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Melt-Sonocrystallization: A Novel Particle Engineering Technique for Solubility Enhancement.

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Abstract

Melt sonocrystallization a novel particle engineering technique to enhance dissolution of hydrophobic drugs and to study its effect on crystal properties of drug. It forms Valdecoxib agglomerates with number of shallow circular pits on the surface leads to increase solubility. Melt sonocrystallization process was developed for valdecoxib in which valdecoxib melt was poured in deionized water maintained at 60^0C and simultaneously subjected to ultrasonic energy. The agglomerates obtained after solidification of dispersed droplets were separated by filtration and dried at room temperature. The agglomerates obtained were evaluated by using Scanning electron microscopy (SEM), Differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), Fourier transformed infrared spectroscopy (FTIR), and solubility. The irregular agglomerates having porous surface were obtained. The agglomerates comprised of crystals having different crystal habits as needles, plates, and some hollow tubes. Saturation solubility increased with the treatment of ultrasonic energy. SEM and XRPD confirmed crystal habit changes.

Keywords: Valdecoxib; Melt sonocrystallization; Saturated solubility; Surface topography; Stability.

Introduction

Particle engineering techniques are developing to modify the physicochemical, micromeritic and biopharmaceutical properties of the drug. Number of particle design techniques are reported, such as spherical crystallization, extrusion spheronization, melt solidification, spray drying, pastillation, solution atomization and crystallization by sonication (SAXS), where simultaneous crystallization and agglomeration occur[1-7] .Valdecoxib is non-steroidal anti-inflammatory, analgesic used in treatment of adult rheumatoid arthritis, primary dysmenorrhea. Valdecoxib shows poor dissolution behavior because of its hydrophobic nature. However, for analgesic action rapid release is preferred. To overcome this problem many workers have attempted to improve properties through suitable particle design techniques[8] .

Ultrasound (US) was introduced in the traditional process of pharmaceutical technology of few years ago. For instance, several workers reported US assisted compaction and US spray congealing of variety of systems where physical modification of structure of drug or excipients was done to improve drug release and compaction properties of drug. Besides these effects on solid, US may also act on a liquid or melt mixtures causing cavitation and extreme molecular motion, which divides the drop of material into number of microdrops of narrow size range. One of the mechanical effects cause by ultrasonification is disaggregation or deagglomeration of the particle assembling. Cavitation is an important phenomenon of ultrasonication. The energy produced due to the collapse of bubbles at very high temperature was responsible for breaking of particles. The so generated shock waves can cause the particle collide into one another with great force since these are similar charge particles problem of agglomeration is greatly reduced[1,2,9] . There are reports on application of ultrasonic (US) energy during crystallization, i.e. sonocrystallization. US energy has been used to achieve nucleation at moderate super saturation during the crystallization process or terminal treatment to achieve deagglomeration and to obtain desired crystal habit. Fini et al. studied US assisted compaction of various drugs with excipients such as cyclodextrin and Eudragit. Significant changes in the crystal properties were observe due to US treatment[10] .The effect of application of US energy on the properties of melt sonocrystallized (MSC) valdecoxib was characterize by scanning electron microscopy (SEM), differential scanning calorimetery (DSC), X-ray powder diffraction (XRPD), infrared spectroscopy and saturated solubility study.

Materials and methods

Materials

Valdecoxib was kindly, supplied by Alembic Pharmaceuticals Ltd. (Vadodara, India). Potassium dihydrogen phosphate and sodium hydroxide of analytical grade were purchase from Quallign and Loba chemicals (Mumbai, India) respectively.

Method of preparation

The drug (2gm) was melted in a vessel on a paraffin oil bath maintained at 190°C. Molten mass was poured in a vessel containing 50ml of deionized water maintained at 60°C using thermostatic water bath and sonicated for 15 minutes using probe ultrasonicator (Ikasonic U 200 s control) at amplitude of 80% and cycle of 0.8 per second. The product obtained after solidification of dispersed droplet was separate by filtration and dried at room temperature. The fraction of MSC valdecoxib agglomerates (–40/+60 #) were used for saturated solubility study.

