

Pellet-Based Drug Delivery Systems: Current Status and Future Prospects

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Abstract: *Pelletization is an advanced drug delivery method that allows modified and site-specific release of medicines. It is useful for drugs with poor taste, low bioavailability, or short half-life. Pellets are small, free-flowing particles prepared by techniques like extrusion-spheronization, powder layering, and hot melt extrusion using natural, semi-synthetic, or synthetic polymers. Oral drug delivery is widely preferred due to its ease and patient comfort. Multiparticulate systems like pellets are superior to single-unit dosage forms as they spread the drug evenly in the gastrointestinal tract. This article discusses pellets, their advantages, preparation techniques, use in controlled/sustained release, suitable excipients, marketed products, and recent research trends. Pelletization technology enables the development of modified-release formulations such as sustained-release, delayed-release, site-specific, colon-targeted, and pulsatile drug delivery systems. Additionally, pellets provide excellent compatibility for combination therapy, allowing incorporation of multiple drugs with differing release profiles into a single capsule or tablet. Recent advancements in coating technologies, polymer science, and nanotechnology have significantly expanded the applications of pellet-based systems in the delivery of poorly soluble drugs, biologics, and personalized medicines. This review highlights the current status of pellet-based drug delivery systems, including formulation methods, characterization techniques, advantages, limitations, and pharmaceutical applications, while also discussing emerging trends and future prospects that may shape the next generation of multiparticulate drug delivery technologies.*

Keywords: Pelletization, Multiparticulate dosage forms, Controlled-release systems, Drug release profile, Extrusion-spheronization, Layering techniques, Spray drying, Hot-melt extrusion, Cryopelletization

I. INTRODUCTION

Pelletization is an innovative approach in modern drug delivery, designed to improve therapeutic efficiency and patient compliance. Pellets are small, spherical units that can deliver drugs in controlled, sustained, or delayed-release patterns within the gastrointestinal (GI) tract. These multiparticulate systems distribute drugs evenly, resulting in better absorption, reduced plasma level fluctuations, and minimal dose dumping. By using suitable polymers and preparation methods, pellets can be engineered for targeted and customized drug release profiles. Pellets are small, spherical drug units designed for controlled, sustained, or delayed release in the gastrointestinal tract. They offer better absorption, stable plasma levels, and reduce dose dumping. By selecting suitable polymers and manufacturing techniques, pellets can be tailored for various release patterns such as pulsed, delayed, or sustained. Pelletization is the process of forming these particles by granulating powdered drugs with excipients to create strong, uniform, and free-flowing units. Multiple drugs or the same drug with different release rates can be combined in one dosage form, like capsules, for better therapeutic results.

History of Pellets-Pellet-based drug delivery systems have evolved significantly since their introduction. Early use began in the 1930s with compressed pellets for sustained drug release in parenteral implants.¹¹ By the 1950s, oral pellet formulations emerged, providing controlled release and improved therapeutic effects over conventional tablets.¹²



The 1960s–1980s saw innovations like Spansule and osmotic systems (OROS), advancing controlled drug delivery technologies.¹³ Today, pellets are valued for improving bioavailability, ensuring uniform drug release, reducing side effects, and enhancing patient compliance.^{14,15} Modern techniques such as extrusion-spheronization, fluid-bed coating, and 3D printing make pellet systems highly relevant to pharmacy practice, supporting personalized medicine and next-generation formulations.^{16,17}

What are Pellets? Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free-flowing, spherical or semi-spherical units, referred to as pellets. They are free-flowing, spherical or semi-spherical solid units with a size range of about 0.5 mm to 1.5 mm and that are intended mostly for oral administration.⁷

Types of Pellets-

1. Based on Drug Release Pattern

Immediate Release Pellets (IR):

Release the drug quickly after administration.

Example: Paracetamol pellets.

Sustained Release Pellets (SR):

Release the drug slowly over an extended period.

Example: Diclofenac sodium SR pellets.

Controlled Release Pellets (CR):

Deliver the drug at a predetermined rate for a prolonged time.

Example: Propranolol CR pellets.

Delayed Release Pellets:

Release the drug after a specific time or at a particular site (e.g., enteric-coated pellets).

Example: Omeprazole enteric-coated pellets.

Pulsatile Release Pellets:

Release drug in bursts at specific time intervals.

Example: Chronotherapeutic pellets for asthma.

2. Based on Composition

- Drug-loaded Core Pellets: Drug distributed throughout the pellet core.
- Coated Pellets: Core pellets coated with polymeric layers for modified release.
- Matrix Pellets: Drug and excipients uniformly mixed to form a matrix structure.

