Sintering of Wax for Controlling Release From Pellets

Received: January 23, 2006; Final Revision Received: April 7, 2007; Accepted: April 11, 2007; Published: September 14, 2007

Reena Singh,[1] S. S. Poddar,[1] and Amit Chivate[1]

[1]Principal K. M. Kundnani College of Pharmacy, Cuffe Parade, Mumbai 400005, India

ABSTRACT

The purpose of the present study was to investigate incorporation of hydrophobic (ie, waxy) material into pellets using a thermal sintering technique and to evaluate the pellets in vitro for controlled release. Pellets prepared by extrusion-spheronization technology were formulated with a water-soluble drug, microcrystalline cellulose, and carnauba wax. Powdered carnauba wax (4%-20%) prepared by grinding or by emulsification was studied with an attempt to retard the drug release. The inclusion of ground or emulsified carnauba wax did not sustain the release of theophylline for more than 3 hours. Matrix pellets of theophylline prepared with various concentrations of carnauba wax were sintered thermally at various times and temperatures. In vitro drug release profiles indicated an increase in drug release retardation with increasing carnauba wax concentration. Pellets prepared with ground wax showed a higher standard deviation than did those prepared with emulsified wax. There was incomplete release at the end of 12 hours for pellets prepared with 20% ground or emulsified wax. The sintering temperature and duration were optimized to allow for a sustained release lasting at least 12 hours. The optimized temperature and duration were found to be 100°C and 140 seconds, respectively. The sintered pellets had a higher hydrophobicity than did the unsintered pellets. Scanning electron micrographs indicated that the carnauba wax moved internally, thereby increasing the surface area of wax within the pellets.

KEYWORDS: Controlled release, pellets, thermal sintering, waxes, theophylline.

INTRODUCTION

Using a multiple-unit dosage form such as pellets as an oral controlled release formulation offers several advantages: pellets disperse freely in the gastrointestinal tract and thus maximize drug absorption, reduce peak plasma fluctuations, and minimize side effects; high local concentrations of drug are avoided; there is flexibility in the development of oral dosage forms as pellets, so different drug substances (eg, incompatible drugs) can be formulated and blended into a single dosage form; and immediate- and controlled-release pellets can be mixed to achieve the desired release pattern. Matrix pellet formulations offer the advantage of a 1-step production procedure, as compared with coated pellets. Researchers have already explored the possibilities of using microcrystalline wax and starch mixtures as excipients for the production of matrix pellets.[1-3]

In 2 studies by Rao et al, controlled release polymeric systems of rifampicin were prepared by mixing the drug and ethylene vinyl acetate copolymer, which were then compressed at room temperature. These matrices were exposed at 60°C, 70°C, and 80°C for 1.5, 3, and 4.5 hours for sintering. The sintering time markedly affected the drug release properties of the ethylene vinyl acetate copolymer matrices. The percent released decreased as the sintering temperature was increased, for all formulations.[4,5] The release followed a diffusive mechanism, with first-order release kinetics. A similar effect was seen when rifampicin was replaced with theophylline[6] and when ethylene vinyl acetate copolymer was replaced with Eudragit RL100 matrices.[7] In another approach, polymeric systems for the controlled release of drugs have been reported where macromolecular drugs and ethylene vinyl acetate copolymer powders were mixed below the glass transition temperature of the polymer and compressed at a temperature above the glass transition point. The macromolecular drug was not exposed to organic solvent during fabrication. Kinetic studies indicated that there was sustained release, and the bioactivity of the macromolecular drug was found to remain unchanged throughout sintering and release.[8] Waxes are one of the excipients being investigated for their use in controlled release pharmaceutical formulations.[9] Waxes are used either as a matrix[10] or as a coating polymer so as to sustain the release of the drug.[11] The use of carnauba wax in combination with Eudragit L100 has been reported. The wax maintained its integrity, while Eudragit L100 slowly eroded the matrix as the drug was released.[12] Carnauba wax was also used in the preparation of microspheres that were spherical and smooth and had an extended release.[13] For transforming solids into fine particles, grinding (impact and shear) is the most common method. It is recognized that waxes (eg, carnauba wax) that are plastic in nature are difficult to grind.[14] Another technique exploited is emulsification. No simultaneous use of waxes and sintering for controlled release has been reported in the literature.

Corresponding Author: Amit Chivate, 103 Indu Apt, Friends Colony, Bhandup (East), Mumbai – 400 042, Maharashtra, India. Tel: +91 22 25688845; E-mail: amitchivate@rediffmail.com

Table 1. Formulation Details and Properties of Unsintered and Sintered (at 100ºC for 3 Minutes) Pellets Prepared Using Ground Wax (180 to 250 μm)*

Batches	Ingredients (%)			Treatment	Hardness-Friability Index	Angle of Repose (°)	Sphericity (%)
	Theophylline	MCC	Carnauba Wax				
B1	46	50	4	Unsintered	51	34	73% ± 5%
				Sintered	52	33	73% ± 4%
B2	44	50	6	Unsintered	49	35	71% ± 5%
				Sintered	51	34	71% ± 4%
B3	40	50	10	Unsintered	43	39	64% ± 7%
				Sintered	45	37	66% ± 6%
B4	30	50	20	Unsintered	36	44	51% ± 7%
				Sintered	38	41	54% ± 6%

*MCC indicates microcrystalline cellulose.

