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Research Paper

Design and Evaluation of Celecoxib Porous Particles using Melt Sonocrystallization

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Purpose. The purpose of the article was to study melt sonocrystallization (MSC) for a drug forming a viscous melt when processed below its glass transition temperature.
Methods. A molten mass of drug was poured in a vessel containing deionized water, maintained at 40°C using cryostatic bath, and sonicated for 1 min using probe ultrasonicator at an amplitude of 80% and a cycle of 0.8 per second. The product obtained after solidification of dispersed droplets was separated by filtration and dried at room temperature. MSC celecoxib was characterized by solubility determination, scanning electron microscopy, differential scanning calorimetry, X-ray powder diffraction, and stability study.
Results. The MSC technique was designed for celecoxib, which undergoes fast solidification. The particles obtained by MSC were porous, irregular in shape, and amorphous in nature. An increase in the apparent solubility was observed for the MSC particles. These amorphous particles also exhibited a higher stability in the amorphous state as compared with particles obtained by melt quenching.
Conclusions. The reported MSC technique for celecoxib demonstrates advantages over other approaches and can be exploited in area of particle design for the amorphization of drugs.

KEY WORDS: celecoxib; melt sonocrystallization; porous amorphous particles; surface topography.

INTRODUCTION

Supersaturation induction, nucleation, and crystal growth are the steps in formation of a particulate solid by crystallization or precipitation from a solution. Particle design techniques cause some variation in the rate of these steps, which can lead to significant alteration in the properties of resultant particulate material. The application of ultrasonic energy during particle formation has been reported in the last decade. In the sonocrystallization process, the nucleation and crystallization steps are modified with a reduced metastable zone and nucleation occurring at a lower degree of supersaturation. Thus, this approach has been applied for systems that are difficult to nucleate (1). Li *et al.* (2) have reported the rapid salting out of various molecules such as spictinomycin hydrochloride, roxithromycin, sucrose, and creatine.

Thompson and Doraiswamy (3) have proposed a mechanism for induction of supersaturation by ultrasound. It was proposed that a cavitation bubble is imploded and a localized hot spot is formed along with extremely large temperature and pressure gradients. In a certain range of temperature and pressure gradients, the solvent exists in the supercritical state, thus resulting in higher solubility. Li *et al.* (2) have reported the formation of very fine crystals caused by rapid nucleation and crystal growth as a result of insonation during the precipitation process. It was proposed that the product obtained resembled that obtained by supercritical micronization. The ultrasonic energy provides microscopic mixing by vibration and cavitation, which promotes nucleation and crystal growth. This study has demonstrated the formation of amorphous particles at an intermediate stage of processing. Insonation of the solution causes significant increase in the intrinsic mass transfer coefficient and interfacial area, which in turn promotes nucleation and crystal growth. Similarly, an increase in mass transfer coefficient occurs as a result of microstreaming, i.e., localized turbulence at the solid–liquid film (4–7).

Recently, Maheshwari *et al.* (8) have reported a novel melt sonocrystallization (MSC) particle design technique where insonation of ibuprofen melt dispersed in water was carried out at ambient temperature. The ibuprofen particles produced included a number of porous tubes and sintered crystals and were shown to have a high specific surface area and an improved dissolution rate. Ibuprofen is a drug with a low glass transition temperature (T_g), and the melt remains in a low viscosity liquid state for a relatively longer period of time (9). Because of this, ultrasonic energy may be applied to the melt during crystallization. In the present study, an attempt has been made to study the effect of insonation of dispersed melt having relatively high viscosity near its T_g. The engineered particles may exhibit properties that may provide biopharmaceutical advantage to the formulator.

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Celecoxib, 4-[5-(4-methyl phenyl)-3-trifluromethyl-1*H*-pyrazol-1-yl] benzene sulfonamide, is a selective COX-2 inhibitor and has been selected as a model drug (10,11). In the present study, celecoxib particles have been produced using the MSC technique. The effect of ultrasonic energy on the properties of MSC celecoxib particles was investigated by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), solubility determination, and stability study.

MATERIALS AND METHODS

Materials

Celecoxib was kindly supplied by Lupin Laboratories (Pune, India). Potassium dihydrogen phosphate, acetronitrile, and methanol used were of analytical grade (Merck, Mumbai, India).

