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Spherical Agglomeration Techniques and their Evaluation Parameters

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Abstract: Spherical agglomeration technique is a specialized and modern method which has been successfully employed to improve flowability, packability, Compressibility, wettability, solubility, and bioavailability of various poorly soluble and poorly Compressible drugs. The different Techniques discussed are Crystallization method, Solvent crystallization method, Quasi- emulsion diffusion method, Ammonia Diffusion method, neutralization method, and solvent agglomeration technique.
This article gives a detailed and comprehensive review about different techniques, its advantages, mechanism and application of Spherical agglomeration Technique along with its Evaluation and Characterization methods. The spherical crystals can be Evaluated using FTIR (Fourier Transformation Infra red technique) DSC (Differential Scanning Calorimetry) X-ray Diffraction and Chromatographical methods. This technique also finds its application in improving taste of bitter drugs and in the preparation of nanospheres, microspheres and nano-particles.

Keywords: Spherical Crystallization, Techniques of Crystallization, Mechanism, Evaluation, Characterization.

INTRODUCTION:

Spherical Crystallization technique is a Particle design technique in which crystallization and agglomeration is carried out simultaneously in one step. This technique has been successfully utilized for improvement of flowability and Compressibility of crystalline drugs. This can be used to prepare crystals of poorly water soluble drugs to increase their solubility and dissolution rate. Therefore, improvement of bioavailability of drugs [1, 2]. Tablets are most stable readily portable and consumed dosage form. Tablets containing sparingly soluble water soluble drugs, the start of dissolution is often delayed by poor wettability of the tablet surface and slow penetration into tablet matrix. This increases dissolution time and release of drug this can be overcome by addition of suitable disintegrant. Spherical Crystallization Technique transforms crystals directly to compact form during crystallization process. It also enables co-precipitation of drugs and encapsulating polymer in the form of spherical particles. Development of novel methods to improve the bioavailability of poorly soluble drugs is a big challenge to formulate solid dosage form. Mechanical Micronization of drugs and use of surfactants during crystallization process are the techniques which are commonly used to improve the Flowability and Compressibility of drugs, by this technique the physio-chemical properties of crystalline drugs can be dramatically improved. This technique can further be used to improve the taste of bitter drugs and to prepare microspheres, nanospheres and nano-particles [3, 4, 5].

Methods of Spherical Crystallization:

1. Conventional Crystallization Process
2. Solvent Change Method
3. Quasi-Emulsion Diffusion Method
4. Ammonia Diffusion Method
5. Neutralization Method
6. Crystal Co-agglomeration Technique

Conventional Crystallization Technique: - (CCT)

Spherical agglomerates are prepared by controlling the physical and chemical properties and can be called as non- conventional crystallization processes [6].

These include:

- Salting out
- Cooling crystallization
- Crystallization using melting

Solvent Change Method [7] **: - (SC)**

This Technique involves simultaneous crystallization and agglomeration of two or more drugs from good solvent and bridging liquid by addition of non- solvent. To obtain fine crystals the solution of the drug and a good solvent is poured into a poor solvent under controlled condition of temperature and speed. The drawback of this technique is it provides fewer yields, due to co-solvency effect of crystallization solvent. Here lesser amount of bridging liquid will produce fine particle where as larger amount of bridging liquid will produce coarse particles.

Different Steps involved in Solvent Change Method

Good solvent + drug added to bad solvent

↓

Formation of Crystals when bridging liquid is added drop wise and with agitation

↓

Precipitated Crystals and aggregates are formed with bridging liquid

↓

Spherical Agglomerates

Quasi-Emulsion Diffusion method [8]**: - (QESD)**

In this technique good solvent diffuses gradually out of Emulsion droplets into surrounding poor solvent area, and poor solvent diffuses into droplets by which the drug crystallizes inside the droplets. Here the affinity between drug and poor solvent is greater than drug and poor solvent. The crystallization of the drug occurs by counter diffusion of good solvent and poor solvent.

Different Steps involved in Quasi-Emulsion Diffusion method:-

Good solvent + drug added to poor solvent

↓

Formation of Emulsion with agitation

↓

Good solvent (Bridging Liquid diffuses out into poor solvent)

↓

Spherical Agglomerates Formed

Ammonia diffusion method [9]**: - (AD)**

Here in this technique the mixture of acetone, ammonia-water and dichloromethane is generally used for crystallization. Here Ammonia-Water acts as bridging liquid and good solvent.

Different Steps involved in Ammonia diffusion method:-

Ammonia-Water + drug

↓ (added to Acetone)

Polymeric solution and Dichloromethane added drop wise

↓

Spherical Agglomerates Formed

Neutralization method [10] **:-(NM)**

Here in this Technique drug is dissolved in good solvent and placed in cylindrical vessel with constant stirring, during stirring aqueous polymeric solution and one neutral solution are added to

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neutralize good solvent, which crystallizes out the drug.

