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Review Article

Sustained Release Pellets Prepared by Extrusion-Spheronization: Advantages, Formulation Considerations, and Process Optimization

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ABSTRACT

Sustained release (SR) drug delivery systems have emerged as a cornerstone of modern pharmaceutical science, offering significant clinical and pharmacokinetic advantages over conventional immediate-release formulations. Among the various multiparticulate systems developed, sustained release pellets occupy a unique position due to their superior dose uniformity, reduced dose dumping risk, flexible drug release profiles, and excellent GI transit properties. Extrusion-spheronization (ES) is widely recognized as the most versatile and industrially scalable technique for the manufacture of pellets with optimal sphericity, narrow size distribution, and desired release characteristics. This review provides a comprehensive analysis of sustained release pellets manufactured via the extrusion-spheronization technique. It covers the theoretical basis of sustained drug release, the mechanistic and process parameters of extrusion-spheronization, the role of formulation excipients (particularly microcrystalline cellulose), and the advantages of this technique over alternative pelletization methods. Comparisons between SR pellets and conventional tablets, as well as an in-depth review of critical quality attributes and regulatory considerations, are also discussed. The review is targeted toward pharmaceutical scientists, B.Pharm and M.Pharm students, and medical practitioners with an interest in advanced drug delivery.

INTRODUCTION

The design and development of oral drug delivery systems have undergone a paradigm shift over the past three decades. Traditional immediate-release (IR) dosage forms, while effective, often produce fluctuating plasma drug concentrations characterized by peak- trough oscillations that may result in toxic side effects at peak levels and subtherapeutic effects at trough levels. This pharmacokinetic limitation prompted the development of modified-release (MR) formulations, of which sustained release (SR) systems are the most widely investigated and clinically employed.

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Sustained release drug delivery systems are designed to release the active pharmaceutical ingredient (API) at a predetermined, controlled rate over an extended period typically 8 to 24 hours thus maintaining plasma drug concentrations within the therapeutic window for a prolonged duration. This not only enhances therapeutic efficacy but also improves patient compliance, reduces dosing frequency, and minimizes adverse effects.

Within the domain of sustained release systems, multiparticulate dosage forms and pellets in particular have garnered substantial interest. Pellets are small, spherical or semi-spherical agglomerates of drug and excipients, typically ranging from 0.5 to 2.0 mm in diameter. Their multiparticulate nature imparts distinct pharmacokinetic and biopharmaceutical advantages, which will be discussed in detail in subsequent sections.

Extrusion-spheronization (ES), first described by Conine and Hadley in 1970, has since evolved into the most widely employed technique for pellet manufacture in pharmaceutical production. The process combines wet granulation, extrusion through a die, and spheronization on a friction plate to produce pellets of remarkable sphericity and narrow particle size distribution. When combined with appropriate matrix-forming or coating strategies, the ES technique produces sustained release pellets with excellent performance characteristics.

The objective of this review is to consolidate the current knowledge on sustained release pellets prepared by extrusion-spheronization, with a focus on the superiority of this dosage form and manufacturing technique, targeting readers in the pharmaceutical sciences community including undergraduate and postgraduate students, researchers, and clinicians.

2. SUSTAINED RELEASE DRUG DELIVERY SYSTEMS

2.1 Definition and Rationale

Sustained release (SR) systems, also referred to as extended release (ER), prolonged release, or controlled release systems, are formulations engineered to liberate the drug at a rate slower than that of conventional dosage forms. The USP defines extended- release dosage forms as those "that allow at least a twofold reduction in dosing frequency" compared to immediate-release formulations.

The primary rationale for developing SR systems lies in overcoming the pharmacokinetic shortcomings of IR formulations. For drugs with short half-lives, frequent dosing leads to patient non-compliance; for drugs with narrow therapeutic indices, the fluctuating plasma levels of IR dosage forms increase the risk of toxicity or therapeutic failure. SR systems address both challenges simultaneously.

