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Melt Solidification Technique: Incorporation of Higher Wax Content in Ibuprofen Beads

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Ravindra Kamble,[1] Manish Maheshwari,[1] Anant Paradkar,[1] and Shivajirao Kadam[2]

[1]Department of Pharmaceutics, Poona College of Pharmacy, Bharati Vidyapeeth Deemed University, Erandwane, Pune-411038, Maharashtra State, India

[2]Department of Pharmaceutical Chemistry, Poona College of Pharmacy, Bharati Vidyapeeth Deemed University, Erandwane, Pune-411038, Maharashtra State, India

ABSTRACT

The purpose of this study was to achieve incorporation of a higher amount of wax during the preparation of ibuprofen beads by a melt solidification technique for better integrity and prolonged drug release by using a combination of waxes. A mixture of cetyl alcohol (CA) and palmitic acid (PA) was used to improve the matrix integrity and drug release. The effect of variables such as CA, PA, and speed of agitation were studied using 3^3 factorial design. Yield, crushing strength, and drug release were analyzed using response surface methodology. The in vitro dissolution test did not show any significant improvement in the drug release. Scanning electron microscopy (SEM) showed that beads were spherical with a smooth surface, but after dissolution became rough and porous. Differential scanning calorimetry (DSC) studies showed that different solidification and erosion properties of waxes are responsible for the inability of waxes to retard drug release even at higher concentration.

KEYWORDS: ibuprofen, palmitic acid, cetyl alcohol, melt solidification, factorial design

INTRODUCTION

Pharmaceutical processing techniques, which offer freedom from organic solvents, are preferred due to stringent global environmental concerns. Hence, many reports are published on techniques such as melt granulation,[1-3] melt extrusion,[4-6] pastillation,[7] melt dispersion,[8-10] and melt solidification.[11-13] Lipids, waxes, and polyethylene glycols are the most favorable carriers for these techniques. Drug is incorporated in these carriers to achieve controlled release,[9,10,12] taste masking,[14] stability improvement, or amorphous form.[15] Design and application of these techniques depend on the physicochemical properties of the drug and excipients, as well as desired properties of the final product. Wax, a common carrier in various melt techniques, contains a wide group of chemicals such as glycerides, fatty acids, fatty alcohols and their esters. These are widely used as release retardants in the design of sustained release beads, tablets, suspensions, implants, and microcapsules. The advantages of waxes include good stability at varying pH and moisture levels, well-established safe application in humans due to their nonswellable and water insoluble nature, minimal effect on food in the gastrointestinal tract, and no dose dumping.[16] Beeswax, carnauba wax, ceresine, microcrystalline wax, Precirol ATO5, and Gelucire 64/02 were evaluated as waxy carriers for melt processing techniques.[8-10]

Ibuprofen, α-methyl-4-(2-methylpropyl)-benzene acetic acid, is a nonsteriodal anti-inflammatory drug used to treat rheumatoid arthritis, osteoarthritis, and mild to moderate pain. Lipophilicty of ibuprofen makes it a suitable candidate for waxy matrices. Paradkar et al[11] have reported that ibuprofen has very low glass transition temperature (t_g<-30°C) and remains in liquid state at low temperature, on the basis of which a novel melt solidification technique (MST) was designed.

The melt solidification/melt dispersion technique basically involves emulsification of the molten mass in the aqueous phase followed by its solidification by chilling. The melt dispersion technique reported by Bodmeier et al[10] and Adeyeye et al[8] for the development of ibuprofen microspheres involves emulsification of the ibuprofen-wax melt at a temperature greater than the melting point of ibuprofen followed by cooling to room temperature. In the melt dispersion technique, the drug:wax ratios were significantly high, from 1:1 to 1:4. The microspheres obtained have drug loading in the range of 15% to 40%, with particle size between 50 and 300 μm.

Ibuprofen melt has low viscosity and the ability to remain in the liquid state for a sufficiently longer period of time so that it can be poured and processed easily even at low temperatures. In such cases emulsification can be performed at temperatures well below its melting point. Therefore, the melt solidification technique to obtain ibuprofen beads was designed where emulsification and solidification of the melt in the aqueous phase was performed at 5°C. The beads exhibited slow drug release, which was attributed to the formation

Corresponding Author: Anant Paradkar, Department of Pharmaceutics, Poona College of Pharmacy, Bharati Vidyapeeth Deemed University, Erandwane, Pune-411038, Maharashtra State, India. Tel: 91-20-2543 7237; Fax: 91-20-2543 9383; E-mail: arparadkar@rediffmail.com.

