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Pharmaceutical Pelletization: A review

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ABSTRACT: Multiparticulates are discrete particles that make up multiple unit system. Pellets exhibit major therapeutic and technical advantages which have established them as an exceptionally useful dosage form. Although pellets have been used in pharmaceutical industry for more than four decades, with the advent of controlled release technology, that the full impact of the inherent advantages of pellet over single unit dosage forms have been realized, not only has focused on refining and optimizing existing pelletization techniques, but also focused on the development of novel approaches and procedures for manufacturing of pellets. The present review outlines the recent findings on the manufacturing and evaluation of spherical pellets published over the past decade. The techniques namely layering, extrusion spheronization, freeze pelletization, cryopelletization have been discussed along with parameters affecting pelletization. Evaluation of quality of the pellets is discussed with reference to the size distribution, shape, surface morphology, specific surface area, friability, tensile strength, density, porosity, disintegration time and in vitro dissolution studies of pellets. The use of multi particulate dosage forms as a promising system for the oral delivery of many therapeutic agents has also been examined in the current review.

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Key words: Multiparticulates, Pelletization, layering, extrusion spheronization, freeze pelletization, cryopelletization.

INTRODUCTIONS:

Generally, multi-particulate formulations or multiple unit-dosage forms (pellets, micro-tablets and granules) are continuously produced since they permit flexibility in development. Thus, multi-particulate dosage forms are pharmaceutical formulations in which the active pharmaceutical ingredient (API) is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet [1]. Pellets, being multiple unit-dosage forms, are widely used as they offer both manufacturing and therapeutic advantages over single-unit solid dosage forms [2]. As

defined by Ghebre-Sellassie, *et al.*[3] pellets are spherical, free-flowing granules with a narrow size distribution, typically varying between 500 and 1500 µm in size for pharmaceutical applications. They are formed as a result of a pelletization process which is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free-flowing, spherical or semi-spherical units.

A SHORT HISTORY OF PELLETS:

Although various industries have routinely utilized pelletization processes since the turn of the 20th century in order to manufacture particles with defined sizes and shapes, it was only in the early 1950's, in response to a desire to sustain the release of drugs over an extended period of time, that the pharmaceutical industry developed a keen interest in the technology [4]. A major breakthrough occurred in 1949 when a pharmaceutical scientist SmithKline and French (SKF) realized the potential application of candy seeds in sustained release preparation and embarked on the development of tiny drug pellets that could be loaded in capsule. In 1964, a new pelletization technique that provided sustained release pellets ranging in size between 0.25 – 2.0 mm was patented by SKF at the same time marumerizer or spheronizer was commercially introduced. The new machine was developed in Japan and could produce large quantity of spherical pellets in short time. The marumerizer and variation of it were subsequently patent in USA. Direct pharmaceutical application of the process for the development of pellets was first published in literature in the early 1970 and the process has been the subject of intensive research ever since. Although pellets have been used in the pharmaceutical industries for more than 4 decades, it has only been since the late 1970s, with the advent of controlled release technology that the advantages of pellets over single – unit dosage forms have been realized [5].

In time, extensive research was conducted to develop pelletization techniques and major resources were allocated towards exploring methods that were faster, cheaper and more efficient both in terms of formulation and processing equipment. The trend is expected to continue in the foreseeable future [6]. There are different techniques applicable for the production of pellets in pharmaceutical industries which are [7,8];

- Powder Layering/Solvent less coating.
- Solution/Suspension Layering.
- Direct powder pelletization.
- Extrusion-Spheronization.
- Spray Drying & Spray Congealing.
- Pelletization by Fluid- Bed Coating.
- Cryopelletization.
- Spherical Agglomeration.
- Freeze Pelletization.
- Agitation (Balling).
- Compression.

Dry powder layering:

The powder layering process is one of the most well controlled and straight forward pelletization techniques. This technique (Fig 1) involves the deposition of successive layer of dry powder of drug or excipient or both on preformed nuclei or core with the help of a binding liquid. During powder layering the binding solution and finely milled powder are added simultaneously to a bed of starter seeds at a pre-determined controlled rate .In initial stages the drug particle are bound to the starter seeds of subsequently to the forming pellets with the help of a liquid bridges originated from sprayed binding liquid. These liquid bridges are replaced by solid bridges derived either from a binder in the liquid medium or from any material. Successive layering of a drug and the binder solution continuous until desired pellet size are reached [4,5]. An important factor that needs to be considered is the particle size of the powder. Micronized particles tend to provide pellets that are smooth in appearance. If the particle size of powder 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.

