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Review Article

Spherical Crystallization: An Overview

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ABSTRACT

Introduction: In 1986, Kawashima developed the spherical crystallization technique for size enlargement of drugs in the field of pharmacy. Spherical crystallization is defined as "An agglomeration process that transforms crystalline drug directly into compact spherical forms for improving the flowability, solubility and compactability".

Methods: General methods for preparing spherical crystallization are spherical agglomeration, emulsion solvent diffusion method, ammonia diffusion method and neutralization method. Factors controlling the process of agglomeration include solubility profile, mode and intensity of agitation, temperature of the system and residence time.

Results: Spherical crystals can be characterized by Optical microscopy, X-ray powder diffraction, Electron scanning microscopy, Fourier Transform Infrared spectrometer (FTIR) and differential scanning calorimeter (DSC).Spherical crystallization has wide applications in pharmaceuticals like improvement of flowability and compressibility of poorly compressible drugs, masking bitter taste of drugs and improving the solubility and dissolution rate of poorly soluble drugs.

Conclusion: Spherically agglomerated crystals can be directly converted into a tablet thus saving time and reducing cost.

Keywords: Spherical crystallization, Compactability, Direct compression, Flowability, Physicochemical properties.

INTRODUCTION

Tablets are the most popular dosage form accounting for 50 % of all oral drug delivery systems and 70 % of all pharmaceutical preparations produced[1]. They are widely used due to special features like unit dosage form with great dose precision, least content variability, lower cost, tamper proof nature and easy administration by patient. Direct compression is a simple and economical technique for manufacture of tablets. It facilitates processing without the need of moisture, heat and involves small number of processing steps, but the technique depends on the flowability, particle size distribution, bulk density and compressibility of crystalline d rug substances. Most of the drugs like NSAIDs exhibiting poor compressibility and flowability are not suitable for direct compression. Several methods have been introduced by researchers for enhancing the flowability and co mpressibility. Recently pharmaceutical companies have adopted modified crystalline techniques for reducing the production cost and enhancing the production process. Spherical agglomeration is one of these novel crystallization techniques[2].

In 1986, Kawashima used the spherical crystallization technique for size enlargement of drugs in the field of pharmacy. Spherical crystallization was defined by Kawashima as "An agglomeration process that transforms crystalline drugs directly into a compacted spherical form for improving the flow ability, solubility and compactability"[3]. It is a nonconventional particle size enlargement technique that involves crystallization and agglomeration using a bridging liquid. This technique enables crystalline form of a drug to be converted into different polymorphic forms having better bioavailability. It also improves the dissolution behavior of drugs with low water solubility. Physicochemical properties (solubility, dissolution rate, bioavailability and stability) and micrometric properties (bulk density, flow properties, compatibility) are modified during the crystallization process.

Spherical agglomerates are prepared to:

- Improve the flowability and compressibility.
- Mask the bitter taste of drugs.
- Increase the solubility and dissolution of poorly soluble drugs.

Spherical crystallization employs three solvents: good solvent (dissolution medium for drug); bridging liquid (medium which partially dissolves the drug and has wetting property) and bad solvent (solvent which is immiscible with the drug substance)[4]. Chow and Leung (1996) showed that agglomeration takes place as the wetted particles collide with each other and the bridging liquid hold the particles together by forming liquid bridges between them. Depending upon the amount of bridging liquid, particles can form either loose flocs or compact pellets.

Various parameters optimized during the process to get maximum amount of spherical crystal are type, amount and mode of addition of bridging liquid, temperature and agitation speed.

