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Research paper

Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot-melt extrusion

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Abstract

The objective of the present study was to investigate the influence of formulation factors on the physical properties of hot-melt extruded granules and compressed tablets containing wax as a thermal binder/retarding agent, and to compare the properties of granules and tablets with those prepared by a high-shear melt granulation (MG) method. Powder blends containing phenylpropanolamine hydrochloride, Precirol® and various excipients were extruded in a single-screw extruder at open-end discharge conditions. The extrudates were then passed through a 14-mesh screen to form granules. The extrusion conditions and the optimum amount of wax to function as the thermal binder were dependent on the properties of the filler excipients. At the same wax level, drug release from tablets decreased in the order of using microcrystalline cellulose (MCC), lactose and Emcompress® as the filler excipient. The observed differences in the dissolution properties of the tablets were due to the differences in the solubility, swellability and density of the filler excipients. Replacing Precirol® with Sterotex® K, a higher melting point wax, resulted in slightly increased dissolution rates, when the extrusion was performed at the same temperature conditions. Hot-melt extruded granules were observed to be less spherical than high-shear melt granules and showed lower values of bulk/tap densities. However, tablets containing MCC or lactose granules prepared by hot-melt extrusion (HME) exhibited higher hardness values. Slower drug release rates were found for tablets containing MCC by HME compared with MG. Analysis of the hot-melt extruded granules showed better drug content uniformity among granules of different size ranges compared with high-shear melt granules, resulting in a more reproducible drug release from the corresponding tablets.

Keywords: Hot-melt extrusion; Melt granulation; Wax; Matrix tablets; Sustained-release

1. Introduction

Lipophilic waxes have been employed as matrix carriers for sustained-release solid dosage forms. In addition to direct compression (DC) and wet granulation, wax matrices can be prepared by fusion (solid dispersion) [1–4] and melt granulation (MG) methods [5–9]. These two methods utilize the molten wax as a binder. The fusion method, which produces granules from a congealed mixture, has been reported to provide slower release profiles compared with the DC or wet granulation method [3]. In a MG process, granules are formed following the melting of the wax due to the heat generated by high-shear friction and the heat conducted from the heating jacket.

Hot-melt extrusion (HME) is another thermal processing technique that has attracted interest as a novel approach for the development of polymeric immediate-, sustained-release or transdermal/transmucosal delivery systems [10–13]. Having been widely used in the plastics industry, this process involves transferring and melting of the polymer inside a heated barrel by a rotating screw. The polymer melt is then pressurized through the die and solidifies into a variety of shapes. Extrudates can be further processed into tablets or granules. HME is a continuous, simple and efficient process. No solvent or water is required, since the molten polymer can function as a thermal binder. The intense mixing and agitation during HME also deaggregates particles and improves the content uniformity of the extrudates. HME generally requires relatively high processing temperatures (greater than 80°C). The excipients and the active ingredients need to be stable under these conditions. Plasticizers, antioxidants and other excipients can be included in the powder blend to improve the processing conditions and stability of each component during extrusion.

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In the current study, wax was used as a thermal binder for the HME process. Waxes are inert and generally have lower melting points than polymers. HME of wax can be conducted at relatively low temperatures. However, inefficient drag flow inside the barrel, due to the low melt viscosity of a wax, makes the extrusion of the waxes a challenging process. To date, few articles regarding HME of wax-containing systems have been published. Nakamichi et al. [14] reported that a wax matrix could be obtained using a twin-screw compounding extruder. Extrusion was performed at temperatures below the melting point of the wax, and the melting of the hydrophobic component was facilitated by the high pressure created from the screws. Using the same type of equipment, Miyagawa et al. [15] produced wax matrix granules of high mechanical strength containing carnauba wax, and investigated the dissolution mechanism [16] and in vivo performance of granules in beagle dogs [17].

A single-screw extruder does not provide such high pressure as a twin-screw extruder. Extrusion of a wax material through the die may be problematic, due to the restriction caused by the die. However, the operation at open-end discharge conditions (no die attached) removes this resistance and makes the wax extrusion a feasible process in a single-screw extruder. The ribbon-shaped extrudates are then passed through a screen to form granules, which then solidify under ambient conditions. The process described above is similar to the preparation of tablets by a dry granulation process. Due to thermal extrusion, the solid bridges formed between particles are induced by the molten wax rather than a dry polymeric binder.

The objective of the present study was to investigate the influence of formulation factors on the physical properties of hot-melt extruded granules and compressed tablets containing wax as a retarding agent, and to compare the properties of granules and tablets with those that were prepared by a high-shear MG method.

2. Materials and methods

2.1. Materials

Phenylpropanolamine HCl (PPA; Spectrum Quality Products, Inc., Gardena, CA), a freely water-soluble compound, was selected as the model drug. Precirol® ATO 5 (glyceryl palmitostearate, Gattefosse, Cedex, France) and Sterotex® K (mixture of hydrogenated castor oil and soybean oil, Abitec Corporation, Janesville, WI) were used as the wax carriers. Three types of filler excipients were evaluated in this study: lactose anhydrate DT NF (Quest International, Hoffman Estates, IL), microcrystalline cellulose (MCC; Avicel® PH 101, FMC Corporation, Philadelphia, PA) and Emcompress® (dibasic calcium phosphate dihydrate, Penwest Pharmaceuticals, Patterson, NY). Various grades of hydroxypropylmethylcellulose (HPMC) E4M, K4M and K15M (The Dow Chemical Company, Midland, MI) were incorporated in some formulations as dissolution rate-adjusting agents.

