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A REVIEW OF PELLETS AND PELLETIZATION PROCESS - A MULTIPARTICULATE DRUG DELIVERY SYSTEM

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ABSTRACT: Multiparticulate drug delivery systems like pellets, granules, micro particles, minitablets etc., prove to be promising and highly flexible systems with ease of formulating with different drug release kinetics. These multiparticulate dosage forms are essential where drug-excipients or drug-drug physicochemical interactions are possible in a single-unit formulation. In present times, pelletization technologies are gaining much attention as they represent an efficient pathway for manufacture of oral drug delivery systems. Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free flowing semi-spherical units. Pellets, being multiparticulate systems, are widely used due to the technological as well as therapeutic advantages over single-unit dosage forms. The present review focus on advantages, disadvantages, formation of pellet growth, different pelletization techniques, characterization, marketed pellets products and also outlines recent developments in the pharmaceutical approaches that have been used to prepare pelletized dosage forms with different techniques like Hot Melt Extrusion-Spheronization, Freeze and Cryopelletization, Microtabletting technology.

INTRODUCTION: Multiparticulate oral drug delivery systems have acquired a center stage in the arena of pharmaceutical research and development; thus provide greater opportunities in extending the first step of future pharmaceutical development.

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Multiparticulate drug delivery systems include pellets, granules, micro particles (like microspheres, microcapsules, nano particles), mini tablets, mini depots, multiparticulate pulsatile drug delivery systems (**Table 1**).

Pelletized dosage forms date back to the 1950s, when the first product was introduced to the market. In 1949, research scientists of SmithKline & French developed tiny drug pellets that are filled into capsules. Since then, these dosage forms have gained considerable popularity because of their distinct advantages such as enhancement of drug dissolution; ease of coating with desirable release characteristics like sustained, controlled, delayed, site-specific or

pulsatile delivery of drug from coated pellets; uniform packing; ease of capsule filling because of better flow properties due to its spherical shape; even distribution in the GI tract and less GI irritation.

TABLE 1: RECENT ADVANCES IN DESIGN OF MULTIPARTICULATE PULSATILE DRUG DELIVERY SYSTEMS

Technology		Description
CODAS Elan	:	Verelan (18), a *Chronotherapeutic Oral Drug Absorption System* for delayed relase action after 4-5 hours after ingestion.
COLAL® by Alizyme Therapeutics Ltd.	:	Drug pellets, tablets or capsules are coated with ethylcellulose and a form of starch called 'glassy amylose'.
Diffucaps ® Eurand	:	Innopran contains a neutral core such as sugar/cellulose spheres layered by propranolol – verapamil and then coated with one or more rate-controlling membranes that releases approximately 4-5 hours after ingestion by polymer coating onto the drug loaded beads.
Diffutab	:	Composed of small beads, each small bead further composed of many layers.
Eurand's Minitabs	:	Tiny cylindrical tablets approx. 2 mm in diameter with the sophisticated drug release control coating membranes.
Eurand's Pulsatile and Chrono Release System	:	Propranolol HCl rate controlled pellets filled into capsules administered at bed time, release the drug after at predetermined lag times such that maximum plasma concentration levels occur in the early morning hours.
Flashtab	:	Oro dispersible tablets containing multiparticulates with drug and rate controlling polymers.
InnoHerb	:	Micropellets or small pellets containing active herbal compounds (phytogranules).
IPDAS	:	*Intestinal Protective Drug Absorption System* - rapidly disintegrating tablets containing controlled release pellets of drug like naproxen.
KV/24	:	Neutral cores coated with drug and one or more rate controlling polymers to attain drug release in a predetermined manner for once a day release profile.
Macrocap®	:	Consists of immediate release pellets made by extrusion- spheronization or by layering powders or solutions on nonpareil seeds.
Multipart®	:	*Multiparticle drug dispersing shuttle*- tablet as carrier for controlled release pellets.
Orbexa®	:	Production of controlled size high drug loaded and density pellets using granulation, extrusion - spheronization techniques, can be coated and filled into capsules. This technology can be used for sensitive drugs such as proteins.
Pelletised tablet	:	Pellets with specific release profiles are compressed to tablets.
Pelletized Delivery System	:	Pellets with specific release profiles are filled into capsules.
PRODAS	:	*Programmable Oral Drug Absorption System* - minitablets in hard gelatin capsule.
PULSYS ™ MiddleBrook Pharmaceuticals	:	Amoxicillin - for improved bactericidal action once daily, a compressed tablet that contains pellets designed to release drug at different regions in the GI tract.
SODAS Elan	:	*Spheroidal Oral Drug Absorption System* contains spheroidal pellets of 1-2 mm diameter, coated with controlled release polymer for once daily use.
Stabilized Pellet Delivery System	:	Diffucaps or minitablets filled into capsules.
TMDS	:	*Time Multiple Action Delivery Systems* - control release rate of multiple pellets within a single tablet.
Multiparticulate mucoadhesive formulations, Delayed release oral polypeptides & Magnetic nanocomposite hydrogels.		

Pellets are small, free flowing, systematically produced, spherical or semi spherical solid units, geometrically defined agglomerates of about size ranging from 0.2 mm to 2.0 mm, obtained from diverse starting materials of fine powders or granules of bulk drugs and excipients utilizing different pelletization techniques [1].

Pellets intended for oral use are administered in the form of hard gelatin capsules or disintegrating tablets (**Figure 1**) which quickly liberate their contents in the stomach and gets distributed throughout the gastrointestinal tract without loss of the depot effect [2, 3]; as the sub unit acts as self-contained depots.

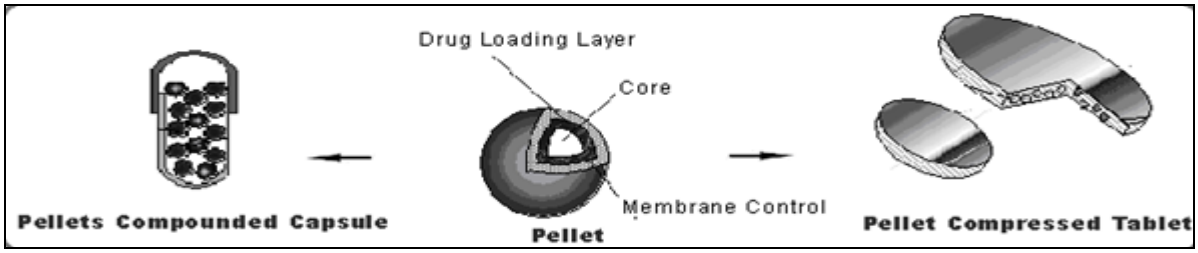


FIGURE 1: SCHEMATIC REPRESENTATION OF PELLETS INTO CAPSULES AND COMPRESSED TO TABLETS

Ideal Characteristics of Pellets: *Core or uncoated pellets* are of uniform spherical shape and smooth surface with improved flow characteristics; high physical strength and integrity; good hardness and low friability for ease and superior properties of coating. They have a narrow particle size between 500 µm to 1000 µm, a prerequisite for efficient coating, prevents segregation during capsule-filling and compression. The high bulk density of pellets plays an important role in achieving content and weight uniformity; reproducible packing of beds and columns. Whereas *functional or non-functional coated pellets* in addition to the above properties; contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits, uniform coating thickness and desired drug release characteristics. Perfect pellets and layers of coating are depicted in **Figure 2**.

