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Preparation and characterization of ibuprofen–cetyl alcohol beads by melt solidification technique: effect of variables

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Abstract

Ibuprofen (IBU) exhibits short half-life, poor compressibility, flowability and caking tendency. IBU melt has sufficiently low viscosity and exhibits interfacial tension sufficient to form droplet even at low temperature. A single step novel melt solidification technique (MST) was developed to produce IBU beads with lower amounts of excipient. Effect of variables was studied using a 3^2 factorial approach with speed of agitation and amount of cetyl alcohol (CA) as variables. The beads were evaluated using DSC, FT-IR and scanning electron microscope (SEM). Yield, micromeritic properties, crushing strength and release kinetics were also studied. Spherical beads with a method yield of above 90% were obtained. The data was analyzed by response surface methodology. The variables showed curvilinear relationship with yield in desired particle size range, crushing strength and, bulk and tap density. The drug release followed non-Fickian case II transport and the release rate decreased linearly with respect to amount of CA in the initial stages followed by curvilinearity at later stages of elution. The effect of changing porosity and tortuosity was well correlated.

Keywords: Ibuprofen; Cetyl alcohol; Melt solidification technique; Factorial design; Response surface methodology

1. Introduction

Ibuprofen (IBU), α-methyl-4-(2-methylpropyl)-benzene acetic acid is a non-steroidal anti-inflammatory drug used to treat rheumatoid arthritis, osteoarthritis and mild to moderate pain. The GI irritation and ulcerogenic effect along with short half-life (1.8–2.0 h) has lead to the design of sustained release formulations of IBU (Arida et al., 1999; Cox et al., 1999). Due to its low melting point and hydrophobic nature many attempts have been made to develop wax based sustained release formulations (Adeyeye and Price, 1991; Adeyeye and Price, 1994; Bodmeier et al., 1992).

Melt dispersion technique has been reported for the development of IBU microspheres. Beeswax, carnauba wax, ceresine, microcrystalline wax, Precirol ATO5, Gelucire 64/02 were evaluated as waxy carriers (Adeyeye and Price, 1991; Bodmeier et al., 1992). In these techniques IBU-wax melt was emulsified and then cooled to obtain microspheres. The drug:wax ratios were significantly high from 1:1 to 1:4 (50–80% wax) with the drug loading in the range of 15–40%.

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IBU forms a low viscosity melt, which due to its low T_g (<−30 °C) remains in liquid state for longer period of time. Solidification of melt can be accelerated by application of shear. On the basis of these properties a single step melt solidification technique (MST) has been developed in our laboratory to obtain non-disintegrating, excipient-free beads of IBU (Paradkar et al., 2003). The drug release from beads was significantly retarded, which may be attributed to the melt solidified bonds formed in the compact beads. In this technique molten IBU was poured in to aqueous phase maintained at 5 °C, with agitation. The beads obtained had poor sphericity and could sustain the release only up to 2 h.

The aim of the present study was to develop sustained release IBU beads employing the strength of melt solidified bond and to impart sphericity with minimum amount of excipient. Process optimization was carried out using response surface methodology. The beads were characterized using scanning electron microscope (SEM), DSC and FT-IR. The effect of variables on the yield, micromeritic properties, crushing strength and various release parameters was evaluated.

2. Materials and methods

2.1. Materials

IBU was kindly supplied by Dr. Reddy's Laboratories (India). Cetyl alcohol (CA), sodium hydroxide, potassium dihydrogen phosphate, ethyl alcohol were of analytical grade (Merck, India).

2.2. Method of preparation of beads

A mixture of IBU (2 g) and CA was melted and stirred on a water bath maintained at 80 °C to form a uniform molten mass. The IBU–CA melt was poured in 100 ml water maintained at 5 °C using cryostatic bath (Haake Phoenix C25P, Germany), and was stirred continuously using constant speed stirrer with propeller blade (Eurostar power control-visc, IKA Labortecnik, Germany). The IBU–CA beads obtained after solidification of dispersed droplets were separated by filtration and dried at room temperature.

Table 1
Experimental design with coded levels and actual values of variables

Batch[a]	Variable X_1: amount of cetyl alcohol (mg)	Variable X_2: speed of agitation (rpm)
1501	150 (−1)[b]	800 (−1)
1502	150 (−1)	1000 (0)
1503	150 (−1)	1200 (+1)
2001	200 (0)	800 (−1)
2002	200 (0)	1000 (0)
2003	200 (0)	1200 (+1)
2501	250 (+1)	800 (−1)
2502	250 (+1)	1000 (0)
2503	250 (+1)	1200 (+1)

[a] Amount of ibuprofen in all the batches was 2 g.
[b] Values in parentheses indicate coded levels.

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

2.3. Evaluation of beads

2.3.1. Yield and drug content

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

2.3.2. Surface topography

IBU–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.

