International Journal on Science and Technology (IJSAT)
E-ISSN: 2229-7677 ● Website: www.ijsat.org ● Email: editor@ijsat.org

Sustained-Release Pellet Techniques: A Review

Ms. Shivanjali D. Nikam[1], Dr. Ravi D. Hole[2]

[1]Research Scholar, Dattakala Institute of Pharmaceutical Science and Research, Swami Chincholi (Bhigwan), Daund, Pune. 413130
[2]Associate Professor, Dattakala Institute of Pharmaceutical Science and Research, Swami Chincholi (Bhigwan), Daund, Pune. 413130

Abstract:
Sustained-release (SR) oral dosage forms are designed to prolong drug release, reduce dosing frequency, maintain therapeutic concentrations and improve patient adherence. Multiparticulate systems, particularly pellets, have attracted considerable interest because they distribute the drug over the gastrointestinal tract and can provide reproducible release when appropriately formulated. Pellets are small, free-flowing, approximately spherical units that may be manufactured by extrusion–spheronization, solution or suspension layering, powder layering, fluid-bed coating, rotary processing and other pelletization approaches. Their release can be modified using matrix formers, polymeric membrane coatings, lipid materials, osmotic components, ion-exchange systems and combinations of these mechanisms. This review summarizes the fundamentals of sustained release pellet systems, pellet properties, major manufacturing techniques, formulation variables, polymers and excipients, mechanisms of drug release, evaluation parameters, advantages and limitations, scale-up considerations, and recent developments. Emphasis is placed on the relationship between pellet structure, coating characteristics and in-vitro drug-release behavior. Proper control of particle size, porosity, drug distribution, coating weight gain, polymer permeability and process parameters is essential for obtaining robust and reproducible sustained-release products.

Keywords: sustained release; pellets; multiparticulate drug delivery; extrusion–spheronization; fluid-bed coating; polymer coating; controlled release.

1. Introduction

Oral sustained-release dosage forms are an important approach for improving the performance of drugs that require repeated administration. Conventional immediate-release tablets may produce relatively rapid increases in plasma drug concentration followed by a decline below the therapeutic range. Repeated dosing can therefore produce fluctuations in concentration and may increase the risk of adverse effects or inadequate therapeutic response. Sustained-release systems are intended to release the drug at a controlled rate for an extended period, thereby reducing dosing frequency and maintaining drug exposure within a desirable range.

Pellets are particularly useful multiparticulate carriers for sustained drug delivery. A pellet is generally a small, spherical or near-spherical agglomerate containing drug and excipients, often in the approximate size range of 0.5–1.5 mm. Multiple pellets can be filled into capsules or compressed into tablets. Because a dosage unit contains many individual subunits, failure of a small number of pellets has less influence on the overall release profile than failure of a single monolithic unit. Multiparticulate systems

may also reduce the risk of local high drug concentrations and can provide more uniform gastrointestinal distribution.

Sustained-release pellets can be designed as matrix pellets, reservoir-coated pellets, or hybrid systems. In matrix pellets, the drug is dispersed in a polymeric or lipid matrix and diffuses or erodes from the matrix. In reservoir systems, an immediate-release drug-loaded core is covered with a functional membrane that controls penetration of gastrointestinal fluid and diffusion of dissolved drug. Combination designs can incorporate an inert core, drug layer, seal coat, functional polymer coat and topcoat. The final release pattern is determined by formulation composition and manufacturing conditions.

The development of SR pellets requires an integrated understanding of drug properties, excipient functionality, pelletization, coating technology and dissolution behavior. Factors such as aqueous solubility, dose, particle size, drug–polymer compatibility, core porosity, coating thickness and polymer permeability strongly influence performance. The objective of this review is to describe the principal pellet techniques used for sustained drug release and the formulation and evaluation principles underlying their successful application.

2. Advantages of Sustained-Release Pellets

Pellet-based systems offer several advantages over conventional single-unit dosage forms. First, multiparticulates are distributed throughout the gastrointestinal tract, which can reduce variability associated with gastric emptying and localized drug release. Second, pellets may be filled into hard gelatin or HPMC capsules and can also be compressed into tablets, providing manufacturing flexibility. Third, release can be modified by changing the matrix composition or membrane coating without substantially changing the total drug dose.