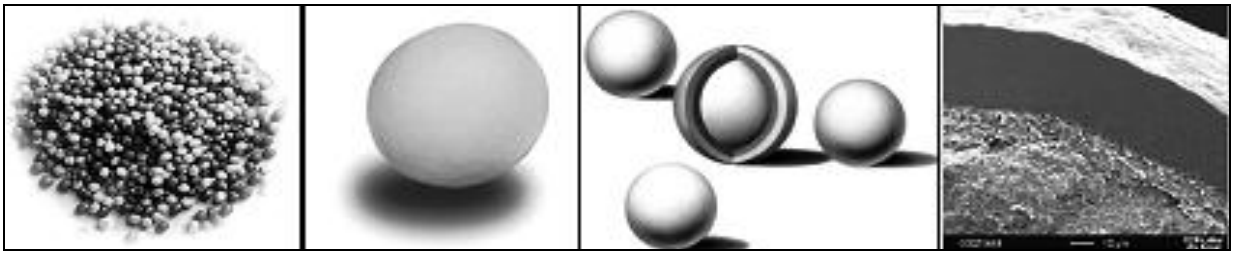


FIGURE 2: (A) PELLETS, (B, C) PERFECT PELLET, (D) COATED PELLET.

Advantages of Pellets: Pellets offer more sophisticated drug-delivery systems as they provide greater advantages over other single unit drug-delivery systems.

a) **Process Advantages:** As subunits various kinds of particles with defined less-porous surface, spherical shape, low surface area to volume ratio are suitable for flexible and uniform drug - polymer coating.

b) **Formulation Advantages:** Pellets offer greater flexibility in the design and development of active ingredient into oral dosage forms like tablets, capsules and suspensions with significant therapeutic advantages over single units [4, 5]. The functional coating usually being applied in a fluid bed coating process provides each subunit with the characteristic drug release properties.

Controlled-release, gastro-resistant, sustained-release or site-specific drug delivery finds a greater advantage of drugs formulated as coated pellets that can be filled into capsules or compressed into tablets. They can be divided into desired dose strengths without formulation or process changes, and can also be blended to deliver even incompatible bioactive agents simultaneously or particles with different release profiles at the same site or at different sites within the gastrointestinal tract. The safety and efficacy of the formulation is higher than that of other dosage forms [6].

c) **Therapeutic Advantages:** When administered orally, pellets pass the pylorus even in the closed state and disperse freely throughout the gastro-intestinal tract and maximize the drug absorption; minimize local irritation of the gastro-intestinal mucosa by certain irritant drugs because of the available drug quantity in a single pellet is considerably small; provides less risk of dose dumping; improves safety and efficacy of a drug; reduce peak plasma fluctuations and minimize potential side effects with improved drug bioavailability [7]; offers reduced variation in gastric emptying rate and transit time which is less dependent on the state of nutrition; reduce inter and intra patient variability [5]; more suitable for fabrication of formulations with acid-sensitive drugs like Erythromycin [8]. As the advantages of pellets over single units became clear, the pharmaceutical industry as a whole started to devote resources to conduct research in pelletization technology, whenever possible, acquire advanced equipment suitable for the manufacture of pellets.

Disadvantages: In accordance with single units, the volume per dose is high because of its high bulk density. Since specific surface area per dose is higher, more amount of coating should be given. Preparation of pellets is a complicated and time consuming process. Inspite of these facts, predominance of advantages with regard to patient compliance, safety and efficacy; pelletization technology is gaining demand in pharmaceutical product manufacturing.

Mechanism of Pellet Formation and Growth: The mechanism of pellet formation and growth is necessary to review by a formulator for the development of formulation in a more skillful perspective and set the trends for future developments in the area of pellets.

Formation of pellet involves adhering of the solid particles or fine powders to each other when they are brought close enough together due to attractive forces such as;

(a) Molecular forces which includes valence forces up to a distance of 10°A and Vanderwaals forces contribute to all intermolecular attractions;

(b) Electrostatic forces produced during size reduction or due to inter-particle friction or contact between the particles which in particular produces permanent adhesion due to development of electrical double layer and;

(c) Magnetic forces rarely observed during pellet formation. The stronger the bond the more efficient is the formation and growth of pellets [9].

The formation of strong bonds between particles is by choice of using viscous binders that develop immobile liquid bridges; or thin adsorption layers either by smoothing surface roughness and increasing particle contact area; or by decreasing the effective interparticle distance and allowing the intermolecular attractive forces to participate in the bonding mechanism. Solid bridges also adopt the tendency of strong bonding by crystallization of dissolved substances, hardening of binders by drying or curing, solidifying melted particles by cooling. The mechanism of pellet formation is shown in **Figure 3**.

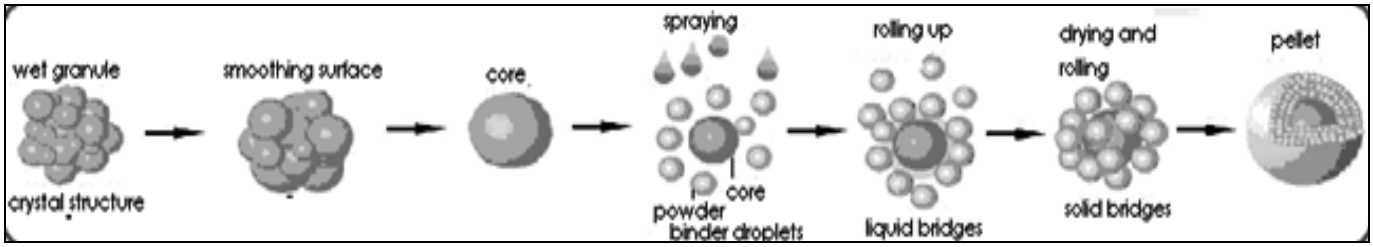


FIGURE 3: MECHANISM OF PELLET FORMATION.

Formation and growth of pellets can be divided into three stages. ***Nucleation,*** the first stage of the pellets growth mechanism is a wet agglomeration process in which powder particles are wetted with binder liquid [10] that distributes throughout the powder particles forming fluidized particles and thus contributes the formation of three-phase pendular nuclei of air-water-liquid attached together by liquid bridges and leads to formation of initial agglomerates [11] shown in **Figure 4**.

The size, rate and extent of nucleus formation is influenced by the size of primary powder particles, viscosity of the bonding particles after binder addition, the ability of wettability of the primary materials, amount of moisture present to form agglomerates and the processing conditions.

