REVIEW ARTICLE

PELLETIZATION TECHNIQUES AND EXTRUSION- SPHERONIZATION: A REVIEW

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Abstract

An oral multiparticulate drug delivery system offers better biopharmaceutical advantages as compared to single unit oral dosage form. The pelletization technique helps in the formation of spherical beads or pellets with a mean diameter of 0.5- 2 *um*. Pellets can be coated for the enhancement of flow and mixing properties, which ultimately reduces segregation and improving physical and chemical properties of fine powder. Different techniques such as Extrusion-Spheronization, drug layering, cryopelletization, hot melt extrusion, spray drying, spray congealing, and freeze drying are successfully discussed in this review. Simple and fast processing and high efficiency obtaining properties made the Extrusion-Spheronization technique superior compared to others. The characterization, evaluation, and importance of pellets with its affecting parameters will also be discussed.

Keywords: Pellets, Pelletization, Extrusion- Spheronization,

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1. INTRODUCTION

Conventionally, pellets have been described as agglomerates that are produced from different types of raw materials. Pellets can be defined as spherical or semi-spherical, free-flowing solid units with a narrow size distribution between 500 and 1500 μm(1). Historically, the word pellet has been used to describe a variety of agglomerates produced by different raw materials(1). Pelletization techniques are playing dominant role in the last two decades in the pharmaceutical field. Pellets are produced primarily for an oral controlled-release dosage form having sustained-release properties (2). They offer not only technological advantages, such as better flow properties, less friable dosage form, narrow particle size distribution, ease of coating, and uniform packing, but also therapeutic advantages like less irritation of the gastrointestinal tract, maximum drug absorption, a lowered risk of side effects associated with dose dumping and uniform distribution in the gastrointestinal tract resulting in a reduction of peak plasma fluctuations (3) (4). Pellets offer a greater degree of flexibility throughout the design and development of oral dosage forms. Pellets usually disperse freely in the gastrointestinal tract and, as a result, maximize the drug absorption, minimize local irritation of the mucosa caused by some irritant drugs, as only a small quantity of drug exists in the single pellet, and reduce patient-to-patient variability(5). The pelletized products can improve the safety and efficacy of the active agent. Pellets have excellent flow and packing properties, resulting in uniform and reproducible fill weight of capsules and tablets(6). Extrusion spheronization was developed in the early 1960s as a pelletization technique. It was used primarily to produce a multiparticulate system for controlled drug release applications. It is especially useful for making dense granules with high drug loading for sustained-release oral solid dosage forms with a minimum amount of excipients. It is a multiple process of wet mass extrusion followed by spheronization to produce uniform-sized spherical particles called spheroids, pellets, or matrix pellets, depending upon the materials as well as the process used for extrusion spheronization. The major advantage over other methods of producing drug-loaded pellets is the ability to incorporate high levels of active ingredients without producing excessively large particles (7). Polymer properties are very important for the controlled release effect of pellets. Different properties, such as pH sensitivity, presence of carboxylic acid, and temperature, are discussed in previous literature. (8).

A hydrophilic polymer like HPMC combined with lactose and water has been used to prepare the pellets by extrusion spheronization(9). It was suggested that hydrophilic polymers, like HPMC, produce highly spherical pellets by disintegration of MCC into small component that improved the dispersion of MCC throughout the lactose(8)**.** Verapamil hydrochloride floating pellets were prepared by the extrusion spheronization process using avicel PH 102, mannitol and kollidon CL. The drug release and floating properties of Verapamil hydrochloride revealed that the effect of compression force showed slower release than the non-compressed pellets. Dissolution performance of Eudragit L100- 55 and Eudragit S 100 based multi-unit controlled release system formulated by extrusion spheronization using poorly soluble drug. Indomethacin pellets were prepared by using blend of Hydroxypropyl cellulose and glyceryl palmito stearateas matrix polymer, methyl crystalline cellulose as spheronization enhancer and sodium lauryl sulphate as pore forming agent(10-12). In previous literature, the lamotrigine pellets were prepared by orifice- ionic gelatin technique by using sodium alginate and calcium chloride. The formulated pellets were evaluated for particle size, entrapment efficiency, *in vitro* drug release, and rheological studies(13).

