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Spherical crystallization –A novel drug delivery system

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Abstract

Today, the tablet is the most popular dosage form, covering around 50% of total oral drug delivery system and accounting 75% of all pharmaceutical preparation produced .It promotes statbility, portability and acceptable patient compliance .The quality of solid dosage form is primarily influenced by micromeritic characteristics such as the shape and size of drug crystal, especially in the case of poorly soluble drugs. To improve the dissolution rate of poorly soluble drugs, fine crystals are referred and this micronisation can change drug powder properties such as wettability, compressibility, packability and flow. Further, it is more beneficial to convert micro crystalline drugs into an agglomerated form using spherical crystallization technique. The resulting spherically agglomerated crystals can be directly prepared into a tablet, thus direct tabletting saves time and reduces cost .General methods of spherical crystallization are spherical agglomeration, emulsion, solvent diffusion method, ammonia diffusion method, neutralization method .The principle steps involved in the process of sc are flocculation zone, zero growth zone, fast growth zone, constant size zone .There is a wide application of spherical crystallization:-improvement of flow ability, compressibility of poorly compressible drug, masking bitter taste of drug, improving solubility and dissolution rate of poorly soluble drug and thus improve bioavailability of drug.

Key-Words: Spherical crystallization, Drug, Techniques

Introduction

Presently, particle design techniques are widely used in pharmaceutical industries to modify primary properties like particle shape, size, crystal habit, crystal form, density, porosity etc. as well a secondary properties like flow ability , compressibility, compact ability, reduction In air entrapment,etc. Spherical crystallization is one of such particle design technique in which crystallization and agglomeration process are carried out simultaneously. Kawashima et al, in 1990, developed spherical crystallization technique .Spherical Crystallization process transforms the fine crystal obtain during crystallization into a spherical agglomerates. Agglomerates formed further improves the flowability and compressibility of pharmaceutical ingredient which enables direct tabletting of drug instead of further processing like mixing , granulation, seiving, drying etc. There are certain parameters which have to be optimized in order to obtain the maximum amount of spherical crystals.

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Application of spherical crystallization in pharmaceuticals:

- For increasing solubility and dissolution rate of poorly soluble drug.
- For masking bitter taste of drug.
- Improve flowability and compressibility.
- Reduces cost of production.

Methods of spherical crystallization

Spherical agglomeration

In spherical agglomeration involve implications of three different solvents, One liquid acts as a perfect solvent for the drug moiety, second liquid is 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

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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 forming 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.

List of solvents used in spherical agglomeration of drugs:

Drugs	Good solvent	Poor solvent	Bridging liquid	Reference
Celecoxib	Acetone	Water	Chloroform	16
Benzoic acid	Ethanol	Water	Chloroform	17
Mefenamic acid	Dimethyl formamide	Water	Chloroform	18
Aceclofenac	Acetone	Water	Dichloromethane	19
Ascorbic acid	Water	Ethyl acetate	Chloroform	20
Aspirin	Acid buffer	Methanol	Chloroform	21
Roxythromycin	Methanol	Chloroform	Water	22
Aminophylline	Ethanol	Chloroform	Water	5
Nabumetone	Ethanol	Water	Cyclohexane	23
Acetyl salycilic acid	Ethanol	Water	Carbon tetrachloride	24
Salicylic acid	Water	Ethanol	Chloroform	25
Dibasic calcium phosphate	Water	Phosphoric acid solution	Citric acid	26
Propyphenazone	Ethanol	Water	Isopropyl acetate	27

List of some drugs on which emulsion solvent diffusion (esd)and ammonia diffusion method(adm)

Drugs	Method	Solvent	Reference
Ibuprofen	ESD	Ethanol, water with sucrose, fatty acid ester	28
Norfloxacin	ADM	Ammonia water,acetone,dichloromethane	23
Acebutalol Hydrochloride	ESD	Water,ethanol,isopropyl acetate	4
Mefenamic acid	ADM	Ammonia water,acetone,dichloromethane	29
Enoxacin	ADM	Ammonia water,acetone,dichloromethane	30

Emulsion solvent diffusion (ESD) method or Quasi ESD Method:

It was first mentioned in 1989. In this method the affinity between the drug and good solvent is stronger than that of the poor solvent.The drug is dissolved in good solvent and dispersed into poor solvent producing emulsion (quasi) droplets, even though the pure solvents are miscible. The good solvent diffuses gradually out of the emulsion droplets into the surrounding poor solvent phase, and the poor solvent diffuses into the droplets by which the drug crystallizes inside the droplets.

The method is simpler than spherical agglomeration method, but the choice of suitable solvent is very critical in order to keep the system emulsified and even diffusion of the poor solute into the dispersed phase is difficult.

Ammonia Diffusion Method

In this method three different solvent mixtures are used (acetone, ammonia water and dichloromethane).These solvents are partially immiscible solvents.Ammonia water acts as the bridging liquid as well as good solvent. Acetone is water miscible but a poor solvent, thus drug precipitate without forming ammonium salts.Water immiscible solvents such as halogenated hydrocarbons or hydrocarbons example dichloromethane induce liberation of ammonia.This method is can be used for amphoteric drugs like Norfloxacin.