2.3.3. 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 scanned over the wave number range of 3600–400 cm^{-1}.

2.3.4. Differential scanning calorimetry (DSC)

Thermograms were obtained using a Mettler-Toledo DSC 821^e instrument equipped with an intracooler (Mettler-Toledo, Switzerland). 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 30–100 °C. Inert atmosphere was maintained by purging nitrogen at the flow rate of 100 ml/min.

2.3.5. Micromeritic properties

Particle size distribution was studied by sieve analysis technique using Ro-tap sieve shaker (Labtronics, India). The beads were subjected to bulk and tap density determination using Tap density tester USP II (Electrolab ETD-1020, India).

2.3.6. Crushing strength

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

2.3.7. Dissolution studies

The dissolution studies were performed using USP 24 type II dissolution test apparatus (Electrolab TDT-06P, India). IBU–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 ± 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, concentration of IBU was determined spectrophotometrically at 222 nm. Analysis of data was done using 'PCP-Disso v2.08' software, India.

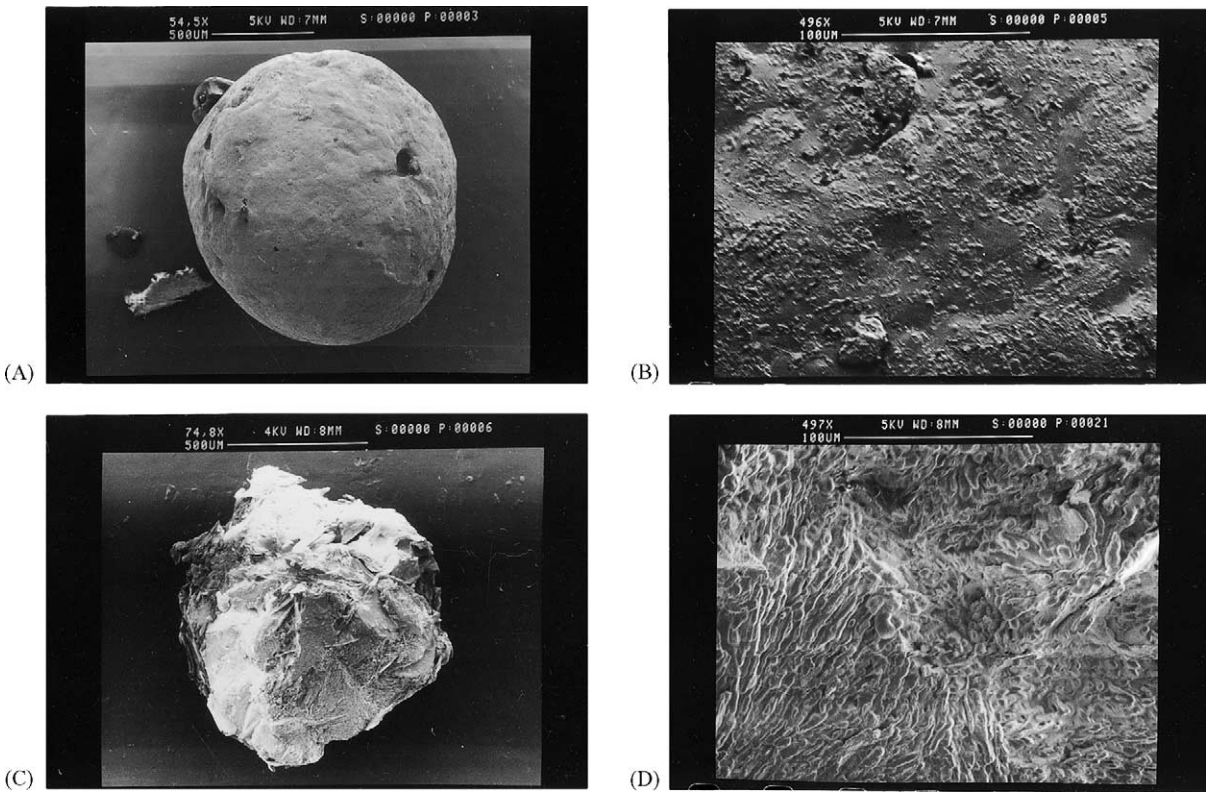

Fig. 1. SEM microphotographs of IBU–CA beads: before dissolution at 54.5× (A), 496× (B); and after dissolution for 9 h at 74.8× (C), 497× (D).

