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Preparation and evaluation of ibuprofen beads by melt solidification technique

Anant R. Paradkar*, Manish Maheshwari, Anant R. Ketkar, Bhaskar Chauhan

Department of Pharmaceutics, Poona College of Pharmacy, Bharati Vidyapeeth Deemed University, Erandawane, Pune 411038, Maharashtra, India

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Abstract

A novel single step melt solidification technique was developed for ibuprofen. DSC studies designed to elucidate the effect of isothermal holding time showed that the extent of crystallization increased with holding time. Agitation speed and polyvinyl alcohol (PVA) were found to reduce the time required for crystallization. The excipient-free, non-disintegrating beads were irregular in shape with high mechanical strength and acceptable flowability. Slow dissolution from beads was attributed to the compactness and higher bond strength of the beads.

Keywords: Ibuprofen; DSC; Melt solidification; Non-disintegrating beads; Slow release

1. Introduction

Particle size enlargement is the most widely used operation in pharmaceutical processing. Though conventional granulation enjoys wide popularity, new techniques such as extrusion-spheronization (Gokonda et al., 1994), spherical crystal agglomeration (Kawashima et al., 1985; Kachrimanis et al., 2000; Paradkar et al., 2002), melt extrusion (White et al., 1987; Gruenhagen, 1996; Sprockel et al., 1997) and melt granulation (Schaefer et al., 1990; York and Rowe, 1994; Johansen et al., 1999) are being studied as alternative techniques to overcome the limitations of conventional granulation. These techniques are mainly designed to decrease the number of unit operations and impart desired primary and secondary properties to the particles.

The materials with low melting point such as waxes were used to obtain microcapsules by solidification (Adeyeye and Price, 1997). Ibuprofen, which is chemically α-methyl-4-(2-methylpropyl) benzene–acetic acid is a non-steroidal analgesic and anti-inflammatory drug. It has poor flow properties, cakes easily and exhibits waxy characteristics with low melting point. Particle size enlargement or improvement in micromeritic properties of ibuprofen has been attempted by different techniques (Gordon and Amin, 1984; Appelgren and Ivarsson, 1987; Ho and Blank, 1990; Chen, 1993; Arida et al., 1999; Cox et al., 1999). One of the earlier reports (Hideji et al., 1981) details a process by which the desired granules may be produced by melting ibuprofen powder and cooling the melt. The solidified melt, which comprised of blocks of crystalline ibuprofen, was subsequently

* Corresponding author. Tel.: +91-20-543-7237; fax: +91-20-543-9383.
E-mail address: arparadkar@rediffmail.com (A.R. Paradkar).

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crushed into granules. This multi step process is time consuming. In the present study, attempt has been made to design a single step melt solidification process to obtain the ibuprofen beads having desired pharmaceutical properties. The effect of process variables was also studied. The properties of the beads were compared with the solid blocks obtained by simple melt solidification.

2. Materials and methods

2.1. Materials

Ibuprofen was kindly supplied by Lupin Laboratories (India). Polyvinyl alcohol (PVA), potassium dihydrogen phosphate, sodium hydroxide pellets and ethyl alcohol were of analytical grade (Merck, India).

2.2. Differential scanning calorimetry (DSC)

Effect of isothermal heating time on crystallization of drug was studied. A Mettler-Toledo DSC 821^e equipped with intracooler, a refrigerated cooling system was used (Mettler-Toledo, Switzerland). Indium standard was used to calibrate the DSC temperature and enthalpy scale. Nitrogen was used as a purge gas through DSC cell at the flow rate of 100 ml/min. Ibuprofen (8–10 mg) was hermetically sealed in an aluminum pan and subjected to different heating and cooling cycles with varying isothermal heating time at −30 °C. Each DSC cycle comprised of four steps as, Step-I: 30 to 100 °C (10 °C/min), Step-II: 100 to −30 °C (−10 °C/min), Step-III: isothermal heating at −30 °C (for 0, 20, 40 and 90 min) and Step-IV: −30 to 100 °C (20 °C/min).

2.3. Melt solidification technique 1 (MST1)

Ibuprofen beads were prepared by melt solidification technique as reported earlier (Hideji et al., 1981). Ibuprofen (5 g) was melted at 80 °C on a water bath and solidified by cooling at room temperature in a dessicator for 24 h. The solidified mass was crushed to −14/+16 mesh size by grinding in a mortar. The granular product was evaluated.

