ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 17, Issue 12, 2024

Online - 2455-3891
Print - 0974-2441

Review Article

REVIEW ON PELLETIZATION: DRY POWDER LAYERING OF PELLETS USING TANGENTIAL SPRAY ROTOR PROCESSOR/INSERT

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Received: 09 September 2024, Revised and Accepted: 16 October 2024

ABSTRACT

Pelletization turns fine powders or granules into small, round pellets for easy flow and handling. These pellets offer advantages such as improved absorption, modified drug release patterns and reduced irritation at application sites. Dry powder layering is gaining popularity in the pharmaceutical industry due to its cost and time efficiency. This method is an effective and straightforward process and can be alternative to liquid-based coating techniques. In recent years, active pharmaceutical ingredient layering onto multi-particulate core materials. One innovative pelletization method uses a rotor processor for powder layering. This process involves applying drug powder onto sugar spheres and spraying a binder solution to achieve uniform distribution and enhance drying efficiency. Compared to traditional methods, this dry powder layering is faster and more energy-efficient, reducing drying time and energy consumption. It is a streamlined and eco-friendly method as no solvent is required which makes it beneficial for pellet coating. This article provides insights on the powder layering technique with innovative fluid bed pelletizing technologies such as rotor processor, glatt powder coater granulator series, tangential spray in the rotary insert, complex perfect sphere insert, and glatt Procell series and their applications.

Keywords: Powder-layering, Glatt powder coater granulator, Rotor insert, Tangential fluid bed, Pellet layering.

 DOI: http://dx.doi.org/10.22159/ajpcr.2024v17i12.52611. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

In the 1950s, pellets as dosage form units emerged in pharmaceuticals, offering faster, cost-effective and efficient processing methods [1]. These small, spherical particles can be created by agglomerating fine powders or granules and can be used in tablet or capsule formulations [2]. Pellets are small, free-flowing granules used in pharmaceuticals, typically ranging from 500 to 2000 µm in size. They make oral medication easier to take and improve patient compliance [3,4]. They ensure consistent bioavailability and enhance drug absorption through a multiparticulate unit system [5]. These are prepared using various technologies such as layering with powder, solution, or suspension, extrusion spheronization, and agglomeration [6]. These methods create granules, pellets, or spheroids, collectively referred to as pelletization or spheronization. Advancements in polymer-based coating excipients, known as film coating, have enabled several benefits like enhancing ease of handling (smooth surface), improving appearance for better compliance, extending shelf-life by shielding from environment elements (moisture, oxygen and light), control drug release (sustained release), directing drug release to specific sites (enteric coating) [7,8]. Fluidized bed technology uses different methods such as top spray, bottom spray, Wurster, and rotor systems [9]. These methods vary based on the direction of spray and distribution of air/gas into the processing chamber [8]. They enable various processes such as granulation, pelletization, drying, coating, and layering can be carried out efficiently. In the layering process, inert spherical cores (starters or non-pareils) are used as a base. Active ingredients in aqueous or organic solutions (suspensions) or powder can be sprayed onto these cores until the formation of pellets of the desired size with optimized drug loading [10].

Common inert excipients include sugar (sucrose maximum of 92%), sucrose, microcrystalline cellulose (MCC, Cellets, Celphere), which are water insoluble and have high abrasion resistance, making them easy to coat [11,12], starch (Suglets, Nu-Pareil PG) [8,13,14], isomalt, anhydrous dibasic calcium phosphate, lactose, tartaric acid, or silicon-based materials and waxes can be used for layering [15,16]. It is found that the yield and some characteristics of resulting pellets are influenced by the original non-pareil properties such as solubility, hardness, and friability. Proportion of beads constitutes about 15–70% of the final product and more preferred range is 20–65% [16]. According to the U.S. Pharmacopeia guidelines, the size specification for pharmaceutical beads typically ranges from 0.5 mm to 1.5 mm. Generally, beads are passed through an 18-20 mesh sieve, although a 20-25 mesh sieve is preferred, with 25-35 mesh being the most desired. Fig. 1 depicts drug delivery platforms using pellets or micropellets [16,17].

The coating process is complicated, governed by several inconstant, making real-time quality monitoring vital for automated production [18]. In general, industrial processes rely on off-line assessment of critical quality attributes. This coating process endpoint is described as the amount of coating application and weight gain, which provides limited data on coating quality (thickness, uniformity, and density) and is inadequate for predicting and responsible for drug release behavior. Real-time process analysis technologies have been adopted to better monitor and control pharmaceutical operations [19]. The non-destructive, in-line measuring tools offer quick feedback, enabling immediate process adjustments, and more effective control of critical quality attributes of final products. Several PAT tools can be used for monitoring and ensure the high quality of coated solid dosage units. These include: (A) spectroscopic methods like near-infrared spectrum [20], raman spectroscopy [21], laser-induced breakdown spectroscopy (LIBS), (B) imaging methods like terahertz pulse imaging (TPI) [22], near-infrared imaging, magnetic resonance imaging, and (C). Microscopic methods such as confocal laser scanning microscope, atomic force microscope, and scanning electron microscope can be used [23-25].

ADVANTAGES AND DISADVANTAGES OF PELLETS

It has ideal shape for coatings due to low surface area, provides higher coating efficiency, and prevents dusting issues. It maintains the compatibility of different drugs, allows for controlled and sustained release of the active ingredient, improving therapeutic outcomes [26],

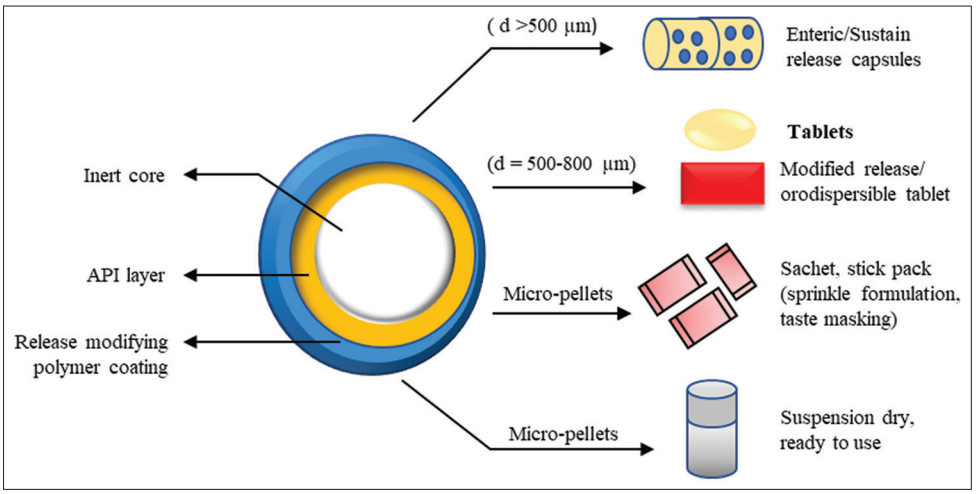

Fig. 1: Drug delivery platforms using pellets or micropellets

easy to adjust doses through combination of different pellets [27]. It protects sensitive drugs from environmental factors, improving shelf life [28]. It has uniform shape along a narrow particle size distribution to accelerate coating. These are distributed evenly in the digestive tract, leading to more consistent drug absorption and reduced risk of local irritation [3,7], minimize the chance of dose dumping liken to single-unit dosage forms. Its consistent size and shape lead to predictable and reproducible bioavailability due to larger surface area as considered to unit dosage forms [3,28]. Disadvantages such as pellet preparation need skilled staff and specialized equipment also time-consuming and quite complex process. Pellets are often rigid, posing challenges for compression into tablets and often requiring encapsulation which may add an additional step as capsule filling [3,26].

