Review Article

Recent Advances in Pelletization Techniques - A Review

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ABSTRACT

Pelletization technologies are efficient pathways for manufacture of oral multiparticulate drug delivery systems compared to single-unit systems in pharmaceutical industry for more than four decades due to their advent of modified release technology, biopharmaceutical advantages like free, more even, predictable dispersion and transportation in the GIT; flexibility for further modification; increased bioavailability of drugs; and hence gaining much attention in recent times. The present review outlines the recent advancements in pelletization techniques such as melt agglomeration, hot melt extrusion - spheronization, freeze pelletization, cryopelletization, CPS™, ProCell™, MicroPx™ fluid bed pelletizing technologies and minitablets.

Keywords: Pelletization Technologies, Modified Release Technology, Hot Melt Extrusion - Spheronization.

INTRODUCTION

Pellets, the multiparticulate drug delivery system has developed a keen interest amongst solid dosage forms to a great extent in the early 1950's in the pharmaceutical industry due to the magnitude of copious advantages offered by their spherical nature, divided on a plurality of sub-units, individual drug delivery device mechanism of each pellet, improved safety and efficacy of the active agent[1]. Smith Kline & French (SKF) in 1949, were the first to develop the potential sustained-release tiny drug pellets that could be loaded into capsules[2]. Pellets are various kinds of subunits with defined less-porous surface, spherical shape and low surface area to volume ratio, suitable for flexible and uniform drug-polymer coating. They offer numerous technological, physiological and therapeutic advantages like predictable distribution and transportation throughout the GIT; maximized drug absorption; less gastric irritation by limiting localized buildup and dose dumping; reduced peak plasma fluctuations and minimized potential side effects with improved drug bioavailability [3]; reduced inter and intra patient variability [4]; more suitable for fabrication of formulations with acid sensitive drugs [5] etc.

Various pelletization techniques include Agitation (Balling), Compaction (Compression and Extrusion/Spheronization), Layering (Powder and Solution/Suspension Layering) and Globulation (Spray drying and Spray Congealing). In recent decades, extensive research conducted to develop pelletization techniques leads in exploring newer techniques such as melt agglomeration, hot melt extrusion - spheronization, freeze pelletization, cryopelletization, CPS™ (Complex Perfect Spheres), ProCell™, MicroPx™ fluid bed pelletizing technologies and minitablets.

Melt Agglomeration AND Hot Melt Extrusion – Spheronization

The techniques *Melt agglomeration* and *Hot Melt Extrusion - Spheronization* find a great advantage to overcome the problems associated with the pellets produced by layering and extrusion-spheronization.

Melt agglomeration is a process where the solid fine particles undergo gradual change in size and shape that result in agglomerates with molten binding liquid that melts due to rise in temperature by heat of friction of the high shear mixer. The binder may be added as molten liquid or as dry powder or flakes and the binder may be heated by means of hot air or by heating jacket above its melting point. As the molten binder solidifies by cooling, dry agglomerates are formed. Melting points of the binders used in melt agglomeration ranges from 50°C to 80°C. Below this range, the binder softens and affects the product quality during manufacture and storage. The formation of agglomerates by this technique involves agitation, kneading and layering.

Hot melt extrusion is one of the most applied processing technologies in the array of plastic, rubber and food industries. It is classified as a molten system under control and semisolid viscous system. In pharmaceutical manufacturing, it is widely employed in the formulation of modified release dosage forms (eg. pellets, granules, tablets, transdermal implants, transmucosal drug delivery systems etc.) as it does not require additional film coating since the drug release is diffusion controlled [6-10]. It is also useful in many interesting aspects such as in-situ salt formation, fast dispersing systems with foam like structures, complex formation in the melt and nanoparticles released from molecular dispersions. It is a simple, efficient, solvent free technique that requires

fewer processing stages and does not require a lengthy drying stage. This technique finds a great advantage for continuous production of spherical shaped pellets with narrow range particle size distribution; drugs that show sign of degradation during processing and storage due to residual water; reduced loss of coating material during the coating process associated with wet mass extrusion process; preparation and delivery of poorly soluble drugs to solid dispersion and solid solution for improved dissolution rate and bioavailability; masking bitter taste of the active ingredient; incorporation of poorly compatible materials into tablets produced by cutting an extruded rod; uniform dispersion of fine particle; good stability at varying pH and moisture levels [11].

