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Fluid Bed Technology: Overview and Parameters for Process Selection

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ABSTRACT
Formulation development is the most emerging and upcoming face of pharmaceutical technology in the current era. It is contemporarily capturing the market leaps and bounds with recent trends and developments with its innovative techniques. The day-to-day advancements in the research have provided an edge to this brilliant branch of pharmaceutical sector for not only uplifting the pharmacy profession but also to conquer the diseased state for nurturing the health and humanity. The fluid-bed technology or air-suspension process is the potential tool to develop newer trends and implications in the sector of formulation development with maximum therapeutic efficacy. The technology is used for granulation/agglomeration, layering and coating of a wide range of particle size. In addition; the technique can be used for the drying process as well. The three patterns of the fluid-bed processes could be characterized by the position/location of the spray nozzle i.e. top spray, bottom spray or tangential spray. This article reviews the three techniques with some innovative fluid bed pelletizing technologies like CPS™, MicroPx™, ProCell™ and discusses their applications, advantages and limitations. These advanced pelletizing technologies are recentely added to complement the actual capabilities of standard fluid bed processing for development of various dosage forms of "Multiple Unit Particulate Systems" (MUPS) with better therapeutic efficacy and economic benefits.

Keywords: Fluid-bed Technology, Pelletization, Granulation, Formulation development, Agglomeration.

INTRODUCTION

The fluid-bed method of wet granulation is well known in the pharmaceutical and other industries as a one-step, enclosed operation. Because several ingredients can be mixed, granulated, and dried in the same vessel, the technique reduces material handling and shortens process times compared with other wet granulation processes. In addition to granulation for tableting, the fluid-bed top-spray method produces highly dispersible granules with a characteristic porous structure that enhances wettability. Such granules are used in powdered food, nutritional, and chemical products. [1] The fluid-bed process often is used for coating and powdered layering (pelletizing) applications. The bottom-spray (Wurster) fluid-bed method is very popular in the pharmaceutical industry for active layering and for coating to modify or control drug release because it produces a superior film compared with other coating techniques. The tangential-spray (rotary) method has been used for granulating and pelletizing with subsequent coating. [2]

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GRANULATION/AGGLOMERATION

Granulated or agglomerated particles are more desirable than fine powders for several reasons. For pharmaceutical products, granulation often is performed

- To improve flowability.
- To improve compressibility for tableting.
- To reduce dust for operator and environmental safety.
- To improve dispersibility.
- To improve uniformity by combining all ingredients together, or by distributing low-dose actives uniformly by dissolving and spraying a solution of actives.

Top-spraying and tangential-spraying typically are the methods chosen for granulation. Process conditions in the bottom-spray technique can be adjusted to produce granules.

Spray Agglomeration

Fluid bed spray agglomeration is also often in colloquial terms referred to as fluid bed granulation. Powders are fluidized and a binder solution or suspension is sprayed onto the fluidized particles, creating liquid bridges which form agglomerates from the powder. [3-4] As soon as the desired size of the agglomerates is achieved, spraying is stopped and the liquid evaporated. The structures created by the liquid bridges are then maintained by solid binder bonds (Fig. 1). Whatever has been liquid inside the agglomerates is now void, as such permitting modified size and porosity of the

agglomerates for their intended function, e.g. for compression into tables or fast dissolving instant drink applications. The lack of kinetic energy in the agglomeration zone results in light structures with plenty of internal capillaries. The usual size range found on the market is approximately 0.2 to 2.5 mm.

Top Spray Fluid Bed Process

Top-spraying is the most well known process for wet granulation, and it has been used in various industries for more than 30 years. A top-spray processor has three components (Fig. 2).

- An air-handling system, which can be equipped with humidification or de-humidification and dew-point control.
- A product container and expansion chamber.
- An exhaust system (including the processor's filter housing).

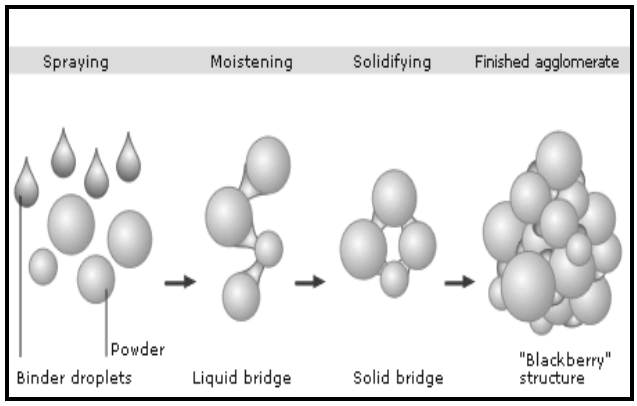

Fig. 1: Process Principle of Spray Agglomeration.

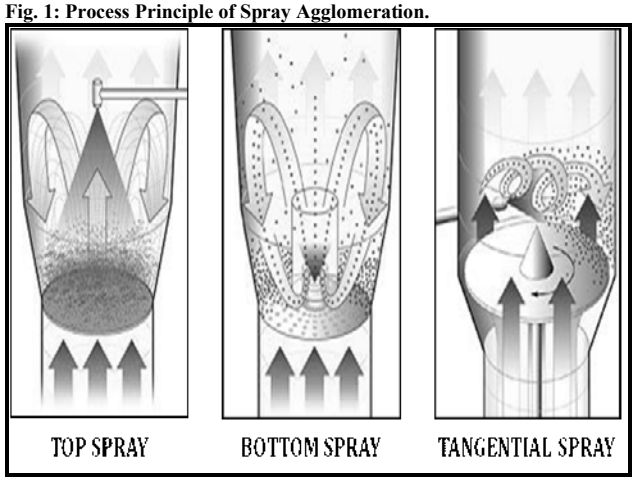

Fig. 2: Different Patterns of Fluid Bed Processing.

Process Variables

Process variables for the top-spray method include the liquid addition rate, inlet air temperature, fluidization air volume, process air humidity, and the atomization air pressure. It should be noted that atomization air volume is the key variable, but it often is gauged by atomization air pressure. [5-6]

The effects of process parameters for top-spraying on the physical properties of the granules were studied. A faster rate of liquid binder addition resulted in a larger average granule size and less-friable granules. An increase in the inlet air temperature caused a decrease in average granule size. In both cases, the effects resulted from an increased ability of the solution to wet and penetrate the solids when the spray rate was increased or when inlet air temperature was decreased. Atomization air pressure also had a significant effect on average granule size. An increase in atomization air pressure resulted in a decrease in average granule size because of smaller liquid droplet sizes. [1, 3]

Fractional factorial design was also developed to evaluate granulations prepared in a top-spray fluid-bed processor and it was concluded that atomization air pressure was the most critical parameter, followed by the liquid addition rate, binder concentration, and inlet air temperature, respectively. Fluidization air volume was found to be statistically insignificant. The authors observed significant interactions between some of the parameters. [2, 4]

In summary, the two most critical process parameters in top-spray fluid-bed granulation are atomization air pressure (volume) and the liquid addition rate. Inlet air temperature, inlet air humidity, and inlet air volume have lesser effects on granule formation; however, good control of all these parameters is important to minimize batch-to-batch variation in production. In addition, the effect of these less-critical parameters may increase as binder strength decreases. Binder type and concentration also play important roles in granule formation, but lie outside the focus of this article. [7-9]

The top-spray process typically is used in three applications:

- Granulating with a binder
- Granulating with water (instantizing)
- Fluid-bed spray-drying.

Generally, granules prepared by the top-spray method are porous and have a loose structure. They disperse well in water and have lower bulk densities compared with granules prepared by high-shear granulation.

