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## A Comprehensive Review: New Approaches in Sustained Release Pellets

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### Abstract:

Sustained release drug delivery systems are gaining momentum due to their potential to maintain constant plasma drug concentrations, reduce dosing frequency, and improve patient compliance. Among these systems, pellet-based formulations produced by extrusion-spheronization have demonstrated significant advantages including uniform size distribution, high sphericity, and smooth surface characteristics. This review highlights the principles of extrusion-spheronization, critical formulation parameters, suitable excipients, evaluation methods, and examples of marketed and experimental sustained release pellets. The technique's ability to process both hydrophilic and hydrophobic drugs makes it highly versatile. The paper further discusses the limitations, regulatory perspectives, and future potential of extrusion-spheronization in advanced drug delivery systems.

**Keywords:** Sustained release drug delivery systems, Spheronization, Drying, Coating.

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### Introduction

In recent decades, oral drug delivery has evolved from conventional tablets and capsules to advanced systems that aim to improve therapeutic efficacy and patient compliance [1].

Sustained release (SR) formulations are particularly advantageous in maintaining a consistent drug concentration in the bloodstream, minimizing side effects, and reducing dosing frequency. Among various SR dosage forms, pellets have emerged as a versatile platform due to their small, free-flowing, spherical structure that ensures uniform distribution in the gastrointestinal tract. [2] The extrusions pheronization

technique has gained prominence as a preferred method for manufacturing multi-unit pellet systems, particularly for SR formulations. This technique allows the incorporation of a wide range of drugs, excipients, and release modifiers while maintaining excellent pellet quality. It offers numerous advantages such as scalability, reproducibility, and the ability to handle heatsensitive materials. [3]

This review focuses on the fundamentals and advancements in sustained release pellets developed through extrusionspheronization. It provides a detailed overview of the technique, formulation considerations,

evaluation parameters, and real-world applications, including the development of pellets for acid-labile drugs like Rabeprazole.

### Overview of Sustained Release Dosage Forms

Sustained release (SR) drug delivery systems are designed to release a drug at a predetermined rate to maintain a constant drug concentration in the bloodstream over an extended period. These systems are especially beneficial for chronic diseases where long-term medication is required. [4]

The primary objectives of SR systems include:

- Minimizing peak-trough fluctuations in drug levels
- Reducing dosing frequency
- Enhancing patient compliance
- Decreasing the risk of side effects [5]

SR formulations typically use polymers, matrix systems, or coating technologies to regulate the release rate of the active pharmaceutical ingredient (API). Among oral SR systems, multiparticulate forms like pellets offer more predictable gastric emptying, reduced dose dumping, and greater flexibility in formulation.

### Advantages of SR Systems:

- Improved therapeutic efficacy
- Reduction in total drug dose and side effects
- Better patient compliance due to reduced dosing frequency

- Minimization of local irritation in the gastrointestinal tract [6]

### Pelletization Techniques

Pelletization is a process of converting fine powders or granules into small, free-flowing, spherical or semi-spherical units, typically ranging from 500–1500  $\mu\text{m}$ . These pellets can be filled into capsules or compressed into tablets.

### Extrusion-Spheronization Technique

Extrusion-spheronization is a widely used technique for preparing multiparticulate drug delivery systems, especially sustained release pellets.

It enables the production of dense, spherical pellets with narrow size distribution—essential for uniform coating and drug release. Key Steps in the Process: [8, 9]

1. Mixing/Wet Massing: Drug and excipients are mixed with a binder to form a plastic mass.
2. Extrusion: Wet mass is extruded through a screen to form cylindrical extrudates.
3. Spheronization: Cylindrical extrudates are rounded into spheres using a rotating friction plate.
4. Drying: Pellets are dried to remove moisture.
5. Coating (Optional): Coating applied for SR or enteric protection.