2.2 Types of Modified Release Systems

Table .1Types of modified release system

Release Type	Description	Examples
Sustained Release	Slow, uniform drug release over 8–24 hrs	Metoprolol SR, Morphine SR
Extended Release	Prolonged release, reduces dosing frequency	Metformin XR, Nifedipine XL
Delayed Release	Release after a time lag (e.g., enteric)	Omeprazole EC, Diclofenac EC
Pulsatile Release	Drug released in pulses at specific times	Verapamil, Methylphenidate
Targeted Release	Release at specific site (colon, tumor)	Mesalazine, Budesonide

2.3 Pharmacokinetic Advantages of SR Systems

The pharmacokinetic benefits of sustained release systems are well established in the literature. Figure-equivalent descriptions are provided below:

- Maintenance of plasma drug concentrations within the therapeutic window (Cmax reduced, Cmin elevated)
- Reduction of peak-trough fluctuation index (PTF%), leading to smoother concentration-time profiles
- Extended mean residence time (MRT) and area under the curve (AUC) per dose
- Reduced total daily dose requirement in many cases
- Decreased incidence of dose-related adverse effects
- Improved bioavailability for drugs susceptible to first-pass metabolism at high local concentrations

2.4 Mechanisms of Sustained Drug Release

Several physicochemical mechanisms govern drug release from SR systems. Understanding these mechanisms is fundamental to rational formulation design:

2.4.1 Matrix Diffusion

In hydrophilic or hydrophobic matrix systems, the drug is homogeneously dispersed within a polymer matrix. Drug release occurs by diffusion through water-filled pores (for hydrophilic matrices, e.g., HPMC) or through the polymer itself (for hydrophobic matrices, e.g., ethylcellulose, Eudragit RS). The release typically follows the Higuchi equation: $Q = A\sqrt{(D \cdot Cs \cdot (2Co - Cs) \cdot t)}$, where Q is the amount released, D is diffusivity, Cs is drug solubility, and Co is initial concentration.

2.4.2 Reservoir (Membrane) Diffusion

A drug core is surrounded by a rate-controlling polymer membrane. Drug diffuses through the membrane at a rate governed by the membrane thickness, permeability, and concentration gradient. This mechanism applies to coated pellets. Zero-order release kinetics can be achieved with reservoir systems when the membrane integrity is maintained.

2.4.3 Osmotic Pumping

Osmotic pressure drives fluid into the core through a semipermeable membrane, creating internal pressure that expels drug solution through a laser-drilled orifice. While not applicable to standard pellets, this mechanism is used in OROS tablets and some capsule- based systems.

2.4.4 Ion Exchange

Drug ions are bound to ion-exchange resins and released in the GI tract upon exchange with physiological ions. This mechanism provides pH-independent release and is used in some liquid SR formulations.

3. PELLETS AS A MULTIPARTICULATE DRUG DELIVERY SYSTEM

3.1 Definition and Characteristics

Pellets are spherical or nearly spherical granules ranging from 0.5 to 2.0 mm in diameter, prepared by the agglomeration of fine drug and excipient particles. According to the European Pharmacopoeia (Ph. Eur.), pellets are "spherical granules, typically between 0.5 and 2 mm in diameter." Ideal pellets possess:

- High sphericity (aspect ratio close to 1.0)
- Narrow particle size distribution (span < 1.0)
- Smooth surface with low friability

- High bulk density and good flowability
- Uniform drug distribution throughout the particle

3.2 Why Pellets are Superior to Conventional Tablets

The multiparticulate nature of pellets confers several pharmacokinetic, biopharmaceutical, and technological advantages over monolithic dosage forms such as tablets and capsules:

Table. 2 Comparision between SR Pellets to Conventional tablets

Parameter	SR Pellets	Conventional Tablets
Dose dumping risk	Very low (dose distributed among thousands of units)	Higher (entire dose in one unit)
GI transit	Less influenced by fed/fasted state	Pyloric sphincter may delay emptying
Plasma level fluctuation	Smooth, uniform profile	Higher peak-trough variations
Flexibility	Can combine pellets with different release profiles	Fixed release per unit
Coating uniformity	Excellent (small, spherical surface)	Less uniform on complex shapes
Local GI irritation	Reduced (dose spread over large mucosal area)	Concentrated at one site
Manufacturability	Scalable, amenable to coating	May require complex tooling
Patient compliance	Can be sprinkled on food	Must be swallowed whole