Granulation with a Binder

Granulation with a film-forming binder probably is the most common wet-granulation technique for preparing tablets in the pharmaceutical industry. This method can be used for both water-soluble and water-insoluble compounds. Some frequently used binders include gelatin, starch, polyvinylpyrrolidone, and high concentrations of sugar. For this type of granulation, the formation and agglomeration of granules depend on the properties of the binder, particularly the type of binder and the concentration of the solution. Process parameters also are important, but they are not as critical as those for granulating with water as the spray medium. [10-13]

Granulation with water (Instantizing)

This process is similar to granulation with a binder; the only difference is that water is the spray medium. Generally, granules produced via instantizing have a loose structure and are somewhat friable. The main advantage of instantizing is that it improves the flowability and dispersibility of fine powders. Because of this, it often is used in the food industry to prepare drink mixes and other dispersible food products. [9-11] Instantizing also can be used to prepare granules for clinical diagnostics, where the choice of binders is limited to com pounds that do not interfere with the chemical reaction or assay, In some cases, when granules are too friable for a particular use, the raw material itself can be dissolved in water and used as a binder to improve granule strength. [14-15]

To form porous granules, instantizing relies on the solubility of the compound in water as well as process conditions. Thus, process parameters are critical for successful instantizing. Controlling and understanding the effects of

psychrometry on granule formation also can be important for reproducibility of the process (e.g., inlet air dew-point control and the calculation of exhaust relative humidity).

Fluid-bed Spray-drying

This concept is based on the similarity between traditional spray-drying and the top-spray fluid-bed process. Both methods atomize liquid droplets into a chamber of hot air to facilitate drying. The process air volume can be adjusted in the top-spray process. By operating with a large air volume, liquid can be spray-dried in the chamber at an inlet air temperature much lower than that used for traditional spray-drying. [16]

In the beginning of the fluid-bed spray-drying process, the liquid flow rate must be low to allow for a high evaporation rate. Once spray-dried particles are formed, the rate of liquid addition can be relatively high because of the combined effect of particle agglomeration and the layering/spray-drying of the liquid. In some cases, inert carriers or particles of the raw material can be used to seed the mixture, thereby inducing the formation of spray-dried particles. [12, 14]

Finished products obtained from fluid-bed spray-drying generally are larger, have better dispersibility and flowability, and exhibit a narrow particle-size distribution compared with products obtained via traditional spray-drying. In one application, fluid-bed spray-drying was used successfully to dry 100 L of a protein solution (3-5% solid concentration) in 2 h. The finished product had a higher dispersibility compared with the same product produced via traditional spray-drying. Furthermore, the protein was not denatured and retained its biological activity. The fluid-bed spray-drying process can be an attractive alternative to freeze-drying or traditional spray-drying of protein-based products. It produces particles with superior dispersibilities compared with those obtained via traditional spray-drying. Fluid-bed spray-drying also offers lower operating costs and shorter process limes compared with freeze-drying.

Tangential Spray Fluid Bed Granulation

The second fluid-bed technique for wet granulation is the tangential-spray (rotary) process, available since the early 1980s (Fig. 2) which depicts a tangential-spray processor. The nozzle is introduced at the side of a product container and is imbedded in the substrate during processing.

The primary feature of a tangential-spray processor is a spinning, variable-speed disk. During processing, three mechanical forces cause particle movement, mixing, and granulating- First, the spinning of the disk generates a centrifugal force. Second, a lifting force is generated by the process air volume that passes through the adjustable disk gap. Third, gravity causes material to fall down onto the disk. These forces, resembling a spiraling helix, provide good mixing and result in granules with good content uniformity. [10-15]

Process Variables

In addition to the variables described for top-spraying, process variables for the rotor include

- Disk speed, which controls centrifugal force
- Disk gap, the distance from the disk to the wall of the processor, which controls the air volume and velocity responsible for the lifting of particles.

Comparison of Top Spraying and Tangential Spraying

Process of wet granulation was performed using tangential-spray granulator and a top-spray granulator. Granules prepared via tangential-spraying were denser and less friable and exhibited a larger particle size compared with those prepared via top-spraying. Subsequent tableting of the granules prepared via both processes resulted in acceptable characteristics (e.g., disintegration time and compressibility). Tangential-spraying is a good choice for producing granules that are to be coated because coating can be carried out within the same machine. Furthermore, granules prepared using the rotor have a surface morphology (less porous and more spherical) that is more suitable for coating than that of granules prepared via the top-spray process. [8-13]

COATING / POWDERED LAYERING (PELLETIZING)

The coating of particles is practiced in various industries for several reasons. For pharmaceuticals, coatings are used

- To mask unpleasant tastes or odors
- For product identification
- To enhance stability (e.g., to act as a moisture barrier)
- To modify or control drug release
- To improve product flowability.

In general, there are two types of coating applications: film coating (using a wax, aqueous, latex, or organic coating system) and substrate layering. The latter produces pellets or spherical forms of a substrate by layering it, in powder or liquid form (e.g., solution, suspension, or emulsion), onto inert carriers such as sugar spheres. [17-18] The pellets are then coated for modified or controlled-release dosage forms. Common coating materials can be grouped into three categories: waxes, water-insoluble polymers, and water-soluble polymers. Water-insoluble polymers can be applied via an organic solvent system or an aqueous system such as latex or pseudolatex dispersions. Because of environmental concerns regarding the use of organic solvents, aqueous dispersions have gained popularity. [11-16]

Multiparticulate Systems

In multi-particulate systems the dosage of the drug substance is in contrast to classical single-unit dosage forms; divided on a plurality of sub-units, typically consisting of thousands of spherical particles with a diameter of 0.05-2.00 mm. Although their manufacture and design is more complex in comparison to single-unit dosage forms, multi-particulate systems offer a magnitude of differing interesting options and advantages to accomplish unique product characteristics and in particular specific drug release patterns. [4, 6-7, 12]

In contrast to single-unit forms, which retain their structure in the digestive tract, the multiparticular, i.e. multiple-unit, preparations consist of numerous sub-units, which disperse after administration. Each single sub-unit acts as an individual modified release entity. As a consequence of this property, the multiple-unit approach offers certain advantages for a modified release dosage form over single-unit, monolithic, preparations.

- Reduced variability of the gastric emptying
- As a consequence lower dependency on the nutrition state
- Minimized risk of high local drug concentrations within the GI-tract
- Lower intra- and inter-individual variability of dissolution of the drug substance
- Lower intra- and inter-individual variability of absorption of the drug substance into the systemic circulation
- Increased residence times within the lower intestine with reduced risk of sudden dose dumping

All three fluid-bed processes (top spray, tangential spray and bottom-spray) can be categorized as standard technologies for coating whereas some innovative fluid bed pelletizing technologies like CPS™, MicroPx™, ProCell™ are recentely added to complement the actual capabilities of standard fluid bed technologies for development of various dosage forms of "Multiple Unit Particulate Systems" (MUPS) with better therapeutic efficacy and economic benefits. [8-16]

STANDARD TECHNOLOGIES

Fluid Bed Coating

Spray coating can be used for all fluid bed systems, be it in batch or continuous operation or if the film is applied from a sprayed solution, suspension or hot melt. For this processing option the parameters have to be chosen to avoid agglomeration, i.e. liquid bridges between the air suspended particles (Fig. 3). If spraying a solution or suspension the liquid only serves as a vehicle to deliver the coating material to the surface of the substrate. For hot melt coating the droplets must be small enough not to form solid bridges. [19-20]

The quality of the coating extensively depends on the statistical residence time of the particles in the coating zone. For a classic fluid bed unit only top-spray coating is possible. Bottom-spray or tangential-spray coating inserts can also be hosted by means of the relevant technical provisions.