Spherical crystallization is preferred mainly due to less number of steps involved and the following other reasons:

- Less equipment and space

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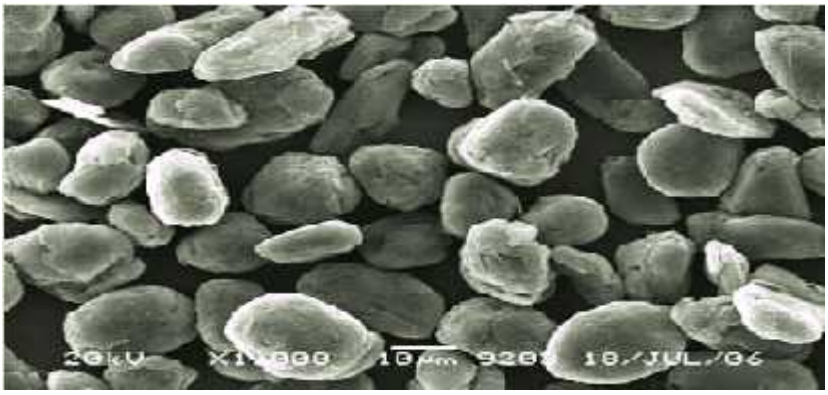


Fig 1. Scanning electron micrograph of spherical agglomerates

Traditional tablet manufacturing procedure involves the following steps [5]:

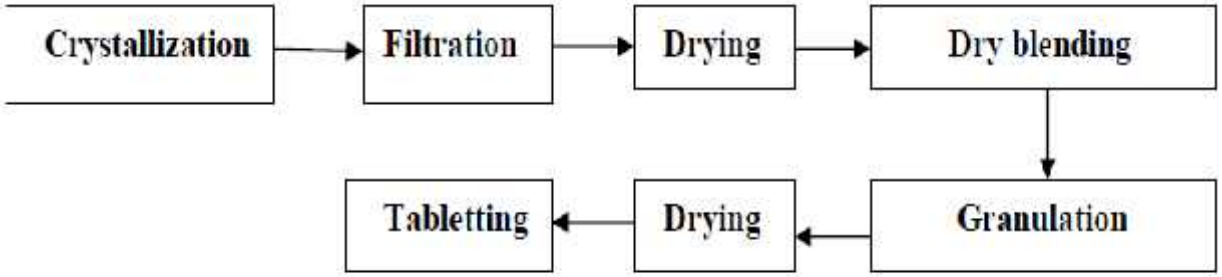


Fig 2. Traditional tablet manufacturing

- Lower labour costs
- Less processing time
- Lower energy consumption

Advantages[6]:

- This technique improves the flowability and compressibility of crystalline drugs.
- Masks the bitter taste of drug.
- Physicochemical properties of drug are dramatically improved for pharmaceutical processes like milling, mixing and tabletting because of their excellent flow and packability
- This technique enables crystalline form of a drug to be converted into different polymorphic form thus attaining better bioavailability.
- It enables subsequent processes such as separation, filtration, drying to be carried out more efficiently.
- It is also used in preparation of microsponges, microspheres and nanospheres, nanoparticles and micropellets as novel particulate drug delivery system
- The agglomerated crystals can be easily compounded with other pharmaceutical powders due to its spherical shape.

Disadvantages:

- Selection of suitable solvents is a tedious process.
- Optimization of processing parameters (temperature, agitation) is difficult.

Principle of spherical crystallization[7]:

- This process involves pouring the saturated solution of the drug in good solvent (first solvent) into poor solvent (second solvent).Third solvent called the bridging liquid is added in small amounts to promote the formation of agglomerates. Bridging liquid wets the crystal surface to cause binding and promotes the formation of liquid bridges between the drug crystals for forming spherical agglomerates.
- Poor and good solvents should be freely miscible and the affinity between the solvents must be stronger than the affinity between drug and the good solvent.
- The bridging liquid should not be miscible with the poor solvent and should preferentially wet the precipitated crystals.

Steps involved in the process of spherical crystallization are flocculation zone, zero, growth zone.

- Flocculation zone: In this zone, bridging fast growth zone and constant size zone[8] Liquid displaces the liquid from the surface of the crystals and these crystals are brought in close proximity by agitation. The adsorbed bridging liquid links the particles by forming bridge between them.
- Zero growth zone: During this growth phase, the entrapped fluid is squeezed out followed by squeezing of the bridging liquid onto the surface of small flocs. Loose floccules are transformed into tightly packed pellet
- Fast growth zone: The fast growth zone of the agglomerate takes place when sufficient bridging liquid has squeezed out of the surface of the small agglomerates. This formation of large size particle after random collision of well formed nucleus is known as coalescence.
- Constant size zone: In this zone agglomerates cease to grow or even show slight decrease in size. Here the frequency of coalescence is balanced by the breakage frequency of agglomeration. The rate determining step in agglomeration growth occurs in zero growth zones when bridging liquid is squeezed out of the pores as the