Characterization

Solubility determination

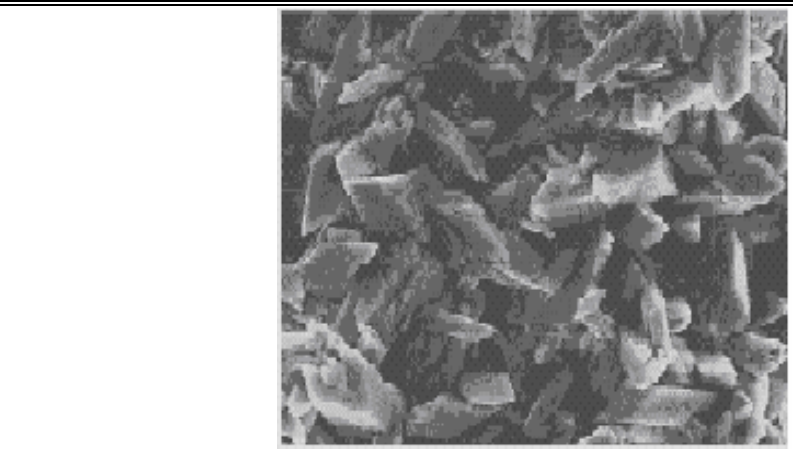
To evaluate increase in solubility of MSC valdecoxib, saturation solubility measurement was carried out. An excess amount of MSC valdecoxib was added to 10 ml of distilled water maintained at 37 ◦C and shaken for more than 24 h. The solutions were then centrifuge at 7000 rpm for 10 min. Supernatant was suitably diluted and analyze by UV-Spectrophotometer at 246 nm.

Fourier transformed infrared spectroscopy

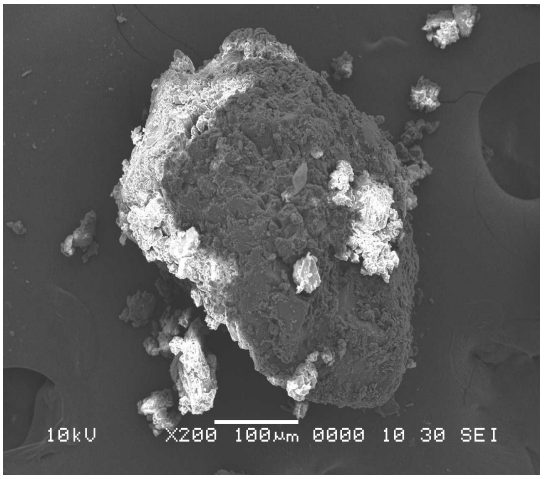
Fourier-transformed infrared (FT–IR) spectra of pure crystalline drug and MSC agglomerates were obtain on Shimadzu 8400 S FT–IR, Japan. The spectra were scan over the wave number range of 3600–400 cm−1.

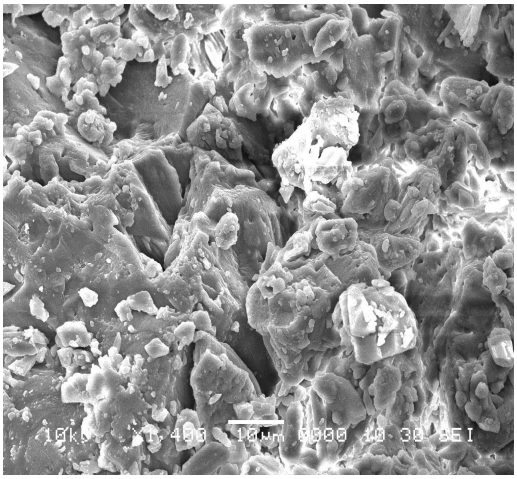
Surface topography

Scanning electron microphotographs of pure crystalline drug, MSC agglomerates were obtained using JEOL-840 Scanning Electron Microscopy .The samples were coated with thin gold–palladium layer by sputter coater unit (VG Microtech, UK). Scanning electron microscope was operating with an acceleration voltage of 10 kV. The photomicrograph was obtained at different magnification (50X, 100X, and 350 X) to study the surface topography.



(A)





(B) **(C)**

Fig. 1: SEM of valdecoxib pure and MSC sample. A) Pure drug at 20 X.B) MSC valdecoxib at 200X. C) MSC valdecoxib at 1400X.

Differential scanning calorimetry (DSC)

Thermograms of pure crystalline drug and MSC valdecoxib agglomerates were obtained using a Mettler- Toledo DSC 821 instrument equipped with an intracooler. Indium standard was used to calibrate the DSC temperature and enthalpy scale. The powder samples were hermetically sealed in aluminum pans and heated at a constant rate

of 20◦C/min, over a temperature range of 20–230 ◦C. Inert atmosphere was maintained by purging nitrogen at the flow rate of 100 ml/min.

