Spherical crystallization –a novel approach to develop microcapsules

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1. Introduction

Spherical crystallization is a novel agglomeration technique to produce various novel drug delivery systems. Spherical crystallization a novel particulate design technique used to improve mixing, filling, and tabletting characteristics, and the bioavailability of pharmaceuticals. This technique has been further developed for use with the polymers, in which the precipitated crystals are designed to form functional drug devices such as microspheres (Kawashima et al., 1989), microballoons (Kawashima et al., 1991), biodegradable nanospheres (Niwa et al., 1993), and microcapsules (Niwa et al., 1994). Finely divided solids in liquid suspension can be agglomerated and separated from the suspending liquid by the addition of a small amount of bridging liquid, which preferentially wets the surface of the solid. Thus surface properties of the crystals and nature of the bridging liquid play an important role in the agglomeration process.

2. Spherical crystallization technique used for preparation of microspheres

Spherical crystallization is a solvent exchange crystallization method in which crystal agglomeration is induced through the addition of a third solvent, termed as "bridging liquid." Virtually any water insoluble liquid is suitable for using as a bridging agent in an aqueous suspension and vice versa. Low viscosity and slight solubility favors its easy distribution to the solid to be flocculated. Density greater than one reduces the possibility of the floc floating on surface of the liquid suspension medium.

The main requirement in the spherical crystallization system is that, it should provide a small amount of bridging liquid. The proportion of bridging liquid in the given system can be determined by plotting a ternary or solubility diagram of the bridging liquid in the given system. In the region above the phase separation curve the system is completely miscible, but in the region just below the separation curve will provide small quantity of bridging liquid.

There are four methods of spherical crystallization, which are as follows

2.1 Simple spherical crystallization method

The process involves the formation of fine crystals and their agglomeration. Crystallization is generally achieved by the change of solvent system or by salting out. The solution of the materials in a “good solvent” is poured in a “poor solvent” under controlled condition, so as to favor formation of fine crystals. Agitating the crystals in a liquid suspension and adding a “bridging liquid”, which preferentially wets the crystal surface to cause binding. The agglomerates may be spherical if the amount of the bridging liquid and the rate of agitation is controlled (Paradkar et al., 1993). Enteric microspheres of Oleonolic acid dihemiphthalate sodium was prepared by spherical crystallization technique using a salting out action of hydroxypropyl methylcellulose phthalate (HP-55), an enteric coating material, was co-precipitated with the drug during the preparation process in which water and ethanol were chosen as good solvents and dichloromethane was used as a bridging agent, while 0.1N sodium chloride (poor solvent) produce salting out action of drug and co

precipitation of additives. Methacrylate resin (Eu-RS PO) and aerosil helped to form spherical and compact enteric microspheres (Kawashima et al., 2003).

2.2 Emulsion solvent diffusion method

By this method spherical crystallization can be carried out using a mixed system of two or three partially miscible solvents i.e., bridging liquid-poor solvent system or good solvent-bridging liquid-poor solvent system. When bridging liquid (or plus good solvent) solution of the drug was poured into poor solvent (dispersing medium) under agitation, quasi emulsion droplets of bridging liquid or good solvent from the emulsion droplet into the dispersing medium induced the crystallization of the drug, followed by agglomeration (Paradkar et al., 1993, Sano et al., 1992).

The quasi emulsion solvent diffusion method of spherical crystallization has been accepted as a useful technique for particle design of pharmaceuticals (Cui et al., 1996). In this process drug and polymers are co precipitated to form functional drug devices according to the polymer properties. i. e. acrylic resin (Eudragit RS, Eudragit RL) and ethyl cellulose (EC) could be used to produce sustained release microspheres (Kawashima et al., 1989, Akbuga 1989, Akbuga 1991).

The preparation mechanism of the emulsion solvent diffusion method is explained by coacervation phenomenon of polymers, which occurred in the system (Cui et al., 1996). When the aqueous solution of the drug was poured in the dispersing phase finally dispersed aqueous droplets were instantly formed, resulting in w/o emulsion. The outer surface of the droplets was immediately covered with a thin shell of crystals, precipitated. Further crystallization occurred in the droplet transformed into spherical agglomerates. The mechanism of emulsion solvent diffusion method is shown in fig 1.

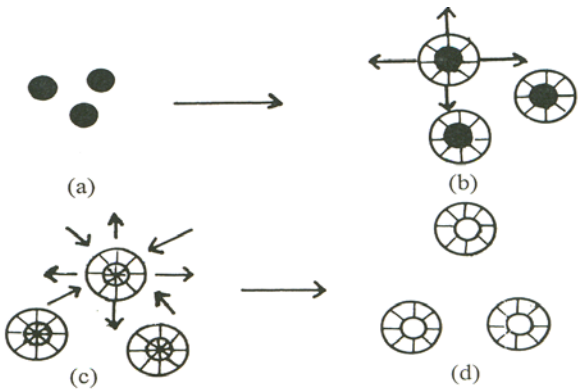

Fig.1: Mechanism of emulsion solvent diffusion method.
(a) Emulsion formation (b) Rapid diffusion of water to outer organic phase
(c) Growth of crystal shell (d) Completion of agglomeration

2.3 Ammonia diffusion system (ADS) method

A novel method for spherical crystallization of amphoteric drug substances was developed. The spherical crystallization of enoxacin, an antibacterial agent was carried out which is slightly soluble in water but soluble in acidic and alkaline solution.

