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Review Article

Spherical Crystallization: A Novel Particle Design Technique

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ABSTRACT

Oral route is the most important route of drug administration. In this route, the solid dosage form specially tablets, are the first choice of patient but due to unfavorable physical and mechanical properties their formulation process becomes problematic. Crystallization is the main process in the pharmaceutical industry for particle formation, Where Spherical crystallization is a novel particle engineering technique developed. Basically, it's single step process used for size enlargement of drug. By which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement of flowability, compactability and bioavailability of crystalline drugs. General methods of spherical crystallization are spherical agglomeration, emulsion, solvent diffusion method, ammonia diffusion method, neutralization method. Spherical crystallization is having 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 drug. Characterization of spherical crystals can be carried out using Optical Microscopy, Scanning Electron Microscopy, X-ray Powder Diffraction, Fourier Transform Infrared spectroscopy and Differential Scanning Calorimetry.

Keywords: spherical crystallization, compressibility, flowbility, solubility.

INTRODUCTION:

Presently tablet is the most popular dosage form of all pharmaceutical preparations produced. Tablet is the most stable readily portable and consumed dosage form. One of the most economical solutions is to find directly compressible formulations and this is especially at interest for large volume products. These have been renewed interest in examining the potential of direct compression tabletting over recent years since in comparison to the used at the more traditional granulation process[1]. Developing novel methods to increase the bioavailability of drugs that inherently have poor aqueous solubility is a great challenge to solid dosage form formulators. Mechanical micronization of crystalline drugs and incorporation of surfactants during the crystallization process are the techniques commonly used to improve the bioavailability of poor soluble drugs[2,3]

Spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement of flowability and compactability of crystalline drugs. [4]

Benefits of spherical crystallization

1. Physicochemical properties of pharmaceutical crystals are mainly improved for pharmaceutical process i.e. milling, mixing and tabletting by using this technique. [5]
2. It can be used for masking of the bitter taste of drug[6].
3. This technique could enable subsequent processes such as separation, filtration, drying, etc. to be carried out more efficiently.[6]
4. Use of this technique leads to conversion of crystalline forms of a drug into polymorphic form that may have better bioavailability.[7]
5. Preparation of microsponges, microspheres and nanospheres, microballoons, nanoparticles and micropellets as novel particulate drug delivery system is possible by it.

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METHODS:

Spherical agglomeration:

In spherical agglomeration involve implications of three different solvents, One liquid acts as a perfect solvent for the drug moiety, second liquid categorized as anti-solvent/poor solvent for chemical moiety and third liquid significantly used as bridging liquid should be added in smaller quantity for promoting the formation of agglomerates. A nearly saturated solution of drug in good solvent is poured in to the poor solvent, provided that the poor and good solvents are freely miscible and affinity between good solvent and poor solvent is stronger than the affinity between the drug and the good solvent, this leads to the formation of crystals immediately. Further third solvent called bridging liquid is added in smaller amount to promote the formation of agglomerates under continuous agitation, the bridging liquid is added. The bridging liquid should not be miscible with the poor solvent and must wet the precipitated crystals. As a result of interfacial tension effects and capillary forces, the bridging liquid act to adhere the crystals to one another forms agglomerates. The spherical agglomeration method has been applied to several drugs and it has been found that the product properties are quite sensitive to the amount of bridging liquid. Relatively less amount of optimum bridging liquid produces plenty of fine crystals and vice versa .Also the choice of bridging liquid, the starring speed and concentration of solute are of importance. Higher stirring rate produces agglomerates that are less porous and more resistant to mechanical stress, porosity decreases as the concentration of the solid increases.[8]

Quasi Emulsion Solvent Diffusion Method:

It involves the formation of quasi- emulsion of solution of drug in good solvent with a non-solvent. The crystallization of drug occurs by counter diffusion of good solvent and poor solvent. Residual good solvent in droplets acts as a bridging liquid to agglomerate the generated crystals. In this process the emulsion is stabilized by the selection of suitable polymer which is required for proper crystallization.[9]

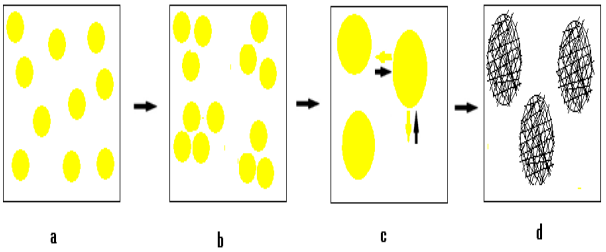

Figure 1: The mechanism of emulsion solvent diffusion method:

a) emulsion formation, b) coalescence of emulsion droplet ,c) diffusion of good solvent to outer phase and poor solvent into of the droplet, d) growth of crystal shell and final agglomerates