LAYERING TECHNIQUES

Layering technology involves applying active substances in layers as a solution, suspension, or powder onto neutral pellets that are at least 100 µm in size using a film coating technique. This process significantly increases the weight of the pellets, often by several 100%, resulting in dust-free, round pellets with a narrow particle size distribution. Dry powder layering can be faster and more efficient than using liquid active ingredients and can achieve weight applications of up to 300% per hour using the rotor process. Following are the properties of pellets produced through fluid bed active material layering such as large layer thicknesses, high active ingredient content, dense and compact structure, good flow behavior, round pellets, perfect for coating, and multi-layering for different active substances [29]. This layering technique is further of two types namely powder layering and solution/suspension layering [26,30].

Powder layering technique

Pelletization uses inert substrates like sugar spheres. A binder solution is sprayed on these spheres to enlarge them, and then active ingredient powder is added in a rotating pan or fluidized bed [31]. In the powder layering method, non-pareil seeds are placed in the rotor bed and tumbled for 5–10 min [32,33]. Then, the seeds are sprayed with a binder solution until they are moist [34]. Tangentially spray the binder solution at a controlled rate while adding the drug and excipient powder mixture [35,36]. Spray the solution until the desired amount of powder is applied. Then, dry the wet pellets [9,27,37]. The powder must be evenly spread onto the seed's surface during rolling to ensure a spherical shape [31].

Initially, drug particles attach to starter seeds and form pellets using liquid bridges created by sprayed liquid. These liquid bridges are later substitute by solid bridges with a binder or any soluble material, including the drug. The drug and binder solution is applied in layers until the pellets reach the desired size. Accurate powder delivery at a set rate must be balanced with the binder liquid application rate [38]. If this balance is not maintained, over-wetting may occur. Dry powder layering, faster and more efficient than liquid methods, achieves high-weight applications quickly, resulting in dense, compact pellets with excellent flow behavior, ideal for multi-layer coatings. The dust generation can occur, reducing product quality and yield. As no solvent drying is required, the powder layering process is faster [39,40]. They do not require solvents, using only a minimal amount of water emulsified with a liquid plasticizer as a binder to facilitate layering on beads [36]. Micronizing the drug before layering improves the efficiency of the layering process and produces smooth pellets that are absolute for film coating. However, micronization can negatively affect the flow, which is crucial for the delivery rate. To maximize the interactions between drug and inert cores a micronized powder, finer the powder, the higher the yield of pellets [41]. This can cause powders to stick to the hopper sides or feed screw and lead to rat holes in hopper. To enhance flow characteristics, glidant can be added to the powder before processing [42]. The rheological nature of the binding liquid, the liquid applying rate, and the drying temperature must be optimized to obtain the desired product temperature. Furthermore, the powder must be delivered at a rate that sustain a balance of the surface wetness of cores and powder adhesion rate [31,40,43]. Fig. 2 depicts drug layered to functionally coated pellets.

To enhance functionality, additional layers of polymers or other materials can be coated onto these pellets. These functional coatings have purposes such as taste masking, moisture protection, modified drug release such as enteric coating, or improve stability of pellets. Fig. 3 depicts fluid bed rotor dry powder layering technology [8,27,28].

Why consider dry powder layering

Dry powder layering can be preferred for pharmaceutical applications because many drugs are chemically unstable in solvents or water. In addition, other processes like Wurster drug layering can be time-consuming [44]. Dry powder layering offers a solvent-free environment, reducing the risk of chemical instability and speeding up the manufacturing process compared to traditional methods. This makes it a favorable choice for the efficient coating of pellets [45-48]. Fig. 4 depicts the new glatt powder feed concept spatial decoupling of fluid bed and powder transfer unit.

The new glatt powder feed concept separates the fluid bed for coating or drying from the powder transfer unit in pharmaceutical manufacturing. This separation improves efficiency by allowing independent control of airflow, and temperature for each unit, optimizing coating, and drying processes without disrupting powder feeding. This innovation reduces downtime, streamlines operations, and boosts productivity in pharmaceutical production.

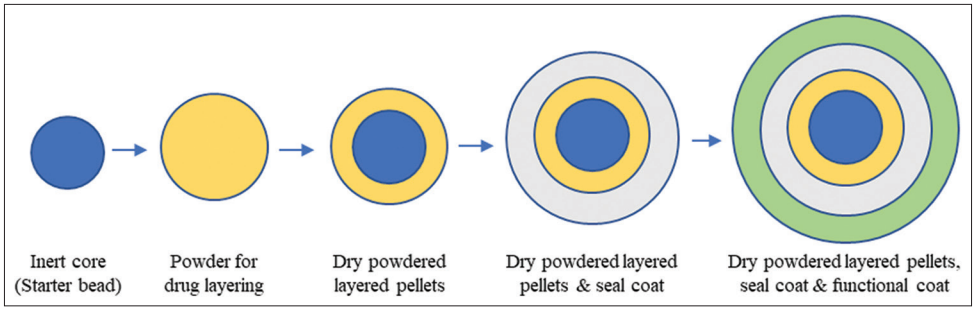

Fig. 2: Drug-layered to functionally coated pellets

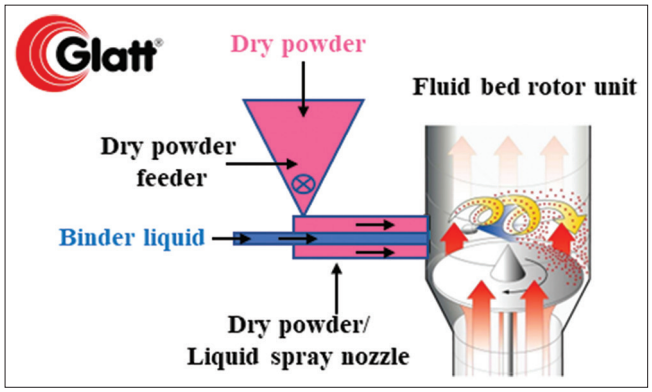

Fig. 3: Fluid bed rotor dry powder layering technology

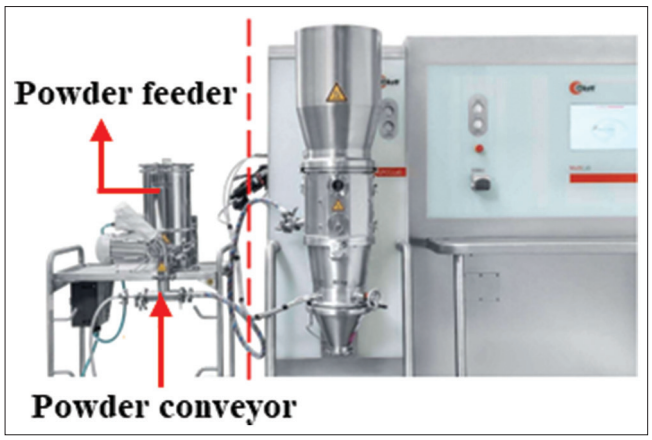

Fig. 4: New glatt powder feed concept spatial decoupling of fluid bed and powder transfer unit

Advantages of powder layering

It is faster and better for moisture- and heat-sensitive actives compared to aqueous or solvent coating but requires careful balancing of powder and binder spraying rate. This method ensures a uniform coating compared to separate additions. It optimizes process conditions, increasing pellet density, and preventing powder loss and agglomeration. After layering, pellets are often coated with film-forming polymers to mask taste, protect from moisture, and modify drug release [49]. If the drug and polymer are incompatible, a seal coat with rapidly dissolving polymers can be done to ensure compatibility and smooth coating for optimal drug release [27].