The present study involved the preparation of fine wax particles by emulsification. These fine carnauba wax particles were incorporated and subsequently sintered thermally for a few minutes. The effects of wax concentration, sintering temperature, and duration on the drug release and physical properties of pellets were studied. A release time from the matrix pellets of 10 to 12 hours was desired.

Materials and Methods

Materials

The active ingredient used in the study was theophylline anhydrous (Cipla Ltd, Goa, India). The matrix material used was carnauba wax (SD Fine Chemicals, Mumbai, India), while microcrystalline cellulose (MCC; SD Fine Chemicals) and talc (SD Fine Chemicals) were used as pelletization facilitators. Other materials used were of analytical grade.

Methods

Preparation of Fine Particle–Sized Carnauba Wax

An emulsification of molten wax (oil-in-water) was attempted to obtain finer particles of carnauba wax. Two phases were prepared: an aqueous phase containing purified water (5000 mL), and a nonaqueous phase containing carnauba wax (500 g). Tween 80 (5 g), employed as an emulsifier, was added to the aqueous phase. Prior to emulsification, water and carnauba wax were heated and maintained at ~90°C. The emulsification was performed by addition of the oily phase to the aqueous phase, maintaining the temperature at 90°C, which minimized the premature solidification of the wax during the mixing of the 2 phases. The 2 phases were homogenized with the help of a high-shear homogenizer (Wadegati, Gujarat, India) at a speed of around 1500 ± 50 rpm for ~5 minutes. The emulsion was then cooled by addition of 5000 mL of purified water maintained at 10°C ± 5°C, which caused the wax globules to congeal. The congealed wax was then filtered off, washed 3 times with 1000 mL of purified water, and vacuum-dried at 40°C for 24 hours. The dried wax was passed through a 200# sieve. The fine wax obtained was used for all subsequent work.

Particle Size Determination of Carnauba Wax

Particle size analysis of wax prepared by grinding or emulsification was performed. The powders were suspended in glycerin, spread on slides, and observed under an optical microscope. The 2 dimensions (ie, length and breadth) of 100 particles (in micrometers) were determined using an ocular micrometer that had been calibrated against a standard-stage micrometer.

Pellet Manufacturing

Pellets were prepared according to the formula given in Table 1. The batch size for each formula was 250 g. Theophylline (80# sieve), MCC (80# sieve), and wax (200# sieve) were mixed in a blender (Karnavati, Mumbai, India). The blend was wet-agglomerated using purified water (60 mL). The wet mass obtained was extruded through a punched metal sieve (1.00 mm) manually. The extrudates obtained were processed in a spheronizer (Fuji Paudal, Osaka, Japan) at a speed of 1000 rpm for 3 minutes. Spheronization speed was optimized in the earlier batches. The pellets were dried in a conventional hot air oven (Thermolab, Mumbai, India) at 50ºC for 4 hours. Pellets were size-classified using 10#/14# sieves to provide a size range of 710 to 1000 μm.

Sintering

Samples of pellets from each batch were subjected to thermal treatment.[15-17] The pellets were placed on aluminum foil and subjected to various temperatures and durations ranging from 90ºC to 120ºC and 60 seconds to 240 seconds, respectively, in an oven (Met Lab, 1500W, Mumbai).

In Vitro Release Studies

The dissolution tests were performed using the US Pharmacopeia rotating basket method. Stirring speed was maintained at 100 rpm. Distilled water was used as a dissolution medium and maintained at 37ºC ± 0.5ºC. Aliquots, each with a 5-mL volume, were withdrawn at regular intervals, filtered, diluted suitably, and assayed spectrophotometrically. The samples were analyzed at 272 nm using a double-beam spectrophotometer (Shimadzu Model No UV 1601, Seoul, Japan) to assay the amount of theophylline released at each time point. Dissolution studies were performed in triplicate, and mean values were taken for each batch.

Volume, Density, and Compressibility

A 50-g sample was put into a 250-mL graduated cylinder of a volume and density apparatus (Shivani Scientific Industries, Mumbai). The volume was noted as being bulk volume or fluff volume. The cylinder was then tapped 1250 times until the volume of the sample was reduced to a constant or consolidated one. Bulk density, tapped density, and Carr's percent compressibility were calculated.[18]

Flow Properties

The static angle of repose was measured according to the standard method. A conical funnel with a diameter of 74 mm at the cone base, a stem length of 33 mm, and a constant diameter of 13 mm was used. This was secured above a paper on a flat horizontal surface such that the axis of symmetry of the funnel was perpendicular to the paper. The powder was carefully poured through the funnel. A conical heap with a consistent height-to-radius ratio was formed. The average height and radius of the heap was noted. Angle of repose (θ°) was calculated from the standard trigonometric relationship.[18]

Sphericity

The sphericity was measured using the optical microscope. The length and breadth of the spherules were measured. A frequency distribution of the ratio of length to breadth of 100 particles was calculated.[19] The sphericity (S) was calculated by the following formula:

$$S = \frac{1}{\sum B^2 \times RF} \times 100 \qquad (1)$$

where B is lower class limit and RF is relative frequency.