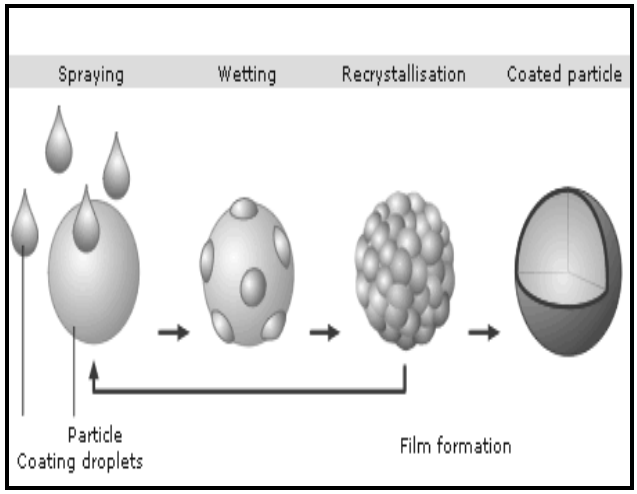

Fig. 3: Process Principle of Fluid Bed Coating.

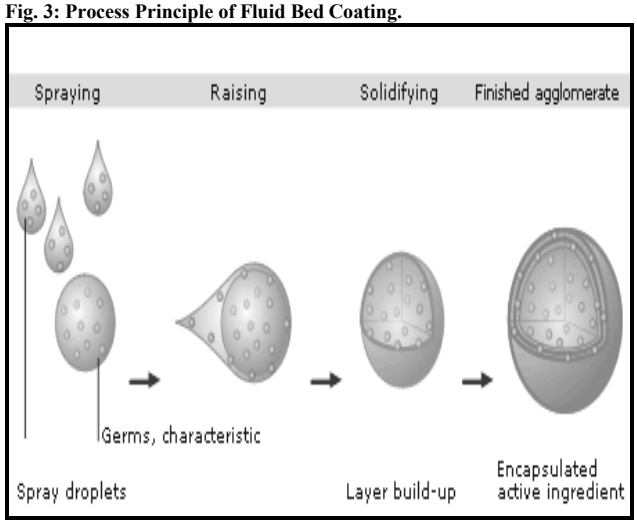

Fig. 4: Process Principle of Spray Encapsulation.

Top Spray Coating Process

Although the top-spray fluid-bed process is widely used for granulation, its use for coating is limited. Top-spraying is the simplest process and offers the highest capacity and lowest capital cost (Fig. 2). It can be used for taste masking, barrier coating, or functional coating. However, it is not a good choice for applications in which film quality (absence of pores) and uniformity of film thickness are important (e.g., for sustained- or controlled-release dosage forms).

This processing option is frequently used by the food, feed and chemical industries as the function of the film mainly serves to improve the general handling or storage times, i.e. time limited protection against moisture, oxygen or light. A perfect film is generally not required for this function, but care must be taken that the droplets do not become too viscous before touching the substrate, in order to maintain a good spreadability. As however neither the particle motion, nor the travel distance of droplet from nozzle to substrate is uniform the film structure is generally rather porous, but nevertheless measuring up to the above described requirements.

Hot-melt coating is one application in which top-spray coating is preferable to tangential-spray or bottom-spray coating. Hot-melt coating applies molten coating materials onto particles. Generally, molten coating materials are waxes or fats with melting points in the range of 50-85°C. The liquid is maintained at a constant temperature during application, typically 40-60°C above the melting point of the material. The quality of the coating depends on the rate at which the coating droplets solidify on the particle surface. Therefore, temperature control is critical in hot-melt coating processes. [11-19]

Various methods of hot-melt fluid-bed coating for producing sustained-release dosage forms were also developed. Compared with the bottom-spray and tangential-spray methods, the top-spray process operated at the highest temperature and gave the best results (i.e., slowest drug dissolution and smoothest coating surface); Effective research has also been pursued using statistical experimental design to study the process variables of a top-spray hot-melt coating process. [16- 17, 19- 20]

The equipment setup for hot-melt coating can be time-consuming because an atomization air heater and nozzle insulation are required. However, because hot-melt coating uses waxes or fats as the coating materials, no evaporation of water or solvent is required. Therefore, high-percentage coatings can be applied in relatively short process times.

Bottom Spray Coating Process

The most commonly known fluid-bed process for coating in the pharmaceutical industry is the bottom-spray (Wurster) process (Fig. 2). Developed by Dr. Dale Wurster in the late 1950s, the technique is well recognized for providing excellent coating uniformity and efficiency. [11-13]

The unique features of bottom-spraying are an air-distribution plate and a partition that together organize fluidization of particles through the partition (coating zone). The nozzle is mounted at the bottom of the product container and is centered in the coating zone. The short distance between the coating materials and particles during the coating process minimizes spray-drying and contributes to high coating uniformity and coating efficiency.

This processing option uses the energies and controls of the fluid bed to create a pneumatic mass transport inside a special insert, which consists of a perforated bottom screen

with defined free areas. Most of the process air is channeled through the center via a tube, as such producing a venturi effect, which sucks the product from outside the partition past the spray nozzle. Leaving the cylindrical partition and entering the conical expansion chamber the particle velocity is dramatically reduced, excess moisture is rapidly evaporated with the dry product returning again and again through the coating zone to receive more coating material. This uniform statistical residence time of all particles in the coating zone results in a very homogenous coating. Due to the high kinetic energy provided by the pneumatic mass flow moist particles are separated, as such allowing the individual coating of even very small particles. Due to the nozzle being positioned directly inside the product and concurrently spraying a premature viscosity change of the coating droplet is avoided. All this features result in the highest possible coating quality, which is imperatively required to produce defined and reproducible drug delivery profiles. [14-15, 17, 19-20]

Process Variables

In addition to the process variables for top-spraying, there are two important variables unique to bottom-spraying: the partition height and the type of air-distribution plate. Partition height is determined by the particle size, the substrate density, and the desired velocity of particles passing into the coating zone. Air-distribution plates are available in various sizes and with whole patterns designed to accommodate a wide range of substrates (from 50µm particles to pellets and tablets). Selection of both the air-distribution plate and the partition height for each particular substrate affects the fluidization of the particles. Wurster has discussed process variables for the bottom-spray process. [11, 13, 16]

Tangential Spray Coating Process

This processing technique is with its physical principles quite similar to bottom-spray coating (Fig. 2), only that the production motion is provided by a motor driven rotor disc. Otherwise, the quality producing parameters are the same:

- Uniform statistical residence time is warranted by defined rotor revolution speed
- The coating material is sprayed concurrently inside the rotating product
- The rolling motion of the particles provides an even higher separation force, as such preventing agglomeration.

However, this high kinetic energy makes it somewhat difficult to coat very small particles and is generally destructive for larger and non-spherical products. The benefits of this processing option are mainly for the layering and subsequent film coating of pellets.

A significant advantage of tangential-spraying over the top-spray or bottom-spray processes is the option of connecting a powder feeder to minimize exposure of compounds to water or solvent. [17] This technique permits the production of pellets with high-dose loading of actives in a relatively short time. Tangential-spraying can be used to produce granules or pellets that require subsequent coating for controlled release. The film quality achieved via tangential-spraying has been shown to be comparable to that obtained via the bottom-spray process. [8-11]

One drawback of tangential-spray coating is the potential for strong mechanical forces during the process. Such forces are beneficial during granulation because they provide good mixing, but they are not desirable during coating because they can cause substrates to break. (Adequate control of these forces can result in a tangential-spray process suitable for granulation or coating/layering applications.)