Solution or suspension layering technique

The solution or suspension layering, the powder and materials are mixed with a solvent and then applied to the pellets. A mixture is sprayed onto a starter core, forming a uniform coating. As the solvent evaporates, the coating material crystallizes, creating solid connections between the core and the layered drug substances or polymers [8]. This process creates a consistent and strong coating on pellets, enhancing both control over how the drug is released and the overall stability of the coating [31,36,50,51].

INTRODUCTION ROTOR TECHNOLOGY

Researchers and process engineers have significantly advanced alternative technologies to apply high active pharmaceutical ingredient (API) loading or functional coatings, reducing coating solvents and processing times. The rotor coater or rotor processor is a new innovative process designed to enhance efficiency and performance [52]. Its distinctive design enables applications in dry powder coating, spherical granulation, and solution or suspension coating. Over the years, the rotor technology has evolved from a flat design to a conical rotor to provide better product movement for efficient coating and simultaneous drying. The rotor processor handles each step from dry API coating and solution coating to drying, all in one unit. In general, there is a sugar sphere needed to transfer products between different equipment for each step. Overall processing time has been significantly reduced, leading to increased productivity. The rotor processor includes a stationary chamber with a rotatable conical rotor or disc in which particles are circulated for coating or powder layering. The rotor's outer edge is very close to the chamber's inner wall. The gap or slits supplies airflow at a specific temperature. An expansion chamber provides housing for drying airflow ducts for moving products inside the rotor chamber [53]. Glatt powder coater granulator (GPCG) has a three-way air-atomizing nozzle where it can operate the dry powder, liquid, and atomizing air simultaneously. The nozzle tip diameter can be changed. This adjusts the spray's velocity and turning the screw will change the spray's width. Fig. 5 depicts fluid bed rotor dry powder layering with combined with liquid/powder feed nozzle [54].

Fluid bed rotor dry powder layering combines a fluid bed processor with a rotor mechanism to apply coatings using liquid or powder feed nozzles [55-57]. This method offers precise control over coating thickness and uniformity, improving product quality. It reduces processing time and energy use through efficient drying. The rotor ensures even coating distribution, enhancing adhesion, and coverage. This technology is valued for improving the overall performance of the coating of pellets [58]. It utilizes a fluidized bed where particles are suspended and coated with layers of dry powder. This process allows for controlled coating thickness and uniform distribution of active ingredients or coatings onto particles. Scaling up ensures efficient production by maintaining consistent process parameters such as airflow, temperature, and powder feed rates. It optimizes coating efficiency and product quality while meeting larger production demands in pharmaceutical [59]. The simplified rotor bed installation includes a new powdered nozzle concept with pneumatic transfer for efficient powder conveying through pipelines [60]. This design spatially decouples the rotor from the fluidization chamber, improving system performance and flexibility [61]. It eliminates the need for a lifting column for powder feeding and features explosion prevention with shock-resistant powder feeding lines up to 12 bar pressure. This streamlined system offers easier cleaning, lower investment costs,

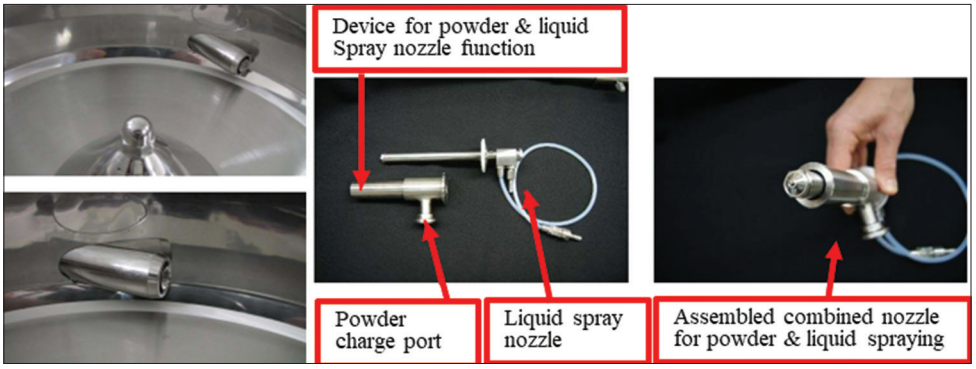

Fig. 5: Fluid bed rotor dry powder layering: combined with liquid/powder feed nozzle

Table 1: Patents with rotor processor/dry powder for pellet coating

Patent number	Patent title	Work	Filing year	References
US005508276A	Duloxetine enteric pellets (produced in fluidized bed equipment (using a rotary processor) or rotating plate equipment)	Drug layering of MCC/sucrose beads, separating layer by HPMC-AS-LF for enteric release by protecting the drug from gastric acid and ensuring it releases in the intestines.	April 16-1996	[101]
US2013/0040066A1	Method for applying a powder coating	Application of two different powder coating layers to a substrate involves the function of a first powder coating layer followed by the function of a second powder coating layer.	Feb 14-2013	[102]
AU2012203203B2	Polymer films for medical devices	Exposing to a solvent causes problem in the device, deposit a coating includes a polymer and an impermeable dispersion of solid onto a substrate (coating by using e-RESS, e-SEDS, or e-DPC methods).	May 30-2012	[103]
USOO5411745A	Powdered layered morphine sulfate formulation	Drug layering on hydrous lactose inert beads for IR release of drug.	May 25-1994	[104]
US2010.0034968A1	Polymer coating process using dry glidant in a rotor processor	Coating or layering with methacrylates (Eudragit polymers) helps prevent agglomeration, ensuring uniform dispersion and stability of the coated material.	Feb 11-2010	[105]

modular components and scalability across industries. It adheres to good automated manufacturing practice (GAMP) guidelines, includes FDA CFR 21 Part 11-compliant electronic records and ensures safety with atmospheres explosible (ATEX-certified solutions) for hazardous areas.

Following mentioned are the equipment's provided by glatt group which can be used for powder layering and various other pelletization processes.

Glatt powder coater granulator (GPCG/GPCGPRO) series

It is a circular single-chamber fluid bed system used for versatile processes such as drying, spray agglomeration, film coating, layering [62], and pelletizing within one plant unit. This system offers high flexibility, ensuring uniformly shaped products with consistent quality. It is meant for continuous operation and ensures the GPCG with a double chamber filter system, allowing uninterrupted processing [63]. It supports multiple insert options such as high-speed Wurster (bottom spray), rotor (tangential spray), CPS inserts, and more [64-68]. The spraying can be adapted for top, bottom, or tangential applications, catering to various fluid bed processes [17,69]. Various batch sizes range from 5 to 1,500 kg, with custom sizes available to meet specific production needs [67,70]. Fig. 6a depicts fluid bed granulator and coater GPCG 300 at the glatt technology center in Weimar, Germany [70].

Glatt procell® Labsystem

It has six versatile modular systems that support fluid bed, spouted bed, and rotor processes. This can perform spray granulation, microencapsulation, spray agglomeration, film coating, hot melt coating, and powder layering. These systems can be operated in continuous or batch modes with top spray, bottom spray, tangential spray, and Wurster process [71]. Fig. 6b depicts mobile glatt fluid bed/spouted bed laboratory unit ProCell® LabSystem at the glatt technology center in Weimar, Germany, with six modular all-rounder systems [41,72,73].

