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THERMAL TREATMENT OF BEADS WITH WAX FOR CONTROLLED RELEASE

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ABSTRACT

Beads prepared by extruder/marumerizer technology were formulated with water soluble drugs, microcrystalline cellulose and several waxy materials. The waxes (10 to 50% by weight) were included in an effort to slow drug release. Subsequent thermal treatment of these beads was applied. Beads were processed to determine the

effect of varying wax level, excipient, active drug, and effect of heat treatment. In-vitro drug release profiles were evaluated for the untreated and thermal treated beads. In general, the simple incorporation of wax into the granulation did not provide the desired controlled release dissolution profile. Thermal treatment of the finished beads, however, resulted in products which behaved in a different manner during dissolution testing and in general provided slower release. Drug release was found to vary with the type and level of wax, drug, excipient, and the thermal treatment.

INTRODUCTION

Beads or pellets are often used for controlled release technology, usually after the application of a specialized coating.[1-4] Uncoated beads composed primarily of microcrystalline cellulose (MCC) have also been shown to exhibit an inert porous matrix type of release[5].

Such matrix behavior was first demonstrated for tablets[6] and later studies by Schwartz et al[7] and Goodhart et al[8] investigated the use of waxes in tablet matrix systems. Other authors have also

investigated waxes to slow drug release[9-14]. Although bead coating with waxes is an established technology, the authors are not aware of any studies on the incorporation of wax materials into bead formulations.

The incorporation of a series of waxy materials into bead formulations prepared by extruder/marumerizer technology is described in the present study. The purposes of the study are to attempt to slow drug release from beads without the use of a coating operation and to determine whether melting of waxes would aid in matrix formation. The effects of wax level, drug concentration, and temperature of the thermal treatment on drug release were evaluated.

MATERIALS AND METHODS

Materials

The active ingredients used in this study are: Chlorpheniramine maleate (CPM), USP and acetaminophen (APAP), USP (both supplied for this study by FMC Corporation, Philadelphia, PA).

The matrix material is microcrystalline

cellulose (Avicel PH-101, FMC Corporation, Philadelphia, PA). The individual waxes are spermaceti (Amend Drug & Chemical Co, N.J.); cetyl alcohol (Ruger Chemical Co., Irvington, N.J.); glyceryl palmitostearate (Precirol from Gattefosse Corporation, Elmsford, N.Y.); glyceryl monostearate (G.M.S, Ruger Chemical Co., Irvington, N.J.); castor wax (The Baker Castor Oil Company, Bayonne, N.J.); stearic acid (Ruger Chemical Co., Irvington, N.J.); polyethylene glycol 8000 (P.E.G. 8000, Fisher Scientific, Pittsburgh, PA) and beeswax (Ruger Chemical Co., Irvington, N.J.).

Pellet Manufacturing

Beads or pellets were manufactured according to the following formula:

Drug	10%
Avicel PH-101	60%
Wax	30%

and the batch size for each formula was 0.5 kg. When the formula was varied, the MCC was increased or reduced to compensate for changes in the drug level or wax level.

The drug, the microcrystalline cellulose and the waxes were blended in a planetary mixer (Kitchen Aid model K 5SS, Hobart Corporation, N.Y). Purified water was added to the mixtures in the planetary mixer to achieve the proper consistency. The wet granulations were passed through an extruder (Model EXDS-60, LUWA Corporation, Charlotte, NC). The extruder was operated at 50 rpm and fitted with 1.5 mm screens. The extrudate was processed in the spheronizer (Marumerizer, Model Q-230, LUWA Corporation) at 1000 rpm. The spheres were collected after 1-2 minutes residence time and dried on paper lined trays in a conventional hot air oven at a temperature of 40°C.

Thermal Treatment

A sample of beads from each of these formulas was subjected to a special thermal treatment by placing the beads in a glass beaker in an oven at 80°C for 30 minutes. Other temperatures were investigated and are noted below for individual waxes. The list of waxes and their melting points are presented in Table 1.

TABLE 1. Melting Points of the Waxes

WAX	MELTING POINT (degrees C.)
Spermaceti	42 - 52
Cetyl alcohol	45 - 50
Glyceryl palmitostearate (Precirol)	52 - 55
Glyceryl monostearate (GMS)	56 - 58
Beeswax	62 - 65
Stearic acid	69 - 70
Castor wax	86 - 88
PEG 8000	-

Dissolution Studies

Dissolution testing was performed before and after thermal treatment in 900 ml distilled water at 37°C using the USP/NF basket method at a rotational speed of 50 rpm over a 2 hour period. A sample of beads of 16/30 mesh fraction was selected for dissolution to eliminate the effect of pellets surface area on drug dissolution. Samples were analyzed by UV spectroscopy (Beckman DU spectrophotometer) at the maximum wavelength of 264

nm for chlorpheniramine maleate and 249 nm for acetaminophen.