Pellets may also improve dose reproducibility because a large population of units contributes to the total release profile. The small size of the individual units can reduce the consequences of accidental dose dumping from one unit. Coated pellets can be engineered to provide sustained release, delayed release, pulsatile release or combinations of these profiles. For drugs that require prolonged exposure but have a suitable dose and stability profile, this flexibility makes pellets attractive for oral controlled-release development.

3. Ideal Characteristics of Pharmaceutical Pellets

An effective pellet formulation should possess adequate sphericity, smooth surface morphology, narrow particle-size distribution, sufficient mechanical strength and low friability. Good flow is required for transfer, capsule filling and coating. A relatively uniform surface is especially important for film coating because variations in surface roughness can cause differences in local coating thickness and consequently alter drug release.

Pellets should also demonstrate adequate porosity to permit controlled penetration of coating solutions or gastrointestinal fluid. However, excessive porosity may increase fluid uptake and accelerate release. Mechanical strength must be balanced against porosity because highly compact pellets may resist processing but can exhibit poor drug release or inadequate coating adhesion. The optimum properties therefore depend on the intended release mechanism and manufacturing process.

4. Drug and Excipient Considerations

The physicochemical characteristics of the drug are central to SR pellet design. Solubility, dose, permeability, particle size, melting point, stability and tendency to interact with polymers influence the choice of technique. Highly water-soluble drugs often require a relatively impermeable or thick functional coating, whereas poorly soluble drugs may need formulation strategies that prevent excessively slow release.

Common pellet excipients include microcrystalline cellulose, lactose, starch, mannitol, dicalcium phosphate and other fillers or binders. Microcrystalline cellulose is widely used in extrusion–spheronization because it provides plasticity and helps retain water during extrusion. Povidone and other binders may improve cohesion. Disintegrants may be incorporated when rapid penetration of fluid into a matrix is required, although their use must be consistent with the intended sustained-release mechanism.

Functional polymers are selected according to their permeability, swelling, erosion and pH-dependent properties. Ethylcellulose is widely used as a water-insoluble diffusion-controlling polymer. Acrylic polymers such as certain ammonium methacrylate copolymers can provide controlled permeability. Hydroxypropyl methylcellulose and hydroxypropyl cellulose may be used as matrix formers or film-forming components. Polyvinyl acetate-based systems can provide sustained release through diffusion and polymer characteristics. Plasticizers such as triethyl citrate or polyethylene glycol may improve film flexibility and reduce brittleness, while anti-tacking agents such as talc can improve coating processability.

5. Major Techniques for Preparation of Sustained-Release Pellets

Several pelletization techniques are available. The choice depends on the drug dose, material properties, desired pellet structure, equipment availability and scale-up requirements. The major techniques include extrusion–spheronization, solution layering, suspension layering, powder layering, fluid-bed pelletization and rotary or centrifugal pelletization. Each method produces characteristic internal structures and surface properties that influence subsequent coating and drug release.

5.1 Extrusion–Spheronization

Extrusion–spheronization is one of the most widely investigated techniques for producing dense, spherical pellets. The drug and excipients are first blended, followed by addition of a suitable quantity of granulating liquid to form a wet mass. The wet mass is forced through a screen or die to form cylindrical extrudates. These extrudates are transferred to a spheronizer, where frictional forces break them into shorter segments and round them into pellets. The pellets are then dried and, when required, coated with a functional polymer.

The technique provides good control over pellet size and can produce mechanically strong units with relatively low friability. Microcrystalline cellulose is particularly useful because of its water-retention and plastic deformation properties. The amount and type of granulating liquid, extrusion speed, screen diameter, spheronization speed and time, and drying conditions can substantially affect pellet density, porosity and shape. Excessive liquid may produce sticky masses, whereas insufficient liquid can result in weak extrudates and irregular pellets.

For sustained release, the drug-containing pellets can be formulated as a matrix using hydrophilic or hydrophobic polymers. Alternatively, the pellets may serve as cores for subsequent film coating. A combination of matrix formulation and membrane coating can provide a more robust release profile.

5.2 Solution Layering

In solution layering, a drug is dissolved in a suitable solvent or vehicle together with binders and other excipients and sprayed onto starter cores. The cores are continuously agitated, usually in a fluidized-bed or other suitable coating system, while the drug solution is introduced. Solvent evaporation leaves a progressively thicker drug layer. Multiple cycles may be used until the desired drug loading is achieved.