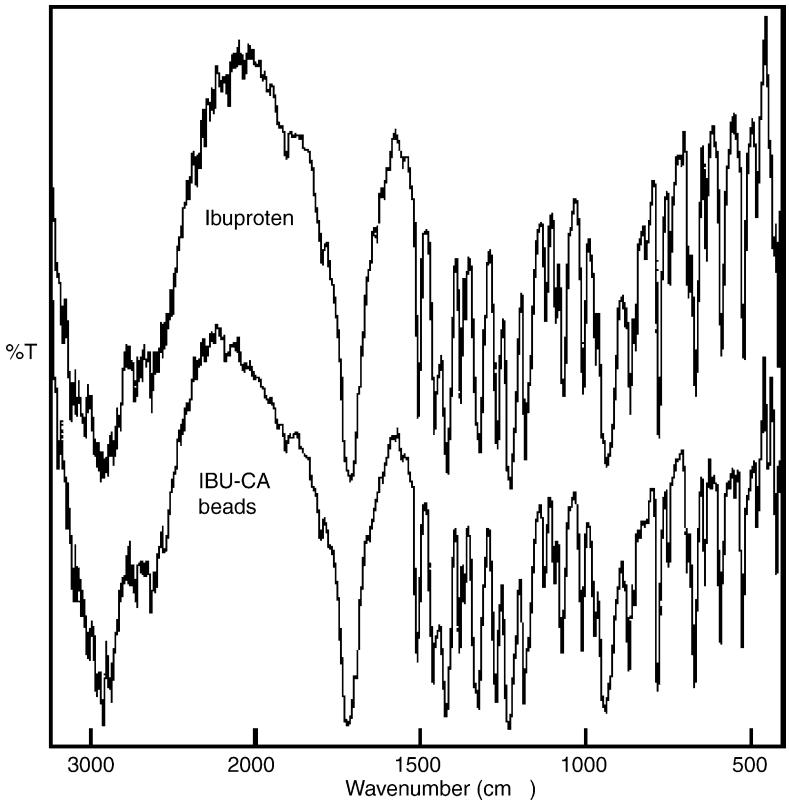

Fig. 2. FT-IR spectra of ibuprofen and IBU–CA beads.

3. Results and discussion

On the basis of our previous study (Paradkar et al., 2003) it was thought that exploiting the strength of melt solidified bonds of IBU along with incorporation of suitable waxy material in small proportion might retard the drug release.

The melt solidification technique involved addition of molten IBU–CA mass to a chilled aqueous phase maintained at 5 °C. During this process, emulsification

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#)	45.460	12.941	3.625	−13.41	–	–	0.990	0.0000
Bulk density (g/cc)	0.514	0.031	0.022	0.010	–	–	0.977	0.0002
Tap density (g/cc)	0.525	0.044	0.027	0.025	0.011	0.010	0.996	0.0008
Crushing strength (g)	184.94	−8.942	19.271	–	−26.00	−10.59	0.989	0.0040
$t_{40\%}$	89.760	9.351	–	–	–	–	0.751	0.0025
$t_{50\%}$	140.47	16.550	–	–	–	–	0.827	0.0007
$t_{60\%}$	202.6	26.181	–	–	–	–	0.832	0.0006
$t_{70\%}$	262.07	38.420	–	21.251	–	–	0.893	0.0012
$t_{80\%}$	338.89	53.433	–	33.790	–	–	0.888	0.0014
$t_{90\%}$	425.18	71.321	–	49.512	–	–	0.877	0.0018

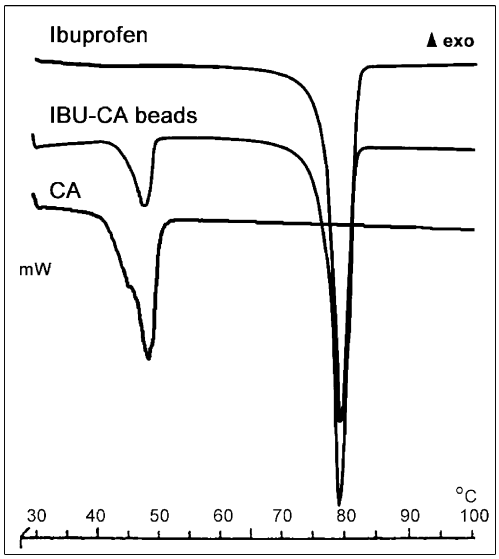

Fig. 3. DSC thermograms of ibuprofen, cetyl alcohol (CA) and IBU–CA beads.

and hardening was achieved within 2–3 min. This fast cooling and high shear caused formation of melt solidified bonds between the drug particles. Low process temperature minimized the drug loss. CA was selected as a waxy excipient in the range of 7.5–12.5% (w/w), due to its ability to solidify simultaneously with IBU under the processing conditions. Waxy flakes of CA were found to separate at higher concentrations and temperatures, and also affected the sphericity.

In the previously reported melt dispersion techniques (Bodmeier et al., 1992; Adeyeye and Price, 1991), emulsification was carried out at higher temperature and then cooled at comparatively faster cooling rates. In the present study aqueous phase was maintained at 5 °C, taking into consideration, the ability of IBU melt to remain in liquid state up to −30 °C.