Spherical crystallization is reduced to:

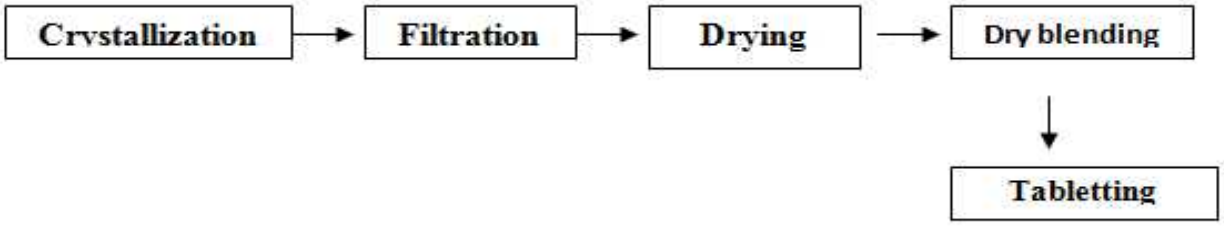
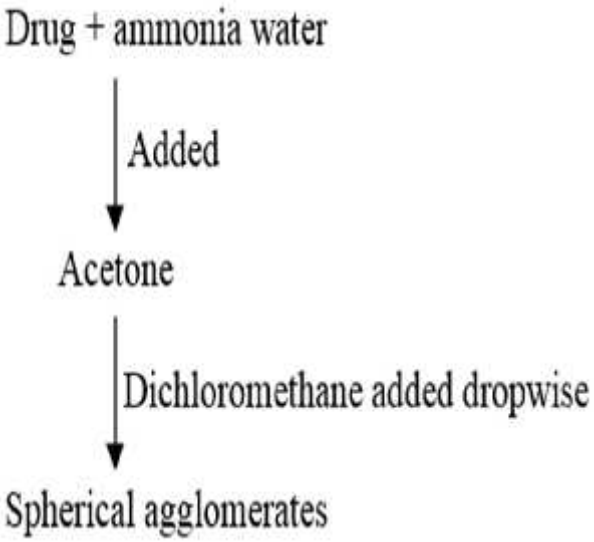
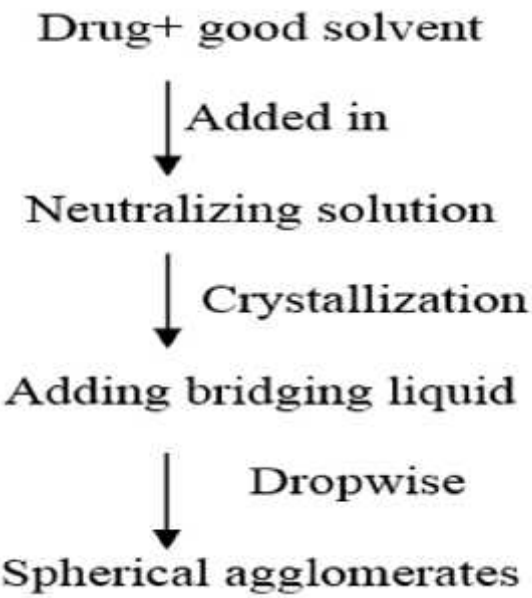


Fig 3. *Spherical crystallization process*



Steps involved in Ammonia Diffusion Method



. Neutralization technique (NT)[12]:

- initial floccules are transformed into small agglomerates.

