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SPHERICAL CRYSTALLIZATION – A NOVEL AGGLOMERATION TECHNIQUE

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Abstract

A greater challenge in solid dosage formulation is the development of spherical agglomerates which increases the solubility and bioavailability of the drug. Spherical crystallization is the novel agglomeration technique that can transform directly the fine crystals into spherical shape. This technique of particle design of drugs emerged as one of the areas of active research industry and gained great interest in the formulation and manufacturing of pharmaceutical dosage forms. Any drug which is considered has been characterized by differential scanning calorimetry, Fourier transformer infrared spectroscopy, X-ray diffractometry and scanning electron microscopy. Process variables such as amount of bridging liquid, stirring time, type of solvent used, duration of stirring were optimized.

Keywords: Spherical crystallization, Agglomeration, Bridging solvents, Dissolution, Bioavailability.

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Introduction

Spherical crystallization is a solvent exchange crystallization method in which crystal agglomeration is induced during the crystallization through the addition of a third solvent, termed the "bridging liquid". The process is performed in a three partially miscible solvent system (good, poor solvent, and bridging liquid). Farnand et al. (1961) suggested that when two immiscible solvents are present and one of the solvents preferentially wets the solid surface, a collision between two wetted particles leads to the formation of a liquid bridge between the particles. This liquid bridge holds the particles together by interfacial tension effects and capillary forces (Kawashima et al., 1984), and by further random collisions large spherical agglomerates can form (Blandin et al., 2000). Zhang et al. (2010) investigated the spherical crystallization process by means of particle vision measurement and microscopy and found the process to be occur in three stages i.e., emulsion formation; nucleation and crystallization; and spheronization.[1]

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, compatibility and bioavailability of crystalline drugs. General methods of spherical crystallization are spherical agglomeration, emulsion solvent diffusion and ammonia diffusion method. The principle steps involved like improvement of flowability and compressibility of poorly compressible drugs, masking bitter taste of drugs and improving the

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solubility and dissolution rate of poorly soluble drug.

Spherical crystallization is a useful particle design technique that can be employed to improve the micrometric properties of pharmaceutical powders. Spherical agglomeration process is a multiple unit process in which crystallization, agglomeration and spheronization can be carried out simultaneously in one step. The resultant crystals can be designated as spherical agglomerates. Spherical agglomeration is a process of formation of aggregates of crystals held together by liquid bridges. The agglomerates are formed by agitating the crystals in a liquid suspension in presence of binding agent. The binding liquid should be immiscible in the suspending medium but capable of cementing the particles to be agglomerated. The properties of the particles so designed vary greatly as compared to the fine crystalline material. These agglomerates were found to have good flowability and compressibility. This technique can also be exploited to increase solubility, dissolution and hence bioavailability of poorly soluble drugs. These modifications allow for the practice of more efficient manufacturing methods that could save time and reduces economic risk.

Use of spherical techniques

Spherical techniques are widely used to make particles spherical since spherical shape possesses properties suitable for their easy manufacturing.

Spherical particles possess suitable properties like

- Improvement in water solubility
- Dissolution
- Bioavailability
- Flowability
- Compressibility
- Dosing problem
- Stability
- Toxicity.

List of solvents used in spherical agglomeration of some drugs

Drugs	Good solvent	Poor solvent	Bridging liquid
Ketoprofen	Sodium hydroxide	Hydrochloric acid	Chloroform
Glibenclamide	Methanol	Water	Chloroform
Naproxen	Acetone	Water	Dichloromethane
Meloxicam	Sodium hydroxide	Hydrochloric acid	Diethyl ether
Aceclofenac	Acetone	Water	dichloromethane
Felodipine	Acetone	Water	Dichloromethane

Mudit dixit *et al;* prepared spherical agglomerates of ketoprofen by neutralization method and were characterized by DSC, IR, X-ray and SEM. Crystallization medium used for spherical agglomerates of ketoprofen consisted of 1M sodium hydroxide; 0.25M hydrochloric acid; chloroform as bridging liquid in the ratio of 20: 55: 25, respectively. The agglomerates of ketoprofen exhibited decreased crystallinity and improved micrometric properties. The dissolution profiles of ketoprofen tablets prepared using spherical agglomerates exhibit greater dissolution behaviour than tablets prepared by powder raw material. Spherical agglomerates exhibit superior compressibility characteristics compared to conventional drug crystals.[2]