Solution layering can provide relatively uniform drug distribution and is suitable when the drug is sufficiently soluble and stable in the selected solvent system. The process requires careful control of spray rate, atomization pressure, inlet air temperature, product temperature and drying conditions. Excessive spray rate may cause overwetting and agglomeration, whereas excessive drying can lead to poor layering or spray-drying of droplets before they reach the cores.

5.3 Suspension Layering

Suspension layering is useful when the drug has limited solubility in the coating vehicle. Drug particles are suspended with binders and other excipients and sprayed onto starter cores. Continuous agitation of the suspension is necessary to minimize sedimentation and maintain uniform drug concentration. The process can reduce the need for organic solvents and can be adapted to aqueous systems.

Particle size of the suspended drug, suspension viscosity, solids concentration, spray rate and drying conditions influence the quality of the drug layer. Appropriate atomization and fluidization are necessary to obtain uniform deposition. The drug-layered pellets can subsequently receive a seal coat and sustained-release membrane.

5.4 Powder Layering

Powder layering involves applying dry drug or excipient powder to moist or adhesive starter cores. A binder solution may be sprayed while powder is simultaneously or sequentially added. The process builds up the pellet through repeated deposition and adhesion. It can be useful for drugs with poor solubility or limited stability in solution.

The major challenges are achieving uniform powder distribution and preventing agglomeration. Powder particle size, binder concentration, spray rate and process airflow affect pellet growth. The technique can be advantageous when avoiding dissolution of the drug is important.

5.5 Fluid-Bed Pelletization and Coating

Fluid-bed technology is widely used for both pellet formation and functional coating. In a fluidized bed, air suspends the particles and provides efficient heat and mass transfer. Drug layering, matrix formation and polymer coating may be performed using top-spray, bottom-spray or related configurations. The bottom-spray Wurster process is particularly important for coating individual pellets because it provides controlled circulation of particles through the spray zone.

For sustained-release coating, an aqueous or organic polymer dispersion or solution is atomized onto fluidized pellets. The coating liquid wets the surface, and solvent evaporation leaves a polymeric film. Coating weight gain, polymer concentration, plasticizer content, spray rate, atomization pressure and drying conditions determine membrane structure. Adequate curing may be required for some polymer systems to stabilize film properties.

5.6 Centrifugal and Rotary Pelletization

Centrifugal or rotary pelletization uses rotational forces to agglomerate and round particles. Wet material is introduced onto a rotating plate or disk, where centrifugal forces and controlled wetting produce spherical pellets. The technique can provide high production rates and may be suitable for scale-up. Process variables include rotational speed, liquid addition rate, feed rate and material composition.

Rotary systems can produce pellets with useful density and mechanical strength. However, formulation development must address the balance between liquid content, pellet growth and agglomeration. Subsequent coating can be used to achieve the required sustained-release profile.

6. Sustained-Release Coating of Pellets

Film coating is one of the most important approaches for converting drug-loaded pellets into sustained-release systems. A functional membrane is deposited around the pellet surface and controls the entry of aqueous medium and diffusion of dissolved drug. The membrane may be water-insoluble but permeable, pH-dependent, or composed of blends of polymers with different permeability.

Ethylcellulose is commonly used because it forms a water-insoluble film through which drug can diffuse. The permeability can be modified by incorporating water-soluble pore-forming materials. Acrylic polymers can similarly provide controlled permeability, and blends allow adjustment of release rate. The coating must be sufficiently continuous to avoid premature release but sufficiently permeable to permit the desired drug flux.

Coating weight gain is an important development parameter. Increasing coating weight generally increases diffusional path length and may reduce the release rate, although the relationship is not necessarily linear. Polymer type, molecular characteristics, plasticizer concentration, curing conditions and pellet surface morphology can alter film integrity. Uniform fluidization and spray conditions are therefore essential.