2.4. Melt solidification technique 2 (MST2)

2.4.1. Preliminary studies

Ibuprofen powder (2 g) was melted on water bath at 80 °C and poured into 100 ml deionised water in a jacketed crystallization vessel. The system was stirred at 1000 rpm using a constant speed stirrer (Eurostar power control-visc, IKA Labortecnik, Germany) with propeller blade to obtain beads. Temperature was maintained at 30 °C using cryostatic bath (Haake Phoenix C25P, Germany). The beads were separated by filtration and dried at room temperature.

2.4.2. Process optimization

Effect of speed on the time required for crystallization was studied in presence and absence of polyvinyl alcohol (0.001%, w/v) at agitation speed between 300 and 1200 rpm.

The final MST2 was designed with speed of agitation 1200 rpm in presence of 0.001% (w/v) PVA. The beads obtained from this batch were subjected to further evaluation.

2.5. Evaluation of beads

2.5.1. Yield and drug content

Beads were weighed after drying and percent yield was calculated considering complete agglomeration of melted ibuprofen. For determination of drug content, beads (100 mg) were triturated and dissolved in 100 ml ethanol by sonication for 30 min. The solution was filtered and after sufficient dilution with phosphate buffer (pH 7.2) analyzed spectrophotometrically at 222 nm (JASCO-V500, Japan). Drug content was calculated from the calibration curve of ibuprofen in phosphate buffer (pH 7.2).

2.5.2. Surface topography

Samples were coated with a thin gold–palladium layer by sputter coater unit (VG-Microtech, UK) and investigated with a Cambridge Stereoscan S120 scanning electron microscope (SEM, Cambridge, UK), which was operated with an acceleration voltage of 10 kV.

2.5.3. Thin layer chromatography (TLC)

The chemical stability of the solidified melts was studied using TLC. The powdered samples were

dissolved in methanol and spotted on 10 cm × 2.5 cm pre-coated glass plates (silica gel GF, 0.25-mm thickness, Analtech), which were developed with solvent system; methanol and water (6:4) and were detected by placing the plates in a chamber containing iodine vapor.

2.5.4. Infrared spectroscopy (IR)

Fourier-transform infrared (FT-IR) spectra were obtained on Jasco V5300 FT-IR. The pellets were prepared on KBr-press (Spectra lab, India). The spectra were recorded over the wave number range of 3600–400 cm^{-1}.

2.5.5. Differential scanning calorimetry (DSC)

The powdered sample of beads obtained by MST2 was hermetically sealed in an aluminum pan and heated between 30 and 100 °C, with the heating rate of 10 °C/min. All other conditions were same as mentioned in Section 2.2.

2.5.6. X-ray powder diffraction (XRPD)

A mass of ibuprofen beads was pulverized in a mortar. The XRPD patterns of samples were recorded by using a Philips PW 1729 X-ray diffractometer. Samples were irradiated with monochromatized Cu Kα radiation (1.542 Å) and analyzed between 2 and 50° (2θ). The voltage and current used were 30 kV and 30 mA, respectively. The range and the chart speed were 2×10^3 CPS and 10 mm/2θ, respectively.

2.5.7. Micromeritic properties

Particle size distribution was studied by sieve analysis technique using Ro-tap sieve shaker (Labtronics, India). Flowability of beads (−16/+24 mesh fraction) was assessed by determination of angle of repose (θ) using fixed funnel method. The beads were subjected to bulk density determination using Tap density tester USP II (Electrolab ETD-1020, India).

2.5.8. Image analysis

For image analysis the images were captured using a stereomicrosope (Carl Zeiss, Germany) attached with a digital camera (Watec, WAT-202, Japan). The captured images were analyzed using Biovis Image Plus Software (Expert Tech Vision, India). Around 50 beads were analyzed. Average diameter and different shape factors such as circularity factor, elongation, roundness and perimeter ratio were determined (Biovis Image Plus, 2002).

2.5.9. Mechanical strength

Crushing strength of beads (−14/+18 mesh fraction) was determined using mercury load cell method (Jarosz and Parrott, 1983).

