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Preparation and Characterization of Flurbiprofen Beads by Melt Solidification Technique

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ABSTRACT

A melt solidification technique has been developed to obtain sustained-release waxy beads of flurbiprofen. Low glass transition temperature (t_g) and shear-induced crystallization of flurbiprofen made it a suitable candidate for melt solidification technique. The process involved emulsification and solidification of flurbiprofen-cetyl alcohol melt at significantly low temperature (5°C). The effect of variables, namely, the amount of cetyl alcohol and the speed of agitation, was studied using 3^2 factorial design. The technique and the beads were evaluated on the basis of process and desired yield, surface topography, Fourier-transform infrared (FT-IR), differential scanning calorimetry (DSC), particle size distribution, crushing strength, and drug release. Average values for process and desired yields were 97% wt/wt and 26% wt/wt, respectively. No interaction was observed between drug and excipient. Multiple regression analysis was carried out, and response surfaces were obtained. A curvilinear relationship was observed between percentage of desired yield and the amount of cetyl alcohol. Linear decrease in crushing strength was observed with increase in the amount of cetyl alcohol. Drug released from the beads followed zero order kinetics. Burst release was shown to a greater extent in beads containing a lower amount of cetyl alcohol. Response surfaces of time required for certain percentage of drug (t_D%) showed that after critical concentration of about 20% of cetyl alcohol (400 mg/batch), no significant release retardant effect was observed.

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KEYWORDS: flurbiprofen, melt solidification technique, factorial design, cetyl alcohol, response surface methodology, zero order kinetics

INTRODUCTION

Attempts are continuously made to reduce the use of organic solvents in the processing of pharmaceuticals. Various particle size enlargement techniques, which offer freedom from solvents include, melt granulation, melt extrusion, melt dispersion, and pastillation.[1-5] Development of new lipophilic excipients has provided impetus to the research in the area of processing techniques involving molten state.[6]

Melt dispersion technique involves emulsification of molten drug or drug-excipient mixture in an aqueous system, followed by cooling. This technique has been applied for lipophilic drugs (eg, ibuprofen).[7,8] Melt dispersion is generally carried out at temperature above melting point of drug. But recently, Paradkar et al[9] demonstrated that ibuprofen has low glass transition temperature (t_g) (<-30°C); hence, ibuprofen melt maintains liquid state for a sufficiently longer period of time, even at very low temperature. Therefore, in such cases melt emulsification can be carried out below the melting point of the drug. On the basis of these properties, a melt solidification technique (MST) for ibuprofen beads was designed, in which emulsification and solidification of the melt in an aqueous phase were carried out at 5°C. The beads obtained using this technique exhibited slow drug release, which was attributed to the formation of melt-solidified bonds. Similarly, the ibuprofen beads containing a low percentage of waxy material cetyl alcohol (up to 12.5% wt/wt) were obtained using MST, in which drug release was further retarded up to 8 hours.[10] Low processing temperature reduces processing time and drug loss because of a decrease in the aqueous solubility of drug.

Flurbiprofen, 2-(2-flurobiphenyl-4yl) propionic acid is a nonsteroidal antiinflammatory drug used to treat rheumatoid arthritis, osteoarthritis, and mild to moderate pain.[11] The gastrointestinal irritation and ulcerogenic effect along with

Table 1. Experimental Design With Coded Levels and Actual Values of Variables*

Batch	Variable X1 Amount of Cetyl Alcohol (mg)	Variable X2 Speed of Agitation (rpm)
3001	300 (–1)	700 (–1)
3002	300 (–1)	900 (0)
3003	300 (–1)	1100 (1)
4001	400 (0)	700 (–1)
4002†	400 (0)	900 (0)
4003	400 (0)	1100 (1)
5001	500 (1)	700 (–1)
5002	500 (1)	900 (0)
5003	500 (1)	1100 (1)

*Values in parentheses indicate coded levels.
†Batch No. 4002 was repeated three times.

the short half-life (3-4 hours) has led to the design of sustained-release formulation of flurbiprofen. But as its melting point (117°C) is above 100°C, conventional melt dispersion technique, which involves melt emulsification above the melting point of the drug, is not possible.