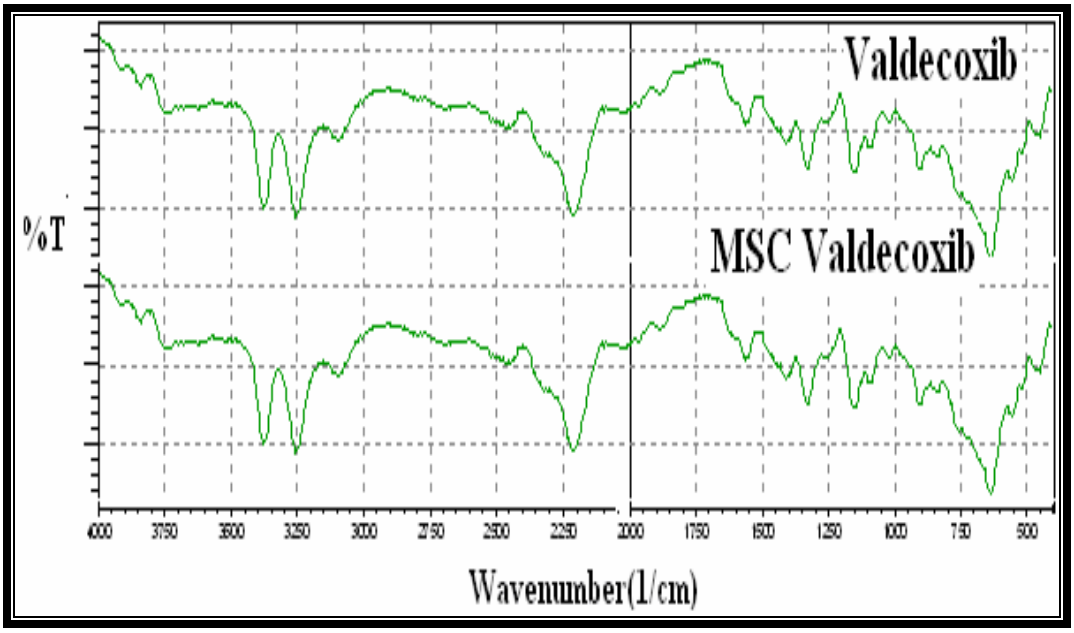


Fig.2: IR spectrum of Valdecoxib pure and MSC Valdecoxib sample.

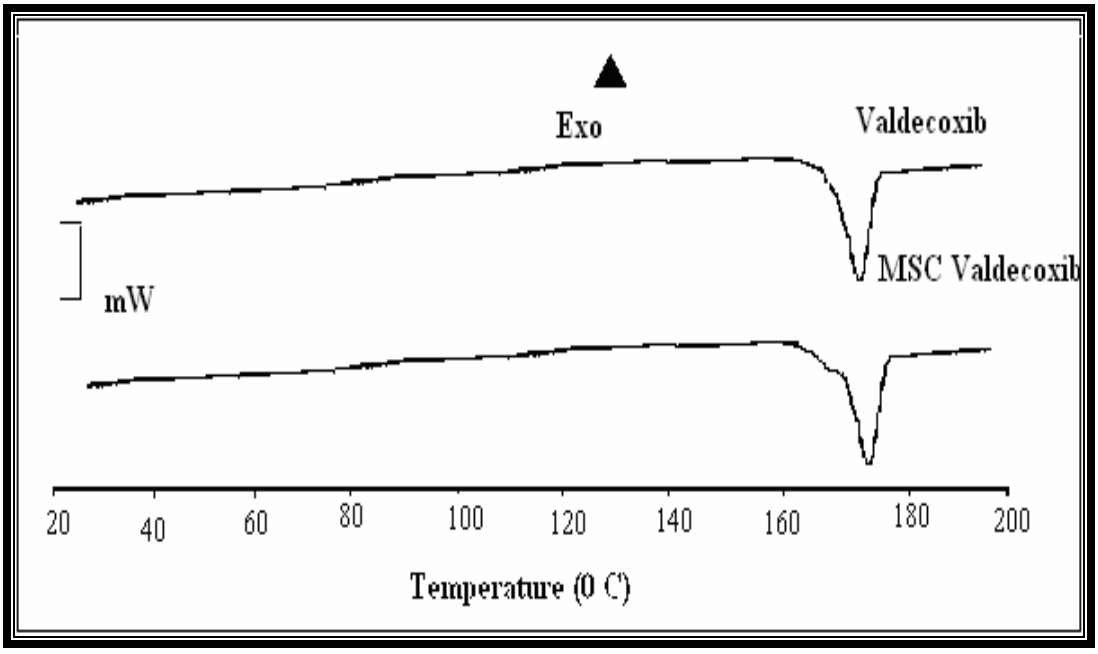


Fig.3: DSC of valdecoxib pure and MSC sample.