Table 1. Experimental Variables and Their Coded Levels With Actual Values

Variables	Levels		
Amount of palmitic acid (mg)	-1 (200)	0 (250)	+1 (300)
Amount of cetyl alcohol (mg)	-1 (100)	0 (125)	+1 (150)
Speed of agitation (rpm)	-1 (800)	0 (900)	+1 (1000)

of melt-solidified bonds.[11] Flurbiprofen, due to its melting point (114-117°C) above the boiling point of water, was never considered as a candidate for the melt dispersion technique. But considering its thermal properties similar to ibuprofen, a low-temperature MST was designed to obtain flurbiprofen waxy beads.[13]

For further retardation of drug release and improvement in sphericity, cetyl alcohol (CA) was incorporated. CA was selected as a waxy excipient due to its ability to solidify simultaneously with ibuprofen under the processing conditions. The inherent strength of the melt-solidified bonds helps to reduce the amount of excipient required to retard the release. Maheshwari et al[12] reported that the higher processing temperature and concentration of CA affected the sphericity, along with the separation of waxy flakes of CA. Similar observations were made by Paradkar et al[13] in the case of flurbiprofen-CA beads where a maximum 25% wt/wt of CA could be incorporated. It was also observed that the threshold amount of CA above which its release retardant effect is maintained increases with time. The maximum amount of wax that could be incorporated in low-temperature MST depends on the properties of the drug, eg, it was 12.5% wt/wt for ibuprofen and 25% wt/wt for flurbiprofen. But this percentage is significantly low as compared with the melt dispersion technique involving high-temperature emulsification.

In the present study, an attempt has been made to increase the proportion of wax by using a combination of waxes, which may impart improved matrix integrity and sustained drug release. Palmitic acid (PA) and CA were selected as release retardants. The effect of variables viz amount of CA, amount of PA, and speed of agitation was studied using 3^3 factorial design. Drug content, yield, crushing strength, and various release parameters were used as dependent variables to study the effect of variables. The morphology was studied using scanning electron microscopy (SEM), differential scanning calorimetery (DSC), x-ray powder diffraction (XRPD), and infrared spectroscopy (IR) to characterize the bead.

Materials and Methods

Materials

Ibuprofen was kindly supplied by Lupin Laboratories (Pune, India). Cetyl alcohol, sodium hydroxide, potassium dihydrogen phosphate, and ethyl alcohol were of analytical grade (Merck, Mumbai, India). Microcrystalline wax 3749 was obtained as a gift sample from Poth Hille and Co Ltd (Stratford, UK). Glyceryl mono-stearte was obtained from Gattefose S.A. (Saint-Priest, Codex, France). Carnauba wax, beeswax, and palmitic acid were purchased from s.d. fine-chem, Ltd (Mumbai, India).

Preparation of Beads

The drug (2 g), PA, and CA were melted on a water bath maintained at 100°C. The homogeneous molten mass obtained 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 a propeller blade (Eurostar power control-visc, IKA Labortecnik, Staufen, Germany). The ibuprofen beads with CA and PA 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 3^3 factorial design. Amount of PA, amount of CA, and speed of agitation were selected as 3 independent variables. Experimental variables and their coded levels with actual values 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 of beads were triturated and dissolved in 100 mL of ethanol by sonication for 30 minutes. The solution was analyzed spectrophotometrically at 222 nm (JASCO-V500, Tokyo, Japan) after sufficient dilution with phosphate buffer (pH 7.2).

Scanning Electron Microscopy

Beads were coated with a thin gold-palladium layer by sputter coater unit (VG-Microtech, Uckfield, East Sussex, 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 and beads were obtained on a JASCO V5300 FT-IR. The pellets were prepared on a KBr-press (Spectra Lab, Mumbai, India). The spectra were scanned over the wave number range of 3600 to 400 cm^{-1}.

Table 2. Processing Conditions and Results of Preliminary Experiments*

Wax	Temperature (°C)						Observation
	5	10	15	20	25	30	
MCW	×	×	×	×	✓	✓	No hardness, no sphericity
MCW + cetyl alcohol	×	×	×	✓	✓	✓	No hardness, no sphericity
Palmitic acid	×	×	×	×	✓	✓	Fine particles
GMS	×	×	×	×	✓	✓	No hardness
Beeswax	×	×	×	×	✓	✓	No hardness, no sphericity
Beeswax + cetyl alcohol	×	×	×	×	✓	✓	No sphericity
Carnauba wax	×	×	×	×	×	×	Solidified irregular particles
Cetyl alcohol + palmitic acid	✓	✓	✓	✓	✓	✓	Spherical satisfactory hard beads

*MCW indicates microcrystalline wax; GMS, glyceryl mono-stearate. × indicates that ibuprofen beads obtained at process temperature were not satisfactory.

✓ indicates that ibuprofen beads obtained at process temperature were satisfactory.

Differential Scanning Calorimetry

Thermograms of ibuprofen, CA, PA, and beads were obtained using a Mettler-Toledo DSC 821^e instrument equipped with an intracooler (Mettler-Toledo, Greifense, Switzerland). Indium standard was used to calibrate the DSC temperature and enthalpy scale. The powdered sample of pure drug, CA, PA, and beads were hermetically sealed in aluminum pans and heated at a constant rate of 10°C/min, over a temperature range of 0°C to 100°C. Inert atmosphere was maintained by purging nitrogen at the flow rate of 100 mL/minute. Similarly, DSC thermograms of beads collected from dissolution studies after 4 hours and 6 hours were also obtained by a similar procedure.