2.5.10. Dissolution studies

The dissolution studies were performed using USP 24 type II dissolution apparatus (Electrolab TDT-06P, India). Ibuprofen beads (−14/+18 mesh fraction) equivalent to 300 mg were placed at the bottom of the dissolution vessel containing 900 ml phosphate buffer (pH 7.2) maintained at 37 ± 0.5 °C and stirred with paddle at 100 rpm. Samples were collected periodically and replaced with dissolution medium. After filtration through Whatman filter paper 41, concentration of ibuprofen was determined spectrophotometrically at 222 nm (JASCO-V500, Japan).

3. Results and discussion

Ibuprofen due to its characteristic properties has been studied extensively for design of particle size enlargement technique. Previously reported melt solidification technique (MST1) for ibuprofen is time consuming particularly in the cooling stage and requires further crushing to obtain desired particle size (Hideji et al., 1981).

DSC studies were carried out to elucidate the energy changes during crystallization from melt. Each DSC cycle comprised of four steps viz. heating, cooling, isothermal heating at −30 °C followed by heating (Section 2.2). The conditions and the transitions for first two steps were same as shown in Fig. 1. It showed a melting endotherm at 76.9 °C. No transition was observed in the cooling step indicating T_g less than −30 °C. The DSC thermograms of third and fourth step of different cycles are shown in Fig. 2. These thermograms showed characteristic exotherm followed by an endotherm indicating crystallization and melting of ibuprofen. The ratio of normalized energies of endotherm to exotherm (Table 1) was found to decrease linearly ($R = 0.985$) indicating increase in the extent of crystallization. Thus, increase in isothermal holding time favored collisions and in turn crystallization

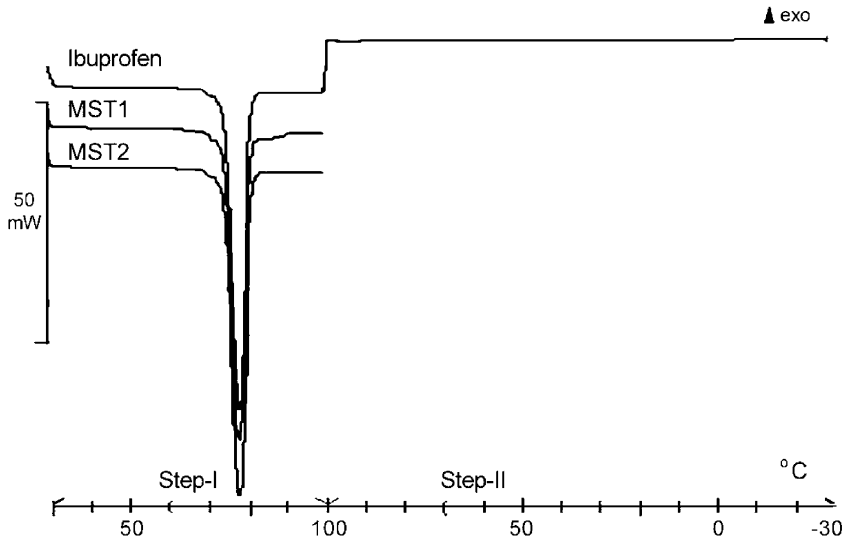


Fig. 1. DSC thermograms of ibuprofen and ibuprofen beads obtained by MST1 and MST2.

of ibuprofen. It revealed that increase in collisions by agitation might cause faster crystallization of ibuprofen melt.

MST1, which did not involve agitation, required significantly longer crystallization time (30–45 min). The solidification resulted in formation of isolated hemispherical beads (Fig. 3), which were crushed into a granular mass.

In case of MST2 as ibuprofen melt is immiscible with water and remains pourable due to its low T_g,