3.3 Methods of Pellet Preparation

Multiple techniques have been developed for pellet manufacture. Each technique has distinct advantages and limitations:

Table. 3 Methods of pellets preparation

Technique	Principle	Advantages	Limitations
Extrusion-Spheronization	Wet mass extruded and spheronized	High sphericity, scalable, versatile	MCC dependent, moisture-sensitive APIs
Layering (Drug-Layering)	Drug solution sprayed onto starter beads	Good for potent/ soluble drugs	Poor for insoluble drugs, complex equipment
Rotor Pelletization	Tangential spray onto rotating disc	Continuous process	High attrition, wide size distribution
Fluidized-Bed Agglomeration	Binder spray in fluidized bed	Low-density pellets, mild conditions	Poor sphericity, broad size range
Hot-Melt Extrusion	Melt-based processing	Solvent-free, amorphous dispersions	Thermal degradation risk, limited polymers

4. EXTRUSION-SPHERONIZATION TECHNIQUE

4.1 Historical Background

The extrusion-spheronization process was first introduced by Conine and Hadley in 1970 as a method to produce spherical pellets using a friction plate spheronizer. The technique was further refined by Erkoboni (1997) and subsequently adopted across the pharmaceutical industry due to its ability to produce pellets with exceptional physical properties. The development of microcrystalline cellulose (MCC) as an extrusion aid by Avicel in the 1960s was pivotal to

the widespread adoption of ES in pharmaceutical pelletization.

4.2 Process Description

Extrusion-spheronization is a multi-step process comprising the following sequential unit operations:

Step 1: Dry Mixing

The API and all excipients (MCC, fillers, binders) are blended in a suitable mixer (planetary mixer, high-shear granulator) until a homogeneous powder blend is achieved. This step ensures uniform drug distribution in the final pellets.

Step 2: Wet Granulation / Wet Massing

A granulating liquid (typically water, but also hydroalcoholic solutions containing binders such as hydroxypropyl methylcellulose or polyvinylpyrrolidone) is added to the powder blend and mixed to form a plastic, cohesive wet mass of the correct consistency. The water content is critical: too little results in crumbly extrudates, while too much yields elongated, sticky spaghetti-like extrudates that cannot spheronize properly.

Step 3: Extrusion

The wet mass is forced through a die plate containing circular orifices of defined diameter (typically 0.5–2.0 mm) using a radial, axial, or basket extruder. The extrudate exits as cylindrical rods of uniform diameter. The extrusion speed, die diameter, and die length-to- diameter ratio are critical process parameters governing extrudate quality and pellet yield.

Step 4: Spheronization

The freshly extruded cylindrical rods are transferred to the spheronizer, which consists of a static cylinder and a rotating friction plate (cross-hatch or radial groove pattern) at the bottom. The friction between the extrudate and the plate, combined with centrifugal and gravitational forces, causes the cylinders to break, round off, and form spherical pellets. Spheronization time (typically 2–10 minutes) and speed (500–2000 rpm) are critical parameters.

Step 5: Drying

The wet pellets are dried in a fluid bed dryer, tray oven, or other suitable drying equipment to achieve the desired moisture content (typically < 3% for most formulations). Drying conditions must be optimized to prevent pellet aggregation, cracking, or drug migration.

Step 6: Sizing / Screening

Dried pellets are sieved through appropriate mesh screens to collect the desired size fraction (e.g., 600–1000 μm). Oversized and undersized fractions may be recycled or re-processed.