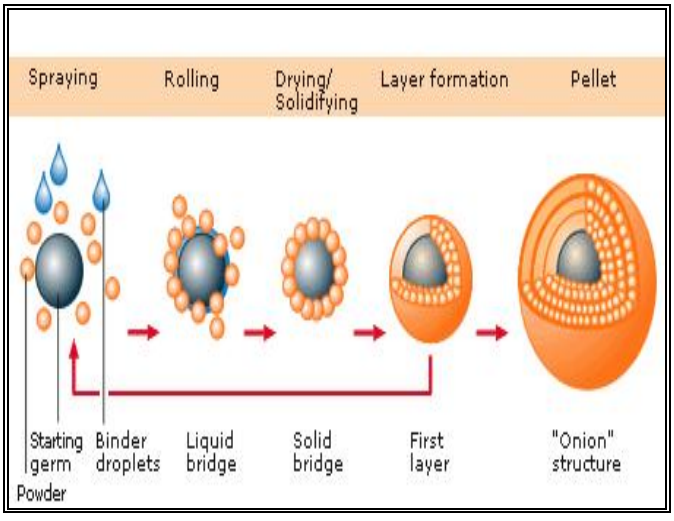

Fig 1. Principle of the powder layering process.

The morphology of the finished pellets also tends to be rough and may adversely affect the coating process and the coated product. Moreover, because particles detach easily from the core they are being layered on owing to frictional forces, yield is usually low. In order to achieve the desired pellet size, successive layering of the powder and binder solution is continued [9].

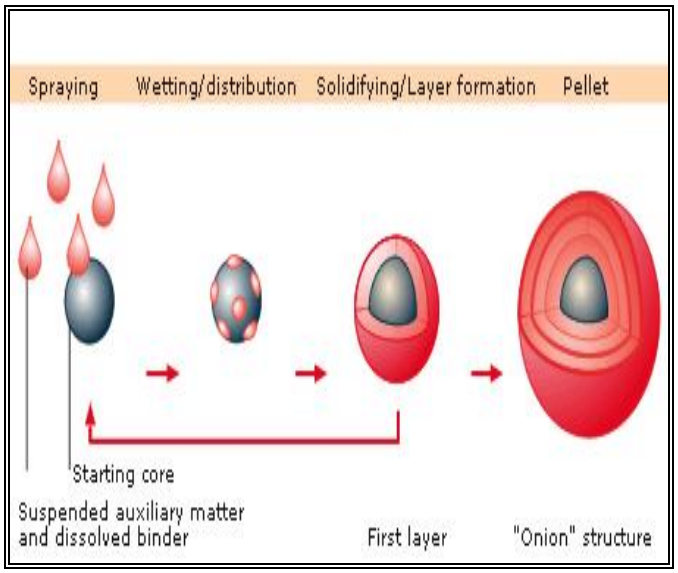

Fig 2. Principle of the solution and suspension layering process.

The first equipment used to manufacture pellets on commercial scale was the conventional coating pan but it has significant limitation that is the degree of mixing is very poor and the drying process is not efficient. Throughout the processes it is extremely important to deliver the powder accurately at a predetermine rate and in a manner that maintains equilibrium between the binder liquid application rate and powder delivery rate is not maintained ,over wetting or dust generation may occur and neither the quality nor the yield of the product can be maximized.

More over the fines may be generated by inter particle and wall to particle friction and appear in the yield. The above problem can be overcome if the application medium is sprayed on the cascading pellets at the end to increase the moisture level at the pellets surface and facilitate layering of fines on to the pellets. For this purpose now it is equipment like tangential spray granulator and centrifugal bed granulator are used [5].

Solution and suspension layering:

This process (Fig 2) uses conventional coating pan or fluidized bed with conventional top spray or Wurster bottom spray to apply drug/binder solution or suspension to solid cores that can be inert materials or granules of the same drug [10,11].

