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RESEARCH PAPER

Melt Granulation and Heat Treatment for Wax Matrix-Controlled Drug Release

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ABSTRACT

The purpose of this study was to evaluate sustained drug release after melt granulation and heat treatment. Theophylline (anhydrous) and phenylpropanolamine hydrochloride (PPA) were used as model drugs. Compritol® 888 ATO (Glyceryl Behenate NF) was incorporated as the wax matrix material. Formulations with drug:wax in 3:1 and 1:1 ratios were evaluated. Tablets were made by dry blending or melt granulation; some of the tablets were heat treated at 80°C for 30 min. Tablets with or without heat treatment were tested for drug release using in vitro drug dissolution. The results showed that melt granulation gave slower drug release than dry blending. Heat treatment further retarded drug release for both dry blending and melt granulation. The drug release rates for theophylline were slower than for PPA at the same wax level and processing method. The drug release profiles were linear using a square root of time scale. In conclusion, melt granulation and heat treatment slowed drug release for the wax matrix-controlled release tablets. Heat treatment of the tablets made by melt granulation further retarded drug release. Heat treatment redistributed the wax, forming a new matrix system with higher tortuosity. The application of melt granulation or heat treatment can successfully retard drug release.

Key Words: Melt granulation; Heat treatment; Wax; Matrix; Controlled release.

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INTRODUCTION

During the past few decades, controlled release formulations have been one of the major focuses in pharmaceutics. Among the controlled release dosage forms, matrix-controlled release systems have been found to be convenient to make, with wax being a popular matrix material. In forming a wax matrix system, melt granulation technology has been used. Flanders et al.[1] investigated the use of melt granulation for sustained release of potassium chloride from tablets. They studied a number of parameters: granulation endpoint temperature, wax level, diluents, cooling rate, and scale of operation. They concluded that reproducible drug release could be achieved by controlling these process variables. Ghaly and coworkers[2] used direct compression and melt granulation (solid dispersion) to prepare wax matrix-controlled drug release formulations. Their results revealed that at 30% and 50% wax levels, the drug release from the tablets made by melt granulation yielded slower drug release than by direct compression.

Heat treatment is also used to further retard drug release.[3] Granules, beads, or tablets are heated at a temperature above the melting point or glass transition temperature of the wax or polymer. Several investigators have shown that heat treatment retards drug release.[4–6] The treatment is easy and convenient to use, and the process can be controlled; therefore, it should be accepted favorably by industry.

Our previous investigation showed that diluents have different effects on tablet integrity during heat treatment and subsequent drug release.[7] The use of dibasic calcium phosphate dihydrate (DCPD) resulted in tablet disfigurement during heat treatment. Microcrystalline cellulose (MCC), lactose, and dibasic calcium phosphate anhydrous (DCPA) kept tablets intact during heat treatment. However, during dissolution, MCC tablets cracked, lactose tablets eroded, DCPA tablets disintegrated, and DCPD tablets remained intact during dissolution. We concluded that the diluent caused these undesirable tablet characteristics and faster drug release. Therefore, in this investigation, the diluents were omitted to simplify formulation and allow a better understanding of the effect of heat treatment.

Melt granulation has been used in Europe for many years[1] and has also been the subject of investigation in the United States. On the other hand, heat treatment is still fairly new in the pharmaceutical field. Because both of these procedures involve melting of the wax, by comparing them, it may expand our knowledge of the heat treatment. The objective of this study was to evaluate the effects of melt granulation and heat treatment on drug release from sustained release products containing no diluents.

Theoretical Consideration

The drug release from a matrix system can be analyzed using a semiempirical equation[8]:

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

In this equation, M_t/M_∞ is the fraction of drug released at time t. Constants k and n describe the system. Constant k is related to the matrix structure, and n is related to the release mechanism. When n approaches 1, the drug release is indicative of zero-order kinetics. When n is 0.5, drug release is the square root of time, which was described by Higuchi.[9] In this special case, the system can be characterized by the Higuchi equation for inert matrix-controlled drug release:

$$Q = \sqrt{\frac{D\varepsilon}{\tau}(2A - \varepsilon Cs)Cst} \tag{2}$$

where Q is the amount of drug released per unit area at time t, D is the diffusion coefficient of the drug in the permeating fluid, and ε and τ are the porosity and tortuosity, respectively. A is the total amount of drug present in the matrix per unit volume, and Cs is the solubility of the drug in the release medium.