Hardness-Friability Index

This was calculated on the basis of the results of the friability test. For this purpose, 10 g of pellets were placed in a Roche friabilator and rotated for 10 minutes at 25 rpm. The pellets were then screened through a 40# sieve to remove the fines generated.[20] The hardness-friability index was calculated as follows:

$$\%HFI = \frac{F_b}{F_a} \times 100 \qquad (2)$$

where F_b and F_a are weights before and after friability treatment, respectively.

Wettability

Pellets from optimized batch B3, both the one that was unsintered and the one that was sintered at 140 seconds, were fixed on a clean, dry glass slide. A 15-μL drop of distilled water was placed carefully with the help of a microsyringe on the pellet. Photographic impressions of the water drop in contact with the pellet were recorded in the static stage.

Differential Scanning Calorimetry

Differential scanning calorimetry (Mettler Toledo, Model No DSC 821^e, Schwerzenbach, Switzerland) scans of theophylline, carnauba wax, and the mixture were performed. A 6-mg sample was heated in a cuvette from 50ºC to 300ºC at a rate of 1°C/10 minutes.

Scanning Electron Microscopy

To understand any changes in the surfaces, the topography of pellets was analyzed with the help of scanning electron microscopy (SEM; Cemeca, Tokyo, Japan). The pellets from optimized batch B3, both the one that was unsintered and the one that was sintered at 140 seconds, were selected. Pellets were mounted on a metal holder with silicon adhesive and then sputter-coated with gold. Pellets were examined with the scanning electron microscope at an accelerating voltage of 20 kV.

Results and Discussion

It can be observed from Figure 1 that mere incorporation of wax into the formulation did not retard the release. A polymer concentration as high as 20% could not sustain the release of drug for more than 3 hours. Hence, the technique of sintering was used to slow the drug's release from the wax matrix.

Preparation of Fine Particle–Sized Carnauba Wax

Size reduction of the wax was attempted either in the solid condition (ie, by grinding) or in the liquid condition (ie, by

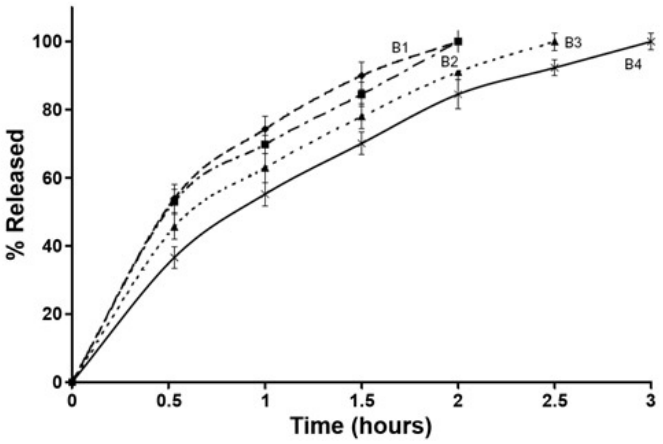

Figure 1. Dissolution profile of various batches of unsintered pellets prepared with emulsified wax (n = 3).

emulsification). The lowest particle size of wax that could be obtained by grinding was in the range of 180 to 250 μm. It was observed that extrusion of wax particles obtained by grinding was difficult. In addition to that, the pellets showed significant differences in terms of shape and integrity. This adversely affected the process of sintering and subsequently the drug release. Therefore, the particle size of carnauba wax needed to be reduced. In the present work, the method attempted for size reduction of carnauba wax was emulsification. Emulsification resulted in fine spherical wax particles. The powder recovery from this was ~99% of the wax load in the emulsion. When the stirring speed was reduced to 1200 rpm or lower, larger spherical particles of wax were formed, which on drying did not pass through a 200# sieve. At a speed above 1500, no further decrease in particle size was observed. By maintaining the temperature of both the aqueous and wax phases at 90°C, we ensured that the wax did not congeal before it could be emulsified into a spherical particle. When the concentration of the surfactant was kept below 1%, a significant change in the particle size and shape was observed. Increasing the concentration to 1.5% did not make much difference; thus, the concentration of the surfactant was optimized at 1%. Carrying out emulsification at the optimized condition resulted in wax particles of 45 to 75 μm.

The nature of the drug and MCC and the fine particle size of wax obtained through emulsification proved to be conducive for pelletization without a need for additional binder. Using wax of finer particle size increased the wax's surface area, which was important to ensure maximum coverage and homogeneity in the pellets. This also helped in improving shape and integrity, which is discussed further below.

Preparation of Pellets

The content of the MCC was optimized from the initial trials to improve the shape and sphericity of the pellets. The spheronization at optimized conditions yielded 85% wt/wt pellets of 710 μm to 1000 μm. This may have been due to the self-binding nature of MCC to hold water. It was observed that desirable pellets could be formed even in the presence of a hydrophobic material like carnauba wax in a concentration as high as 20%. The pellets prepared with ground wax were irregular in shape and had low sphericity. They were also mechanically weaker. Results can be seen in Table 1. The findings can be attributed to the irregular shape of the wax particles, which might have resulted in irregular distribution of wax, thus hampering the spheronization process. When dissolution studies were performed for unsintered batches containing the ground wax, the release was similar ($P < .05$) to that of batches prepared with the spherical wax particles. The only difference was the presence of a high standard deviation for the pellets prepared with ground wax. A similar phenomenon was observed with sintered batches. A high standard deviation can be observed in Figure 2, which can be correlated to uneven distribution of wax particles in the pellets. The pellets prepared from wax obtained through emulsification showed better shape and sphericity, which was attributed to the fine particle size of the pellets.