3.1. Preliminary characterization

The process yield of various batches was in the range of 86–93%. It was not affected by the variables. Entrapment efficiency of various batches was in the range of 90–96%. The IBU–CA beads obtained were spherical with smooth surface. SEM photomicrograph of the beads (Fig. 1) revealed the presence of pinholes on the surface with smooth texture imparted by CA.

The FT-IR spectrum showed characteristic peaks for ibuprofen—IR (KBr) cm^{-1}: 1720 (C=O stretch-

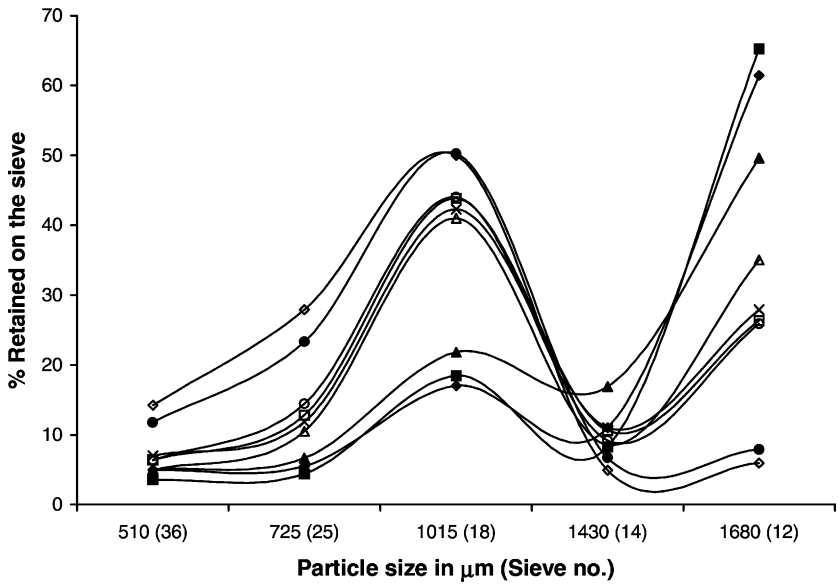

Fig. 4. Particle size distribution curves for IBU–CA beads for different batches: 1501 (◆); 1502 (■); 1503 (▲); 2001 (×); 2002 (□); 2003 (●); 2501 (△); 2502 (○); and 2503 (◇).

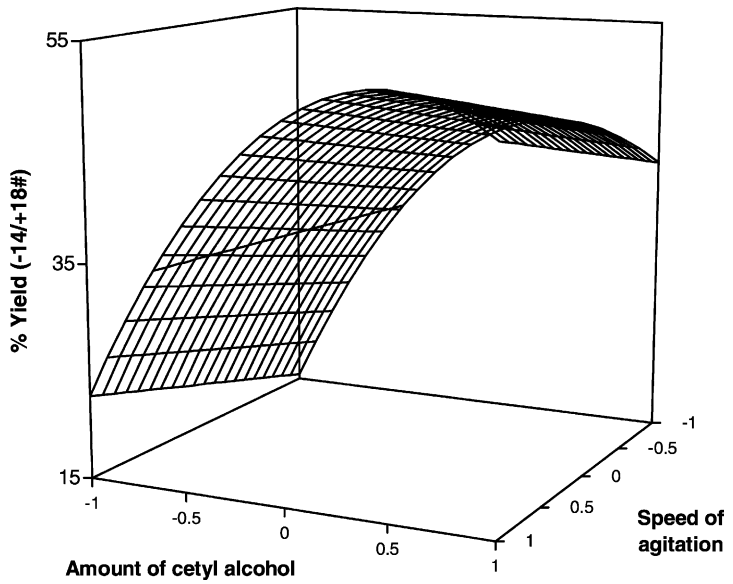

Fig. 5. Effect of variables on the percent yield of IBU–CA beads, in the desired size range of −14/+18#.

ing), 2955 (bonded O–H stretching) (Fig. 2). DSC thermogram of ibuprofen–CA beads (Fig. 3) showed two endotherms at 47.2 and 76.6 °C due to the melting of cetyl alcohol and ibuprofen respectively, indicative of absence of any interaction between the drug and the excipient.