The basic aim of this work was to investigate suitability of melt solidification technique for obtaining sustained-release beads of flurbiprofen. Hence, the proposed technique has been designed with emulsification and solidification at 5°C. Because of the ability of cetyl alcohol (CA) to solidify simultaneously with flurbiprofen under the processing condition, it was selected as an emulsifier and release retardant. The effect of speed of agitation and amount of CA on the properties of beads was studied using 3^2 factorial design. Process optimization was carried out using response surface methodology. The beads were characterized using scanning electron microscope (SEM), differential scanning calorimetry (DSC), powder x-ray diffraction (PXRD), and Fourier-transform infrared (FT-IR). The effect of variables on the yield, micromeritic properties, crushing strength, and various release parameters were evaluated.

MATERIALS AND METHODS

Materials

Flurbiprofen was a gift from FDC Limited, Mumbai, India. Cetyl alcohol, sodium hydroxide, potassium dihydrogen phosphate, and ethyl alcohol were of analytical grade (Merck, Mumbai, India).

Methods

Differential Scanning Calorimetry

To judge the suitability of drug for MST, DSC study was carried out. A DSC thermogram of flurbiprofen was obtained using Mettler-Toledo DSC 821^e instrument equipped with an intracooler (Mettler-Toledo, Greifensee, Switzerland). Indium standard was used to calibrate the DSC temperature and enthalpy scale. Flurbiprofen was hermetically sealed in an aluminum pan and subjected to 3 different heating and cooling steps: Step I, 20°C to 150°C (10°C/min); Step II, 150°C to -30°C (-10°C/min); Step III, -30°C to 150°C (10°C/min).

Preparation of Beads

A mixture of flurbiprofen (2g) and CA was melted and stirred on a water bath maintained at 120°C to form a uniform molten mass. The flurbiprofen-CA melt was poured in 100 mL water maintained at 5°C using cryostatic bath (Haake Phoenix C25P, Karlsruhe, Germany) and was stirred continuously using a constant speed stirrer with propeller blade (Eurostar power control-visc, IKA Labortecnik, Staufen, Germany). The flurbiprofen-CA beads obtained after solidification of dispersed droplets were separated by filtration and dried at room temperature.

Effect of Variables

To study the effect of variables, batches were prepared using 3^2 factorial design. Speed of agitation and amount of CA were selected as 2 independent variables. Coded and actual values of variables for each batch and experimental design are given in **Table 1**.

Evaluation of Beads

Yield and Drug Content

Beads were weighed after drying and process yield and desired yield (-14/+18 sieve fraction) were calculated. For determination of drug content, 100-mg beads were triturated and dissolved in 100 mL ethanol by sonication for 30 minutes. The solution was analyzed spectrophotometrically at

247 nm (JASCO-V500, Tokyo, Japan) after sufficient dilution with phosphate buffer (pH 7.2).

Surface Topography

Flurbiprofen-CA beads were coated with a thin gold-palladium layer by sputter coater unit (VG-Microtech, UK), and the surface topography was analyzed with a Cambridge Stereoscan S120 scanning electron microscope (Cambridge, UK) operated at an acceleration voltage of 10 kV.

Infrared Spectroscopy

Fourier-transform infrared (FT-IR) spectra of drug, CA, and beads were obtained on JASCO V5300 FT-IR. The pellets were prepared on KBr-press (Spectra Lab, Mumbai, India). The spectra were scanned over the wave number range from 3600 to 400 cm^{-1}.

Differential Scanning Calorimetry

Thermograms of flurbiprofen and flurbiprofen-CA beads were obtained using a Mettler-Toledo DSC 821^e instrument equipped with an intracooler. Indium standard was used to calibrate the DSC temperature and enthalpy scale. The powdered sample of beads was hermetically sealed in an aluminum pan and heated at a constant rate of 10°C/min, over a temperature range of 30°C to 120°C. Inert atmosphere was maintained by purging nitrogen at the flow rate of 100 mL/min.

X-ray Powder Diffraction

A mass of flurbiprofen beads was pulverized in a mortar. The x-ray powder diffraction (XRPD) patterns of samples were recorded using a Philips PW 1729 x-ray diffractometer (Legroupe Interconnexion, Saint-Juile, Qubec, Canada). 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 cycle per second and 10 mm/2θ, respectively.

Particle Size Distribution

Particle size distribution was studied by sieve analysis technique using Ro-tap sieve shaker (Labtronics, Pune, India).

Crushing Strength

Crushing strength of granules (-14/+18 mesh fraction) was determined using the mercury load cell method as described by Jarosz and Parrott[12] on specially fabricated crushing strength apparatus (Seema Enterprises, Pune, India).