RESULTS AND DISCUSSION

The manufacturing of beads was successful for all formulations, with the exception of the preparation containing polyethylene glycol 8000 at a 30% level. This formula was processed in the marumerizer for only a 0.5 minute residence time because of sticking to the plate and wall of the marumerizer during processing.

The results with all other waxes, however demonstrated that waxes can be incorporated into pellets using extruder/marumerizer technology. The physical properties such as size and bed density are similar to the control beads, and the particle size distributions for these pellets represent a narrow distribution.

Figure 1 shows the dissolution profile for beads containing 10% CPM in Avicel PH-101 without wax. This profile was considered as the control and dissolution is essentially complete after 30 minutes. Beads appear to remain intact after the two hour dissolution test; this phenomenom would be

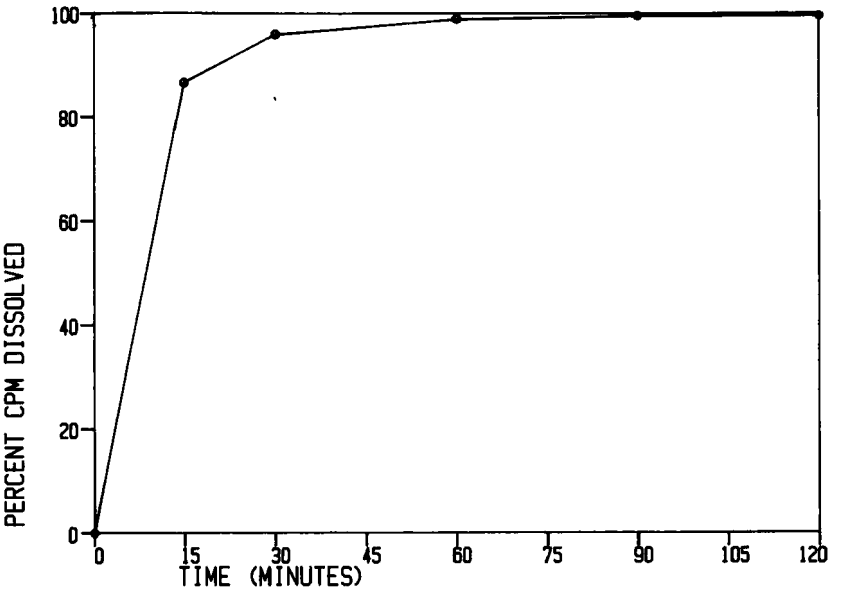

FIGURE 1. Dissolution profile of 10% CPM beads (control).

expected of an inert matrix release system[15]. This is also consistent with previously reported results on microcrystalline cellulose beads[16,17]. This profile was not reduced by the simple incorporation of wax; i.e, all beads with wax, tested before thermal treatment, yielded the same dissolution profile as that in Figure 1.

After the 80°C thermal treatment, beads with four of the waxes exhibited slower dissolution profiles. The four waxes were: spermaceti, Precirol, beeswax and castor wax (see Figure 2).