A hot melt extrusion – spheronization line consists of a *feed hopper, extruder with 3 distinct sections in the heating barrel - feed zone, transition zone, metering zone and spheronizer*. Extrusion is carried out in a rotating screw in the heating barrel preferably single screw extruder due to relatively low cost, credibility and ruggedness [12-13] (Figure 1 and 2). The process is similar to wet granulation, except that the binder is in molten state and does not require water or solvent to liquefy it. The process proceeds in 4 steps.

(a) Feeding into extruder and melting or plasticizing the solid material in which drug is dispersed in a thermal carrier usually a low melting point wax or polymers (starting from high molecular weight to low molecular weight polymers) eg. vinyl polymers (polyvinylpyrrolidone, polyvinylpyrrolidone-vinyl acetate); copovidone; polyethylene oxide; polyethylene glycol; acrylates; cellulose derivatives (carboxy methyl cellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate succinate, cellulose acetate, cellulose acetate phthalate); gelucire 50/13; poloxamer 188; carnauba wax; glyceryl stearate; microcrystalline wax; paraffin wax; stearic acid; stearic alcohol; bees wax; cetyl palmitate; guar gum; xanthan gum; sodium alginate; cyclodextins. Release mechanisms favored are (i) *diffusion mechanism* for formulations with water-insoluble polymers such as ethylcellulose or carnauba waxes (ii) *both by diffusion and erosion* with water-soluble polymers such as hydroxypropylcellulose.

(b) Conveying of mass, flow through the die and shaping of molten content into uniform cylindrical segments by extruder.

(c) Spheronization of extrudes at high temperature to deform by softening and assist uniform spheroids.

(d) Solidifying spheroids to get the desired shape spheroids, exit from the die and downstream processing. The endplate die connected to the end of barrel determines the shape of extruded products[14-16].

The factors that influence hot-melt extrusion and spheronization: *(a) Process Parameters:* barrel temperature, feed rate, screw speed, motor load, melt pressure, design of the extruder die and operating parameters of the extruder *(b) Product Parameters:* nature of extrudates selectively thermoplastic, composition of extrudates like drug and its melting point, physical and chemical properties of thermal carriers like drug polymer miscibility, polymer stability and function of final dosage form since they get transformed to molten state during the process at low temperature, porosity of the extrudes which influences drug release. In case of thermolabile constituents, incorporation of plasticizer brings down degradation and improves flexibility of the polymer components by reducing the tensile strength and glass transition temperature. Functional excipients such as release modifiers, bulking agents, processing agents also play a key role in formulations by hot melt extrusion[14, 17].

A few disadvantages are requirement of high energy input, handling and storage of the lower-melting-point binders, instability for heat-labile materials with higher-melting-point binders as it requires high melting temperatures.