Sintering

To retard the release of the drug, pellets were sintered for different time intervals at various temperatures. The sintering time markedly affected the drug release properties of the carnauba wax matrices. The release of theophylline for batches B1 to B4 after sintering at 100°C for 240 seconds is shown in Figure 3. All the pellets were exposed to 240 seconds so as to maximize the movement of molten wax in the matrix. There was no significant difference in the release of theophylline ($P < .05$) at the same wax concentration when the pellets were sintered in the range of 90°C to 120°C. The wax

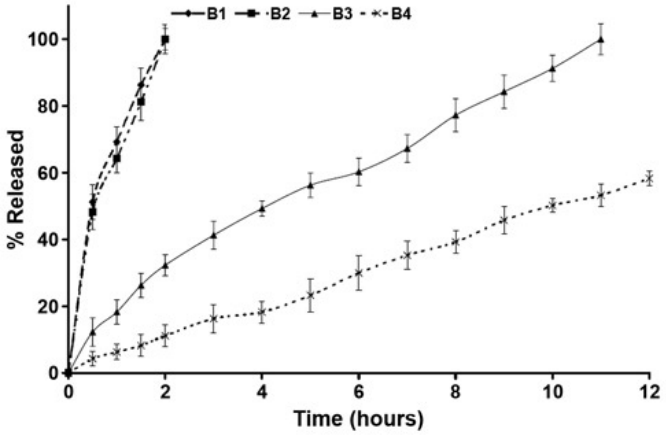

Figure 2. Dissolution profile of sintered batches prepared with ground wax (n = 3).

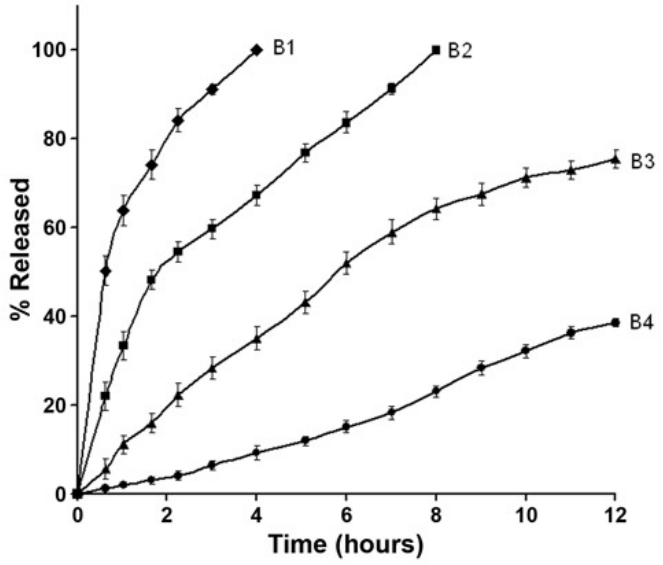

Figure 3. Dissolution profile of sintered batches prepared from emulsified wax (passed through a 200# sieve). Batches were sintered at 100°C for 240 seconds.

concentration did play a significant role in the release of the drug. At higher concentrations, release rates decreased. Complete release was observed for batches B1 and B2 in 4 and 8 hours, respectively. The release was incomplete at the end of 12 hours for batches B3 and B4. Only 78% and 43% of the drug was released at the end of 12 hours for batches B3 and B4, respectively. As complete release was observed at 8 hours for batch B2 and 78% release was observed at the end of 12 hours for batch B3, we decided to use batches B2 and B3 for further modification to obtain complete release in 12 hours. Evaluation of the physical properties of matrix pellets of theophylline before and after sintering revealed differences in their micromeritic properties, which are depicted in Table 2. Although sintered pellets showed a negligible change in sphericity, surfaces were smoother, which is discussed below in detail. As indicated by Figure 1, drug release was not retarded for more than 3 hours by simple incorporation of wax particles into pellets.

Unsintered pellets showed erosion during dissolution, which might have been due to the disintegrating property of MCC as well as the lack of cohesive bond between the neighboring wax particles (ie, there was no uniform matrix formation). On sintering, wax particles melted and penetrated the empty spaces, forming a continuous sheet around the drug and other materials present in the pellets, which increased the surface area of wax and thus indicated a nearly monolithic formation. In other words, sintering increased the percentage area of pellets covered, thereby improving the flow property. This thereby decreased the exposure of the drug to the dissolution medium, and hence the release of the drug was retarded. Although on sintering no change in the size, shape, or mass of pellets was noted, the improvement in the continuity of wax, approaching a type of monolith, reduced erosion and enhanced drug retardation. It is a fact that the true volume of materials remains constant. Therefore, it could be inferred that the void volume remained constant during sintering. This indicated maintenance of porosity. Thus, changes due to sintering might be in tortuosity and in the increase in continuity of wax layers.