X-ray Powder Diffraction

Samples of ibuprofen and ibuprofen beads were prepared by pulverizing in a mortar. The XRPD patterns of samples were recorded by using a Philips PW 1729 x-ray diffractometer (Legroupe Interconnexion, Saint-Juire, Clubac, Canada). Samples were irradiated with monochromatized Cu Kα radiation (1.542 Å) and analyzed between 2 and 60° (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.

Particle Size Distribution

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

Crushing Strength

Crushing strength of beads (−14/+18 mesh fraction) was determined using the mercury load cell method as described by Jarosz and Parrott[17] on a specially fabricated crushing strength apparatus (Seema Enterprises, Pune, India).

Dissolution Studies

The dissolution studies were performed using United States Pharmacoepeia 26 type II dissolution test apparatus (Electrolab TDT-06P, Mumbai, India). Ibuprofen beads (−14/+18 mesh fraction) equivalent to 300 mg of drug were placed in the dissolution vessel containing 900 mL of 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(s**.**d. fine-chem, Ltd, Mumbai, India , concentration of ibuprofen was determined spectrophotometrically at 222 nm. Analysis of data was done using PCP Disso v2.08 software (Poona College of Pharmacy, Pune, India).

Results and Discussion

Low-temperature emulsification offers advantages such as increased yield, fast processing, and high drug content. As compared with melt dispersion using high-temperature emulsification, which can incorporate up to 400% wt/wt wax, the low-temperature melt solidification could incorporate only 12.5% to 25% wt/wt wax. Preliminary experiments were performed using different waxes alone and in combination at different temperatures. The processing conditions and results of the preliminary study are summarized in Table 2. The processing temperature required for emulsification was found to increase with the melting point of the wax. Waxes having a melting point above 65°C, eg, carnauba wax, microcrystalline wax, and beeswax, could not be processed up to 20°C, even in combination with a low temperature melting wax like CA. Incorporation of high melting wax alone is not possible at low temperature and therefore an attempt was made in combination with low melting wax like CA. PA was selected for use in combination with CA from preliminary study. Though PA alone failed to yield beads, in combination with CA it was emulsified at 5°C.

Drug content of various batches was in the range of 77.33% wt/wt to 86.58% wt/wt. Standard deviation of average drug

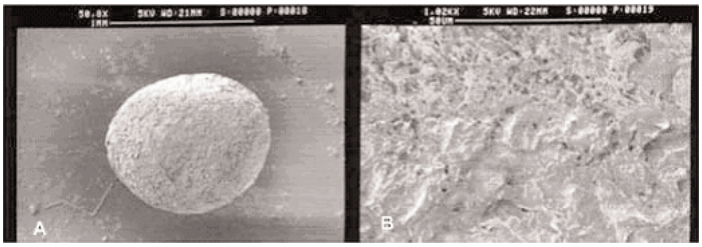

Figure 1. SEM photographs of ibuprofen beads at ×50 (A) and ×1000 (B).

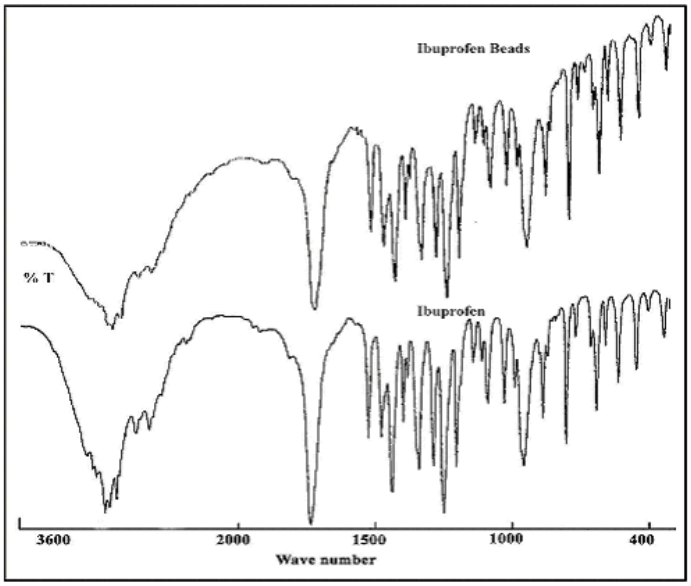

Figure 2. FT-IR spectra of ibuprofen and ibuprofen beads.