Direct powder pelletization:

The technique (Fig 3) uses high shear mixers and centrifugal fluid-bed or rotary fluid-bed granulators to apply agglomeration liquid direct to a powder mixture of a drug and excipients followed by pelletization by means of a rotating disc. A binder can be added as a liquid (wet pelletization) or as a molten binder before or during the process (melt pelletization) [12].

Extrusion-Spheronization process:

This is the most employed technique (Fig 4) as it offers the advantage to incorporate high amounts of active pharmaceutical ingredient, without producing an excessively large particle of drug-loaded pellets apart from being more efficient than the other techniques for producing pellets [13]. Extrusion can be defined as the process of forcing a material through an orifice or die under controlled conditions thus forming cylinders or strands called extrudates. During spheronization, these extrudates are broken into small cylinders and consequently rounded into spheres (pellets). Hence, extrusion/spheronization is a multiple-step process capable of making uniformly sized spherical particles referred to as pellets and involving the following sequential steps like Dry Blending/Mixing, Wet Mixing/Granulation, Extrusion, Spheronization, Drying and Optional Screening [14,15]. The end product from each of the steps is shown Fig 5 and 6. The pellets manufactured via extrusion/spheronization have a high process yield, narrow size distribution, good sphericity and low friability [16,17,18].

As mentioned previously extrusion/spheronization is a multi-step process (Fig 5). Each phase of the process (except for dry mixing and wet massing which are often performed in the same equipment type) requires highly specialized equipment, which can be a disadvantage in terms of expenses. Furthermore, each production step is a distinct process and involves control over a number of process parameters in order to obtain pellets of required quality. In recent years a lot of research was also dedicated to the influence of formulation variables on the success of extrusion/spheronization (Fig 6).

Dry mixing:

Obtaining a uniformly blended dry powder mix of active ingredient (s) and excipient (s) is the first step in any process involving agglomeration of particles. Dry

mixing, followed by wet massing or granulation is usually performed in the same equipment (batch-type mixer/granulators). Commonly used types reported in the literature are: planetary mixers, high-shear mixers and sigma blade mixers [19-23].

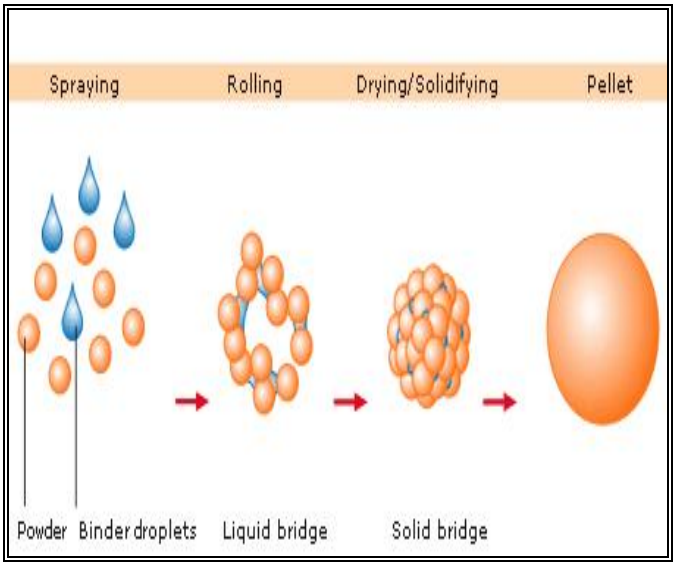

Fig 3. Principle of the direct pelletization process.

Wet massing:

The wet massing step of extrusion/spheronization involves the addition of a granulation liquid in much higher amounts than those required for conventional granulation [24]. The amount of granulation liquid has a crucial role in the success of extrusion and spheronization and should therefore be included as a variable during formulation development. In addition, temperature generation during wet massing can promote water evaporation and significantly influence pellet properties [25,26].