A mixture of three partially immiscible solvent i.e., acetone-ammonia water-dichloromethane was used as a crystallization system. In this system ammonia water acts as a bridging liquid as well as a

good solvent for enoxacin. Acetone is water miscible but a poor solvent, thus enoxacin gets precipitated by solvent change without forming ammonium salt. Water immiscible solvents such as hydrocarbons or halogenated hydrocarbons e.g., dichloromethane induces liberation of ammonia water (Kawashima et al., 1990).

It is assumed that acetone in the solvent enters into droplet of ammonia water which is liberated from the acetone-ammonia water-dichloromethane system, and consequently, enoxacin dissolved in ammonia water is precipitated while the droplets collect the crystals (I). Simultaneously ammonia in the agglomerate diffuses to the outer organic solvent phase and its ability as a bridging liquid becomes weaker (II), then the size of the agglomerates is determined (III). The technique could be applied to other amphoteric drug, which has the same properties as enoxacin (Kawashima et al., 1990).

2.4 Neutralization method

This process involves the formation of fine crystals and their agglomeration. The spherical crystallization of tolbutamide an antidiabetic drug was reported by this technique. The drug was dissolved in sodium hydroxide (NaOH) solution. Aqueous solution of hydroxy propyl ethyl cellulose and hydrochloric acid was added to neutralize sodium hydroxide solution of tolbutamide and crystallize out the tolbutamide. The bridging liquid was added dropwise followed by agglomeration of the tolbutamide crystals.

The agglomerates of tolbutamide prepared by neutralization technique were found to have more specific surface area, more wettability and hence better dissolution rate as compared to the agglomerates prepared by the other methods of emulsion solvent diffusion, solvent change etc. The agglomerates prepared by neutralization method were instantaneously permeated with water showing shrinkage and greater wettability. The reason for this superior wettability of agglomerated crystals and tablets is that, at the time of crystallization and agglomeration processes, hydrophilic hydroxyl propyl methylcellulose in the crystallization solvent adheres firmly to the agglomerated crystals.

3. Application

The spherical crystals of drugs like furosemide, Ibuprofen and ketoprofen were directly modified during spherical crystallization using acrylic polymers to prepare microspheres. The microspheres so obtained showed prolonged release and improved bioavailability (Paradkar et al., 1993).

Spherical crystallization could provide remarkable advantages over conventional microspheres preparation method, in which drug and polymers are co precipitated to form functional drug devices according to polymer properties. However, further application of quasi emulsion spherical crystallization method is to produce solvent disposition system with poorly water soluble drug to improve dissolution rate. In the spherical crystallization process the preparation of microspheres and solvent desposition system were combined into one step (Cui et al., 2003). Biodegradable nanospheres of D.L. lactide/ glycolide copolymers can also prepare by emulsification solvent disposition method (Niwa et al., 1993).

The spherical crystallization technique can be modified to a simple and less expensive process to prepare spherical matrices of prolonged release drugs as an alternative to spray-congealing method. The advantage of this technique includes the avoidance of harmful organic solvents and additives such as polyisobutylene used in the process of micro-encapsulation phase separation. Further this

process did not require elevation of the temperature of the system as in the phase separation method. The resultant matrix spheres were directly compressible without damaging their structure, due to their characteristic sponge-like texture, unlike microcapsules (Hasegawa et al., 1984).

Effect of drug properties on physical and release characteristics of Eudragit microspheres prepared by spherical crystallization technique was studied by Julide Akbuga and Nazan Bergish- ten compounds having different solubilities and molecular weights were evaluated for incorporation into Eudragit microspheres using the spherical crystallization technique. The effects of drug-related factors on the properties of Eudragit microspheres, the suitability of the technique to entrap the active compounds with different physicochemical properties were investigated. Microspheres prepared with slightly and very slightly soluble drugs such as salicylic acid, naproxen, piroxicam, indomethacin and methylprednisolone indicated controlled-release properties. Solubility is not the main factor in highly drug loading capacity. Timolol maleate and methylprednisolone, the compounds of very soluble and very slightly soluble respectively, showed very low drug loading capacities. The entrapment of the active compound within the microspheres was highly dependent on the acidic or basic characteristics of the drug. Weakly basic drugs as acetaminophen and propranolol HCl showed low drug loading capacity. Moreover poor drug incorporation was observed with drugs having lower pKa values. Adjustment of pH in aqueous phase to minimize drug solubility resulted in increased drug contents within the microspheres in the case of ionizable drugs. Increase or decrease in molecular weight of the active compound has no significant effect on drug loading capacity. The surface of the Eudragit microspheres examined under scanning electron microscope, changed from a smooth texture at low drug loadings to a honey-comb like structure containing small holes at high loading at pH 1.2.

4. Conclusion

The spherical crystallization could simplify the traditional manufacturing process for sustained release preparations having solid dispersion structure. It is also indicated that present method was suitable for preparing the sustained release enteric microspheres for poorly water soluble drug. Spherical crystallization provides a method of crystal modification, which not only changes the flowability and compressibility of crystal but can also be utilized as a tool to increase or control the rate of dissolution. Thus this technique can be successfully used in formulation of prolonged release system. In conclusion the spherical crystallization technique can be used successfully to prepare microspheres with Eudragit, ethyl cellulose or other polymers.

5. References

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