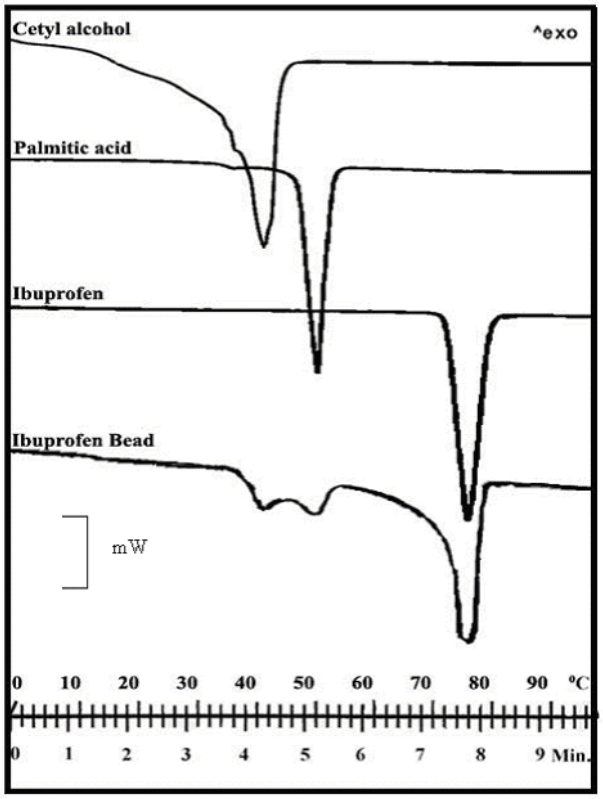

Figure 3. DSC thermograms of cetyl alcohol, palmitic acid, and ibuprofen.

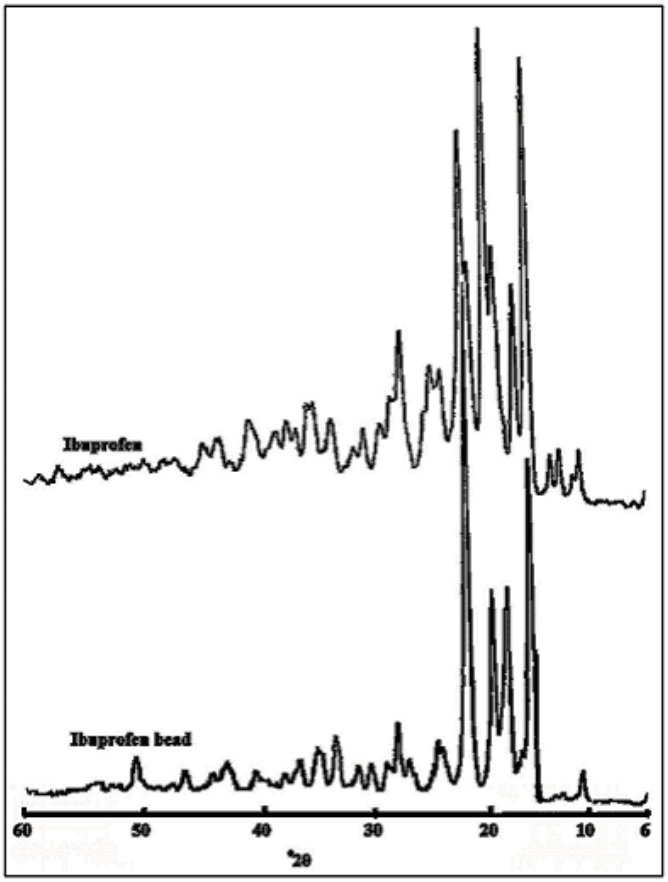

Figure 4. X-ray powder diffraction pattern of ibuprofen and ibuprofen beads.

content is ± 1.13 ($P < .05$). No significant difference was found between the drug content of various batches.

The beads obtained were spherical with smooth surface. An SEM photograph of ibuprofen beads is shown in Figure 1. The beads were compact with uniform surface coating and did not contain any pinholes.

The FT-IR spectra of ibuprofen and ibuprofen beads (Figure 2) showed characteristic peaks of ibuprofen at 1720 cm^{-1} and 2920 cm^{-1}, due to carbonyl and hydroxyl stretching respectively. DSC thermograms of ibuprofen and ibuprofen beads are shown in Figure 3. The DSC thermogram of ibuprofen showed a melting endotherm at 77.6°C with normalized energy of 118.22 J/g. The thermogram of ibuprofen beads showed 3 endotherms at 42.4°C, 50.5°C, and 74.2°C with energies 7.87 J/g, 8.27 J/g, and 85.58 J/g attributing to melting of CA, PA, and ibuprofen respectively. The ibuprofen melting onset temperature decreased due to the presence of CA and PA in the beads. X-ray powder diffractrograms (Figure 4) of ibuprofen and ibuprofen beads have not shown a significant difference in the d (interplannery distance), spacing values with slight decrease in peak intensity, which could be due to dilution effect.