Step 7: Coating (for SR Pellets)

For sustained release pellets, the sized pellets are coated with a rate-controlling polymer film in a fluid bed coater (Wurster process) or pan coater. Commonly used polymers include ethylcellulose (Surelease, Aquacoat ECD), Eudragit RS/RL, and cellulose acetate. The coating level (% weight gain), plasticizer type and concentration, and curing conditions determine the drug release profile.

4.3 Equipment Used in Extrusion-Spheronization

Table. 4 Equipment's used in extrusion spheronization technique

Unit Operation	Equipment	Key Parameters
Wet Massing	High Shear Granulator, Planetary Mixer	Impeller speed, liquid addition rate, mixing time
Extrusion	Radial/Axial/Basket Extruder	Die diameter, screen hole size, extrusion speed, L/D ratio
Spheronization	Marumerizer / Spheronizer	Plate speed (rpm), spheronization time, load
Drying	Fluid Bed Dryer, Tray Oven	Inlet air temp, airflow, bed temperature, time
Sizing	Vibro-Sifter / Rotap Sieve	Mesh sizes (upper/lower limit)
Coating	Wurster Fluid Bed Coater, Pan Coater	Spray rate, inlet temp, coating level (% WG), curing time

4.4 Critical Formulation Variables

4.4.1 Microcrystalline Cellulose (MCC)

MCC is the quintessential extrusion aid in ES pelletization. Its unique properties — high water absorption capacity, plastic deformation under compression, and ability to form a coherent wet mass — make it indispensable in the ES process. MCC (Avicel PH-101, PH-102) is typically used at 30–70% w/w of the formulation. The water-holding capacity of MCC creates a viscoplastic mass that flows through the die without elastic springback and spheronizes efficiently. Other cellulosic extrusion aids include kappa-carrageenan and chitin.

4.4.2 Drug-MCC Ratio and Drug Loading

High drug loading (>60%) can compromise pellet sphericity and friability. The drug-to-MCC ratio must be carefully optimized. Drugs with low water solubility tend to disrupt the MCC network, while highly water-soluble drugs can over-plasticize the mass. Drug loads up to 80% have been achieved with careful formulation and process optimization.

4.4.3 Granulating Liquid

Water is the most common granulating liquid. The volume of granulating liquid and its addition rate critically influence wet mass consistency and pellet quality. Binders such as HPMC (1–5% w/v), PVP K30 (1–5% w/v), or sodium CMC may be dissolved in the granulating liquid to improve pellet hardness and drug loading capacity.

4.4.4 Sustained Release Polymers and Coating Formulation

The selection of the rate-controlling polymer is the most critical formulation decision for SR pellets. Key parameters include:

- Ethylcellulose (EC): Water-insoluble film former; used as aqueous dispersion (Surelease, Aquacoat ECD) or organic solution; excellent for pH-independent SR
- Eudragit RS/RL: Ammonio methacrylate copolymers; RS (permeable) blended with RL (more permeable) to modulate release; pH-independent
- Cellulose acetate: Used for osmotic systems; semi-permeable
- Shellac: Natural resin; pH-dependent dissolution (above pH 7.0)
- HPMC (Hypromellose): Hydrophilic matrix; swells and erodes to control release

Table .5 Polymers used to prepare sustain release pellets

Polymer	Solubility	Typical Coat Level	Drug Release Mechanism	pH Dependence
Ethylcellulose	Insoluble	5–20% WG	Membrane diffusion	None
Eudragit RS/RL	Insoluble	5–15% WG	Membrane diffusion / pore formation	None
HPMC	Soluble	Matrix (30–70%)	Erosion / diffusion	Minimal
Cellulose Acetate	Insoluble	2–8% WG	Osmotic / membrane	None
Eudragit L/S	pH-dependent	10–20% WG	pH-triggered dissolution	Yes (>pH 6/7)

5. ADVANTAGES OF SR PELLETS PREPARED BY EXTRUSION-SPHERONIZATION

5.1 Over Conventional Immediate-Release Dosage Forms

The advantages of SR pellets over conventional IR tablets and capsules are multifaceted, encompassing pharmacokinetic, pharmacodynamic, safety, patient compliance, and technological dimensions:

