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COMMUNICATION

Effect of Diluents on Tablet Integrity and Controlled Drug Release

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ABSTRACT

The objective of this study was to evaluate the effect of diluents and wax level on tablet integrity during heat treatment and dissolution for sustained-release formulations and the resultant effect on drug release. Dibasic calcium phosphate dihydrate (DCPD), microcrystalline cellulose (MCC), and lactose were evaluated for their effect on tablet integrity during drug dissolution and heat treatment in wax matrix formulations. A newly developed direct compression diluent, dibasic calcium phosphate anhydrous (DCPA), was also evaluated. Compritol® 888 ATO was used as the wax matrix material, with phenylpropanolamine hydrochloride (PPA) as a model drug. Tablets were made by direct compression and then subjected to heat treatment at 80°C for 30 min. The results showed that MCC, lactose, and DCPA could maintain tablets intact during heat treatment above the melting point of wax (70°C–75°C). However, DCPD tablets showed wax egress during the treatment. MCC tablets swelled and cracked during drug dissolution and resulted in quick release. DCPD and lactose tablets remained intact during dissolution and gave slower release than MCC tablets. DCPA tablets without heat treatment disintegrated very quickly and showed immediate release. In contrast, heat-treated DCPA tablets remained intact through the 24-hr dissolution test and only released about 80% PPA at 6 hr. In the investigation of wax level, DCPD was used as the diluent. The drug release rate decreased as the wax content increased from 15% to 81.25%. The dissolution data were best described by the Higuchi square-root-of-time model. Diluents showed various effects during heat treatment and drug dissolution. The integrity of the tablets was related to the drug release rate. Heat treatment retarded drug release if there was no wax egress.

Key Words: *Controlled release; Diluents; Heat treatment; Wax matrix.*

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INTRODUCTION

Wax has been extensively investigated for sustaining the release of drugs (1–6). The sustaining effect by simply incorporating wax into the granulation is not sufficient, especially for a highly soluble drug. Heat treatment of wax beads reported by Ghali et al. (6) showed that the treatment can retard chlorpheniramine maleate release. Since then, a few reports that utilize heat treatment to retard further the drug release from a polymer matrix or a coating have appeared in the literature (7–10). Generally, the heat treatment is done above the glass transition temperature or melting point of the polymer. The polymer probably penetrates and redistributes through the matrix system or coating on heat treatment. The resultant effect is to form a fine and stronger network and therefore retard the drug release. Heat treatment has been shown to be a promising method for sustained release; however, the effects of diluents on heat treatment have not been reported.

For matrix controlled-release systems, the drug dissolution rate is related to the matrix surface area. In the investigation of the effect of tablet integrity on the dissolution rate of sustained release, wax matrix aspirin tablets (ZORprin®, Boots Pharmaceuticals, IL) by Mandal (11) demonstrated that the split tablets consistently gave faster release over time, with a 50% higher release at 6 hr. The Higuchi diffusion model predicts that drug release from a diffusion-controlled system is related to its surface area. Broken tablets have larger surface areas and therefore exhibit faster release. Tablet integrity plays an important role in controlling drug release from a matrix controlled-release system. The application of heat treatment requires that tablets remain intact. However, the effects of diluents on heat treatment and tablet integrity have not been reported.

The objective of this study was to evaluate the effect of wax level and diluents on tablet integrity during dissolution and during heat treatment and the corresponding effects on drug release.

MATERIALS AND METHODS

Phenylpropanolamine hydrochloride (PPA; Amend Chemical, Irvington, NJ), a highly water soluble decongestant and appetite suppressant, was used as a model drug. Compritol® 888 ATO (glyceryl behenate, NF; Gattefosse, France), with a melting range of 70°C–75°C was incorporated as the wax matrix material. The three most commonly used diluents were used: dibasic calcium phosphate dihydrate (DCPD; DI-TAB®, Rhone-Poulenc, NJ), microcrystalline cellulose (MCC; Avicel® PH-102, FMC Corp., Princeton, NJ), and lactose (Fast Flo®, Sheffield, UK).

For a comparison with DCPD, dibasic calcium phosphate anhydrous (DCPA; Fujicalin®, Fuji Chemical Industrial Co., Englewood, NJ), a newly developed direct-compression excipient, was also evaluated for tablet integrity. According to the manufacturer, DCPA is highly compressible and promotes rapid dissolution.