Responses obtained from the batches of factorial design experiments were subjected to multiple regression

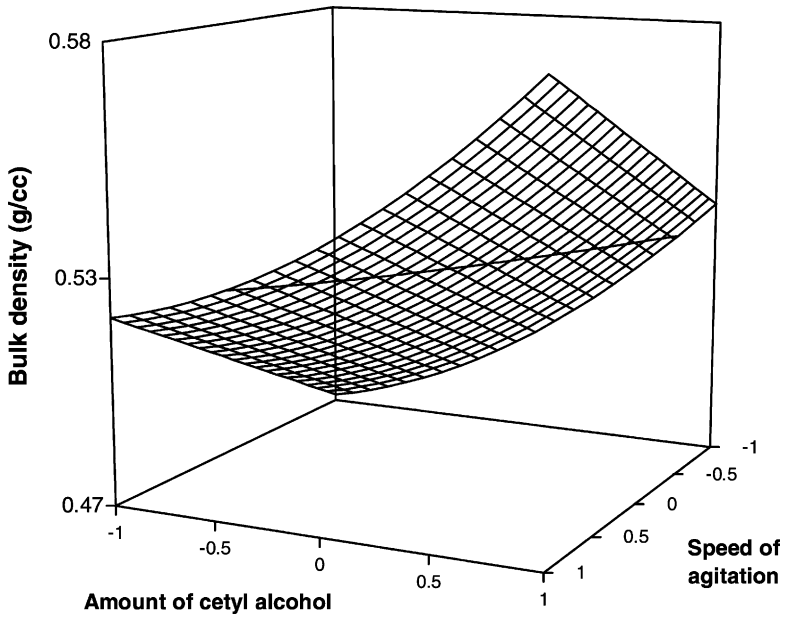

Fig. 6. Effect of variables on the bulk density of IBU–CA beads.

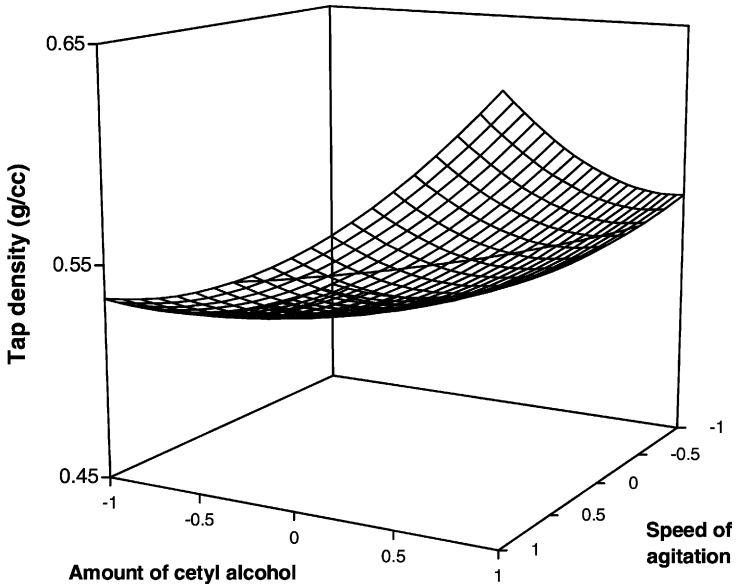

Fig. 7. Effect of variables on the tap density of IBU–CA beads.

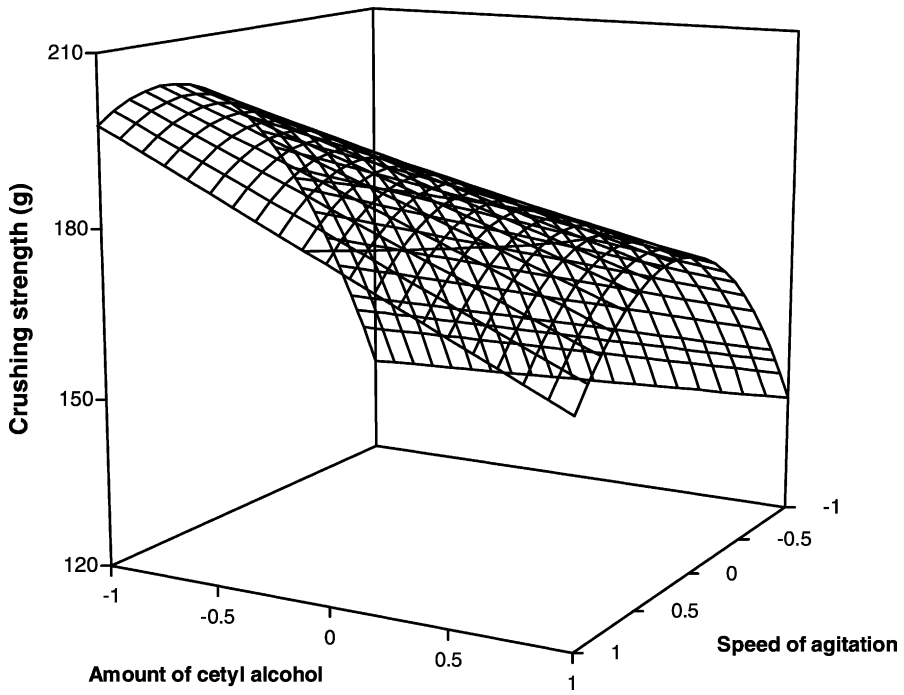

Fig. 8. Effect of variables on the crushing strength of IBU–CA beads.