Table 1. Comparison of Major Pelletization Techniques

Technique	Main principle	Key advantages	Major limitations
Extrusion–spheronization	Wet mass → extrusion → rounding	Spherical, strong pellets; good control	Requires suitable wet-mass properties
Solution layering	Drug solution deposited on starter cores	Uniform drug layering	Solubility/solvent constraints
Suspension layering	Drug suspension deposited on cores	Useful for poorly soluble drugs	Suspension stability and agglomeration
Powder layering	Powder adhered using binder	Avoids dissolving drug	Uniform deposition can be difficult
Fluid-bed coating	Atomized polymer deposited during fluidization	Excellent coating control; scalable	Process-sensitive and equipment-intensive
Centrifugal pelletization	Rotational forces form pellets	High throughput potential	Formulation/process optimization needed

7. Mechanisms of Drug Release from Sustained-Release Pellets

Drug release from pellets may occur through diffusion, polymer swelling, erosion, dissolution, osmotic pressure or combinations of these mechanisms. In a hydrophobic membrane system, gastrointestinal fluid enters through pores or by diffusion through the polymer, dissolves the drug and allows dissolved molecules to diffuse outward. In a hydrophilic matrix, the polymer hydrates and forms a gel layer through which the drug diffuses. The gel may gradually erode, adding an erosion component to release.

The Higuchi model is often used to describe diffusion-controlled release from certain matrix systems. Zero-order models are used when a nearly constant release rate is achieved, while first-order behavior describes release related to the amount of drug remaining. Korsmeyer–Peppas analysis can be used to help characterize release mechanisms when appropriate. Model fitting should be interpreted together with formulation structure and experimental observations rather than relying only on correlation coefficients.

8. Evaluation of Sustained-Release Pellets

Pellets are evaluated for physical, chemical and biopharmaceutical performance. Important physical tests include particle-size distribution, shape and sphericity, bulk and tapped density, angle of repose, flow properties, friability, crushing strength and moisture content. Microscopic examination and imaging methods can be used to assess surface morphology and coating uniformity.

Drug content and content uniformity are essential quality attributes. Differential scanning calorimetry, infrared spectroscopy and other compatibility or solid-state techniques may be used during development to evaluate drug–excipient interactions and physical changes. For coated pellets, coating thickness and weight gain are monitored to maintain reproducibility.

In-vitro dissolution is the principal performance test for sustained-release pellets. Appropriate dissolution media, apparatus, agitation conditions and sampling intervals should be selected to discriminate among formulations. The resulting release profile is compared with the target profile and may be analyzed using kinetic models. Stability studies should examine physical appearance, drug content, moisture, coating integrity and dissolution performance under relevant storage conditions.

9. Factors Affecting Drug Release

Drug release is affected by pellet size, porosity, drug loading, polymer concentration, polymer permeability, coating thickness, plasticizer level, and pore former content and curing conditions. Smaller pellets have a higher surface-area-to-volume ratio and may release drug differently from larger pellets when formulation and coating are otherwise comparable. Increased porosity may increase liquid penetration and accelerate release.

The solubility of the drug is another major determinant. Highly soluble drugs can diffuse rapidly through a porous coating, requiring greater resistance from the membrane. Poorly soluble drugs may show slow release because dissolution within the pellet becomes the limiting step. The pH and ionic composition of the dissolution environment can also influence drug solubility and polymer behavior.

Process variables are equally important. In coating operations, spray rate, atomization, inlet temperature, airflow and product temperature affect film formation. In extrusion–spheronization, liquid level and mechanical energy determine pellet structure. Consequently, formulation and process variables should be optimized together rather than independently.

10. Advantages and Limitations

Sustained-release pellets offer dose flexibility, good gastrointestinal distribution, reduced dosing frequency and multiple options for tailoring release. They can be filled into capsules or compressed into tablets and can combine immediate- and sustained-release populations to produce biphasic profiles. Multiparticulates can also reduce the influence of a single unit on the overall dosage-form performance.

Despite these benefits, pellet manufacturing can be more complex than conventional tablet compression. Multiple processing steps may be required, including pelletization, drying, drug layering and functional coating. Specialized equipment and process control may increase manufacturing costs. Film coating can be sensitive to environmental and processing conditions, and small changes in coating thickness or polymer structure may produce significant differences in release. Scale-up must therefore maintain comparable fluidization, spray distribution and drying conditions.

11. Scale-Up and Quality-by-Design Considerations

Modern development of sustained-release pellets increasingly applies Quality by Design principles. Critical quality attributes may include pellet size, sphericity, drug content, coating thickness, mechanical strength and dissolution profile. Critical material attributes include polymer grade, drug particle size, excipient properties and moisture content. Critical process parameters can include extrusion pressure, spheronization speed, spray rate, atomization pressure, airflow and product temperature.