Preparation of Celecoxib Particles

The drug (1 g) was melted using a paraffin oil bath maintained at 170°C. The molten mass obtained was poured in a vessel containing 25 mL of deionized water maintained at 40°C using cryostatic bath (Haake Phoenix C25P, Karlsruhe, Germany), and sonicated for 1 min using probe ultrasonicator (IKASONIC U 200 S control, IKA Labortechnik, Staufen, Germany) at an amplitude of 80% and a cycle of 0.8 per second. The product obtained after solidification of the dispersed droplets was separated by filtration and dried at room temperature.

Melt quenched glass was prepared by heating the celecoxib powder in an aluminum pan, and the melt was solidified by cooling on an ice bath (12).

Characterization

Yield and Drug Loss

Particles were weighed after drying, and percent yield was calculated. The loss of the drug in the aqueous phase during the process was determined using the high-performance liquid chromatography (HPLC) method (13).

The HPLC system specifications were as follows: pump, PU-1580 (Jasco, Tokyo, Japan); injector, autosampler CAS-1555 (Jasco); column, RP C_{18} 250 × 4.6 mm (Kromasil® 5 μm, Flexit Jour Lab. Pvt., Pune, India); detector, UV/Vis (UV-1575, Jasco). Data acquisition and analysis was carried out using the Borwin/HSS 2000 software (LG 1580-04, Jasco). The mobile phase used was aqueous potassium dihydrogen phosphate (pH 4.8, 0.01 M) and acetronitrile (45:55 v/v). Flow rate was kept at 1.0 mL/min. The column was maintained at ambient temperature, and the eluant was monitored at a wavelength of 252 nm.

Solubility Determination

Solubility was determined by placing an excess sample in 10 mL of phosphate buffer (pH 7.2), maintained at 37°C, and shaken for 48 h. The solution was then centrifuged at 7000 rpm for 10 min, and the supernatant was suitably diluted and then analyzed by HPLC (13).

Scanning Electron Microscopy

Particles were coated with a thin gold–palladium layer by sputter coater unit (VG-Microtech, West Sussex, UK), and the surface topography was analyzed with a Cambridge Stereoscan S120 scanning electron microscope (SEM, Cambridge Instruments, Cambridge, UK) operated at an acceleration voltage of 4 kV.

Differential Scanning Calorimetry

Thermal profiles of pure and MSC celecoxib were obtained using a Mettler-Toledo DSC 821^e instrument equipped with an intracooler (Mettler-Toledo, Greifensee, Switzerland). An indium standard was used to calibrate the differential scanning calorimetry (DSC) temperature and enthalpy scale. The samples were hermetically sealed in aluminum pans and heated at a constant rate of 10°C/min, over a temperature range of 0–200°C. An inert atmosphere was maintained by purging with nitrogen at a flow rate of 100 mL/min.

X-Ray Powder Diffraction

Samples of pure and MSC celecoxib particles were prepared by pulverizing with a pestle and mortar. X-ray

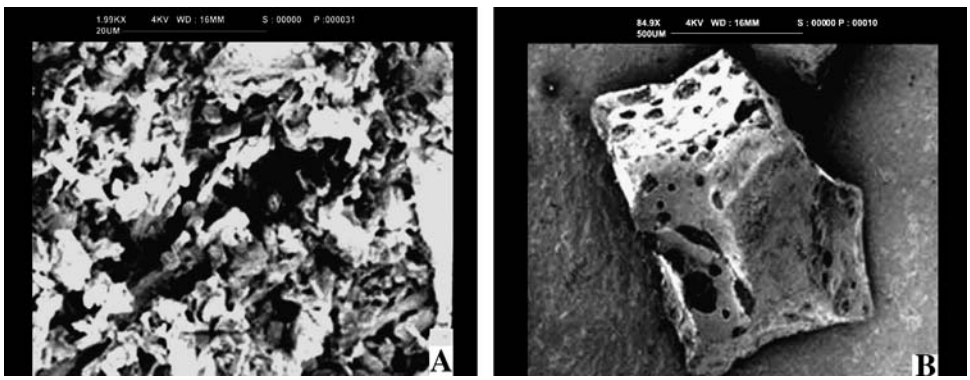

Fig. 1. Scanning electron microscopy (SEM) photographs. (A) Celecoxib crystals. (B) Melt sonocrystallized (MSC) celecoxib particle.