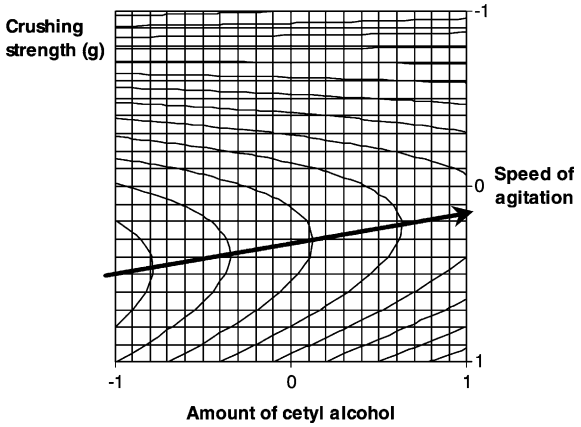

Fig. 9. Contour plot indicating shift in the threshold speed (indicated by arrow) for crushing strength, with change in the amount of CA.

analysis using 'PCP-Disso v2.08' software. The data was fitted in the Eq. (1).

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

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

3.2. Micromeritic properties

The particle size distribution for different batches is shown in Fig. 4. The beads in the range of −14/+18# are suitable for capsule filling, hence the yield in this fraction was selected for the further studies. The effect of variables on the yield in the desired particle size range is shown in Fig. 5. Batches processed at lower levels of both the variables favored larger particle size (Fig. 4). The yield in desired range increased with increase in the amount of CA and the speed of agitation. The positive coefficient for X_2 could be attributed to droplet size reduction with shear leading to increase in the yield.

CA reduces droplet coalescence causing reduction in particle size. Therefore yield in the desired size range increases with increase in amount of CA up to certain level, above which undersize fraction is favored resulting in decreased yield of desired fraction.

Both the variables showed curvilinear increase in the bulk and tap densities of the beads (Figs. 6 and 7). Increase in the amount of CA and the speed of agitation favored formation of fines, which occupy the voids, causing better packing.

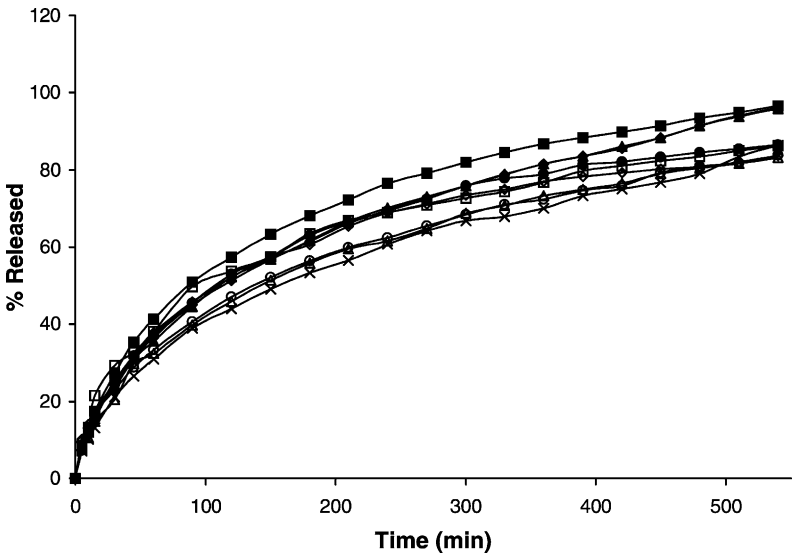

Fig. 10. Dissolution profiles of IBU–CA beads from different batches: 1501 (◆); 1502 (■); 1503 (▲); 2001 (×); 2002 (□); 2003 (●); 2501 (△); 2502 (○); and 2503 (◇).