Extrusion:

The extrusion phase comprises forcing of the wet plastic mass through a small orifice (extrusion die), thus forming cylinders or strands with a breadth corresponding to the die diameter and a length which depends on material properties and extruder type [27]. Extruders have a part which transports the wet mass towards the extrusion screen and a die which shapes the extruded material. Several extruder types are used. Different authors classified them into screw, gravity and piston type extruders (Fig 1.7) based on the material feeding mechanism; some authors grouped them into four types (screw; sieve and basket; roll and ram extruders)[28] and recently researcher classified them into extruders with pumping (ram, axial screw) and wiping action (sieve and basket, roll, radial screen).[29]

Screw feed extruders (Fig 7) consist of one or two rotating screws which push the moistened mass from the material feeding zone towards the extrusion screen. Based on the extrusion screen design, screw feed extruders are classified into axial, dome, or radial types. The major advantages of screw feed extruders are a higher throughput rate, ease of changing different screen types and ease of cleaning [30]. Gravity feed extruders the wet mass is transported towards the extrusion screen by means of gravitational force and several types are in use: rotary cylinder, rotary gear and radial. Piston feed extruders or ram extruders are mainly used as laboratory extruder or for extrusion of specialized materials which require strict in-process control [29].

Spheronization:

A spheronizer consists of a bowl with a stationary cylindrical wall and a fast-rotating bottom plate with grooved surface to increase the friction. During the initial stage of spheronization extrudates are broken into small cylinders and after a relatively short period of time spherical pellets are formed. The spheronized material moves outwards to the wall due to centrifugal forces, followed by collision and climbing up the stationary wall. Then the particles fall back onto the rotating disk which due to its angular motion pushes the mass again towards the wall, creating a typical “rope-like” formation (Fig 8) which is considered crucial for successful spheronization [26]. The transformation from cylinder-shaped extrudate to a sphere occurs in various stages. Two models have been proposed to describe the mechanism as shown graphically in Fig 9.

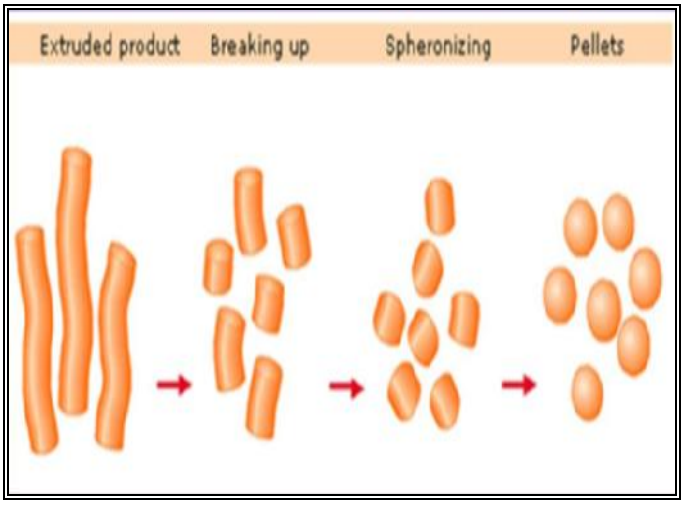

Fig 4. Extruded product spheronizing process.

The transition of cylindrical into spherical shape occurs via several stages, as proposed by two models: suggested that after the initial breaking of the extrudates, cylinders are initially rounded at the edges, followed by formation of dumbbell-like granules and finally spherical pellets are formed (Fig 9.a),[27] while some author described an alternative model where cylinders are rounded at the edges but additionally bent, followed by twisted dumbbell formation which initiates particle breaking into two parts with a cavity on their flat side and further rounding into spheres (Fig 9.b) [31]. Which mechanism will dominate most likely depends on the formulation, while granulation liquid level and spheronization process parameters influence whether the spheronization step will result in pellets with a broad size distribution, dumbbells, agglomerated material or spherical granules with a narrow size distribution [10]. The main spheronization variables affecting pellet characteristics are: material load, residence time, spheronizer type, geometry of spheronization plate, peripheral velocity (rotational speed of the friction plate combined with the plate diameter) [27].