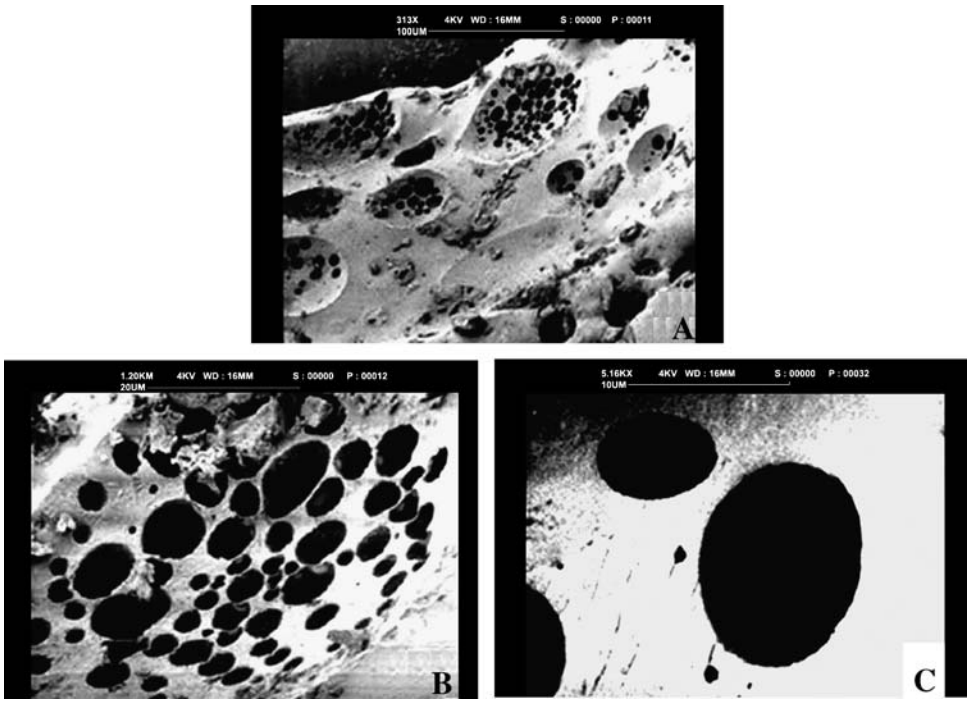

Fig. 2. SEM photographs of MSC celecoxib at different magnification.

powder diffraction (XRPD) patterns were recorded by using a Philips PW 3710 X-ray diffractometer (Philips, Eindhoven, Netherlands). The samples were irradiated with monochromatized Cu Kα radiation, generated at 1.54239 Å wavelength, at 30 kV and 30 mA. Afterward, the samples were step-scanned at 0.05° interval, from 4.00° to 60.00° (2θ), at the rate of 4.00° min^{-1}.

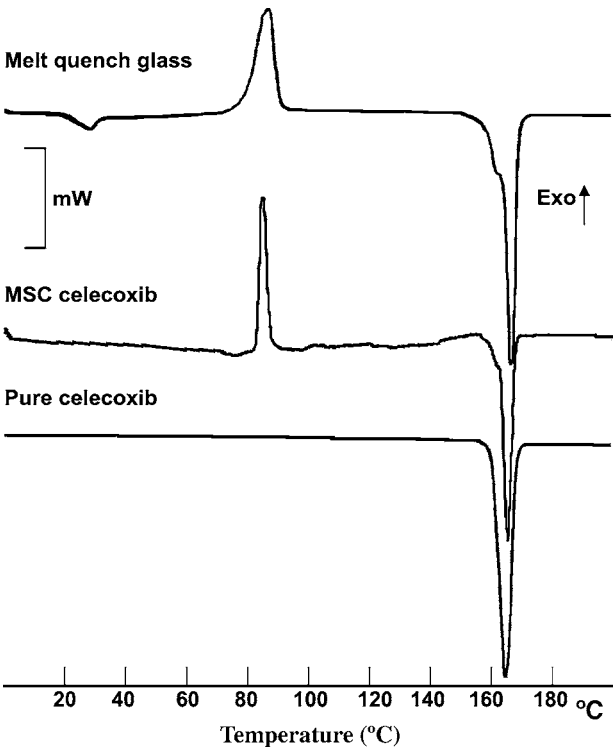

Fig. 3. Differential scanning calorimetry (DSC) profiles of various solid state forms: melt quench glass of celecoxib, MSC celecoxib, and pure celecoxib.