Sachin kumarpatil *et al;* prepared direct compressible tablets of glibenclamide, the agglomerates which showed appropriate hardness, friability, and weight variation and disintegration time with improved drug release than conventional marketed tablets. The agglomerates were prepared effectively by using emulsion solvent diffusion. Flowability, compressibility and elastic recovery were dramatically improved for all agglomerates. Polymers like PVP, PEG, β-CD, EU were used and their average diameter was increased than raw crystals but decreased than agglomerates without additives due to reduction in the interfacial tension between bridging liquid and crystals. The direct compression of spherical crystallization of GLM with selective additives is a satisfactory method to improve compressibility as well as dissolution and bioavailability of GLM. Hence the tablets prepared with the agglomerates of glibenclamide may reduce the total dose of drug and could improve the patient compliance by reducing the dose- related side effects.[3]

Damineni Saritha *et al*; prepared naproxen agglomerates using simple spherical crystallization technique which exhibited improved micrometric properties, bioavailability and dissolution rate of

agglomerates than compared to the pure naproxen. Anti-inflammatory studies were conducted in Wistar strain male albino rats and naproxen agglomerates showed more significant activity than the pure form of naproxen. It was found that the solubility of naproxen was more in buffer than water which can be owed to its poor water solubility in lower pH. The results of *in vivo* studies demonstrated that naproxen agglomerates showed better anti-inflammatory activity than pure drug, thus confirming the better therapeutic efficacy of naproxen agglomerates.[4]

Alladisaritha *et al;* improved the dissolution rate of meloxicam spherical agglomerates which are prepared by neutralization method of agglomeration. The obtained agglomerates were spherical in shape and dissolution rates were faster than conventional crystals. In their study it was proved that the optimized spherical agglomerates provided a rapid anti inflammatory activity and faster onset of action when compared with the pure drug. Other evaluation parameters such as solubility studies, drug content, dissolution studies, optical microscopy, differential thermal analysis etc were evaluated. It was concluded that this technique might be applicable for producing oral solid dosage forms of meloxicam with improved dissolution rate.[5]

SarfarazMd *et al;* obtained aceclofenac-disintegrant agglomerates prepared by a novel crystallo-co-agglomeration(CCA) technique which was characterized by improved solubility, flowability, packability and compression rates resulting in successful direct tableting without capping. Disintegrants like sodium starch glycolate, crospovidone, croscarmellose sodium were used in different concentrations as the crystallization medium. The improved compaction properties of the agglomerated crystals were due to their fragmentation occurred during compression. The dissolution rates of aceclofenac from the aceclofenac-disintegrant agglomerates were enhanced significantly by increasing the amount of disintegrant which showed a better sustainability.[6]

A.R.Tapas *et al*; prepared felodipine spherical agglomerates using quasi emulsion solvent diffusion technique using a three solvent technique. It was proved that the enhancement in the dissolution rate of spherical agglomerates than the pure drug might be due to the presence of polymer, Inutec SP1, which was a polymeric surfactant with high HLB value, hence its solubility in a lipophilic or a hydrophobic phase is extremely low. It was concluded that the improved wetting and dissolution characteristics was due to the concentration of oil and water interfaces of the polymeric surfactant and hydrophobic particles of the aqueous dispersions. The micrometric properties and the dissolution profile of the drug were dramatically affected by this technique.[7]

Conclusion

In recent times, particle engineering/design techniques are widely used in pharmaceutical industries to modify primary characteristics like particle size, shape, crystal habit, density, porosity as well as secondary characteristics like flowability, compressibility, compactibility etc. Improvement in the efficiency of manufacturing process and dissolution rate along with micrometric properties were appreciable using this agglomeration technique. The different methods used to prepare spherical agglomerates of different drugs were successful in its approach and proved its efficiency in novel drug delivery systems.

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