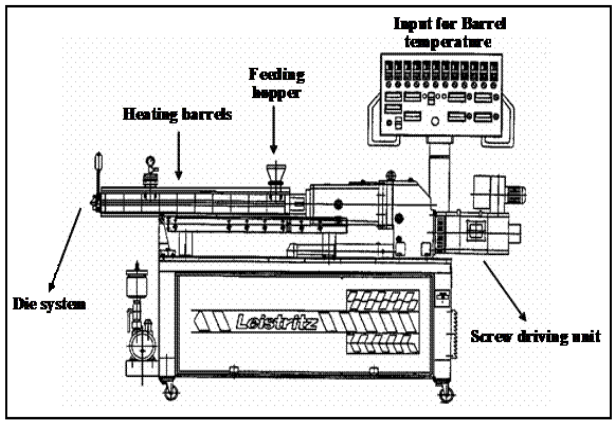

Figure 1: Micro-18 Twin Screw Co-Rotating Leistritz Extruder

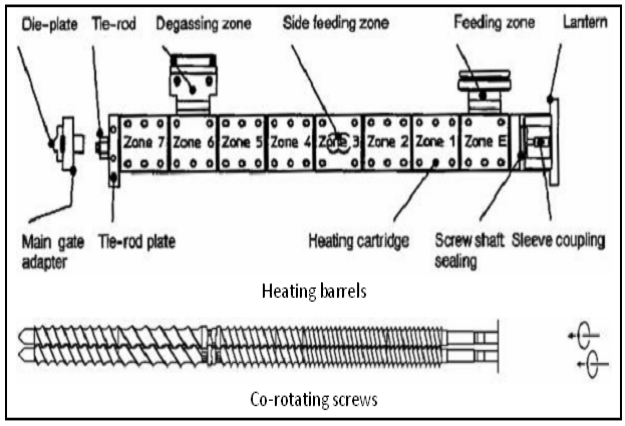

Figure 2: Heating barrels and Co-rotating screws for Hot-Melt Extruder

Freeze Pelletization

It is an advanced and a most simple technique for the production of spherical pellets by introducing droplets of immiscible molten solid carrier/ matrix containing additives like disintegrants, diluents, surfactants and release modifiers with or without drug into an inert liquid column. The droplets are introduced using needles or nozzles or atomizer into the inlet column of liquid and dropped from a certain height, so that droplets remain intact as they fall into the liquid column. The process can be scaled-up by increasing the number of nozzles (to several hundred) based on the desired rate of production and they can be static or vibrated electrically.

Size of needle gauge ranges from *16-31* depending on the size of the pellets desired. These droplets move either to the top or bottom of the column depending on their density with respect to liquid in the column [18].

Based on the movement of molten-solid droplets, two apparatus are designed. The former *Freeze pelletizer I,* with an inlet at the top for introducing droplets and these droplets settle at the bottom of the column as the density of the matrix droplet is more than the liquid column. *Freeze pelletizer II* is used when the carrier droplet density is less than the liquid column which has an inlet at the bottom and the droplets solidify at the top (Figure 3).

The column is *24 inches* long and made of borosilicate glass. It is divided into two portions; initial portion with a temperature of 25^0C *to* 100^0C, a region where the droplets are introduced. The second is cooling portion at which the droplets solidify and form spherical pellets; having a temperature 0^0C *to* -40^0C maintained using cooling mixture such as acetonitrile - dry ice or salt-ice.

The carriers used should be solid at room temperature and have melting point below 100°C in order to minimize degradation of the active constituent. The molten solid matrices may be *hydrophilic* or *hydrophobic.* For *freeze pelletizer I*, *hydrophilic carrier matrices* used are polyethylene glycol; polyvinyl alcohol; low melting point sugars like xylitol, dextrose, sorbitol, maltose; water soluble polyoxyethylene derivatives; polyethylene-propylene glycol copolymers; polyethylene oxide derivatives; PEG-PEO derivatives. For *freeze pelletizer II*, *hydrophobic solid carrier matrices* used are glyceryl monostearate; glyceryl palmitostearate; glyceryl dibehenate; ethylene glycol palmitostearate; cetostearyl alcohol; cetyl alcohol; stearyl alcohol; cholesterol; hydrogenated vegetable oils; phospholipids; lanolin; triglycerides; long chain fatty acids or hydrocarbons; hard fat; cocoa butter and waxes.

In case of hydrophilic carriers, hydrophobic liquid column and for hydrophobic carriers, hydrophilic column is used. For *freeze pelletizer I, hydrophobic liquid columns* used are low density oils such as silicone oils, mineral oils, vegetable oils, aliphatic long- chain hydrocarbons and for *freeze pelletizer II, hydrophilic columns* such as liquid polyethylene glycols with molecular weight 200-600, propylene glycol, glycerin, ethyl alcohol, water are used. These carriers are melted at a temperature 5-10°C higher than the melting point of the carrier solids. For sustained release pellets containing mixture of hydrophilic and hydrophobic solids, liquids that are immiscible with both hydrophilic and hydrophobic molten solids are used as cooling liquid in the column [18-20].

This technique involves less process variables and also offers several advantages like production of non-porous spherical pellets with narrow particle size range which are feasible for further coatings like delayed; colon targeted and sustained release coatings. Since the pellets are solid at room temperature, they do not require drying [18].