Tangential spray in the rotary insert and complex perfect sphere (CPS) technology

The product container has cylindrical walls, a solid spinning disc, adjustable height, speed, and an immersed nozzle. Definite importance should be placed on the production of pellets by direct pelletization and various processes such as solutions or suspension layering and powder layering, with a higher content of active pharmaceutical ingredients is achievable, particle with narrow size distribution, high bulk density can be obtained [30,74-82]. Fig. 6c and d depict tangential spray in rotor insert (Glatt) [54,83]. The process inserts are ideal for producing pellets by direct pelletizing and various types of powder layering. Rotor process inserts with the tangential nozzle is installed directly in the product bed [84,85]. The adaptable air gap of the rotor allows the proper airflow to be selected at any time. The flexible rotor processor allows the coating of different APIs in separate layers to ensure chemical compatibility. This technology makes IR pellets, MR pellets, granules, or multiple particles with a lot of active ingredients quickly and efficiently. This can achieve up to 500% weight gain and product yields of over 95% with high bulk density. The overall processing time is significantly reduced, and productivity is enhanced by minimizing the need for storage during intermediate stages [53].

Fig. 6: (a) Fluid bed granulator and coater GPCG 300 at the glatt technology center in Weimar, Germany (b). Mobile glatt fluid bed/spouted bed laboratory unit ProCell® LabSystem at the glatt technology center in Weimar, Germany, with six modular all-rounder system (c and d). Tangential spray in rotor insert (Glatt)

ADVANTAGES OF ROTOR-BASED POWDER LAYERING

The rotational movement ensures even distribution of the powder onto the cores, which results in uniform coating thickness and is used for consistent drug delivery characteristics. It is scalable and suitable for both laboratory-scale and industrial-scale production, accommodating varying batch sizes as required [86]. The operators can control parameters such as rotation speed, powder flow rate, and application time to tailor the coating process according to specific formulation requirements [87]. This technique can be used for various applications including modified-release formulations, taste masking, and improving drug stability of drugs. It combines mixing, granulation, and coating into a single operation using a conical rotor apparatus. This approach is valued for its efficiency, providing precise control over particle size, coating uniformity, and overall product quality in a streamlined process. It reduces time, less materials (solvents), leading to lower inventory, and higher active content simply, it enhances efficiency and productivity. It provides higher yields than other granulators and coaters, allows precise control over process parameters and product movement for uniformity, flowability, and density and enables multiple actives in the same beads for an "all in one processing" unit [17,79].

CRITICAL PROCESS PARAMETER (CPP'S) AND IMPACT

The batch size and amount of core beads determine the quantity of material processed and affect the uniformity of the coating. Larger batches may require more precise control to maintain coating quality [27,88-90]. The speed of rotor (rpm) influences the mixing and distribution of the coating material. Too high or too low speed can cause uneven coating or agglomeration of pellets, also low speed affects mixing of liquid and the material [8,9]. Particle size and surface area affect pellet fluidization pattern and velocity and can affect the thickness of the coating. Compared to smaller or lighter pellets, larger or heavier pellets produce a thicker film and release at a slower rate due to their longer residence time in the spray zone [8]. Air flow rate and temperature through the slit affect the drying efficiency and uniformity of the coating; proper control prevents defects such as the peeling or cracking of pellets [91]. Drying air speed, drying time (min), bed temperature, and temperature of product (inlet and outlet air temperature) (°C) influence the efficiency and speed of the drying process, affecting the final product pellets quality [87]. Binder to powder addition rate ratio is crucial for achieving a balanced and effective coating [92]. The improper ratios can lead to weak adhesion or excessive buildup of layering onto pellets [93,94]. Furthermore, it can lead to loss of drug through the exhaust system and sticking on the drying chamber wall like a cake [95]. Spray rate of binder (g/min) determines the amount of binder applied, affecting the coating's adhesion and uniformity of pellets. An appropriate spray rate ensures a consistent and well-adhered coating on the pellets [66,96]. Angle of powder application (spraying nozzle) affects the distribution and coverage of the coating material on the pellets [21,96,97]. Percent (%) yield after processing indicates the efficiency and effectiveness of the coating process, with higher yields indicating better performance of pellets [76,98-100].

CRITICAL QUALITY ATTRIBUTES (CQA'S) AND IMPACT

The particle size distribution (PSD) <100 mm is very cohesive and may lead to agglomeration and uneven coating. It affects drug release and

Table 2: Case studies powder layering technique

Sr. no	Drug and excipients	Rationale and method used to formulate pellets	Results	References
1	Piroxicam as model drug, sugar, avicel PHP101:lactose (5:1), Polyvinyl pyrrolidone 10 w/w %, HMC 8 w/w%, Eudragit L30, L100, NE30D, acryl-eze, Triethyl citrate/ Polyethylene glycol 6000, 5% Glyceryl monostearate	To minimize GIT adverse effects of drug and evaluate effects of enteric coating using and powder layering technique to meet USP28 criteria.	TEC compared to enteric suspension is superior to PEG in related to drug release in acidic medium. Eudragit NE30D is highly adhesive, results in spray nozzle clogging, and is time-consuming, making it not recommended. The PL process can continue until the desired particle size is reached. The enteric polymer coating layers showed an average drug loading of 90.4±4.7%, better sphericity, a mean pellet 80% yield, and coating times of 1 h for the drug layer and 20 min for the enteric polymer. This technique is efficient, rapid, and easy to clean.	[106]
2	Satranidazole as the model drug, locust bean gum: xanthan gum (LBG: XG), locust bean gum: chitosan gum (LBG: CG), PVP K30, Isopropyl alcohol	To evaluate and optimize amount of combination of natural polysaccharides by response surface design to meet colonic release by powder layered pellets.	The coating formulation showed locust bean gum xanthan gum mixture in 2:1 (20%) is effective for colonic release. LBG and XG can be the most efficient polymer to control the release property in that an increased quantity of xanthan gum affects the discharge rate of drug by reducing the amount of locust bean gum. The effective way for optimizing the pellet as alternate to conventional formulations may be response surface method.	[107]
3	Azithromycin as model drug, Eudragit RL30D, L30-55 (1:4 w/w), avicel CL-611, PVP K90, Triethyl citrate	To evaluate dual effect of pH dependent polymer for taste masking and enhance absorption of drug by dry suspension layering method using (Glatt GPCG1, Germany)	The coated pellets with Eudragit RL30D, Eudragit L30-55 (1:4 w/w) avoid drug release in oral for 1h, showed promise for taste masking and completely released in 0.1 M HCl.	[62]
4	Indomethacin as model drug, sugar, avicel PH 101, L-HPC, lactose (1:1:1), Eudragit NE30D, opadry, sodium dodecyl sulfate, talc, PVP K30, Polyethylene glycol 400/8000	To formulate and *in-vitro* characterization of enteric coated pellets using centrifugation (rotary fluid bed granulation) or powder layering technique to reduce GIT and CNS disturbances produced by drug.	PL method is chosen because of the difficulty in managing the drug powder with 1–3 μm in size and attractive features of the powder layering technology.	[41]
5	Fenofibrate as model drug, Eudragit RS PO/E100, Eudragit RS PO/RL PO, Eudragit NE30D/HPMC, and EC/HPMC), aerosil 200, sucrose/starch non-pareil seeds, HPMC as binder solution	To improve the oral bioavailability of drug by using powder layering technique of the modified-release formulation and Compare with commercial sustained release and Immediate release pellets.	The powder laying process is stable and reproducible, producing homogeneous products having a 90% layering efficiency, 70% drug loading with 0.6 g/mL bulk density of and has spherical shape of drug-loaded cores.	[64]
6	Theophylline as model drug, methocel E15LV, HPC-L as binder Eudragit RS/RL100, TEC, castor oil as plasticizer	To evaluate and compare pellets by both suspension and powder layering using a bottom spray coater and tangential rotary granulator.	The binder level if increases lead to lower porosity and a smoother pellet surface. The rotary granulator's tumbling and colliding motion produced pellets with higher density, lower porosity, and smoother surfaces compared to those made with a bottom spray coater. Reduced void spaces of the drug layer, decreasing pellet porosity and pore size are observed by higher binder concentrations. The solid particles from a concentrated solution are tightly bound to starting seeds resulted in smoother pellet surfaces. In the rotary granulator, pellets roll in a spiral fashion under centrifugal, fluidizing air, and gravitational forces, leading to higher density, lower porosity, and smoother surfaces compared to bottom spray coater pellets. At lower binder concentration leads to little rapid initial dissolution. Higher levels of Eudragit coating increased drug release from powder-layered pellets compared to suspension-layered pellets. The suspension layering process leads to hydration and transforms the theophylline anhydrous to hydrate form, reducing dissolution time.	[65]

(Contd...)