2.2. Formulations

The composition of formulations and their methods of preparation are listed in Table 1. The levels of PPA and wax were maintained at 15 and 30%, respectively, except for formulation F4, which contained a higher loading of both drug and wax. Formulations F1–F3 consisted of PPA, Precirol® and different types of filler excipients. These formulations were prepared by HME, MG and DC methods. In formulations F5–F7, 10% of different grades of HPMC was incorporated, while the filler excipient, lactose, was reduced to 45% to modify the drug release properties of the tablets. For formulation F8, Precirol® was replaced with Sterotex® K as the wax carrier, while other ingredients were maintained at the same level as formulation F1. For all formulations, PPA and wax were initially passed through an 80- and a 60-mesh screen, respectively, before mixing with the filler excipients. The powder mixtures were blended in a twin-shell blender (Patterson-Kelley Co., Inc., East Stroudsburg, PA) for 20 min prior to processing.

2.3. HME process

The dry blends of drug, wax and filler were processed in a single-screw extruder (C.W. Brebender Instrument, Inc., S. Hackensack, NJ) using open-end discharge conditions. The extruder is composed of three sections: the feeding, melting and metering sections. The temperature at the feeding section was kept at 55°C. The melting and metering sections were maintained at 60°C, except for formulation F2 containing Emcompress®, which required a lower processing temperature of 50°C in both sections. The screw speed was set at 30–40 revs./min. The powder blend was fed from the hopper and transferred by the screw from the feeding section to the melting and metering sections. The ribbon-shaped extrudates were then passed through a 14-

Table 1
Composition of tablet formulations containing PPA prepared by DC, HME and MG[a]

	F1	F2	F3	F4	F5	F6	F7	F8
PPA	15	15	15	20	15	15	15	15
Precirol®	30	30	30	40	30	30	30	–
Sterotex® K	–	–	–	–	–	–	–	30
Lactose	55	–	–	–	45	45	45	55
Emcompress®	–	55	–	–	–	–	–	–
MCC	–	–	55	40	–	–	–	–
HPMC E4M	–	–	–	–	10	–	–	–
HPMC K4M	–	–	–	–	–	10	–	–
HPMC K15M	–	–	–	–	–	–	10	–
Total	100	100	100	100	100	100	100	100

[a] Formulations F1–3 prepared by HME, MG, and DC; formulations F4–8 prepared by HME only.

mesh screen into granules and cooled at ambient temperature.

2.4. MG

MG was conducted in a high-shear mixer containing a heating jacket (Model RSI 3VG, Robot Coupe Scientific Industrial Division, Ridgeland, MS). Warm water (60°C) was circulated inside the heating jacket of the mixer. The powder blend was loaded into the bowl and mixed by impellers at the speed range of 1500–2000 revs./min. A temperature probe was immersed in the powder bed inside the bowl to monitor the product temperature and to ensure that the final temperature reached the melting point of the wax. The MG process was terminated either when the powder was transformed into granules of a desired size range, or if no further growth in granule size took place. The granules were collected and passed through a 14-mesh screen.

2.5. DC and tabletting of granules

Tabletting was conducted using a Carver laboratory hydraulic press (Fred S. Carver, Inc., Menomonec Falls, WI). Aliquots of 1 g of powder blend or granules formed from HME and MG processes were compressed at a force of 2000 kg using a 14 mm normal concave punch set. Formulation F1 containing Precirol® and lactose prepared by HME was additionally compressed at 1000 and 3000 kg.

2.6. Granule size distribution

The granule size distribution was determined by sieve analysis methods using four sieves, including 20, 30, 40 and 60 meshes. Aliquots of 30 g of granules were introduced into the sieves and they were shaken for 5 min. The granules retained on each sieve were accurately weighed.

2.7. Bulk density, tap density and angle of repose

Approximately 30 g of granules were weighed and poured into a graduate cylinder. The volume occupied was recorded as the bulk volume. The cylinder was then tapped for 200 times to determine the tap volume. The bulk density (BD) and tap density (TD) were calculated by dividing the weight of granules with the corresponding volume. The Carr's index (CI) was calculated by using the following equation (Eq. (1))

$$CI = (TD - BD) \times 100/TD \quad (1)$$

The angle of repose was determined by measuring the height (H) and diameter (D) of the cone formed by the granules flowing through a funnel. The angle of repose was calculated as $\tan^{-1}[2H/D]$.

2.8. Tablet hardness and friability

Six tablets were randomly selected and tested for their hardness (Hardness tester, Heberlein). The friability was determined as the percentage weight lost of six tablets after rotating in the drum of a friabilator (Vanderkamp, Model 10801, Van-Kel Industrial, Inc., Chatham, NJ) at 25 revs./min for 4 min.

2.9. Dissolution

The dissolution studies were conducted using the USP XXIV dissolution Apparatus I (basket method; Vankel 6010, Vankel Industries, Inc., Edison, NJ). Purified water (500 ml) maintained at 37°C was used as the dissolution medium. The rotation speed of the baskets was set at 100 revs./min. Aliquots of 3 ml of the filtered dissolution medium were withdrawn at 1, 2, 4, 6, 8 and 12 h time points. The drug concentration was determined using a diode array spectrophotometer (Model 8452A, Hewlett–Packard Company, Wilmington, DE) at 258 nm.