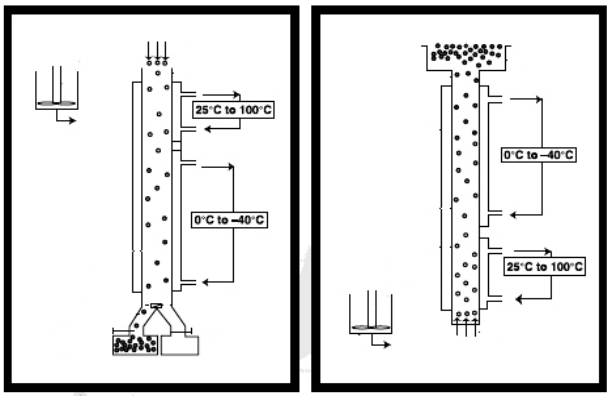

Figure 3: Freeze pelletizer I and II.

Cryopelletization

It is a technique by which freeze dried or lyophilized pellets are formed by solidifying the droplets of aqueous or organic solutions, suspensions or emulsions using liquid nitrogen as the fixing medium. The technology was initially developed for the nutrition industry to lyophilize viscous bacterial suspensions. It is also used to produce drug loaded pellets for immediate and controlled release formulations. The main advantage of this technique is production of highly porous pellets. The cryopelletizer is shown in Figure 4. The procedure permits instantaneous and uniform freezing of the processed material owing to rapid heat transfer that occurs between the droplets and liquid nitrogen.

The equipment consists of a container equipped with: perforated plates, a reservoir, conveyor belt with transport baffles and storage container. Below the perforated plate, a liquid nitrogen reservoir with a varying speed conveyor belt is present with transport baffles dipped in it. The perforated plates generate droplets that fall and freeze instantaneously as they come in contact with the liquid nitrogen (solidifying medium) below and by the residence time provided by the conveyor belt due to its varying speed. The frozen pellets are transported into a -60^0C storage container and dried in a freeze dryer to remove water or organic solvents [18, 21- 23].

Droplet formation is a critical step in cryopelletization. The factors that influence the size and shape of droplets

are: formulation variables, equipment design and process variables.

(a) Formulation Variables: *Viscosity* and *solid content* of the liquid formulation should be high enough and not exceed a critical limit which depends on the formulation. The *surface tension* of the liquid influences droplet formation and size; smaller droplet can reduce the surface tension by the use of surfactants.

(b) Equipment related Variables: The *distance between the perforated plate and the reservoir* is arranged in such a way that it allows the drops to become spherical before it comes in contact with liquid nitrogen. To achieve smaller size pellets, the *diameter of the perforation* in the perforated plate should be small.

(c) Process Variables: The *amount of liquid nitrogen* required for manufacturing a given quantity depends on the solid content and *temperature of the solution or suspension* being processed. The liquid nitrogen should be continuously stirred to prevent agglomeration, when it is desirable to have pellets with diameter less than 2 mm.

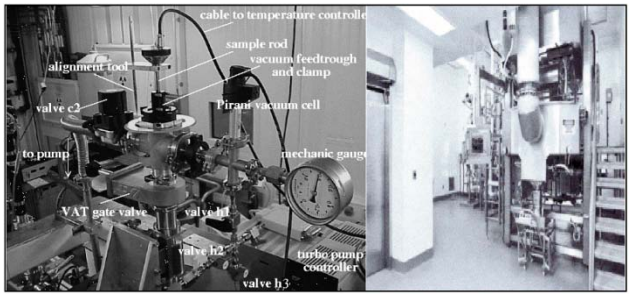

Figure 4: A) Cryopelletizer B) Cryogranulator used to form Technosphere Insulin Pellets prior to Lyophilization

CPS™ (Complex Perfect Spheres) Pelletizing Technology

In the year 2000, this technology was invented by *Glatt GmbH in Binzen, Germany*; an advanced fluid bed rotor and a direct pelletization technology for the production of matrix type pellets and micropellets. The process equipment consists of a *modified fluid bed rotor system* with a conical shaped rotating disc and additional devices for direct movement of particles. This is a *batch process* suitable for drug layering by drug solution, suspension, emulsion etc. on starter cores as well as dry powder layering to achieve a particular drug layer quality. The layering liquid can be aqueous or organic with or without functional compounds. As an option, dry powder may be fed into the process. In powder layering, the endpoint of the pelletization can be measured with the help of torque at the CPS™ rotor. Densification of the particles is achieved by means of a characteristic rolling movement of particles and thereby the application of different forces particularly centrifugal forces on the arising pellet cores by the form and speed of the rotating disc [24-27].