The void spaces between the primary particles are occupied by the binder solution added and form as lens-like rings by liquid bridges at contact points of two adjacent particles and results in pendular agglomerates.

Hence, this state is referred to as *pendular* state (**Figure 4**). In this state liquid to the void volume ratio is low. The surface tension of the liquid and the negative suction pressure generated at the liquid bridges causes attraction between the powder particles. The formation of liquid bridges depends on distribution and surface geometry of the two adjacent particles.

The next state in nucleation is *funicular* state, where liquid and air pockets are dispersed continuously throughout the agglomerate instead of liquid bridges depicted in **Figure 4**.

In *capillary* state, all the void space in agglomerate is fully occupied by liquid due to the strong bonds formed between the particles by interfacial forces and capillary pressure. These bonds wane as the liquid evaporates. The characteristic feature of this state is the liquid does not completely surround the agglomerate and there by cannot form nuclei (**Figure 4**).

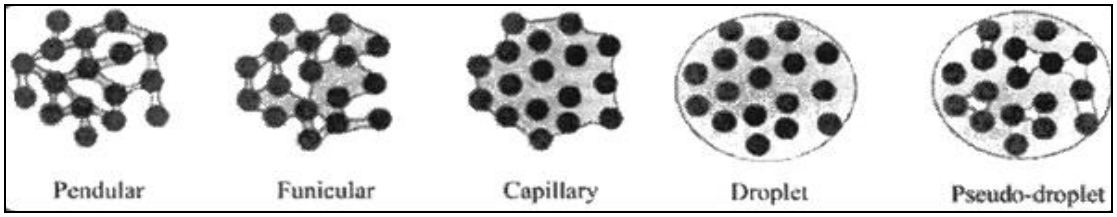


FIGURE 4: DIFFERENT STAGES OF NUCLEATION.

The next state is *droplet*, identified when liquid completely surrounds onto the agglomerate with no interparticle capillary bonds. The primary particles are brought together only by the surface tension of the droplet and the liquid envelops the agglomerates.

During nucleation the mass and number of nuclei in the system changes with time [12].

Next to nucleation is *transition phase* with two major mechanisms; coalescence and layering[13]. Coalescence itself refers to collision. During *Coalescence phase* (**Figure 5**), the nuclei collide with each other due to random movement and results in formation of large-sized particles [14]. Due to this, the number of nuclei is reduced but the total mass of the system remains constant. During collision, fines and fragments of particles are produced due to size reduction by breakage, attrition and shatter. The successive addition of these fines and fragments on surface of nuclei is called *layering* (**Figure 5**). Due to this the number of nuclei remains constant, but the total mass of nuclei in the system increases due to increasing particle size with time [9].

Consecutive coalescence and layering continues till the decline of number of favourable collisions and may lead to a reduction in the rate of growth of the pellets. At this point the third phase, the ball growth is reached [9].

Ball growth phase is the final step of pellet formation. In this, slow growth of agglomeration is affected by *abrasion transfer* as illustrated in **Figure 5**, a mechanism involving the transfer of materials formed on one granule to another in either direction without any particular priority. A change in size of particles undergoes as long as the materials for transfer exist. There is no change in total number or mass of the particles [9].

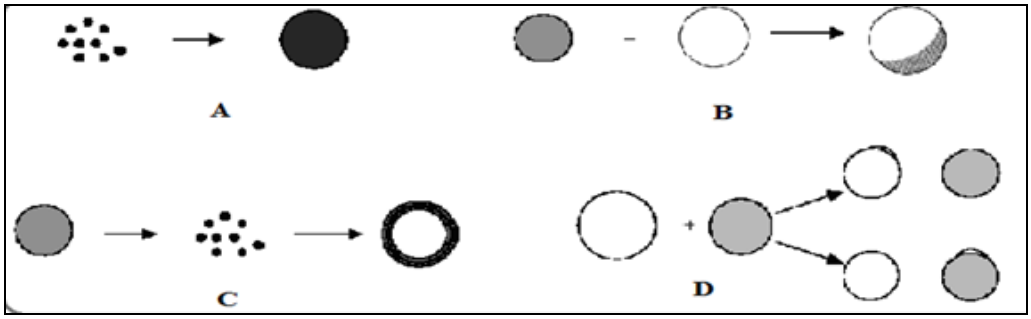


FIGURE 5: STAGES IN PELLET GROWTH MECHANISMS. (A) NUCLEATION, (B) COALESCENCE, (C) LAYERING (D) ABRASION TRANSFER

Pelletization techniques- Equipment- Process Variables: Manufacturing of pellets include different techniques based on the application and the requirement of manufacturers [13] (**Figure 6**).

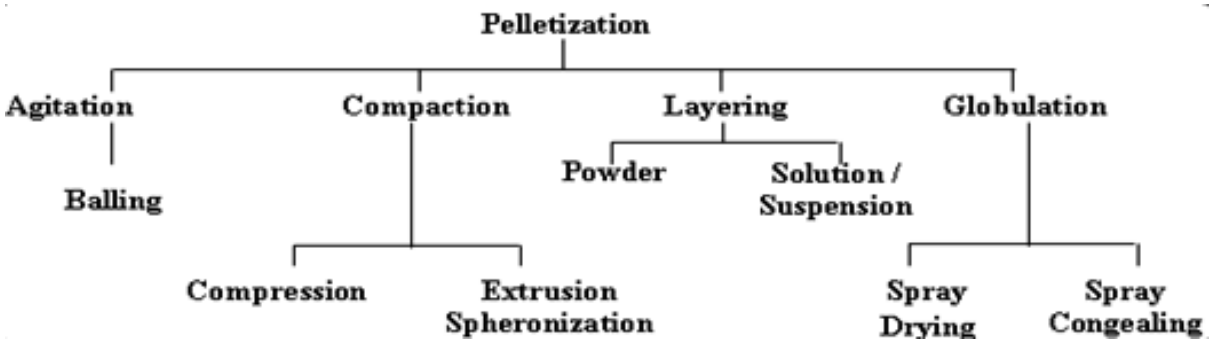


FIGURE 6: DIFFERENT PELLETIZATION TECHNIQUES.

a. **Agitation :**

i. **Balling:** In this technique, liquid in required amount is added prior to or during agitation stage to finely divided particles and this mass under continuous rolling or tumbling motion results in spherical particles. Equipment used is pans, discs, drums, or mixers.

b. **Compaction:**

i. **Compression:** A pelletization process in which mixtures or blends of active ingredients and excipients are compacted under pressure to obtain pellets of definite shape and size [15, 16]. These pellets are of narrow size distribution and can be filled into capsules.

ii. **Extrusion - Spheronization:** A multi-step process invented by Nakahara, in 1964 [17] (**Figure 7**). The main benefit of this is to fabricate drug loaded spheres with high drug content up to 90% [18]. This process involves dry mixing of the active compound with excipients to achieve a homogeneous powder, wet massing of dry mixture with binder, granulation of wetted mass, extrusion of the wetted mass into a spaghetti-like extrudates, transfer of the mass to spheronizer to produce spheroids, drying of the wet pellets in a dryer and at the end screening to obtain required particle size. This is also referred to as cold mass extrusion – spheronization.

c. **Layering:** A well-controlled pelletization technique in which drug is layered onto starter seed materials (coarse material or nonpareil) in powder, solution or suspension form with the aid of binder that assists heterogeneous pellets, consists of an inner core region and an outer shell region of a different composition [19, 20]. The nonpareil seeds must have spherical shape, smooth surface, uniform particle size distribution for uniform coating [21].