Table 2: ***(Continued)***

Sr. no	Drug and excipients	Rationale and method used to formulate pellets	Results	References
7	Lansoprazole model drug, aqueous acrylic enteric system (Acryl-EZE 93F19255), sugar spheres, 3% L-HPC as binder, sucrose, corn starch as filler	To evaluate the performance of drug (acid labile) by powdered layered technology (PLT) and aqueous enteric coting of pellets.	The dry PLT can be used to prepare more stable pellets of acid labile drug. Acryl-EZE 93F19255 offers enteric protection in acidic conditions (pH 0.1N HCl) and pH 4.5 while allowing for immediate drug release in phosphate buffer (pH 6.8).	[85,108]
8	Ketoprofen as model drug, sustain release polymer ethyl cellulose, enteric polymer shellac (1:3 ratio with 6 w/w%), sugar spheres, talc, aerosil 200	Development of HGC for extended release pellets using powder layering technique in a rotary centrifugal granulator and study the effect both polymers.	By using shellac, it decreased the release of drug in acidic medium to minimize the localized side effect. The release properties with 3% w/w ethyl cellulose and 7% w/w shellac coating showed minimize release up to 10 h in acidic condition.	[95]

bioavailability by influencing the surface area and dissolution rate of drug [8]. Bulk density influences flow properties, dosage uniformity, and ensuring accurate dosing during manufacturing process [8]. Particles having smooth surface are chosen over an irregular surface. The irregular surface can increase surface area and the coating solution captured in the pores cannot function as a release barrier. The favored particle shape is spherical with a 1:1 aspect ratio. The cubic or plate-like shaped drug substances that likely to compact easily are selected substrates for drug layering and needle-like shape drug substances are undesirable. It affects coating uniformity and drug release by ensuring even application and predictable release profiles of drug [8,42]. Residual solvent concentration, content uniformity, and drug release from coated pellets determine efficacy and patient compliance by controlling the release rate of the drug and ensuring it meets therapeutic needs [99]. To produce successful powder layered pellets, factors should be considered like balancing the powder and binder application rates. The drug assay, content uniformity, and drug release properties are essential quality attributes that must be closely monitored to ensure the coating process is effective and the product meets quality standards. In addition, coating thickness and uniformity are important because they directly impact these quality attributes [23,99].

CHALLENGES ENCOUNTERING THE PROCESS AND WAYS TO OVERCOME THEM

1. When the binder spray rate is higher compared to the powder addition rate, the bed becomes overly wet, leading to agglomeration issues. To improve layering efficiency and prevent pellet agglomeration, the ratio between binder spray rate and powder addition rate is crucial to optimize. The binder spray rate must be adjusted based on the surface area of the pellets to ensure even distribution without causing excessive wetness of the product.
2. In a fluid bed dryer, although fluidization is efficient, uneven coating distribution can occur due to blind spots. In the case of the rotor-processor's rotating disk and upward air forces create vigorous agitation that eliminates these blind spots, resulting in even drug layering and uniform coating of the product.
3. To control drug or excipient dissolution on a coating surface, adjust the inlet air temperature and spray rate. Applying a seal coat prevents drug migration into the sustaining coat and protects drug-layered pellets from drug loss during cleaning and migration into the functional membrane.
4. Consistent coating thickness is important for reliable drug release, which may be influenced by the pellet's surface area. Therefore, using uniform-sized pellets reduces coating variability. The porous drug-layered pellets improve drug migration into the coating due to their larger surface area.
5. The high rotor speeds cause pellets to slide rather than rotate in a rope-like motion when the binder is added, leading to uneven binder distribution and pellet clumping while low speeds result in uneven binder distribution. Hence, optimum speed should be carried during the process.

A LIST OF PATENTS RELATED TO ROTOR PROCESSOR/DRY POWDER FOR PELLET COATING

Following Table 1 contains a list of patents related to rotor processors and dry powder technique for pellet coating

SOME RECENT CASE STUDIES ON POWDER LAYERING TECHNIQUE

The researcher has explored this technology, and the following Table 2 data provides a summary of powder layering.

CONCLUSION

Pelletization with dry powder layering using a rotor offers a high-yield, efficient method for drug delivery. It provides faster and simpler coating compared to traditional methods, ensuring uniform powder distribution and high binder efficiency. This dry method creates dense, compact pellets with excellent flow, suitable for multi-layer coatings, and is faster and more efficient than liquid coating. The GPCG system features a versatile three-way air-atomizing nozzle, capable of handling dry powder, liquid, and atomizing air simultaneously, allowing for precise adjustments in spray velocity and width. The rotor-based pelletization process, with adjustable airflow and direct nozzle insertion, enables efficient production of high-density pellets and granules with up to 500% weight gain and yield over 95%, while eliminating intermediate transfers and storage. The rotational movement ensures uniform coating, precise control over parameters, and efficient, scalable production, enhancing productivity and product quality.

ACKNOWLEDGMENT

The authors express gratitude to glatt system private limited (GSPL, India) for supporting and guiding for publication of this article.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Ritik Ramdhani: Writing – original draft, Data dissemination and graphics, Formal Analysis, Methodology, Validation. Purnima Amin: Supervision, Investigation, Writing – review and editing, Validation, Conceptualization, Methodology, and Suraj Bhatt: Supervision, Investigation, Writing – review and editing.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Patel HP, Patel JK, Patel PR, Patel MP. Pellets: A general overview. Int J Curr Res Rev. 2010 Jun 6;2(20):21-31.
2. Khambat SB, Kale AS. A Review extended release oral drug delivery system and Multiparticulate Drug Delivery Systems (MDDS). Int J Sci Res Sci Technol. 2020 Feb 5;7:84-92.
3. Srinivasarao K, Jyothirmai KS, Rao NR. Pellets and pelletization techniques: A review. Int J Res Pharm Chem. 2017;7(2):141-7.

