Evaluation of Spherical Crystallization as a Particle Size Enlargement Technique for Aspirin

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Received 25 March 1996

Spherical crystallization of asprin by solvent change methods was carried out in a crystallization system composed of acid buffer (pH 2.5), methanol and chloroform. The agglomerates contained salicylic acid less than the I.P. limits prescribed. Agglomeration process significantly improved the flow properties of the drug. The agglomerates were characterised by Scanning Electron Microscopy, X-ray diffractometry, DSC and IR. The agglomerates obtained had irregular edges consisting of tightly packed lathe type crystals with broken edges. The agglomerates have lower crystallinity as compared to powder but no change was observed in the crystal form.

SPHERICAL crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step. It involved selective formation of aggregates of crystals held together by liquid bridges.[1] Spherical crystallization technique has been successfully utilised for improvement of flowability and compressibility of crystalline drugs,[2] preparation of microsponges[3] and microspheres[4], and masking of bitter taste[5]. But literature survey has revealed that no attempt has been made to exploit the potential of spherical crystallization as an alternative granulation technique for drugs sensitive to moisture. Spherical crystallization can be achieved by various methods viz. simple spherical crystallization by solvent change[6] or pH change method[7], emulsion solvent diffusion method[8], ammonia diffusion method.[9] In the present study solvent change method is adopted for spherical crystallization of aspirin as a model drug sensitive to moisture.

Methanol and Acid buffer I.P. of pH 2.5 were selected for crystallization considering the solubility of drug and stability. Chloroform was selected as a bridging liquid. The composition of crystallization system was determined by ternary phase diagram. The solution of a drug (2g) in methanol (8 ml) was added to crystallization vessel containing 8.4 ml acid buffer and 1.8 ml chloroform. The system was stirred with a three blade propeller at a speed of 600 r.p.m. Agglomerates were dried for 20 min. at 65° and then placed in a dessicator for 24 h. The amount of salicylic acid formed was then determined by the method described by Edwards et al.[10]

Agglomerates were evaluated for particle size distribution (seive analysis), bulk density (tapping cylinder method) and flowability (fixed funnel method). The agglomerate was observed under magnification of 20X on Nikon stereoscopic 200 m binocular microscope. It was also observed under 45 X and 200 X magnification in a Scanning Electron Microscope (Jeol, JSM, 5200 Japan). The powder was observed under magnification of 10 X, on Nikon polarising microscope.

The crystalline form of the agglomerated aspirin was determined using an X-ray diffractometer (Philips), with CuKα = 1.542 A.° The speed used was 0.5° 2θ/sec. Range was 2X10^4 cps. Total count was 2 sec. The slit width was 0.3 mm. The DSC scans were recorded using Perkin-Elmer DSC system, in

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the temperature range of 30°- 200° with a heating rate of 10°/min. for agglomerates as well as the powder. The I.R. spectrum of both the powder as well as spherical agglomerates was determined on F.T.I.R. spectrophotometer (Perkin-Elmer, Model 1600) using nujol.

During spherical crystallisation the drug crystals were immediately surrounded by the bridging liquid chloroform. Thus, the drug was exposed to the aqueous phase for a very short period of time, hence if the drug is crystallised in the aqueous phase containing suitable amount of chloroform, agglomerates of aspirin containing significantly lower amounts of salicylic acid could be obtained. The average amount of salicylic acid formed in the spherical agglomerates immediately after drying was found to be 0.07% which is well below the limits specified by I.P. (which is 0.1%). The mode, mean geometric diameter and geometric standard deviation were determined by plots of % cumulative oversize versus particle size on probability - log paper. The decrease in the angle of repose from 47.12° to 31.13° indicates improved flow properties of agglomerates as compared to aspirin powder. The aspirin powder has higher bulk density and thus lower porosity as compared to spherical agglomerates. The powder is more tightly packed and thus arch formation will occur when it flows through the hopper. On the other hand the flowability of spherical agglomerates is greater than that of aspirin powder sample. It was seen that the agglomerates of aspirin prepared by spherical crystallization method were not perfectly spherical and had irregular edges. The powder crystals were rectangular lathes, with randomly broken edges. The particle size of the crystals was not uniform. Many smaller particles were adsorbed onto the surface of the larger particles. Many small irregular shaped particles were also present. Scanning electron microscopy of spherical agglomerates revealed that the agglomerates were irregular spheres, with rectangular lathe type crystals forming a majority of percentage. All the particles were tightly and densely packed. Due to the packing of smaller irregular particles in between the rectangular larger particles; a close dense packing was possible. This close packing led to a decrease in the interparticular void spaces and increased particle-particle interaction. The broken edges of the lathe type crystals could be due to the shear imparted by the stirrer during the spherical agglomeration process.