The concentration of the binder is based on choice of the drug because it influences physical as well as mechanical properties of pellets and drug release from coated pellets. Commonly used binders include gelatin, povidone, carboxymethyl cellulose, hydroxyl propyl methylcellulose, hydroxypropyl cellulose, Sodium CMC, malto-dextrins.

Layering is classified into three categories: direct pelletizing, powder layering and solution or suspension layering [22].

i. **Direct pelletization:** It is a process in which homogeneous pellets are formed without any detectable core (**Figure 7**). It is carried out in high shear mixers and fluidized bed equipment [7].

ii. **Powder Layering:** In this process dry powder of drug or excipients or both is sprayed with binding liquid and results in deposition of sucessesive layers on preformed nuclei or cores (**Figure 7**). Equipment used is tangential spray/centrifugal/rotary fluidized bed granulator [23, 24], conventional coating pan.

iii. **Solution/Suspension layering:** In the case of Solution/Suspension layering, growth of pellets involve deposition of successive layers of solution and/or suspension of drug substance and binders on existing nuclei, which may be inert substrate seed, crystal or granule of the same drug. The drug particles are dissolved or suspended in solvent, with or without binder. Droplets of the binding liquid spread on to the surface of the nuclei. During drying, the liquid evaporates. Then, the dissolved substances crystallize out and capillary forces formed draw the particles towards each other and towards the inert seed, forming solid bridges (**figure 7**).

Materials suitable for use as starter cores in the production of coated pellets include sugar spheres consisting of saccharides and its derivatives (sugars, sucrose-starch mixtures, oligosaccharides, polysaccharides), microcrystalline cellulose spheres, pure drug crystals, polymers such as plastic resins, inorganic substances (silica glass, hydroxy-apalite), organic substances (activated carbon, acids like citric, fumaric, tartaric, ascorbic acids etc) [25].

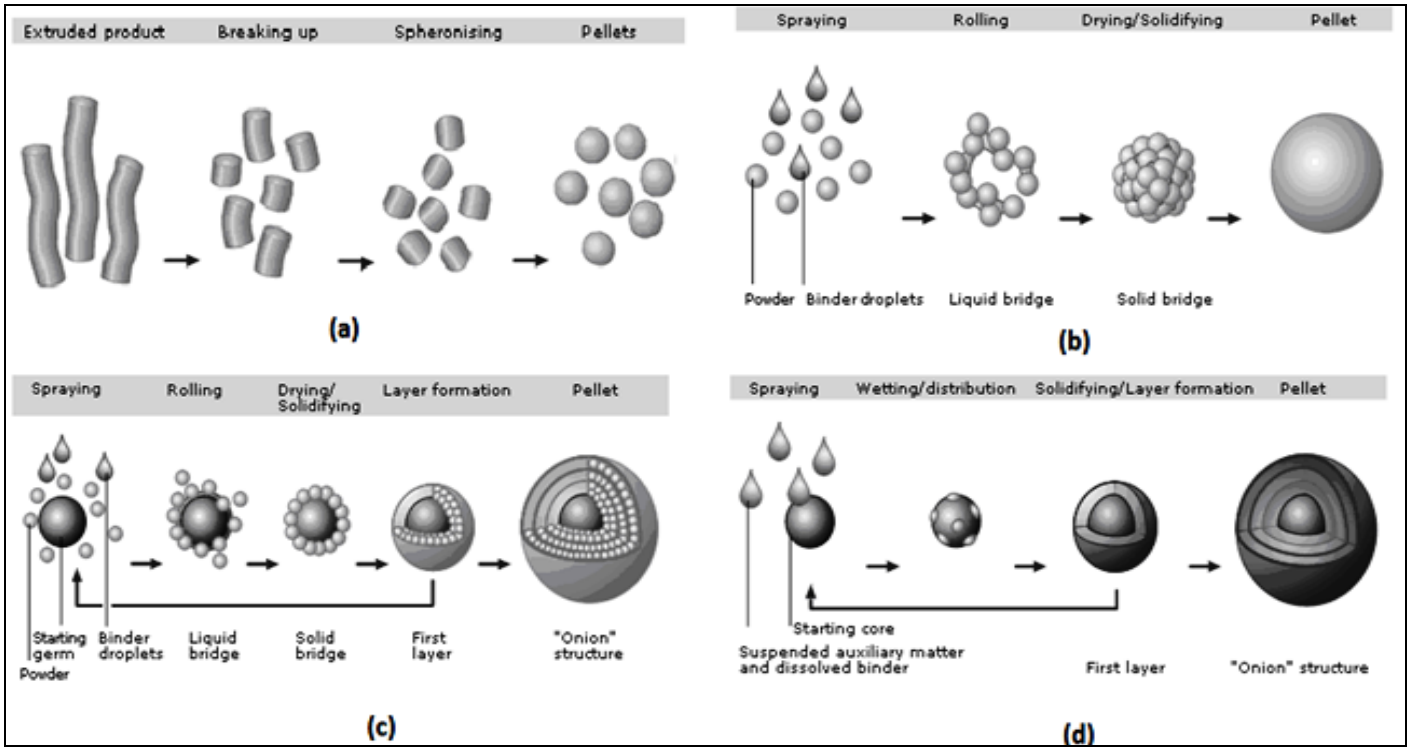


FIGURE 7: PRINCIPLE OF (A) EXTRUSION – SPHERONIZATION (B) DIRECT PELLETIZING (C) POWDER LAYERING (D) SOLUTION/ SUSPENSION LAYERING PROCESS

Layering is carried out in Fluid bed systems. These are of three types [26] shown in **figure 8**.

1. **Granulator, Top-spray** process is preferred when a taste masking coating is being applied and granulation of drug(s) combined with excipient(s). Additionally it is suitable for the application of hot melt coating. The long expansion chamber allows the particles to decelerate in a high velocity fluidized air stream for much longer period as well as minimized agglomeration. The nozzle positioned in such a way to achieve uniform spray without spray-drying.

2. **Wurster, Bottom spray** process is preferred for the application of modified-release coating to a wide variety of multiparticulates; also suitable for drug layering when the drug dose is in low to medium range. Bottom spray coater consists of (a) product container with bottom fitted perforated plate for fluidization of particles (b) Wurster positioned at the bottom in such a way to assert flower shaped circulation of particles (c) spray nozzle.