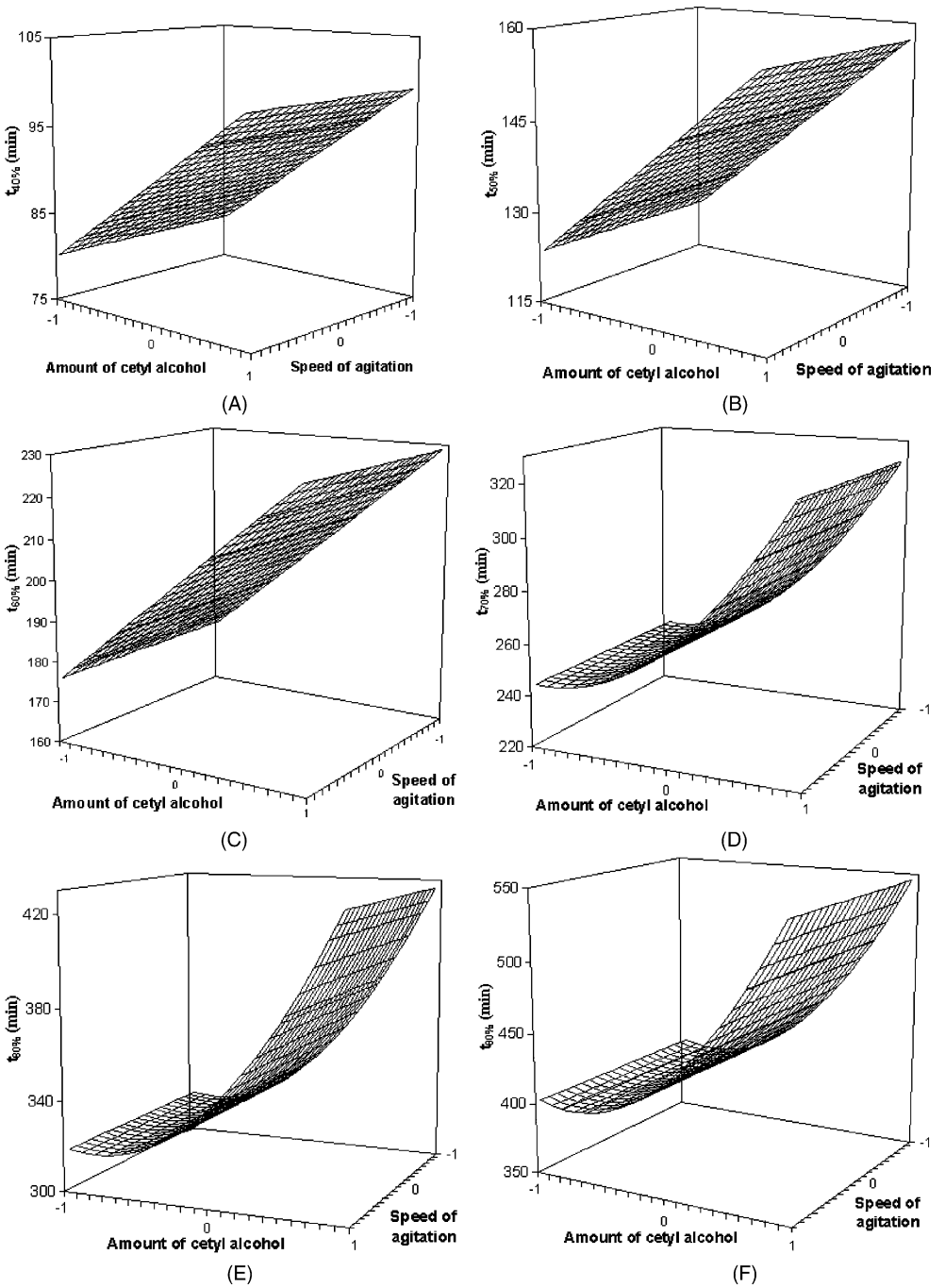

Fig. 11. Effect of variables on the drug release profile of IBU–CA beads: $t_{40\%}$ (A); $t_{50\%}$ (B); $t_{60\%}$ (C); $t_{70\%}$ (D); $t_{80\%}$ (E); $t_{90\%}$ (F).

3.3. Crushing strength

Crushing strength, which is the force required to deform the beads, as determined by mercury load cell method was in the range of 137–198 g. The mechanical strength of the beads was significantly lower as compared to earlier report for excipient-free beads obtained by MST (310 g) (Paradkar et al., 2003). Increase in the amount of CA, decreases the number of melt solidified bonds between IBU particles, responsible for mechanical strength of the beads, hence a decrease in crushing strength. This effect was more pronounce at higher speed of agitation (Fig. 8). The rate of solidification of IBU is shear dependent. As the speed increases above certain threshold level it solidifies much faster than CA, which may cause non-uniform distribution of CA in IBU beads. This was also evident from the preliminary experiments, which showed separation of CA in the form of flakes at higher concentrations. As shown in Fig. 9, this threshold speed decreased with increase in the amount of CA.

3.4. Drug release studies

The drug dissolution profiles for various batches are shown in Fig. 10. The dissolution profiles were fitted in Eq. (2) (Korsmeyer et al., 1980).

$$\frac{M_t}{M_\infty} = kt^n \tag{2}$$

Where k is a constant incorporating structural and geometric characteristics of the drug dosage form; n is the release exponent indicative of the drug release mechanism; and M_t/M_∞ (fraction of drug released) is the function of time t. The release exponent n, was found to be ~0.5 indicative of non-Fickian case II transport. This might be due to simultaneous effect of surface erosion and diffusion of drug through the solvent filled pores.

