STM JOURNALS

Research & Reviews: A Journal of
Pharmaceutical Science

ISSN: 2229-7006
Volume 16, Issue 1, 2025
January–April
DOI (Journal): 10.37591/RRJoPS

https://journals.stmjournals.com/rrjops

Review RRJoPS

A Literature Review on Extrusion/Spheronization – A Pelletization Technology

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Abstract

Extrusion-spheronization is a leading pelletization technology, widely favored for its economic and commercial viability. It is a cost-effective method suitable for large-scale production, making it the most efficient approach for oral drug delivery. This process provides multiple benefits, such as improved flow characteristics, lower friability, a narrow particle size range, easier coating, consistent packing, reduced likelihood of dose dumping, and more predictable gastric emptying. Pellets usually measure between 0.5 and 1.5 mm in size. The formation of these pellets involves several stages, including nucleation, coalescence, layering, and abrasion transfer. Additionally, processes like attrition, breakage, and fragmentation contribute to the size reduction of pellets. Pelletization techniques include agitation (balling), compaction (compression, extrusion-spheronization), layering (powder or solution/suspension), and globulation (spray drying and spray congealing). Among these, extrusion-spheronization is the most prominent due to its versatility and process efficiency. Extrusion-spheronization involves distinct steps: it comprises dry mixing, wet massing, extrusion, spheronization, and drying. Various formulation factors (moisture content, granulating fluid, excipients, drugs), process parameters (spheronization time, speed, temperature), and equipment variables (mixer, extruder, extrusion screen) influence pellet quality. Pellet characterization is crucial and includes particle size distribution (PSD), surface area, sphericity, friability, and dissolution. This technology not only ensures efficient drug delivery but also facilitates the production of robust, high-quality pellets for pharmaceutical applications. Extrusion/spheronization is the most promising pelletization technology because it is both economic and commercial. Due to its affordability for large-scale production, extrusion spheronization is currently the most efficient method for oral drug delivery. Numerous benefits are available, including improved flow characteristics, a less friable dosage form, a narrow particle size distribution, ease of coating, and uniform packing. Pellets usually range in size from 0.5 to 1.5 mm. The mechanism of pellet formation involves nucleation, coalescence, layering, and abrasion transfer. Mechanisms and techniques for pelletization include agitation (balling), compaction (compression, extrusion spheronization) layering (powder, solution/suspension), and globulation (spray drying, spray congealling) described in the next section of this literature. It outlines the procedures involved in extrusion spheronization (dry mixing, wet massing, extrusion, spheronization, and drying). It also discusses the variables, such as formulation, process (moisture content, granulating fluid, excipients, drugs) equipment parameters (spheronization time, spheronization speed, spheronization temperature), and equipment parameters. (Mixer, extruder, extrusion screen that affects pellet formation. The description of pellet characterization, including PSD, surface area, sphericity, friability, and

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Received Date: December 24, 2024
Accepted Date: January 27, 2025
Published Date: February 01, 2025

Citation: Nandlal B. Savaliya, Chetan H. Borkhataria, Chintankumar J. Tank, Harshal A. Sadhariya. A Literature Review on Extrusion/Spheronization – A Pelletization Technology. Research & Reviews: A Journal of Pharmaceutical Science. 2025; 16(1): 61–71p.

dissolution is given at last.
Keywords: Pelletization, spheronization, extrusion, pelletization technique, characterization of pellets

INTRODUCTION

One of the most well-liked multi-particulate dose forms is pellets. Pelletization refers to the process of forming spherical, free-flowing pellets from powders or granules. The size range of pellets typically falls between 500 µm and 1500 µm. Multiparticulate dosage forms, such as pellets, offer several advantages over single-unit forms, including controlled drug release, improved flow properties, reduced risk of sudden drug release (dose dumping), enhanced stability by coating, improved bioavailability by minimizing variability and improved drug efficacy through consistent gastric transit [1, 2].

FORMATION AND MECHANISM OF PELLETS

Understanding the underlying mechanisms of pellet formation and growth is crucial for selecting and optimizing the pelletization process. The key events involved in pellet formation and development include nucleation, coalescence, layering, abrasion transfer, and size reduction [1].