3. **Rotor, Tangential spray** process is suitable for the application of modified-release film coating to a wide range of multiparticulate products. It is ideal for drug layering when the dose is medium to high. It is also useful as a spheronizing process for producing spheres**.**

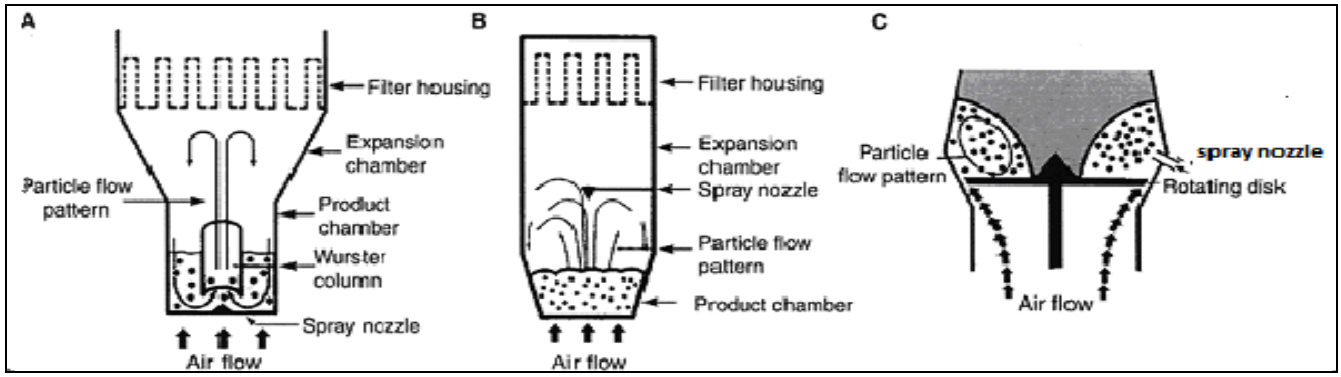


FIGURE 8: (A) PRINCIPLE OF BOTTOM SPRAY BATCH FLUID COATING. (B) PRINCIPLE OF TOP SPRAY BATCH FLUID COATING. (C) PRINCIPLE OF TANGENTIAL SPRAY BATCH FLUID COATING.

TABLE 2: CHOICE OF FBP USED IN DIFFERENT PROCESSING TECHNIQUES

APPLICATION	EQUIPMENT
Drying	Top spray
Spray granulation/drying	Top spray, bottom/Wurster, rotor
Pelletizing	
Solution/suspension layering	Top spray, bottom/Wurster, rotor
Dry powder layering	Rotor
Direct pelletization	Rotor
Coating (fine particles/pellets)	
Organic solvent	Top spray, bottom/Wurster, rotor
Water based	Top spray, bottom/Wurster, rotor
Hot melt	Top spray, bottom/Wurster, rotor

d. **Globulation:** Globulation or droplet formation includes spray drying and spray congealing [27, 28].

i. **Spray drying:** Drug entities in solution or suspension form are sprayed, with or without excipients, into a hot air stream to generate dry and highly spherical particles. It is generally employed to improve the dissolution rates and there by enhance the bioavailability of poorly soluble drugs.

ii. **Spray congealing:** A process in which a drug is allowed to melt, disperse, or dissolve in hot melts of gums, waxes, fatty acids, etc., and is sprayed into an air chamber where the temperature is below the melting points of the formulation components, to provide spherical congealed pellets under appropriate processing conditions.

Recent advances in Pelletization Techniques

1. **Hot-melt Extrusion and Spheronization:** It is a solvent free technique finds a great advantage for drugs that show sign of instability due to residual water during processing and storage. Consequently no additional film coating is needed to attain controlled release and hence release is favored by; (a) diffusion mechanism for formulations with water-insoluble polymers such as ethylcellulose or carnauba waxes; and (b) both by diffusion and erosion with water-soluble polymers such as hydroxypropyl cellulose. This technique is employed for the production of pellets, specific rate release dosage forms like tablets, capsules, transdermal implants etc. A hot melt extrusion line consists of a feed hopper, extruder with 3 distinct sections in the heating barrel and spheronizer. Extrusion is carried out in a rotating screw extruder preferably single screw extruder due to relatively low cost, credibility and ruggedness [29] (**Figure 9 and 10)**.

The process proceeds in 4 steps;

(a) Melting or plasticizing a solid material in which drug is dispersed in a thermal carrier usually a low melting point wax or polymer e.g. vinyl polymers (polyvinylpyrrolidone, polyvinyl pyrrolidone-vinyl acetate); copovidone, polyethylene oxide; polyethylene glycol; acrylates; cellulose derivatives include carboxy methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate succinate, cellulose acetate, cellulose acetate phthalate; guar gum; xanthan gum; sodium alginate; cyclodextrins..

(b) Shaping of molten content into uniform cylindrical segments by extruder.

(c) Spheronization of extrudes at high temperature to deform by softening and assist uniform spheroids.

(d) Solidifying spheroids to get the desired shape spheroids.

The factors that influence hot-melt extrusion and spheronization: nature of extrudates selectively thermoplastic; composition of extrudates like drug and its melting point, physical and chemical properties of thermal carriers since they get transformed to molten state during the process; porosity of the extrudes which influences drug release. In case of thermolabile constituents, incorporation of plasticizer brings down degradation and improves flexibility of the polymer components by reducing the tensile strength and glass transition temperature. Functional excipients such as release modifiers, processing agents also play a key role in formulations by hot melt extrusion.