Because, in most cases, $2A \gg \varepsilon Cs$, Eq. (2) can be simplified to

$$Q = \sqrt{\frac{D\varepsilon}{\tau}2ACst} \tag{3}$$

Or, simply,

$$Q = kt^{1/2} \tag{4}$$

Therefore, a linear relationship with a slope of k is expected if Q is plotted vs. square root of time ($t^{1/2}$).

To characterize the matrix system, τ and ε factors should be studied. From Eqs. (3) and (4), τ can be calculated as follows:

$$\tau = \frac{2D\varepsilon ACs}{k^2} \tag{5}$$

The porosity (ε) includes the void space due to air (ε_a) and the void space due to dissolving of the soluble materials (ε_d) in the matrix. ε_a and ε_d can be calculated using true densities.

$$\varepsilon_a = 1 - \frac{\rho_b}{\rho} \tag{6}$$

$$\varepsilon_d = \sum_{i=1}^{n} \frac{V_i}{V_b} = \sum_{i=1}^{n} \frac{M_i/\rho_i}{V_b} \tag{7}$$

where ρ_b is the bulk density of the tablet; ρ is the true density of the materials in the formulation; V_i, M_i, and ρ_i are the true volume, mass, and true density of the soluble component I; V_b is the bulk volume of the matrix, and n is the number of different soluble materials in the matrix.

MATERIALS AND METHODS

Theophylline, anhydrous (Boehringer Ingelheim KG, Germany), or phenylpropanolamine hydrochloride (PPA) (FMC, Philadelphia, PA) was incorporated with Compritol® 888 ATO (Glyceryl Behenate NF, Gattefosse, France) in a 3:1 or 1:1 ratio, whereas the tablet was maintained at 400 mg. The batch size was 400 g. In dry blending, drug and wax were mixed in a 2-quart P-K blender for 10 min. Then the mixture was compressed using a Manesty single station F press with $\frac{3}{8}$-inch tooling set. In melt granulation, the wax was melted at 80°–85°C, and the drug was added to the molten wax while stirring. The drug–wax suspension was then cooled to room temperature and resolidified. The resultant solid was pulverized in a mortar, passed through a #16 sieve screen, and then compressed to form tablets.

Heat treatment of the tablets was conducted by placing the tablets in an oven in which the temperature was maintained at 80°C. After a period of 30 min, the tablets were removed and cooled at room temperature. Dissolution testing of these tablets occurred at least 24 hr later.

Dissolution of theophylline tablets was performed using the USP paddle method with a rotation speed of 100 rpm. The dissolution medium was purified water at 37° ± 0.5°C, and the drug was assayed at 272 nm. Dissolution of the PPA tablets was conducted using the USP basket method with purified water at 37° ± 0.5°C and with a rotation speed of 100 rpm. The samples were analyzed for the drug at 256 nm.

Dissolution data were fitted to Eq. (1) using the Microsoft SigmaPlot® program. Then the percentage released was converted to the amount of drug released per unit area Q by dividing the amount with the surface area of the tablet. Q vs. the square root of time was then analyzed.

The true density of the ingredients was measured by using a pycnometer (Micromeritics AccuPyc) with helium as the permeating gas. Then the porosity of the tablets was calculated using Eqs. (6) and (7). The diffusion coefficient for theophylline is 6.3×10^{-6} cm^2/sec.[10] The diffusion coefficient for PPA is approximated using the phenylpropanolamine base, which has a value of 1.82×10^{-6} cm^2/sec.[11] The solubility is 1 g/120 mL for theophylline and 1 g/1.1 mL for PPA.[12]

RESULTS

Compression

All the dry blending formulations exhibited poor flowability; therefore, the tablets were made by manually turning the press. All the melt granulated batches, except the one with 3:1 theophylline:wax, which was made manually, have good flow; and the tablets were made with power. Melt granulation resulted in better flowability.