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

Table 3. Summary of Regression Results for the Measured Responses*

	Coefficient												
Parameters	β_0	β_1	β_2	β_3	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}	β_{123}	r^2	***P***
Crushing strength	66.97	-13.31 (.000)	-13.24 (.000)	4.07 (.000)	-	-	-	7.55 (.008)	3.42 (.000)	-	4.69 (.014)	0.8459	.0000
Yield (-14/+18)	33.64	-	-6.08 (.000)	-2.39 (.000)	-	-3.09 (.008)	-	2.86 (.000)	-	-2.18 (.005)	-	0.6985	.0019
T10	16.37	1.39 (.004)	-2.79 (.000)	-	-3.17 (.001)	-3.28 (.000)	-2.82 (.000)	-1.38 (.019)	-	-	-	0.5898	.0000
T40	129.79	-	-14.36 (.000)	-5.72 (.014)	-9.23 (.008)	-16.00 (.000)	-14.64 (.002)	-7.86 (.012)	9.95 (.015)	-	-	0.7280	.0003
T60	231.74	-	-20.43 (.000)	-11.46 (.013)	-	-8.58 (.000)	-19.27 (.001)	-11.64 (.008)	22.02 (.012)	-	-	0.7661	.0001
T70	294.14	-	-22.61 (.000)	-14.97 (.015)	-	-16.58 (.000)	-19.32 (.002)	-13.07 (.009)	29.68 (.008)	-	-	0.8270	.0000
T80	356.74	-11.66 (.007)	-23.14 (.000)	-18.78 (.001)	-	-	-23.48 (.001)	-15.37 (.004)	38.20 (.000)	-10.77 (.013)	-12.92 (.021)	0.7854	.0005

*Values in parentheses indicate *P* value associated with each term. Hyphens indicate that particular coefficient is not in equation.

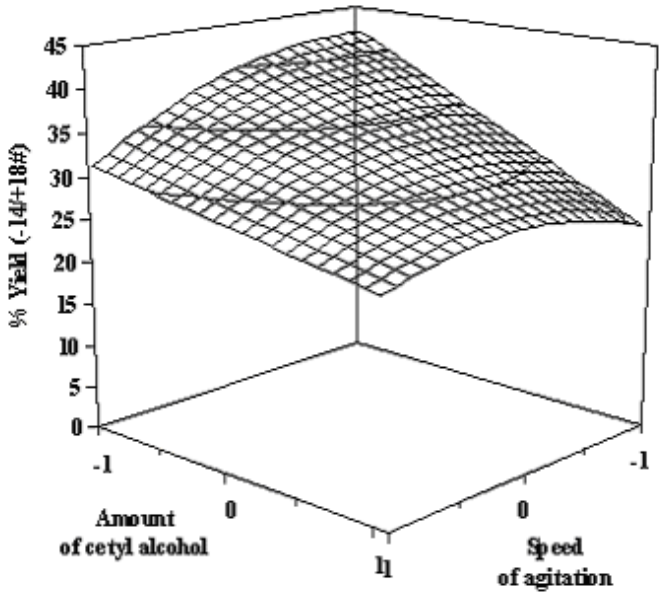

Figure 5. Effect of variables on the percent yield of ibuprofen beads in the desired size range of -14/+18#.

using PCPRSM software **,** Poona College of Pharmacy Pune, India . The data were fit into the following equation:

$$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_{12}X_1X_2 + \beta_{13}X_1X_3 + \beta_{23}X_2X_3 + \beta_{11}X_1X_1 + \beta_{22}X_2X_2 + \beta_{33}X_3\,X_3 + \beta_{123}X_1X_2X_3 \quad (1)$$

Insignificant effects were removed by the backward elimination method and adequacy of the fitted model was checked by analysis of variance (ANOVA). The results of multiple regression analysis are summarized in Table 3. The response surface plots were generated using the graph mode of the PCPRSM software.

The process yield of various batches was in the range of 84.53% to 92.68% wt/wt. The beads in the 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 19.06% and 62.78% wt/wt. Effect of variables on the desired yield is shown in Figure 5. A curvilinear response to the speed of agitation and linear decreasing relation with amount of CA was observed. It revealed that desired yield decreases with amount of CA, but increases due to an increase in the speed of agitation up to a certain level of agitation above which it favors decrease in the desired yield.

Reduction in particle size occurred due to increased shear with speed of agitation. The yield of undersize fraction (less than #18) increased after a certain level of agitation and caused a decrease in the desired yield. Reduced coalescence due to CA caused reduction in particle size, hence desired yield decreased with increase in the amount of CA.

Crushing strength, which is the force required to crush the beads, was in the range of 44.56 to 108.38 g. Effect of variables on crushing strength is shown in Figure 6. A linear relation was observed between the crushing strength and the formulation variables. It was revealed that crushing strength decreases with increase in amount of wax, but a slight increase in crushing strength was experienced due to an increase in the speed of agitation. Crushing strength of the beads was significantly lower as compared with earlier