4. Hirjau M, Nicoara AC, Hirjau V, Lupuleasa D. Pelletization techniques used in pharmaceutical fields. Pract Farm. 2011;4(3-4):206-11.
5. Chen T, Li J, Chen T, Sun CC, Zheng Y. Tablets of multi-unit pellet system for controlled drug delivery. J Control Release. 2017;262:222-31. doi: 10.1016/j.jconrel.2017.07.043, PMID: 28774838
6. Korakianiti ES, Rekkas DM, Dallas PP, Choulis NH. Optimization of the pelletization process in a fluid-bed rotor granulator using experimental design. AAPS PharmSciTech. 2000;1(4):71-5. doi: 10.1208/pt010435
7. Kumari MH, Samatha K, Balaji A, Uma Shankar MS. Recent novel advancements in pellet formulation: A review. Int J Pharm Sci Res. 2013;4(10):3803-22.
8. Teng Y, Qiu Z. Fluid bed coating and granulation for CR delivery. In: Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice. United States: Wiley; 2010. p. 115-27.
9. 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(7):687-94. doi: 10.3109/03639049709150770
10. Deb R, Ahmed AB. Pellets and pelletization techniques: A critical review. Int Res J Pharm. 2016;4(4):90-5. doi: 10.7897/2230-8407.04414
11. Mohylyuk V, Styliari ID, Novykov D, Pikett R, Dattani R. Assessment of the effect of Cellets' particle size on the flow in a Wurster fluid-bed coater via powder rheology. J Drug Deliv Sci Technol. 2019;54:101320. doi: 10.1016/j.jddst.2019.101320
12. Nguyen TT, Anton N, Vandamme TF. Oral pellets loaded with nanoemulsions. In: Nanostructures for Oral Medicine. Amsterdam: Elsevier Inc.; 2017. p. 203-30.
13. Muley S, Nandgude T, Poddar S. Extrusion-spheronization a promising pelletization technique: In-depth review. Asian J Pharm Sci. 2016;11(6):684-99. doi: 10.1016/j.ajps.2016.08.001
14. Gryczová E, Rabišková M, Vetchý D, Krejčová K. Pellet starters in layering technique using concentrated drug solution. Drug Dev Ind Pharm. 2008 Dec;34(12):1381-7. doi: 10.1080/03639040802130046, PMID: 18618309
15. Zakowiecki D, Szczepanska M, Hess T, Cal K, Mikolaszek B, Paszkowska J, *et al*. Preparation of delayed-release multiparticulate formulations of diclofenac sodium and evaluation of their dissolution characteristics using biorelevant dissolution methods. J Drug Deliv Sci Technol. 2020;60:101986. doi: 10.1016/j.jddst.2020.101986
16. Kállai-Szabó N, Lengyel M, Farkas D, Barna ÁT, Fleck C, Basa B, *et al*. Review on starter pellets: Inert and functional cores. Pharmaceutics. 2022;14(6):1299. doi: 10.3390/pharmaceutics14061299, PMID: 35745872
17. Majeed SM, Al-Shaheen MK, Al-Zidan RN, Mahmood SM. Multiple Unite Pellet Systems (MUPS) as drug delivery model. J Drug Deliv Ther. 2020;10(6):231-5. doi: 10.22270/jddt.v10i6.4389
18. Možina M, Tomaževič D, Leben S, Pernuš F, Likar B. Digital imaging as a process analytical technology tool for fluid-bed pellet coating process. Eur J Pharm Sci. 2010 Sep 11;41(1):156-62. doi: 10.1016/j.ejps.2010.06.001, PMID: 20541010
19. Naidu VR, Deshpande RS, Syed MR, Wakte PS. Real-time imaging as an emerging process analytical technology tool for monitoring of fluid bed coating process. Pharm Dev Technol. 2018 Jul 3;23(6):596-601. doi: 10.1080/10837450.2017.1287730, PMID: 28121263
20. Avalle P, Pollitt MJ, Bradley K, Cooper B, Pearce G, Djemai A, *et al*. Development of Process Analytical Technology (PAT) methods for controlled release pellet coating. Eur J Pharm Biopharm. 2014;87(2):244-51. doi: 10.1016/j.ejpb.2014.01.008, PMID: 24503256
21. Behzadi SS, Toegel S, Viernstein H. Innovations in coating technology. Recent Pat Drug Deliv Formul. 2008;2(3):209-30. doi: 10.2174/187221108786241633, PMID: 19075909
22. Porter SC. Coating of Pharmaceutical Dosage Forms. Netherland: Elsevier; 2020. p. 551-64.
23. Feng H, Mohan S. Application of process analytical technology for pharmaceutical coating: Challenges, pitfalls, and trends. AAPS PharmSciTech. 2020;21(5):179. doi: 10.1208/s12249-020-01727-8, PMID: 32596747
24. Korasa K, Vrečer F. Overview of PAT process analysers applicable in monitoring of film coating unit operations for manufacturing of solid oral dosage forms. Eur J Pharm Sci. 2018;111:278-92. doi: 10.1016/j.ejps.2017.10.010, PMID: 29020609.
25. Knop K, Kleinebudde P. PAT-tools for process control in pharmaceutical film coating applications. Int J Pharm. 2013;457(2):527-36. doi: 10.1016/j.ijpharm.2013.01.062, PMID: 23380626
26. Ranjitha KS, Ganesh NS, Megha J, Chandy V. A study on pellets, pelletization techniques and its evaluation parameters-a review. World J Pharm Pharm Sci. 2021;10:850-63.
27. Afsana KGA, Ariful IK. Formulation and evaluation of domperidone pellets prepared by powder layering technology. Asian J Pharm. 2010;4:41-7.
28. Gaur PK, Mishra S, Bhardwaj S, Kumar SS, Bajpai M, Verma A, *et al*. Recent developments for oral time controlled drug delivery by pelletization techniques: An overview. Int J Pharmcol Pharm Sci. 2015 Jul 21;1(4):283-95.
29. Glatt Process Technologies Food, Feed and Fine Chemicals. Layering of Active Substances for Food, Feed and Fine Chemicals. Glatt Technologies Food, Feed and Fine Chemicals; 2022 Sep 21.
30. Sirisha VR, Vijaya Sri K, Suresh K, Reddy GK, Devanna N. A review of pellets and pelletization process-a multiparticulate drug delivery system. Int J Pharm Sci Res. 2013;4(6):2145-58.
31. Pundlikrao Ige P, Patil N, Khadse SC, Ige PP. Review on novel granulation techniques. World J Pharm Res. 2016;5:1-6.
32. Singh SK, Durrani MJ, Karnachi AA, Khan MA. Optimization and characterization of controlled release pellets coated with an experimental latex: I. Anionic drug. Int J Pharm. 1995;125(2):243-55. doi: 10.1016/0378-5173(95)00135-6
33. Bathool A, Vishakante GD, Khan MS, Gupta VK. Pelletization as a key tool for oral drug delivery: A review. J Pharm Res. 2011;4(10):3282-6.
34. Park ES, Lee DS, Kwon SY, Chi SC. A new formulation of controlled release amitriptyline pellets and its *in vivo*/*in vitro* assessments. Arch Pharm Res. 2003;26(7):569-74. doi: 10.1007/BF02976883, PMID: 12934651
35. Yadav N, Verma A. Pharmaceutical pellets: A versatile carrier for oral controlled delivery of drugs. Indian J Pharm Educ Res. 2016;50(3s):S146-60. doi: 10.5530/ijper.50.3.27
36. Shelke TT, Aher UD, Patel EP. Recently used technologies in Pellet Formulation-A Review. PharmTutor. 2017;5(7):22-30.
37. Patel NV, Patel JK, Shah SH, Patel JN. Central composite design for the formulation and optimization of a multi-unit potential colonic drug delivery system of budesonide for ulcerative colitis. Pharmazie. 2011 Mar;66(2):124-9. PMID: 21434575
38. 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(7):687-94.
39. Nastruzzi C, Cortesi R, Esposito E, Genovesi A, Spadoni A, Vecchio C, *et al*. Influence of formulation and process parameters on pellet production by powder layering technique. AAPS PharmSciTech, 2000;1(2):14-25.
40. Cerea M, Foppoli A, Maroni A, Palugan L, Zema L, Sangalli ME. Dry coating of soft gelatin capsules with HPMCAS. Drug Dev Ind Pharm. 2008 Nov;34(11):1196-200. doi: 10.1080/03639040801974360, PMID: 18720149
41. Kovacevic J, Mladenovic A, Djuris J, Ibric S. Evaluation of powder, solution and suspension layering for the preparation of enteric coated pellets. Eur J Pharm Sci. 2016 Mar 31;85:84-93. doi: 10.1016/j.ejps.2016.01.018, PMID: 26796145
42. Eskandari S, Varshosaz J, Akhavanfarid G, Hafizi G. Formulation and *in-vitro* characterization of extended release pellets of indomethacin using powder-layering technique. Res Pharm Sci. 2009;2(2):67-75.
43. Heinicke G, Matthews F, Schwartz JB. The effects of substrate size, surface area, and density on coat thickness of multi-particulate dosage forms. Pharm Dev Technol. 2005;10(1):85-96. doi: 10.1081/pdt-49670, PMID: 15776816
44. Engels S. Dry Polymer Layering Using a Rotor Processor (Patent No. US20100034967A1). U.S.; 2010.
45. Pundlikrao Ige P, Patil N, Khadse SC, Ige PP. Review on novel granulation techniques. World J Pharm Res. 2016;5:1-6.
46. Scoggins M, Sidwell R, Crawford R. Innovative Reformulation of a Complex, High-Drug-Load, Modified Release Dosage Form with Reduced Dosing Frequency. Pennsylvania: Clinical Leader; 2021.
47. Vaphare AM, Banerjee DSK, Gadhave MV, Gaikwad DD. Pelletalization Techniques: A Review. Asian J Pharm Res Dev 2014;2(3):103-114.
48. Zaman M, Saeed-Ul-Hassan S, Sarfraz RM, Batool N, Qureshi MJ, Akram MA, *et al*. Pellets and pelletization: Emerging trends in the pharma industry. Acta Pol Pharm Drug Res 2016;73:1415-25.
49. Tomuta I, Leucuta SE. Use of experimental design for identifying the most important formulation and technological variables in pelletization by powder layering. J Drug Deliv Sci Technol. 2004;14(3):215-21. doi: 10.1016/S1773-2247(04)50103-X
50. Kandukuri JM, Allenki V, Eaga CM, Keshetty V, Jannu KK. Pelletization techniques for oral drug delivery. Int J Pharm Sci Drug Res. 2009;1(2):63-70.
51. Taylor D. Feasibility of Taste-masking a Highly Soluble Drug Via