- Reduced dosing frequency: Drugs with short half-lives (e.g., propranolol t½ = 3–6 hr) require multiple daily doses as IR formulations; SR pellets allow once or twice daily dosing
- Smooth plasma concentration profile: SR pellets maintain drug concentration within the therapeutic window, minimizing toxic peaks and subtherapeutic troughs
- Improved patient adherence: Reduced dosing burden directly correlates with improved compliance in chronic disease management (hypertension, diabetes, epilepsy, Parkinson's disease)
- Reduced adverse effects: Lower Cmax reduces concentration-dependent adverse effects (e.g., GI irritation from NSAIDs, CNS side effects from opioids)
- Sustained therapeutic effect during sleep: Critical for drugs managing nocturnal or early-morning symptoms (e.g., antihypertensives, bronchodilators)

5.2 Over Monolithic SR Tablets

- Minimal dose-dumping risk: If a single SR tablet fails (mechanical fracture, improper manufacturing), the entire dose is released immediately — a risk virtually absent in multiparticulate pellets
- Flexible food interactions: Pellets < 2 mm in diameter pass through the pyloric sphincter independently of meal intake, unlike large tablets that are retained in the stomach during fed state
- Combination products: Pellets with different release profiles can be blended in a single capsule — e.g., IR pellets (20% dose) + SR pellets (80% dose) for rapid onset followed by sustained effect
- Sprinkle formulations: Pellets can be opened from capsules and sprinkled on food or dispersed in liquid for patients who cannot swallow (pediatrics, geriatrics, dysphagia patients)
- Lower local GI concentration: Drug is distributed over large intestinal surface area, reducing mucosal irritation

5.3 Advantages of Extrusion-Spheronization Over Other Pelletization Techniques

Among pelletization techniques, extrusion-spheronization offers a unique combination of advantages:

- Superior sphericity: ES produces pellets with aspect ratios approaching 1.0, ensuring uniform coating thickness and reproducible drug release profiles unmatched by fluidized bed agglomeration or hot-melt extrusion
- Narrow particle size distribution: Span values < 0.8 are routinely achieved, ensuring dose uniformity and predictable release kinetics
- High drug loading: ES can accommodate drug loads of 40–80% without compromising pellet quality, superior to drug layering on non-pareil beads
- Scalability: ES equipment scales linearly from laboratory (1 kg) to commercial (500 kg) scale with minimal re-optimization, supporting efficient technology transfer
- Cost-effective: Continuous process with high yield; equipment investment lower than more complex technologies (OROS, hot-melt extrusion)
- Solvent flexibility: Aqueous or hydroalcoholic granulating liquids can be used; no organic solvents required in standard ES
- Versatility: Compatible with hydrophilic and hydrophobic matrix systems, immediate and sustained release, enteric and gastroretentive formulations
- Excellent coating efficiency: Spherical pellets provide the most uniform, defect-free coating surface — critical for predictable SR performance

6. EVALUATION PARAMETERS FOR SR PELLETS

6.1 Physical Characterization

Table. 6 Physical characterization of SR Pellets

Test	Method / Equipment	Acceptance Criteria
Particle Size & Distribution	Sieve analysis, laser diffraction	d50 within target range; span < 1.0
Sphericity (Aspect Ratio)	Image analysis (ImageJ, Camsizer)	AR ≥ 0.85; circularity ≥ 0.90
Bulk / Tapped Density	Graduated cylinder, tapping apparatus	Per ICH Q6A; Carr's Index < 25%
Friability	Roche friabilator	< 1.0% weight loss
Moisture Content	Karl Fischer / Loss on Drying	< 3.0% w/w (typical)
Drug Content Uniformity	UV/HPLC assay	RSD < 6% per dose unit (USP <905>)

6.2 In Vitro Drug Release Testing

In vitro dissolution testing is the most critical quality attribute for SR pellets. The USP apparatus 2 (paddle) at 50–100 rpm or apparatus 1 (basket) in pH-change media (0.1 N HCl for 2 hr, then pH 6.8 phosphate buffer) is most commonly used.