1.1. Pelletization techniques

Different formulation techniques were used in pervious literature. The followings are Pelletization by extrusion & spheronization, Drug layering (dry powder layering & solution and suspension layering), Cryopelletization, Globulation, Compression, Freeze Pelletization, Balling, Hot melt extrusion(14).

1.2. Extrusion and Spheronization

Extrusion spheronization was developed in the early 1960s as a Pelletization technique. The extrusion-spheronization process is frequently used in the pharmaceutical industry to make uniformly sized spheroids(15). It is particularly useful for making dense granules with high drug loading for controlled-release oral solid dosage forms with a minimum amount of excipients (16).These days this technology has gained attention because of its simple and fast processing and high efficiency.

Extrusion spheronization is a multi-step compaction process comprising of following steps.

1.3. Dry mixing

Dry mixing of all ingredients is prepared to get homogeneous powder dispersion or mixer using different types of mixers like twin shell blender, high shear mixer, tumbler mixer and planetary mixer (12).

1.4. Wet Massing

This process of powder dispersion is done to produce a sufficient plastic mass for Extrusion. It is similar to the wet granulation method but the granulation and point is determined by the behavior of the wetted mass during the extrusion operation. The most commonly used granulator is planetary mixer or sigma blade mixer or high shear mixer and Horbat mixer (17).

1.5. Extrusion

This is a technique of applying pressure to a mass until it flows through an opening and determine two dimension of an agglomeration of particles. This process is the major contributing factor in the final particle size of the pellets. In this method the wetted mass is passed through the extruder to form rod shaped particles of uniform diameter(15). The extrudate must have enough plasticity to deform but not so much that the extrudate particles adheres to other particles when rolled during spheronization process. The granulation solvent serves as the binding agent to form the granules and as the lubricating during the extrusion(18).

1.6. Spheronization

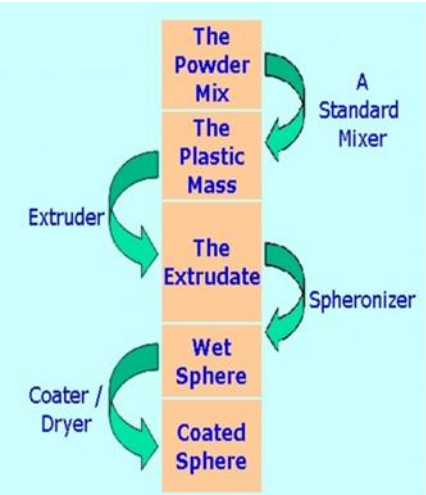
Spheronization method was first introduced by Nakahara in 1964. The formation of pellets depends on the formulation of extrudates. The equipment used is spheronizer, also called as merumerizer, is simple equipment consisting of a bowl with fixed side walls and fast rotating bottom plate or disk(15). The sphericity of the pellets depends on the frictional forces applied i.e. force generated by particle-to-particle and particle-to-equipment interaction. The spheronization of a product usually takes 2-10 mins. The extruded granulation must have combined characteristics of cohesiveness, firmness and plasticity(19). This operation has been divided into three stages such as breaking of extrudate, agglomeration of broken segments and smoothing of particles (20, 21).

1.7. Drying

To get desired moisture content in pellets a drying stage is required. The pellets can be dried at room temperature or at elevated temperature in a tray dryer or in a fluidized bed dryer. According to studies freeze drying retains the shape and size and the granules whereas oven drying produces rough granules due to uneven shrinkage of wet powder (9).

1.8. Screening

Screening may be necessary to achieve the desired size distribution and for this purpose sieves are used. In case of pellets prepared by extrusion spheronization, screening is essentially required after manufacturing, in order to avoid pellets having high size polydispersity index(22, 23)