### Process Flow:

Raw Materials  $\rightarrow$  Wet Massing  $\rightarrow$  Extrusion  $\rightarrow$  Spheronization  $\rightarrow$  Drying  $\rightarrow$  Coating (optional)  $\rightarrow$  Final Pellets

**Table 1: Formulation Variables and Excipients [10, 11]**

Excipient Roles	Examples	Excipient Roles	Examples	Excipient Roles	Examples
Diluent		Improves binding and plasticity		Microcrystalline cellulose (MCC)	
Binder		Forms plastic mass		PVP K30, HPMC	
Poreformer		Alters drug release		Lactose, Mannitol	

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Release retardant	Sustained release matrix	Ethyl cellulose, HPMC K100M
Plasticizer	Improves coating flexibility	Diethyl phthalate (DEP)
Solvent	Used in granulation or coating	Water, Methylene dichloride

### Case Study: Rabeprazole SR Pellets [12]:

Rabeprazole sodium is an acid-labile proton pump inhibitor. SR pellets are produced by layering the core drug onto MCC-based pellets, followed by enteric and sustained release coatings. Coating polymers include Eudragit L100 and ethyl cellulose.

### Evaluation Parameters of Pellets [14]

1. Particle Size Distribution: Sieve or laser diffraction analysis

2. Sphericity and Surface Morphology: SEM, image analysis

3. Flow Properties: Angle of repose, bulk/tapped density, Carr's Index

4. Moisture Content: LOD or Karl Fischer titration

5. Drug Content Uniformity: UV or HPLC

6. In Vitro Release Studies: USP apparatus I/II, pH 1.2 and 6.8 media

**Table 2: Marketed Formulations and Examples**

Drug	Brand Examples	Coating Type
Rabeprazole	Rabicip L, Rabium SR	Enteric + SR
Diclofenac Sodium	Diclo SR	SR coating
Omeprazole	Omez, Ocid	Enteric + SR
Theophylline	Theolair SR	Matrix or layered SR

### Challenges and Limitations [15]

- Moisture sensitivity during wet massing
- Optimization complexity (speed, binder, screen size)
- Equipment cost for small scale
- Scale-up reproducibility

### Recent Trends and future scope in Pelletization Technology [16, 17]

#### Recent Trends

#### a. Use of Natural and Biodegradable Polymers

These materials offer biocompatibility and reduce long-term toxicity. Natural gums (e.g., xanthan, guar, gellan gum), chitosan, and alginates are beinused as matrix formers for eco-friendly sustained release.

**b. Co-processed Excipients:** MCC-lactose, MCC-dicalcium phosphate combinations

enhance pellet strength, flow, and sphericity. Reduce the need for binders or plasticizers.

#### c. Hot-Melt Extrusion (HME)

A solvent-free, continuous process gaining popularity for heat-stable drugs. Allows fine control over drug dispersion and release kinetics.

#### d. Multi-layered and Multiparticulate Systems

Pellets with dual or triple layers (e.g., immediate + sustained + enteric) to treat complex diseases like GERD or chronic infections.

#### e. Incorporation of Nanoparticles into Pellets

Nanoparticles embedded into pellets for targeted delivery or enhanced solubility of poorly water-soluble drugs.

#### f. 3D Printing in Pellet Manufacturing

Though in early research, extrusion-based 3D printing can produce customized, layered, and programmable-release pellets.

#### **g. Design of Experiments (DoE) and QbD**

DoE and Quality by Design (QbD) principles help optimize process variables (speed, binder ratio, drying time) to improve reproducibility and quality control.

#### **Future Scope in Pelletization Technology [18, 19]**

**a. Personalized Medicine:** Pelletization allows customization of doses and combinations — ideal for age-specific or patient-specific treatments.

#### **b. Pediatric and Geriatric Formulations:**

Small, tasteless pellets in sprinkle capsules or suspensions can improve compliance in children and elderly.

**c. Colon-targeted Delivery:** pH-sensitive coatings and time-dependent systems for diseases like IBD and colorectal cancer.

**d. Artificial Intelligence (AI) in Formulation Design:** Machine learning models will predict optimal excipient combinations, release profiles, and stability parameters.

#### **e. Sustainability and Green Pharmacy:**

Use of solvent-free, low-energy, and biodegradable systems will align with environmental goals and regulatory pressure.

#### **f. Regulatory Harmonization:**

Future guidelines (USFDA, EMA, CDSCO) may support pellet-based drug delivery as a preferred system due to its modular, safe, and reproducible nature.

#### **Conclusion**

Extrusion-spheronization is a scalable and reliable technique to produce sustained release pellets with consistent quality. With advancements in polymers, excipients, and

coating methods, the technique continues to be widely used for oral drug delivery. Its role in developing combination, pediatric, and targeted therapies is expanding, aligning with current trends in personalized medicine.

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