Stability Study

A stability study of MSC celecoxib was performed at ambient temperature and under accelerated conditions of 40°C/75% relative humidity (RH) for up to 30 days. Samples are packed in sealed glass vials. These samples were characterized using DSC and XRPD at intervals throughout the duration of the study.

RESULTS AND DISCUSSION

During a preliminary study, it was observed that upon addition to the aqueous phase, the viscous celecoxib melt did

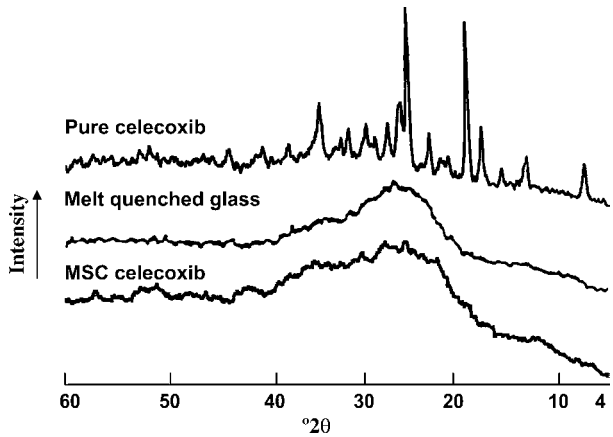

Fig. 4. X-ray diffractograms of various solid state forms of celecoxib: MSC celecoxib, melt quench glass, and pure celecoxib.

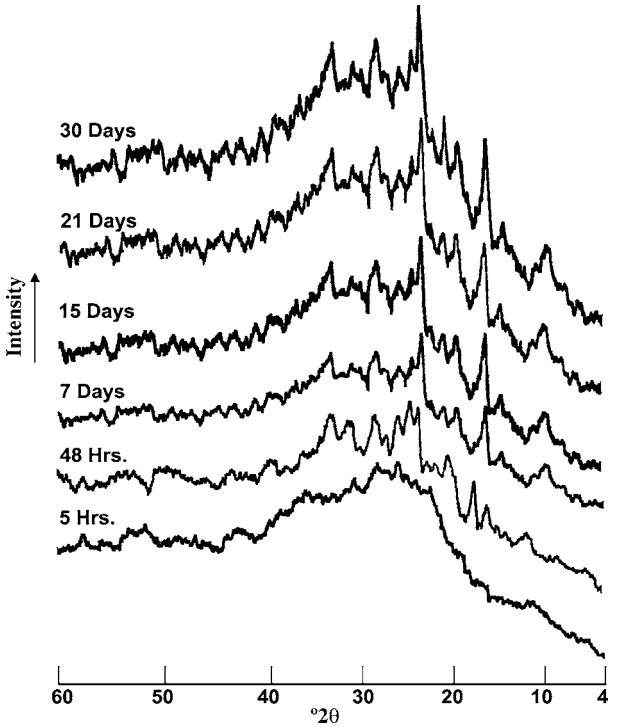

Fig. 5. X-ray diffractograms of stability samples stored at room temperature.

not remain on the liquid surface, and during its movement down through the aqueous phase, the application of the ultrasonic energy led to the formation of highly porous particles. The particles formed were in the range of 100 μm to 1.1 mm. MSC was carried out at 40°C, which is approximately 10–15°C below the reported T_g of celecoxib (51–54°C) (12). The high viscosity and rapid transformation of celecoxib melt to the solid state restricted the conversion of celecoxib melt into fine droplets, even during the application of ultrasonic energy. The effect of the ultrasonic energy on the chemical stability of the product was examined by HPLC. Chromatograms of the MSC celecoxib did not show any additional peaks, indicating the absence of chemical degradation during the process.

The process yield of celecoxib particles was in the range of 89.32–92%. The loss of the drug in the aqueous phase was found to be less than 0.1% w/w. The saturation solubilities of pure and MSC celecoxib in phosphate buffer (pH 7.2) were 5.16 and 6.23 μg/mL, respectively. The increase in solubility is attributed to the amorphization of celecoxib during MSC, which has been confirmed by other techniques. The amorphous form, being the high-energy state caused by the lack of long-range order, produces a greater molecular mobility and thermodynamic escaping tendency, leading to faster dissolution rates and higher solubility. Chawla *et al.* (14) also reported an increase in the solubility of celecoxib in water as a result of amorphization (pure celecoxib, 3.56 μg/mL; amorphous celecoxib, 4.66 μg/mL).

