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EVALUATION PARAMETERS FOR SPHERICAL AGGLOMERATES FORMED BY SPHERICAL CRYSTALLISATION TECHNIQUE.

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ABSTRACT

Spherical crystallization is the novel agglomeration technique that can transform directly the fine crystals produced in the crystallization process into a spherical shape. It is the particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transform crystals directly into compacted spherical form. This technique of particle design of drugs has emerged as one of the areas of active research currently of interest in pharmaceutical manufacturing and recently came into the forefront of interest or gained great attention and importance due to the fact that crystal habit can be modified during the crystallization process. In consequence of such modifications in the crystal habit certain micrometric properties and physicochemical properties can also be modified .As this technique forms the spherically agglomerated crystals showing significant effect on the formulation and manufacturing of pharmaceutical dosage form. Therefore it is necessary to evaluate and characterized these spherically agglomerated crystals by using the different parameters so as to differentiate it from the raw crystals.

KEYWORDS

Spherical crystallization, flowability, compactability, physicochemical properties.

INTRODUCTION

In 1986, Kawashima et al used the spherical crystallization technique for size enlargement of the drug in the field of pharmacy. Spherical crystallization was defined by Kawashima as “An agglomeration process that transforms crystals directly in to a compact spherical forms during the crystallization process.” It also enables co-precipitation of drug and encapsulating polymer in the form of spherical particle [1,2] .

Following are the methods used to prepare the spherical crystals.

1. Spherical Agglomeration method (SA)
2. Quasi-Emulsion Solvent Diffusion method (QESD)

3. Ammonia diffusion system (ADS)
4. Neutralization Technique (NT).
5. Traditional crystallization process.

Spherical crystallization is the novel agglomeration technique that can transform directly the fine crystals produced in the crystallization process into a spherical shape. It is the versatile process that enables to control the type and the size of the crystals. It is the particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transform crystals directly into compacted spherical form. This technique of particle design of drugs has emerged as one of the areas of active research currently of interest in pharmaceutical manufacturing and recently came into the forefront of interest or gained great attention and importance due to the fact that crystal habit (form, surface, size and particle size distribution) can be modified during the crystallization process. In consequence of such modifications in the crystal habit certain micrometric properties (bulk density, flow property, compactability) and physicochemical properties like solubility, dissolution rate, bioavailability and stability) can also be modified. It is also possible to prepared novel particulate drug delivery system like microsponges, microspheres and nanaospheres, microbaloons, nanoparticles and micro pellets by using these techniques. This technique may enable crystalline form of a drug to be converted into different polymorphic form and thus attain better bioavailability and improving the dissolution behavior of some drugs that are characterized by low water solubility and a slow dissolution profile.

By using this technology, physicochemical properties of pharmaceutical crystals are dramatically improved for pharmaceutical process i.e. milling, mixing and tabletting because of their excellent flowability and packability.

The process is simple and inexpensive enough for scaling up to a commercial level. It reduces time and cost by enabling faster operation, less machinery and fewer personnel. It gives importent advances in tabletting technology, especially the introduction of number of directly compressible excipients. The spherically agglomerated crystals can be prepared in tablet form or compounded directly into a pharmaceutical system without further processing such as granulation [3,4] .

As these techniques forms the spherically agglomerated crystals showing significant effect on the formulation and manufacturing of pharmaceutical dosage form. Therefore it is necessary to evaluate these spherically agglomerated crystals by using the different parameters. From the literature survey following parameters were used for the evaluation of spherically agglomerated crystals.

Flow Property

Flow property of the material depends on the force developed between the particle, particle size, particle size distribution, particle shape, surface texture or roughness and surface area. Flowability of the agglomerates is much improved as the agglomerate exhibits lower angle of repose then that of single crystals. Studies on spherically agglomerated aspirin crystals revealed that, the angle of repose of agglomerated crystals was 31.13^0 while that of unagglomerated crystals was 47.12^0 .This improvement in the flowability of agglomerates could be attributed to the significant reduction in inter-particle friction, due to their spherical shape and a lower static electric charge. [5]

Following are the methods used for determination of flow property:

Angle of repose

Angle of repose is the common method used for determination of flow property. The angle of repose is the angle between the horizontal and the slop of the heap or cone of solid dropped from some elevation. Values for angle of repose $\leq 30^0$ usually indicate free flowing material and angle $\geq 40^0$ suggested a poor flowing material.