Nucleation

This is the initial stage where small particles or agglomerates begin to form because of the interaction between fine powders or granules. It marks the starting point of the pellet formation process (Figure 1).

Figure 1. Nucleation.

Coalescence

During coalescence, the formed nuclei or agglomerates begin to merge or fuse together, leading to the growth of the pellets. This process helps in the formation of larger, more stable particles (Figure 2).

Figure 2. Coalescence.

Layering

In this stage, additional material (such as binder solution or powder) is added to the growing pellet to increase its size. The material coats the surface of the pellet, contributing to its growth and structural integrity (Figure 3).

Figure 3. Layering.

Abrasion Transfer

Abrasion transfer occurs when smaller particles are transferred onto the growing pellet during the agglomeration process. This helps in smoothing the surface and increasing the pellet size (Figure 4).

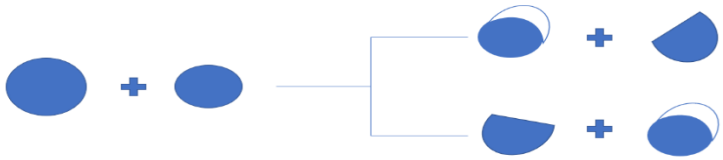

Figure 4. Abrasion transfer and mechanism of size reduction.

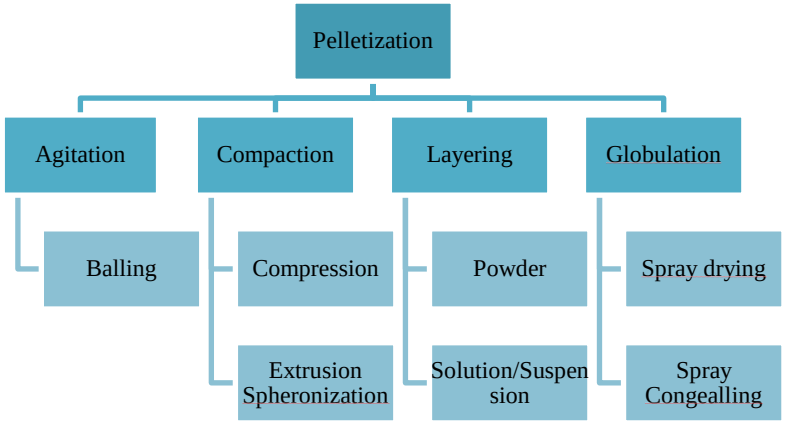

Figure 5. Various pelletization techniques.

BALLING

Pellets are formed through a process known as balling, which involves the rolling and tumbling of materials within equipment, such as pans, discs, drums, or mixers (Figure 5) [3].

LAYERING [1]

Pelletization by layering involves the systematic application of successive layers of drug entities, which can be derived from solutions, suspensions, or dry powders, onto preformed nuclei. These nuclei may consist of crystals or granules made from the same material or an inert starter material [1].

In powder layering, fine powders are applied to seed particles using a binding liquid, while in solution/suspension layering, active substances are sprayed onto the core as a liquid and dried simultaneously. These methods are commonly used in pharmaceutical manufacturing for controlled-release formulations.

EXTRUSION/SPHERONIZATION

The spheronization technique emerged in the early 1960s as a method for pelletization. For the formulation of controlled and modified-release systems, it is essential to achieve a uniform coating and free-flowing properties, which require a consistently smooth surface and a narrow size distribution. The primary objective of this process is to produce pellets or spheroids that are uniformly sized and possess a high drug-loading capacity. Extrusion spheronization is a multi-step process that begins with a pre-consolidation phase through extrusion, followed by the spheronization stage to create spherical particles known as spheroids, pellets, beads, or matrix pellets, depending on the materials and techniques employed. This technology has gained significant popularity in recent years due to its user-friendliness, rapid processing capabilities, and high efficiency. Consequently, efficient extruders are crucial for transforming the desired characteristics into uniform fragments that can be rounded into pellets with a narrow size distribution [3].