Tablet Manufacture

The drug and the excipients were mixed in a twin shell blender for 10 min, and then the mixtures were compressed with a Manesty single-stroke F press with a 3/8-inch flat beveled edge tooling set. Tablet weight was set to 400 mg, and the target tablet hardness was 8–10 Kp.

Tablets were subjected to heat treatment at 80°C in an oven (NARCO, model 630, National Appliance Company, Portland, OR) for 30 min. After removing the tablets from the oven, the tablets were allowed to cool at room temperature, and dissolution was performed at least 24 hr after the treatment. The dissolution of tablets, with or without heat treatment, was performed in triplicate using the USP 23 basket method. The baskets were rotated at 100 rpm. The medium was 500 ml purified water maintained at 37°C ± 0.5°C. Samples were withdrawn at a specified time through 35 μ Full Flow™ filters (Vankel Industries, Inc., Edison, NJ). In the case of the diluent DCPA, 0.2 μ filters (high-performance liquid chromatography grade; Sun International Trading, Ltd., Wilming-

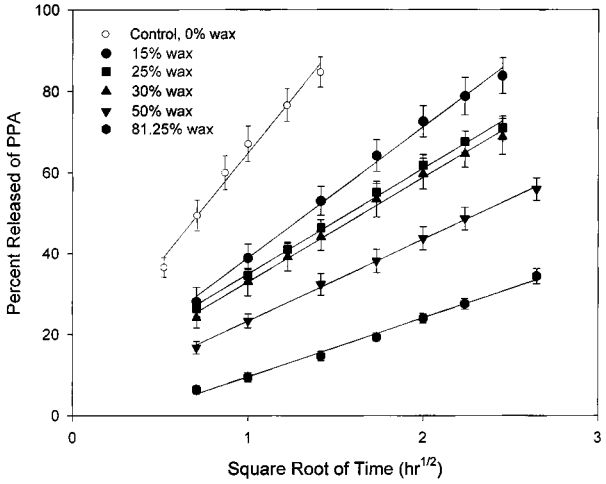

Figure 1. Effect of wax level on the dissolution of PPA.

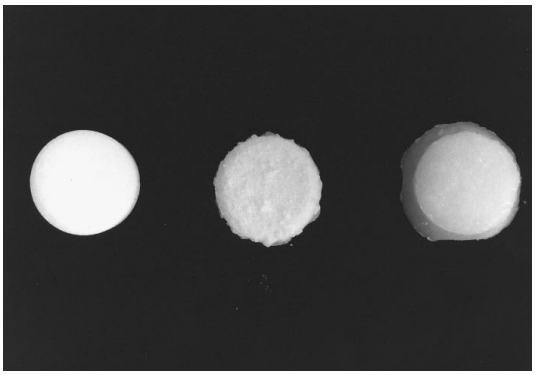

Figure 2. Tablet morphology after heat treatment: (a) intact tablet; (b) wax egress, nonsmooth surface; (c) wax spread.

ton, NC) were used to eliminate the interference of the fine powders in the material. Drug absorbance was measured at 256 nm using a UV spectrophotometer (Shimadzu UV-1601, Kyoto, Japan).

Formulations

For evaluating the effects of wax content, DCPD was used as the diluent. As the wax level increased from 0%, 15%, 25%, 30%, and 50% to 81.25%, DCPD correspondingly decreased from 81.25% to 0% to maintain a constant tablet weight. For evaluating the effects of diluent, wax was maintained at 25%, and individual diluent or a combination of two diluents was set at 56.25%. The remaining 18.75% was the drug (at a constant dose of 75 mg).

RESULTS AND DISCUSSION

Wax Level

The tablets were manufactured successfully except for the formulations with 50% and 81.25% wax. At the 50% wax level, the compaction failed due to punch sticking and capping problems. Tablets were compacted by manually turning the wheel of the press. Tablet hardness was only about 4 Kp. Poor flow occurred for the formulation with 81.25% wax. Punch sticking was so serious that

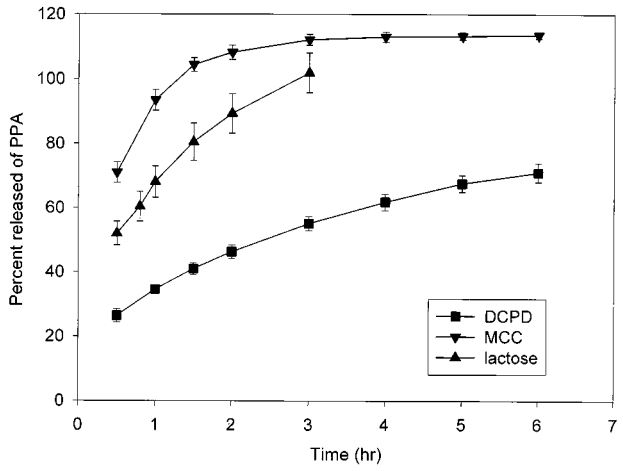

Figure 3. Effect of diluents on the dissolution of PPA tablets.