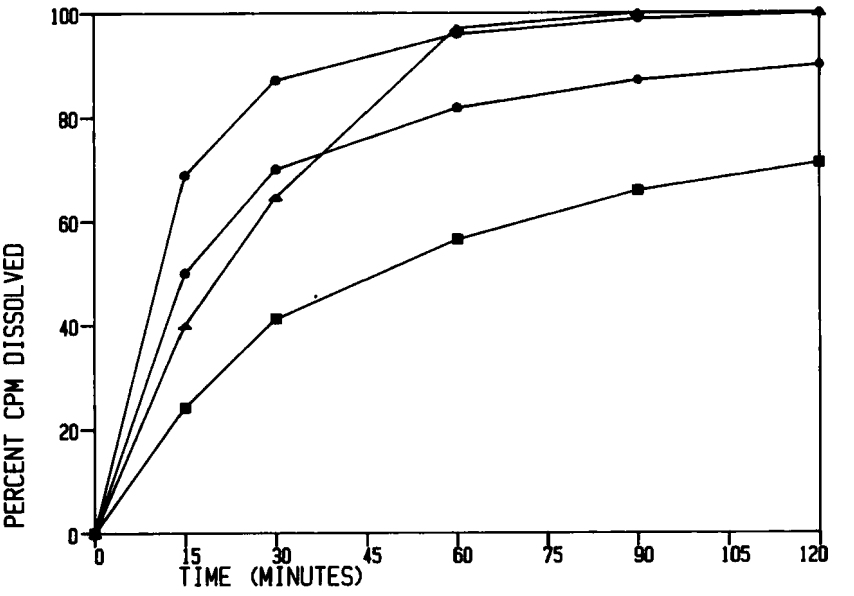

FIGURE 2

Dissolution profiles of 10% CPM / MCC beads with 30% wax. After thermal treatment. (▲) Precirol; (■) spermaceti; (●) beeswax; (○) castor wax.

The melting and resolidification of these waxes, due to the thermal treatment, have apparently resulted in a redistribution of the wax throughout the beads and a possible change in nature of the pores within the beads. This is indicated in the scanning electron photomicrographs in Figure 3 (a) and 3 (b). Further investigation of this phenomenon is underway.

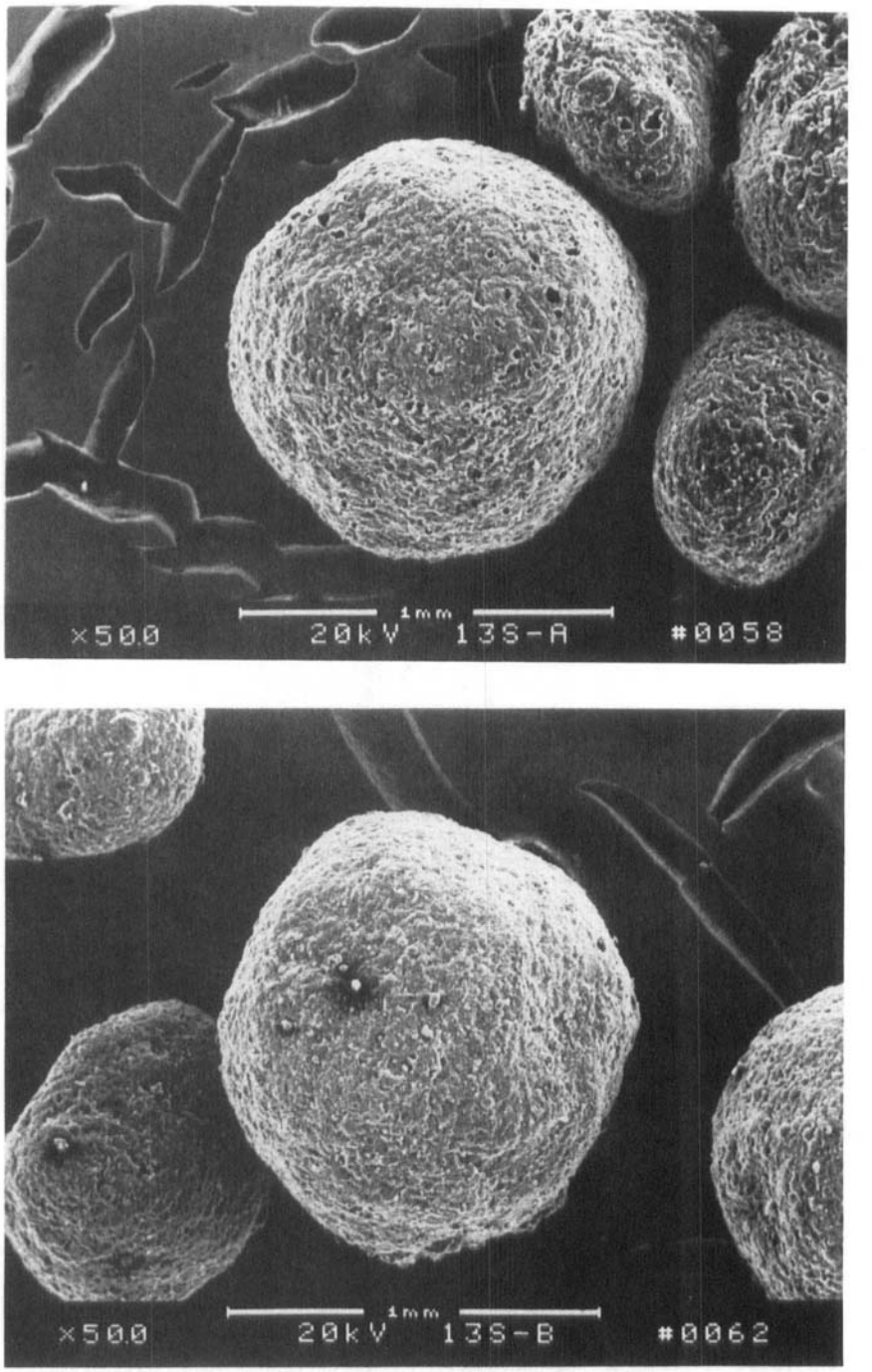

FIGURE 3

Scanning electron micrograph of 10% CPM / MCC beads with 10% Precirol. (a) after thermal treatment; (b) untreated (X50).