The angle of repose can be obtained from the equation:

$$Tan\theta = h/0.5d$$

Where h-height of the cone, d-diameter of cone.

Compressibility or Carr index

A simple indication of ease with which a material can be induced to flow is given by application of compressibility index.

$$I = (1-V/Vo)\ 100,$$

Where V = the volume occupied by a sample of the powder after being subjected to a standardized tapping procedure and Vo = the volume before tapping. Value below 15% indicates good flow characteristics and value above 25% indicate poor flowability.

Hausner ratio

It is calculated from bulk density and tap density.

Hausner ratio = Tapped density / Bulk density, Values less then 1.25 indicate good flow (20% Carr index.) and the value greater then 1.25 indicates poor flow (33% Carr index.). If it is between 1.25-1.5 added glident normally to improve flows.

Density [6]

Density of the spherical crystals is the mass per unit volume.

$$Density = M/V.$$

Densities are of the following types,

True density (ρ): It is the ratio of the mass to true volume (Vt) i.e. the total volume of the solid particle, which excludes of the voids and interparticle pores to the mass of the particle. It is measured by displacing the liquid in which they are insoluble by using Helium densitometer or Relative density method.

$$True\ density = M / Vt.$$

Granular density (ρ g): It is the ratio of the mass to granular volume (Vg) i.e. the cumulative volume occupied by particles including all intraparticulate (but not interparticulate) voids to the mass of the particle. It may influence compressibility, tablet porosity; dissolution. Basically two methods are available to determine granular density. In one intrusion fluid is mercury and other is the solvent of low surface tension (benzene) in which the granules are not soluble.

$$Granular\ density = M / Vg.$$

Bulk density (ρ b): It is the ratio of the mass to bulk volume (V b) i.e. the total volume occupied by the entire powder mass under the particular packing achieved during the measurement. It is determined by using the graduated cylinder.

$$Bulk\ density = M / V\ b\ .$$

Tap density: It is the ratio of weight of sample in gm to tapped volume of sample in ml. It is measured by using tap density apparatus.

Tap density = weight of sample in gm./tapped volume of sample in ml.

Porosity [7]

Porosity of granules affects the compressibility. Porosities are of two types intragranular porosity and intergranular porosity and these are measured with the help of above densities.

Intragranular porosity = 1- Granular density /True density.
Intergranular porosity = 1- Bulk density / Granular density.
Total porosity = 1- Bulk density / True density.

Packability

Improve packability has been reported for agglomerates prepared by spherical crystallization. The angle of friction, shear cohesive stress and shear indexes are lower then that of single crystals, which can improve the packability of the agglomerates. Kawashima, Y., et al. prepared spherical agglomerates of two solvent systems and compared with those of original powder of the drug. It was found that the packability of agglomerates was improved compared with those of the original crystals and that the agglomerated crystals were adaptable to direct tabletting. [8,9]

Packability was assessed by analysis of the tapping process with the Kawakita (I) and Kuno (II) method and using the parameter a, b,1/b, k in the equation:

$$N/C = 1/(ab) + N/a \quad \text{.....I}$$

$$C = (Vo-Vn)/Vo, \quad a = (Vo-V\infty)/Vo.$$

$$\rho f - \rho n = (\rho f - \rho o) \cdot \exp(-kn) \quad \text{.....II}$$

Where, N =Number of tapping.
C =Difference in volume (degree of volume reduction.)
a and b = constant for packability and Flowability
Vo = Initial volume.
Vn = Final volume after n th tapping.
V∞ = Powder bed volume at equilibrium.
ρ f, ρ n ,ρ o = Apparent densities at equilibrium, nth tapped and initial state respectively

Constant a describe the degree of volume reduction at the time of tapping and called as compactability. 1/b is considered to be a constant related to cohesion and is called cohesiveness. The compactability a and cohesiveness 1/b are obtained from the slop 1/a and the intercept 1/ab of the plot of modified Kawakitas equation. The smaller value of parameter a and higher value of parameter b indicate improve packability and flowability of the spherical crystals. The large value of parameter (k) in kunos equation for the agglomerates indicated that the rate of their packing was much higher then that of primary crystals.