Bottom-spray coating compared with the top-spray and tangential-spray coating processes. Analyzing the surface topography of the pellets through the scanning electron microscopy using all three fluid-bed processes; it was observed that for film coating (using aqueous and organic solvents), the bottom-spray process produced a smoother and more uniform coating compared with top-spraying. It has further been demonstrated, in terms of the amount of coating deposited, bottom-spraying provided a higher coating efficiency than did top-spraying. [21-24]

The differences in film quality produced by the three fluid-bed coating processes are more pronounced when an organic solvent system is used (as opposed to an aqueous dispersion latex system). The latent heat of vaporization of organic solvents generally is lower than that of water. Thus, spray-drying is more problematic for the top-spray process using an organic solvent system rather than an aqueous system. [14-19]

The position of the spray nozzle is important. Both the bottom-spray and tangential-spray processes have a nozzle imbedded in the product during the coating process. For top-spraying, the nozzle is at the top of the chamber, and coating material is sprayed in a counter-current direction to product and airflow. There is a tendency for spray-drying of the material during top-spray coating, which leads to lower coating efficiency and quality when compared with bottom-spraying and tangential-spraying. [25-26]

Spray Encapsulation

When different excipients are mixed during the liquid phase and spray granulated afterwards; it results in granules with an excellent stochiometric distribution of all ingredients (Fig. 4). By fine tuning of the process parameters, liquids can also be embedded in the solid matrix as small microcapsules. Liquid microcapsules can also be imbedded in a spray agglomeration process. [21-23]

Pelletizing

Fluid bed technology offers different methods of pelletizing depending upon the functionality of the products and the given properties of the substrate.

Direct Pelletizing

Direct Pelletizing involves manufacturing of pellets directly from powder. Powder is mixed and moistened and the powder bed set into centrifugal motion (fluid bed pelletizing in the rotor).The impact and acceleration forces that occur in this process result in the formation of agglomerates (Fig. 5), which become rounded out into uniform and dense pellets and are then dried. Another alternative for direct pelletizing is spray granulation.

Pellets can be automatically dosed and filled into capsules or compressed to form tablets using a suitable formulation. The even shape and surface provide ideal conditions for application of a precise film, in order to achieve controlled release. Some of the specific properties of the pellets developed by direct pelletizing are round shape with well defined surface; Ideal flow behaviour and dosability; Narrow particle size distribution with low abrasion. [27-31]

Pelletizing by Layering

A starting grain or a pellet can be presented as the starting material. The pellet is built up to the required size and active ingredient content on a layer-by-layer basis by spray application of the layering substance. Powder and binders, suspensions or solutions make suitable layering substances.

The layers are densely and quickly applied during powder layering in the rotor (fluid bed pelletizing), whereby different types of layers can be formed. [32-35]

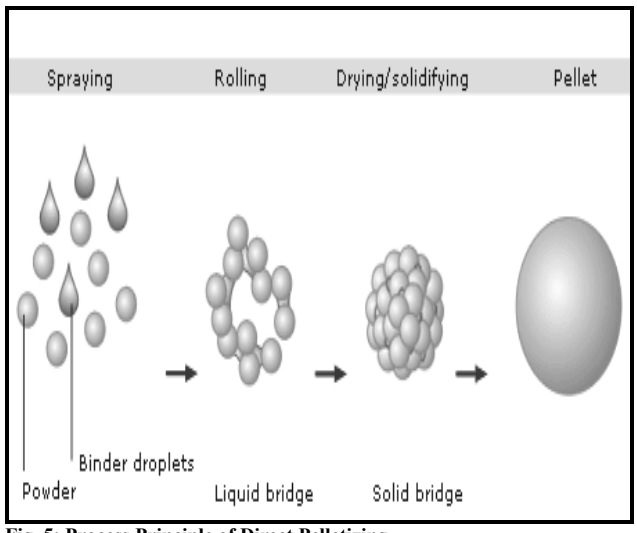

Fig. 5: Process Principle of Direct Pelletizing.

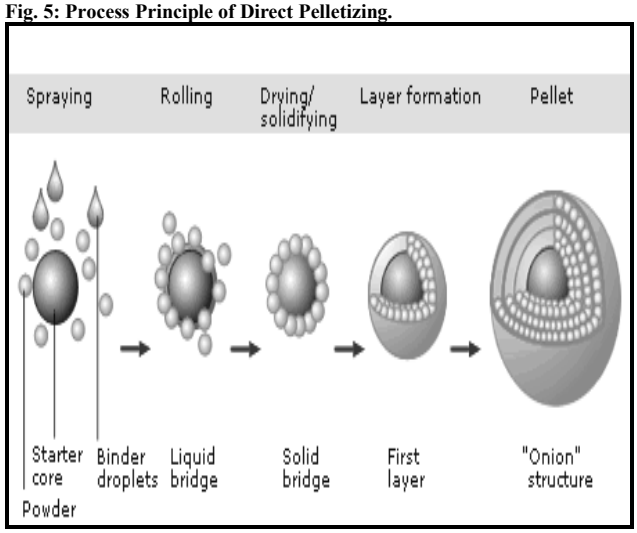

Fig. 6: Principle of the Powder Layering Process.

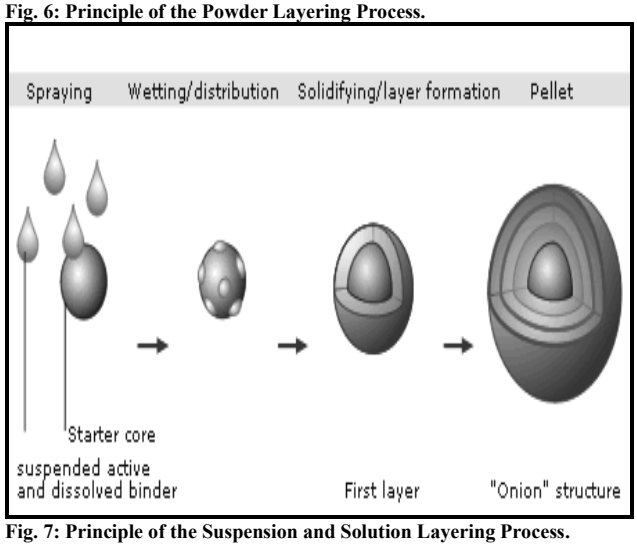

Fig. 7: Principle of the Suspension and Solution Layering Process.

Active ingredients can be applied in powder form (Fig. 6) or solution form (Fig. 7) on a layer-by-layer basis onto a carrier, and so unite wide-ranging different functions in a single pellet. Layer-by-layer pellet build-up; around a given starting core provides layered round pellets of dense and even surface with ideal dosability, low hygroscopicity, narrow grain size distribution. The process of layer-by-layer build-up of ingredients give an edge in formulation development allowing different active ingredients to be coated at different layers to tailor-made the release as well as to maximize the therapeutic benefits. [29-35]

Pelletizing by Spheronizing

This processing option is the eldest known industrial pelletizing technique. First all ingredients are blended, then by adding liquid a wet dough is formed, which is passed through an extruder with defined dye sizes. If a thick-wall extruder (approx. 4 mm) is used and the ratio liquid/solids is well adjusted the extrudates break up into 1mm particles during the beginning of spheronization, warranting a high yield of homogenously sized pellets. However, minimum particle size is limited to about 500µ. Despite a high reproducibility this is a somewhat tedious process as it involves many process steps, i.e. dry blending, wet massing, extrusion, spheronization, drying and involves different equipment with a large total product contacting surface [36-39]. The mentioned process led to development of spherical pellets from granulates (Fig. 8) or extruded products (Fig. 9). Needless to say that the surface of the produced pellets will be smooth; as the intensive rolling movement is involved in the production of the same. The uniform particle size allow for an equally uniform subsequent functional coating. In many pharmaceutical applications the uniform particle size is often only achieved if the formulation includes 20-50% of microcrystalline cellulose. [23-34]

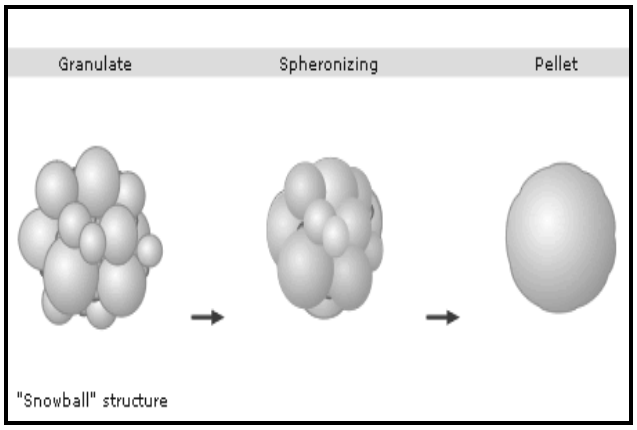

Fig. 8: Principle of the Granulate Spheronizing Process.