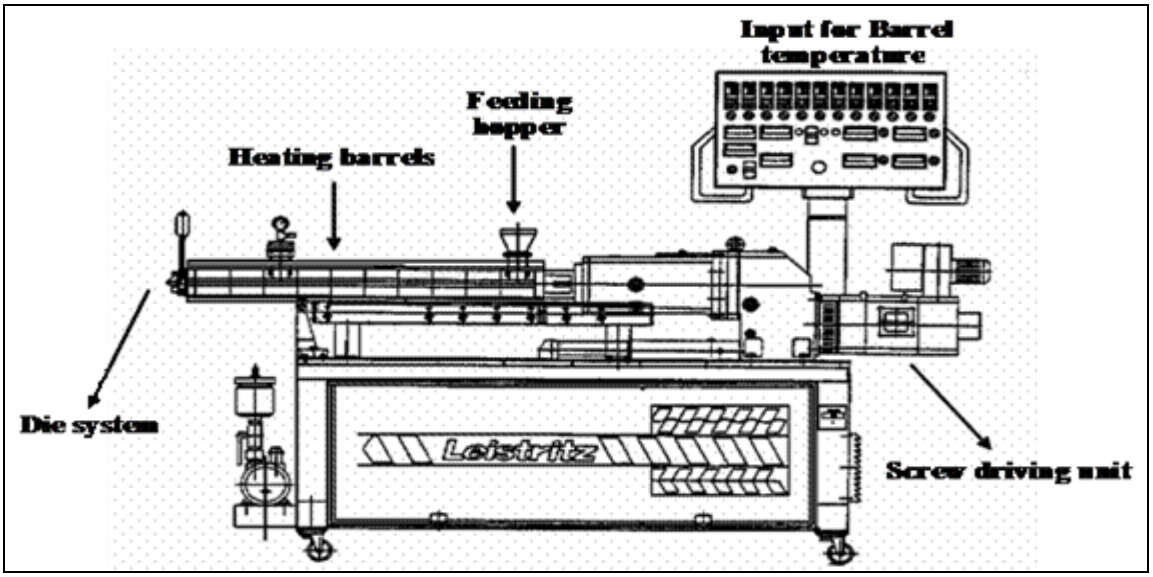


FIGURE 9: MICRO-18 TWIN SCREW CO-ROTATING LEISTRITZ EXTRUDER

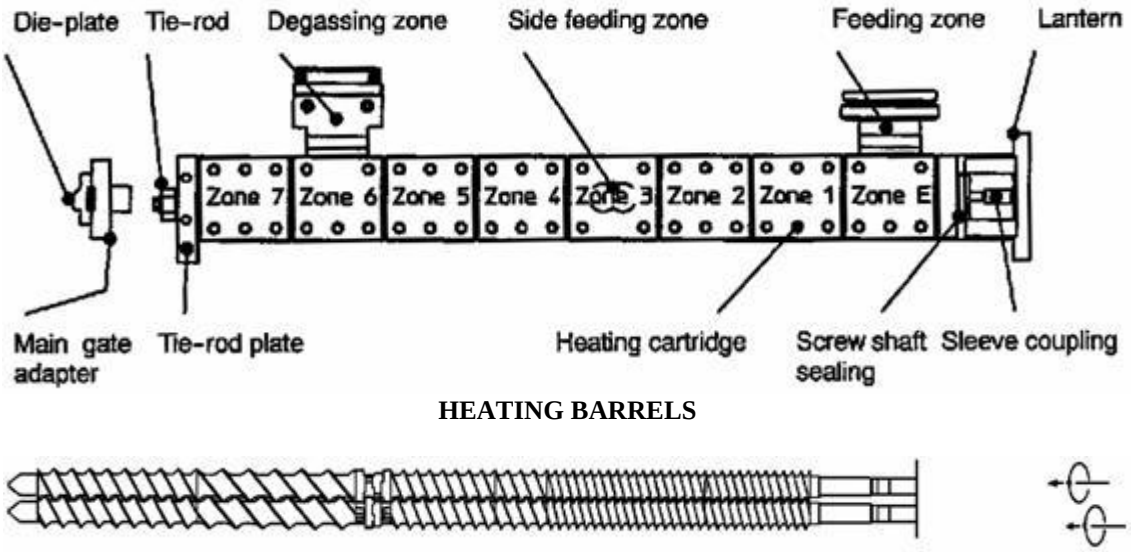


FIGURE 10: HEATING BARRELS AND CO-ROTATING SCREWS FOR HOT-MELT EXTRUDER

2. **Freeze Pelletization:** It is an advanced and a most simple technique for the production of spherical pellets by introducing droplets of immiscible molten solid carrier/matrix containing additives like disintegrants, diluents, surfactants and release modifiers with or without drug that is introduced into an inert liquid column. These droplets move either to the top or bottom of the column depending on their density with respect to liquid in the column [30].

Based on the movement of molten-solid droplets, two apparatus are designed. The former Apparatus I with an inlet at the top for introducing droplets and the droplets settle at the bottom of the column as the density of the matrix droplet is more than the liquid column (**Figure 11**).

Apparatus II is used when the carrier droplet density is less than the liquid column which has an inlet at the bottom and the droplets solidifying at the top **(Figure 11)**.

The column is 24 inches long and made of borosilicate glass. It is divided into two portions; initial portion with a temperature 25^{o}C to 100^{o}C, a region where the droplets are introduced. The second is cooling portion at which the droplets solidify and form spherical pellets; having temperature 0^{o}C to -40^{o}C maintained using cooling mixture such as acetonitrile - dry ice, or salt-ice.

The carriers used should be solid at room temperature and molted at its melting point. The molten solid matrices may be hydrophilic (polyethylene glycol; polyvinyl alcohol; low melting point sugars like xylitol, dextrose, sorbitol, maltose; water soluble polyoxyethylene derivatives; polyethylene- propylene glycol copolymers; polyethylene oxide derivatives; PEG-PEO derivatives) or hydrophobic (glyceryl monostearate; glyceryl palmitostearate; glyceryl dibehenate; ethylene glycol palmitostearate; cetostearyl alcohol; cetyl alcohol; stearyl alcohol; cholesterol; hydrogenated vegetable oils; phospholipids; lanolin; triglycerides; long chain fatty acids or hydrocarbons; hard fat; cocoa butter and waxes).

In case of hydrophilic carriers, hydrophobic liquid column and for hydrophobic carriers, hydrophilic column is used. Hydrophobic liquid column include silicone oils, mineral oil, vegetable oils, aliphatic long- chain hydrocarbons and hydrophilic columns are liquid polyethylene glycols with molecular weight 200-600, propylene glycol, glycerin, ethyl alcohol, water.

The main advantage of this technique is production of non-porous pellets with narrow particle size range which are feasible for further coatings like delayed; colon targeted and sustained release coatings.

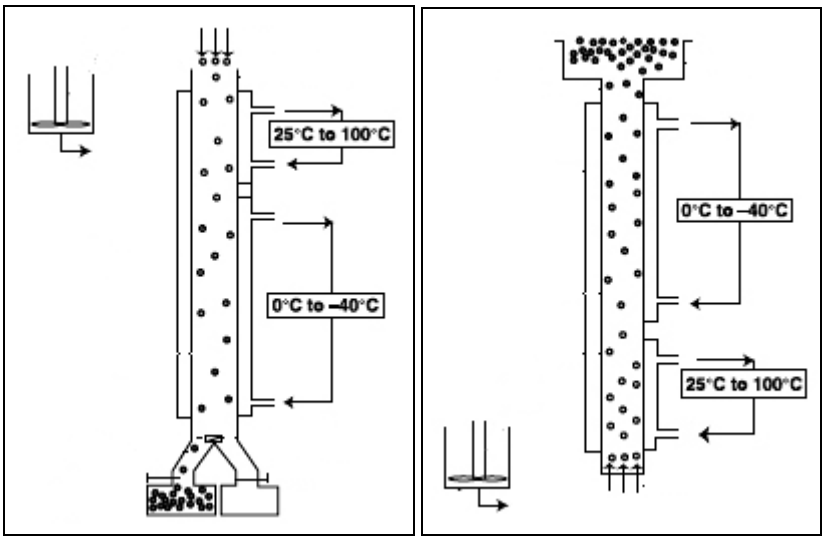


FIGURE 11: SCHEMATIC OF APPARATUS I AND APPARATUS II

3. **Cryopelletization:** It is a technique by which freeze dried or lyophilized pellets are formed by solidifying the droplets of aqueous or organic solutions, suspensions or emulsions using liquid nitrogen. The equipment has a perforated plate below which a liquid nitrogen reservoir with a varying speed conveyor belt is present with transport baffle dipped in it. Pellets are frozen by the residence time provided by the conveyor belt due to its varying speed. The frozen pellets are transported into a -60^{o}C storage container and dried in a freeze dryer [31, 32]. The factors that influence the size and shape of droplets are equipment design, process variables, solid content and viscosity of the droplets. The distance between the perforated plate and the reservoir is arranged in such a way that it allows the drops to become spherical before it comes in contact with liquid nitrogen.