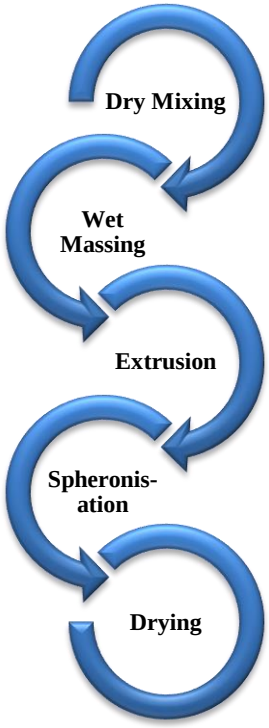

Figure 6. Steps during the extrusion spheronization.

STEPS USED IN EXTRUSION/SPHERONIZATION

Step 1. Dry Mixing

Homogeneous powder dispersion is achieved using various mixing equipment, including twin shell mixers, high-shear mixers, tumbler mixers, and planetary mixers [3].

Step 2. Wet Massing

Planetary mixers are employed to achieve a sufficient plastic mass of mixed powders. During this stage, granulation techniques that are traditionally utilized for producing compression products are implemented [4]. This process is typically done in a batch mixer/granulator. Sigma blade mixers, Horizontal or Vertical high shear mixers, Planetary mixers, and other batch-type processors are examples. In contrast, continuous mixers, such as high shear twin screw mixer/extruders[4] and the Nica M6 instant mixer [5, 6].

Step 3. Extrusion

The wet mass is converted into rod-shaped particles in these. The wet mass is forced through dies and formed into small cylindrical particles of uniform diameter. Under their weight, the extrudate particles turn at identical lengths [6]. Screw, sieve and basket, roll, and ram extruders are the four main classes of extruders that can be used to carry out the extrusion process, they are used not only in the pharmaceutical industry but also in the food, ceramics, and polymer industries. It is also possible to prepare extrudate for further processing using the extrusion method. By mixing the powder and granulation liquid inside the extruder's barrel, this technique allows for the continuous preparation of granules using a screw extruder (Figure 6) [7].

Step 4. Spheronization

During the spheronization process, extruded materials are transformed into spherical particles due to frictional forces generated by the interaction between the particles and the spheronizer. Initially, the extrudate, which starts as rod-shaped pellets, undergoes several stages of transition to achieve a spherical shape. Once introduced into the spheronizer, centrifugal forces cause the extrudate to move

toward the equipment's walls. The extrudate fragments into smaller, more uniform pieces under ideal circumstances. Due to attrition and the quick movement of the bottom plate or disc, each piece's length quickly equals its diameter in most cases (Figure 7) [6].

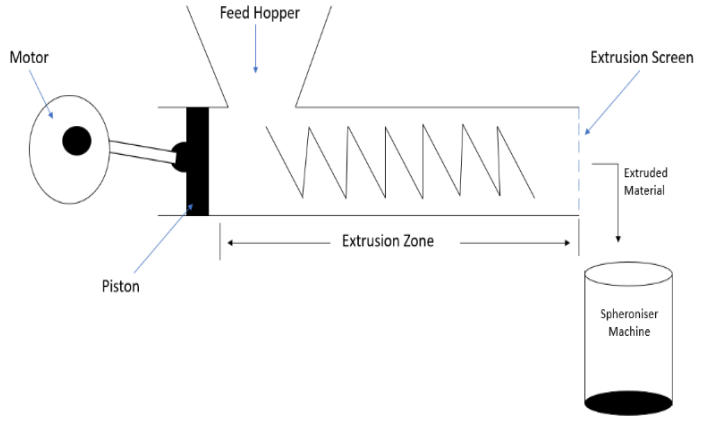

Figure 7. Schematic representation of extrusion spheronization machine.

Step 5. Drying

The drying of the final extruded material is carried out in any type of dryer, such as a tray dryer, etc.[6] As various drying methods have many benefits. Because removing the water makes a significant difference [6]. In a static bed, tray drying takes a bit of time. This makes it the most likely scenario for a drug to migrate toward the surface and recrystallize [8].