2.10. Content assay of drug and excipients in granules of different size ranges

Granules of two size ranges (20–40 mesh and 60–100 mesh) from formulations F1 to F3 were ground into fine powder. Water was added to the powder and the mixture was stirred to dissolve the PPA. The amount of PPA in the filtered solution was quantitated by UV spectroscopy. Precirol® and Emcompress® in the granules of different size ranges from formulation F2 were separated using the solubility approach and the content of each component was determined gravimetrically. Precirol® is freely soluble in dichloromethane. PPA is freely soluble in ethanol but not soluble in dichloromethane, while Emcompress® is nonsoluble in both solvents. One gram of powdered granules was first spiked with 4 ml dichloromethane for four times and the supernatant containing dissolved Precirol® was filtered by a 0.22 μm membrane filter into an aluminum pan. The solvent was evaporated off and the weight gain of the pan was the mass of Precirol®. The remaining nondissolved solids composed of PPA and Emcompress® were further rinsed with ethanol to remove PPA. The Emcompress® solids were dried at 40°C to a constant weight. The content of each ingredient was expressed as the percentage of the amount recovered from the granules over the theoretical value.

3. Results and discussion

3.1. Influence of wax level and filler excipient type on the extrusion process

The extrudability of the materials is generally characterized by the extrusion torque during the process, material output rate and the physical appearance of the extrudates. The influence of the Precirol® level on the extrudability of the powder blend was determined by varying the percentage of wax in the formulation and using Emcompress® as the

filler excipient. The extrusion temperature was maintained at 60°C. At the 20% Precirol® level, the powder blend could not be extruded due to the high extrusion torque (greater than 60 N m) accompanied with loud noise that was caused by the friction between the non-meltable materials in the formulation and the wall of the extruder barrel. Raising the barrel temperature did not improve the process. The extrusion noise was diminished when a 45% wax level was included in the formulation, however, the material was discharged from the screw as dripping semisolids, resulting from a decrease in the viscosity of the mixture at the increased wax level. A 30% wax level was found to be suitable for extrusion without creating a high torque value or forming flowable semisolids.

To investigate the influence of excipient type on the extrusion process, the wax level was maintained at the 30% level. All formulations containing lactose as the filler (F1, F5 through F8) could be extruded without any difficulties at 60°C, which was just above the melting point of Precirol® (57°C). Extrudates were discharged at low torque (values ranging from 5.0 to 12.0 N m) in the form of soft ribbons, approximately 0.5–1 inch in length. No color change in the extrudates was observed, indicating that the active ingredients and excipients were stable during the extrusion process.

The formulation containing Emcompress® (F2) was found to be sensitive to the processing temperature. At 60°C, the extrudates were softer compared with the extrudates containing lactose (F1). Extrusion at 45°C resulted in powdery extrudates and incomplete melting of the wax. The optimal extrusion temperature for F2 was found to be 50°C, which produced extrudates of similar quality to the extrudates from F1. This indicated that melting of wax during extrusion could also take place at temperatures lower than the melting temperature of the wax with a single-screw extruder. This phenomenon was previously observed by Nakamichi et al. [14] who used a twin-screw extruder.

At 60°C, the extrudates from the formulation containing MCC (F3) were found to be more fragile and formed smaller ribbons compared with extrudates containing lactose or Emcompress®. Increasing the extrusion temperature to 80°C did not improve the physical strength of the extrudates. A difference in the density of the materials may influence the properties of the extrudates. Of the excipients used in this study, Emcompress® had the highest TD of 1.0 g/ml [18], and lactose had a slightly lower value of 0.81 g/ml [19]. However, the TD of Avicel® is only 0.45 g/ml [20]. Therefore, among the three materials, MCC is the most bulky ingredient. Since the molten wax has a fixed volume, the increased surface areas of the MCC formulation resulted in a lower probability of inter-connecting wax particles, which would account for the formation of highly friable extrudates. To confirm this hypothesis, formulation F4 containing PPA/MCC/Precirol® at a 1:2:1 weight ratio was generated by calculations using TD values, simulating the volume fraction of each component in formulation F1 (the TDs of PPA and Precirol® were determined to be 0.66 and 0.50 g/ml, respectively). The resulting appearance of extrudates from formulation F4 was very similar to that of extrudates containing the lactose or Emcompress®.

3.2. Physical properties of granules and tablets prepared by HME and MG

Two processes for preparing granules from ribbon-shaped hot-melt extrudates were compared, namely, passing the extrudates through a 14-mesh sieve when they were warm and soft versus grinding extrudates when they were cold and hard. Due to the plasticity of the cold extrudates, granules prepared by the second method were composed of a mixture of both large and fine particles. In comparison, the first method produced granules with a more uniform particle size. It was thus decided to prepare all hot-melt extruded granules by passing the material through the screen when the extrudates were warm and flexible following the discharge from the extruder.

The size distribution of granules containing different filler excipients prepared by HME and MG is presented in Fig. 1. For hot-melt extruded granules, the fractions of large granules (size greater than 20 mesh) and fine particles (smaller