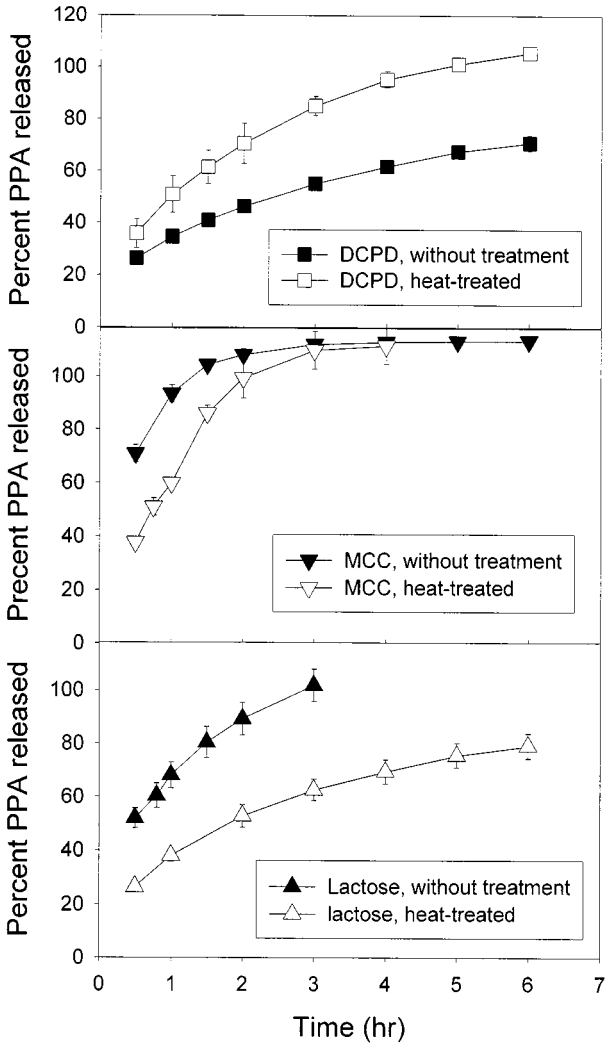

Figure 4. Effect of heat treatment on drug dissolution.

Table 1

Tablet Integrity During Drug Dissolution and Heat Treatment

Diluents	Dissolution of Untreated Tablets	Heat Treatment	Dissolution of Treated Tablets
DCPD DI-TAB	Intact	Wax egress	Intact
MCC Avicel	Swelling and cracking	Intact	Swelling and cracking
Lactose	Erosion or intact	Intact	Erosion or intact
DCPA Fujicalin	Disintegration	Intact	Intact

10% magnesium stearate acetone suspension had to be applied to lubricate the upper and lower punch faces to form a tablet manually. The maximum tablet hardness decreased as the wax content increased. Figure 1 shows the dissolution profiles of tablets with different wax contents. Increasing the wax content led to a corresponding decrease in the rate of drug release, as expected. The drug release profiles are linear with the square-root-of-time scale, which indicates that the drug release proceeded via a diffusion-controlled process.

Heat treatment of these DCPD tablets with 15% to 30% wax resulted in egress of wax (Fig. 2b) and faster release of the drug (data not shown). Although the treatment of 50% wax tablets also caused wax egress and spreading (see Fig. 2c), drug release was slower after the treatment. Thermal treatment of 81.25% wax tablets resulted in total melting of the wax tablet (no tablet structure).

Diluent Effect

The compression of all the formulations was successful. The dissolution profiles show MCC tablets had the fastest release; DCPD showed the slowest release; and lactose was in between (Fig. 3). During the dissolution, MCC tablets swelled and broke apart, but DCPD and lactose tablets were intact after the 24-hr dissolution test.