PARAMETERS INFLUENCING THE PELLET QUALITY

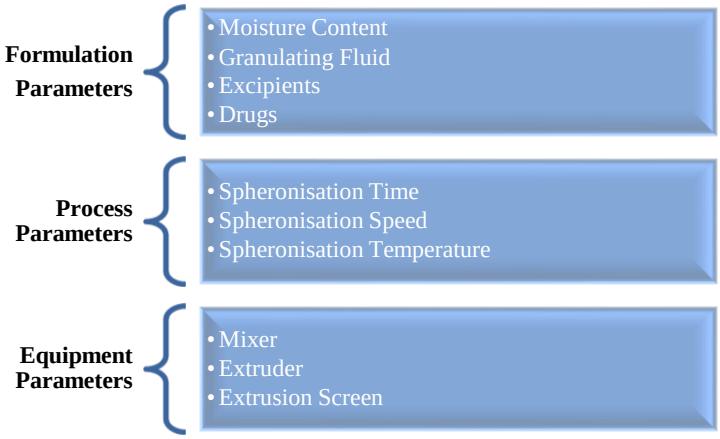

Figure 8. Parameters influencing the pellet quality.

FORMULATION PARAMETERS

Moisture Content

Tomer and Newton (1999) the liquid of choice in extrusion/spheronization systems is typically water, as previously stated. Success depends on how it behaves during the process [9]. The majority of extrusion formulations involve pressures that also cause water to move. It's critical to know how to limit and control water circulation as well as its effects. According to Lustig-Gustafsson et al. (1999), a limited water level range could be troublesome for the development of an extrusion/spheronization formulation, especially during the scale-up process [10]. The most significant aspect of the extrusion

process variables is water content, which has a significant impact on the spheres' quality [1]. According to Tomer & Newton, 1999 water movement during extrusion is critical to the process. This allows water to soften the mass and migrate to the die walls, acting as a lubricant (Figure 8) [9].

Granulating Fluid

Tomer & Newton (1999) mentioned that the liquid of choice in extrusion/spheronization systems is typically water [9]. It was reported by Dreu et al. (2005) that using ethanol or ethanol-water mixtures as granulation liquids during the extrusion-spheronization process produces pellets with mechanical and structural properties that differ significantly from those created using only water.

It has been demonstrated that the combination of ethanol, ethanol/water mixtures, 2-propanol, and 2-propanol/water mixtures produces pellets with significantly different mechanical and structural properties [11]. The inclusion of ethanol in the wetting liquid, according to Hamedelniel et al., decreased the amount of active agent that was released during the first phase of the dissolution process while also lowering the hardness of the pellets.

Excipients

According to Law & Deasy, 1997 Extrusion-spheronization may employ a variety of excipient classes, with potential effects on the yield and quality of the pellets produced as well as on the drug release properties of those pellets. It was anticipated that adding silicates would increase the mix's plasticity and encourage rounding during spheronization, resulting in pellets with the desired improved sphericity. This effect, however, was only perceptible in the case of Kaolin, Talc, and Veegum, indicating that the trend is not commonplace in this class of materials [12].

Prior studies have revealed that Avicel PH-101 appears to be an ideal matrix material for the preparation of low-drug-loading pellets; these beads remain intact during dissolution testing in water [13]. According to Ghali et al. (1989), the Avicel RC-581 appears to be better suited to the preparation of pellets containing a high drug dose [13].

Pelletization using MCC to defer the release of the drug from a formulation containing MCC, Pectin, and Chitosan. As MCC levels dropped, the rate at which drugs were released also increased [14]. During the pellet preparation process, MCC loses its swelling properties, which prevents pellet disintegration and complicates drug contact with the dissolution fluid. With poorly soluble drugs like Ibuprofen, this effect of MCC becomes more pronounced. To produce pellets of these types of medications, Pectin, and Chitosan, which are polysaccharides for pelletizing, can be suitable alternatives to MCC or even a better choice [14].

DRUGS

For the preparation of pellets of various materials, including natural extract, bacterial culture, drugs, etc., one can use the extrusion/spheronization technique. Additionally, one can prepare various types of pellets (immediate release, modified release) [1].

Mesoporous silica was used to create immediate-release pellets of carbamazepine [15]. Hydrochlorothiazide and piroxicam, which are insoluble, are combined with modified starch to create immediate-release pellets (high-amylose, crystalline, and resistant starch) [16]. Using novel latex-like Ethyl acrylate (EA) and methylmethacrylate materials, controlled-release ibuprofen pellets were created (MMA) [17].