Various methods used for preparing spherical crystals are:

- Traditional crystallization method
- Solvent change method (SA)
- Quasi-Emulsion Solvent Diffusion method (QESD)
- Ammonia diffusion system (ADS)
- Neutralization Technique (NT)
- Crystal-co-agglomeration technique (CCA)

Traditional crystallization method: Spherical agglomerates are produced in this method by controlling physical and chemical properties and can be called as non typical spherical crystallization processes. These are:

- Salting out precipitation
- Cooling crystallization
- Crystallization under melting

Solvent change method[9]: Saturated solution of drug in a good solvent is poured into the poor solvent under controlled conditions of temperature and speed to obtain fine crystals. These crystals are agglomerated in the presence of bridging liquid. The poor solvent has miscibility with good solvent but low solubility with solvent mixture. Increasing the stirring rate reduces the agglomeration due to increasing disruptive forces. Higher stirring rate produces agglomerates that are less porous and more resistant to mechanical stress. Porosity decreases with the increase in the concentration of solid. Viscosity of continuous phase has an effect on the size distribution of the agglomerates. Type of bridging liquid has an influence on the rate of agglomeration and the strength of the agglomerates. Drawback of this method is that it provides low yield because the drug shows significant solubility in the crystallization solvent. This method is not applicable to water insoluble drugs. Fig. 2 explains the different stage s involved in preparing spherical agglomerates by solvent change method.

Quasi Emulsion Solvent Diffusion Method[10]: Drug is dissolved in a good solvent and this solution is dispersed into the poor solvent, producing emulsion (quasi) droplets, even though the pure solvents are miscible. Good solvent diffuses gradually out of the emulsion droplet into the outer poor solvent phase. Counter-diffusion of the poor solvent into the droplets induces crystallization of the drug within the droplet due to decreased solubility of the drug in the droplet containing the poor solvent. This technique is usually applied for the preparation of microspheres. Fig. 3 explains the different stages involved in preparing spherical agglomerates by quasi emulsion solvent diffusion method

Ammonia Diffusion Method[11]: Ammonia-water is used as the good solvent and bridging liquid. Bad solvent is s elected depending upon the drug's solubility in that solvent. Ammonia water exists as the immiscible phase forming droplets. Counter diffusion process across the droplet involves movement of poor solvent into the ammonia out of the droplet. Agglomeration takes place