The other four waxes (stearic acid, GMS, cetyl alcohol and PEG 8000) are not effective in reducing dissolution even with the 80°C thermal treatment. They give the same dissolution profiles as the control formula (Figure 1). The effectiveness of the individual waxes does not appear to be related to the melting point.

Thermal treatment of the bead at a temperature

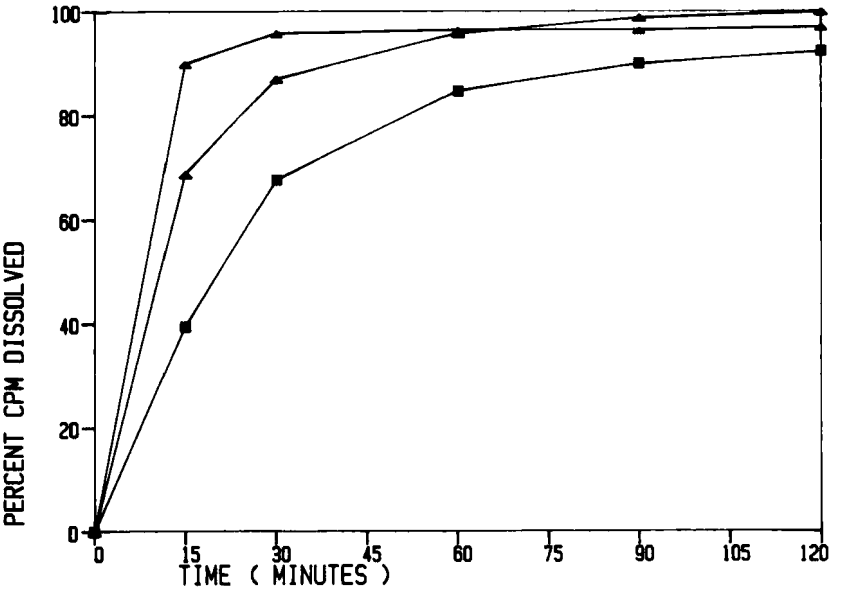

FIGURE 4

Dissolution profiles of 10% CPM / MCC beads with 30% castor wax (temperature effect). (△) control; (▲) oven 80 degrees; (■) oven 88-92 degrees.

closer to the wax melting points resulted in some expected results. The formula with 30% spermaceti was tested for dissolution after thermal treatment at a temperature of 50°C and, as expected, drug release was slower than the control. The 50°C treatment does not slow drug release to the same extent as the 80°C heat treatment. The same trend was observed with beeswax.

For castor wax, because its melting point is above 80°C, the beads that were treated thermally at a temperature of 90°C show a slower release profile than beads treated at a temperature of 80°C as shown in Figure 4.

Wax Concentration

When the wax level was varied, for one of the waxes, expected changes in the drug release were observed (after thermal treatment). The dissolution profiles for 10%, 30% and 50% Precirol levels are shown in Figure 5, and it is apparent that beads with the highest percent of wax exhibit the slowest drug release. This was also confirmed for stearic acid, but the results are not as dramatic.