Gupta & Khan, 2011 prepared the controlled-release matrix pellets of Olanzapine Sawicki, 2001 Prepared the controlled-release floating pellets of Verapamil and Norverapamil to determine their pharmacokinetics [18, 19]. To regulate the release of propranolol hydrochloride from pellets, hot-melt coatings of polymers like golyglycolysed glyceride (GelucireR 50/02) and glycerol palmitostearate

(precirolR ATO5) are used by Sinchaipanid et al. (2004) [20].

To improve the solubility of paliperidone and provide a stable concentration of the drug in blood the ascending controlled-release pellets were prepared by Yang et al. (2018) [21]. Kan et al. (2015) Prepared the salvianolic acid B micro-porous osmotic pump pellets with appropriate In vitro release profiles needed to create a reliable *IVIVC* [22]. Celphere® 102 and Suglet® were used as the core seeds in the design of the sustained-release pellet formulation of Domperidone, while Kollicoat® SR 30 D was used as the rate-regulating polymer [23].

Szewczyk et al. (2020) used Mesoporous silica as a polymer to prepare the cefazolin pellets for a dual-purpose medication delivery system [24].

EQUIPMENT PARAMETERS

Mixer

At both the extrusion and spheronization stages, it was observed that the mixer type had a greater impact on the paste behaviors than the projected mixer shear strain rate [25].

Extruder

A study conducted by Baret J.P. Remon and Newton (1992) found that when water movement is considered, the use of a ram extruder to evaluate the ability of formulations to create spherical granules from gravity feed extruders has been proven as a good approach [26]. When a formulation is transferred from the ram to the gravity feed extruder, less water will be needed, which may be explained by this water movement. A study revealed that the quality of spheres obtained by gravity feed extruders is slightly narrower as compared to twin screw extruders [27].

Extrusion Screen

Vervaet et al. (1994) studied how the quality of the final pellets is influenced by using an extruder equipped with a screen having a length-to-radius (L/R) ratio between 2 and 4. Pellets with an L/R ratio of 2 where a loosely bound extrudate with significant surface flaws is produced. Even at lower water concentrations, smooth and well-bound extrudates were produced by pellets with an L/R ratio of 4 [28].

PROCESS PARAMETER

Spheronization Time

The quality of the spheres is profoundly influenced by the spheronization period [29]. The spheronization Period also has an impact on the spheres' roundness. The spherical spheres are likewise produced by a longer spheronization period [30].

Spheronization Speed

According to Bölcskei et al., spheronization speed also profoundly affects the quality of pellets [29]. More spherical particles were created at high speed and extended time [6]. The friction plate's speed and the residence time had the greatest effects on the shape of the pellets. The pellets appeared rounder when the speed and time were increased [5].

Spheronization Temperature

Extrusion temperature should be controlled for the following reasons: a. there are heat-sensitive active ingredients; b. liquid-phase rheology is important, either due to liquid-phase migration being promoted by a lower viscosity at higher temperatures, or the formation of micelles; c. particle softening may be an issue; and d. evaporation of the liquid phase (Le. water) from the extrudate, particularly from its surface, may affect the spheronization [31].

EVALUATION OF PELLETS

Particle Size Distribution

The particle size distribution (PSD) plays a crucial role in influencing the rheological properties of the wet powder mass during extrusion [31]. Lactose particle size has previously been demonstrated to be an important factor in preparing a uniform, consistent extrudate [32]. Increasing the size of the lactose particle used to have a significant effect on the force-displacement profile, exacerbating extrusion to occur at high pressures under forced flow conditions [33]. With the sonicated MCC dispersions in the various liquids, it was possible to observe a decrease in particle size and a wider size distribution of all the MCC grades [34].

Surface Area

The release rate of pellets is significantly influenced by their surface area, which is determined by factors, such as particle size, shape, porosity, and surface texture [1]. The findings suggest that incorporating the model drug into MCC containing extrusion/spheronization wet masses with a larger surface area increases its water sensitivity [9].