Tablet Integrity

Tablets with 3:1 drug:wax were intact after heat treatment and eroded slightly during dissolution due to the dissolving of the drug that comprises the majority of the tablets. Tablets with 1:1 drug:wax showed wax spread after heat treatment; however, the tablets remained intact during dissolution.

Effect of the Drug:Wax Ratio

Figure 1 (tablets were made by dry blending) shows that the formulation with 3:1 theophylline:wax gave faster drug release than the one with 1:1 drug: wax. Pure theophylline compacts released the entire drug within 2 hr.

Processing Methods

The effect of processing methods on the release of theophylline and PPA from tablets made by dry blending and melt granulation is shown in Figs. 2–5. Melt granulation gave slower drug release than dry blending for both theophylline and PPA,

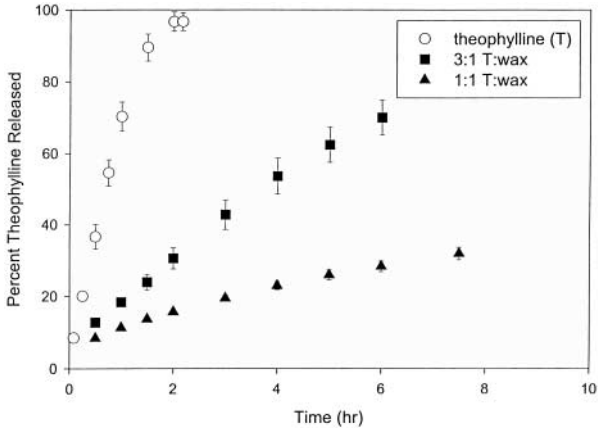

Figure 1. Effect of drug:wax ratio on theophylline release.

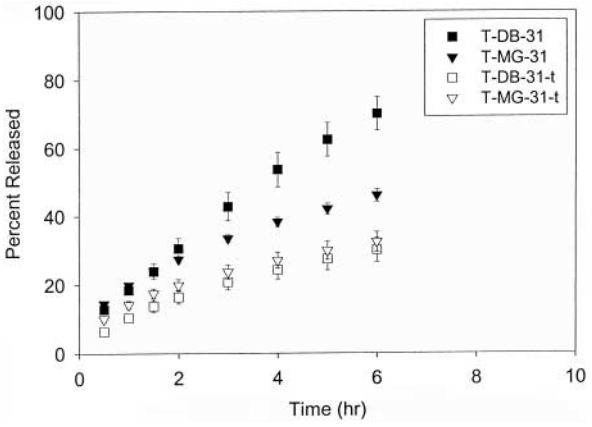

Figure 2. Effect of heat treatment on theophylline (T) release. DB, dry blending; MG, melt granulation; 31, 3:1 drug:wax; t, heat-treated.

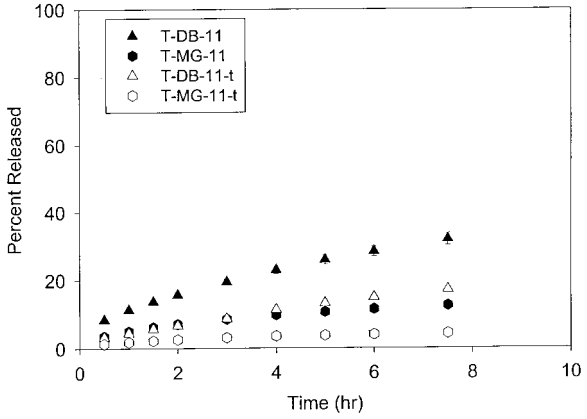

Figure 3. Effect of heat treatment on theophylline (T) release. DB, dry blending; MG, melt granulation; 11, 1:1 drug:wax; t, heat-treated.