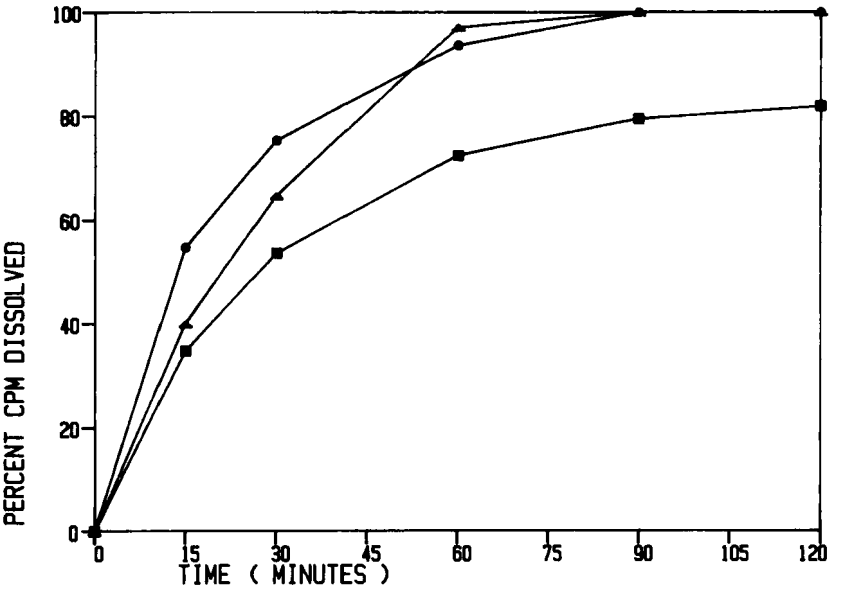

FIGURE 5

Dissolution profiles of 10% CPM / MCC beads with Precirol. After thermal treatment. (●) 10% Precirol; (▲) 30% Precirol; (■) 50% Precirol.

Drug Model

In order to determine if wax incorporation might have a more general application, another formula with a different drug model (acetaminophen) was investigated. Figure 6 shows the dissolution profile for a 30% stearic acid level, which was not effective in decreasing the release of the 10%

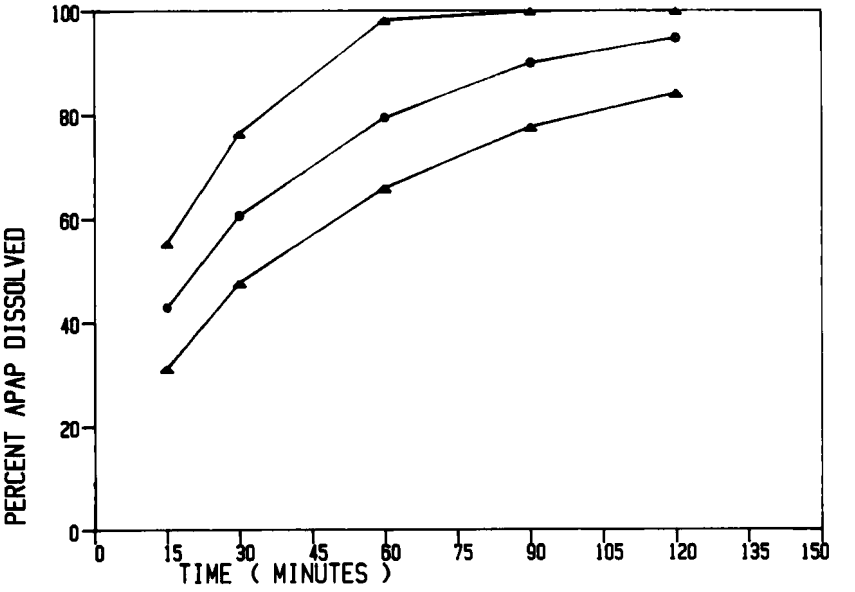

FIGURE 6

Dissolution profiles of 30% APAP / MCC beads. (○) control without wax; (△) 30% stearic acid, untreated; (▲) 30% stearic acid, after thermal treatment.

chlorpheniramine maleate but does have an effect when the beads contain 30% acetaminophen. The figure shows the profiles for a control bead without wax, untreated beads with wax, and thermally treated beads with the wax. The latter shows the slowest release.

It is interesting to note that the wax beads without thermal treatment are faster in drug release

than the control. This observation supports previous results in our laboratories indicating that the addition of most ingredients to drug / Avicel beads appears to increase the drug release slightly and interrupt the matrix formation. In this case, also, it appears that the addition of stearic acid to the inert matrix of drug with microcrystalline cellulose will interfere with the bond formation of the microcrystalline cellulose and will therefore increase the drug release slightly.

CONCLUSIONS

The results of this investigation show that beads prepared with specific quantities of waxy material can be processed via extruder/marumerizer technology. Although drug release from these beads is not affected by simple incorporation of a wax into the bead granulation, brief thermal treatment does slow the release. The effect, however, is not sufficient to provide a controlled release product. In general, the drug release from beads is dependent on the wax selected, the wax level and the degree of thermal treatment.

The present technique of bead formulation with

wax appears to have potential in production, since the waxes are simply added to the blended powders prior to granulation. Further studies to cause a slow release with these beads are indicated and will be reported in a separate communication.

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