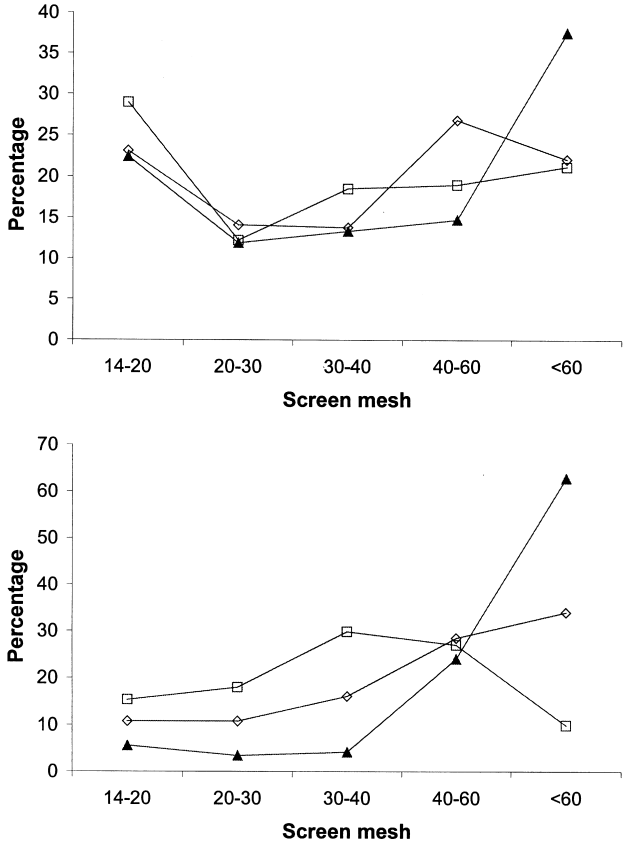

Fig. 1. Particle size distribution of granules containing different filler excipients prepared by HME (top) and MG (bottom). (□) 15% PPA, 30% Precirol, and 55% lactose; (▲), 15% PPA, 30% Precirol, and 55% MCC; (◇), 15% PPA, 30% Precirol, and 55% Emcompress.

Table 2
BD, TD, CI and angle of repose of granules prepared by HME or MG using Precirol® as the thermal binder[a]

Method	Filler	BD (g/ml)	TD (g/ml)	CI	Angle of repose (°)
HME	Lactose	0.48	0.61	21.31	36.2
	MCC	0.36	0.50	28.00	37.6
	Emcompress	0.63	0.78	19.23	34.6
MG	Lactose	0.53	0.65	18.46	36.5
	MCC	0.39	0.53	26.42	37.7
	Emcompress	0.70	0.83	15.66	34.9

[a] $n = 3$.

than 60 mesh) were still higher compared with that of the mid-size granules (between 20 and 60 mesh). The large granules were produced from passing the extrudates through a 14-mesh screen. The size distribution of batches containing lactose and Emcompress® were similar, however, granules containing MCC showed a higher fraction of fine particles, due to the fragile nature of the extrudates.

For the MG method, only granules containing lactose demonstrated a narrow particle size distribution, with greater than 50% of the granules in the size range of 30–60 mesh. Granules containing Emcompress® had a higher fraction of smaller particles. The larger difference in the density of Emcompress®, when compared with other components, did not favor granule-growth during high-shear processing. Granules containing MCC had an even higher fraction of fine particles than granules prepared by HME. The decreased efficiency of heat conduction in high-shear mixing compared with the HME process may account for the incomplete granulation, while with HME, the compression of materials by the rotating screw helped facilitate the binding of the powder particles to form agglomerates.

The BDs and TDs, CI and angle of repose of the respective granules are summarized in Table 2. While the angles of repose were similar irrespective of the preparation method, granules prepared by the HME process exhibited lower values of density and higher values of CI as compared with granules prepared by MG. The granules prepared by MG were more spherical, due to the centrifugation and spheronization steps that occurred during the granulation process. Centrifugation also resulted in a densification of the granules. Although hot-melt extrudates were densified by the rotating screw during the extrusion process, the wide granule size distributions of the hot-melt extruded granules and the irregular shape from passing the warm extrudates through a 14-mesh sieve could lead to decreased values in bulk/TDs.

The hardness data shown in Table 3 demonstrated higher values for the hardness of tablets from granules prepared by HME than by those prepared by MG. This indicated a stronger wax network formed from hot-melt extruded granules. Due to the superior compressibility and bonding capacity of MCC, tablets containing this filler were harder than lactose- or Emcompress®-containing tablets for both granulation methods. The friability data in Table 3 demonstrated that tablets from all batches were non-friable. No trends were evident with regard to the method of preparation or filler types.

3.3. Influence of formulation variables and compression force on drug release from tablets prepared from hot-melt extruded granules

The release of PPA from wax matrix tablets prepared by HME was dependent on the type of filler. A plot of the percentage of drug release versus the square root of time for tablets (F1–3) compressed from hot-melt extruded granules (20–40 mesh) is presented in Fig. 2. A linear relationship ($r > 0.999$) between the release percentage and the square root of time indicated that the drug release properties of the tablets were in good agreement with the diffusion model, as described by the Higuichi equation [21] for all three types of filler. The lowest release rate was seen with tablets containing Emcompress®, while MCC tablets

Table 3
Hardness and friability of tablets containing granules prepared by HME or MG compressed at 2000 kg by the Carver lab press

	Filler	HME	MG	Significance[a]
Hardness (kg)	Lactose	14.00 ± 1.38	11.27 ± 1.39	$P < 0.05$
	MCC	> 16	13.98 ± 1.39	$P < 0.05$
	Emcompress	11.73 ± 1.32	11.12 ± 1.69	$P > 0.05$
Friability (%)	Lactose	0.103	0.047	
	MCC	0.034	0.028	
	Emcompress	0.111	0.140	

[a] Statistical analysis was performed by one-way ANOVA.