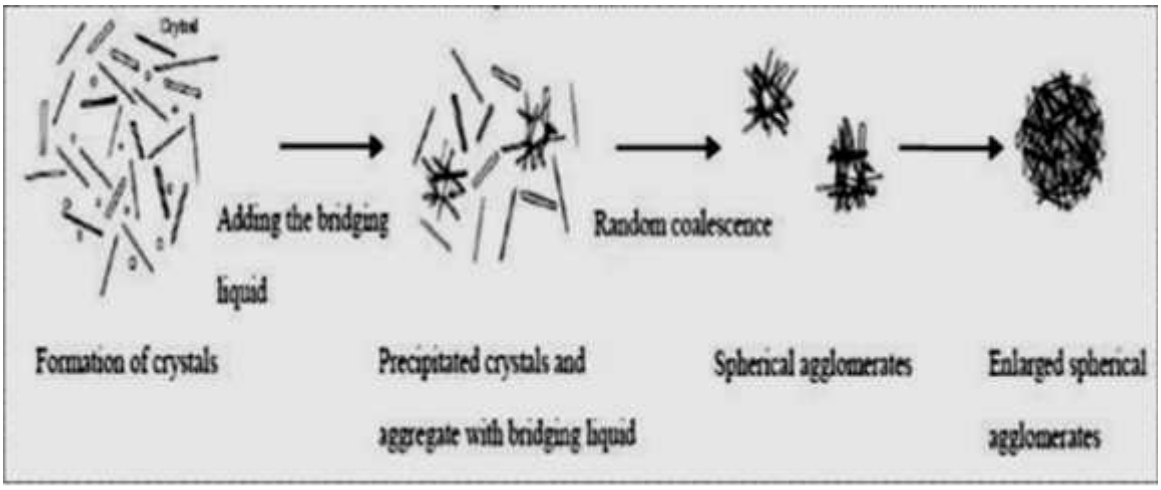


Fig 4 . Solvent Change Method

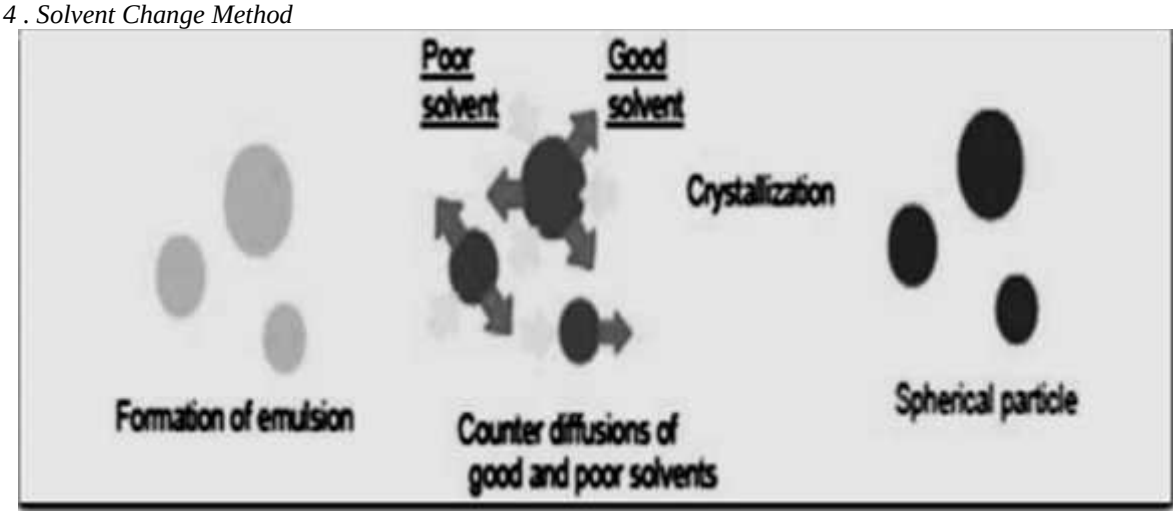


Fig 5. Quasi Emulsion Solvent Diffusion Method

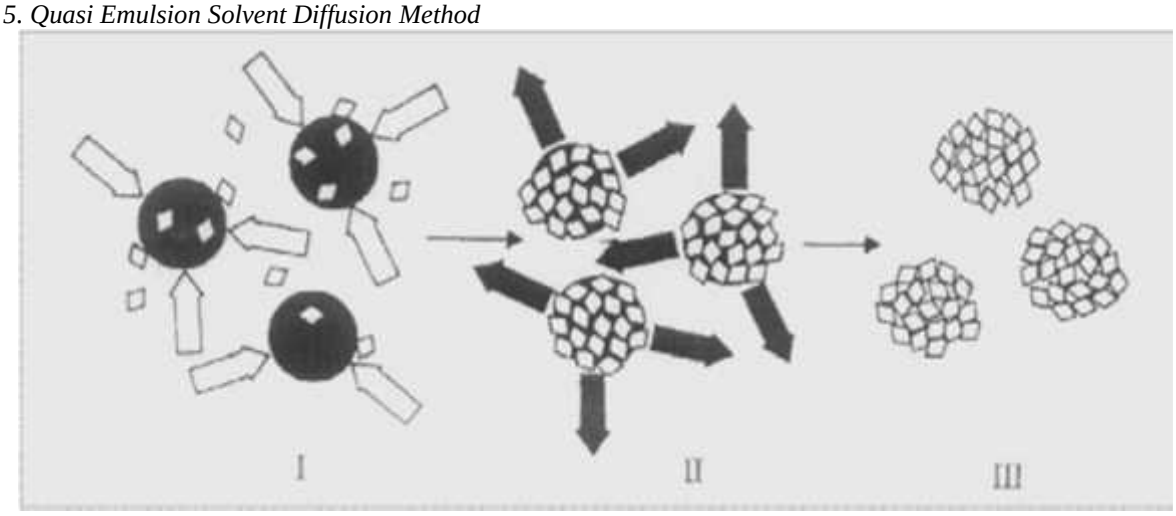


Fig 6. Ammonia Diffusion Method

inside the droplet as the drug precipitates slowly in ammonia water and cause s growth of crystal.

