ORIGINAL ARTICLE

MODIFICATION OF DRUG RELEASE FROM ACETAMINOPHEN GRANULES BY MELT GRANULATION TECHNIQUE – CONSIDERATION OF RELEASE KINETICS

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ABSTRACT

Acetaminophen granules have been formed by a melt granulation process with the objective of retarding drug release for prolonged action formulations. The waxes used were goat wax, carnuba wax and glyceryl monostearate. In the melt granulation procedure, acetaminophen powder was triturated with the melted waxes and passed through a sieve of mesh 10 (aperture size 710µm). The content of wax in resulting granules ranged from 10 to 40%w/w. Acetaminophen granules were also formed by the convectional method of wet granulation with starch mucilage (20%w/w). The granules were subjected to *in-vitro* drug release tests. The release data were subjected to analysis by three different well-established mathematical models (release kinetics) namely, – zero order flux, first order, and the Higuchi square root of time relationship. The convectional granules exhibited an initial zero order flux (first 55%) followed by a first order release profile (the remaining 45%). The pattern of drug release from the melt granulations was consistent with the first order kinetic and the Higuchi square root of time relationship, indicating a diffusion-controlled release mechanism. The first order release rate constant of the convectional granules was $1.95 \pm 0.02h^{-1}$. After melt granulation (wax content, 20%w/w) the rate constants dropped drastically to $0.130 \pm 0.001h^{-1}$ (goat wax), $0.120 \pm 0.003h^{-1}$ (carnuba wax), and $0.130 \pm 0.002h^{-1}$ (glyceryl monosterate) indicating that all three waxes were equivalent in retarding drug release from the melt granulations.

Keywords: Goat wax, melt granulation, diffusion controlled release mechanism, retard release.

INTRODUCTION

The need to improve dosage convenience and hence patient compliance has led to the search for various ways of modifying drug release from solid dosage forms. Film coating of drug particles is often used but it involves preliminary spheronisation and the use of organic solvents, which are expensive and hazardous. Hence, other techniques such as melt granulation have been explored, (Schaefer *et al*., 1990; York and Row, 1994; Jonansen *et al*., 1999). In the melt granulation approach, the drug powder is triturated with the melted wax followed by screening to form wax coated drug particles or a solid dispersion of the drug in the wax. Drugs have been incorporated in these lipid carriers to achieve controlled release (Adeyeye and Price, 1994; Bodmeier *et al*., 1992; Maheshwari *et al*., 2003), taste masking (Robson *et al*., 1999), and for enhanced stability (Paradkar *et al*., 2004). Design and application of these techniques depend on the physico-chemical properties of the drug and excipients, as well as desired properties of the final product. Wax, a common carrier in various melt techniques, contains a wide group of chemicals such as glycerides, fatty acids, fatty alcohols and their esters. These are widely used as release retardants in the design of sustained release tablets, suspensions, beads, implants, and microcapsules. Bees wax, carnauba wax, ceresine, microcrystalline wax, Precirol ATO5, and Gelucire 64/02 are examples of waxes that have been evaluated as carriers for the sustained release of drugs using the melt processing technique (Adeyeye and Price, 1991;1994; Bodmeier *et al*., 1992).

A multi-unit dosage form consists of drug particles of different release profiles. Hence, in the present study the melt granulation technique has been employed to obtain slow release granules of acetaminophen (model of drug with a short biological half life) for prolonged action formulations. Of particular interest in this investigation is the use of a locally sourced wax material (goat wax) in this area of application. Its potential in retarding drug release from the melt granulations was compared with the performances of the more expensive and less readily available carnuba wax, and glyceryl monostearate. The release profiles of conventional granules of acetaminophen were compared with those of the melt granulation in order to assess the impact of the technique.

MATERIALS AND METHODS

Materials

Goat wax (mp 58-60^{0}C) was extracted by heat expression from the adipose tissues in the peritoneum of a sacrificed he-goat (*Capra hircus*). The wax is normally discarded as a waste when a goat is sacrificed as protein food for human consumption hence before now it had no commercial value.

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Table 1: Flow and packing properties of the granules

Wax conc (%w/w)	Angle of repose (0^0)	Bulk density (g/cm^3)	Tap density (g/cm^3)	Compressibilty (Carr's) index (%)
Carnuba wax				
0	12.3±1.2	0.35±0.02	0.58±0.02	39±2.2
10	17.2±1.1	0.34±0.03	0.57±0.04	40±2.1
20	18.6±1.4	0.63±0.02	0.84±0.01	25±3.2
25	20.5±1.1	0.58±0.03	0.69±0.02	16±1.8
30	25.8±1.2	0.61±0.04	0.72±0.01	15±1.6
40	28.7±1.5	0.59±0.02	0.69±0.02	14±1.8
Goat fat				
0	12.3±1.2	0.35±0.02	0.58±0.03	39±2.2
10	-	0.32±0.03	0.60±0.03	46±2.5
20	-	0.53±0.03	0.70±0.02	24±2.1
25	-	0.54±0.01	0.69±0.02	22±2.2
30	-	0.56±0.02	0.73±0.01	23±2.4
40	-	0.520.03	0.71±0.02	26±2.6
Glyceryl monostearate				
0	12.3±1.2	0.35±0.02	0.58±0.02	39±2.2
10	-	0.40±0.03	0.56±0.04	28±2.4
20	-	0.44±0.02	0.67±0.02	34±2.2
25	-	0.46±0.01	0.69±0.02	33±2.9
30	-	0.46±0.02	0.62±0.03	25±2.7
40	-	0.45±0.01	0.56±0.01	19±1.9

Note: 0% wax refers to the conventional granules and - means no flow of granules from the funnel in the measurement of angle of repose.