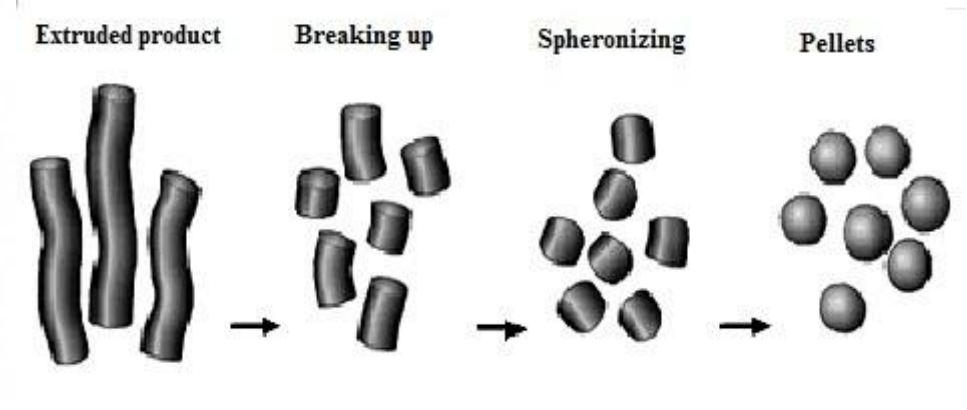


Figure I- Sketch diagram of Extrusion and Spheronization process(1),**Figure II-** Principle of Spheronization process(12)

Table I-List of drugs used for preparation of sustained release pellets by extrusion-spheronization

SR NO	DRUG	POLYMERS	EXCIPIENTS	REFERENCE
1	**Propranolol**	EC,HPMC	MCC, Avicel 101	(24)
2	**Indomethacin**	HPC, GPS	MCC, SLS	(14)
3	**5 Amino- salicylic acid**	Eudragit RL PO, Eudragit RS PO, Pectin	MCC, Lactose	(25)

4	**Roxithromycin**	HPMC, Eudragit L30,D55,NE30 Carbopol 934	MCC, Lactose	(26)
5	**Ibuprofen**	Eudragit S100, HPMC	MCC, Starch	(20)
6	**Ibuprofen**	Eudragit RL PO, Eudragit RS PO,	PVP, MCC	(17)
7	**Piroxicam**	HPMC	PVP, MCC	(27)
8	**Venlafaxine**	HPMC,HPC, EC	MCC, Lactose	(9)
9	**Paracetamol**	HPMC,PEG1500	MCC,PVP	(28)
10	**Ibuprofen, Theophylline**	Acacia, Tragacanth	Corn starch, MCC	(29)
11	**Theophylline**	Gelucire, Instamodel	MCC	(30)

1.9. **Hot Melt Extrusion**:

This method is a newly modified variation of extrusion spheronization method. Here a combination of drug substance and excipients are converted into a molten or semi-molten state and subsequently shaped using appropriate equipment to provide solid spheres or pellets. This is a simple, efficient and continuous process in which fewer processing stage involves. It does not need lengthy drying stage since it does not require addition of water or other solvent, in disparity to granulation process(31, 32).

1.2.1. Drug Layering:

The layering process is one of the most well-controlled and straight forward Pelletization techniques. The process comprises of deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei which may be crystals or granules of same material or inert starter seeds. The process of solution/ suspension layering consists of preparing a solution or suspension of drug particles and other components in application medium. The dissolved material crystallizes forming solid bridges between the cores and initial layers of drug substance and polymer. Process is continued until desired layer of drug or polymer is formed(33). An important factor that needs to be considered when suspensions are used as opposed to solutions is the particle size of the

drug. Micronized drug particles tend to provide pellets that are smooth in appearance, a property that is extremely desirable during subsequent film coating, particularly for controlled release applications. If the particle size of the drug in the suspension is large, the amount of binder required to immobilize the particles onto the cores will be high, and, consequently, pellets of low potency are produced. The morphology of the finished pellets also tends to be rough and may adversely affect the coating process and the coated product(34). Moreover, because particles detach easily from the core they are being layered on owing to frictional forces, yield is usually low.

In powder layering method, the binding liquid helps in forming successive layers of dry powder of drug and other components on starting cores by forming liquid bridges which are eventually replaced by solid bridges(35). In order to achieve the desired pellet size, successive layering of drug and binder solution is continued(36). The first equipment used to manufacture pellets on a commercial scale was the conventional coating pan, but it has significant limitations as pelletization equipment. The degree of mixing is very poor, and the drying process is not efficient(37). Other equipment's used for powder layering process are: Tangential Spray granulator Centrifugal Fluid Bed granulator.