Neutralization Method

This method drug is characterized by dissolved in good solvent and placed in the cylindrical vessel with constant stirring. While stirring an aqueous polymer solution along with a neutral solution is added which neutralize the good solvent and eliciting drug crystallization, bridging liquid is added drop wise with a definite constant rate, which causes agglomeration of crystals

Steps involved in spherical crystallization

Four steps involved in the growth of crystals and agglomerates, proposed by Bermer and Zuider Wag,is as followed

Flocculation zone

In this zone, bridging liquid displaces the liquid from crystals surfaces and tends to agglomerate with agitation. The adsorbed bridging liquid links the particles by forming lens bridge between them, due to which loose flocs are formed.

Zero growth zone

This zone is characterized by converting the loose flocs in to tightly packed pellets, during which the entrapped fluid is squeezed out, followed by squeezing of bridging liquid on to the surface of small flocs.This causes poor space in the pellets. The driving force for conversion is due to the agitation that resulted into pellet-pellet and pellet-stirrer collision. It is the rate determining step of reaction governed by rate of agitation.

Fast growth zone

The growth of agglomerates takes place as bridging liquid get squeezes out from the small agglomerates. This formation of large particles following random collision of well formed nucleus is known as coalescence. Successful collision occurs only if the nucleus has slightly access moisture which imparts plasticity on nucleus. The growth of agglomerates also takes place due to the successive addition of materials on formed nuclei.

Constant sized zone

Now agglomeration growth is ceased or may decrease in size due to attrition, breakage and shatter. In this zone frequency of collision is balanced by the breakage frequency of agglomeration.

Factors affecting the process of spherical crystallization

Temperature of the system

Temperature has significant influence on the shape, size and texture of the agglomerates .The solubility of drug is affected by the temperature change.

Mode and intensity of agitation

The extent of mechanical agitation along with the amount of bridging liquid determines the rate of formation and size of agglomerates. The stirring speed must be optimized. High speed agitation is necessary to disperse the bridging liquid through the system. But in some cases increasing stirring rate, may cause reduction in agglomerate formation due to increased disruptive forces. Higher stirring rates produces agglomerates that are less porous and more resistant to mechanical stress.

Amount of bridging liquid

The spherical agglomeration method has been applied to plenty of drugs,and it has been observed that the properties of spherical agglomerates were very much sensitive to the amount of bridging liquid

Choice of solvent

The choice of solvent depends on the solubility profile of drug. A mutually immiscible three solvent system consisting of good solvent, poor or anti solvent and bridging liquid are necessary. The proportion of solvent to be used is determined by carrying out solubility studies and constructing triangular phase diagram to define the region of mutual immiscibility by using ternary diagram.

esidence time

The time for which the agglomerates remain suspended in reaction mixture effect the agglomerates strength.

Advancement in spherical crystallization process

Use of polymers and surfactants

The presence of additives like polymeric material 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. Spherical agglomeration in the presence of these additives may reduces the processing time,improves the bioavailability of drug ,improves the micrometric properties of drug.

Use of polyvinylpyrrrolidine in preparing spherical crystals of Celecoxib, improved micromeritic properties, as well as improved solubility and dissolution rate. However, in vivo studies are required to confirm these results. Studies revealed that crystallization and agglomeration of pure drugs(without excipients)shows poor compressibility and handling qualities. Addition of polymers such as HPMC, PEG, EG, AND PVP has shown the improved properties.

Crystal-co-agglomeration (CCA) technique

Spherical crystallization has been restricted to size enlargement of single large dose drugs. Crystal-co-agglomeration technique is one of the novel particles designing technique developed by Kadam et al, to overcome the limitations of spherical crystallization. It is a single step process enlarging the size of single, two or more drugs, may be of small does or large doses and in combination or without combination of diluents. CCA has been applied for spherical agglomeration of - By using talc, placebo beads have been prepared by Limzerwala. Brom hexine hydrochloride-talc:Gadekar and Jadhav have developed the process for size enlargement of low dose bromhexine hydrochloride (BXH) using talc as a diluents. Ibuprofen-talc: use of talc has been made by Pawar in the agglomeration of ibuprofen, a high dose drug. Naproxen-starch:Recently, starch and Na-starch glycolate has been used in preparation of rapidly disintegrating agglomerates of naproxen by the CCA process.

References

1. Kawashima Y. Spherical crystallization as a novel particle design technique for oral drug delivery system. Chin Pharm J 1989;41:163-72
2. Kulkarni P.k. and Nagavi B.G., spherical crystallisation . Indian J.Pharm.Ed36(2002)66-71
3. Paradkar A.R.Pawar A.P,Mahadik K.R.,and Kadam S.S..Spherical crystallization,a novel particle design technique,Indian Drugs.31(1998)229-233
4. Kawashima Y,Cui F,Takeuchi H,Hino T,Niwa T,Kiuchi.k.Parameters determining the agglomeration behavior and micromeritic properties of spherically agglomerated crystals prepared by spherical crystallization technique with miscible solvent system.1995,Int J.Pharm 119:139-147.
5. Kawashima Y,Aoki S,Takenaka H,Miyake .Y.Preparation of spherically agglomerated crystals of Aminophylline. J.Pharm Sci1984;73(10):1407-10