X-ray powder diffractometry (XRPD)

Samples of valdecoxib and MSC valdecoxib were prepared by pulverizing in a mortar. The XRPD patterns of samples were recorded by using a Philips PW 1830 X-ray diffractometer. Samples were irradiated with monochromatized Cu Kα radiation (1.542 A°) for measuring the 2ø range 4 to 60° with reproducibility of ± 0.001° on a diffractometer. The XRD patterns were recorded automatically using rate meter with the time constant of 2 X 10^2 pulses per second and the scanning speed of 2° (2θ)/min.

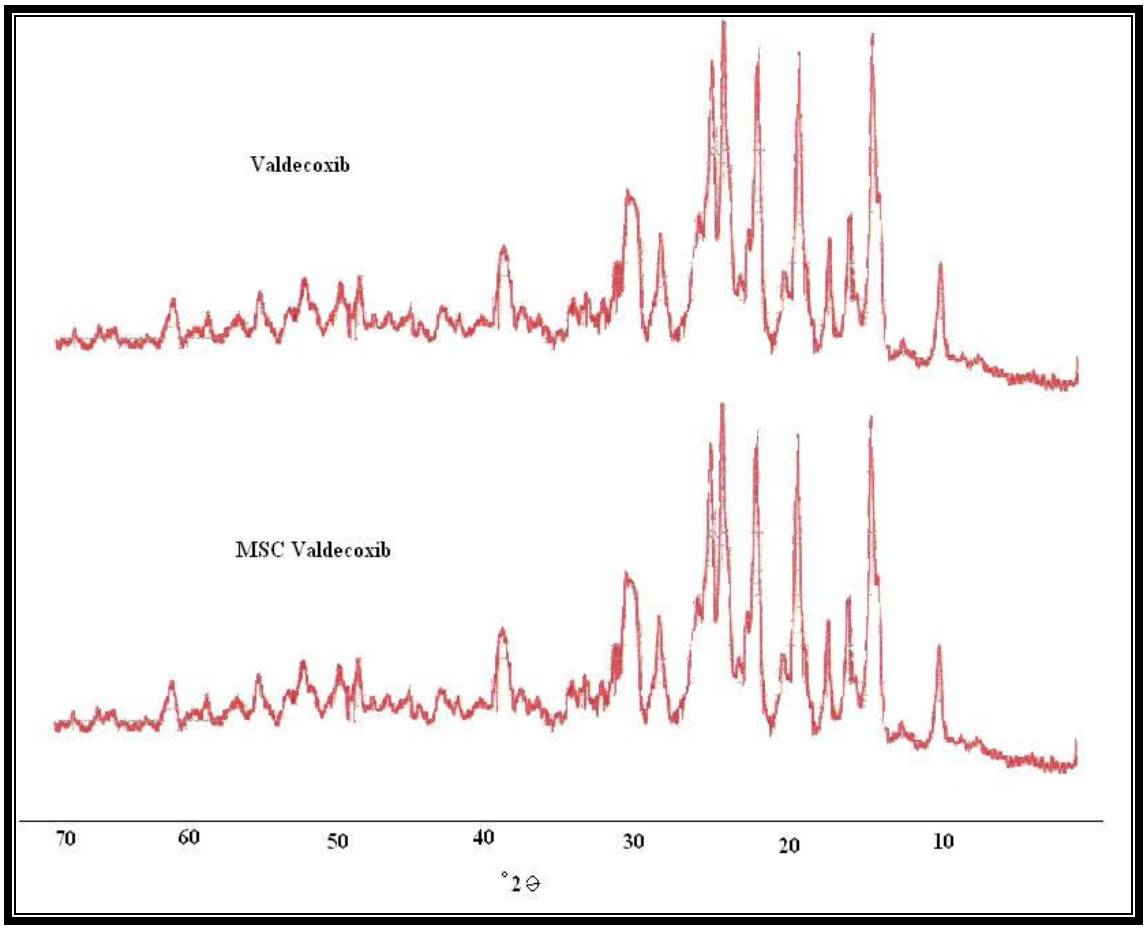


Fig. 4: XRPD of Valdecoxib and MSC Valdecoxib sample.