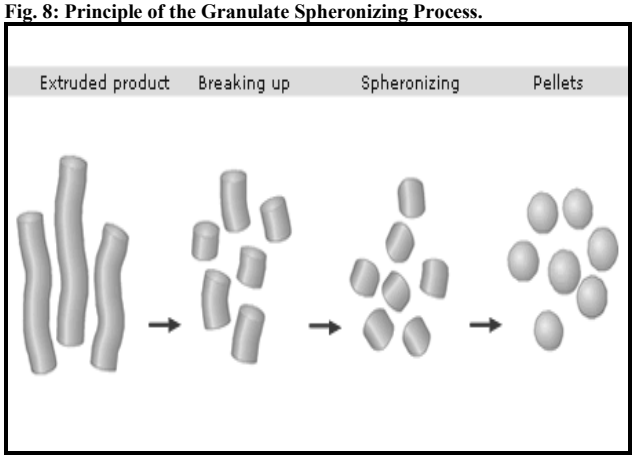

Fig. 9: Principle of the Extruded Product Spheronizing Process.

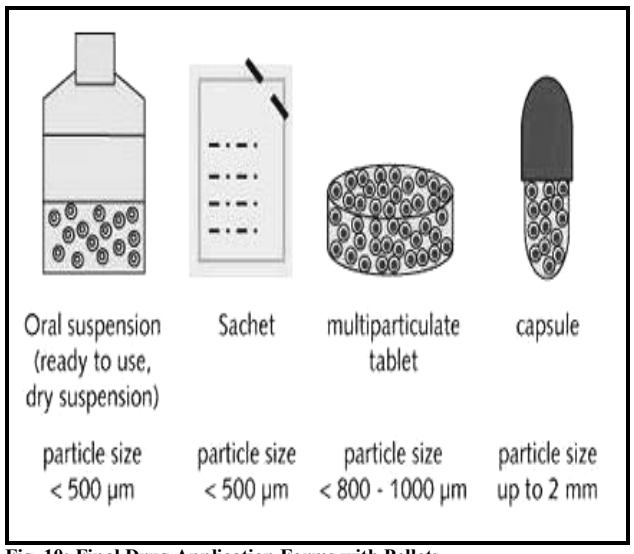

Fig. 10: Final Drug Application Forms with Pellets.

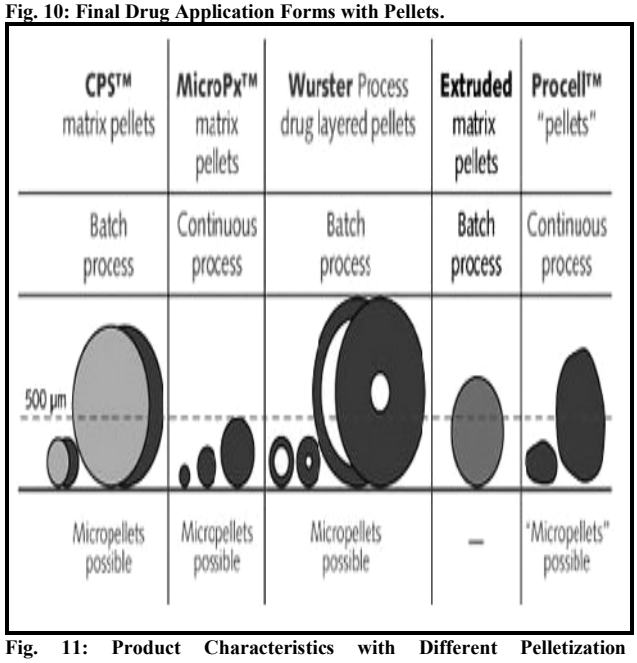

Fig. 11: Product Characteristics with Different Pelletization Technologies.

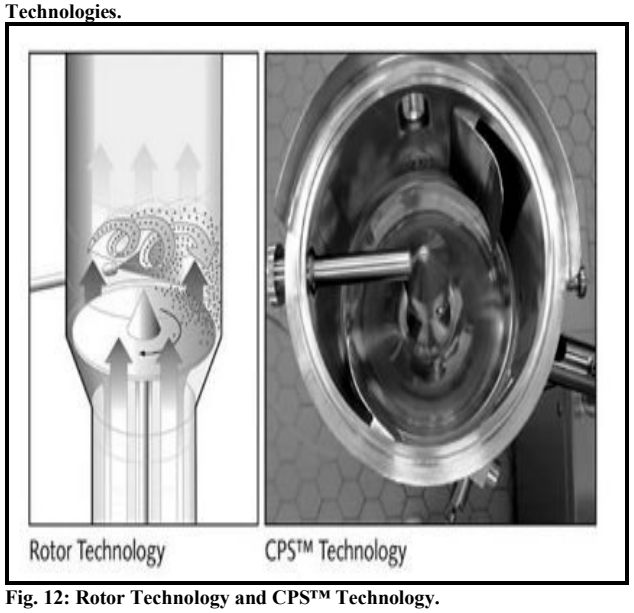

Fig. 12: Rotor Technology and CPS™ Technology.

A round pellet from moist granulates and extruded products will be having the properties of round and even shape for optimum dosability, ideal flow behaviour, compact structure, low hygroscopicity, high bulk density with dense surface and narrow grain size distribution with low abrasion.

INNOVATIVE TECHNOLOGIES

The well explained multiparticulate pellet units can be formulated to different drug application forms (Fig. 10); the most conventional form is the capsule. Pellets may further be compressed to tablets; after disintegration of the tablet in the stomach the pellets are set free acting as multiparticulates. Pellets having a particle size < 500 µm can be applied as oral suspensions without providing a sandy mouth feel. To achieve such small pellet sizes particular technologies providing micropellets are required (Fig. 11).

With classic fluid bed drug layering and coating technologies like the Wurster and the Rotor technology such pellet particle sizes are basically achievable taking into account that the Wurster process is limited to drug layering approaches; an optimized Rotor technology could lead to an even better performance than the existing one. [30-39]

In addition to said existing and established pelletizing technologies, some recent advanced and innovative technologies have been explored allowing new formulation options and product qualities. In particular, unique benefits and opportunities such as a small pellet size range of 100-500 µm, uniformity of particle size distribution, smooth particle surface, high density and high drug loading are achievable.

CPS™ Technology (Controlled Release Pelletizing Technology)

CPS™ Technology is a direct pelletization process resulting in matrix type pellets. Release characteristics of API from CPS™ pellets depend both on the pellet formulation and on the pelletizing process. The CPS™ technology is an advanced fluid bed rotor technology allowing the preparation of matrix pellets with particular properties in a batch process; extremely low dosed and high potent drug can be formulated to CPS™ matrix pellets as well as high dosed APIs; the drug concentration can vary from < 1% up to 90%. Due to its modifications compared to the established Rotor system the CPS™ Technology works with a conical shaped rotating disc and additional devices ensuring a directed particle movement (Fig. 12).