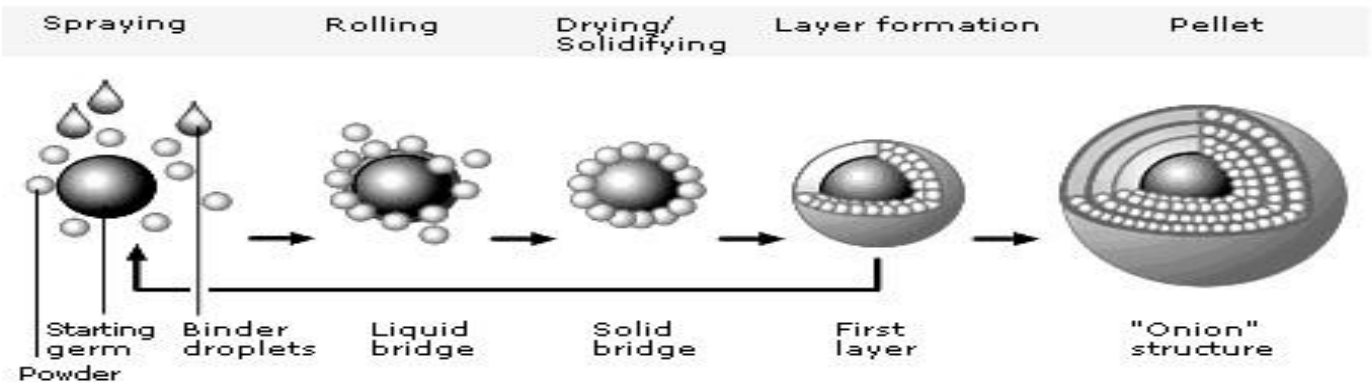


Figure III- Dug layering by using suspension(6)

C**ryopelletization**:

Cryopelletization is a process whereby droplets of a liquid formulation are converted into solid spherical particles or pellets by using liquid nitrogen as the fixing medium at -1600C. The procedure permits instantaneous and uniform freezing of the material(12). The rapid heat transfer that occurs between the droplets and liquid nitrogen is

responsible for the same. The pellets are dried in conventional freeze dryers. Generally, 3-5 kg of liquid nitrogen is required for preparation of 1 kg pellets(38).

Melt Spheronization:

Melt spheronization is a process whereby a drug substance and excipients are converted into a molten or semi molten state and subsequently shaped using appropriate equipment to provide solid spheres or pellets. The drug substance is first blended with the appropriate pharmaceutical excipients, such as polymers and waxes, and extruded at a predetermined temperature(39). The extrusion temperature must be high enough to melt at least one or more of the formulation components. The extrudate is cut into uniform cylindrical segments with a cutter. The segments are spheronized in a jacketed Spheronizer to generate uniformly sized pellets(40).

Globulation:

Globulation, or droplet formation, consists of two related processes, spray drying and spray congealing. They involve atomization of hot melts, solutions, or suspension to generate spherical particles or pellets(5).

Spray Drying:

During spray drying, drug entities in solution or suspension are sprayed, with or without excipients, into a hot stream of air to generate dry and highly spherical particles. As the atomized droplets come in contact with hot air, evaporation of the application medium occurs. This drying process continues through a series of stages whereby the viscosity of the droplets constantly increases until finally almost the entire application medium is evaporated and solid particles are obtained(41).Though the technique is suitable for the development of controlled-release pellets, it is generally employed to improve the dissolution rates and the bioavailability of poorly soluble drugs. Also, this method is applied for processing heat sensitive pharmaceutical s, such as: amino acids, antibiotics, ascorbic acid, liver extracts, pepsin and similar enzymes.

The spray-dried powder particles are homogenous, approximately spherical and nearly uniform in size. The design and operation of the spray drier can influence a great number of the characteristics of the final product, such as particle size and size distribution, bulk density, porosity, moisture content, flow ability and friability (42).

Spray Congealing:

Spray-Congealing is a process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes, fatty acids or other melting solids. The dispersion is then sprayed into a stream of air and other gases with a temperature below the melting point of the formulation components. Under appropriate processing conditions, spherical congealed pellets are obtained (38).

Compression:

Compression is one type of compaction technique for preparing pellets. Typically, pellets are produced for administering in a capsule dosage form after manufacturing with desired modified release properties. However, they can be compressed into tablets as well. Pellets of definitive sizes and shapes are prepared by compacting mixtures or blends of active ingredients and excipients under pressure. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablet manufacturing(43)

Balling:

Balling is the pelletization process in which pellets are formed by a continuous rolling and tumbling motion in pans, discs, drums or mixers. The process consists of conversion of finely divided particles into spherical particles upon addition of appropriate amounts of liquids (44).