3. Based on Manufacturing Method

- Extrusion - Spheronization Pellets
- Solution/Suspension Layered Pellets
- Powder Layered Pellets
- Cryopellets (Freeze Pelletization)
- Hot Melt Extrusion Pellets
- Direct Compression Pellets

Advantages of Pellet Based System-

1. Improved Bioavailability & Uniform Drug Distribution

- Uniform dispersion in the GI tract: Pellets disperse evenly throughout the gastrointestinal tract, maximizing absorption and reducing mucosal irritation—a key benefit over single-unit dosage forms.⁸



- Reduced intra- and inter-subject variability: Multi-particulate systems deliver more stable plasma drug levels by minimizing variability in transit and absorption.
- Enhanced bioavailability due to increased surface area: Coating drugs onto many small pellets boosts dissolution rates and enhances absorption, especially for poorly soluble drugs.¹⁰

2. Reduced Dose-Dumping & Side Effects

- Individual drug reservoirs: Since each pellet acts as its own release unit, the risk of sudden or complete dose dumping is significantly lowered.¹⁰
- Controlled and sustained plasma levels: Extended or modified-release pellet formulations maintain therapeutic levels longer, reducing dosing frequency and improving safety.⁹
- Minimized gastrointestinal irritation: Coating pellets can protect the GI lining by preventing direct contact between irritant drugs and the stomach—particularly useful with enteric or modified-release designs.⁹

3. Masking of Unpleasant Taste and Odor

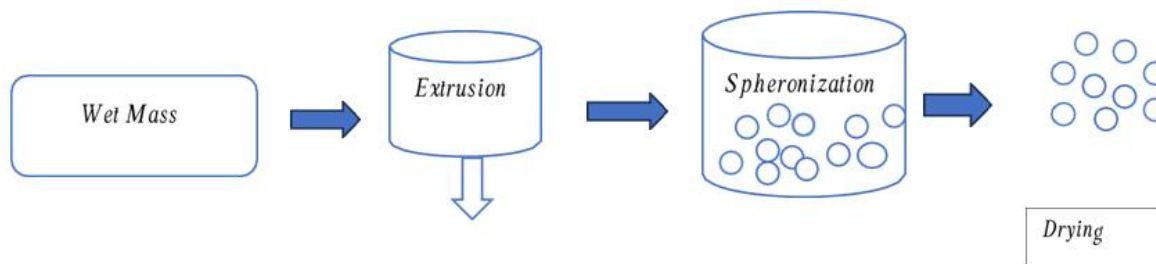
- Pellets with coating for taste masking: Applying polymer coatings on pellets effectively hides bitter or unpleasant tastes of active ingredients.⁹
- Coatings offer additional functional benefits: Beyond taste masking, coatings can also improve stability, prevent interactions, and enable targeted or controlled drug release profiles.¹⁰

4. Flexibility in Dosage Form Design

- Many dosage options: Pellets can be filled into capsules, embedded in tablets, or even packed as sachets or suspensions—enhancing design flexibility.¹⁰
- Combination therapies and multi-layered release: Different pellets can carry varied release profiles or different drugs entirely—perfect for designing fixed-dose combination therapies or sequential release systems.⁹
- Improved manufacturability: The excellent flow properties of uniform spherical pellets facilitate processes like capsule filling, tableting, and molding.
- Adaptable for special patient groups: Pellet formulations are especially suitable for pediatric and geriatric patients, offering easy dose adjustment, swallowing ease, and better compliance

Pelletization Techniques-

1. Extrusion-Spheronization is a common method for making pellets. First, the drug and other ingredients are mixed with a liquid to form a wet mass. This mass is pushed through a small opening (die) to make thin strands. These strands are then rolled in a spheronizer to form small round pellets. Finally, the pellets are dried to remove moisture.



This method is popular because it makes smooth, uniform pellets with good flow, which are useful for controlled-release and multi-unit dosage forms.