Ammonia Diffusion Method:

In this method ammonia water act as a good solvent and bridging solvent, other components of this method are bad solvent and hydrocarbon/halogenated hydrocarbon (acetone). The hydrocarbon is miscible with the system but it reduces the miscibility of ammonia water with bad solvent. The fraction of ammonia water is the system that exists as an immiscible phase forms droplet. The counter diffusion process across the droplet involves movement of bad solvent into and ammonia out of the droplet. The droplet collects the crystals as a drug in ammonia water precipitates slowly and growth of agglomerates occurs. List of various drugs on which Emulsion solvent diffusion, spherical agglomeration and Ammonia diffusion method has been tried for improving physicochemical properties.[9]

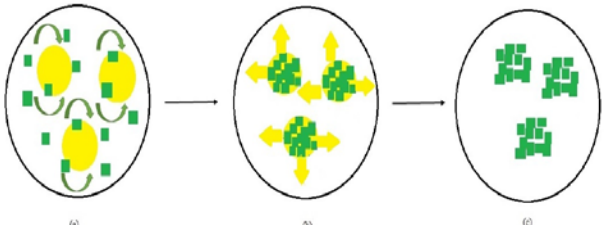

Figure 2: Ammonia diffusion method for preparation of spherical crystallization: a) movement of poor solvent into the droplet, b) movement of ammonia out of the droplet, c) the drug crystals precipitate in ammonia water slowly and agglomerates are grown.

Neutralization Method:

This process involves the formation of fine crystals and their agglomeration. The spherical crystallization of antidiabetic drug tolbutamide was reported by this technique. The drug was dissolved in sodium hydroxide solution. Aqueous

solution of Hydroxypropyl methylcellulose and hydrochloric acid was added to neutralize sodium hydroxide solution of tolbutamide, which was then, crystallized out.[10] besides above mentioned methods there are some other traditional methods for the crystallization which are carried out by controlling the physical and chemical properties and also called as the non-typical spherical crystallization process. These methods include Salting out precipitation, cooling crystallization and crystallization from the melting. [11]

Table 1: Solvent systems in preparing spherical agglomeration of drugs

Drug	Solvent system			Technique	References
Flubiprofen	Acetone	Water	Hexane	SA	12
Salicylic acid	Ethanol	water	Chloroform	SA	13
Aspirin	Acid buffer	Methanol	Chloroform	SA	14
Fenbufen	THF	Water	Isopropyl acetate	SA	15
Nabumetone	Ethanol	Water	Cyclohexane	SA	16
Naproxen	Acetone-ethanol	Water	Chloroform	SA	17
Roxythromycin	Methanol	Water	Chloroform	SA	18
Mebendazole	Acetone	Water	Hexane, octanol, Dichloromethane	SA	19
Valsartan	Acetone	Water	Chloroform	SA	20
Celecoxib	Acetone	Water	Chloroform		21
Ascorbic acid	Water	Ethyl acetate	Ethyl acetate	SA,ESD	22
Aspartic acid	Methanol	Water	-	SA	23
Ibuprofen	Ethanol	Water	Ethanol	SA	24
Ibuprofen-paracetamol	Dichloromethane	Water	Dichloromethane	CCA	25
Benzoic acid	Ethanol	Water	Chloroform	SA	26
Aceclofenac	Acetone	Water	Dichloromethane	SA	27
Indomethacin	Dimethyl formamide	Water	Chloroform	SA	28
Indomethacin meprizole	Ethyl acetate	Water	Ethyl acetate	CCA	29
Ibuprofen-talc	Dichloromethane	Water	Dichloromethane	CCA	30
Glibenclamide	Dichloromethane	Water	Chloroform	SA	31
Tranilast	Acetone	Water	Dichloromethane	SA	32
Aminophylline	Ethanol	Water	Chloroform	SA	33
Bromohexin Hcl	Dichloromethane	Water	Dichloromethane	CCA	34
Ketoprofen	Isopropyl acetate	Water	Chloroform	SA	35
Propiphenazone	Ethyl alcohol	Water	Isopropyl acetate	SA	36
Acetyl salicyclic acid	Ethanol	Water	Carban-tetrachloride	SA	37
Ketoprofen-talc	Dichoromethane	Water	Dichloromethane	CCA	38