Stampf volumeter measurements allow calculation of the rearrangement constant.

$$(Vn-V\infty)/(Vo-V\infty) = (1-Kn) -0.25$$

Where, n = The number of taps.

Vo = Initial volume of powder.

Vn = the volume after n th taps.

V∞ = Final volume.

After transformation of equation regression analysis was performed. The relationship between the variable can be described in term of linear equation (y =1+Kn.) or a exponential model (y = Exp (1+Kn.), where the slop of the curve is the rearrangement constant. If the constant is too small, the compression during tablet pressing can give rise to brittle fracture and plastic flow in certain regions before a close rearrangement has been achieved in other regions.

Compression Behavior Analysis

Good compactibility and compressibility are essential properties of directly compressible crystals. The compaction behavior of agglomerated crystals and single crystals is obtained by plotting the relative volume against the compression pressure. Spherical agglomerates possess superior strength characteristics in comparison to conventional crystals. It is suggest that the surface are freshly prepared by fracture during compression of agglomerates, which enhances the plastic inter particle bonding, resulting in a lower compression force required for compressing the agglomerates under plastic deformation compared to that of single crystals.

Compaction behavior of agglomerated crystals were evaluated by using following parameters:

Heckel Analysis [10,11]

The following Heckel's equation was used to analyze the compression process of agglomerated crystals, and assessed their compactibility.

$$\ln [1/(1-D)]=KP+A$$

Where: D is the relative density of the tablets under compression Pressure and K is the slope of the straight portion of the Heckel Plot, and the reciprocal of K is the mean yield pressure (Py).

The following equation gives the intercept obtained by extrapolating the straight portion of the plots.

$$A=1n [1/(1-D0)]+B$$

Where: D0 is the relative density of the powder bed when P=0.

The following equation gives the relative densities corresponding to A and B.

$$DA=1-e -A$$

$$DB=DA-D0$$

Stress Relaxation Test

In this test put specific quantity of spherical agglomerated crystals sample in a die specific diameter the surface of which was coated with magnesium stearate in advance, then used the universal tensile compression tester to compress the samples at a constant speed. After the certain limit of pressure attained, the upper punch was held in the same position for 20 min, during which measured time for the reduction amount of the stress applied on the upper punch. [12]

The result was corrected by subtracting from this measurement the relaxation measured without powder in the die under the same conditions. The following equation finds the relationship between relaxation ratio Y(t) and time t, calculated the parameters As and Bs, and assessed relaxation behavior. [13,14]

$$t/Y(t)=1/AsBs-t/As$$

$$Y(t)=(P0-Pt)/P0$$

Where: P0 is the maximum compression pressure, and Pt is the pressure at time t.

Tablet Elastic Recovery Test

In this test put specific quantity of spherical agglomerated crystals sample in a die specific diameter the surface of which was coated with magnesium stearate in advance, then used the universal tensile compression tester to compress the samples at a constant speed. Then measured

the thickness of each tablet under maximum pressure (Hc) and at about 24 h after tablet ejection (He). The following equation was used to calculate the elastic recovery ratio (ER).

$$ER=[(He-Hc)/Hc] \times 100$$

About 24 h after the tablet was ejected, its weight, diameter, and thickness were measured, and its apparent density (ρa) calculated. The following equation was used to calculate internal tablet porosity (ε) from true density (ρt), which was measured with an air comparison pycnometer

$$\varepsilon=1-\rho a/\rho t$$

Tablet Tensile Strength Test

The prepared tablets from agglomerated crystals were kept in a desiccator (silica gel) for about 24 h, and then a hardness tester was used to measure a load across the diameter of each tablet at a specific compression speed to find the hardness F when crushing. The following equation was then used to calculate the tensile strength T . [15]

$$T=2F/\pi dL$$

Where: d and L are a tablet's diameter (m) and thickness (m).