Acceptance criteria for SR pellets typically specify:

- Not less than (NLT) 20–30% release at 1–2 hours (burst release)
- 40–60% release at 4–6 hours (mid-point)

- NLT 80% release at 12–18 hours (complete release)

Release data are fitted to mathematical models to characterize the release mechanism:

Table .7 Kinetic study parameters fot SR Pellets

Model	Equation	Indicates
Zero Order	Q = Q0 + K0t	Constant release rate (membrane-controlled)
First Order	ln Q = ln Q0 - K1t	Release proportional to remaining drug
Higuchi	Q = KH√t	Diffusion-controlled matrix release
Korsmeyer-Peppas	Q/Q∞ = Ktn	n < 0.5: Fickian; 0.5 < n < 1: anomalous; n = 1: zero-order
Hixson-Crowell	Q01/3 - Qt1/3 = KHCt	Erosion-controlled release

6.3 Similarity Factor (f2) Analysis

The f2 similarity factor, as defined by the FDA, is used to compare dissolution profiles between test and reference batches. An f2 value between 50 and 100 indicates similarity between two profiles and is a regulatory requirement for post-approval changes and scale-up. The formula is: f2 = 50 × log{[1 + (1/n)Σ(Rt - Tt)²]^-0.5 × 100}, where Rt and Tt are the mean percentage dissolved at each time point for reference and test, respectively.

7. SELECTED DRUG PRODUCTS AND CASE STUDIES

7.1 Marketed SR Pellet Products

Table. 8 Marketed products

Product (Brand)	Drug	Indication	Pellet Technology
Theo-Dur Sprinkle	Theophylline	Asthma / COPD	SR matrix pellets in capsule
Toprol-XL (metoprolol SR)	Metoprolol succinate	Hypertension, Heart failure	ES pellets with HPMC
Verapamil SR (Verelan PM)	Verapamil HCl	Hypertension, Angina	Coated SR pellets
MS Contin (Morphine SR)	Morphine sulfate	Chronic pain	SR matrix pellets
Dexedrine Spansule	Dextroamphetamine	ADHD	Ion exchange + coated pellets
Omeprazole DR	Omeprazole	GERD, Peptic ulcer	Enteric-coated pellets (ES- based)

7.2 Representative Research Examples

Numerous studies have validated the superiority of ES-derived SR pellets. Highlighted examples include:

- Mutalik et al. (2008) prepared SR pellets of metformin HCl using MCC and HPMC K4M matrix; ES-produced pellets showed superior sphericity, drug loading of 70%, and first-order release over 12 hours
- Wagner et al. (2011) compared ES pellets to drug-layered beads for diltiazem SR; ES pellets demonstrated better content uniformity (RSD < 2%) and more reproducible release profiles upon coating with ethylcellulose
- Barreto et al. (2014) demonstrated that ibuprofen SR pellets prepared by ES and coated with Eudragit RS:RL (1:2) achieved excellent pH-independent release over 8 hours with low friability (< 0.5%)
- Kambayashi et al. (2016) used design of experiments (DoE) to optimize ES parameters (spheronizer speed, time, water content) for

pellets with aspect ratio > 0.90 and 80% drug release at 12 hours

8. CHALLENGES AND LIMITATIONS

8.1 Formulation Challenges

- MCC dependence: ES is heavily reliant on MCC as an extrusion aid; APIs that disrupt MCC network (e.g., highly soluble salts, high-melting waxy materials) pose challenges
- Low drug loading for certain APIs: Potent drugs requiring very low doses may not provide sufficient mass for pelletization
- Hydrolysis-sensitive APIs: Water used as granulating liquid can degrade moisture-sensitive drugs (e.g., aspirin, β-lactams)
- Waxy or lipophilic drugs: These reduce water absorption of MCC, producing poorly formed extrudates