APPLICATION OF SPHERICAL CRYSTALLIZATION IN PHARMACEUTICALS:

1. To improve the flowability and compressibility:

The formulation of tablet is optimized to achieve goals. The focus today in the business is better drug delivery concepts, but also makes the simple standard formulations as economical as possible to produce. One of the most economical solutions is to find directly compressible formulations and this is especially at interest for large volume products. These have been renewed interest in examining the potential of direct compression tabletting over recent years since in comparison to the used at the

more traditional granulation process. Such manufacturing of the tablets involves simple mixing and compression of powders which gives benefits like time and cost saving[39]. An interesting alternative is to manufacture larger particles in situ by agglomeration of the small crystals during the crystallization. In addition, it has been revealed that agglomerates have properties that make suitable for direct compression tableting. Crystals could be generated employing any of the available techniques like sublimation, solvent evaporation, vapor diffusion, thermal treatment and crystallization from melt precipitation by change in pH, growth in presence of additives or the grinding[40]. Thus the novel agglomeration technique that transforms crystals themselves directly into a compacted spherical form during crystallization process has been desired [41]. The use of spherical crystallization as a technique appears to be efficient alternative for obtaining suitable particles for direct compression[42,43]. Due to different crystal habit many drugs show inconvenient flowability and compressibility. So these problems can be solved by converting them into a agglomerated crystals by changing the crystal habit and spheronization so as to increase the flowability and compressibility. Various drugs of which flow and compressibility are Improved.

2. For masking bitter taste of drug:

Microcapsules are prepared to mask the bitter taste of the drug. They are suitable for coating granules, since spherical material can be uniformly coated with a relatively small amount of polymer. Microcapsules of following drugs were prepared for masking of bitter taste. Various drugs of which taste masking has done.

3. For increasing solubility and dissolution rate of poorly soluble drug:

Spherical crystallization has been described as a very effective technique in improving the dissolution behavior of some drugs having low water solubility and a slow dissolution profile. Various drugs of solubility and bioavailability is improved.

CHARACTERIZATION:[44]

1. Physico Chemical characterization of Agglomerates:

a. Thin layer chromatography:

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.

b. Fourier Transform Infrared spectrometer:

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 solvation

c. Differential scanning calorimeter:

DSC measures the heat loss or gain resulting due to physical or chemical changes within a sample could be obtained from thermo grams using instrumental software. If a mixture of drugs and polymer is agglomerated together then change in properties of agglomerates can be studied with DSC. It is also useful to determine thermal degradation, purity, polymorphism, salvation, Dehydration, Dissociation, Decomposition, and Phase transfer, Glass transition, Heat capacity and drug-excipients compatibility. Crystal of samples heated (25-200°C) at the rate of 10°C/min in crimped hemetically sealed aluminum pans under nitrogen atmosphere. Calorimeter was calibrated using Indium & lead standards

2. Particle shape & surface topography:

a. Geometrical properties of agglomerates

Geometrical properties of spherical crystals can be determined by image processing system. Around 300 particle of different range size fraction were run over with an optical pen. The system determines the smallest (Dmin) and the largest (Dmax) diameter of each individual particle. A Parameter R was developed, which indicates the roundness of the particles sovereignty of the size of the particle. A value of R near 1 is indicative of perfectly spherical agglomerate.

b. Electron Scanning Microscopy

The surface topography, type of crystals (polymorphism and crystal habit) of the spherical agglomerates & the conventional crystals is analyzed by using scanning electron microscopy. Using an image analyzer micrographs of more than 100 particles were transformed into the software and the shape factor is specified as 4π (area/perimeter).

c. X-ray Powder Diffraction

This is an important technique for establishing batch-to-batch reproducibility of a crystalline form. The form of crystal in agglomerates determine by using technique. An amorphous form does not produce a pattern. The X-ray scattered in a reproducible pattern of peak intensities at distinct angle (2θ) relative to the incident beam. Each diffraction pattern is characteristics of specific crystalline lattice for a compound. X-ray diffractometer is operated at 40kV, 30mA, and a scanning speed of 0.06°/min over the range of 5-40 2θ using Cu kα1 radiation of wavelength of 1.540 A°.

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