Different Steps involved in Neutralization method:-

Good solvent + drug added to neutralizing solution

↓

Formation of Crystals

↓

Bridging Liquid added drop wise

↓

Spherical Agglomerates Formed

Crystalo- Co-agglomeration Technique [11]: **- (CCA)**

This Technique is a modification of spherical crystallization technique in which excipients or other drug is used to make spherical crystals and agglomerates. The agglomeration is done using a bridging liquid.

Different Steps involved in Crystal co-agglomeration Techniques

Good solvent + drug (agitation)

↓

Bridging Liquid (homogeneous solution)

↓

Bad solvent

↓

Spherical crystals and Agglomerates Formed

Table 1: List of various drugs on which Spherical crystallization technique has been attempted so far

S. No	Name of the Drug	Method	Solvent Systems used	Ref.
1	Acebutalol Hcl	QESD	Water, Ethanol, Isopropyl acetate	50
2	Aceclofenac	SA	Acetone, Water, DCM	52
3	Acetyl Salicylic Acid	SA	Ethanol, Water, Carbon tetra Chloride	27
4	Aminopylline	SC	Ethanol, Chloroform, Water	15
5	Ampicillin Trihydrate	ADM	Ammonia Water, Acetone, DCM	03
6	Ascorbic Acid	SA	Water, Ethyl acetate, Chloroform	37
7	Aspartic Acid	SA	Water, Methanol	50
8	Aspirin	SA	Acid buffer, Methanol, Chloroform	10
9	Benzoic Acid	SA	Ethanol, Water, DCM	47
10	Bromhexine Hcl	CCA	DCM, Water, DCM	56
11	Buccillamine	SA	Ethanol, DCM, Water	41
12	Carbamezapine	QESD	Ethanol, Water, IPA	43,55
13	Cefuroxime Axetil	QESD	Acetone, Water, IPA	54
14	Celecoxib	SA	Acetone, Water, Chloroform	01
15	DCP	SA	Water, Phosphoric Acid, Citric Acid	51
16	Enoxacin	ADM	Ammonia Water, Acetone, DCM	01
17	Etoricoxib	QESD	Acetone, Chloroform, Water	57
18	Fenbufen	SA	THF, Water, IPA	02
19	Flurbiprofen	SA	Acetone, Water, Hexane	22
20	Glibenclamide	QESD	Methanol, Chloroform, Water	23
21	Griseofulvin	QESD	DCM, Water, DCM	21
22	Ibuprofen	SA QESD NA	Ethanol, Water, Ethanol Ethanol, Water with sucrose, FAE 01M NaoH, 0.07M Hcl, IPA	30 34 40
23	Indomethacin	QESD SC	Methanol, DCM, D.Water N,N DMF, Water, Chloroform	25 39
24	Ketoprofen	NA	1 M NaoH, 0.25 M Hcl, Chloroform	42
25	Mebendazole	SA	Acetone, Water, Hexane/Octanol	49
26	Mefenamic Acid	SA ADM NA	DMF, Water,CCl_4 / Chloroform Ammonia Water, Acetone, DMF 01 M NaoH, 0.7 M Hcl, IPA	24 05 39
27	Nabumetone	SA	Ethanol, Water, Cyclohexane/n-hexane	53
28	Naproxen	SA	Acetone/Ethanol, Chloroform, Water	28
29	Norfloxacin	ADM	Ammonia Water, Acetone, DMF	29
30	Pioglitazone Hcl	QESD	Methanol, Chloroform, Water	44
31	Propiophenazone	SA	Ethyl alcohol, Water, IPA	12
32	Roxithromycin	SA	Methanol, Chloroform, Water	23
33	Salicylic Acid	SA	Water, Ethanol, Chloroform	36
34	Tanilast	SA	Ethanol, Acetone, Water, Chloroform, DCM	35
35	Theophylline	SA	Ethylenediamine, Aq. Nacl, Water	26
36	Tolbutamide	QESD	Ethanol, Water, IPA	31
37	Valsartan	SC	Methanol, Water, DCM	20

The Steps involved in Spherical Crystallization Process are [12]**:-**

Flocculation Zone:-Here loose open flocs of particles are formed. In this zone bridging liquid displaces the liquid from the surface of the crystal and crystals are brought in close proximity by agitation.

Zero- growth Zone: - Loose flocs get converted into highly packed pellets in which liquid entrapped is squeezed out followed by squeezing out bridging liquid onto the surface of the small flocs.

Fast growth Zone:-The formation of large size article following random collision of well formed nucleus is called coalescence. Successful collision occurs if surface has slightly excess moisture.