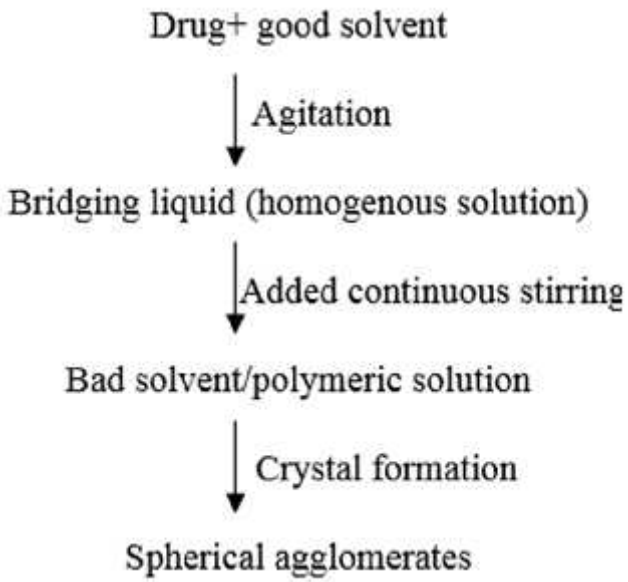
This method is usually meant for amphoteric drugs which cannot be agglomerated by conventional methods. Fig. 4 explains the different stages of spherical agglomerates prepared by ammonia diffusion method.

Neutralization technique (NT)[12]: Drug crystals are precipitated by neutralization of the base with acid. Drug is dissolved in alkaline solution and then poured into an acidic solution containing polymers and bridging liquid under constant agitation. Spherical crystals of tolbutamide and phenytoin have been prepared by this technique

Crystal-co-agglomeration technique (CCA)[13]: It is a modification of the spherical crystallization technique in which drug is crystallized and agglomerated with an excipient or with another drug. This process enables design of agglomerates containing two drugs or poorly compressible drug in combination with diluents and is restricted to water insoluble large-dose drugs only. Difference in the physicochemical properties of drug molecules and excipients is a major challenge in the selection of the solvent system for the crystal-co-agglomeration technique.

Factors controlling the process of agglomeration[14]:

- Solubility profile: Selection of solvent depends upon the solubility characteristics of the drug. The proportion of solvent to be used is determined by carrying out solubility studies and constructing a ternary phase diagram.
- Mode and intensity of agitation: High speed agitation is necessary to disperse the bridging liquid throughout the system. Change in the agitation pattern or fluid flow will affect the shape of agglomerates. The extent of mechanical agitation and the concentration of bridging liquid determines the rate of formation of agglomerates and their final size.
- Temperature of the system: It has a significant influence on the shape, size and texture of the agglomerates. The effect of temperature on spherical crystallization is probably due to its effect on the solubility of drug substance.
- Residence time: It is defined as the time for which agglomerates remain suspended in the reaction mixture. Residence time affects the strength of agglomerates.
- Amount of bridging Liquid[14]: Median diameter of agglomerated crystals increases with decrease in the amount of bridging liquid in the three-solvent system. Insufficient bridging liquid produces plenty of fines and excess produces very coarse particles.



Steps involved in crystal-co-agglomeration technique

The common excipients used in spherical crystallization are polymers and surfactants. Presence of additives like polymers and surface active agents whose surfaces are not similar to the crystal surfaces can influence molecular aggregation during crystallization. The viscosity of the medium and surface tension is reduced by the surfactants which affect the nucleation process. Studies have revealed that crystallization and agglomeration of pure drugs shows poor compressibility and handling qualities. Addition of polymers such as HPMC, PEG and PVP has improved the properties of spherical agglomerates. It has been reported that PVP improved the micromeritic properties, solubility and dissolution rate of spherical crystals of Celecoxib.

Improvement of Physicochemical Properties of Drug by Spherical Crystallization Methods[55]:

Particle size and shape: Spherical crystallization causes a change in the crystal habit of drugs thereby improving their physicochemical properties.

Density: Density of drug substances decreases with an increase in the volume of agglomerates.

Stability: Stability of drug substances changes due to polymorphism taking place.

Flowability: Flowability of agglomerates is improved, exhibiting lower angle of repose due to significant reduction in inter-particle friction compared to that of crystalline drug.