Optimization With Batches B2 and B3

It is notable that the release rate of theophylline from carnauba wax matrices is inversely related to the time of sintering. Complete release of drug was achieved in 7 and 10 hours when batch B3 was sintered at 100ºC for 60 and 120 seconds, respectively, as shown in Figure 4. Sintering for 180 or 240 seconds did not yield a complete drug release; only 78% of the drug was released in 12 hours. Complete release of drug was achieved in 3 and 6 hours when batch B2 was sintered at 100ºC for 60 and 120 seconds, respectively. Sintering for 180 or 240 seconds yielded a complete release of the drug in 8 hours. This indicated that the 6% wax concentration is insufficient for sustaining the release of the drug for 12 hours even after sintering. Thus, no further modification was tried on batch B2. Batch B3 was further studied and modified for optimization of the drug release for 12 hours. The pellets were treated at 100°C for 140 and 160 seconds so as to have faster release in comparison to that of the 180-second-treated pellets, as shown in Figure 5. The release of the drug was complete for the 140- second-treated pellets, while 94% ± 1.2% was released for the 160-second-treated pellets. Thus, almost complete release of drug was observed when the pellets were treated. In short, it can be said that drug release decreased as sintering time increased for all formulations, which is in accordance with the literature studied.[4,5] But for these formulations no significant difference in release within the batch was

Table 2. Properties of Unsintered and Sintered (at 100ºC for 3 Minutes) Pellets Prepared Using Emulsified Wax (200 μm)

Batches	Treatment	Hardness-Friability Index	Angle of Repose (°)	Sphericity (%)
B1	Unsintered	57	29	76% ± 3%
	Sintered	90	27	80% ± 1%
B2	Unsintered	60	28	79% ± 3%
	Sintered	93	26	81% ± 2%
B3	Unsintered	62	28	80% ± 3%
	Sintered	94	26	81% ± 2%
B4	Unsintered	66	27	81% ± 3%
	Sintered	96	24	81% ± 1%

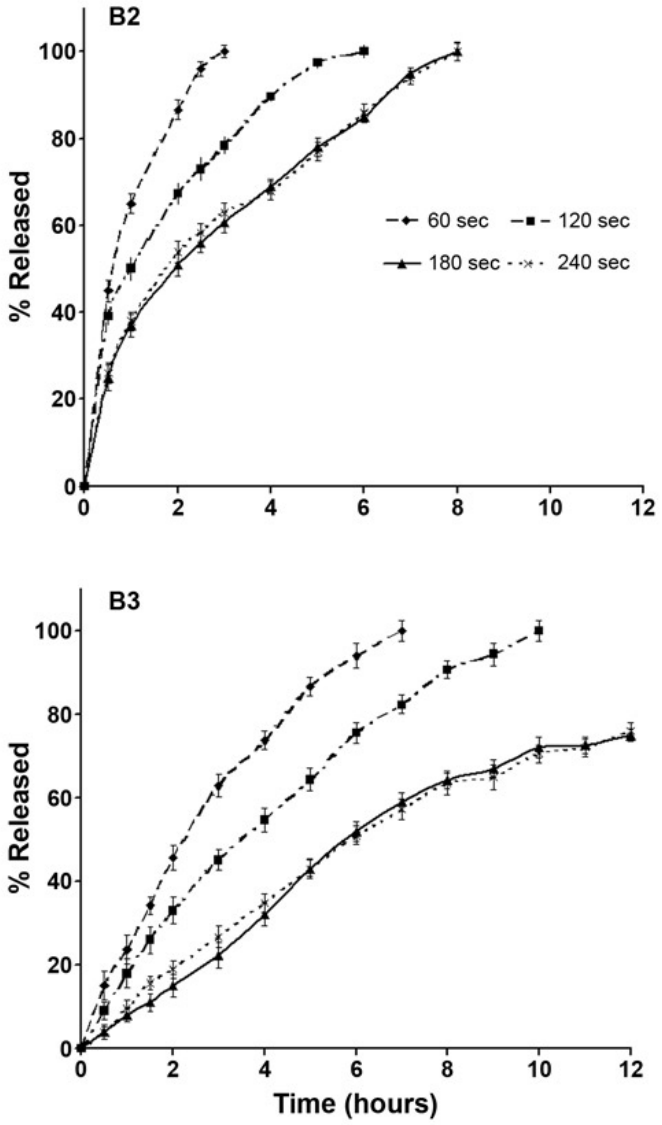

Figure 4. Dissolution profile of sintered batches B2 and B3 prepared from emulsified wax (passed through a 200# sieve) at 100ºC for various durations.

obtained when sintering lasted either 180 or 240 seconds. The minimum duration of sintering resulting in maximum release retardation appears to have been 180 seconds, as is evident from all the release profiles. Thus it can be inferred from the findings above that the time taken by the wax to heat up, melt, and fuse with neighboring particles would be at least 180 seconds. Thereafter there would be no improvement in matrix structure to favorably extend the drug release.

Kinetic Treatment

The coating of wax acted as a diffusion barrier and thus had a retarding effect on the drug release from pellets. The release data for pellets were further analyzed to find out whether they

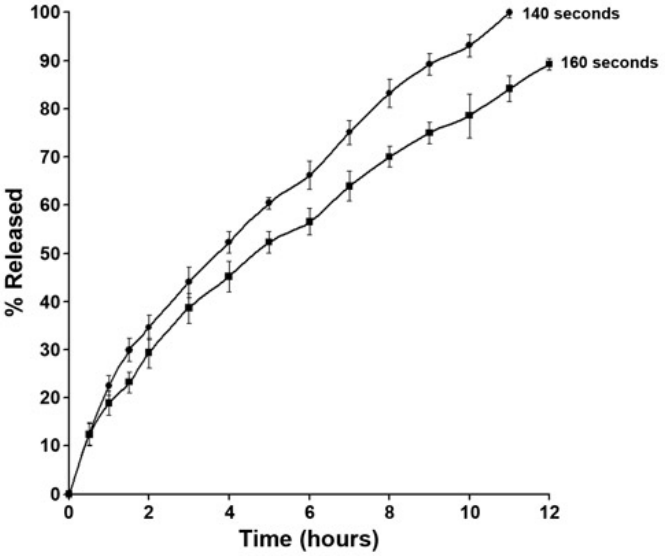

Figure 5. Dissolution profile of batch B3 sintered at 100ºC for 140 and 160 seconds (n = 3).