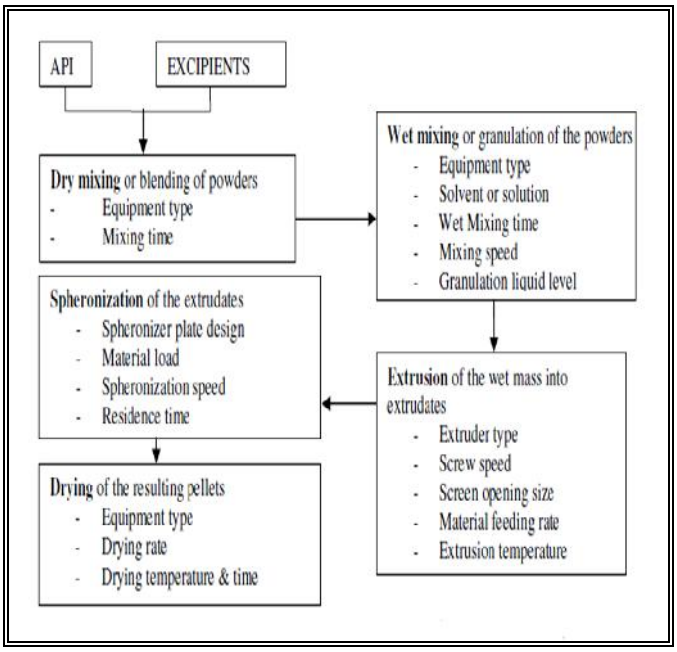

Fig 5. Extrusion/spheronization process flow chart with individual processing variables.

Drying:

Wet pellets are mostly dried in an oven or fluid-bed, although micro-wave and freeze drying have been also used to study the influence of drying method on pellet properties. The main differences between oven and fluid-bed drying are the rate of granulation liquid evaporation and the way how the material is handled during drying: during oven drying in a static bed liquid evaporates from the material over longer period of time, while during fluid-bed drying the turbulent motion of dried material in a heated air stream promotes significantly faster drying [32].

PELLET PROPERTIES:

The properties of pellets are listed in Fig 10, together with different evaluation methods [33].

ADVANTAGES OF PELLETS:

Therapeutic Advantages of Pellets made by the ES Process [34-38] are;

Easy to coat. Improved product appearance and the core are pharmaceutically elegant. Separation of incompatible drugs and delivered in a single dosage form by encapsulating them. Reduced risk of dose dumping. Ability to mix pellets with different release rates. It improves safety and efficacy of a drug. Even distribution over the gastro-intestinal tract. Pellets offer reduced variation in gastric emptying rate and transit time. Reduced risk of local irritation in the gastro-intestinal tract.

Less variable bio-availability. Particles of 1mm or less behave more like liquids in terms of gastric emptying. For immediate release products larger surface area of pellets enables better distribution, dissolution and absorption.

Physical advantages of Pellets made by the ES Process [34] are;

Improved flow characteristics. Narrow particle size distribution (PSD). Uniform packing characteristics. Dust free. Low friability.

Additionally**,** the production of controlled-release multi-particulate oral dosage forms using spheroids, designed to deliver drugs at a specific site within the gastrointestinal tract or over an extended period of time, leads to a series of therapeutic advantages over conventional oral dosage forms such as tablets or capsules.

PRODUCT CHARACTERISTICS OF THE PELLETS:[34]

The characteristics are Round pellets, Good flow behavior, Easy to dose, Good dispensability, Compact structure, High bulk density and dense surface.

INFLUENCE OF PROCESS VARIABLES:

Operational variables may affect several important pellet properties, which can render a pellet either suitable or

unsuitable for use. In the current study, the different process variables were studied for the preparation of pellets. The process variables considered were granulation liquid, extruder speed, spheronization time, spheronization speed, spheronization load [39].

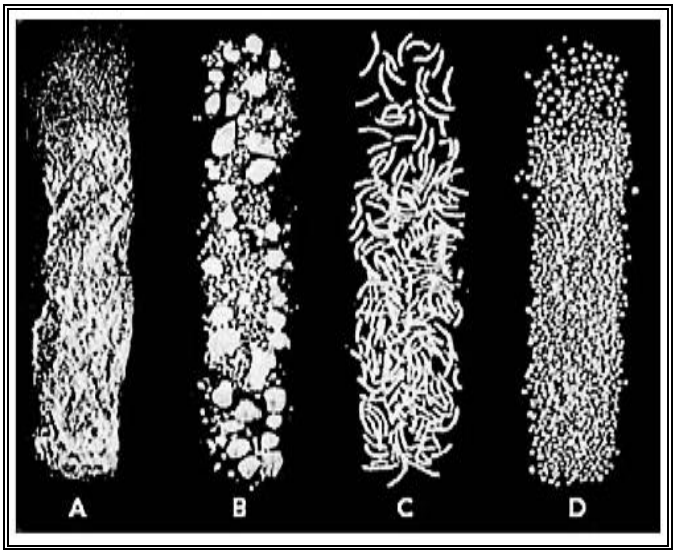

Fig 6. Product produced by the first four extrusion/spheronization process steps: (a) powder from dry mixing, (b) granules from granulation, (c) extrudate from extrusion, and (d) spheres (pellets) from spheronization.