Inert starting beads are not required for the CPS™ Technology; typically, microcrystalline cellulose powder is used as a basic excipient; moreover, other functional excipients like polymers, disintegrants, solubilizers and the like can be part of the CPS™ formulations in combination with the API. The starting powder (blend) is wetted with the pelletizing liquid until a defined stage of moisture will have been achieved; at this time, spherical pellets begin to form (Fig. 13). The pelletizing liquid can be water and/or organic solvents which may also contain functional compounds. As an option, dry powder may be fed into the process. [23-24, 26-27, 30, 33, 35, 38-40]

With the help of torque measurement at the CPS™ rotor the endpoint of the pelletization can be defined. By means of a characteristic rolling particle movement and thereby the application of different forces, in particular of centrifugal forces on the arising pellet cores, a defined densification of the particles can be reached. Finally the pellets are dried in the CPS™ or in a classical fluid bed dryer configuration.

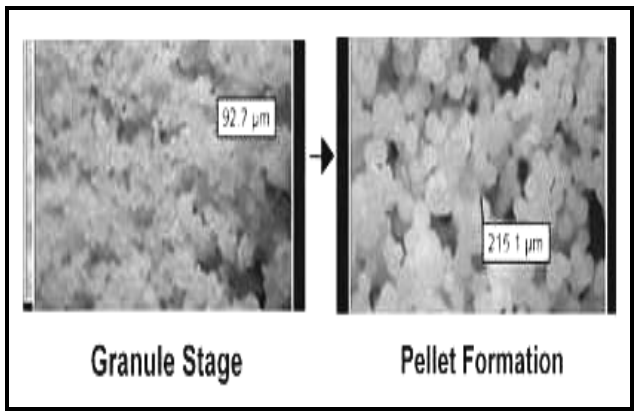

Fig. 13: CPS™ Pelletizing Process in Progress.

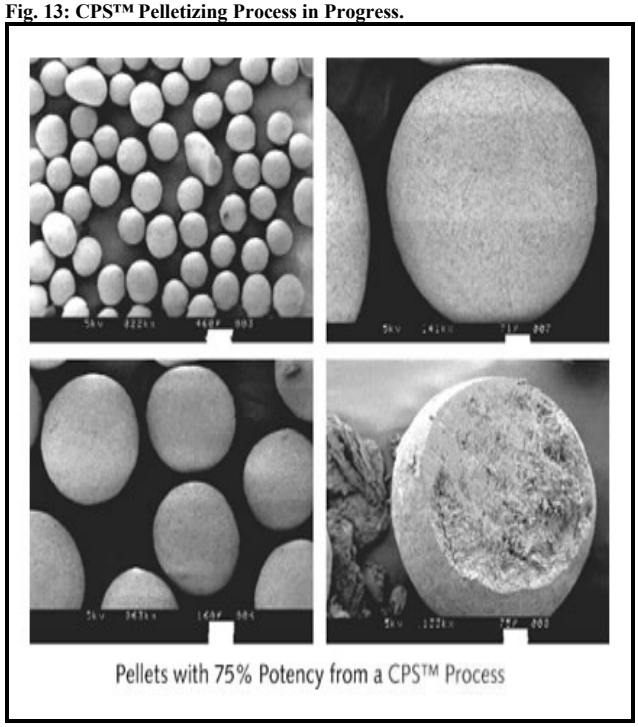

Fig. 14: CPS™ Matrix Pellets

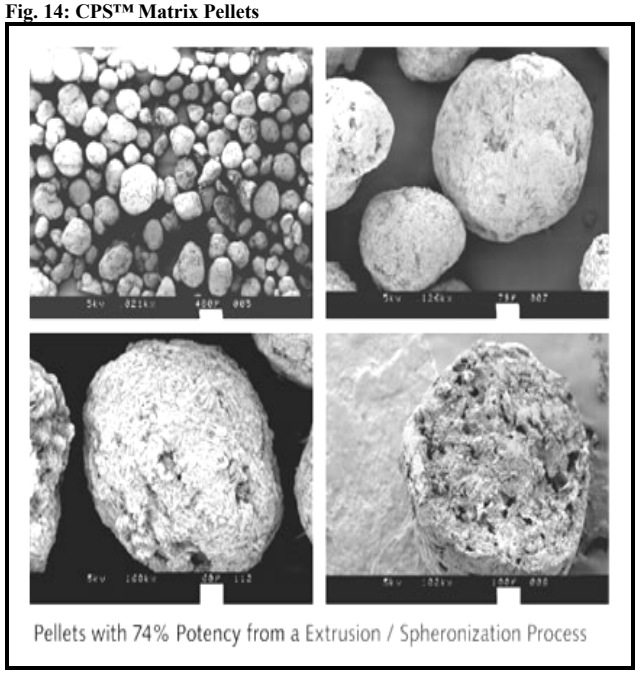

Fig. 15: Pellets from an Extrusion / Spheronization Process.

Fig. 14; shows the characteristics of CPS™ pellets containing 75% of an API in comparison with the same pellet formulation manufactured by extrusion (Fig. 15); the CPS™ pellets provide a higher density due to the particular spheronization process; their surface is smoother than the one of the extruded pellets and therefore provides ideal prerequisites for coating applications. Some specific and outstanding product characteristics of CPS™ pellets are as follows

- Spherical and smooth pellet surfaces which is best suited for coating applications
- High density / low porosity of pellets with low attrition and friability
- Broad potency range for APIs
- Dust free surfaces of the pellets having mean particle size range in between 100-1500 µm with narrow particle size distribution.
- Controlled drug release from the CPS matrix

MicroPx™ Technology

The MicroPx™ Technology is a fluid bed agglomeration process resulting in matrix type pellets. Particle size could be rather small, e.g. < 400 µm together with a high drug loading of typically 95% (Fig. 16). Functional pharmaceutical excipients, e.g. for bioavailability enhancement or controlled drug release can be integrated in the pellet matrix.

The MicroPx™ Technology is a continuous fluid bed process: again, for the pelletization, no starting cores are required. Typically, all formulation components like the API, pharmaceutical binder(s) and other functional ingredients are contained in a liquid which is fed into the MicroPx™ process via spray guns; the spraying liquid can be a solution, suspension, emulsion or the like. [24, 26-27, 30, 33, 37]

The design of the MicroPx™ technology is shown in Fig. 16; in the pilot and the commercial scale a rectangular shaped processing chamber provides an ideal product flow. The fluidizing air is led through a inlet air distribution plate into the processing area; by this means a directed air stream is provided allowing a directed product transport over the inlet air distribution plate towards the classifying unit. One or more spray guns are mounted in the air distribution plate. A set of cartridge filters will blow back dust into the processing area in a controlled manner. At the front of the processing chamber an on-line classification unit known as zig-zag sifter is mounted in order to continuously discharge well-sized product from the continuous process and in order to keep product still being too small in size in the process. By adjustment of the classification air flow the particle size of the "good" product which must be discharged from the process is defined. A number of channels, each of them having a number of edges, are used for the classification; a narrow particle size distribution is achieved. [21-22, 25, 27, 30, 33, 35-40]

The direct pelletization process starts with spraying the API containing liquid into the empty MicroPx™ fluid bed unit. Initially, powder is generated by spray drying; the powder is stepwise agglomerated to seeds. The online provided seeds are continuously layered with droplets from the bottom spray nozzles ending up in onion-like structured micropellets.