Dissolution Studies

The dissolution studies were performed using United States Pharmacopeia 26 type II dissolution test apparatus (Electrolab TDT-06P, Mumbai, India). Flurbiprofen-CA beads (-14/+18 mesh fraction) equivalent to 300 mg drug were placed in the dissolution vessel containing 900 mL phosphate buffer (pH 7.2), maintained at 37°C ± 0.5°C, and stirred at 100 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper 41, the concentration of flurbiprofen was determined spectrophotometrically at 247 nm. Analysis of data was done using PCP Disso v2.08 software (Poona College of Pharmacy, Pune, India).

RESULTS AND DISCUSSION

Melt solidification and melt dispersion techniques basically involve emulsification of melt followed by solidification of the droplets. The melt should be immiscible with the external phase and undergo emulsification with low shear. In melt dispersion technique, emulsification of melt is carried out at temperature above the melting point of the drug. But our recent report[9] on ibuprofen has shown that melt remains in liquid state up to a very low temperature and for a sufficient length of time, so that it can be emulsified below its melting point. On the basis of this, MST was designed to obtain ibuprofen beads.[9] Because of its high melting point (114-117°C) flurbiprofen was never considered as a candidate for melt dispersion technique; however, in the present study flurbiprofen waxy beads were obtained by MST.

Thermal properties of flurbiprofen were studied using DSC (**Figure 1**). DSC thermogram showed a sharp melting endotherm at 117°C. On cooling to -30°C, the melt did not exhibit any exotherm due to crystallization. Reheating of the mass again up to 150°C has shown t_g at -4.65°C and crystallization exotherm at 54.63°C. The normalized energy of crystallization and fusion were 44.6 J/g and 95.9 J/g, respectively. Thus, flurbiprofen maintains its liquid state for a sufficient period of time even at very low temperature.

In order to study crystallization from melt, the molten mass was poured into a petri dish and placed in a dessicator. The crystallization started after about 15 to 20 minutes. The time required for crystallization of melt was significantly affected

Figure 1. Effect of heating and cooling treatments on flurbiprofen: Step I, 20˚C to 150˚C; Step II, 150˚C to −30˚C; Step III, −30˚C to 150˚C. Heating and cooling rates were 10˚C/min.

by the shear provided during agitation. But the beads obtained were not spherical. CA was selected as the waxy excipient; it works as a release retardant and emulsifier, imparting sphericity to the beads and resulting in sustained drug release.

During MST, the molten mixture of flurbiprofen and CA (15-25% wt/wt) was emulsified in the aqueous phase maintained at 5°C. The emulsified melt was solidified during agitation. The solidification properties and proportion of waxy excipient play an important role in designing the technique. Faster or slower solidification of wax as compared with drug may cause separation of waxy flakes. At processing temperature (5°C), use of more than 25% wt/wt of CA has shown separation of waxy flakes.

Drug content of various batches was in the range of 72.82% wt/wt to 81.17% wt/wt. Standard deviation of average drug content is ±1.06 ($P < .05$). No significant difference was found between the drug content of various batches.

The beads obtained were spherical with a smooth surface. SEM photomicrographs of flurbiprofen beads, before and after dissolution are shown in **Figure 2**. The beads were compact with uniform surface coating and did not contain any pinholes. SEM photomicrographs of flurbiprofen beads containing different percentages of cetyl alcohol (**Figure 3**) revealed that the surface texture of beads becomes smoother as the percentage of CA is increased.

The FT-IR spectra of flurbiprofen- and melt-solidified beads (**Figure 4**) showed characteristic broad peak of flurbiprofen in the range of 2500 to 3500 cm^{-1} due to hydrogen bonding. The characteristic peaks of flurbiprofen at 1698 cm^{-1} and 2920 cm^{-1} were due to carbonyl and hydroxyl stretching, respectively.

DSC thermogram of flurbiprofen and flurbiprofen beads are shown in **Figure 5**. DSC thermogram of pure drug has shown a melting endotherm at 117°C with normalized energy of 93.4 J/g. The thermogram of flurbiprofen beads showed 2 endotherms at 50.4°C and 111.2°C, with energies of 16.1 J/g and 81.0 J/g, respectively. These may be attributed to melting of CA and flurbiprofen, respectively. The flurbiprofen melting onset temperature decreased because of the presence of CA in the beads. X-ray powder diffractrograms of drug and beads have shown no significant difference in the inter planar distance (d) values and a slight decrease in peak intensity in the PXRD spectra of beads, possibly as a result of the dilution effect.