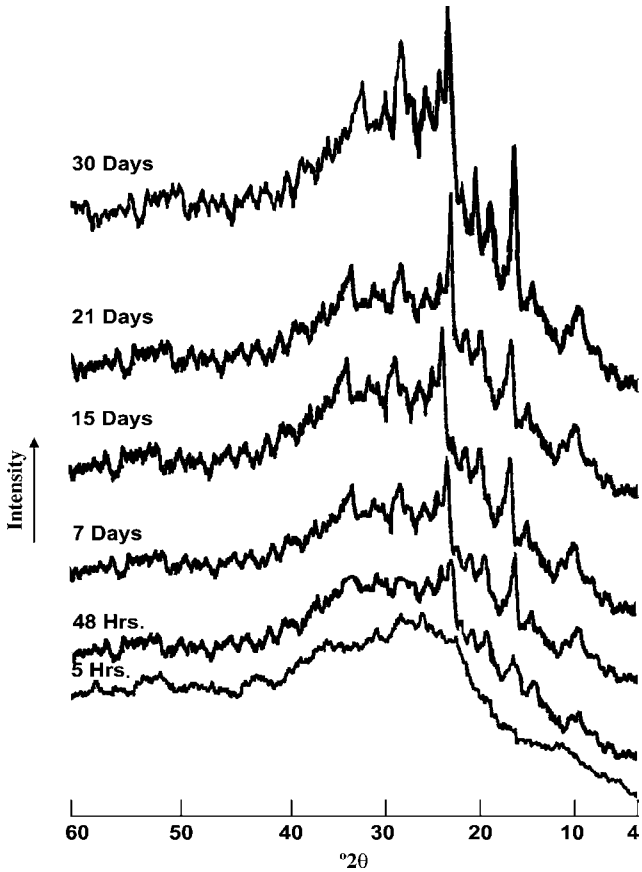

Fig. 6. X-ray diffractograms of stability samples stored 40°C/75% relative humidity (RH).

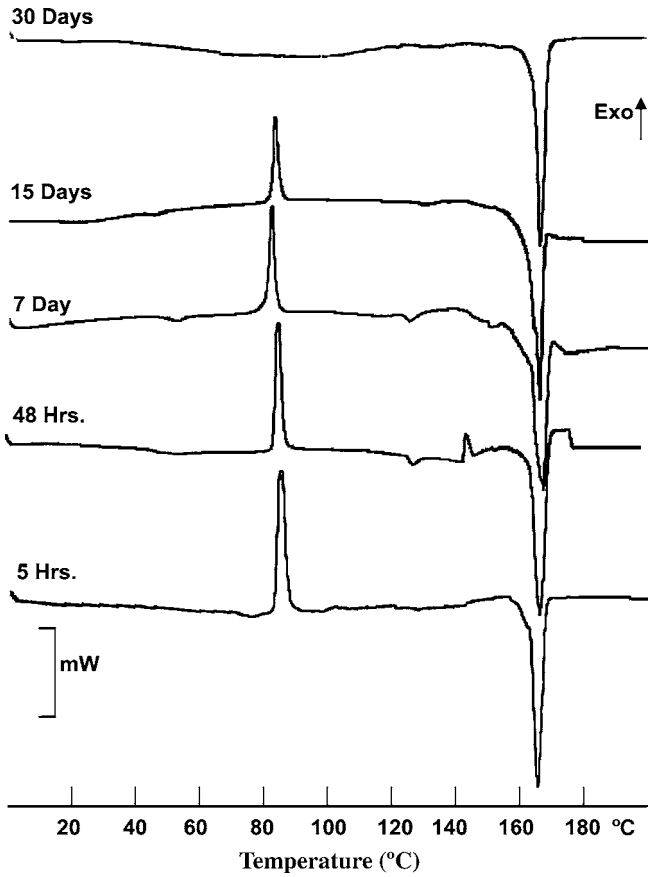

Fig. 7. DSC profiles of stability samples stored at room temperature.