8.2 Process Challenges

- Critical water content window: The range of water content that produces optimal wet mass consistency is narrow; small deviations lead to non-spherical or broken pellets
- Scale-up complexity: While generally scalable, ES requires careful re-optimization of spheronization parameters during scale-up
- Coating variability: Spray rate, atomization air pressure, and bed temperature must be tightly controlled to ensure uniform coating; under-coating leads to dose dumping
- Curing requirements: Ethylcellulose-coated pellets often require post-coating curing (40–60°C for 12–24 hr) to achieve stable and reproducible release profiles

9. REGULATORY CONSIDERATIONS

Sustained release pellets, as modified-release dosage forms, are subject to stringent regulatory requirements. Key regulatory guidelines governing their development and approval include:

- ICH Q6A: Specifications — Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
- FDA Guidance for Industry: Extended Release Oral Dosage Forms — Development, Evaluation, and Application of In Vitro/In Vivo Correlations (IVIVC)
- FDA Guidance: Scale-Up and Post-Approval Changes (SUPAC-MR) for modified-release dosage forms
- EMA Guideline on Quality of Oral Modified Release Products
- ICH Q8/Q9/Q10: Pharmaceutical Development, Quality Risk Management, and Pharmaceutical Quality System

Establishing an in vitro-in vivo correlation (IVIVC) for SR pellets is highly desirable from a regulatory perspective, as a validated IVIVC allows dissolution testing to serve as a surrogate for in vivo bioavailability studies in certain post-approval changes. Level A IVIVC, which establishes a point-to-point relationship between in vitro dissolution and in vivo absorption, represents the gold standard.

10. FUTURE PERSPECTIVES

The field of SR pellets prepared by extrusion-spheronization continues to evolve rapidly.

Several emerging trends and technologies are expected to shape the future of this dosage form:

- Hot-melt extrusion-spheronization (HME-S): Combining HME (solvent-free, thermoplastic processing) with spheronization to produce amorphous solid dispersions in pellet form — of particular relevance for BCS Class II drugs
- Continuous manufacturing (CM): The pharmaceutical industry is transitioning from batch to continuous processing; twin- screw extruders with in-line spheronization represent a promising platform for continuous SR pellet manufacture
- 3D printing of pellets: Selective laser sintering and fused deposition modeling are being explored for on-demand, personalized SR pellet production with programmable release profiles
- Nanotechnology integration: Nanoparticle-loaded pellets combining the advantages of nano-drug delivery (solubility enhancement, targeting) with the multiparticulate benefits of pellets
- Colon-targeted SR pellets: pH-sensitive and microbially-triggered coatings on ES pellets for targeted delivery to the large intestine in IBD, colorectal cancer, and local colon infections
- IVIVC-guided formulation: Advanced mechanistic PBPK modeling tools will enable more rational design of SR pellet formulations with predictable in vivo performance

11. CONCLUSION

This review has provided a comprehensive and critical analysis of sustained release pellets prepared by the extrusion-spheronization technique. The multiparticulate nature of pellets, combined with the superior physical and technological properties conferred by the ES process, makes this combination one of the most powerful and versatile platforms in modern pharmaceutical drug delivery.

SR pellets prepared by ES demonstrate unequivocal advantages over conventional IR dosage forms and monolithic SR tablets — including predictable, dose-dump-resistant release profiles; flexible pharmacokinetic engineering; improved patient compliance; and superior coating uniformity. Among pelletization techniques, ES stands out for its ability to produce pellets of exceptional sphericity, narrow size distribution, and high drug loading, combined with its scalability, cost-effectiveness, and compatibility with both matrix and reservoir SR designs.

While challenges related to MCC dependence, water-sensitive APIs, and coating uniformity remain areas of active research, ongoing innovations in continuous manufacturing, HME-spheronization, and IVIVC modeling are steadily expanding the applicability and precision of ES-derived SR pellets. For pharmaceutical scientists, B.Pharm and M.Pharm students, and clinicians engaged in rational drug delivery design, a thorough understanding of this technology is not only academically essential but clinically consequential.

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