fit zero-order kinetics, first-order kinetics, or the Higuchi mechanism. The analysis revealed that the drug release did not fit first- or zero-order kinetics. When the square root of time vs percent drug released for the optimized batch was plotted, it was apparent that the release occurred via a matrix diffusion-controlled process, as shown in Figure 6. The pattern of drug release from sintered pellets was linear with the square root of time. The linear correlation coefficient of the profiles shown in Table 3 indicated that the drug release from the sintered carnauba wax matrix was via diffusion.

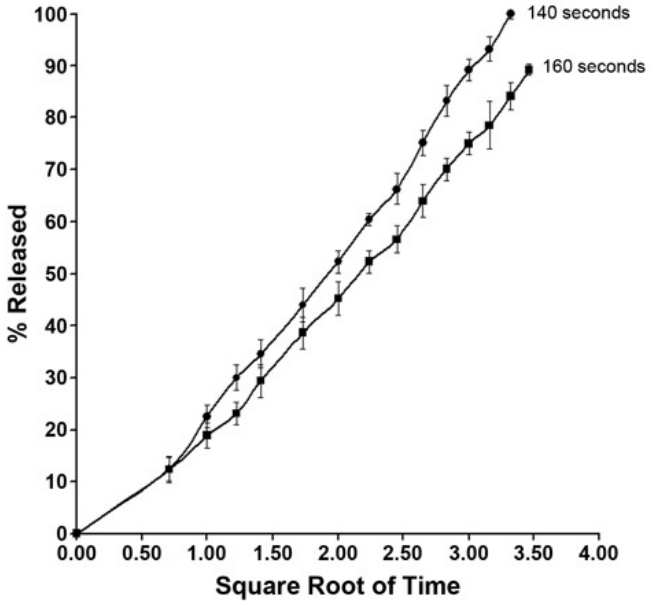

Figure 6. Higuchi treatments for batch B3 sintered at 100ºC for 140 and 160 seconds (n = 3).

Table 3. Kinetic Treatment for Batch B3 Sintered at 100°C for 140 and 160 Seconds*

	140 Seconds			160 Seconds		
Treatment	r^2	n	k (h^{-1})	r^2	n	k (h^{-1})
First order	0.5654	—	—	0.5771	—	—
Zero order	0.9697	—	—	0.9683	—	—
Diffusion (Higuchi)	0.9922	—	—	0.9904	—	—
Korsmeyer-Peppas model	0.9914	0.5996	0.2221	0.9961	0.5769	0.2389

*k indicates release rate constant; n, diffusional release exponent; r^2, correlation coefficient.

To gain some insight into the drug release mechanism, a very simple and semi-empirical equation to describe drug release from polymeric systems, the power law (Korsmeyer-Peppas model), was also applied[21,22]:

$$\frac{M_t}{M_\infty} \equiv kt^n \qquad (3)$$

Here, M_t and M_∞ are the absolute cumulative amount of drug released at time t and infinite time, respectively; k is a constant incorporating structural and geometric characteristics of the device; and n is the release exponent, indicative of the mechanism of drug release.[21] Thus, Equation 3 implies 2 meanings, $n = 0.5$ (indicating diffusion-controlled drug release) and $n = 1.0$ (indicating swelling-controlled drug release). Values of n between 0.5 and 1.0 can be regarded as indicating the superposition of both phenomena (anomalous transport). It is important to remember that the 2 extreme values for the exponent n, 0.5 and 1.0, are valid for only slab geometry. For spheres and cylinders, different values have been derived,[22,23] as listed in Table 3. Unfortunately, this fact is not always taken into account, leading to misinterpretations of experimental results. The n values obtained were 0.5996 and 0.5769 for 140- and 160-second-treated samples. Thus, it can be concluded that the release of the drug from sintered matrix pellets was due to anomalous transport, which is well supported by the literature.[24-26]

Wettability

Figure 7 shows that the contact angle for sintered pellets was greater than that of the unsintered pellets. This indicated an improvement in hydrophobicity in the sintered pellets. As is apparent, the surface of the unsintered pellets consisted of particles from the entire formula (ie, the dominance of wax was much less). When a drop of liquid was placed on an unsintered pellet, the advancing liquid might have encountered a surface with fewer waxy areas and probably a large number of microscopic cracks, leading to a smaller contact angle. In contrast, the larger contact angle for sintered pellets indicated resistance to the advancing liquid. This could be explained only by increased dominance of wax and existence of a smoother surface—that is, having fewer microscopic cracks because of the melting and spreading of wax.