2. **Factor affecting Pelletization technique**

Moisture content

It is one of the significant parameter for pellet growth in pelletization technique. Moisture in the wet mass bring cohesiveness to the powder so that the wet mass can be extruded and spheronize to give spherical shape. High moisture contents lead to agglomeration of pellets during spheronization process which is one of the technique of pelletization due to excess of water in the surface of pellets and low moisture content lead to generation of fines with large variation in size distribution (45).

Rheological characteristics

The Rheological condition of the wet mass determines the flow ability in extruder Optimum rheological condition leads to good flow ability in order to extrude the wet mass variation in rheology make improper and non-uniform extrusion (46).

Solubility of excipients and drug in granulating fluid

A soluble drug get dissolve in a granulating liquid .Thus increasing the volume of liquid phase lead to over wetting system of agglomeration of pellet sand increase in wetting liquid increases plasticity but induces sticky mass(47).

Composition of granulating fluid

According to studies a minimum of 5 % of granulation liquid have to be water in order to produce pellets(48). Some researchers used water and dilute acetic acid in different powder to liquid ratio and concluded that mass fraction can be increased up to 100% by using dilute acetic acid for granulation step in place of dematerialized water (18). Aqueous polymer dispersion containing Eudragit, Hydroxy Propyl Methylcellulose (HPMC), Poly vinyl pyrrilodine (PVP) and Gelatin is used in the moistening liquid.

Physical properties of starting material

Formulation variable such as type and content of starting material, type of filler and particle size of constituent have the effect on the pelletization process. Quality of pellets depend not only composition but also on different grades of the same product. The swelling property of material used in pelletization technique decides the release rate of the drug in pellets (23).

Speed of the spheronizer

The speed of the spheronizer affects the size, hardness, sphericity and density of pellets, High speed gives high sphericity, lower friability, smooth surface and higher crushing strength (49).

3. **Drying technique and drying temperature**

It is important to get proper size, shape and flow of pellets and it must be reproducible and consistent in all the batches. Variation in pellet's size, shape and flow will lead to difference in physicochemical properties of final dosage form like weight variation, improper filling etc, which will further affect the therapeutic efficiency of the delivery system. Wider particle size distribution may lead to variation in the dose of drug delivery. Variation in shape may lead to variation in flow and compressibility(29).

Extrusion screen

The quality of the extrudate is greatly influenced by the characteristics of the orifice of the screen. An increase in orifice dimension resulted in increased mean pellet size. The increase in orifice depth decreased with the presence of water at the extrudate surface, increasing the extrusion force and then had a negative effect on granulometric distribution and on shape(32).

4. Advantage of Pelletization Technique

- Pellets are less susceptible to dose dumping than reservoir type single unit formulation.
- Plasma profile variability, variation in gastric emptying rates and over all transit time and can be reduce by producing pellets.
- Pelletization produces spheroids with excellent loading capability active ingredient without producing extensively large particle.
- Pellets can be used for taste masking of drugs.
- Pellets reduce peak plasma fluctuation and minimize the side effect without lowering the drug bioavailability.
- Pelletization produces spheroids with high loading capacity of active ingredient without producing large particles.
- Pellets disperse freely in GI tract and therefore greater absorption of the active drug occurs (50).

5. Disadvantage of pellets

- Pellets are rigid and so cannot be compressed into tablets. It can be encapsulated into capsules.
- The production of pellets is expensive and need specialized equipment.

Pellets production process is difficult.

6. CONCLUSION

The evolution of oral drug delivery has been significantly marked by the transition from traditional single-unit dosage forms to sophisticated multiparticulate systems. This review has comprehensively explored the landscape of

pelletization techniques, underscoring their pivotal role in formulating oral multiparticulate drug delivery systems that offer superior biopharmaceutical properties. Pellets, characterized by their spherical geometry and narrow size distribution (typically 0.5-2.0 mm), are not merely intermediate products but are sophisticated delivery vehicles in their own right. They provide distinct therapeutic advantages, including predictable gastric emptying, reduced risk of dose dumping, minimized local irritation of the gastric mucosa, and the flexibility to combine incompatible active pharmaceutical ingredients (APIs) or to deliver different release profiles within a single dosage form. The core of this review lies in the critical examination of the various technologies employed to manufacture these pellets. The spectrum of techniques from established methods like drug layering to specialized processes such as cryopelletization, spray drying, spray congealing, and freeze drying demonstrates the field's adaptability in addressing diverse physicochemical and biopharmaceutical challenges. Each technique offers unique capabilities for handling moisture-sensitive, heat-labile, or poorly compressible drugs, thereby expanding the formulation toolbox for scientists.