The SEM photographs of the pure celecoxib particles and MSC particles are shown in Fig. 1. The MSC particle is irregular in shape, with a number of shallow circular pits on the surface. There are also pockets on which shear has been applied to the extent of creating deep circular holes, which can be observed as black spots (Fig. 2A) as well as smaller pores at the center of the surface. These particles did not show any visual crystal structure (Fig. 2B). An image of the particle at high magnification (Fig. 2C) showed a uniform surface, and no individual crystal structure was observed.

MSC ibuprofen showed porous fine tubes, and some sintered crystals were observed (8). The tubular structures were formed as a result of stretching of the sticky melt, but the relatively viscous and rapidly solidifying melt of celecoxib did not undergo crystallization. Ibuprofen, which has a low T_g (less than −30°C) and a slow rate of crystallization, showed the formation of crystals when subjected to MSC at room temperature, which is well above its T_g. Thus, the properties of the particles are significantly affected by the processing temperature and the properties of the melt.

The DSC thermal profiles of pure, melt quenched, and MSC celecoxib are shown in Fig. 3. The DSC scan of pure celecoxib showed a single endotherm at 163°C, with a normalized energy of 91.25 J/g ascribed to drug melting. Melt quenched celecoxib exhibited a small change in the heat capacity at 51.8°C, identified as the T_g, an exotherm as a result of crystallization at 95.63°C, with a normalized energy of 61.89 J/g, and a melting endotherm at 165.6°C. The recrystallization exotherm is relatively broad, with an onset temperature of 80.0°C and an end set at 95.0°C. The thermal trace of MSC celecoxib gave a recrystallization peak at 92.1°C, with a normalized energy of 58.33 J/g, followed by a melting endotherm at 165.69°C. The melting endotherm is sharp but asymmetric, which may be caused by the presence of different crystal structures. These observations are in accordance with the change in the thermal properties of ibuprofen after MSC, where the broadening and asymmetry are ascribed to different crystal sizes and crystal habits of ibuprofen (8).

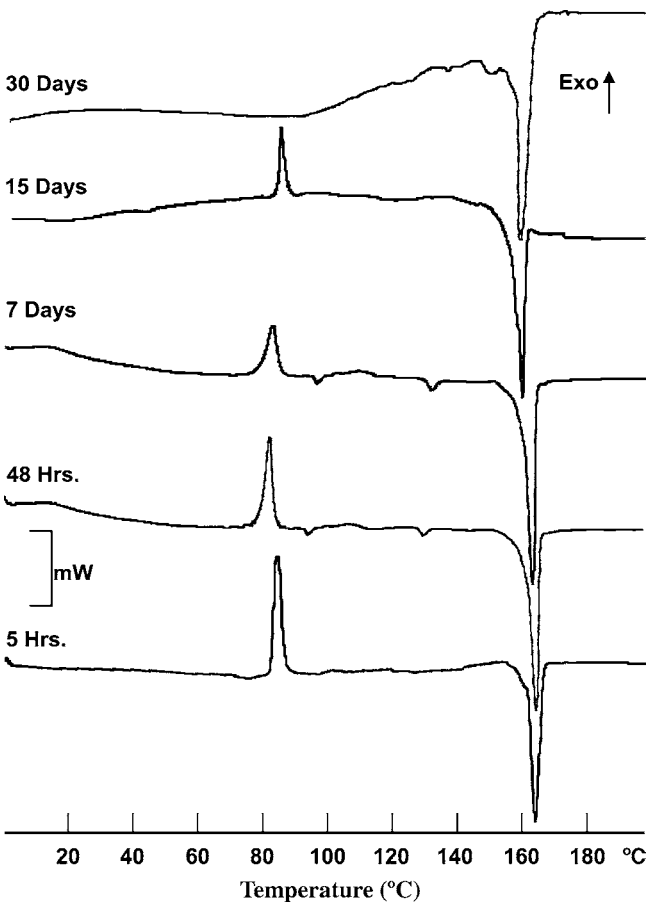

Fig. 8. DSC profiles of stability samples stored at 40°C/75% RH.