Sphericity and Roundness

The roundness of a pellet is a critical characteristic. During the spheronization process, the particles undergo various shape transitions, starting as cylinders and progressing through stages, such as cylinders with rounded edges, dumbbell shapes, and elliptical forms, eventually achieving nearly perfect spheres. This roundness is determined using computer-aided image analysis, which calculates it based on the pellet's projected area and perimeter (Figure 9) [7].

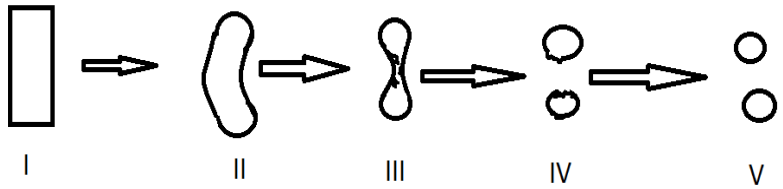

Figure 9. Pellet forming mechanism: I. Cylinder; II. Cylinder with Rounded Edges; III. Dumb-Bell Shape; IV. Ellipse; V. Sphere.

Density

Bulk and tap densities of pellets are measured to assess the uniformity of their particle size distribution [7]. By measuring the displacement with He or Hg, it is possible to determine the true density of pellets, which evaluates their porosity [7].

Friability

A solid's propensity to crumble into smaller pieces when put under stress or contact, particularly when being rubbed, is referred to as its friability. Spheres are considered acceptable if their friability is less than 0.2% [28]. A friability is reduced as an increase in the size of the extruder screen size [6]. The low friability may provide mechanical resistance during subsequent pharmaceutical processes, such as coating or tablet compression [24].

Disintegration

To have rapid absorption, there must be rapid disintegration. According to Vervaet et al., the most popular excipient for pellets made by extrusion/spheronization is microcrystalline cellulose (MCC)[7]which has good binding properties and gives the wet mass the necessary plasticity [35]. The drug is indeed released through diffusion through an insoluble inert matrix because MCC-based pellets do not disintegrate. Martin S. and Peter K (1995) used a 40% IPA and water mixture as a granulating liquid to make MCC pellets and discovered that the liquid dissolved quickly. When compared to pellets obtained with less IPA in the mixture, these phenomena are caused by the pellets

disintegrating quickly and completely [36].

Chamsai & Sriamornsak (2013) prepared the MCC pellets containing PEG 400, polysorbate 80, and croscarmellose sodium (CCS) for rapid disintegration of pellets and found that when compared to formulations containing PEG 400 and/or polysorbate 80, which disintegrated within 90 seconds and had increased drug dissolution, MCC pellets that did not disintegrate and showed slow drug dissolution [35].

Lundqvist A'b' et al. found that using a high-density disintegrating agent prolongs the disintegration process [37]. The friability test should be carried out as per the details given in the official book (Pharmacopoeia).

Dissolution

For solid dosage forms given orally, this test is intended to assess compliance with the dissolution requirements. In this test, the drug release from the given formulation at a specific time and under specific circumstances is measured. The detailed test procedure and other information are readily available in official books (Pharmacopoeia).

Sousa et al. found that drug and filler solubility and film coating may influence the drug release profiles [38]. Some other parameters relate to a drug's release profiles, such as hardness, composition, and drug loading [7].

CONCLUSIONS

Extrusion/spheronization is the most promising pelletization technology because it is both economic and commercial. As a result of the various drawbacks associated with the conventional technique, extrusion/spheronization produces better results. Extrusion spheronization, a flexible method for creating pellets with useful properties, has several advantages over other pelletization techniques in terms of productivity, product quality, easy processing, and quick turnaround. This method is increasingly being explored in pharmaceutical drug delivery to tackle specific challenges, including masking unpleasant tastes, enhancing the solubility and bioavailability of drugs, and enabling the controlled and sustained release of medications.

ABBREVIATIONS

PSD: Particle Size Distribution
MCC: Micro Crystalline Cellulose
CCS: Crosscarmellose Sodium
IPA: Isopropyl Alcohol
PEG: Polyethylene Glycol
L/R ratio: Length to Radius ratio
EA: Ethyl Acrylate
MMA: Methyl Methacrylate

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