to get effective utilization of drying of air. As rate of air flow rises, drying rate also rises and its value also rises. If drying of air is kept in touch with substance which is to be dried, a optimum heat and transfer of mass done and hence value of drying minimizes. Flowing rate of air must be optimum for efficient drying.

**In coating process:**

**Related to spraying nozzle**

1. **Distance of spraying nozzle:**

Effectiveness of coating based on viscosity of material. Coating material should not be too viscous to get dried before reach to the fluidized particles e.g. spheres, tablets, particles, and granular surfaces.

2. **Droplet size:**

Droplet size is important point to affect quality of coat. So it should optimum.

3. **Spray rate:**

It must be of optimum for effective coat forming.

4. **Pressure of Spray:**
Atomizing of coat forming solution based on force of a spray, hence for optimum atomizing droplets size must be developed. The nozzles generally used are 0.8 mm, 1 mm and 1.2 mm based on material used and type of release profile required.

Miscellaneous:
1. Moisture must not be available in case of hygroscopic substances. Moisture content can be controlled by using dehumidifier.
2. Method utilized for coating must be based on the reason for which it is utilized. Eg. Sustained Release, Extended Release, etc.
3. Drying time may be measured on basics of substance and standard of a coat targeted.

Product parameters:

A. In drying process:

1. Early moisture content of substance must be less to avoid increase in time of drying.
2. Batch size- It must be optimum depending on occupancy of equipment.

B. In coating stage:

1. Coating agent.

Coat forming material must be selected based on coat forming class needed e.g. functional coating, sugary spraying, delayed coating etc. Medium must be chosen based on characteristics of the coat forming material.

2. Starting material:

Dimension of tablets marginally impacts the coat forming procedure. In powder coat forming the size of particles, shapes and strength impacts the coat forming procedure.

Active substance choosing criteria for oral modified release delivery system: 11
The bio-pharmaceutical investigation of active substance needs idea on the principle of absorption of active substance from GIT, absorption ability, molecular weight of active substance, pKa, solubility at wide range of pH and apparently coefficient of partition prior to its utilization in modified release system. Table 1 shows general factors for ideal active candidate selecting while the table 2 shows the general pharmacokinetics parameters for drug selection.

The release profile requirement is depend on the BCS class of active substance. If formulator needs to formulate the Class 1 drug (Highly soluble and Highly permeable) then he needs to use high viscous release controlling polymer as compare to design formulation for Class IV drug.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Preferred values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight or size</td>
<td>Less than 1000</td>
</tr>
<tr>
<td>PKa</td>
<td>Non ionized moiety more than 0.1% between pH 1 and 7.8.</td>
</tr>
<tr>
<td>Solubility</td>
<td>More than 0.1µg/ml between pH 1 and 7.8.</td>
</tr>
<tr>
<td>Apparent partition coefficient</td>
<td>Higher</td>
</tr>
<tr>
<td>Mechanism of absorption</td>
<td>Diffusion</td>
</tr>
<tr>
<td>General absorption ability</td>
<td>From all GI parts.</td>
</tr>
<tr>
<td>Release</td>
<td>Irrespective of enzymes or pH.</td>
</tr>
</tbody>
</table>

The pharmaco-kinetic investigation need basic idea of the active substance terminal elimination half-life, absolute bioavailability, overall clearance, achievable first-pass metabolism & targeted constant state amounts for trough & peak.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute bioavailability</td>
<td>Preferably 75% or more.</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>Within 0.5 and 7.9 hrs.</td>
</tr>
<tr>
<td>Apparent volume of distribution</td>
<td>The smaller the $V_d$, the larger will be the amount of drug</td>
</tr>
<tr>
<td><strong>Elimination rate of constant</strong></td>
<td>Needed for design.</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Total clearance</strong></td>
<td>Should not depend on dose.</td>
</tr>
<tr>
<td><strong>Intrinsic rate of absorption</strong></td>
<td>To be more than rate of release.</td>
</tr>
<tr>
<td><strong>Therapeutic concentration (C_{ss})</strong></td>
<td>The minimum the C_{ss} and less the V_{d}, the larger will be the amount of active substance needed.</td>
</tr>
<tr>
<td><strong>Toxic concentration</strong></td>
<td>The lesser the amount of MTC and MEC, the safe the dosage form. Useful for active substances with very small half-life.</td>
</tr>
</tbody>
</table>

In this report, an evaluation is done on multiple unit active substance delivery system to target time and/or site specific dissolution pattern of zolpidem tartarate. The drug, Zolpidem Tartarate is a Sedative-Hypnotic Drug (Imidazopyridine class). It have a less biologically half life of 0.2 to 1.9 hr, with 6.25 - 12.5 mg daily dose and 70-80% bioavailability. The reason for selecting this drug candidate is there is not any marketed preparation of Zolpidem Tartarate in multiparticulate form in India, and is the very famous drug to the US market in sedative hypnotic’s category than the other barbiturates and the benzodiazepines which gives various advantages as compare to conventional formulation of Zolpidem tartarate.