The process is characterized by a permanently balanced ratio of spray drying and layering of already existing seeds. Well-sized pellets are continuously discharged out of the process through a rotary valve after classification by the zig-zag

sifter. In order to allow spray drying besides the layering of existing pellets the product bed in the process must not be too high; this requirement is also true when the directed product flow towards the sifter should be put into effect.

Besides the classical fluid bed operating parameters such as inlet air volume, inlet air temperature, atomization air pressure and liquid feed rate the classification air volume defining the particle size of the discharged product is characteristic for the MicroPx™ process. As a certain degree of spray drying is an important requirement for the performance of the continuous pelletization process it is easily understandable that the product temperature is typically higher than in a Wurster layering or coating process where losses of product by spray drying must be absolutely avoided.

Here are some potential outstanding product characteristics of MicroPx™ pellets:

- Spherical and smooth pellet surfaces those are ideal for coating applications like taste masking controlled release coating etc.
- High density / low porosity of pellets with high drug loading: typically 95%
- Low attrition and friability with dust free surfaces.
- Mean particle size range: 100-500 µm with narrow particle size distribution.
- Inclusion of bioavailability enhancers, controlled release polymers etc.

Comparison of CPS™ Technology and MicroPx™ Technology

MicroPx™ technology is the most feasible technology when particles with drug loading > 90 % must be provided in a particle size range of 100-400µm; such small pellets are needed frequently for taste-masking applications but also for the compression of pellets into tablets.

CPS™ is also able to provide a similar particle size range, typically lower API loads are intended and reached; a regular API load range is from 1-75%. As the densification can be well controlled by the adjustment of the CPS™ processing parameters particularly by the form and speed of the rotating disc. The CPS™ matrix pellets are most appropriate for a modified drug release from the matrix. Any functional coating can in addition be applied onto the CPS™ matrix pellets in order to achieve a particular in vitro dissolution profile. Both processes are appropriate to provide high valuable pharmaceutical products with unique properties. [27-37]

ProCell™ Technology

The ProCell™ Technology is a spouted-bed type pelletizing process for the preparation of very high concentrated pellet-shaped particles; ideally, no additional excipients may be required for the formation of ProCell™ particles; in this case particles consisting of pure API are reached.

Particles are fluidized in the ProCell™ spouted bed by vertical process airflow: the process air enters the processing chamber through slots at the side and not through the usual bottom screen or inlet air distribution plate as in conventional fluid bed processing (Fig. 17). The cross section of the processing chamber becomes significantly broader towards the top, resulting in a sharp decrease of the fluidizing velocity of the process air. This effect provides a controlled flow pattern and circulation of the particles in the processing chamber. Spray nozzles are usually arranged in the bottom spray position; right in between the two inlet air slots; in this position they spray at the point of the highest energy input inside the unit. [19, 24, 27, 29-30, 32, 37, 39]

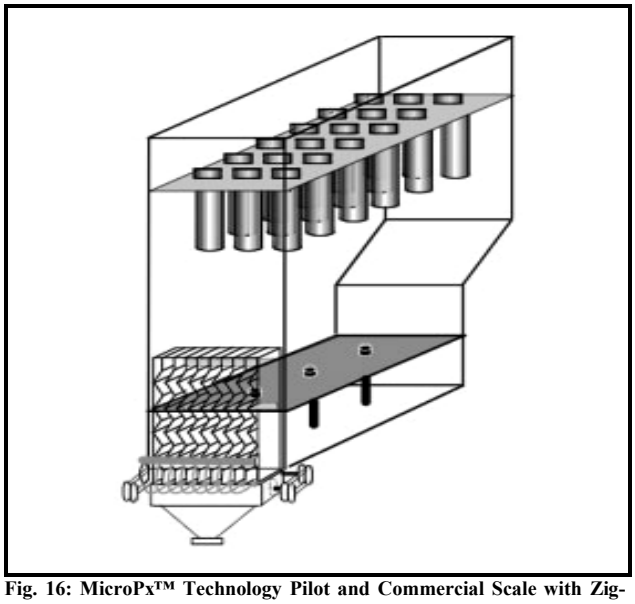

Fig. 16: MicroPx™ Technology Pilot and Commercial Scale with Zig-Zag-Sifter.

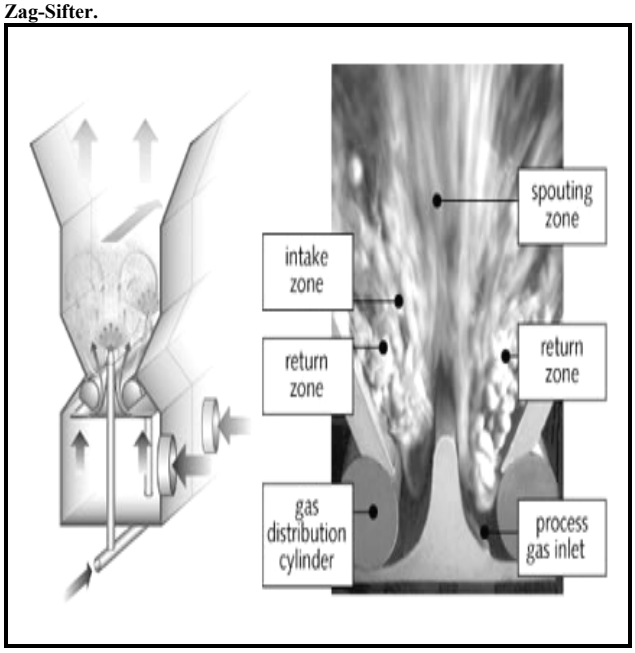

Fig. 17: ProCell™ Technology and Spouted Bed Fluidization Pattern.

The ProCell™ Technology is a direct granulation and pelletizing process: again like with the CPS™ and the MicroPx™ technology. No inert starting beads are required and either, solutions, suspensions, emulsions or the like, containing the API, can be processed. ProCell™ Technology performs in the most effective way when a melt of a material is processed, as in this case neither water nor organic solvents have to be evaporated; the formation of granules and pellets takes place by means of spray solidification and agglomeration. By this means, high through-puts and cost effective processes are possible. The continuously arising product quantities can be fractionated online by means of a zig-zag-sifter or offline by means of a sieving unit. In any case, separated material can be recirculated into the ongoing

process; product losses are minimized in this way. Specific product characteristics of ProCell™ granules and pellets are as follows

- High density / low porosity of particles with very high drug load up to 100%
- Mean particle size range from 50-1500 µm with optimum narrow particle size distribution
- Low attrition and friability justifying its suitability for processing of particular products with inherent stickiness

CRITERIA FOR PROCESS SELECTION

Selection of a suitable fluid-bed process for a particular granulation or coating application is based on several factors. Each process has its own advantages and disadvantages. Some of the criteria used to choose the right process for a given application include the following. [31-40]

Capacity Requirement

For an application that demands a large capacity, the top-spray process has an advantage over the tangential-spray and bottom-spray processes.

Physical Properties of Raw Materials

For granulation of a product that contains several ingredients with significant differences in bulk densities, the tangential-spray process can provide better mixing than can the top-spray process.

Finished Product Requirement

For a coating application that requires a high degree of reproducibility and high quality of film, such as a controlled-release dosage form, the bottom-spray process is advantageous.

Capital cost (if considering equipment purchase). The top-spray process is the simplest of the three methods. Thus, the equipment cost is lowest.

Productivity or Process Time

This factor depends on each application. The top-spray process offers the highest capacity. However, in top-spraying, it may take longer to achieve the target coating level because the coating material will be spray-dried to some degree. Hot-melt coating is a notable exception.

Coating or Loading Level

The bottom-spray process is a very effective way to produce substrate-layered pellets because of its high coating efficiency. The tangential-spray process is a good alternative to the bottom-spray process for high-dose loading applications.