Powder Layering with Fine Particle Ethyl Cellulose. In: AAPS Annual Meeting. USA: American Association of Plastic Surgeons; 2015.
52. Meenakshi B, Harsha S. Multiple unit particulate system: Pelletization techniques: An overview. Int J Pharm Erudition. 2012;2(2):28-39.
53. Kovacevic J, Ibric S, Djuris J, Kleinebudde P. Application of the design of experiments in optimization of drug layering of pellets with an insight into drug polymer interactions. Int J Pharm. 2016 Jun 15;506(1-2):312-9. doi: 10.1016/j.ijpharm.2016.04.030, PMID: 27094356
54. Kristensen J, Hansen VW. Wet granulation in rotary processor and fluid bed: Comparison of granule and tablet properties. AAPS PharmSciTech. 2006;7(1):E153-62. doi: 10.1208/pt070122, PMID: 28290037
55. Winkler M. Rotor Technology for Dry Powder Coating. Israel: Freund Publishing House Ltd.; 2022 Jun 17.
56. Faculty of Pharmacy, Division of Pharmaceutical Chemistry and Technology, Discipline of Industrial Pharmacy, Astra Zeneca. Dry Powder Layering of High Viscosity Polymers Using A Fluidized Bed Rotor Granulator. Helsinki: University of Helsinki; 2014.
57. Cerea M, Nespoli S, Del Curto MD, Foppoli A, Maroni A, Gazzaniga A. Design and preparation of zero-order prolonged release systems based on hydrophilic polymers obtained with a non-uniform drug distribution. AAPS J. 2012:1.
58. Gauthier P, Cardot JM, Beyssac E, Aiache JM. Study of the influence of coating methods on lipid spheres manufactured on rotor fluidized bed process. Pharm Dev Technol. 2018;23(6):655-62. doi: 10.1080/10837450.2017.1356331, PMID: 28714756
59. Sauer D, Cerea M, Dinunzio J, McGinity J. Dry powder coating of pharmaceuticals: A review. Int J Pharm 2013;457:488-502.
60. Smikalla M, Mescher A, Walzel P, Urbanetz NA. Impact of excipients on coating efficiency in dry powder coating. Int J Pharm. 2011 Feb 28;405(1-2):122-31. doi: 10.1016/j.ijpharm.2010.12.001, PMID: 21145382.
61. Kablitz CD, Harder K, Urbanetz NA. Dry coating in a rotary fluid bed. Eur J Pharm Sci. 2006 Feb;27(2-3):212-9. doi: 10.1016/j.ejps.2005.10.001, PMID: 16290285
62. Foppoli AA, Maroni A, Cerea M, Zema L, Gazzaniga A. Dry coating of solid dosage forms: An overview of processes and applications. Drug Dev Ind Pharm. 2017;43(12):1919-31. doi: 10.1080/03639045.2017.1355923, PMID: 28707494
63. Ahtola M. Dry Powder Layering of High Viscosity Polymers Using a Fluidized Bed Rotor Granulator. Master's thesis; 2014.
64. Chen Y, Liu Y, Wu C, Pan X, Peng T. Dry suspension containing coated pellets with pH-dependent drug release behavior for the taste-masking of azithromycin. AAPS PharmSciTech. 2022;24(1):21. doi: 10.1208/s12249-022-02484-6, PMID: 36526883
65. Menendez CJ. A Novel Approach for the Manufacturing of Extended Release [Pellets Doctoral Dissertation]. Ohiolink Electronic Theses and Dissertations Center, University of Cincinnati; 2003.
66. Li F, Zheng X, Bao Y, Chen T, Zeng J, Xu X, *et al*. Fenofibrate modified-release pellets with lag phase and high oral bioavailability. Drug Des Dev Ther. 2019;13:141-51. doi: 10.2147/DDDT.S179266, PMID: 30613135
67. Sinchaipanid N, Chitropas P, Mitrevej A. Influences of layering on theophylline pellet characteristics. Pharm Dev Technol. 2004;9(2):163-70. doi: 10.1081/pdt-120030246, PMID: 15202575
68. Yamamoto K, Shao Z. Process Development, Optimization, and Scale-up. Netherlands: Elsevier; 2017. p. 77-792.
69. Missaghi S, Young C, Fegely K, Rajabi-Siahboomi AR. Delayed release film coating applications on oral solid dosage forms of proton pump inhibitors: Case studies. Drug Dev Ind Pharm. 2010 Jan 21;36(2):180-9. doi: 10.3109/03639040903468811, PMID: 20070183
70. Jones DM, Rajabi-Siahboomi AR. Fluid bed technology, process robustness, and scale-up. In: Multiparticulate Drug Delivery: Formulation, Processing and Manufacturing. Cham: Springer; 2017. p. 65-93.
71. Robert, Pisek O, Planinsek M, Tus S, Srčič. Influence of rotational speed and surface of rotating disc on pellets produced by direct rotor pelletization. Pharm Ind. 2000;62(4):312-9.
72. Laboratory Systems in the Glatt Technology Center Weimar. Lab Scale for Calcination, Drying, Granulation, Microencapsulation, Coating. Glatt Technologies Food, Feed and Fine Chemicals; 2022 Dec 14.
73. Glatt Process Technologies Food, Feed and Fine Chemicals. Designs and Series of Fluid Bed and Spouted Bed Systems. Glatt Technologies Food, Feed and Fine Chemicals; 2022 Sep 23.
74. Tsotsas E, Mujumdar AS. Modern Drying Technology, Product Quality and Formulation. Vol. 3. United States: Wiley; 2011.
75. Pulgamwar GV. Fluid bed technology: A review. Int J Pharm Res Biosci. 2015;4:89-110.
76. Foppoli A, Cerea M, Palugan L, Zema L, Melocchi A, Maroni A, *et al*. Evaluation of powder-layering vs. spray-coating techniques in the manufacturing of a swellable/erodible pulsatile delivery system. Drug Dev Ind Pharm. 2020;46(8):1230-7. doi: 10.1080/03639045.2020.1788060, PMID: 32597251
77. Wargo DJ. Near-Infrared Analysis and Process Control of Pharmaceutical Pelletization Processes. United States: Duquesne University; 2009.
78. Langner M, Zhou B, Priese F, Wolf B. Statistical investigation of rotary fluidized bed agglomeration process with tangential spray and in-line particle size measurement for PAT process control. Processes. 2023 Apr 1;11(4):1066. doi: 10.3390/pr11041066
79. Srivastava S, Mishra G. Fluid bed technology: Overview and parameters for process selection. Int J Pharm Sci Drug Res. 2010;2(4):236-46.
80. Suhrenbrock L, Radtke G, Knop K, Kleinebudde P. Pellet layering: Scale-up considerations using different kinds of processing equipment. Drug Dev Ind Pharm. 2012 Dec;38(12):1494-503. doi: 10.3109/03639045.2011.653815, PMID: 22452570
81. Pollinger-Tieg C. Development and Investigation of Propranolol HCl Pellets Coated with Poly (Vinyl Acetate) Based Polymer Films for Sustained Release Applications [PhD dissertation]. Halle: Martin Luther University Halle-Wittenberg; 2012.
82. Bhairy SR, Habade BM, Gupta SK, Ghodke VR, Girkar YK, Kuchekar SK. Pellets and pelletization as Multiparticulate Drug Delivery Systems (MPDDS): A conventional and novel approach. Int J Inst Pharm Life Sci. 2015 5;83:79-126.
83. Pasic M. Study to Design Stable Lansoprazole Pellets. [PhD dissertation]. Germany: University of Freiburg; 2008.
84. Glatt Integrated Process Solutions. Available from: https://www.glatt.com/wp-content/uploads/2021/03/glatt_bro_ptp_026_ws_2019-04_en.pdf
85. Priese F, Frisch T, Wolf B. Comparison of film-coated retarded release pellets manufactured by layering technique or by bed rotor pelletization. Pharm Dev Technol. 2015 Jun 1;20(4):417-25. doi: 10.3109/10837450.2013.879883, PMID: 24483364
86. McGinity JW, Felton LA. Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms. United Kingdom: Informa Healthcare; 2008. p. 488.
87. Chen H, Rustagi S, Diep E, Langrish TA, Glasser BJ. Scale-up of fluidized bed drying: Impact of process and design parameters. Powder Technol. 2018 Nov 1;339:8-16. doi: 10.1016/j.powtec.2018.07.087
88. Jeon IJ. In: Neubert R, Süß W, Kleinebudde P, editors. Development and Formulation of Carbomer 934P-Containing Mucoadhesive Pellets by fluid-bed Techniques. Halle: Martin-Luther-Universität Halle-Wittenberg; 2007. Available from: https://opendata.uni-halle.de/bitstream/1981185920/9510/1/prom.pdf
89. Maniyar D, Kadu P, Baig MI. Critical variables affecting the layering method of pelletization. Future J Pharm Sci. 2023 Aug 14;9(1):68. doi: 10.1186/s43094-023-00522-z
90. Dumpala R, Patil C. A review on pellets and pelletization techniques. Int J Trend Innov Res. 2020;2(4):9-21.
91. Wesdyk R, Joshi YM, Jain NB, Morris K, Newman A. The effect of size and mass on the film thickness of beads coated in fluidized bed equipment. Int J Pharm. 1990;65(1-2):69-76. doi: 10.1016/0378-5173(90)90011-R
92. Seo KS, Bajracharya R, Lee SH, Han HK. Pharmaceutical application of tablet film coating. Pharmaceutics. 2020 Sep 1;12(9):853. doi: 10.3390/pharmaceutics12090853, PMID: 32911720
93. Gupta VK, Beckert TE, Price JC. A novel pH- and time-based multi-unit potential colonic drug delivery system. I. Development. Int J Pharm. 2001;213(1-2):83-91. doi: 10.1016/S0378-5173(00)00649-9
94. Iyer RM, Augsburger LL, Parikh DM. Evaluation of drug layering and coating: Effect of process mode and binder level. Drug Dev Ind Pharm. 1993;19(9):981-98. doi: 10.3109/03639049309062996
95. Suresh K, Sharma S. Pellets and palletisation: A review article. J Orient Res Madras 2021;6(8):XCII-XLII:113-118.
96. Pai R, Pai A, Srivastava B, Kohli K. Development and in vitro evaluation of ketoprofen extended release pellets using powder layering technique in a rotary centrifugal granulator. Comb Chem High Throughput Screen. 2011;14(2):138-45. doi: 10.2174/138620711794474042, PMID: 21118082
97. Bouffard J, Dumont H, Bertrand F, Legros R. Optimization and scale-up of a fluid bed tangential spray rotogranulation process. Int J Pharm. 2007 Apr 20;335(1-2):54-62. doi: 10.1016/j.ijpharm.2006.11.022, PMID: 17166677
98. Song Y, Zhou T, Bai R, Zhang M, Yang H. Assessment of the coating quality in a top-spray fluidized bed coater: An experimental study. Powder