   To achieve smaller size pellets, the diameter of the perforation in the perforated plate should be small. The liquid nitrogen should be continuously stirred to prevent agglomeration. The surface tension of the liquid can be reduced by the use of surfactants. The main advantage of this technique is production of highly porous pellets. The cryopelletizer is shown in **Figure 12**.

Microtablets: Nordmark Arzneimittek GmbH & Co. KG developed microtablets, a modern multiple unit dosage form with diameter and height 2 mm X 2 mm by compaction and compression. High speed rotary tabletting machine equipped with 10 - 19 multi-tip tabletting tools that produce 1- 2 million microtablets per hour. This design offers flexibility to compress active drug with poor compression properties in large concentrations and high mass uniformity.

These compressed core microtablets can be matrix forms or functionally coated to get the desired release profiles. One or more microtablet formulations containing different active ingredients can be filled into capsules at varying dosage strengths. Microtablets are supplied as stickpacks or filled into capsules. These formulations can be used in the therapies of pain relief, AIDS, oncology, hormones, pediatrics, etc. Various marketed formulations include Pancreatin Microtablets enteric coated with Kollicoat ®MAE 30 DP (Nordmark), Omeprazole (Ratiopharm), Sodium valproate (Desitin), Ferrous sulfate (Teofarma), Dimethyl-fumarate (Biogen).

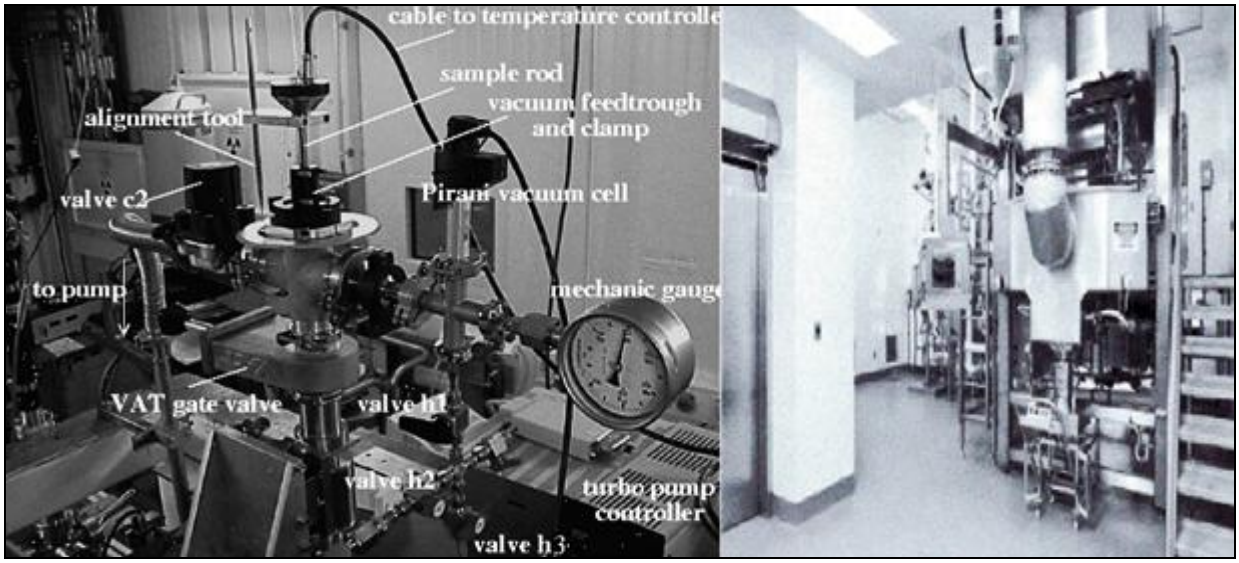


FIGURE 12: A) CRYOPELLETIZER; B) CRYOGRANULATOR USED TO FORM TECHNOSPHERE INSULIN PELLETS PRIOR TO LYOPHILIZATION

Characterization of Pellets: Pellets are evaluated for certain quality measures, which reflect the suitability and endurance of material during various operations like filling, transportation and handling.

The most common physical characteristics evaluated are:

1. **Pellet size and size distribution,** determined by sieve analysis which is simple and economical; microscopy methods like Scanning electron microscopy (SEM) and laser diffraction [33, 34]. This characteristic feature of pellets affects coating and rate of drug release. Another method to determine the size of pellets is estimation of fret diameter obtained from four different angles. In all cases, the size data was best fitted by a normal distribution.

2. **Shape** influences flow of pellets during coating, filling into capsules and dies. The most common method of analysis is by ring gap analyzer; scanning electron microscopy (SEM) for qualitative and quantitative analysis [35]. Visual inspection of pellets by microscope and stereomicroscope also determine shape of pellets. Another method to determine spherical shape (sphericity) is by taking optimum size pellets, stained with dye solution in a petri dish and dried on a hot air oven. Each pellet is recorded for two dimensional image i.e., length and width using camera lucida fixed to an optical microscope and circulatory factor(s) was calculated using the equation $S = P^2/(12.56 * A)$; where A is the area (cm^2) and P is the perimeter(cm) of circular tracing. Circularity, another parameter to determine shape is calculated as $4\pi A/P^2$, wh*ere A is projection area and P is projection perimeter*.

3. **Surface area** has an effect on drug release and results in batch to batch variability. To ensure the production of consistent shape pellets, surface area is analyzed by particle size distribution, gas adsorption (BET method-Brunauer, Emmett & Teller) and air permeability method [35]. *Surface roughness* is analyzed by fractal geometry of particle obtained by microscopy with image analysis and SEM. This property influences flow and packing of pellets [35].

4. **Porosity** influences rate of drug release from the pellets by affecting the capillary action of the dissolved drug; analysed qualitatively by scanning electron microscopy and quantitatively by mercury porosimetry [36]. The sample is introduced into the chamber, degassed, and then completely covered with mercury. Pressure is applied and the volume of mercury that penetrates into the pores is recorded. Pore radius is given by Washburn equation:

   R = 2 g [cos q] / P; Where g = 480 ergs/cm3, q= 140^{o}, r = pore radius, p = mercury-intrusion pressure.