Study of Plasticity and Compressibility

For this study use single, flat punches 10mm in diameter, furnished with strain gauge and a displacement transducer compression tools. The strain gauge allows the pressure forces on the upper and lower punches to be followed with force-measuring equipment. The equipment transducer was fitted over the upper punch. The tablets were pressed from the control and denoted samples with 0.5% magnesium stearate as a lubricant. A total of 100 tablets were pressed electrically in continuous operation. During tablet pressing, the data were collected by computer. The energy parameters of 10 tablets were fixed for the calculation of plasticity and compressibility values. The measurements were repeated three times during the pressing.

Plasticity (Pls-m) was determined by Stamm-Mathis

$$\text{Plasticity (Pls-m)} = E2/E2+E3X100\ (\%)$$

Where, E2=effective work which includes the useful works invested in deformation and the friction during processing, E3=is the degree of elastic recovery during processing.

E2 AND E3 could be calculated from the force displacement curve. If the plasticity value is near 100,the material has plastic property.

Compressibility [Pr(mass)] was calculated via the following equation.

$$\text{Compressibility [Pr (mass)]} = sx/Wspec = sx/(E2/m)\ X\ (Pa\ /JKg\ -1\ )$$

Where sx = Tensile strength, Wspec = expresses effective work (E2) invested into the compression of the unit mass of substance (m) at a given compress force [16] .

Mechanical Strength

Spherical crystals should posses good mechanical strength as that directly reflects the mechanical strength of compact or tablet. It is determine by using the following two methods,

Tensile strength

Tensile strength of spherical crystals is measured by applying maximum load required to crush the spherical crystal. This method is a direct method to measure the tensile strength of spherical crystals.

Crushing strength[17]

It was measured by using 50ml glass hypodermic syringe. The modification includes the removal of the tip of the syringe barrel and the top end of the plunger. The barrel was then used as hallow support and the guide tube with close fitting

tolerances to the plunger. The hallow plunger with open end served as load cell in which mercury could be added. A window was cut into the barrel to facilitate placement of granule on the base platen. The plunger acted as movable plates and was set directly on the granules positioned on the lower platen as the rate of loading may affect crushing load (gm). Mercury was introduced from reservoir into the upper chamber at the rate of 10 gm/sec.untile the single granule crushed; loading time was <3 minutes. The total weight of the plunger and the mercury required to fracture a granule was the crushing load. Minimum of 10 granules were tested and the average load in gm was taken as the crushing strength.

Friability test

Tak Ho and John A Hersy used method, which consolidate the attrition and sieving process in to a single operation. Granules along with the plastic balls placed on a test screen. The sieve was then subjected to the usual motion of a test sieve shaker provided the necessary attrition on the granules. The weight of powder passing through the sieve was recorded as function of time. The friability index was determined from the slop of the plot of % weight of granules remaining on the sieve as a function of time of shaking.

Friability of agglomerates were determined by using formula,

$$\text{Friability } (X) = \{1-W/Wo\}/100$$

Where, Wo = Initial weight of the crystalline agglomerates placed in sieve and W = Weight of the material which does not passed through sieve after 5 min.

The study was continued up to 25min. by analyzing the sample for every 5-minute data was fitted in a linear equation and the constant K and C were determined.

$$Y = KP + C$$

Where, C = constant will depends on % fines produced in the initial stages of testing and K = will reflect overall friability of agglomerates

Wettability

The wettability depends on the crystallinity and elementary crystal size of the agglomerated crystals. As the contact angle decreases the wettability increases. Crystals with low crystallinity are more wettable then crystals with higher crystallinity.

Following methods were used to determined wettability spherical crystals.

Determination of density: Density of saturated solution of drug and spherical crystals in water was determined using a relative density bottle.

Determination of surface tension: Surface tension of saturated solution of drug and spherical crystals in water was determined employing stalagmometer.

Determination of porosity: Thickness and diameter of prepared tablet of drug spherical crystals was determined using vernier caliper and porosity was calculated from apparent density of the tablet.

Determination of contact angle: A drop (50ml) of saturated solution of drug and spherical crystals in water was placed on the tablet surface and height of the drop was measured. The wettability is determined by following formula.

Where, $B=\rho g/2\gamma$ (γ = surface tension of saturated solution of formulation in water; dyne/cm; ρ = density of saturated solution of formulation in water, gm/cm 3), ε = porosity of tablet, h = height of liquid drop in cm.