Flow and Other Properties of Pellets

The densities and Carr's compressibility of sintered pellets were between 0.72 and 0.82 g/cm^3, and 5% and 7%, respectively. The low values of Carr's index (less than 15%) indicate good flowability of the spheroids for all batches, since the angle of repose of all the formulations was less than or equal to 30° (±0.13°-0.59°).[27] As these figures reveal, sintered pellets had a packing property superior to that of unsintered pellets. The average percent hardness index of sintered pellets and unsintered pellets was 93 and 71, respectively, which indicated that sintered pellets were harder than unsintered ones. The low hardness obtained when the pellets were unsintered as well as when they were sintered at a low temperature indicated that the main forces holding the particles together were probably Van der Waals and mechanical forces caused by the interlocking of irregularities on the surface of the particles making the pellets. Increasing the temperature and/or time of exposure to a particular degree during sintering boosted the hardness, because of the fusion of wax particles or formation of welded bonds among the particles. These and the forces mentioned earlier contributed to the final hardness of the sintered pellets. The Van der Waals, mechanical force, and the welded bonds would therefore help to reduce the subsequent wear and tear from handling, especially during transport and packaging.

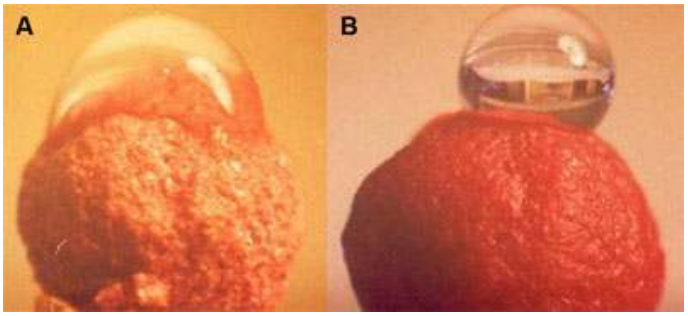

Figure 7. Photomicrographs showing contact of water with (A) unsintered pellet and (B) sintered pellet.

Differential Scanning Calorimetry

Differential scanning calorimetry plots in Figure 8, corresponding to the qualitative composition of the drug formulations, verified the identity of each of the components and indicated the absence of interaction or complexation throughout the process of pelletization and sintering.

SEM

The SEM photographs in Figure 9 indicate that wax particles did flow and improve the matrix structure on thermal treatment. The sintered surface appears smoother than the unsintered surface. This is the reason for the increase in the hydrophobicity of sintered pellets, which caused the increase in the release extension.

CONCLUSION

On thermal sintering of the pellets, the wax changed from finely divided particles to films and sheaths, as reflected by the wax's non-eroding nature during dissolution and as shown in improved drug release retardation. By selecting the proper wax-to-drug ratio and sintering condition, we formulated an effective controlled-release dosage form using a model therapeutic (ie, theophylline). During sintering, the drug did not undergo any degradation or complexation by which its release could be retarded.

ACKNOWLEDGMENT

The authors are grateful to Cipla (Goa, India) for the supply of theophylline.

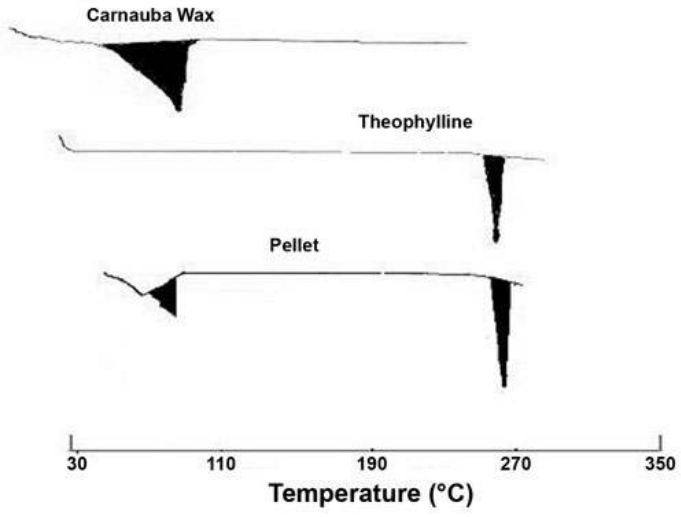

Figure 8. Differential scanning calorimetry scan of carnauba wax, theophylline, and sintered pellet at 100°C.

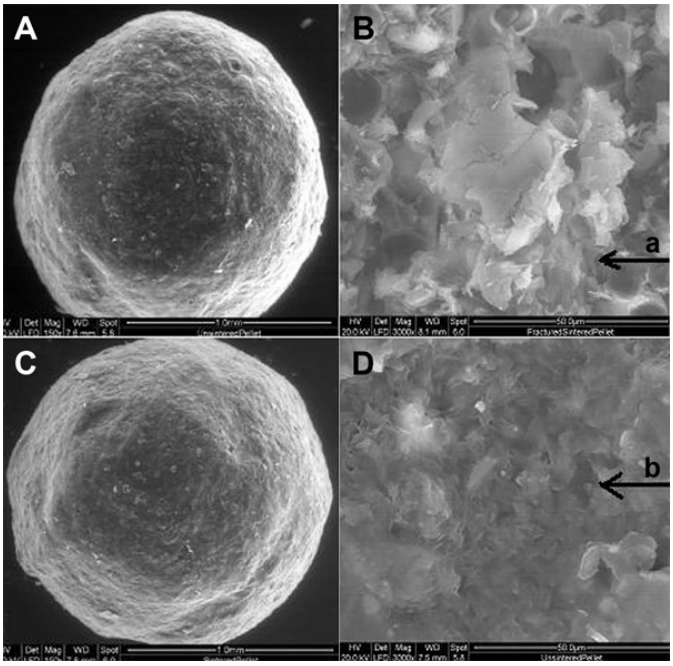

Figure 9. Scanning electron microscope images of (A) unsintered pellet (low magnification); (B) unsintered pellet (high magnification); (C) sintered pellet (low magnification); and (D) sintered pellet (high magnification). (a) indicates rough surface; (b), smoother surface.