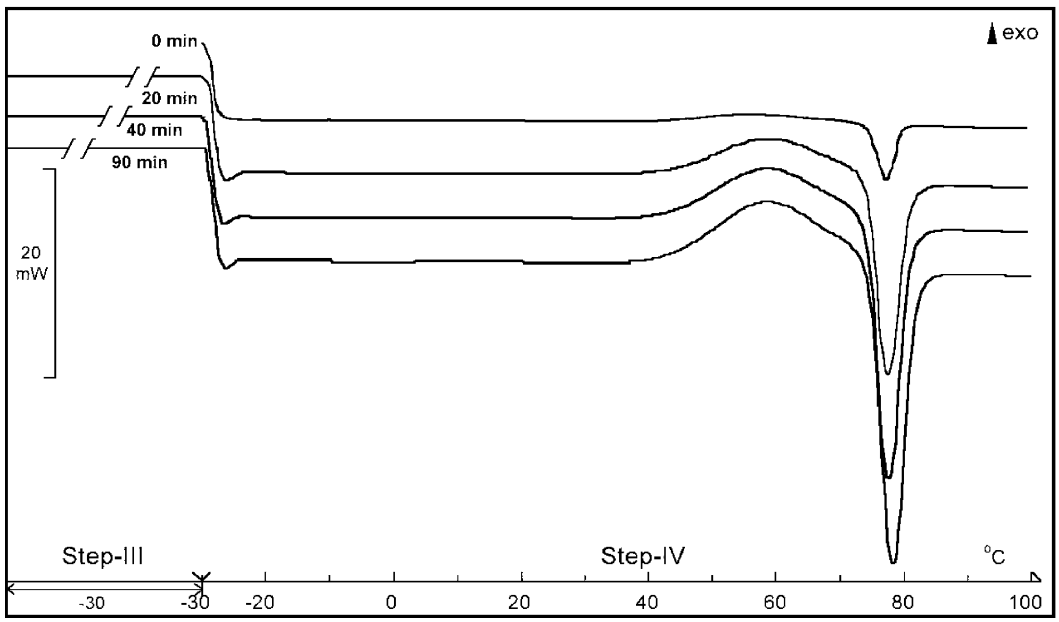


Fig. 2. Effect of isothermal holding time on DSC thermograms of ibuprofen.

Table 1
Transitions in DSC thermograms of ibuprofen

Isothermal heating time at −30 °C (min)	Normalized energy of exotherm, E1 (J/g)	Normalized energy of endotherm, E2 (J/g)	Ratio of E2/E1
0	6.29	8.56	1.361
20	16.43	21.9	1.333
40	23.31	29.1	1.248
90	30.55	35.4	1.158

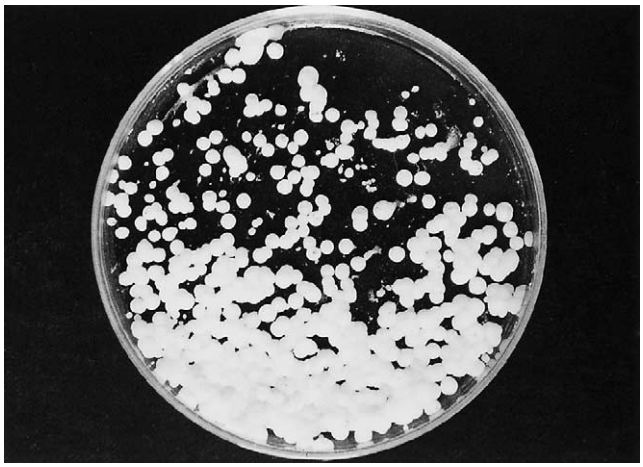


Fig. 3. Photograph of ibuprofen beads obtained by MST1.