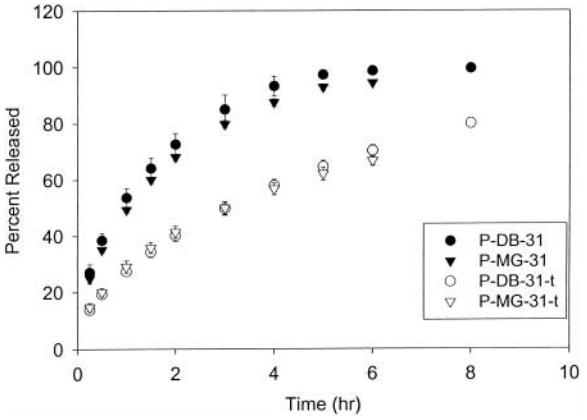

Figure 4. Effect of melt granulation on PPA (P) release. DB, dry blending; MG, melt granulation; 31, 3:1 drug:wax; t, heat-treated.

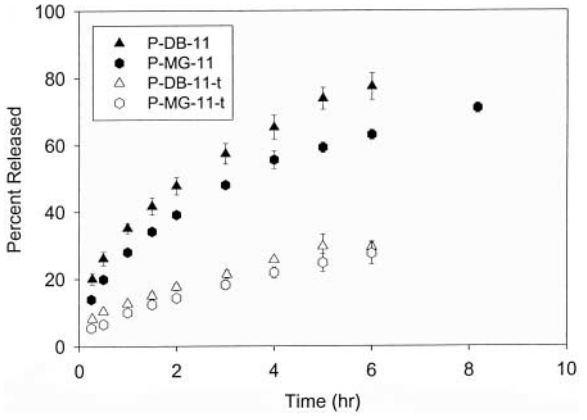

Figure 5. Effect of processing methods and heat treatment on PPA release. DB, dry blending; MG, melt granulation; 11, 1:1 drug:wax; t, heat-treated.

especially for the formulations with 1:1 drug:wax (Figs. 3 and 5).

Heat Treatment

The drug releases are slower after heat treatment for both drugs, both processing methods, and at the two drug levels (Figs. 2–5).

Drug Solubility

The release of theophylline is slower than that of PPA at the same wax levels and processing method (see Figs. 6 and 7).

Drug Release Mechanism

When the drug release data are fitted to Eq. (1) using SigmaPlot® linear regression program, n is better represented by 0.5 (square root of time) as opposed to 0 (zero order) or 1 (first-order kinetics) (Table 1), with r^2 being higher than 0.9. For all the formulations, constant k decreased after heat treatment.

After converting the percentage released to the amount released per unit area Q, dissolution data were analyzed using a square root of the time plot. Linear regression results are reported in Table 2. The r^2's are very close to 1, indicating a good linear fit. For the same formulation, slopes for the melt granulation data are smaller than for dry blending. When the wax level increases and drug level decreases, the slope decreases. After heat treatment, the slopes become smaller.

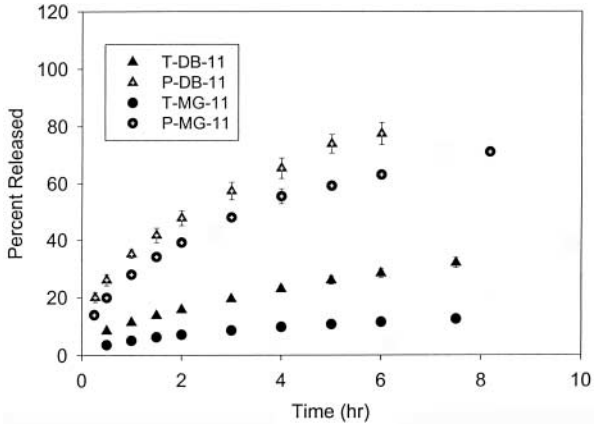

Figure 6. Effect of drug solubility on drug release (drug:wax, 1:1). T, theophylline; P, PPA; DB, dry blending; MG, melt granulation; 11, 1:1 drug:wax.