Powder bed hydrophilicity test: The powder bed hydrophilicity test was done to confirm the wettability of the spherical crystals by placing the spherical crystals on a sintered glass disk forming the bottom of glass tube on which methylene blue

crystals were placed. The whole device was brought into contact with water. The time taken for the capillary rising of water to the surface so as to dissolve methylene blue crystals was noted. The shortest rising time would correspond to the most hydrophilic drug leading to good wettability [18] .

Solubility :Solubility study was carried out in distilled water and dissolution medium by using flask shaker method. Excess raw crystals and different spherical agglomerated crystals were introduced into a 25 ml bottle containing 10 ml distilled water (pH 7 ± 0.1) and dissolution medium. All suspensions were protected from the light by wrapping the flask with aluminum foil. The flask was shaking for 24 hours at room temperature. The content of each flask was then filtered through a Whatman filter paper. The filtrate was then diluted with distilled water or dissolution medium and determined content by using suitable analytical method. [19,20]

Dissolution Rate

The dissolution rate, bioavailability of agglomerated crystal depends on particle size, particle density and specific surface area of the agglomerated crystals. It has been elucidated that the dissolution of agglomerates increases as apparent specific surface area increases. Tabletting compacts partially breaks the agglomerated crystals and thus the average particle size is reduced. Comparative study of dissolution behavior between agglomerated crystals and unagglomerates was done. If agglomerated crystals showed change in wettability or crystalline form then dissolution study is must. If spherical crystallization was carried out in presence of surfactant then improvement in dissolution rate was observed. But compression also increases the particle density, which may adversely affect dissolution. Specific surface area of crystals is found to depend on the method used for spherical crystallization. Therefore it necessary to evaluate the intrinsic dissolution rate of agglomerated crystal sand raw crystals. [21]

Particle Size And Size Distribution

Size of the particle and their distributions can be determined by simply sieve analysis. Now with the help of Ro-Tap sieve shaker particle size analysis can be determined. In advance technology image-analyzer is used to determined size and volume of the particle.

Where, x i = Weight retained in gm.

dpi = Average particle size (mm)

Moisture uptake study: The study indicates the behavior of uptake of moisture by drug and the prepared spherical crystals, which affect the stability. The weighted quantity of drug and spherical crystals were placed in crucible at accelerated condition of temperature and humidity, 40 C ± 1 0 C and 75% ± 3% respectively. The gain in weight of drug and spherical crystals were measured [22] .

Characterization Of Spherical Agglomerates: Particle shape/surface topography: Following two methods are used

Optical microscopy: The shape of the spherical agglomerates is studied by observing the spherical agglomerates under a optical microscope. The observations are made under the observation like 10X, 45X, 60X etc.

Electron scanning microscopy: The surface topography, type of crystals (polymorphism and crystal habit.) of the spherical agglomerates is analyzed by using a scanning electron microscopy.

Thin layer chromatography: To know the chromatographic behavior, the TLC study was carried out in mentioned mobile phase and the Rf value was determined and compared the Rf value of drug with the spherical crystals. This study was carried out to check the interaction between the drug and the polymer and also to confirm the stability of drug in solvents.

X-ray powder diffraction: X-ray powder diffraction is an important technique for establishing batch-to-batch reproducibility of a crystalline form. The form of crystals in agglomerates was determined by using this technique. An amorphous form does not produce a pattern. The X-ray to scatter in a reproducible pattern of peak intensities at distinct angle (2θ) relative to the incident beam. Each diffraction pattern is characteristics of a specific crystalline lattice for a given compound.

Fourier Transform Infrared spectrometer (FTIR): It was done for identification of the drug present and also to identify whether the drug has undergone polymorphism. It is much more useful for distinguishing between solvates and anhydrous form then for identifying polymorphs because of the addition of new stretching frequencies resulting from the salvation.

Differential scanning calorimeter (DSC): DSC measures the heat loss or gain resulting from physical or chemical changes within a sample. If a mixture of drugs and polymer is agglomerated together than change in properties of agglomerates can be studied with DSC.It is also useful to determine thermal degradation, purity, polymorphism, salvation, and drug-excipients compatibility .

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