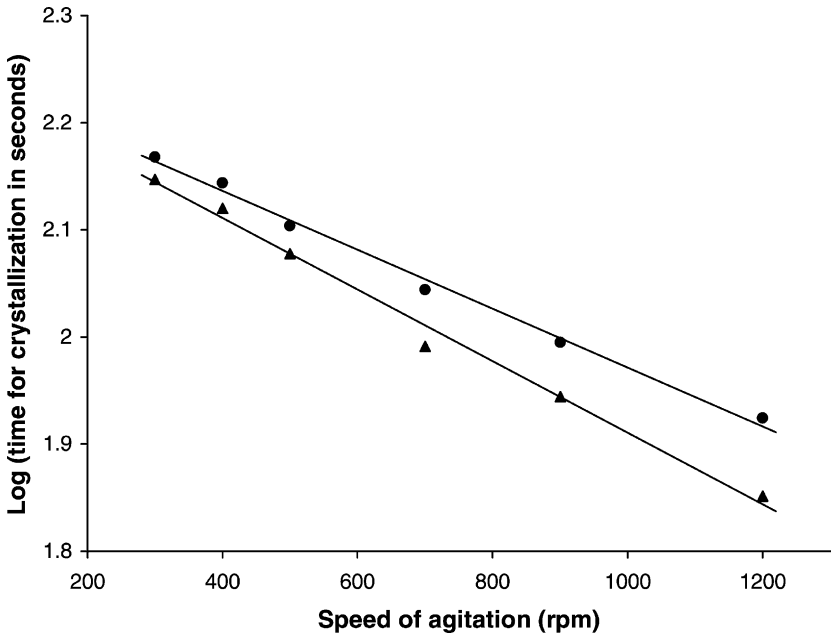


Fig. 4. Effect of speed of agitation on crystallization time of ibuprofen: (●) without PVA; (▲) with PVA (0.001%, w/v).

it can be dispersed easily into droplets by agitating in water. The preliminary experiment at the agitation speed of 1000 rpm resulted in faster solidification of ibuprofen melt, in the form of beads in 1.5–2.0 min. This was in accordance with the hypothesis made on the basis of DSC studies. As shown in Fig. 4, the time required for crystallization decreased logarithmically with increase in speed of agitation.

It was observed that at lower speeds, significantly larger beads were obtained. Also there was a significant loss of ibuprofen due to adherence of solidified mass to the propeller blades. Incorporation of 0.001% (w/v) PVA to the system due to its surfactant nature reduced the losses due to sticking to propeller blade. PVA also reduces the droplet size, thereby, increasing the surface area, which in turn increases effective shear per unit volume. Thus, it also reduced the time for crystallization in case of MST2 (Fig. 4).

TLC of both the samples showed $R_f = 0.6$ and the characteristic peaks in the IR spectra were IR (KBr) cm^{-1}: 1720 (C=O stretching), 2955 (bonded O–H stretching) (Fig. 5). DSC thermograms of beads obtained by MST1 and MST2 (Fig. 1) showed melting endotherms at 76.8 and 76.6 °C, respectively. In addition to this, no difference was observed in the *d*-values in the XRPD pattern of MST2 (Fig. 6). The intensities of X-ray diffraction were slightly higher for MST2 confirming no transition during processing.

The yield of beads by MST2 was in the range of 92–94% (w/w) with drug content of 97–99% (w/w). Microphotographs of beads are shown in Fig. 7. The beads obtained by MST2 were dense, irregular in