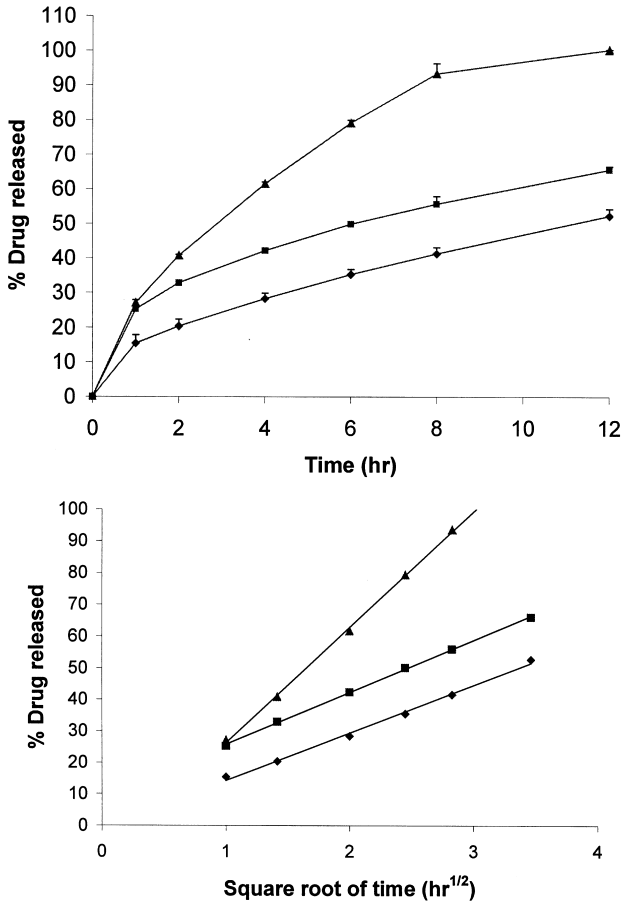

Fig. 2. Influence of filler excipient on the release of PPA from tablets containing hot-melt extruded granules using USP Method I at 100 revs./min in 500 ml purified water, maintained at 37°C. (▲) 15% PPA, 30% Precirol, and 55% MCC; (■), 15% PPA, 30% Precirol, and 55% lactose; (◆), 15% PPA, 30% Precirol, and 55% Emcompress. (Top) Percentage drug released versus time; (bottom), percentage drug released versus square root of time.

showed the fastest release rate. Emcompress® is insoluble, non-swelling, and the tablets remained intact throughout the dissolution process. Drug release was by diffusion through the small inter- and intra-granule spaces. The lactose-containing tablets were softened and exhibited a single crack on the sides of tablets during the dissolution process. Drug diffusion was promoted due to the pores and channels that were created following the solubilization of the lactose. The MCC-containing tablets released approximately 80% of the PPA within 6 h. MCC absorbed water into the tablet through capillaries, leading to swelling and eventual disintegration of the tablets. New surfaces were thus created for drug diffusion to occur. This finding is in agreement with El-Shanawany [4] who reported a faster release of nitrofurantoin from wax tablets containing MCC than from tablets containing Emcompress® prepared by a fusion method.

The influence of compressional force on the release of tablets containing lactose prepared by HME is showed in Fig. 3. Compressional force had no significant effect on the release of PPA tablets containing lactose ($P > 0.05$ for both release rate and percentage of drug release in the first 6 h). A similar observation was reported for PPA direct compressed wax tablets [22] and for wax tablets containing chlorpheniramine maleate [23].

The drug release profiles of tablets containing different grades of the rate-adjusting agent, HPMC, are showed in Fig. 4. The inclusion of HPMC in the tablet formulations led to an acceleration in drug release, in all cases. Although the high viscosity grades of HPMC are often used as controlled-release matrix carriers, the combination with Precirol® did not display a combined effect. The immiscibility between the hydrophobic wax and the hydrophilic HPMC may hamper the performance of each material to function as a retardant. The continuity of hydrophobic domains of wax was interrupted by the swelling of the cellulosic polymer, leading to a faster dissolution rate of PPA, than from tablets containing no HPMC. The significant increase in drug release from wax granules containing hydroxypropyl cellulose (HPC) compared with NaCl and Eudragit L-100 was reported by Miyagawa et al. [15,17]. The swelling of the HPC promoted drug release in the wax systems.

The tablets containing HPMC E4M completely eroded and disintegrated during the dissolution study, resulting in a rapid release rate of the PPA. The K grades of HPMC, which display a faster hydration rate than the E grade, formed a gel layer surrounding the tablet cores during the dissolution process and this gel layer impeded the penetration of water. The gel layer of HPMC K15M was more viscous and less erodible, providing a stronger barrier for drug diffusion, and resulting in the slowest drug release rate. For all tablets that contained HPMC, the dissolution data were found to fit the Higuchi model and the first-order kinetics model to an equal extent ($0.99 < r < 0.999$ for

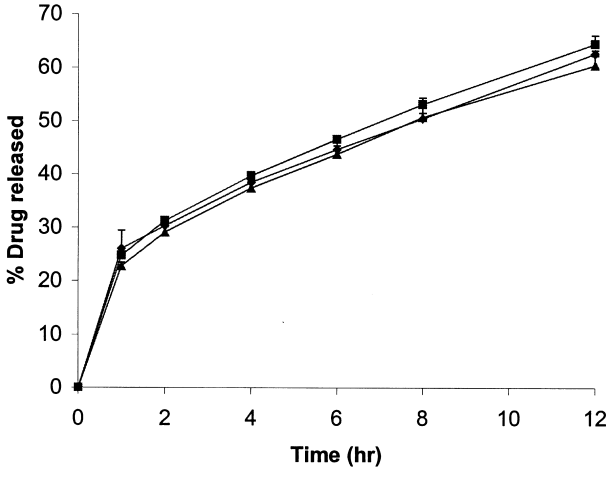

Fig. 3. Influence of compression force on the release of PPA from tablets containing hot-melt extruded granules using USP Method I at 100 revs./min in 500 ml purified water, maintained at 37°C. The tablets composed of 15% PPA, 30% Precirol, and 55% lactose compressed at: (■), 1000 kg; (◆), 2000 kg; (▲), 3000 kg.