Various batches of flurbiprofen CA beads were prepared as per 3^2 design. Responses obtained from the batches of factorial design experiments were subjected to multiple regression analysis using PCP Disso v2.08 software. The data were fitted into Equation 1.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{12} X_1 X_2 \qquad (1)$$

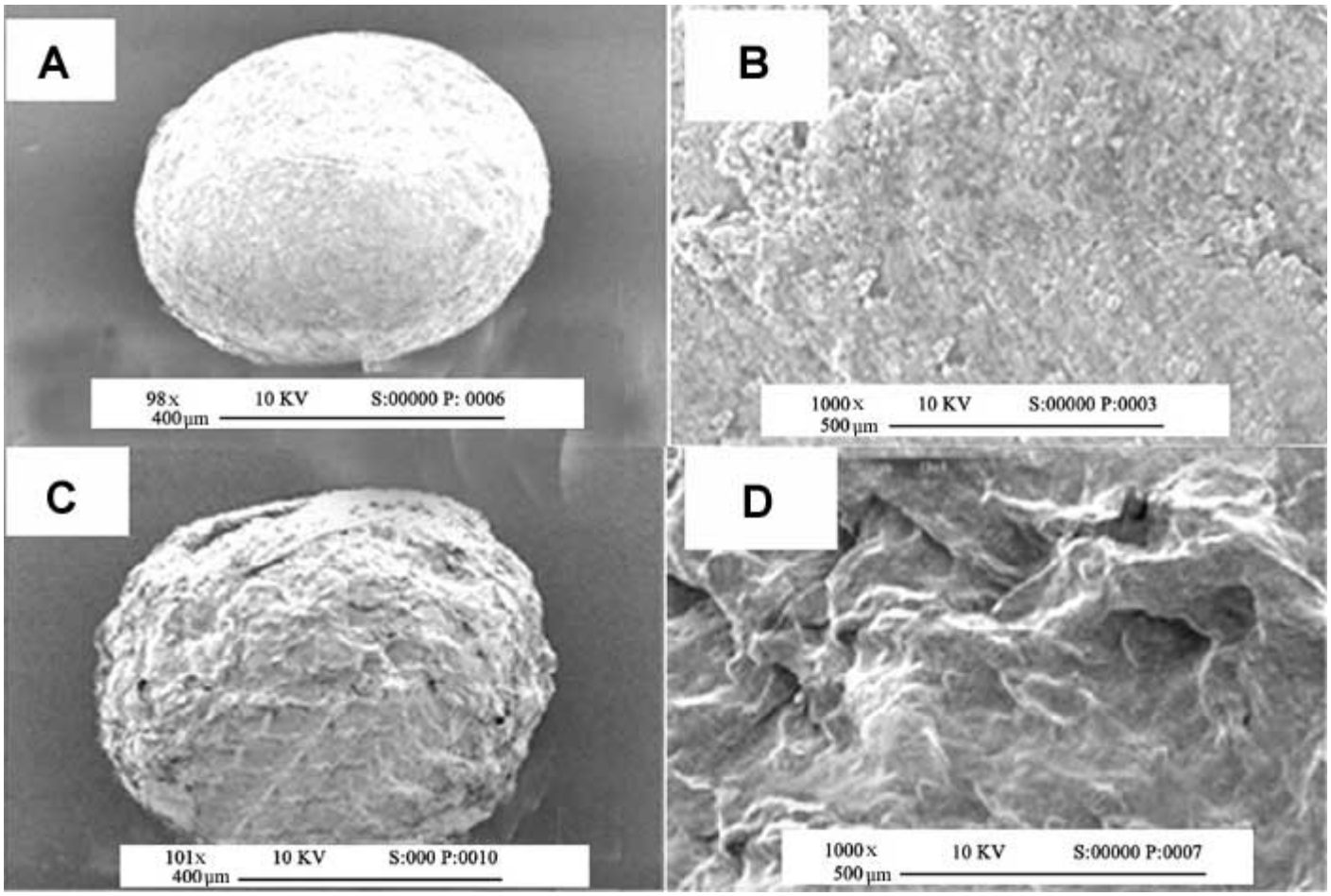

Figure 2. SEM photomicrographs of flurbiprofen CA beads: (A) before dissolution at original magnification 98x, (B) before dissolution at original magnification 1000x, (C) after dissolution at original magnification 101x, and (D) after dissolution at original magnification 1000x.