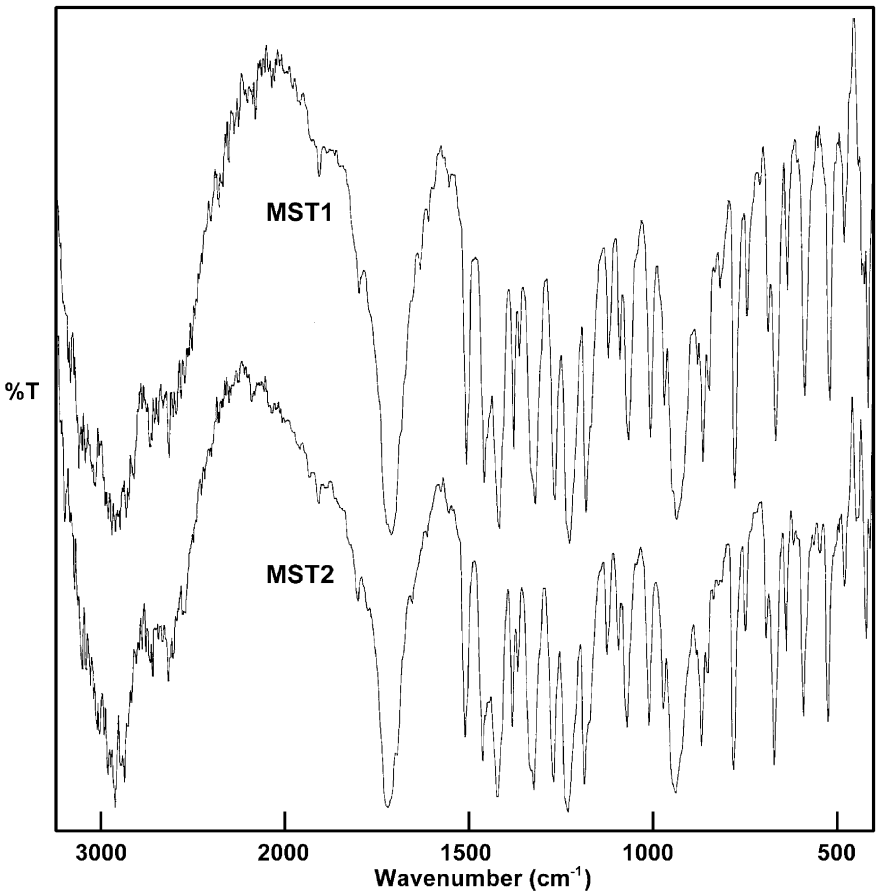


Fig. 5. FT-IR spectra of ibuprofen beads obtained by MST1 and MST2.

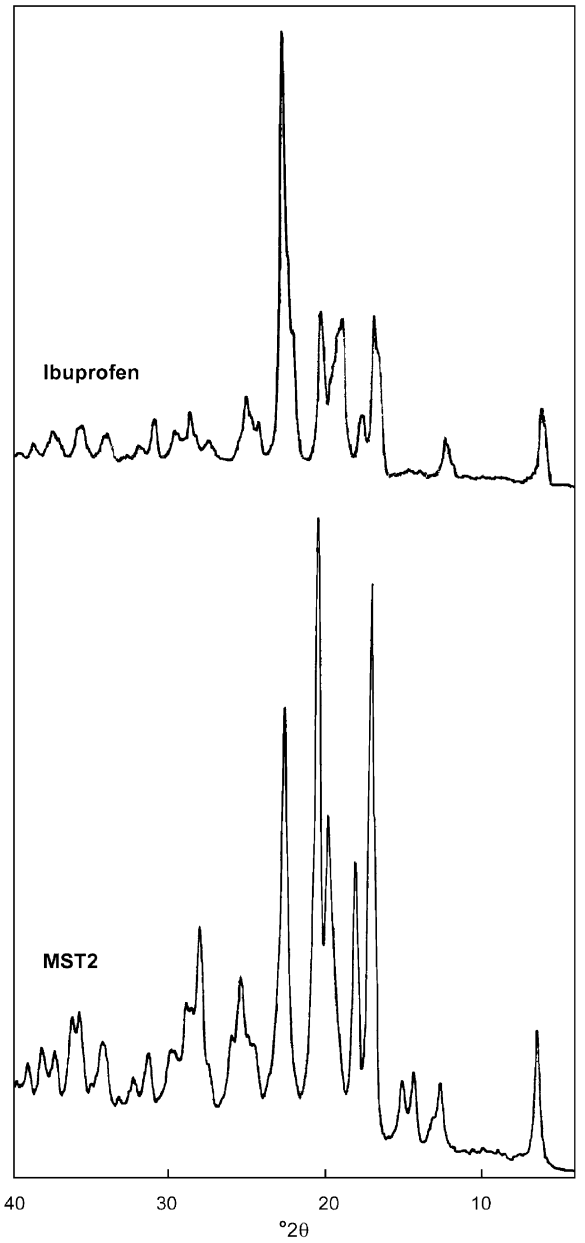
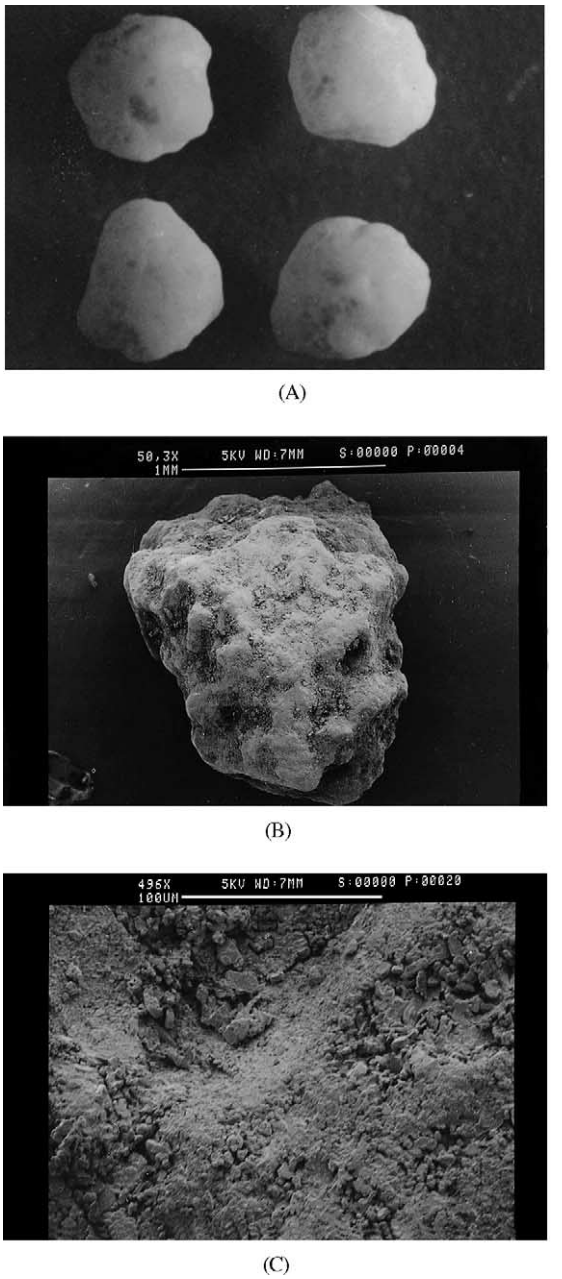