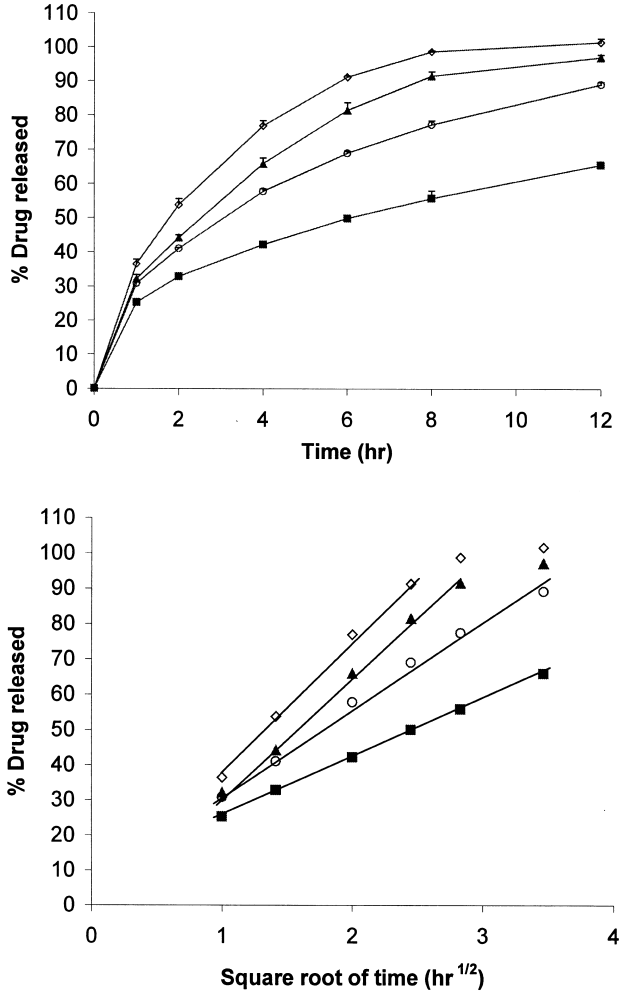

Fig. 4. Influence of HPMC on the release of PPA from tablets containing hot-melt extruded granules using USP Method I at 100 revs./min in 500 ml purified water, maintained at 37°C. (◇) 15% PPA, 30% Precirol, 45% lactose and 10% HPMC E4M; (▲), 15% PPA, 30% Precirol, 45% lactose and 10% HPMC K4M (F6); (○), 15% PPA, 30% Precirol, 45% lactose and 10% HPMC K15M; (■), 15% PPA, 30% Precirol and 55% lactose (no HPMC). (Top) Percentage drug released versus time; (bottom), percentage drug released versus square root of time.

both models). This finding demonstrated that the release mechanism of PPA from wax tablets containing hydrophilic polymer is controlled by a combination of both diffusion and erosion.

Replacing Precirol® with Sterotex® K as a wax carrier resulted in an approximately 5% increase in drug release, as shown in Fig. 5. The slight increase in the dissolution of Sterotex® K tablets may be attributed to the different melting points of the two waxes. The differential scanning calorimetry (DSC) thermograms showed multi-melting points of Sterotex® K at 55, 60, 68 and 83°C. For Sterotex® K, the fractions that had higher melting points than that of Precirol® may not be molten during HME, which could weaken the bonding of powder particles in the extruded granules.

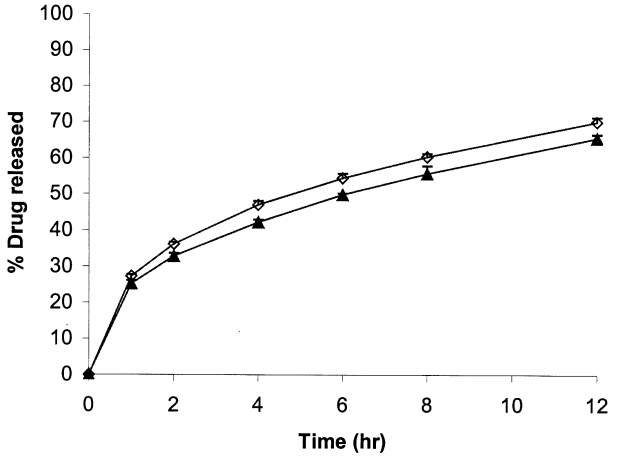

Fig. 5. Influence of wax carrier on the release of PPA from tablets containing hot-melt extruded granules using USP Method I at 100 revs./min in 500 ml purified water, maintained at 37°C. (▲) 15% PPA, 30% Precirol, and 55% lactose; (◇), 15% PPA, 30% Sterotex K, and 55% lactose.

3.4. Influence of granulation methods on drug release from wax matrices

Due to the differences in the particle size distribution of granules prepared by HME and MG, comparisons of these two methods were made using tablets prepared from granules of the size range, 20–40 mesh. Dissolution profiles of tablets prepared by DC or from granules produced by HME and MG containing either lactose, Emcompress® or MCC as filler excipients, are shown in Figs. 6–8, respectively. Regardless of the type of filler, tablets prepared by DC exhibited a faster release rate than those prepared by the HME and MG methods. The wax was presented as individual particles in the direct compressed tablets, compared with the granules prepared by HME or MG where the wax was in the molten stage during the granulation process. The

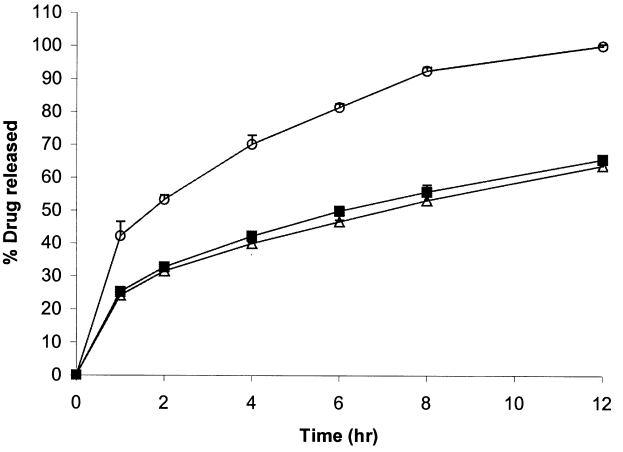

Fig. 6. Influence of the method of preparation on the release of PPA from tablets compressed at 2000 kg using USP Method I at 100 revs./min in 500 ml purified water, maintained at 37°C. The tablets containing 15% PPA, 30% Precirol and 55% lactose were prepared by DC (○); or from granules prepared by HME (■) and MG (△).