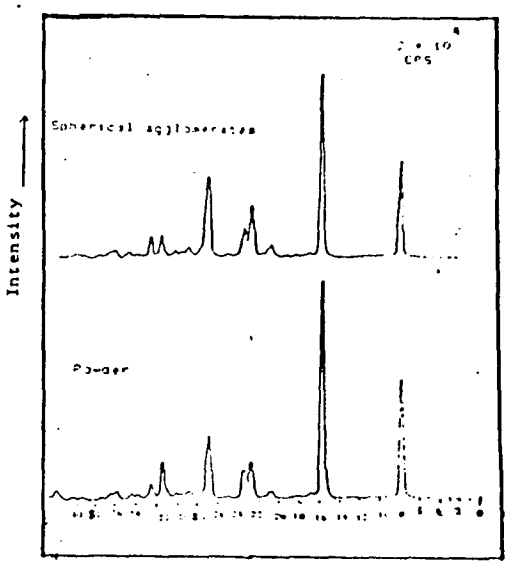

Fig. 1 : Powder X-ray Diffractogram of Aspirin Powder and spherical agglomerates

The d spacing values of the peaks in the diffractograms of powder and agglomerates do not exhibit any significant difference suggesting no change in the crystal form of the drug, and this fact is also supported by SEM studies. The relative diffraction intesities of the agglomerates are slightly lower than that of the powder, indicating slight decrease in the crystallinity of the drug after spherical crystallisation process. X-ray diffractograms of powder and agglomerates are depicted in Figure 1.

The DSC of powder as well as agglomerates show an endotherm at 136° which is melting point of aspirin. The initial decomposition and final temperature also show no significant difference indicating no polymorphic change. I.R. Spectra of powder and spherical agglomerate does not show any significant variation.

The present study has shown that the spherical agglomeration of aspirin using water-methanol-chloroform blend is an inexpensive and satisfactory method for its particle size enlargement. This tech-

n. :ue can significantly improve the flow properties of aspirin without causing change in crystal form. The process would be a better alternative to slugging of moisture sensitive drugs. The agglomerates should be further subjected to evaluation of stability and compressibility.

The authors wish to thank University Grants Commission, New Delhi, for the sanction of minor research project to ARP, and to Li-Taka Pharmaceuticals, Pune for gift sample of aspirin.

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Structural Education of Columbin, A Diterpene Isolated from The Rhizomes of *Artistolochia albida*

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Received 21st May 1996

The Isolation and structure elucidation of columbia have been reported from Aristolochia albida as well as from Aristolochiaceae family for the first time possessing antisnake venom activities, the structure of which was determined by special (UV, IR, ^{1}H-NMR, ^{13}C-NMR, MS) and elemental analysis. This is the first report of biological activities of Columbin.

THE presence of sterol and D-glucose [1], the *in vivo* antisnake venom activities of a furanoid diterpene[2] isolated from the rhizomes of Aristolochia albida Duch (family : Aristolochiaceae) were previously reported from this laboratory. The present article describes the structure elucidation of this biologically active furanoid diterpene lactone which has been characterized as columbin on the basis

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