Fig. 6. X-ray powder diffraction patterns of ibuprofen and ibuprofen beads obtained by MST2.



(A)

(B)

(C)

Fig. 7. Photomicrographs of ibuprofen beads obtained by MST2: (A) Stereomicropy at 62.5× (B) SEM at 50.3× (C) SEM at 496×.

shape with rough surface. The particle size distribution curve is shown in Fig. 8. The micromeritic and mechanical properties of the beads obtained by MST2 are summarized in Table 2. The beads exhibited satisfactory flowability and significantly high crushing strength. Mechanical strength of a solid material depends on the number of bonds formed and strength of the individual bond. In conventional granulation these bonds are formed due to precipitated binder

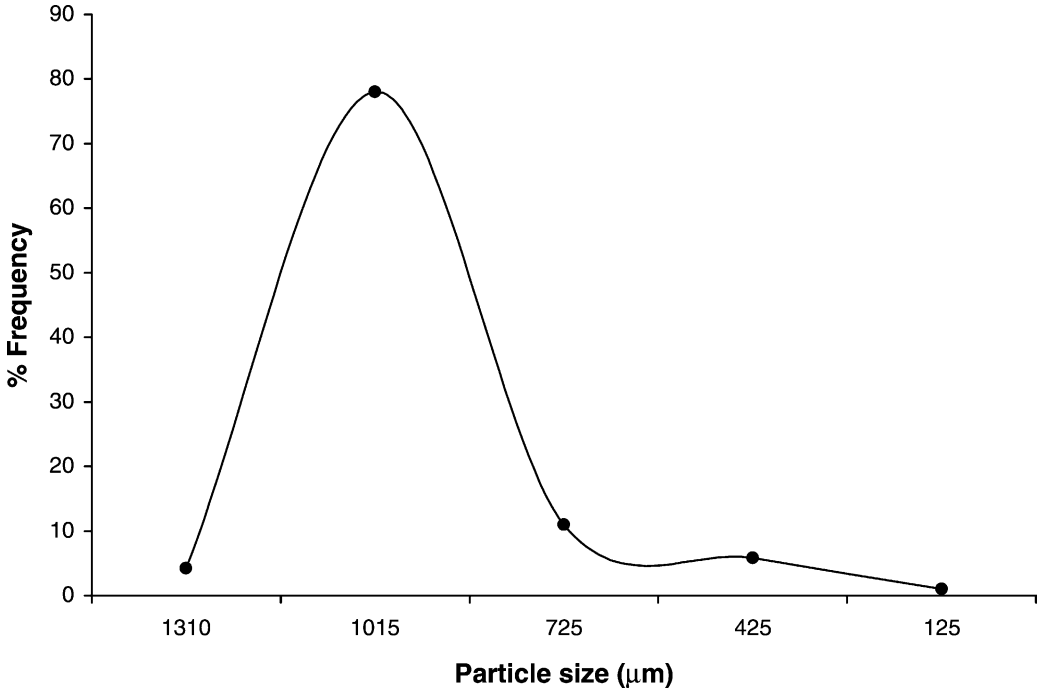


Fig. 8. Particle size distribution curve of ibuprofen beads obtained by MST2.