Packability: Angle of friction, shear cohesive stress and shear indexes are lower than that of crystalline drug thereby improving the packability of the agglomerates.

Compaction Behavior of Agglomerated Crystals: Spherical agglomerates possess superior strength characteristics compared to crystalline drug.

Wet ability: Wettability depends on the crystallinity and elementary crystal size of the agglomerated crystals. Wettability increases with decrease in the contact angle. Crystals with poor crystallinity are more wettable than crystals with higher crystallinity.

Solubility: Changes in the internal energy of the molecules play an important role in increasing solubility. Improved solubility of spherical agglomerates may be due to a change in the crystal form, crystal habit and structure. Surface modification can change the surface properties and the reactivity of drug particles.

Dissolution Rate and Bioavailability: Prepared agglomerated crystals with appropriate particle size, solubility, particle density and specific surface area increases the dissolution rate and bioavailability of drug[56].

Evaluation of spherical agglomerates: Micromeritic properties: Improvement in the flowability of agglomerates could be attributed to the significant reduction in inter-particle friction due to their spherical shape and lower static electric charge[57]. Methods used for determination of flow properties are

Angle of repose(θ): It can be obtained from the equation:

$\theta = \tan^{-1} h/r$

where h-height of the cone, r- radius of cone.Values for angle of repose: ≤ 30 indicate free flow and ≥40 indicate poor flow.

Compressibility or Carr index: Compressibility index calculated by:

Table 1 summarizes the different techniques and solvents used in preparing spherical agglomeration of drugs.

Drug	Solvent system			Technique
	Good solvent	Bad solvent	Bridging liquid	
NSAIDS				
Aceclofenac[16]	Acetone	Water	Dichloromethane	SA
Aspirin[17]	Acid buffer	Methanol	Chloroform	SA
Acetylsalicyclic acid[18]	Ethanol	Water	Carbon tetrachloride	SA
Celocoxib[19]	Acetone	Water	Chloroform	SA
Fenbufen[20]	THF	Water	Isopropyl acetate	SA
Flubiprofen[21]	Acetone	Water	Hexane	SA
Ibuprofen[22]	Ethanol	Water	Ethanol	SA
Ibuprofen-Paracetamol[23]	Dichloromethane	Water	Dichloromethane	CCA
Ibuprofen-Talc[24]	Dichloromethane	Water	Dichloromethane	CCA
Indomethacin[25]	Dimethyl Formamide	Water	Chloroform	SA
Indomethacin Mepirizole[26]	Ethyl acetate	Water	Ethyl acetate	CCA
Ketoprofen[27]	Isopropyl acetate	Water	Choroform	SA
Ketoprofen-Talc[28]	Dichloromethane	Water	Dichloromethane	CCA
Mefenamic acid[29]	Ammonia-water	Acetone	Ammonia-water	ADM
Naproxen[30]	Acetone-ethanol	Water	Chloroform	SA
Antibiotics				
Ampicillin trihydrate(ATH)[34]	Ammonia water	Acetone	Dichloromethane	ADM
Cefuroxime Axetil[35]	Acetone	Water	Dichloromethane	ESD
Enoxacin[36]	Ammonia-water	Acetone	Ammonia-water	ADM
Norfloxacin[37]	Ammonia-water	Acetone	Ammonia-water	ADM
Roxythromycin[38]	Methanol	Water	chloroform	SA
Antihelminthic				
Mebandazole[39]	Acetone	Water	Hexane	SA
Anti allergic				
Tranilast[40]	Acetone	Water	Dichloromethane	SA
Anti hypertensive				
Felodipine[41]	Acetone	Water	Dichloromethane	ESD
Anti epileptic				
Carbamazepine[42]	Ethanol	Water	Chloroform	ESD
Antifungal				
Gresiofulvin[43]	Dichloromethane	Water	Dichloromethane	ESD
Bronchodialator				
Aminophylline[44]	Ethanol	Water	Chloroform	SA
Theophylline[45]	Ethylene diamine	Sod. Chloride	Water	SA
ß-adrenergic blockers				
Acebutalol HCl[46]	Ethanol	Water	Isopropyl alcohol	ESD
Antidiabetic				
Glibenclamide[47]	Dichloromethane	Water	Chloroform	SA
Tolbutamine[48]	Ethanol	Water	Isopropyl alcohol	ESD, NT