Amount of Granulation Liquid:

The liquid content in the wetted mass, along with its distribution, is very important in that it can dramatically alter pellets properties, such as size, shape, density, and friability. The plasticity of the wetted mass is closely associated with its moisture content. Lower moisture levels may increase friction in the extruder, causing forced flow during extrusion as the wetted mass is not sufficiently lubricated at the die surface [40]. The severity of shark skinning is increased with decreasing moisture levels. Plasticity of the pellets may be decreased and the pellets would not round up completely [41]. The extrudate stays dumb-bell shaped or oval shaped in the final product. Friability of the pellets is increased and pellet size is reduced.[42] The amount of fines generated during spheronization is increased. On the other hand, excess moisture in the wetted mass may lead to smooth extrudate that doesn't break easily during spheronization.[43] Agglomeration into larger pellets occurs due to the presence of excess moisture on the surface of the particles as they round up. The pellets may be too soft due to excess plasticization, contributing to agglomeration [40].

Extrusion speed:

The throughput of extrusion and the quality of the final pellets depend on the speed of the extruder. Higher extrusion speeds result in an increased compression force on the wetted mass in the extruder. This results in increased surface impairments on the extrudate, such as shark skinning [44].

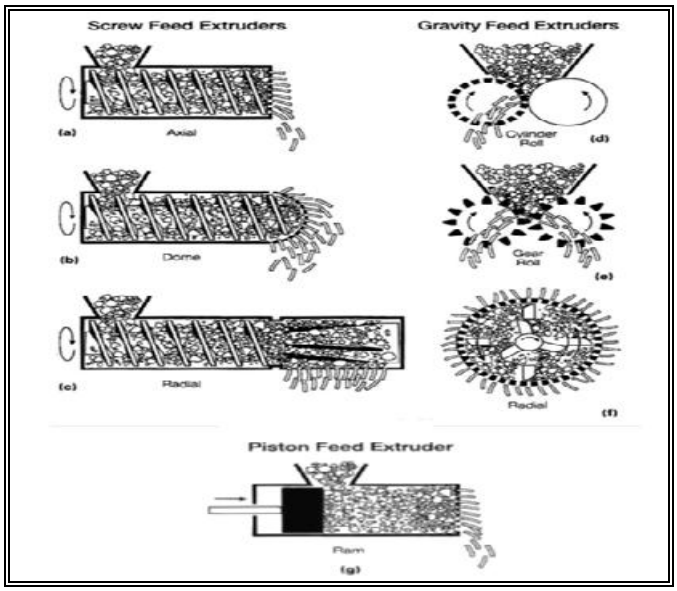

Fig 7. Schematic diagram of extruder types used in extrusion/spheronization: screw feed (a. axial-, b. dome- and c. radial- type), gravity feed (d. cylinder, e. gear and f. radial- type) and piston feed (g. ram) extruders.

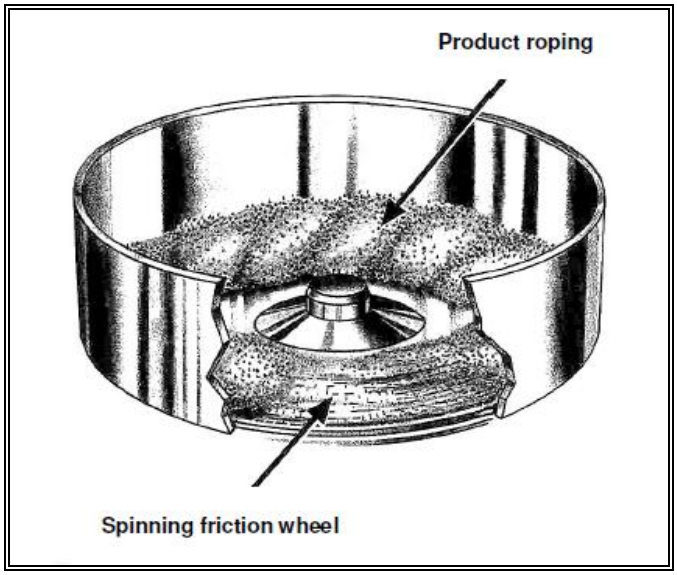

Fig 8. Schematic representation of the "rope-like" motion during spheronization.