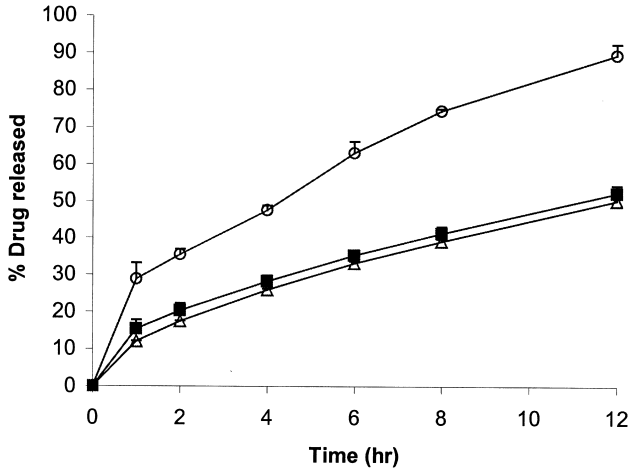

Fig. 7. Influence of the method of preparation on the release of PPA from tablets compressed at 2000 kg using USP Method I at 100 revs./min in 500 ml purified water, maintained at 37°C. The tablets containing 15% PPA, 30% Precirol and 55% Emcompress were prepared by DC (○); or from granules prepared by HME (■) and MG (△).

absence of the melting process may result in an increase in the porosity of tablets prepared by DC and enable the dissolution media to rapidly penetrate into the core to facilitate drug dissolution and diffusion [24]. The wax tablets prepared by DC required post-thermal treatment in order to obtain prolonged release [25]. In HME and MG, the coating of the molten wax over the surface of drug or filler particles was achieved during processing, and resulted in an increase in surface hydrophobicity which hindered the entrance of water into the tablets.

As shown in Figs. 6 and 7, no significant difference in drug release was found for tablets prepared by HME and MG when lactose or Emcompress® was used as the filler

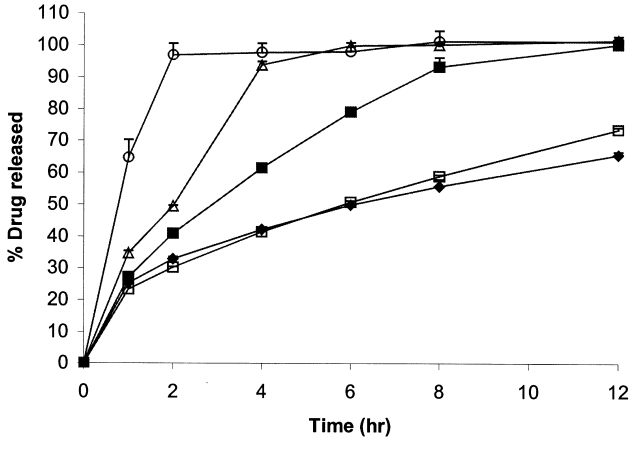

Fig. 8. Influence of the method of preparation on the release of PPA from tablets compressed at 2000 kg using USP Method I at 100 revs./min in 500 ml purified water, maintained at 37°C. Symbols listed are: (1), the tablets containing 15% PPA, 30% Precirol and 55% MCC prepared by DC (○); compressed from granules produced by HME (■), and MG (△); and (2), the tablets containing 20% PPA, 40% Precirol, and 40% MCC (□); 15% PPA, 30% Precirol, and 55% lactose (◆) prepared by HME.

($P > 0.05$ for both release rate and percentage of drug release in the first 6 h). In comparison, a slower release rate was found for tablets containing MCC prepared by HME as seen in Fig. 8. As discussed previously, the formulations containing MCC had insufficient wax as the binder due to the bulky nature of MCC. During HME, however, intensive mixing and compression by the extruder screw would increase the contact between solid drug/filler particles and the molten wax, resulting in a more effective coating of drug and filler by available wax. This would delay the swelling of MCC, and hence delay tablet disintegration and result in a decrease in drug release.

When the composition of the PPA–MCC–wax formulation was readjusted to simulate the volume fractions of components in formulation F1 containing lactose, the release rate of PPA from the resultant formulation (F4) was significantly decreased compared with that for formulation F3, as seen in Fig. 8. The release profile of formulation F4 in the first 6 h was similar to the release profile of formulation F1. The tablets did not disintegrate during the dissolution process. Only cracks in the tablets were observed after the dissolution test. This indicated that increasing the wax level in the MCC formulations increased the strength of binder network, which suppressed the swellability of the MCC in the dissolution media. The results also demonstrated that the difference in solubility, swellability and density of filler excipients should be considered when comparing release profiles of tablets containing these materials.