There is not any controlled release formulation of Zolpidem Tartarate available. But recently Sanofi, Aventis has taken the patent on the AMBIEN CR controlled release product of Zolpidem which is available in the tablet form. The reason for formulating this modified release formulation of zolpidem tartarate is to maintain the sleep for those people who could not maintain the recommended sleep of 8 hrs.

From the technical view, floating delivery system of drug and mucoadhesive drug delivery of drug coated pellets is a much suitable and useful approach to enhance a residential time of gastric mucosa. The active zolpidem tartrate is weak acid with a pKa value 6.2. The solubility of zolpidem tartrate has been reported to be altered by the pH of different digestive fluids to a considerable extent i.e. zolpidem tartrate disperse easily in stomach but not completely in the intestine. Due to the above reported fact about zolpidem tartarate it may be useful to design
mucoadhesive active transfer which enhances residence time for gastric mucosa and releases active substance in proximal GIT where absorption of zolpidem tartrate is more confined.

OPTIMIZATION: FUNDAMENTAL CONCEPTS.  

Optimization utilizing design of experiments is a systematic, effective tool which is useful for the designing of medicinal doses & for research & development activity. The word optimized simply implicated to prepare as perfect and efficient as much. Optimizing of a product or processes is determining the experimental situations results in optimal performance.

In factorial design, all factors are evaluated in all suitable combinations and are consider as most effective in calculating the impact of individual variables and its interactions utilizing fewer experiments. Uses of such concept in development of formulation had plays important view in knowing relation between a in-dependent variables and the responses. The responses are dependent on independent variables which are controllable. The contour plotting give a visual presentation of the units of the response.

Optimization strategy

The new strategy for conducting optimistic evaluations in medicinal doses could be shown by optimization planning. The stages included in optimizing approach are as follows;

1. Problem definition
A optimizing issue (e.g., active substance releasing from doses) should be wisely mentioned and understood.

2. **Selection of parameters and levels**

The in-dependent variables chosen must be quantitative and easy to control. A stages of every variables are either decided from before practical or pilot study. Selection of parameter and level to be efficient to gather a more knowledge with less trials. If more number of in-dependent variables are available, a primary screening for farcical variables to be done. Levels for every parameter must not to narrow nor very wide.

3. **Design of practical protocol**

Depending on the selection of in-dependent variations and response proposed useful statistical process is chosen.

4. **Design and evaluation the dosage units**

Dosage unit is designed based on required quantity of trials and checked for targeted parameter.

5. **Predicting optimize formulation**

An optimum formula is determined using mathematical optimization or search process. This is generally facilitated using computer software.

6. **Validation of optimize formulation**

An expected optimum composition is designed and responses were checked and cross-checked.
1.2 Problem on hand:

The present work is related to modified release pattern of Zolpidem or its salts thereof consider to release over a predetermined time interval, related to biphasic profile of drug release, in which initial phase is immediate release phase and the second phase is modified release phase which will avoid taking multiple dosage form per day and also to improve stability, patient comfort and compliance.
1.3. Research Objectives:

- Development of modified release drug delivery system of zolpidem or its salts over a predetermined time period, based on biphasic dissolution profile (i.e. immediate release followed by modified release)
- To improve stability of product and patient compliance.
- To reduce dose dumping of zolpidem tartarate.
- To achieve unique release pattern of zolpidem tartarate pellets
- To improve residence time in stomach.
1.4. Scope of Research Work

This research is useful to study biphasic dissolution behaviour of single drug substance by applying DoE approach. In future, this research work will become reference for biphasic drug release pattern by using modified drug delivery.
1.5. Organization:

This research activity performed under the guidance of Dr. J. R. Baheti, at Department of Pharmaceutics, S. N. J. B.’s Shriman Sureshdada Jain College of Pharmacy, Chandwad and Kamla Nehru College of Pharmacy, Butibori, Nagpur (Maharashtra).