The response surfaces for time required for 40–90% drug release ($t_{x\%}$) are shown in Fig. 11. The response surfaces showed characteristic pattern. As only the particles in the desired size range (−14/+18) were

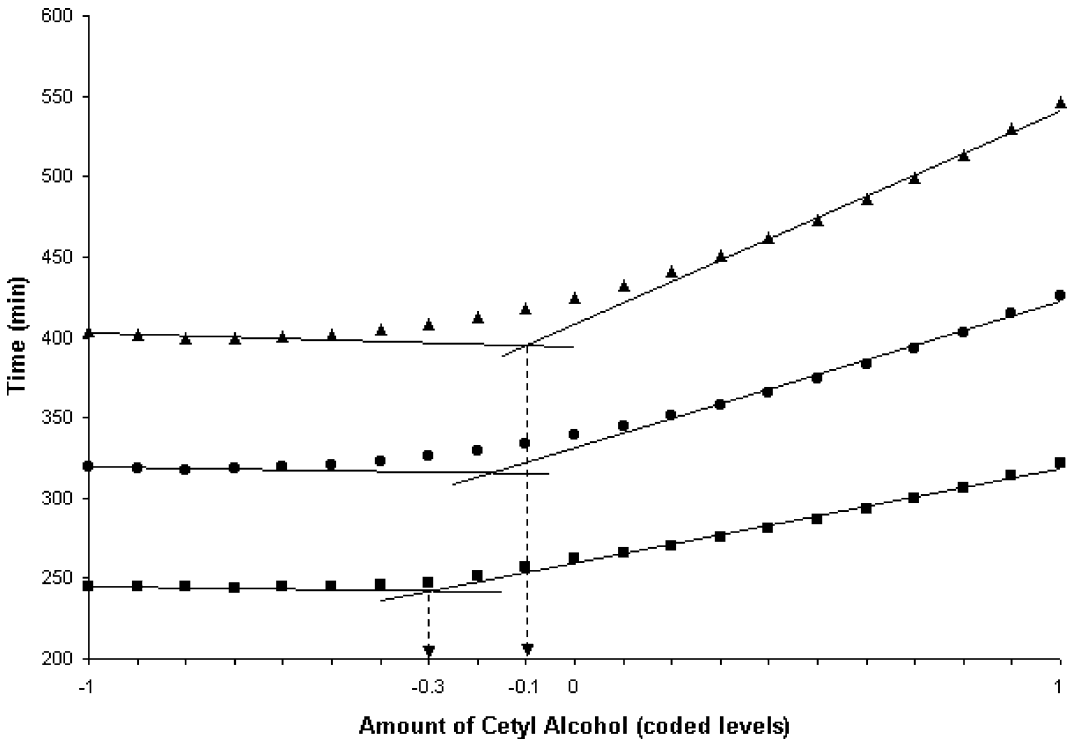

Fig. 12. Effect of amount of CA on $t_{x\%}$ of IBU–CA beads: $t_{70\%}$ (■); $t_{80\%}$ (●); $t_{90\%}$ (▲).

selected for release studies, the effect of speed of agitation was not seen. The release of IBU was significantly affected by amount of CA, but the effect differed with time. A linear response with positive coefficient was observed up to 60% drug release (Fig. 11A–C).

After 70% drug release the effect became curvilinear. The threshold amount of CA, above which the release retardant effect is maintained, increases with time as shown in Fig. 12. As shown in Fig. 1C and D, integrity of the beads is disturbed with the release of drug. As the drug leaches out from the beads, the matrix integrity could not be maintained at lower levels of CA and the release retarding effect of CA below the threshold amount is lost. As indicated in Fig. 12, the threshold above which a linear decrease in the release rate occurs with increase in amount of CA, increases from 185 mg for $t_{70\%}$ (coded level '−0.3') to 195 mg for $t_{90\%}$ (coded level '−0.1'). In other words, $t_{70\%}$ increases linearly only for batches containing more than 185 mg CA, whereas $t_{90\%}$ increases linearly above 195 mg CA. Thus the matrix integrity is well maintained above 195 mg or approximately zero level batches throughout the complete drug elution.

Thus, determination of threshold concentration of the release retardant could serve as a guideline for designing of beads with desired release profile. Response surfaces for yield, crushing strength and micromeritic properties were curvilinear with curvature near the center. Hence, considering the release profiles and other parameters, the batches near center of the experimental design may be considered optimum.

4. Conclusions

The IBU–CA beads were spherical with smooth surface and good micromeritic properties. Significant release retarding effect for more than 9 h, was achieved with lower concentrations of CA between 10 and 15% (w/w). Multiple regression analysis along with response surface methodology helped to study the effect of variables on the micromeritic and release properties. Calculation of optimum amount of CA to maintain the matrix integrity with good release retarding effect was possible with the help of 3^2 factorial design. Melt solidification thus yields controlled release IBU–CA beads in single step operation, at lower CA concentrations. The inherent strength of melt solidified bonds of IBU helped to reduce the amount of excipient required to retard the release.

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