While moderate, surface roughness encourages extrudate to break into consistent pieces to form uniform sized pellets, more pronounced surface impairments lead to production of lower quality pellets with a wider size

distribution and generation of fines due to uneven breakage of the extrudate in the spheronizer [45]. In contrast to these studies there was no significant effect of extrusion speed on the properties of the pellets. This may be because the materials were tolerant to the changes in the extrusion forces in the ranges studied [46,47].

Spheronizer speed:

Several researchers have reported the effect of spheronizer speed on the pellets size [46,48-50]. An increase in the spheronization speed yields more spherical pellets and results in increased bulk densities due to improved packing properties. Spheronization speeds below a minimum threshold may not result in the rounding of the extrudate, resulting in rod-shaped structures. High spheronization speeds increase attrition and likely to result in the generation of fines and, depending on the binding properties of the formulation, the formation of agglomerates with those fine particles. Pellet characteristics influenced by the spheronizer speed include sphericity, density, friability, size distribution, amount of fines generated, porosity, flow rate, and surface structure. An optimized spheronization speed is necessary to achieve spherical pellets with a narrow size distribution.

Spheronization time:

The residence time in the spheronizer is one factor that must be optimized to obtain a superior product. According to some studies, a longer spheronization time was responsible for increased pellets size,[51] increased sphericity of the pellets,[52] increased density[53] and a narrow particle size distribution [54]. In contrast, some researcher, report no change in the shape and density of the beads with increasing spheronization time. The yield in the targeted size range, however, was reported to be lowered by an increase in the spheronization time [55].

Spheronizer load:

Spheronizer load has been shown to affect the properties of pellets with a wide range of tolerance [56-58]. Only under extreme conditions does the spheronizer affect the properties of the pellets significantly. When the batch size is too low, particle-particle interactions are minimized and particle to friction plate interactions are more. This causes a reduction in the size of the pellets due to the abusive nature of the friction plate. At high spheronizer loads, particle to plate interactions are low. The particle to particle interactions are dominant and opportunities for agglomeration are greater. The resultant pellets are consequently larger in size.

CHARACTERISATION OF PELLETS:[55-59]

In order to meet the requirements of pellet yield, size distribution, surface area, shape, surface roughness, density and friability, including the reproducibility of morphologic properties of the pellets, pellets were tested.

Pellet yield:

The coated pellets (20 g) were sieved for 5 min on sieve shaker equipped with series of sieves of pore opening as 1400, 1000, 710, 500 and 250 µm sieves (Sieve No. 12, 16, 22, 30 and 60 respectively). The pellet yield was calculated based on the pellet fraction between 710 and 1400 µm and presented as a percentage of the total pellet weight. This size fraction was used for all further measurements.

Size Analysis:

The most common and widely used method for determination of size is sieve analysis. The reasons for its extensive use are simplicity, low costs, low time consuming. Sieving, using sieve shaker is one of the fundamental methods for determining the size distribution of pellets. In this method test sieves ranging from sieve no. 12 to 60 are arranged in descending order. A 20 g quantity of the pellets is placed on the top sieve and the set-up is shaken for 5 min.