However, the central theme that emerges from this analysis is the preeminence of the Extrusion-Spheronization technique. Its superiority is attributed to a combination of factors that align perfectly with industrial and pharmaceutical requirements. The process is characterized by:

High Efficiency and Throughput: It allows for the incorporation of a high drug load (often exceeding 80%) and enables continuous, large-scale production, making it economically viable.

Superior Pellet Quality: It consistently produces pellets with exceptional sphericity, narrow size distribution, high density, and smooth surface characteristics. These attributes are crucial for subsequent coating processes and for achieving reproducible drug release kinetics.

Versatility: It applies to a wide range of drugs and excipients, offering robust formulation development options.

The review has also highlighted that the success of extrusion-spheronization, like all pelletization techniques, is not automatic but is instead highly dependent on the intricate interplay of numerous formulation and process variables. Parameters such as the composition and rheology of the wet mass, the type and concentration of binders and spheronizing agents (like microcrystalline cellulose), extruder screen size, spheronizer speed and residence time, and drying conditions must be meticulously optimized. Failure to control these can lead to pellets with poor morphology, low yield, or inconsistent drug release. Furthermore, the characterization and evaluation of pellets are paramount to confirming their quality and performance. Key attributes such as particle size distribution, shape and sphericity, friability, tensile strength, porosity, and density directly influence critical downstream processes like coating, encapsulation, and, ultimately, the *in vivo* drug release and absorption. A robust quality control protocol,

incorporating these evaluations, ensures the production of a reliable and effective final product. In essence, this review confirms that the choice of pelletization technique is a strategic decision that dictates the quality, performance, and manufacturability of the final dosage form. While alternative methods hold value for niche applications, extrusion-spheronization stands as the gold standard for producing high-quality pellets for oral drug delivery. Future advancements will likely focus on process analytical technology (PAT) for real-time monitoring and control, the development of novel excipients tailored for continuous manufacturing, and the application of these techniques to novel therapeutics like biologics and nanomedicines. The continued evolution and refinement of pelletization technologies, led by the versatile and efficient extrusion-spheronization process, promise to deliver even more sophisticated and patient-friendly pharmaceutical products in the years to come

7. References:

1. Supriya P, Rajni B, Rana A. Pelletization techniques: A literature review. International Research Journal of Pharmacy. 2012;3(3):43-7.
2. Sunil B. PPaAB. General Review on pelletization. Int J Pharma World Res. 2013;1(4):1-18.
3. Evodokia S. DM, Paraskevas P. and Nikolsaos H. Optimization of the pelletization process in a fluid bed granulator using experimental design. AAPS Pharm Sci Tech. 2000;1(14):1-5.
4. vikash K, kumar Ms, amit L, Vikas, ranjiy S. Multiple unit dosage form- Pellet and pelletization techniques:An overview. International journal of Research in Ayurveda and pharmacy. 2011;2(1):121-5.
5. Bathool A, Vishakante GD, Khan MS, Gupta VK. Pelletization as a key tool for oral drug delivery: A review. Journal of Pharmacy Research. 2011;4(10).
6. Lavanya K, Senthil V, Rathi V. Pelletization technology: a quick review. Int J Pharm Sci Res. 2011;2(6):1337-55.
7. Tomer G, Podczeck F, Newton J. The influence of model drugs on the preparation of pellets by extrusion/spheronization: II spheronization parameters. International journal of pharmaceutics. 2002;231(1):107-19.
8. Lakshmi.p.k SBa. Extrusion Spheronization - A review. international journal of Pharm Tech Research. 2010;2(4):2429-33.
9. Kumar MS, Das B, Raju SVSR. Formulation and evaluation of multi unit Pellet system of Venlafaxine Hydrochloride. Journal of Pharmaceutical and Biomedical Sciences. 2012;18(5):1-12.
10. Wlosnewski JC, Kumpugdee-Vollrath M, Sriamornsak P. Effect of drying technique and disintegrant on physical properties and drug release behavior of microcrystalline cellulose-based pellets prepared by extrusion/spheronization. Chemical Engineering Research and Design. 2010;88(1):100-8.
11. Baloju, Srikanth, Chandrashekar Vemula, Srinivas BKarna, Sudheer. Nifedipine Sustained Release Pellets Formulation Development and Evaluation. Pharmascient. 2013;2(1):12-7.
12. Kandukuri JM, Allenki V, Eaga CM, Keshetty V, Jannu KK. Pelletization techniques for oral drug delivery. Int J Pharm Sci Drug Res. 2009;2:63-70.
13. Bhoir S, Agrawal S. Pelletization of Lamotrigine solid dispersion for improved solublization. international journal of Pharmaceutical sciences and research. 2011;2(9):2380-6.
14. AravindaRam A, Gowda D, Khan MS, Vishwanath B. Development and evaluation of indomethacin matrix pellets for controlled release. Elixir International journal. 2012;46:8248-54.
15. f.Erkoboni D. Pharmaceutical technology. New york: Marcel Dekker, Incorporation; 2003.
16. GSI D. Pharmaceutical pelletization technology. Marcel Dekker Incorporation. 1989;37:30-100.