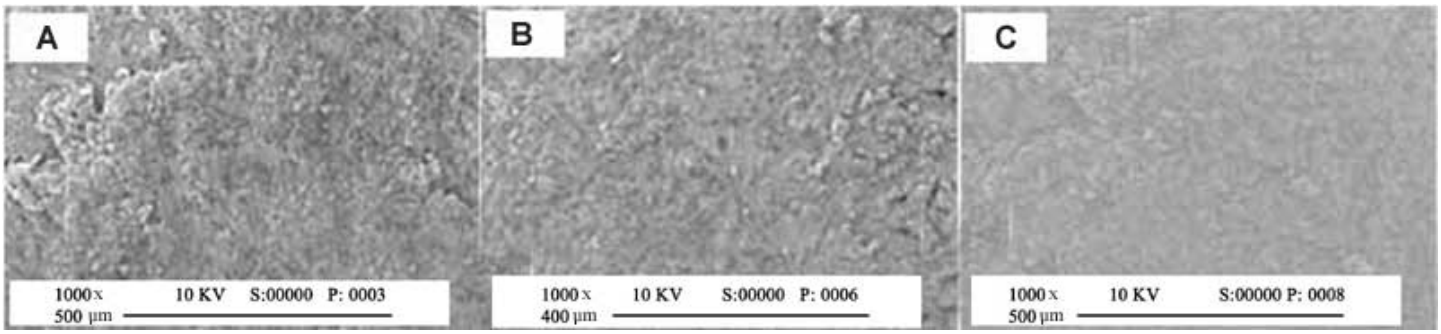

Figure 3. SEM photomicrographs of surfaces of different batches: (A) batch 3001, (B) 4001, and (C) 5001.

The response surface plots were generated after removal of insignificant variables by backward elimination method, and the adequacy of fitted model was checked by analysis of variance (ANOVA). The results of multiple regression analysis are summarized in **Table 2**.

The process yield of various batches was in the range of 94.78% to 98.71% wt/wt. The beads in the size range of -14/+18 are suitable for capsule filling; hence, yield in this range was considered as desired yield. The desired yield of beads from various batches was between 14% and 39% wt/wt. The effect of variables on the desired yield is shown in **Figure 6**. The desired yield revealed a curvilinear response to the amount of CA but experienced only a slight increase due to an increase in the speed of agitation over the range studied.

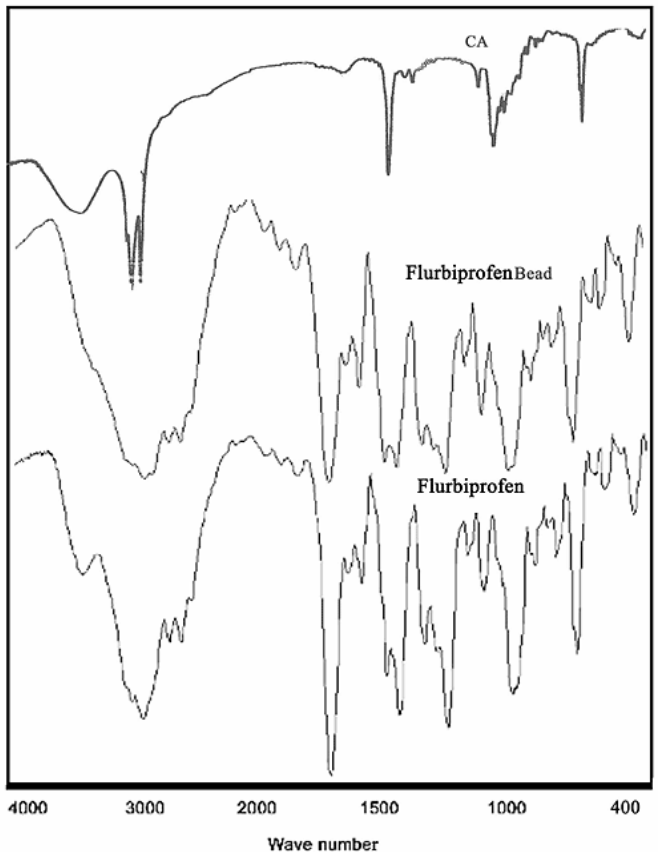

Figure 4. FT-IR spectra of flurbiprofen and flurbiprofen beads.