This process is suitable for drug dose ranging from low to high. It is ideal for functional coating and taste masking coating applications. The ideal features of pellets attained by this process includes spherical shape with mean particle size range: 100 - 1500 µm, narrow particle size distribution: > 90% between 700 - 900 µm, yield typically > 90 %; smooth surface- an ideal substrate for coating applications; drug loading from < 0.1% - 90%; low attrition and friability; high density and low porosity; dust free surfaces. The densification of particles is by means of rolling particle movement.

Figure 5: CPS™ pelletizing equipment- Lab scale and Production scale

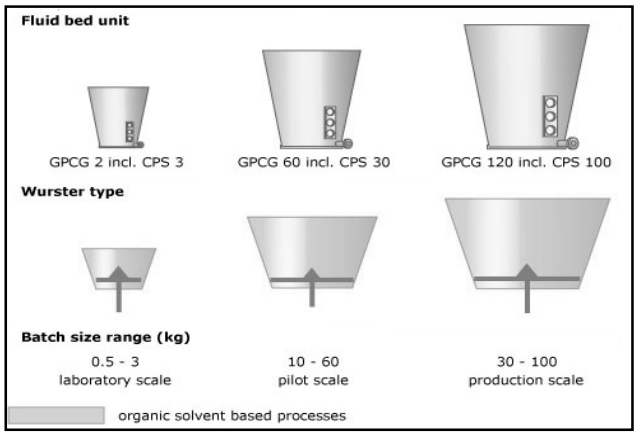

Figure 6: CPS™ pelletization Fluid Bed Capabilities

ProCell™ Technology

This is a *spouted-bed type continuous agglomeration technology* where particles are fluidized in the ProCell™ spouted bed by vertical airflow process. 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.

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; where in this position they spray at the point of the highest energy input inside the unit [25, 26, 28].

The ProCell™ Technology is a *direct granulation and pelletizing process*. No inert starting beads are required and solutions, suspensions or emulsions 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 so that product losses are minimized in this way.

It is used for the manufacture of very high concentrated, almost spherical pellets with high density and low porosity, resulting in matrix type granules and micropellets with low attrition and friability.

It is originally performed as hot-melt granulation process that provides an interesting and economic option without the need to evaporate water or organic solvents. Drug loading is upto 100% i.e., no additional excipients may be required for the formation of ProCell™ particles due to the design of the process chamber and its unique processing characteristics. The mean particle size range is adjustable over a broad size range from 50-1500 µm. The agglomeration process is in particular suitable for products with inherent stickiness.

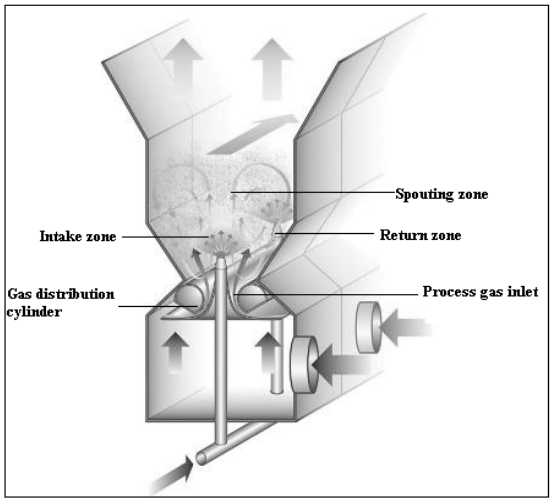

Figure 7: Equipment and process scheme of ProCell™ Technology

MicroPX™ Fluid Bed Technology

It is a *continuous fluid bed pelletizing technology* where aqueous-based liquids can be processed for this novel pelletization process – resulting in matrix type, onion-like micropellets by spray solidification and agglomeration. Glatt Pharmaceutical Services offers the Glatt MicroPx™ at both the lab and pilot scales at its center in *Binzen, Germany*. Throughput approximately for *Glatt Pharmalab is 0.5 – 1 kg/hr* and *MicroPx Pilot Plant in GPCG 60 basic unit is 2.0 – 10 kg/hr*.