17. M.R.Abbaspour, Sadegi F, Garekani HA. Preparation and characterization of ibuprofen pellets based on Eudragit RS PO and RL PO or their combinayion. International journal of Pharmaceutics. 2005;303:88-94.
18. Steckel.H, F M-N. Production of chitosan pellets by extrusion spheronization. Europian journal pharmaceutics and biopharmaceutics. 2004;57:107-13.
19. Tho I, Kleinebudde P, Sande SA. Extrusion/spheronization of pectin-based formulations. II. Effect of additive concentration in the granulation liquid. AAPS PharmSciTech. 2001;2(4):63-72.
20. Krogars K, Heinämäki J, Vesalahti J, Marvola M, Antikainen O, Yliruusi J. Extrusion–spheronization of pH-sensitive polymeric matrix pellets for possible colonic drug delivery. International journal of pharmaceutics. 2000;199(2):187-94.
21. Gao Y, Hong Y, Xian J, Lin X, Shen L, Zhang X, et al. A protocol for the classification of wet mass in extrusion–spheronization. European journal of pharmaceutics and biopharmaceutics. 2013;85(3):996-1005.
22. Sri KV, Suresh K, Reddy GK, Devanna N. A review of pellets and pelletization process- A multiparticulate drug delivery system. International Journal of Pharmaceutical Sciences & Research. 2013;4(6).
23. Koo OMY, Heng PWS. The influence of microcrystalline cellulose grade on shape and shape distributions of pellets produced by extrusion-spheronization. Chemical and pharmaceutical bulletin. 2001;49(11):1383-7.
24. Srisha v, Vijaaya Sri K, Devanna N, Suresh K. Multiple unit extended release pellets of Propranolol Hydrochloride: Preparation and characterization. International Journal of Pharmacy & Pharmaceutical Sciences. 2013;5(3).
25. Akhgari, Abbas, Abbaspour, Mohammadreza, Moradkhanizadeh, Meysam. Combination of Pectin and Eudargit RS and Eudragit RL in the Matrix of Pellets Prepared by Extrusion-Spheronization for Possible Colonic Delivery of 5-Amino Salicylic Acid. Jundishapur Journal of Natural Pharmaceutical Products. 2013;8(2):86.
26. Li K, Zeng X, Tang X, Cui Y, Yu Y. Development of membrane-matrix hybrid sustained-release pellets loaded with roxithromycin. Asian Journal of Pharmaceutical Sciences. 2008;3:110-21.
27. Rajesh N. Design and Evaluation of Controlled Release of Piroxicam from the Pellets of Microcrystalline Cellulose and Hydroxypropylmethyl Cellulose Blends. International Journal of PharmTech Research. 2010;2(2):1465-73.
28. Issa MG, Pessole L, Takahashi AI, Andréo Filho N, Ferraz HG. Physicochemical and dissolution profile characterization of pellets containing different binders obtained by the extrusion-spheronization process. Brazilian Journal of Pharmaceutical Sciences. 2012;48(3):379-88.
29. Akhgari A, Abbaspour MR, Pirmoradi S. Preparation and evaluation of pellets using acacia and tragacanth by extrusion-spheronization. DARU Journal of Pharmaceutical Sciences. 2011;19(6):417.
30. Jain S, Shah S, Rajadhyaksha N, Singh P, Amin D, PS P. Once a Day Pellets of Theophylline by Extrusion Spheronization Technique Using Gelucire® Matrix. Iranian Journal of Pharmaceutical Sciences. 2010;6(4):235-43.
31. TW W, WS C, PWS H. Handbook of Pharmaceutical Granulation Technology. DM P, editor: Taylor & Francis Group; 2005.
32. Rahman MA, Harwansh R, Biswas R, Mirza MA. Hot melt extrusion and freeze pelletization: Better alternative for drugs having stability problem due to presence of water. International journal of Pharmacy and reserach. 2011;1(11):22-31.
33. Kumari MH, Samatha K, Balaji A, Shankar M. Recent novel advancement in pellet formulation : A review. International Journal of Pharmaceutical Sciences & Research. 2013;4(10).
34. Sousa J, Sousa A, Podczeck F, Newton J. Influence of process conditions on drug release from pellets. International journal of pharmaceutics. 1996;144(2):159-69.
35. Nastruzzi C, Cortesi R, Esposito E, Genovesi A, Spadoni A, Vecchio C, et al. Influence of formulation and process parameters on pellet production by powder layering technique. AAPS PharmSciTech. 2000;1(2):14-25.
36. Sachdeva V, Alam MS, Kumar R, Kataria MK. Oral multiunit pellet extended release dosage form: A review. International Current Pharmaceutical Journal. 2013;2(10):177-84.
37. Ozarde Y, Sarvi S, Polshettiwar S, Kuchekar B. Multiple-Unit-Pellet System (MUPS): A Novel Approach for Drug Delivery. Drug Invention Today. 2012;4(12).
38. HA A, KH S, . Multiparticulate Oral Drug Delivery. HA A, KH S, editors. New York: Marcel Dekker Inc; 1994.