Heat treatment of MCC and lactose tablets resulted in intact, smooth, and waxy tablets (Fig. 2a). The treatment of DCPD tablets, however, produced wax egress (Fig. 2b), and tablets were not smooth. As a result, the dissolution of treated MCC and lactose tablets produced slower release, whereas DCPD tablets showed faster release after the treatment (Fig. 4). The reason for this difference may be due to the wax and drug diffusing out of DCPD tablets during the treatment. The drug exposed on the surfaces of the tablets dissolved immediately and resulted

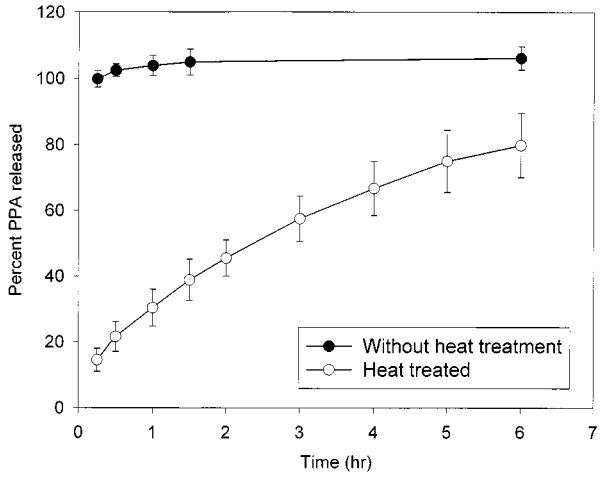

Figure 5. Dissolution profiles of DCPA tablets.

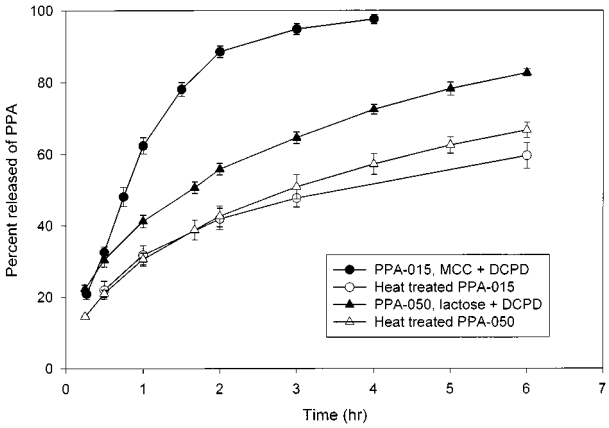

Figure 6. Dissolution profiles of PPA tablets with a diluent combination of DCPD with MCC or lactose.

in a higher burst effect and faster release. The heat treatment may cause the wax to redistribute, form fine matrix structures, and therefore retard the release for MCC and lactose tablets. After heat treatment, DCPD and lactose tablets remained intact during dissolution, whereas MCC tablets cracked. Integrity observations for the tablets are summarized in Table 1.

When DCPA was used as the diluent, heat treatment of the tablets was successful (tablets were intact). The dissolution of non-heat-treated tablets showed immediate release (Fig. 5)* since the tablets disintegrated immediately. After heat treatment, the tablets were intact throughout the 24-hr dissolution run, and the drug release was much slower than that without the treatment.

It is of interest that, even though DCPD and DCPA represent the same chemical, the hydrate had very different effects in terms of tablet integrity and drug dissolution rate. The crystal form and particle size may play a big role in keeping the tablet intact during heat treatment. Heat treatment has a dramatic effect on retarding drug dissolution for DCPA tablets.

Since MCC and lactose can keep tablets intact during heat treatment and DCPD can maintain tablets intact during drug dissolution, the combination of MCC or lactose with DCPD could keep tablets intact during both heat treatment and drug dissolution. The combination of 10% MCC or lactose with 46.25% DCPD prevented wax egress during heat treatment and prevented tablets from cracking or eroding during dissolution. Therefore, sustained release was successfully achieved (Fig. 6).

* The DCPA material contained fine powders; 35-μ filters were not good enough to block the fine powders, and the filtrate showed much higher absorbance than expected. After passing through 0.2-μ filters, the absorbance correctly reflected the concentration of PPA.

CONCLUSION

Tablet integrity during dissolution or heat treatment depends on the diluent(s) used and the wax levels and was directly related to the drug release rate for these wax matrix, controlled-release formulations. Therefore, the choice of appropriate diluents is critical for successful formulation and processing to achieve a sustained-release effect.

The release of PPA could be adequately sustained by using appropriate levels of wax with appropriate diluent(s). The higher the wax content, the slower the drug released, and the more difficult was the manufacturing process. Heat treatment above the melting point of wax can retard the drug release if there is no wax egress. Utilization of heat treatment can achieve a similar sustained-release effect at lower wax levels and with easier processing.

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