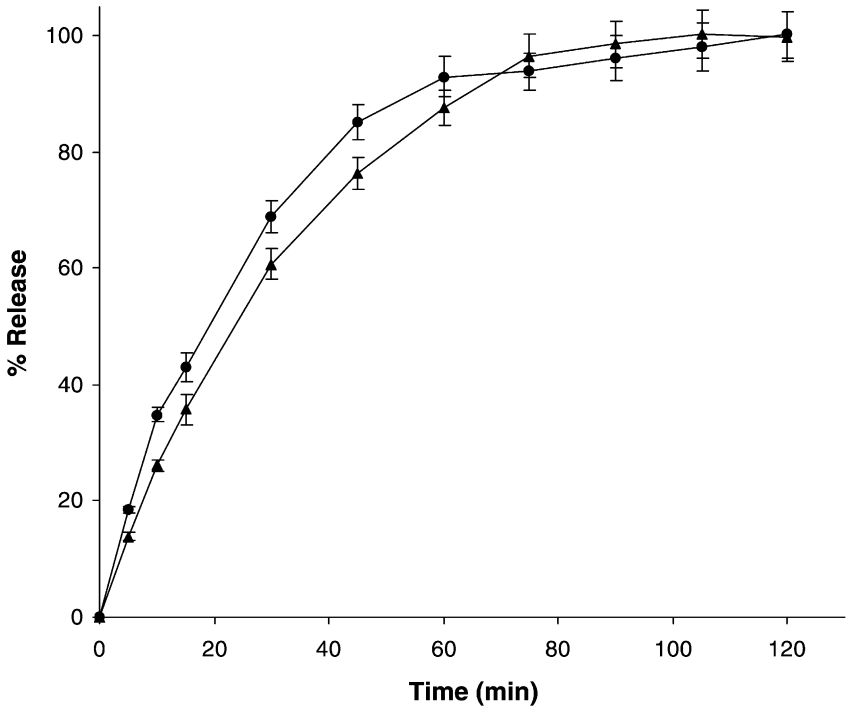


Fig. 9. Dissolution profiles of ibuprofen beads obtained by MST1 (●) and MST2 (▲).

Table 2
Micromeritic and mechanical properties of ibuprofen beads obtained by MST2

Parameter	Value
Diameter (μm)	995.2 ± 43.1
Circularity factor	1.370 ± 0.157
Elongation	1.131 ± 0.142
Roundness	0.722 ± 0.043
Perimeter ratio	0.849 ± 0.025
Angle of repose (°)	33.43 ± 0.46
Bulk density (g/cm^3)	0.469 ± 0.018
Tap density (g/cm^3)	0.527 ± 0.019
Crushing strength (g)	309.7 ± 31.5

joining the two particles. In beads obtained by melt solidification technique, the bonds were formed by the solidified melt of the ibuprofen itself. These high strength bonds may be responsible for high compactness and mechanical strength of the beads.

The dissolution profile of beads obtained by MST1 and MST2 did not show any significant difference (Fig. 9) as both the techniques involve formation of melt-solidified bonds. The slow release of drug from non-disintegrating beads of ibuprofen may be attributed to high mechanical strength and compactness of the mass.

The present technique involves solidification of ibuprofen melt in presence of significantly low concentration of PVA in water (1 mg/100 ml). Due to water solubility of PVA, hydrophobic nature of the melt and a very high water:melt ratio (100:2) the chances of partitioning of PVA in the solidified melt are negligible. The beads passed the official standards prescribed for pure ibuprofen. Hence, the beads obtained by MST2 could be claimed as non-disintegrating, excipient free beads.

4. Conclusion

Ibuprofen due to its low melting point, significantly low T_g, and water immiscibility of melt, was subjected to particle size enlargement by MST2. The crystallization time was lowered with increase in speed and addition of PVA. As compared to conventional size enlargement techniques and MST1, MST2 offers a single step process with significantly low processing time yielding excipient-free, slow release, non-disintegrating beads. This technique can be further explored for improvement of sphericity and extended release with the aid of proper additives and process variables.

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