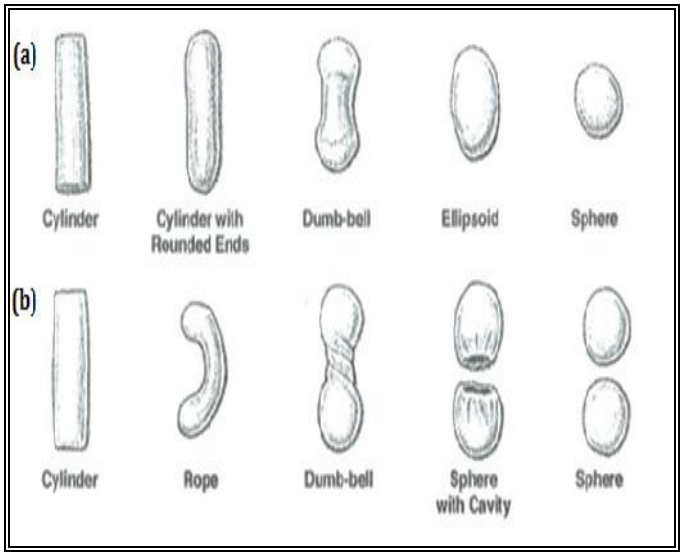

Fig 9. Schematic representation of different pellet formation stages during spheronization.

The weight of material retained on each sieve is determined.The modal class fraction was the size fraction obtained from sieving with the highest weight of pellets. The average diameter is calculated using the equation:

Avg diameter = [∑(% retained) × (mean aperature)]/ 100 …… (1)

Shape Analysis:

At least 20 pellets from each batch were randomly selected for shape analysis from fraction obtained after size analysis by sieving. The pellets were mounted on a surface of motic microscope, and the images of the pellets were captured. The area of the images and the maximum and minimum radii were calculated, and from these the various shape factors were calculated.

Densities of Pellets:

An accurately weighed quantity (5 g) of the pellets (W), was carefully poured into the graduated cylinder and the bulk volume (V_o) was measured. Then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 100 tabs and after that, the volume (V_f) was measured and operation was continued till the two consecutive readings were equal. The bulk density, and tapped density were calculated using the formulae**.**

Bulk density (ρ_b) = Weight (W)/ Bulk Volume (V_0) ……... (2)

Tapped Density (ρ_t) = Weight (W)/ Tapped Volume (V_0) ……. (3)

Compressibility Index and Hausner's ratio:

In recent years the compressibility index and the closely related Hausner's ratio have become the simple, fast, and popular methods of predicting pellets flow characteristics. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of pellets.

Compressibility Index (%) = $[(\rho_t - \rho_b)/\rho_t]\times100$ …… (4)

Hausner's ratio = ρ_t / ρ_b …… (5)

Flow Rate and Angle of Repose:

The flow rate and angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of pellets or granules and the horizontal plane.

Flow Rate (g/s) = Weight of Pellets/ Time …….. (6)

Angle of Repose, θ (°) = $Tan^{-1}(h/r)$ …….. (7)

Where, θ is angle of repose, h is height of pile and r is radius of pile. A funnel was fixed at a height approximately of 2-4 cm over the platform. The loose pellets (10 g) was filled in a funnel and passed along the wall of funnel, till the cone of the pellets formed. The angle of repose was determined by measuring the height of the cone of pellets and radius of the heap of pellets.

Pellet Friability Test:

About 10 g of pellets (Fs) was placed in friability test apparatus together with 20 glass beads. The sample was subjected to falling shocks for 4 min at a rotational speed of 25 rpm and fines collected by sieving through 250 µm mesh. The weight difference was obtained by weighing the pellets retained above 250 µm (Fa) and compared to the initial weight of the sample and percentage of friability determined using the following equation;

Friability (%) = [(Fs – Fa)/ Fs] × 100 …….. (8)

Pellet Disintegration Test:

The pellet disintegration in water was evaluated by a tablet disintegration test apparatus. About 100 mg pellets were placed along with a plastic disc in each tube and they were inserted in the disintegration test apparatus maintained at 37°C ± 1°C. Disintegration test was carried out three times for each formulation, and results were expressed with the standard deviations.

CONCLUSION:

Pelletization plays an important role in designing of various oral immediate or controlled delivery systems. Suitability of its technique due to numerous advantages, Pelletizatin has been included in special position in the Pharmaceutical Industry and moreover its use in production of multiparticulate oral controlled release dosage forms overtaking granulation. Now a day, extrusion spheronization and melt extrusion spheronization demonstrates a significant approach for novel drug delivery system, which in term would be able to design suitable novel dosage forms of drugs that will have more patient convenience, therapeutic safety and efficacy.

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