REFERENCES

1. Sellassie IG, Gordon RH, Fawzi MB, et al. Evaluation of a high-speed pelletization process and equipment. *Drug Dev Ind Pharm.* 1985;11: 1523–1541.

2. Ghebre-Shellasie I. Pellets: a general overview. In: Ghebre-Shellasie I, ed. *Pharmaceutical Pelletization Technology.* New York, NY: Marcel Dekker Inc; 1989:6–7.

3. Vervaet C, Baert L, Remon J. Extrusion spheronisation: a literature review. *Int J Pharm.* 1995;116:131–146.

4. Rao BS, Cheruvu PS, Sudha KS, et al. Studies on release of rifampicin from sintered matrix tablets. *Indian J Pharm Sci.* 2001; 63:371–378.

5. Rao BS, Seshasayana A, Himasankar K, et al. Design and evaluation of ethylene vinyl acetate sintered matrix tablets. *Indian J Pharm Sci.* 2003;65:496–502.

6. Kondaiah A, Prakash K. Design of controlled release non-erodible polymeric matrix tablets of theophylline using sintering technique. *Indian J Pharm Sci.* 2002;64:239–243.

7. Rao BS, Seshasayana A, Himasankar K, et al. Design and evaluation of eudragit RL 100 sintered matrix tablets. *Indian J Pharm Sci.* 2004;66:202–207.

8. Cohen J, Siegel RA, Langer R. Sintering technique for the preparation of polymer matrices for the controlled release of macromolecules. *J Pharm Sci.* 1984;73:1034–1037.

9. Zhou F, Vervaet C, Remon JP. Matrix pellets based on the combination of waxes, starches and maltodextrins. *Int J Pharm.* 1996;133:155–160.

10. Zhang YE, Tchao R, Schwartz JB. Effect of processing methods and heat treatment on the formation of wax matrix tablets for sustained drug release. *Pharm Dev Technol.* 2001;6:131–144.

11. Pandey VP, Kannappan N, Manavalan R, Subburaj T. Sustaining pattern of phenformin hydrochloride using various polymers and waxes. *Boll Chim Farm.* 2002;141:361–366.

12. Walia PS, Stout PJ, Turton R. Preliminary evaluation of an aqueous wax emulsion for controlled release coating. *Pharm Dev Technol.* 1998;3:103–113.

13. Huang HP, Mehta SC, Radebaugh GW, Fawzi MB. Mechanism of drug release from an acrylic polymer-wax matrix tablet. *J Pharm Sci.* 1994;83:795–797.

14. Ghaly ES, Sepulveda S. *In-vitro* evaluation of sustained release ibuprofen microspheres. *P R Health Sci J.* 1996;15:97–100.

15. El-Shanawany S. Sustained release of nitrofurantoin from inert wax matrices. *J Control Release.* 1993;26:11–19.

16. Kondaiah A. Design of controlled release non-erodible polymeric matrix tablets of theophylline using sintering technique. *Indian J Pharm Sci.* 2002;64:239–243.

17. Luk CL, Jane HL. Sintering in pharmaceutics. In: Swarbrick J, Boylan JC, eds. *Encyclopedia of Pharmaceutical Technology.* vol. 14. New York, NY: Marcel Dekker; 1996:87–101.

18. Mehta AM. Evaluation and characterization of pellets. In: Sellassie IG, ed. *Pharmaceutical Pelletization Technology.* New York, NY: Marcel Dekker; 1989:241–263.

19. Eriksson M, Nyström C, Alderborn G. The use of air permeability for the assessment of external surface area and sphericity of pellitised granules. *Int J Pharm.* 1993;99:197–207.

20. Nasipuri RN, Omotosho JA. Influence of surfactant-treated starch on the disintegration and dissolution of sulphadiazine tablets. *J Pharm Pharmacol.* 1985;37:212–213.

21. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. *Int J Pharm.* 1983;15:25–35.

22. Ritger PL, Peppas NA. A simple equation for description of solute release, II: Fickian and anomalous release from swellable devices. *J Control Release.* 1987;5:37–42.

23. Ritger PL, Peppas NA. A simple equation for description of solute release, I: Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. *J Control Release.* 1987;5:23–36.

24. Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. *Eur J Pharm Sci.* 2001;13:123–133.

25. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Adv Drug Deliv Rev.* 2001;48:139–157.

26. Sezer AD, Akbuga J. Controlled release of piroxicam from chitosan beads. *Int J Pharm.* 1995;121:113.

27. Gordon RE, Rosanske WT, Fonner DE, Anderson NR, Banker GS. Granulation technology and tablet characterization. In: Lieberman HA, Lachman L, Schwartz JB, eds. *Pharmaceutical Dosage Forms: Tablets.* New York, NY: Marcel Dekker; 1990: 245–348.