Table I. Transitions in DSC Profiles of MSC Celecoxib Stored at Room Temperature

Duration	Crystallization temperature, T_C (°C)	Normalized energy of exotherm (J/g)	Melting temperature, T_M (°C)	Normalized energy of endotherm (J/g)
5 h	92.10	58.33	165.69	99.93
48 h	89.86	56.66	168.03	86.35
7 days	82.89	47.38	164.83	100.20
15 days	83.73	34.62	166.95	80.60
30 days	–	–	167.24	103.24

DSC = differential scanning calorimetry and MSC = melt sonocrystallized.

The XRPD patterns of pure drug, melt quenched, and MSC celecoxib are shown in Fig. 4. The diffractrogram of the pure drug showed sharp and well-defined diffraction peaks. The melt quenched glass produces a halo pattern typical of an amorphous material, where the broad and diffuse maxima are caused by a random arrangement of the constituent molecules. The diffractrogram of MSC celecoxib also showed a diffused pattern, but with an indication of some low intensity peaks in the region of 26° 2θ. The presence of these low intensity peaks is attributed to the presence of a small amount of microcrystalline structures formed in the domains, which received less ultrasonic energy during solidification or crystallization as a result of the plasticizing effect of water. However, quantification of crystalline content is difficult at such low percentage in the mixture.

The solid-state stability of MSC celecoxib was studied at room temperature and at 40°C/75% RH for a period of 30 days using XRPD and DSC as characterization parameters (see Figs. 5–8). The increase in crystallinity during storage at

Table II. Transitions in DSC Profiles of MSC Celecoxib Stored at 40°C/75% RH

Duration	Crystallization temperature, T_C (°C)	Normalized energy of exotherm (J/g)	Melting temperature, T_M (°C)	Normalized energy of endotherm (J/g)
5 h	92.10	58.33	165.69	99.93
48 h	86.83	52.66	164.83	87.35
7 days	76.02	32.36	167.32	82.34
15 days	81.28	25.44	166.90	89.32
30 days	–	–	168.00	82.00

the accelerated conditions is higher compared with the sample stored at room temperature, which is attributed to the higher mobility of the molecules at elevated temperature and in the presence of moisture, leading to crystallization.

The DSC traces of the samples stored at room temperature and 40°C/75% RH are shown in Figs. 7 and 8, respectively, and the derived thermal data are summarized in Tables I and II. Analysis of the sample immediately after production (5 h) did not reveal a glass transition, but stored samples exhibited a T_g value in the range of 52–58°C, indicating that molecular relaxation had occurred during storage. The recrystallization exotherm for samples stored at room temperature occurred in the range of 82.89–92.10°C as compared with 76.02–92.10°C for samples stored at 40°C/75% RH, with higher normalized enthalpy for this exotherm for samples stored at room temperature. The thermal profiles of the samples stored under both conditions showed a decrease in the exotherm during storage of up to 30 days, indicating transformation into the crystalline form, but the XRPD data did not show a complete crystallinity gain, indicating a slower crystal transformation. The rate of transformation is faster in the case of samples stored at 40°C/75% RH. This is consistent with the XRPD data, indicating higher mobility of the molecules at elevated temperature and in the presence of moisture. The difference in the normalized energies for melting endotherms might be as a result of the different rates of relaxation, which cause different crystal structures having different melting temperatures.

The DSC profiles also exhibit low-energy endotherms at 128.6 and 154.32°C, which may be attributed to the transformation to a stable polymorph. The samples stored at 40°C/75% RH also show an additional endotherm, as compared with those stored at room temperature. The DSC trace of the sample stored for 30 days at room temperature showed a sharp and symmetric endotherm. Paradkar *et al.* (12) formed amorphous celecoxib using melt quench technique, which, after storage, showed complete reversal to the crystalline phase after 15 days. Therefore, in comparison with these results, MSC processed remains in the amorphous state for longer periods. The stabilization of the amorphous form has been achieved in the absence of any stabilizing excipients such as polyvinylpyrrolidone (PVP), which acts to increase the T_g and thus prevents the conversion into the crystalline form. Thus, the MSC technique provides an opportunity for particle design for the amorphization of celecoxib and other potential drug substances.

CONCLUSIONS

In present study, celecoxib porous particles were obtained by the MSC technique, which is a combination of melt solidification and ultrasonication. This technique has an advantage of producing particles with desired biopharmaceutical properties without the addition of excipients. Therefore, this promising technique should be further exploited for the preparation of amorphous porous materials.

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