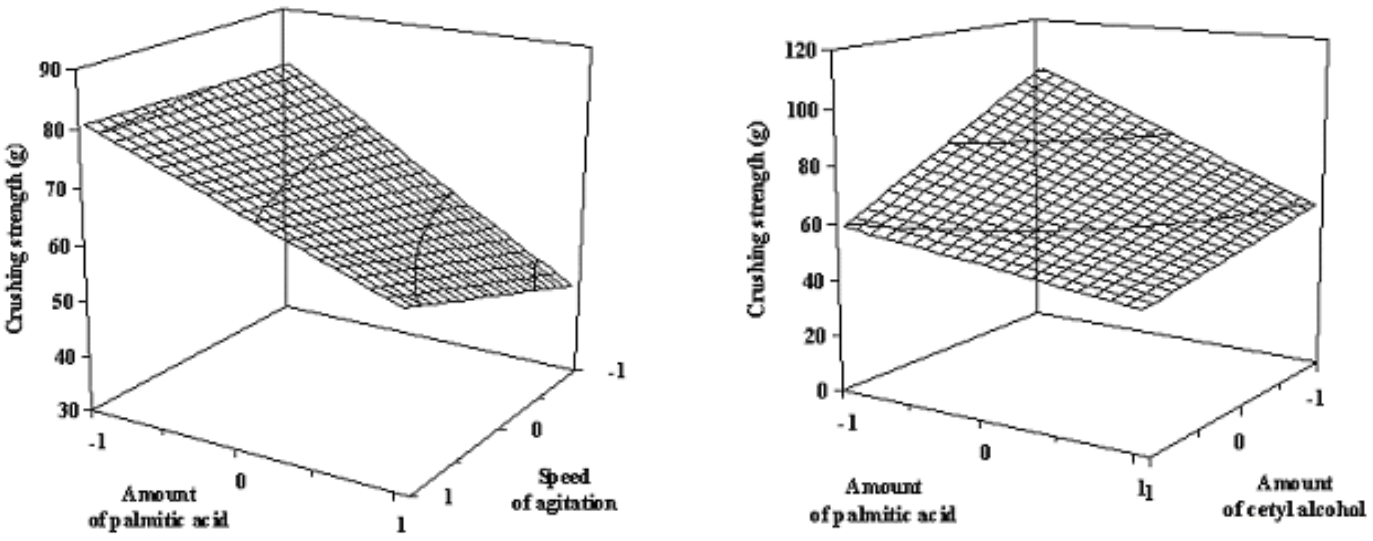

Figure 6. Effect of variables on crushing strength of ibuprofen beads.

reports for excipient-free beads 310 g and ibuprofen-CA beads 198 g.[11,12] Crushing strength of the bead depends on the number of bonds formed by the solidified melt of ibuprofen itself and strength of the individual bond. Incorporation of waxes reduces the number and strength of melt solidified bonds, exhibiting reduction in crushing strength. Rate of ibuprofen solidification is shear dependent hence the number of bonds formed increases with agitation resulting in increased crushing strength.

The dissolution data analysis was performed using PCP Disso v2.08 software. The dissolution data were fitted well in the Korsmeyer–Peppas equation.[18]

$$\frac{M_t}{M_\infty} = kt^n, \qquad (2)$$

where k is a constant incorporating structural and geometric characteristics of the drug dosage form, n is the release exponent, indicative of drug release mechanism, and M_t/M_∞ (fraction of drug released) is the function of time t. The release exponent was found to be ~0.5 indicative of the Higuch matrix diffusion.

Response surfaces for time required for 10%, 60%, and 80% drug release are shown in Figure 7. As the effect of PA on dissolution was insignificant, response surfaces were plotted taking into consideration the variables viz amount of CA and speed of agitation. A curvilinear relation was observed with both the variables initially. The effect of CA on drug release differed with time, following a curvilinear relationship up to $t_{60\%}$ and further linearity with negative coefficient. But the effect of speed of agitation remains curvilinear throughout. Speed of agitation affects particle size and mechanical strength of the beads. As only the particles in the desired size range were selected for drug release studies, its effect was not seen. Curvilinear response obtained in the release study is due to the strength of beads, but as the speed of agitation increases above a threshold level, ibuprofen solidifies much faster than the wax, which causes nonuniform distribution of the wax, hence a decrease in crushing strength of beads.

It was observed that not only hydrophobicity but also melting point of wax is equally important for sustaining the drug release. For example, the higher the melting point, the later the active substance is released, indicating that the melting point of Gelucire was the most influential factor on the release of potassium chloride.[19]

Sutananta et al[20] have demonstrated that the composition of lipids and the processing conditions significantly affect the performance of the matrix after aging. The matrices composed of mixtures of different glycerides are affected more during aging as compared with the single glyceride. This is due to the slower crystallization of some components during aging. Therefore, Roussin and Duddu[21] made an attempt to avoid aging problems by enhancing the crystallization rate by addition of a nucleation enhancer like glyceryl mono-stearate.

Maheshwari et al[12] have reported that 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. Incorporation of higher melting wax is expected to allow drug release over a relevant time scale by improving the integrity of the system. But contradictory to a previous report,[11] the higher melting wax could not significantly prolong the release as compared with previously reported ibuprofen-CA beads.