5. **Bulk Density and tap density** affects potency of finished product, produces segregation during mixing and leads batch to batch variation. The bulk density was calculated by the ratio of weight to the occupied volume and is measured by automated tapper or a pycnometer [37, 38, 39, 40].

6. **True density** indicates extent of densification or compactness. Air- comparison pycnometer, helium pycnometer or solvent displacement method are different methods of analysis.

7. **Friability and hardness** helps to withstand subsequent coating and high attrition during coating. Roche friabilator, Erweka friabilator, Pharma Test friabilator are different equipment used. The % friability of pellets should be less than 0.08% [41, 42]. Relative hardness of the pellets is determined by using Kaul pellet hardness tester.

8. **Tensile strength is** determined by using tensile apparatus with a 5 kg load cell. The radius of pellets is recorded and these pellets were strained continuously until failure occurs. Further load is recorded. The tensile strength is calculated by applying the value for the failure load (F) and the radius of the pellets (R) by the formula $\sigma_{f(s)} = 0.4F/\pi R^2$.

9. **Flowability** is determined by angle of repose. If $\Theta<30°$-excellent Flowability and $\Theta>40°$- poor flow ability.

10. ***In-vitro Dissolution Testing*** most commonly is by USP I (basket) and USP II (paddle) apparatus to study the release pattern of the coated pellets [43].

Mechanism of Drug Release from Pellets: The mechanism of drug release from pellets can occur in the following ways:

1. **Erosion:** Some coatings are designed to erode gradually with time, thereby releasing the drug contained within the particle.

2. **Osmosis:** In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.

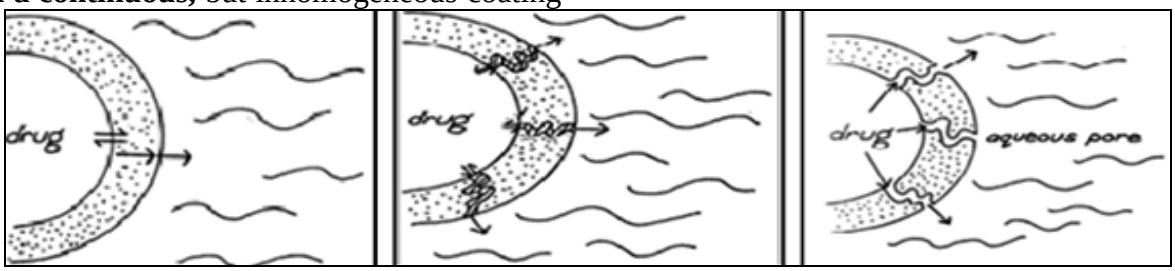
3. **Diffusion*:*** On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Three different release mechanisms were identified from pellet dosage forms coated with polymers insoluble in GIT through diffusion.

1. ***Diffusion of solution through the continuous plasticized polymer phase*;** assumes that the polymer forms a phase in which the plasticizer and other additives are homogeneously dispersed. The diffusion of a solute molecule within an amorphous polymer phase is an activated process involving the cooperative movements of the penetrant (drug) and the polymer chain segments around it. It is by this stepwise process that hindered molecular diffusion occurs. The frequency with which a diffusion step occurs depends on the size and shape of the drug, tightness of the bonds between adjacent polymer chains and the stiffness of the polymer chain. Further below its glass transition temperature (Tg), less permeable is the polymer. Plasticizers lower the Tg, increase free volume and increase diffusivity. Accordingly, this mechanism is dominant in continuous film, flexible polymers which lacks pores. Overall permeability of the polymer to the drug will depend on the ability of the drug to partition into the polymer as well as its ability to diffuse through the polymer (**Figure 13**).

2. ***Solution/diffusion through plasticizer channels*;** occurs when the plasticizer is not uniformly distributed in the coating polymer and its content is high. The plasticizer takes the form of a continuous phase in the form of patched channels. Diffusivity in the plasticizer will generally be lower than in water since plasticizers tend to be relatively viscous (**Figure 13**).

3. ***Diffusion through aqueous pores*** **intervenes when a continuous,** but inhomogeneous coating layer is punctuated with pores. This mechanism is more likely to be operative for the coatings formed from aqueous dispersions and when the pellets come in contact with an aqueous medium. These pores fill with solution thus facilitating the diffusion of the drug. During the coating and curing processes, the pseudolatex particles often do not fuse completely, thereby creating a porous coating. The pores may be of 1µm size and the release mechanism is illustrated in **Figure 13**.



(a) **(b)** **(c)**

FIGURE 13: DRUG RELEASE FROM COATED PELLETS VIA (A) SOLUTION/DIFFUSION THROUGH THE POLYMER FILM (B) SOLUTION/DIFFUSION THROUGH PLASTICIZER CHANNELS (C) DIFFUSION THROUGH AQUEOUS CHANNELS

TABLE 3: MARKET PRODUCT OF PELLETS

S. No.	PRODUCT	DRUG	COMPANY
1	Bontril SR	Phendimetrazine Tartrate	Carnick laboratories, Inc
2	Brexin L.A	Chlorpheniramine Pseudoephedrine	Savage Laboratories, Bangalore
3	Catazyme S	-	Organon pharmaceuticals, USA
4	Compazine	Prochlorperazine	Smith & French, Mumbai
5	Cymbalta	Duloxetine Hydrochloride	Eli Lilly and Company, USA
6	Dilgard XL 180	Diltiazem hydrochloride	Smith kline & French, Mumbai
7	Elixophyline	-	CIPLA Ltd, Ahamadabad
8	Fastin	Phentermine	Berlex Laboratories, USA
9	Hispril	Diphenylpyraline	Berlex Laboratories, USA
10	Ibugesic S.R 300	Ibuprofen	CIPLA Ltd, Ahamadabad
11	Inderal	Propranolol Hydrochloride	Astrazeneca US Ltd.
12	Indocrin S.R	-	Merk Sharp, Mumbai
13	Nexium	Esomeprazole	Astrazeneca US Ltd.
14	Nicobid T.S	Niacin	U.S Vitamin, USA
15	Omez	Omeprazole	Dr. Reddys lab, Hyderabad
16	Ornade	Chlorpheniramine & phenylpropanolamine	Smithkline & French
17	Prevacid	Lansoprazole	Takeda
18	Prilosec	Omeprazole	Astrazeneca US Ltd.
19	Sporanox	Itraconazole	Janssen
20	Theobid SR	Theophylline	Glaxo

CONCLUSION: The brief review on pellets and pelletization concludes pelletized dosage forms as one of the most promising and efficient pathway of novel and multiparticulate drug delivery systems. This technology has remained much of an art for many years due to its process, formulation and therapeutic advantages over single unit drug delivery systems. In addition, hot-melt extrusion and spheronization, freeze pelletization, cryo-pelletization, microtabletting technologies provides a wide scope to produce pellets. Today, pelletization is challenging and growing technique to develop pelletized dosage forms for a wide range of drugs which are unstable or have compatibility problems with excipients and hence the market for these dosage forms is growing rapidly and gaining popularity in an impressive rate.

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