Results and discussion

Melt sonocrystallization, which is combination of melt solidification and ultrasonication, has advantages of melt solidified bonds and hard surface. This hardened surface has enabled the particles to withstand high sonication shear and maintain integrity even in highly porous form. Ultrasonication has been reported to cause spontaneous nucleation at relatively low degrees of super saturation, due to increase in number of collisions. Similarly, ultrasonication enhanced collisions in molecules of the melt favors nucleation rather than crystallization. Thus, it may be conclude that MSC is a promising technique to obtain porous, amorphous material with high stability. Melt sonocrystallization (MSC) process was designed for valdecoxib, which undergoes slow and shear independent crystallization. Processing temperature was an important factor in the design of the technique. Application of ultrasonic energy to the molten mass significantly increases kinetic energy of the molecules and number of collisions causing faster crystallization of the drug. Application of ultrasonic energy has caused complete crystallization in less than 30s.Watanabe et al. (2001) has demonstrated decrease in recrystallization time of indomethacin with increase in grinding time. During preliminary study, it was observe that the melt was immediately disperse into fine droplets and remained in the upper portion of the vessel. Larger agglomerates were formed from the melt droplet at the top of liquid surface, which received less US energy. The percentage of these large agglomerates was not more than 10% (w/w). The process yield of various batches was in the range of 84–91% (w/w). Loss of drug in aqueous phase was found to be less than 2% (w/w) though it showed to be increase with increase in sonication time. Crystal morphology influences pharmaceutical engineering and biopharmaceutical parameters as solubility and dissolution characteristic of drug powder. Scanning electron microphotographs of the crystalline valdecoxib and valdecoxib treated with US energy are shown in Fig. 1.

The crystalline drug is in the form of rhombic shape (Fig. 1.A). Application of US energy to crystalline drug in suspension form resulted agglomeration of crystalline drug with number of shallow circular pits on the surface, cracks in the crystals, reduction in particle size and surface roughness with porous nature. MSC valdecoxib agglomerate shown in Fig.1 (B). MSC valdecoxib agglomerates are irregular in shape with pores nature (Fig. 1C).

The IR spectra of valdecoxib (Fig.2) showed band at 3377.12 cm^{-1} is due to N - H stretching. The band at 1161 cm^{-1} due to stretching vibrations of S = O bond. Band in between 3100 – 3000cm^{-1} is due to Aromatic C – H stretching and bending vibration in

between 1450 – 1400 cm^{-1}. The C – O of Isoxazolyl stretching shows peaks at 1350 – 1300 cm^{-1}. MSC samples showed spectrums as that of pure drug hence no chemical changes occur in MSC valdecoxib.

The DSC curve of Valdecoxib (Fig.3) was typical of a crystalline anhydrous substance with a sharp melting endotherm (Tonset=164.8 8C, Tpeak=176.8 8C) ascribed to drug melting. The melting endotherm is sharp but asymmetric, may be due to presence of different crystal structures. These observations are in confirmation with change in thermal properties of ibuprofen after MSC, where broadening and asymmetry is ascribed different crystal size and crystal type of ibuprofen (Paradkar, A. R. and Maheshwari, M., 2005).

In the X-ray diffractogram of Valdecoxib powder (Fig.4), sharp peaks at a diffraction angle (2θ) of 12.26, 15.88, 19.88, 22.08, 23.92^0 are present and it suggests that the drug is present as a crystalline material. There was no change observed in the d-spacing value.

Saturated solubility of crystalline Valdecoxib was found to be 10.42±0.017 µg/ml, whereas for MSC Valdecoxib agglomerates, it was found to be 17.17±0.010 µg/ml. Solubility of MSC Valdecoxib has been significantly higher than the original powder, it may be due to decrease in size of the individual crystals, forming the agglomerates.

Conclusion

Valdecoxib agglomerates has yielded, comprising of irregular in shape having rough surface with pores obtained by MSC technique, The MSC Valdecoxib agglomerate has shown some number of shallow circular pits on the surface, cracks in the crystals of the drug and has shown significantly higher specific surface area and thereby increase in saturated solubility

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