DISCUSSION

Tablet Integrity

Tablets with a 3:1 drug:wax ratio remained intact after heat treatment, even though they had no diluent in the formulation. Therefore, MCC and lactose are

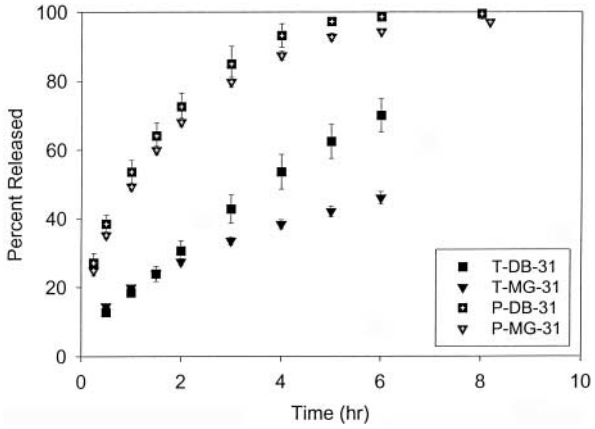

Figure 7. Effect of solubility on drug release (drug:wax, 3:1). T, theophylline; P, PPA; DB, dry blending; MG, melt granulation; 11, 1:1 drug:wax.

Table 1. Curve-fitting results of the theophylline and PPA group.

	Before heat treatment			After heat treatment		
Batch ID[a]	k	n	r^2	k	n	r^2
T-DB-31	0.188	0.743	0.998	0.111	0.554	1.00
T-DB-11	0.129	0.440	0.995	0.0542	0.546	0.998
T-MG-31	0.200	0.462	1.00	0.145	0.446	1.00
T-MG-11	0.057	0.370	0.996	0.0176	0.467	0.994
P-DB-31	0.531	0.402	0.990	0.281	0.510	0.999
P-DB-11	0.352	0.447	0.999	0.142	0.402	0.995
P-MG-31	0.496	0.390	0.983	0.293	0.469	0.998
P-MG-11	0.285	0.448	0.995	0.105	0.524	0.999

[a]T, theophylline; P, phenylpropanolamine hydrochloride; DB, dry blending; MG, melt granulation; 31, 3:1 drug:wax, 11, 1:1 drug:wax.

Table 2. Linear regression results of dissolution data vs. square root of time.

	Before heat treatment		After heat treatment	
Batch ID[a]	Slope[b]	r^2	Slope[b]	r^2
T-DB-31	30.7	0.989	12.1	1.00
T-DB-11	6.81	0.998	3.97	0.999
T-MG-31	15.6	0.999	10.6	0.999
T-MG-11	2.62	0.998	0.886	0.995
P-DB-31	46.8	0.996	28.6	0.999
P-DB-11	18.6	0.998	5.66	0.992
P-MG-31	42.0	0.991	26.9	0.997
P-MG-11	16.2	0.992	4.14	0.999

[a]T, theophylline; P, phenylpropanolamine hydrochloride; DB, dry blending; MG, melt granulation; 31, 3:1 drug:wax; 11, 1:1 drug:wax.
[b]Unit: $mg/cm^2/hr^{1/2}$.

Table 3. Tablet porosity and tortuosity.

	Before heat treatment		After heat treatment	
Batch ID[a]	ε_{total}	τ	ε_{total}	τ
T-DB-31	0.739	0.251	0.751	1.56
T-DB-11	0.493	2.15	0.497	6.30
T-MG-31	0.724	1.01	0.726	2.18
T-MG-11	0.498	14.5	0.441	125
P-DB-31	0.734	3.32	0.737	8.80
P-DB-11	0.515	8.92	0.501	96.0
P-MG-31	0.747	4.00	0.747	9.73
P-MG-11	0.498	11.7	0.482	179

[a]T, theophylline; P, phenylpropanolamine hydrochloride; DB, dry blending; MG, melt granulation; 31, 3:1 drug:wax, 11, 1:1 drug:wax. True densities (g/cm^3) used in the calculations of porosity: theophylline, 1.4932; PPA, 1.2456; Compritol, 1.0131.

not essential components. As long as there are enough solid materials from the formulation in the molten wax mixture, the tablets will remain intact. Tablets with 1:1 drug:wax did not remain intact after heat treatment, because the amount of wax was too high, preventing the drug from adsorbing the molten wax. Some of the wax seeped out from the bottom of the tablets.