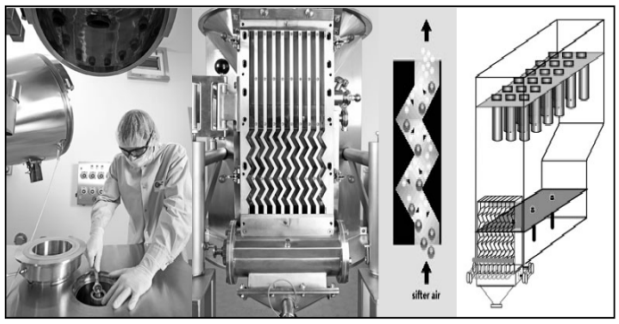

Figure 8: MicroPx™ fluid bed technology

This technology is most feasible for taste-masking applications; controlled release formulations; compression of pellets into tablets; production of spherical, smooth surfaced, high density-low porosity, high drug loaded particles (> 90%) with a particle size range of 100-500 µm with low attrition and friability. No starter cores are required. API, pharmaceutical binder(s) and other functional ingredients are contained in a spraying liquid (solution, suspension or emulsion) which is fed into the MicroPx™ process via spray guns. The process is a high-through put, cost effective process as the product losses are minimal due to the recirculation of the material into the ongoing process.

The design of the MicroPx™ technology is shown in Figure 8. The equipment consists of a rectangular shaped processing chamber, a konidur inlet air distribution plate, bottom spray guns, cartridge filters and on-line classification unit. Various parameters that influence fluid bed are inlet air volume, inlet air temperature, atomization air pressure and liquid feed rate. Processing chamber provides an ideal product flow and the fluidizing air is directed into it via an inlet air distribution plate. This process is characterized by a permanently balanced ratio of spray drying and layering of existing seeds. Spray guns may be one or more, mounted in the air distribution plate. The dust is blow back into the processing area in a controlled manner by a set of cartridge filters. An on-line classification (zig-zag sifter) is mounted in front of the processing chamber continuously discharge well-sized pellets out of the process through a rotary valve. The particle size of the discharged pellets depends on the adjustment of classification air flow. As a certain degree of spray drying of pellets is required when the product flows towards the sifter, this process is said to have a permanently balanced ratio of spray drying and layering

of existing seeds. Inorder to prevent excessive spray drying, the product bed must not be too high for easy and continuous performance of the pelletization process [25- 30].

Mini and microtablets

Nordmark Arzneimittek GmbH & Co. KG developed microtablets, a modern multiple unit dosage forms with diameter and height 2 mm X 2 mm by *compaction and compression*. High speed rotary tabletting machine is equipped with 10 - 19 multi-tip tabletting tools that produce 1 - 2 million microtablets per hour. This design offers flexibility to compress active drug with poor compression properties in large concentrations and high mass uniformity. These compressed core microtablets can be matrix forms or functionally coated to get the desired release profiles. One or more microtablet formulations containing different active ingredients can be filled into capsules at varying dosage strengths. Microtablets are supplied as stickpacks or filled into capsules. These formulations can be used in the therapies of pain relief, AIDS, oncology, hormones, pediatrics, etc. Various marketed formulations include Pancreatin Microtablets enteric coated with Kollicoat®MAE 30 DP (Nordmark), Omeprazole (Ratiopharm), Sodium Valproate (Desitin), Ferrous Sulfate (Teofarma) and Dimethylfumarate (Biogen).

The *Eurand minitabs*, a unique technology, contains tiny tablets that can be filled into capsules as a final dosage form. These tablets contain gel forming excipients that control drug release rate. Successive layers may be further coated to control the release rate. The main advantages of this technology are high drug loading with more accurate dosing and formulation of combination products with a wide range of release rate designs. The capsules can be opened and the contents used as a "sprinkle" formulation [31, 32].

CONCLUSION

Formulation design and development is the most promising and impending face of innovative pharmaceutical technologies in the current epoch for exploring newer formulations with high-quality. Recent and advanced pelletizing technologies like melt agglomeration, hot melt extrusion, freeze pelletization, cryopelletization, minitablets, CPS™, MicroPx™ and ProCell™ represent potential and efficient pathways not only in achieving better therapeutic and financial benefits but also product throughputs such as a small pellet size of < 500 µm, uniformity of particle size distribution, smooth particle surface, high density and high drug loading. In conclusion, these novel technologies due to their unique benefits, in particular are achieving a prominent role in new chemical entity and generic development.

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