Table I provides an overview of the three fluid-bed coating processes based on several properties. The table is organized into three groups: process, product, and economic considerations. For both process and economic considerations, the top-spray process is the most desirable. However, for product applications in which film quality, coating uniformity, and coaling efficiency are important, the bottom-spray and tangential-spray processes are more desirable than the top-spray process. [34, 37, 39-40]

In certain applications, one technique is favored over the other two methods. For example, the top-spray process generally is a good choice for hot-melt coating, and bottom-spraying generally is the method of choice for controlled-release coating. Tangential-spraying should be considered for producing pellets of high-dose actives.

Fluid-bed technology offers a wide range of applications for both granulation and coating. The three types of fluid bed processes (top-spray, bottom-spray and tangential-spray) all have unique features. Each method has its advantages and limitations depending on the application. An understanding of each fluid-bed process, the properties of raw materials, and finished product requirements will aid formulators in selecting the optimal process for a given applications.

Table 1: Comparison of the three Fluid bed Coating Processes (where 1 = Least Desirable and 3 = Most Desirable).

S. No.	Parameters	Fluid Bed Process		
		Top Spray	Bottom Spray	Tangential Spray
1.	**Process consideration**			
	Simplicity	3	2	1
	Nozzle access	3	1	2
	Scale-up issues	3	2	1
	Mechanical stress	3	2	1
2.	**Product considerations**			
	Surface morphology	1	3	3
	Coating uniformity	2	3	3
	Layering Efficiency	1	3	3
	Product coating capacity	2	3	3
3.	**Economic consideration**			
	Space requirement	2	1	3
	Equipment capacity	3	2	1
	Equipment cost	3	2	1

The innovative fluid bed pelletizing technologies; CPS™, MicroPx™, ProCell™, potentially complement the actual capabilities of existing fluid bed technology as an added advantage. New possibilities for drug product development are demonstrated using advanced fluid bed technologies leading towards better therapeutic benefits and financial outcomes. The new era of innovative fluid bed technologies has potential not only for line-extensions of new chemical entity development but also for the by-pass of existing specific patent landscape in the generic business. Utilizing all the available fluid bed process technologies different product qualities related with different product throughputs and manufacturing cost are realizable.

REFERENCES

1. Leuenberger H, Luy B, Struder J. New development in the control of a moist agglomeration and pelletization process. STP Pharma Sci. 1990; 6: 303-309.
2. Ylirussi J, Rasanen E, Rantanen J, Mannermaa JP. The characterization of Fluidization Behavior Using a Novel Multichamber Microscale Fluid Bed. J. Pharma Sci. 2004; 3: 780-791.
3. Vuppala MK, Parikh DM, Bhagat HR. Application of powder-layering technology and film coating for manufacture of sustained-release pellets using a rotary fluid bed processor. Drug Dev Ind Pharm. 1997; 23: 687-694.
4. www.chemicalonline.com; Accessed on 15.11.2010.
5. Gu L, Liew CV, Heng PW. Wet spheronization by rotary processing: a multistage single-pot process for producing spheroids. Drug Dev Ind Pharm. 2004; 30: 111-123.
6. www.engineering.uakron.edu; Accessed on 15.11.2010.
7. Banks M, Aulton ME. Fluidized bed granulation - A Chronology. Drug Dev Ind Pharm. 1991; 17: 1437-1463.
8. Kristensen J, Schaefer T, Kleinebudde P. Direct pelletization in a rotary processor controlled by torque measurements, I: influence of process variables. Pharm Dev Technol. 2000; 5: 247-256.
9. Kristensen J, Schaefer T, Kleinebudde P. Direct pelletization in a rotary processor controlled by torque measurement, II: effect of changes in the content of microcrystalline cellulose. AAPS Pharm Sci. Tech. 2000; 2: E24.
10. Aulton ME. "Pharmaceutics: The science of dosage form design", Edn 2, Churchill Livingstone, Edinburgh, 2002, pp. 373.
11. www.glatt.com; Accessed on 10.11.2010.

12. Kristensen J. Direct pelletization in a rotary processor controlled by torque measurements, III: investigation of microcrystalline cellulose and lactose grade. AAPS Pharm Sci Tech. 2005; 6: E495-E503.
13. Vertommen J, Kinget R. The influence of five selected processing and formulation variables on the particle size, particle size distribution, and friability of pellets produced in a rotary processor. Drug Dev Ind Pharm. 1997; 23: 39-46.
14. Ansel C, Allen LV, Popovich NG. "Pharmaceutical dosage form and Drug delivery system", Edn 8, B.I Publications, India, 2005, pp. 193, 243.
15. Swarbrick J, Boylan JC, "Fluid bed dryer, granulator and coaters", Encyclopedia of pharmaceutical technology, Volume- 6, Marcel Dekker INC, New York, 1992, pp. 171-173.
16. Watano S, Sato Y, Miyanami K, Murakami T, Oda N. Scale-up of agitation fluidized bed granulation. Part 1: preliminary experimental approach for optimization of process variables. Chem Pharm Bull (Tokyo). 1995; 43: 1212-1216.
17. Othomer DF. Fluidization: Background, History and Future of Fluid bed systems. Reinhold publishing corporation, New York. 1956; 102-115.
18. Holm P, Bonde M, Wigmore T. Pelletization by granulation in a roto-processor RP-2. Part 1: effects of process and product variables on granule growth. Pharm Technol Eur. 1996; 8: 22-36.
19. www.cjtech.co.kr; Accessed on 10.11.2010.
20. www.kurimoto.co.jp; Accessed on 10.11.2010.
21. Jager KF, Bauer KH. Effects of material motion on agglomeration in the rotary fluidized bed granulator. Drugs Made Ger. 1982; 25: 61-65.
22. www.bepex.com; Accessed on 10.11.2010.
23. Meshram R, Bajaj A. "Solid dispersion and enteric coating of pancreatin enzyme using fluidized bed coating and other techniques" Indian Drugs. 2005; 42(12): 792-796.
24. www.wurster.net; Accessed on 10.11.2010.
25. Vazquez ER. "Optimization of drying end point measurement for the automation of Fluidized bed dryer using FT-IR Spectroscopy" M.Sc Thesis, University of Puerto Rico , Mayaguez Campus, 2004.
26. www.fritzspecialty.com; Accessed on 10.11.2010.
27. Robinson RL, Hollenbeck RG. Manufacture of spherical acetaminophen pellets: comparison of rotary processing with multiple-step extrusion and spheronization. Pharm Technol. 1991; 15: 48-56.
28. www.kurimoto.co.jp; Accessed on 12.10.2010.
29. www.drytecheng.com; Accessed on 12.10.2010.
30. Petersen FJ, Worts O, Schaefer T, Sojka PE. Effervescent atomization of aqueous polymer solutions and dispersions. Pharm Dev Technol. 2001; 6: 201-210.
31. www.eliteboilers.com; Accessed on 12.10.2010.
32. Lachman L, Lieberman HA, Kanig JL, "Granulation" , The Theory and practice of industrial pharmacy, Edn 3, Verghese Publishing House, Bombay, 1991, pp. 58-59.
33. www.glattair.com; Accessed on 15.11.2010.
34. European Pharmacopeia. Strasbourg, France: Council of Europe; 2002.
35. www.niroinc.com; Accessed on 15.11.2010.
36. www.engr.pitt.edu; Accessed on 15.11.2010.
37. www.pharmaceutical-equipment.com; Accessed on 15.11.2010.
38. Turkoglu M, Hem, Sakr A. Evaluation of rotary fluidized-bed as wet granulation equipment. Eur J Pharm Biopharm. 1995; 41: 388-394.
39. www.equipnetindia.com; Accessed on 15.11.2010.
40. www.swensontechnology.com; Accessed on 15.11.2010.