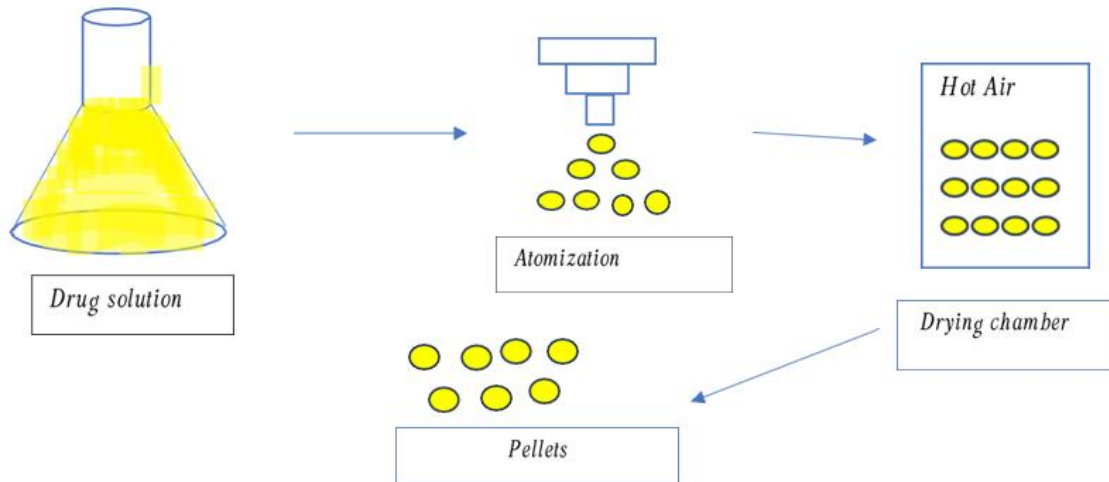
2. Solution/Suspension Layering is a pelletization method where the drug is either dissolved in a solvent to form a solution or dispersed to create a suspension. This liquid is then sprayed onto small inert cores, known as non-pareil seeds, using a coating pan or fluid bed coater. The process is repeated in layers until the desired pellet size is obtained. This technique is especially useful for low-dose and heat-sensitive drugs. It is commonly used to prepare taste-masked and enteric-coated pellets for improved patient compliance and targeted drug release.



3. Powder Layering is a pelletization technique where powdered drug particles are layered onto small inert cores using a binding solution. This process is carried out in a coating pan or fluidized bed under carefully controlled conditions to ensure uniform coating and pellet size. One major advantage of this method is that it allows higher drug loading compared to solution layering. It is widely used in the production of both immediate-release and controlled-release pellets for various pharmaceutical applications.

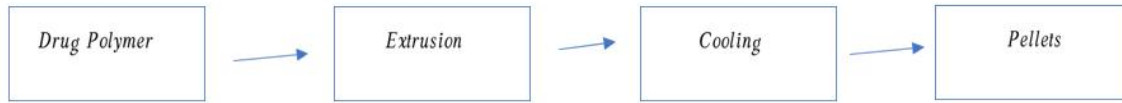


4. Spray drying involves atomizing a drug solution or suspension into a hot drying chamber, where rapid solvent evaporation leads to the formation of solid pellets or microparticles. In contrast, spray congealing uses a melted drug–excipient mixture that is atomized into a cooling chamber, where the droplets solidify into pellets upon cooling. Both techniques are advantageous as they are suitable for thermo-labile and solvent-sensitive drugs.



5. Hot-melt extrusion involves blending the drug with excipients and melting the mixture under controlled heat and pressure. The molten mass is then extruded through a die and cut into uniform pellets. This solvent-free method offers several advantages, including enhanced drug solubility and improved bioavailability, making it particularly suitable for formulating poorly soluble active pharmaceutical ingredients (APIs).





6. **Cryopelletization** involves introducing droplets of a drug solution or suspension into liquid nitrogen or another cryogenic medium, where they undergo rapid freezing to form solid pellets. These frozen pellets are then freeze-dried to remove moisture while preserving their structure. This technique minimizes thermal degradation, making it highly suitable for thermosensitive drugs



Current Applications of Pellet Based Systems-

Application Area	Benefits
Oral Dosage Form	Capsules, MUPS, tablets, sachets—enhanced control over release and dosing flexibility
Combination Therapy	Multiple actives with different release profiles in one dose
Pediatrics & Geriatrics	Flexible dosing, easier swallowing, better compliance
Marketed Products	Esomeprazole (MUPS), Vimovo, Omeprazole & Pantoprazole pellets, Dexlansoprazole DDR

Challenges and Limitations

Pellet-based drug delivery systems face numerous technical and logistical challenges throughout their development and production. Manufacturing complexity and costs often escalate due to the need for specialized, precision-controlled equipment, such as extruders, spheronizers, and fluidized bed dryers. These processes demand meticulous control over parameters like raw material properties, extrusion pressure, spheronization speed, and drying conditions, all of which critically influence final pellet characteristics such as size, shape, porosity, and surface morphology .

Scale-up from laboratory to industrial production amplifies these challenges. For instance, the compaction of multi-unit pellet systems (MUPS) into tablets can compromise the integrity of the pellets and lead to poor content uniformity, unless careful measures are taken, like using cushioning excipients or optimizing process flow. Similarly, during extrusion–spheronization, even small variations in equipment or operating parameters can lead to significant deviations in pellet size distribution and dissolution behavior.

Stability concerns add another layer of complexity, particularly for moisture-sensitive APIs. High humidity can plasticize coating films—especially those made from polymers like Eudragit—lowering their glass transition temperature (Tg) and rendering them brittle or prone to cracking. This adversely affects mechanical integrity, dissolution profiles, and overall product performance .

Taken together, these challenges highlight the intricate balancing act required during pellet formulation—juggling material science, process engineering, scale-up feasibility, and product stability to ensure reliable, reproducible, and high-quality therapeutic outcomes.