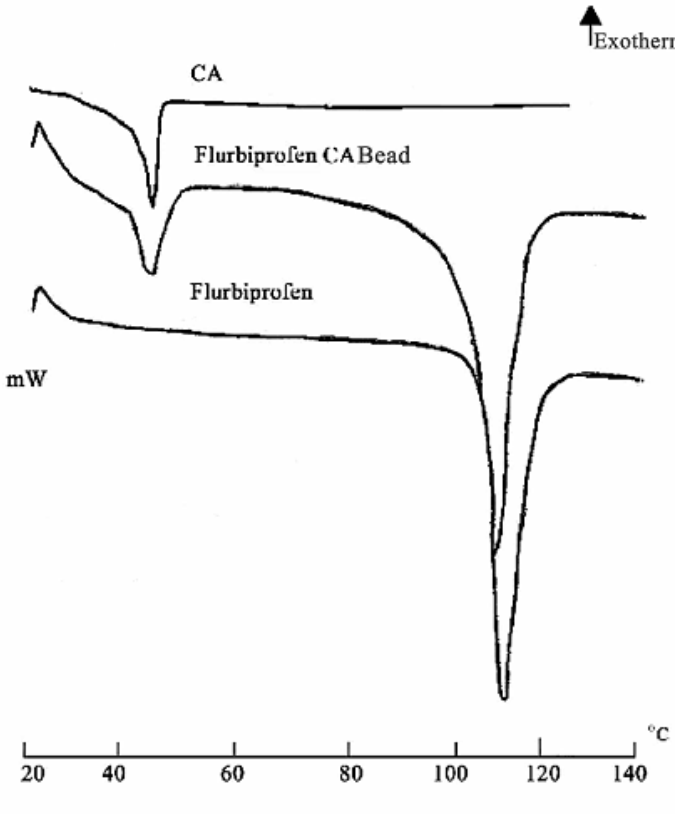

Figure 5. DSC thermograms of flurbiprofen and flurbiprofen beads.

Table 2. Summary of Regression Results for the Measured Responses*

Parameters	Coefficients							
	β_0	β_1	β_2	β_{11}	β_{22}	β_{12}	r^2	P
% Yield (−14/+18#)	30.6	−0.788 (.0016)*	1.246 (.0032)	−8.785 (.0002)		−2.12 (.0000)	0.9879	0.0004
Crushing Strength	74.74	−10.13 (.0009)	4.60 (.0000)				0.9767	0.0000
$t_{50\%}$	419.48	46.74 (.0000)		−23.44 (.0069)			0.9688	0.0001
$t_{90\%}$	822.79	77.36 (.0007)		−45.36 (.0013)			0.9906	0.0000

*Values in parentheses indicate *P* value associated with each term.
† t is the time required for 50 % and 90 % release of the drug.

Particle size distribution curves for various batches are shown in **Figure 7**. Reduction in particle size occurs because of increased shear with speed of agitation. Reduced coalescence due to CA causes reduction in particle size; hence, the desired yield increases with an increase in the amount of CA up to a certain level, above which the undersize fraction (<18) increases and causes a decrease in the desired.

The force required to crush the beads was in the range of 60 to 90g. The effect of variables on crushing strength is shown in **Figure 8**. Crushing strength of the beads depends on the number of bonds formed by the solidified melt of flurbiprofen itself and the strength of the individual bond. Incorporation of CA reduces the number and strength of melt-solidified bonds exhibiting reduction in crushing strength. The rate of solidification of drug is shear dependent; hence, the number of bonds formed increases with agitation, causing an increase in crushing strength. The dissolution profiles of various batches are shown in **Figure 9**. The dissolution study was carried out in phosphate buffer (pH 7.2). The dis-

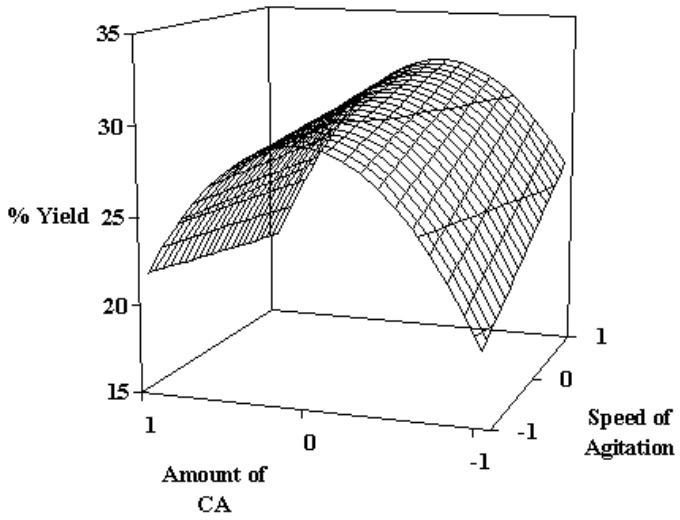

Figure 6. Effect of variables on the percentage of desired yield of flurbiprofen beads.