Drug:Wax Ratio

For an inert matrix-controlled release system, the porosity of the matrix is the void space plus the space occupied by the soluble materials. Therefore, an increase in the soluble contents in the formulation means higher porosity, resulting in faster drug release. Formulations with 3:1 drug:wax have higher soluble contents than those with 1:1 drug:wax, because the total weight of the tablets is the same. In addition to the porosity factor, formulations with 3:1 drug:wax have less rate-controlling reagent than the formulations with 1:1 drug:wax, and this should also contribute to faster drug release.

Processing Methods

For melt granulation, the drug was suspended in the molten wax and allowed to resolidify. Because wax coats the drug during this process, the matrix formed by melt granulation process would be different from that formed by simple dry blending. The matrix formed in melt granulation showed higher tortuosity, and this resulted in slower drug release. The calculated values of the matrix porosity and tortuosity are given in Table 3.

Drug Solubility

According to the Higuchi equation, the drug release from an inert matrix system is proportional to the square root of solubility. The solubility of theophylline is about 8.3 mg in 1 mL water, whereas PPA is freely soluble in water (909 mg/mL water). Therefore, the ratio of the slopes of the PPA formulations to the slopes of the theophylline formulations should be about 10, if all the other parameters remain constant. However, the particle shape and the particle size also affect the tortuosity of the matrix.[13] Therefore, if the drug is changed, other variables such as τ in the rate law will also change. Immersing the same matrix (such as the tablet shells after complete drug loss) in different drug solutions would produce matrix systems with a constant tortuosity for different drugs.[13]

Heat Treatment

The tablets made by melt granulation without heat treatment and the heat-treated tablets made by

dry blending both involved one melting process. However, they did not give the same dissolution results. Therefore, the effect of heat treatment is not simply a melting phenomenon.

Comparison of the drug dissolution profiles from the tablets made by dry blending with heat treatment to the tablets made by melt granulation but without heat treatment resulted in decreased drug release, but to a larger magnitude with heat treatment when the formulation contained 75% drug and 25% wax. This indicates that heat treatment is more efficient in forming the wax matrix system than melt granulation.

Heat treatment of the tablets above the melting point of wax caused the wax to melt and redistribute. After cooling to room temperature, the wax resolidifies and forms a new matrix. Previous investigation[14] using scanning electron microscopy demonstrated that, after heat treatment, the matrix structure changed with the wax covering the tablet surfaces. The analysis of the dissolution data revealed that the tortuosity of the matrix increased after heat treatment (Table 3). Therefore, heat treatment changed the distribution of the wax and formed a new matrix system with higher tortuosity, resulting in decreased drug release.

Both the melt granulation and heat treatment retarded drug release. Melt granulation slowed drug release possibly by forming intragranule bonds. Heat treatment of the tablets made by the melt granulation method at the temperature above the melting point of wax further retarded drug release. This may be due to the intergranule bonds formed during heat treatment, which made the matrix more tortuous.

CONCLUSIONS

Dry blending and melt granulation resulted in different drug release profiles for the same formulation. Melt granulation resulted in slower drug release. Heat treatment retarded drug release from tablets formed by dry blending and melt granulation. The drug release from the wax matrix tablets was best described by the Higuchi square root of time equation. Heat treatment retarded drug release mainly by increasing the tortuosity of the matrix. Both melt granulation and heat treatment involve melting the wax; however, the effects on the matrix formation and drug release are not the same. Both melt granulation and heat treatment can sustain drug release from the wax matrix-controlled release tablets. The simpler method of heat treatment is more efficient in retarding drug release, especially at lower wax content.

For both theophylline and PPA, heat treatment of the wax matrix tablets successfully sustained drug release, even at the high drug levels (50% and 75%). The simple formulations in this study can be applied to different strengths by adjusting the tablet weight.

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