SA = Spherical Agglomeration, ESDS = Quasi-Emulsion Solvent Diffusion System, ADS = Ammonia Diffusion System, NT = Neutralization Technique, CCA = Crystal-co-agglomeration technique

I = (1-V/Vo) 100

Where V = Volume occupied by a sample of the powder after being subjected to standardized tapping procedure and Vo = the volume before tapping. Value below 15% indicates good flowability 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 than 1.25 indicate good flow and the value greater than 1.25 indicates poor flow.

Friability test: Tak Ho and John A Hersy method is used and determined by formula

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

where

Wo = Initial weight of the crystalline agglomerates placed in sieve

W = Weight of the material retained on sieve after 5 minutes.

Mechanical Properties: Tensile strength of spherical agglomerates is determined by compressing 500 mg of crystals using hydraulic press at different forces (kg/cm2) for 1 min. The hardness of each compact is measured using

Pfizer hardness tester. Crushing strength of agglomerates is determined by using modified Jarosz and Parrot's mercury load cell method[58].

Wettability: Wettability depends on the crystallinity and elementary crystal size of the agglomerated crystals. The methods used to determine wettability are:

- Determination of density: Density of saturated solution of drug and spherical crystals in water is determined by using a relative density bottle.
- Determination of surface tension: Surface tension of saturated solution of drug and spherical crystals in water is determined by employing a stalagmometer Determination of porosity: Thickness and diameter of prepared tablet of drug spherical crystals is determined by using vernier callipers. Porosity of tablet is calculated from the apparent density of the tablet.
- Solubility studies: Solubility studies are carried out in distilled water and dissolution medium by using
- Flask shaker method. Spherical agglomerated crystals are introduced into a flask containing distilled water and dissolution medium. The flasks are shaken for 24 hours at room temperature. The filtrates are then diluted with the respective medium and content is determined by a suitable analytical method [59].
- Dissolution studies: Dissolution of spherical agglomerates is determined by using the official dissolution apparatus and comparative studies are done for agglomerated crystals and non agglomerate [60]. Dissolution rate and bioavailability depends on the particle size and density and specific surface area of the agglomerated crystals.
- Particle Size and Size Distribution: Size of the particle and their distributions can be determined by simple sieve analysis with the help of a Ro-Tap sieve shaker.
- Compression Behavior Analysis: Good compactibility and compressibility are the 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. Compaction behavior of agglomerated crystals can be evaluated by using following parameters:
- Heckel Analysis: The following Heckel's equation is used to analyze the compression process of agglomerated crystals and assessed their compactibility.
- In [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.

Moisture uptake study: This study indicates the behaviour of uptake of moisture by drug and the prepared spherical crystals which affects their stability. Weighed quantity of drug and spherical crystals are placed in crucibles at accelerated conditions of temperature and humidity, 40 0C ± 1 0C and 75% ±3% respectively. Gain in weight of drug and spherical crystals are measured.

Characterization of Spherical Agglomerates[62]:

- Optical microscopy: The shape of spherical agglomerates is studied by observing them under optical microscope.
- 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: TLC studies are carried out and the Rf value is determined. Rf value of drug and spherical crystals are compared. This study is carried out to check if there is any interaction between the drug and the polymer. It also helps in determining the stability of drug in different solvents.
- X-ray powder diffraction: Each diffraction pattern is characteristics of a specific crystalline lattice for a given compound. The form of crystals in agglomerates is determined by using X-ray powder diffraction technique. This is an important technique for establishing batch-to-batch reproducibility of a crystalline form.
- Fourier Transform Infrared spectrometer (FTIR): It is mainly used for identification of drug and its different polymorphic forms. It is also used for distinguishing solvates and anhydrous form of drug.
- Differential scanning calorimeter (DSC): DSC measures the heat loss or gain resulting from physical or chemical changes within a sample. It is also useful to determine thermal degradation, purity, polymorphism and drug-excipients compatibility.

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