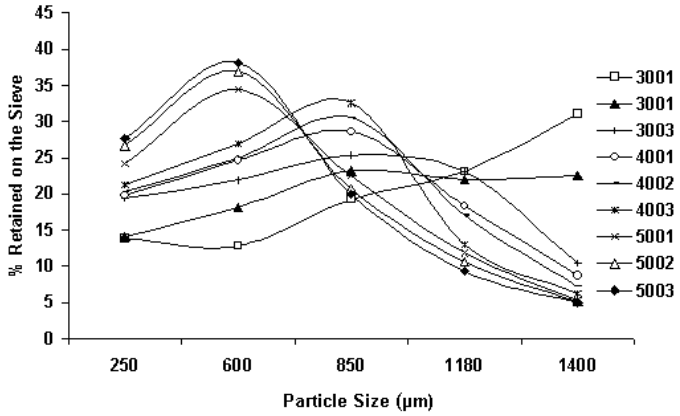

Figure 7. Particle size distribution curves for flurbiprofen CA beads for different batches.

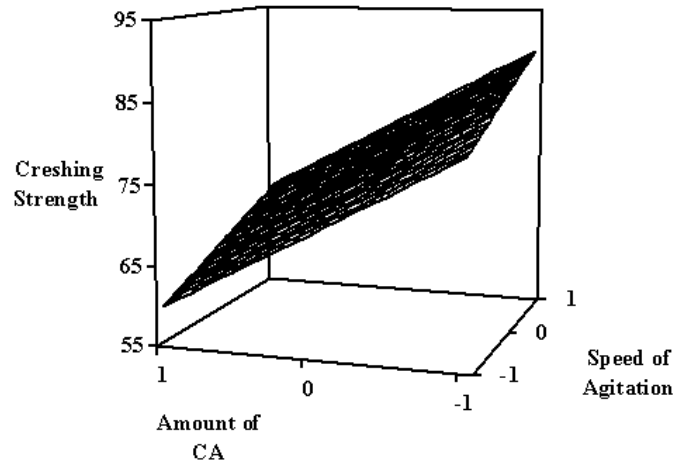

Figure 8. Effect of variables on crushing strength of flurbiprofen beads.

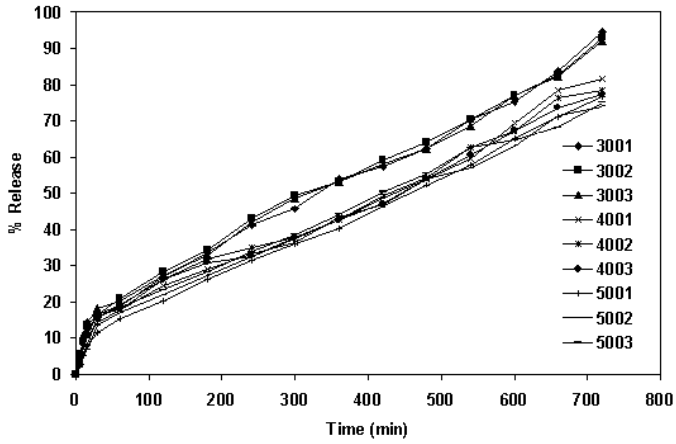

Figure 9. Dissolution profile of flurbiprofen beads from different batches.

solution data analysis was carried out using PCP Disso v2.08 software.

The drug release profiles revealed that about 10% to 15% of drug is released within the first 30 minutes. This finding may be attributed to fast dissolution of drug on the surface. In a similar way, significantly faster release was obtained from beads containing a lower percentage of CA. The release controlling effect of CA decreases after 8 to 9 hours for beads containing a lower percentage of it. SEM photomicrographs of beads and bead surface (**Figure 2**) obtained after dissolution for 12 hours showed slight surface erosion of the beads with a number of holes. The drug release from flurbiprofen beads followed zero order kinetics after initial burst. In the waxy matrix, constant resistance for drug release could have been maintained because of balance between erosion and movement of dissolution front to the interior.