In the present study, the matrix comprises 3 waxy materials viz CA (45°C), PA (53°C), and ibuprofen (78°C) itself, hav-

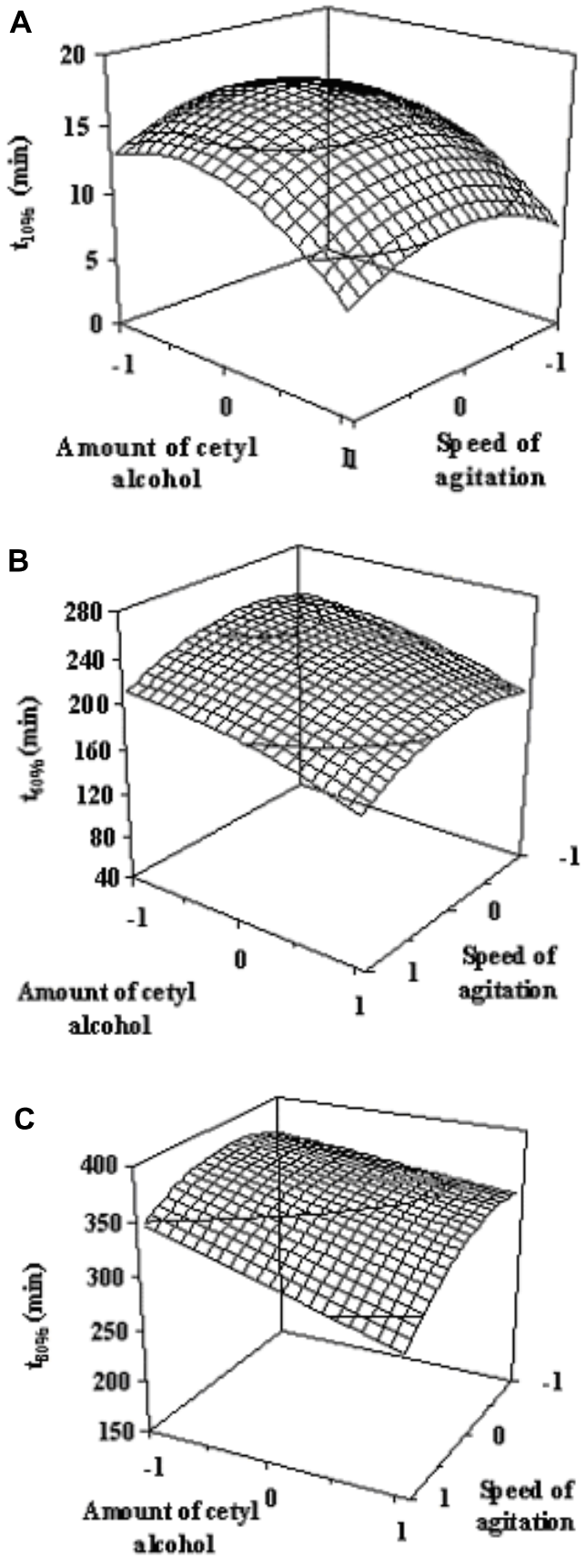

Figure 7. Effect of variables on the drug release profile of ibuprofen beads: $t_{10\%}$ (A), $t_{60\%}$ (B), $t_{80\%}$ (C).

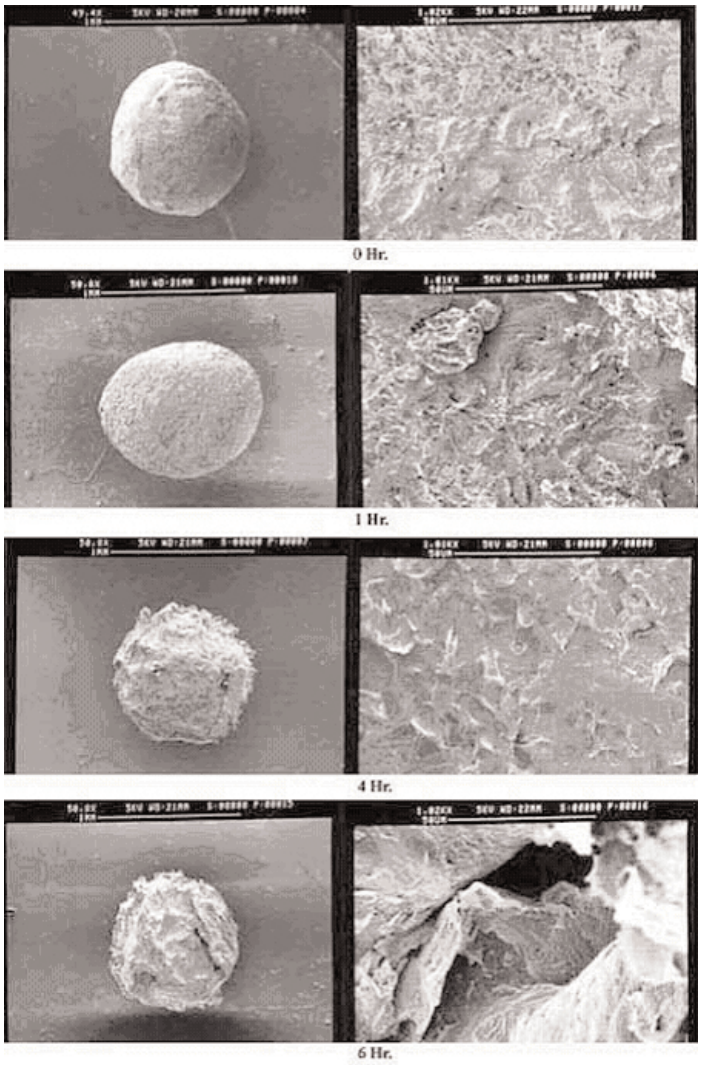

Figure 8. SEM photographs of ibuprofen beads before and after dissolution for different time periods.