Technol. 2024 Apr 15;439:119663. doi: 10.1016/j.powtec.2024.119663
99. Pawar A, Bahulikar SR. Design and development of tangential spray rotogranulation mechanism. Int J Sci Technol Eng. 2016;2:1036-41.
100. Agrawal S, Fernandes J, Shaikh F, Patel V. Quality aspects in the development of pelletized dosage forms. Heliyon. 2022;8(2):e08956. doi: 10.1016/j.heliyon.2022.e08956, PMID: 35243077
101. Dreu R, Luštrik M, Perpar M, Žun I, Srčič S. Fluid-bed coater modifications and study of their influence on the coating process of pellets. Drug Dev Ind Pharm. 2012 Apr;38(4):501-11. doi: 10.3109/03639045.2011.617754, PMID: 21962028
102. Anderson R, Oren PL, Ogura T, Fujii T. Duloxetine Enteric Pellets United States Patent (19). Japan: Shionogi and Co Ltd.; 1996 Apr.
103. Thompson TS, Barker ER. Method for Applying a Powder Coating United States (12) Patent Application Publication. United States: Sherwin Williams Co; 2013 Feb.
104. Taylor D, Mcclain JB. Polymer Films for Medical Device Coating Australian Patent. Durham: MiCell Technologies Inc.; 2014 Oct.
105. Oshlack B, Pedi F Jr. Powder-layered Morphine Sulfate Formulation United States Patent 19. United States: Purdue Pharma LP; 1995 May.
106. Engels SM. Polymer Coating Process Using Dry Related U.S. Application Data Glidant in A Rotor Processor (60) Provisional Application No. 61/087,083; 2008.
107. Varshosaz J, Tavakoli N, Serri A. Preparation and *in vitro* characterization of piroxicam enteric coated pellets using powder layering technique. Pharm Dev Technol. 2009;14(3):305-11. doi: 10.1080/10837450802626288, PMID: 19519183
108. Mazumder R, Mahanti B, Majumdar S, Pal R, Chowdhury AD. Response surface method for optimization of prepared satranidazole powder layered pellets. Futur J Pharm Sci. 2021 Dec;7(1):190. doi: 10.1186/s43094-021-00337-w
109. Young J, Kurt CF, Rajabi RA. ACRYL-EZE Application Data Aqueous Acrylic Enteric System Application of Powder Layering Technology and Aqueous Enteric Coating of Lansoprazole. Harleysville, PA: Colorcon Inc.; 2016 Nov.