Constant growth Zone: - Here size of the agglomerate formed ceases . The rate determining step in agglomerates growth occurs in zero growth zones. The strength of agglomerates is determined by interfacial tension between bridging liquid and continuous phase, contact angle and ratio of volume of bridging liquid and solid particles.

Factors controlling the Process of Agglomeration [5]**:-**

Temperature of the System:-

Temperature has significant role to play and has great influence on final shape, size and texture of agglomerates. This may be due to the fact that temperature affects the solubility of drug in ternary system.

Solubility profile:-

The proportion of solvent used is determined by carrying out solubility studies and constructing triangular phase diagram to define region of mutual immiscibility by using ternary diagram.

Mode and Intensity of Agitation:-

The Extent of Mechanical agitation in conjugation with amount of bridging liquid determines the rate of formation of agglomerates and its final size. Generally high speed agitation is necessary to disperse bridging liquid throughout the system.

Residence Time:-

The time for which agglomerates remain in reaction mixture is residence time and it affects the strength of agglomerates.

Evaluation parameters for spherical agglomerates:-

Flow Property [13]**:-**

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. Following are the methods used for determination of flow property

Angle of repose [14]**:-**

Angle of repose is the common method used for determination of flow property. The angle of repose can be obtained from the equation:

$\tan \theta = 2h/d$ Where h-height of the cone, d-diameter of cone.

Compressibility or Carr's index [14]**:-**

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%

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indicates good flow characteristics and value above 25% indicate poor flowability.

Hausner ratio [14]**:-**

It is calculated from bulk density and tap density as follows

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

Packability[15,16]**:-**

Improve packability has been reported for agglomerates prepared by spherical crystallization. The angle of friction, shear cohesive stress and shear indexes are lower than 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.

Compression Behaviour Analysis:-

Good Compactibility behavior and Compressibility are essential properties of directly Compressible agglomerates. The Compaction behavior of Crystals is obtained by plotting the relative volume against the Compression Pressure.

Spherical agglomerates possess superior strength in comparison to conventional crystals.

Tablet Elastic Recovery Test [17]**:-**

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

ER= [(He-Hc)/Hc] x100

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

ε=1-ρa/ρt

Tablet Tensile Strength Test:-

The prepared tablets from agglomerated crystals can be kept in desiccators (silica gel) for about 24 h, and then a hardness tester can be 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 can be used to calculate the tensile strength T.

T=2F/πdL

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 can be fitted over the upper punch. The tablets can be pressed from the control and denoted samples with 0.5% magnesium stearate as a lubricant. A total of 100 tablets could be pressed electrically in continuous operation. During tablet pressing, the data is collected by

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computer. The energy parameters of 10 tablets can be fixed for the calculation of plasticity and compressibility values. The measurements are repeated three times during the pressing.

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

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.

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.

Mechanical strength:-

Spherical crystals should posse's good mechanical strength as that directly reflects the mechanical strength of compact or tablet. It can be determine by using the Crushing strength, Friability test.

Wettability:-

The wettability depends on the crystalline and elementary crystal size of the agglomerated crystals. The Crystals with low Crystallinity are more wettable then crystals with higher crystallinity. Following methods can be used to determined wettability of spherical crystals.

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

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

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

Solubility [18]**:-**

Solubility can be determined quantitatively using distilled water and other solvent (acid or base) at room temperature (250c).

Dissolution Rate [19]**:-**

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. If agglomerated crystals shows change in wettability or crystalline form then dissolution study is must. If spherical crystallization is carried out in presence of surfactant then improvement in dissolution rate is must. 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.

Moisture Uptake Study:-

The study indicates the behaviour of uptake of moisture by drug and the prepared spherical crystals, which affect the stability.

Equipments for the Characterization of Spherical Agglomerates:-

1) **For Particle shape/surface topography** Optical microscopy and Electron scanning microscopy are used.

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2) **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. Each diffraction pattern is characteristics of a specific crystalline lattice for a given compound.

3) **Fourier Transform Infrared spectrometer (FTIR):** 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.

4) **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 then change in properties of agglomerates can be studied with DSC.

Conclusion:-

The Spherical agglomeration is a specialized particle design technique which could shorten and improve the tablet manufacturing process and thus could reduce cost. Agglomerates thus produced shows excellent improvement in physio-chemical properties. The main concern is that the residual organic matter used should be properly checked and monitored as per the regulatory requirements. This is certainly technique of the future.

- If different Techniques could be Compared and Evaluated for Single drug using different additives and the technique showing best results is selected on the basis of improvement in physio-chemical and micrometric properties of poorly water soluble drugs with low bio-availability. This will certainly help in choosing best Technique and additive for the particular drug.

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