39. c.case C. Pharmaceutical extrusion technology. New york: Marcel Dekker, Incorpoation; 2003.
40. Lindén M. Hot-melt Extrusion of Modified Release Pellets-Influence of the formulation and extrusion process on extended-and enteric release profile. Gothenburg, Sweden: Chalmers university of technology; 2012.
41. Wan LS, Lai W. Factors affecting drug release from drug-coated granules prepared by fluidized-bed coating. International journal of pharmaceutics. 1991;72(2):163-74.
42. M C, SC W. Handbook of Pharmaceutical Granulation Technology: Taylor & Frabcis Group; 2005.
43. Elias NM, Sharmin S, Ahmed I. Development & in vitro evaluation of sustained release pellets of diltiazem hydrochloride using ethyl cellulose & hydroxy propyl methyl cellulose polymer. International journal of Pharmaceutical studies and Research. 2012;3(1):8-17.
44. Pai R, Kohli K, Shrivastava B. Compression and evaluation of extended release matrix pellets prepared by the extrusion/spheronization process into disintegrating tablets. Brazilian Journal of Pharmaceutical Sciences. 2012;48(1):117-29.
45. K F, J N, R R. The influence of moisture content on spheronization of extrudate processed by ram extruder. international journal of pharmaceutics. 1993;97:79-86.
46. P H, J N, R R. The application of capillary rheometry to the extrusion of wet powder masses. international journal of pharmaceutics. 1987;35:235-42.
47. Vervaet C, Baert L, Remon JP. Extrusion-spheronisation A literature review. International journal of pharmaceutics. 1995;116(2):131-46.
48. Millili G, Schwartz J. The strength of microcrystalline cellulose pellets: the effect of granulating with water/ethanol mixtures. Drug Development and Industrial Pharmacy. 1990;16(8):1411-26.
49. Wan LS, Heng PW, Liew CV. Spheronization conditions on spheroid shape and size. International journal of pharmaceutics. 1993;96(1):59-65.
50. Dash V, Behera S, Agarwal R, Sinha N. Pelletization technique in drug delivery system. Journal of Current Pharmaceutical Research. 2012;9(1):19-25.