ing significantly different melting points. Crystallization of these materials was performed by chilling at 5°C, reducing the possibility of crack generation due to the difference in the rate of crystallization. The SEM photographs of the beads obtained at different time intervals during dissolution studies are shown in Figure 8. The DSC thermograms of the beads and beads obtained after dissolution are shown in Figure 9. The results of transitions in the DSC thermogram of ibuprofen are summarized in Table 4. The surface topography of the beads revealed that as the dissolution time increased, the surface erosion of the beads increased. SEM photographs of the beads showed rough surface after 1 hour dissolution when ~20% to 25% of drug and a significant amount of CA was leached out. But after 4 hours, bead surface has shown a significant change in appearance. The surface texture becomes smooth indicating the nature of the wax at the surface to be different from what it was in the initial stages. The DSC thermogram, showing that percentage of CA has decreased significantly whereas that of PA was still high, supported this observation.

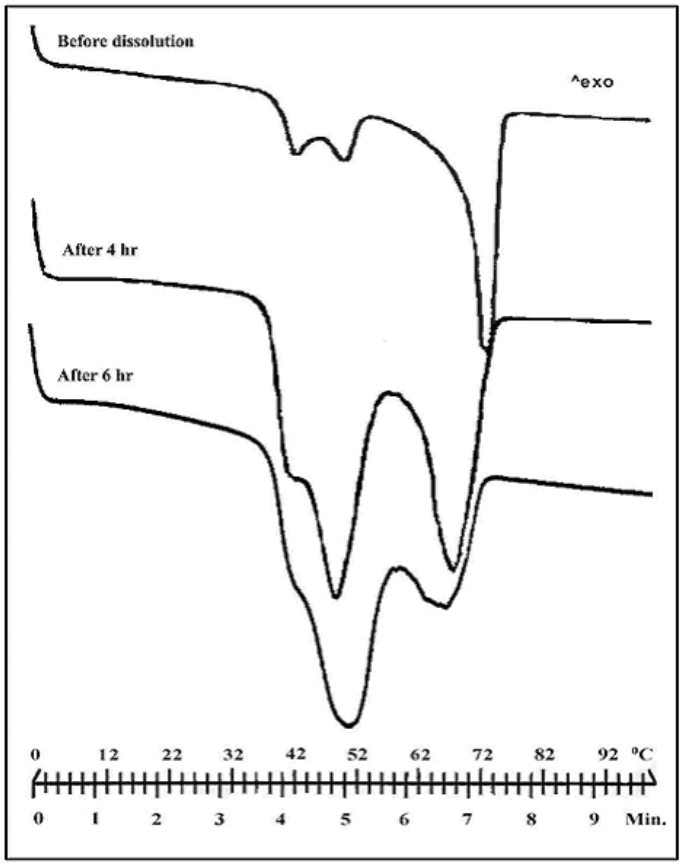

Figure 9. DSC thermogram of ibuprofen beads: before dissolution, after 4 hours, and after 6 hours.

In the initial stage, erosion of low-melting component CA occurs significantly. The CA might be concentrated near the surface due to its slower solidification as compared with PA. Hence the matrix may be considered to have been made up of PA rich inner core and CA rich outer surface. Further dissolution of drug causes formation of large cracks on the bead surface and at this stage the drug release is not controlled by waxes, indicating rather that the increase in wax percentage causes faster drug release. Though it cannot be explained completely with the present data, it may be related to the size of the channels formed after erosion. It is clear that in the mixture of waxes, each wax exhibits different solidification and erosion rates and due to which no significant improvement in the release retardation was observed after increasing the proportion of the waxes in the beads.

CONCLUSION

In an attempt to prolong drug release using a combination of waxes, it was observed that no significant improvement in the release retardant activity was observed in the beads containing a higher percentage of waxes. It may be attributed to the difference in the solidification and erosion behavior of the waxes. Therefore, it was concluded that waxes for the combination should be selected on the basis of their erosion and solidification behavior.

Table 4. Transition in Differential Scanning Calorimetry Thermogram of Ibuprofen

	Normalized energy for melting (J/g)		
Dissolution time	**Cetyl alcohol**	**Palmitic acid**	**Ibuprofen**
0 hour	7.87	8.27	85.58
4 hour	2.76	22.68	41.82
6 hour	1.52	38.42	24.03

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