Future Prospects of Pellets Based Drug Delivery System-

1. The future of pellet-based drug formulations holds transformative potential, driven by an integration of advanced technologies and personalized therapeutic strategies. 3D printing, particularly direct powder extrusion (DPE) and multi-material additive manufacturing, enables precise, on-demand fabrication of pellets with complex geometries and tailored release profiles—circumventing traditional limitations tied to filament preparation and expanding flexibility in drug loading and release design. Such techniques support the creation of polypills, combining multiple active ingredients with distinct kinetics into a single dosage form, opening avenues for individualized treatments.
2. Targeted drug delivery, particularly for colon-specific release, is receiving renewed focus through innovative formulation strategies. For instance, the combination of pH-responsive materials with 3D printing has produced colon-targeted tablets encapsulating budesonide in “pill-in-pill” architectures, achieving improved dose accuracy and localized delivery, potentially enhancing treatments for inflammatory bowel diseases. Broader strategies for colon-targeted delivery, such as microflora-triggered systems, osmotic capsules, and pressure-dependent mechanisms, are also under exploration to optimize site-specific therapeutic outcomes.
3. Integrating nanotechnology with pellet systems is another exciting frontier. Emerging research highlights the use of solid lipid nanoparticles, mesoporous silica nanoparticles, and dendrimers as functional coatings or loading platforms, enabling controlled release, enhanced stability, and organ-specific targeting—all of which are especially promising in oncology, vaccine delivery, and treating inflammatory disorders.
4. Altogether, these innovations mark a shift toward truly personalized medicine, where dosage forms are precisely manufactured to match individual patient needs, release requirements, and therapeutic targets. Yet, realizing this vision hinges on overcoming challenges related to regulatory frameworks, scale-up feasibility, and ensuring reproducible quality control in complex, multilayered systems.

II. CONCLUSION

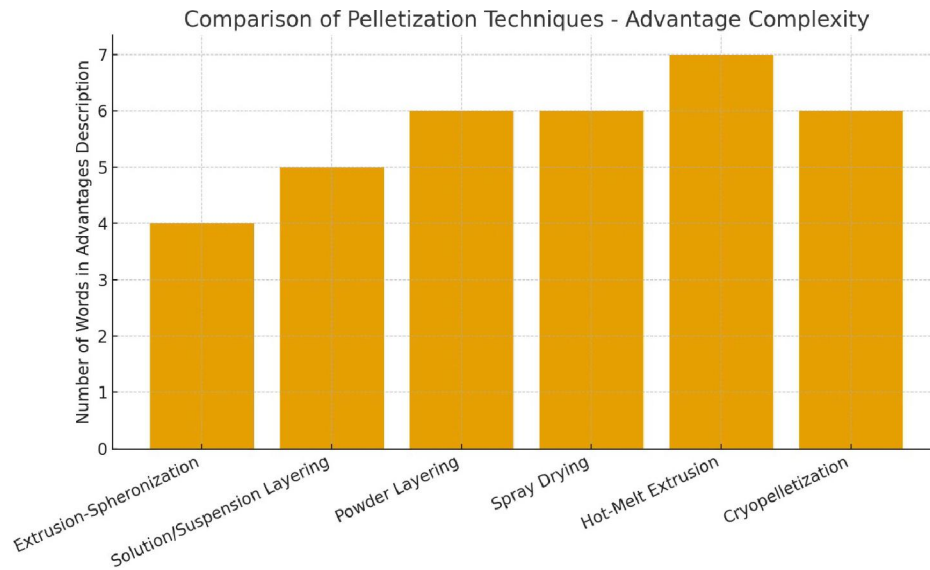
Pellet-based drug delivery systems have emerged as a versatile and innovative approach in modern pharmaceuticals, offering significant advantages such as controlled drug release, improved bioavailability, reduced risk of dose dumping, and enhanced patient compliance. Current applications span oral dosage forms, combination drug therapy, and specialized formulations for pediatric and geriatric patients, with several successful marketed products like omeprazole and pantoprazole pellets validating their clinical utility. Advancements in manufacturing techniques, including 3D printing, nanotechnology-based coatings, and personalized medicine strategies, are expected to further enhance the precision and therapeutic performance of these systems. As research progresses, pelletized formulations will continue to play a pivotal role in pharmaceutical innovation, addressing complex drug delivery challenges while improving patient adherence and treatment outcomes.

ACKNOWLEDGEMENT

The author sincerely thanks the respected teachers and faculty members of the Department of Pharmacy for their valuable guidance, support, and encouragement during the preparation of this review paper. The author is also grateful to the institution for providing the necessary academic facilities and resources. Special thanks are extended to all researchers and authors whose published literature has contributed to the successful completion of this student review paper.



Result Obtained



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