3.5. Influence of granule size on the PPA content and the dissolution profiles of tablets prepared by HME and MG

The non-uniform distribution of drug content over different sizes of granules has been documented for conventional wet granulation [26], high-shear mixing [27] and fluidized-bed granulation [28]. Variations in drug content were seen when the active ingredient had a low solubility in the granulation liquid. In the fluidized-bed method, the density of components and the affinity of components to the binder solution should also be considered. In this study, the PPA content in different sizes (20–40 mesh and 60–100 mesh) of wax granules prepared by HME and MG was determined and the results are shown in Table 4. Among the granules containing different filler excipients, only those containing MCC had a uniform drug distribution for both granulation methods. A larger difference in the content distribution of PPA between two sizes of granules was found in the granules containing Emcompress® compared with those containing lactose. The immiscibility of PPA and wax was excluded as a possible factor since the drug content was uniform for the MCC formulations. The density of components appeared to contribute to the deviation. The uniform drug distribution among MCC-containing granules was possibly due to the TD of the MCC being very similar to that of PPA and Precirol®. The higher density of lactose and

Table 4
Comparison of the content distribution of each component in the granules of two different sizes prepared by HME and MG[a]

Method	Filler	Component	20–40#	60–100#
HME	Lactose	PPA	94.44 ± 0.87	85.40 ± 1.15
	Emcompress	PPA	95.50 ± 0.89	78.67 ± 0.56
		Precirol	96.58 ± 0.97	88.18 ± 1.38
		Filler	96.14 ± 1.03	107.57 ± 1.76
	MCC	PPA	100.95 ± 0.47	98.44 ± 0.74
MG	Lactose	PPA	100.03 ± 0.67	79.28 ± 0.67
	Emcompress	PPA	123.97 ± 4.33	60.03 ± 1.32
		Precirol	100.70 ± 0.30	74.47 ± 1.31
		Filler	93.28 ± 1.00	122.89 ± 0.45
	MCC	PPA	100.29 ± 0.21	101.75 ± 0.10

[a] Data expressed as the percentage of the amount of the ingredient analyzed from the granules over its theoretical value. A 100% content on both size granules indicated a uniform distribution.

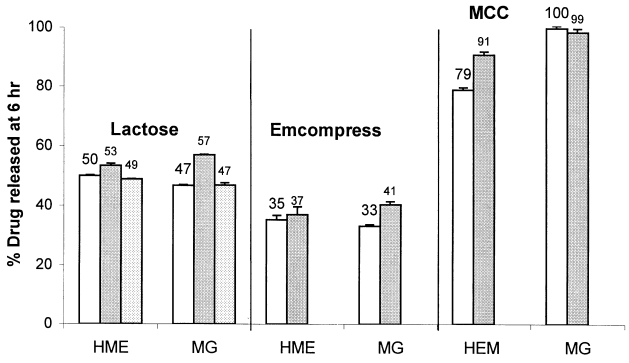

Fig. 9. The percentage PPA released at 6 h from tablets containing 15% PPA, 30% Precirol and 55% filler excipient prepared by HME and MG using USP Method I at 100 revs./min in 500 ml purified water, maintained at 37°C. (□) Tablets compressed from granules within 20–40 mesh only; (■), tablets compressed from granules within 60–100 mesh only; and (▤), tablets compressed from granules within 20–40 mesh but size-reduced to less than 60 mesh.

Emcompress® led a to greater tendency towards segregation during granulation. In these formulations, the molten wax was prone to bind PPA, and formed granules, leaving a high percentage of the filler excipient in the fine particles. This resulted in a higher PPA and wax content in the larger granules than in the small granules. The data in Table 4 confirmed the distribution pattern of components in the large and small granules containing Emcompress®.

A comparison of the two methods of granulation showed that HME produced granules with a more uniform drug content over the two granule size ranges compared with the MG process. During extrusion, the intensive mixing and pressure generated by the screw limited the segregation of the materials. Following extrusion, the filler, PPA and wax were compressed as uniform extrudates and separation of these components was less likely to occur. The subsequent sieving process produced granules as portions of the extrudates, therefore, granules of different sizes were more likely to maintain a similar composition to that of the extrudates.

The dissolution profiles of PPA-containing tablets compressed from granules of 20–40 and 60–100 mesh were compared. As showed in Fig. 9, tablets containing lactose or Emcompress® from small granules had more drug released after 6 h compared with the tablets prepared from larger granules. However, between two methods of granulation, the differences in the release profiles of tablets containing different sizes of granules were less for HME. A more uniform distribution of components in the hot-melt extruded granules of different sizes may result in more consistent release profiles of respective tablets by HME than those by MG.

To elucidate whether the granule size affected the dissolution of PPA wax tablets, the lactose-containing granules of 20–40 mesh were reduced in size and passed through a 60-mesh screen. The size-reduced granules were compressed into tablets and the dissolution profiles were compared with tablets compressed from the original size range. As shown in Fig. 9, tablets compressed from the size-reduced granules produced drug release profiles that were similar to those from tablets containing the large granules, regardless of the methods of granulation. These results indicate that the size of the granules did not affect the dissolution rate of PPA from lactose-containing tablets. Since the PPA content was relatively uniform for tablets containing MCC, the difference in the percentage drug release at 6 h of tablets prepared from the two size ranges of hot-melt extruded granules may be caused by the higher wax content in the larger granules.

In summary, HME by single-screw extruder was shown to be a viable method to prepare sustained-release wax granules that can be compressed into tablets. The low melting point of the wax enabled the extrusion to be performed at relatively low temperatures. The release rate of a drug from wax matrices can be modified by the selection of the filler excipients or by the addition of hydrophilic polymers to the powder blend. When compared with the traditional MG method, HME produced harder tablets. Furthermore, better content uniformity among granules of different size ranges was obtained from the HME process compared with granules prepared by MG. This offers an advantage for using HME to prepare wax granules for tablets containing low-dose drug when the densities of the excipients in the formulation are different from that of the active ingredient.

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