Design of experiments can be used to identify interactions among formulation and process factors and to establish a design space. Process analytical technologies, such as in-line or at-line monitoring of temperature, moisture and particle behavior, can improve process understanding. Robust scale-up requires attention to equipment geometry and mass- and heat-transfer characteristics rather than simply increasing batch size proportionally.

12. Recent and Emerging Approaches

Current research in multiparticulate drug delivery includes functional polymer blends, aqueous coating systems, novel excipients, osmotic approaches, mucoadhesive concepts and combinations of immediate- and sustained-release pellets. Hot-melt extrusion and related solvent-free approaches have also been investigated for poorly soluble drugs and polymeric matrices. Advanced manufacturing and process monitoring may improve control of pellet structure and release.

The increasing use of physiologically based dissolution and absorption models may help link in-vitro release to expected in-vivo performance. Three-dimensional manufacturing and precision pelletization are additional areas of interest, although their routine industrial application depends on scalability, reproducibility and regulatory acceptance. Future development is expected to focus on robust, solvent-efficient and patient-centered systems capable of delivering drugs at predictable rates.

13. Conclusion

Sustained-release pellets are versatile multiparticulate drug-delivery systems capable of reducing dosing frequency and improving the consistency of drug exposure. Extrusion–spheronization, solution and suspension layering, powder layering, fluid-bed processing and centrifugal pelletization provide different routes to obtain suitable pellet cores and drug-loaded units. Among these, extrusion–spheronization is particularly useful for matrix pellets, while solution or suspension layering followed by functional film coating is highly suitable for reservoir-type systems.

Successful development depends on coordinated control of drug properties, excipient selection, pellet morphology, coating composition and process parameters. Polymer permeability, coating weight gain, porosity and curing conditions are particularly important determinants of release. Comprehensive physical characterization, dissolution testing, kinetic analysis and stability assessment are essential for

product development. With appropriate process understanding and quality-by-design approaches, sustained-release pellets can provide reproducible and adaptable oral drug-delivery platforms.

REFERENCES:

1. Ghebre-Sellassie I. Pharmaceutical Pelletization Technology. New York: Marcel Dekker; 1989.
2. Gandhi R, Naik SR, Khatri S. Extrusion-spheronization: a review. Pharm Technol. 1999.
3. Dukić-Ott A, Thommes M, Remon JP, Kleinebudde P, Vervaet C. Production of pellets via extrusion-spheronisation without microcrystalline cellulose: a critical review. Eur J Pharm Biopharm. 2009;71:38–46.
4. Parikh DM. Handbook of Pharmaceutical Granulation Technology. 3rd ed. Boca Raton: CRC Press; 2016.
5. Jones DM. Solution and suspension layering. In: Ghebre-Sellassie I, editor. Pharmaceutical Pelletization Technology. New York: Marcel Dekker.
6. Cole G, Hogan J, Aulton M, editors. Pharmaceutical Coating Technology. London: Taylor & Francis.
7. Felton LA. Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms. 3rd ed. New York: Informa Healthcare; 2012.
8. Siepmann J, Siepmann F. Mathematical modeling of drug delivery. Int J Pharm. 2008;364:328–343.
9. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci. 2001;13:123–133.
10. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983;15:25–35.
11. Higuchi T. Mechanism of sustained-action medication. J Pharm Sci. 1963;52:1145–1149.
12. Lieberman HA, Lachman L, Schwartz JB, editors. Pharmaceutical Dosage Forms: Tablets. 2nd ed. New York: Marcel Dekker.
13. Aulton ME, Taylor KMG, editors. Aulton's Pharmaceutics: The Design and Manufacture of Medicines. Elsevier.
14. Allen LV, Ansel HC. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Wolters Kluwer.
15. Qiu Y, Chen Y, Zhang GGZ, Yu L, Mantri RV, editors. Developing Solid Oral Dosage Forms: Pharmaceutical Theory and Practice. 2nd ed. Academic Press; 2017.
16. Jannin V, Lemagnen G, Gueroult P, Larrouture D, Tuleu C. Multiparticulate drug delivery systems. Adv Drug Deliv Rev. 2021.
17. Nair AB, Jacob S. A simple practice guide for dose conversion between animals and human. J Basic Clin Pharm. 2016;7:27–31.
18. World Health Organization. WHO Expert Committee on Specifications for Pharmaceutical Preparations: guidelines and related quality considerations. Geneva: WHO.