The effect of variables on the time required to dissolve 50% and 90% drug is shown in **Figure 10**. Speed of agitation mainly affects particle size of the bead. But because dissolution studies were carried out at a particular fraction, speed was not found to affect drug release. The amount of CA affects drug release, and the relation is curvilinear in all cases. It The time required to release a certain percentage of drug increases with the amount of CA but that after reaching a particular concentration of CA, the effect can no longer be seen. The critical concentration of CA above which the release remains unaffected is about 20%.

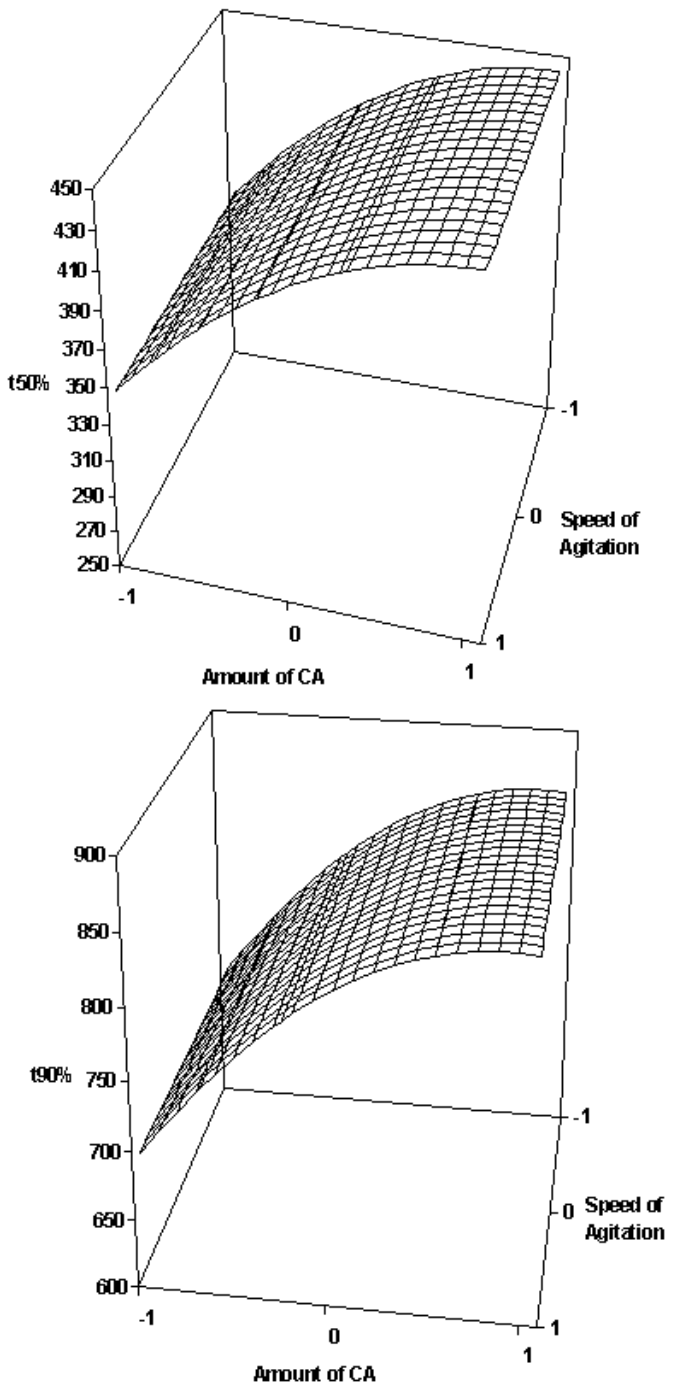

Figure 10. Effect of variables on the drug release profile of flurbiprofen beads. t is the time required for 50% and 90% release of the drug.

CONCLUSION

A low temperature MST has been developed in the present study to obtain flurbiprofen beads, a drug having a melting point above 100°C. The beads obtained by this simple, one-step processing technique have shown sustained drug release up to 12 hours. The flurbiprofen beads were spherical with smooth surface and good micromeritic properties. Drug release followed zero order kinetics. No evidence of polymorphic transition was observed. The amount of CA affects the drug release up to a critical amount with no further significant release retardant effect. The inherent strength of melt-solidified bonds of flurbiprofen helped to reduce the amount of excipient required to retard the release.

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