Details of the extraction method and purification have been described elsewhere (Okor, 1988). It is whitish in colour and consists mainly of triglycerides and cholesterol. The odorous fraction can be removed by heating under reflux at a high temperature (95°C) for 1h. Carnuba wax (Halewood Chemicals Ltd, England) is a fine waxy solid with melting point of 80-88°C, yellowish in colour. Glyceryl monosterate (GMS, MGS-F 75, white to yellow beads, mp 54-57°C, HLB = 1.5, lot no. 2054) was kindly supplied by Nikko Chemical Co Ltd (Tokyo, Japan). Maize starch (BDH) was used as binder. The test drug, acetaminophen, was supplied by BDH (Poole, UK) having m.p. 169-170°C. Although sustained release formulations are usually applied to potent drugs with short biologic half-life, acetaminophen was selected because of its availability and ease of assay.

Methods

Granulation technique

The wax material (20g) was melted in a stainless steel container in a water bath at temperature higher than the melting point of the wax material (i.e. 90°C). The acetaminophen powder (100g) was then added to the melted wax and mixed well, then allowed to cool to room temperature (range 26-30°C). The mass was pressed through a sieve of mesh 10 (aperture size; 710µm). Convectional acetaminophen granules were produced by wet granulation technique using starch mucilage (20%w/v) as binder fluid and dried on a tray in a hot air oven (Kottermann, Germany). The granules were stored in air tight container at room temperature. The release profiles of the melt granules were compared with those of the conventional granules.

Physical characterization of the granules

The packing properties were determined by measuring the difference between bulk density (BD) and the tapped density (TB) using standard procedures (Richards, 1972a). In the procedure, a 30g quantity of granule sample was placed into 250ml clean, dry measuring cylinder and the volume, V_0 occupied by the sample without tapping was determined. After 100 taps using Stampfvolumeter (Model STAV 2003 JEF, Germany), occupied volume, V_{100} was also determined. The bulk and tap densities were calculated from these volumes (V_0 and V_{100}) using the formula: Density = Weight of sample/Volume occupied by sample. From the data compressibility index (CI) values of the granules were calculated as CI = {(TB-BD)/ (TB} × 100%

Table 2: Values of linear regression coefficient (R^2) when the data were analysed according to the zero order, first order and Higuchi models.

Models	Coating materials		
	Goat wax	Carnuba wax	Glyceryl monosterate
Zero order			
0	0.6730	0.6730	0.6730
10	0.7767	0.7584	0.7473
20	0.8221	0.9212	0.8457
25	0.8421	0.8349	0.8855
30	0.8530	0.8697	0.8336
40	0.8560	0.8638	0.8520
First order			
0	0.8886	0.8886	0.8886
10	0.9073	0.9570	0.9285
20	0.9879	0.9901	0.9498
25	0.9758	0.9854	0.9774
30	0.9840	0.9437	0.9266
40	0.9841	0.9733	0.9724
Higuchi			
0	0.8081	0.8081	0.8081
10	0.9858	0.9295	0.9304
20	0.9860	0.9943	0.9959
25	0.9943	0.9931	0.9795
30	0.9934	0.9901	0.9769
40	0.9920	0.9853	0.9810

(Carr, 1965). The flowability of the granules was determined by measuring the angle of repose formed when a sample of the powder or granules (40g) was allowed to fall freely through the stem of a funnel to a horizontal bench surface (Richards, 1972a).

Photomicroscopy of powder and granule samples

Samples of the acetaminophen powder and its granules were spread thinly on a slide and examined with a light microscope (Model 745917 Kyowa, Tokyo) at various magnifications up to ×40. Photomicrographs of representative fields of view were taken to study particle structure.

Dissolution test

A sample of the granules (500mg) was filled into a capsule shell and placed in a single cylindrical basket (aperture size 425nm, diameter 20mm; height 30mm), which was immersed in 800ml of leaching fluid (0.1N hydrochloric acid maintained at 37 ± 2°C). The fluid was stirred at 100rpm with a single blade GallenKamp stirrer (Model APP No 4B 5784A. Cat No: SS530). Samples (5ml) were withdrawn from the leaching fluid at the following time intervals (mins) 5, 10, 15, 30, 45, 60, 120, 180, 240, 300, 360, 420, 480, 540, 600 replacing with an equal volume of drug-free dissolution fluid. The samples were suitably diluted with a blank solution fluid (i.e. 0.1N hydrochloric acid). The samples were then filtered with whatman No. 3 filter paper before they were analysed for content of acetaminophen spectrophotometrically at λmax, 245nm (Model Spectronic 21D, Bausch and Lomb, USA). The amounts released were expressed as a percentage of the initial amount of drug in the granule samples. The determination was carried out in triplicate and the mean results reported.

Analysis of data

The data were analysed on the basis of zero order, (cumulative percentage of drug released vs time), first order (log cumulative percentage of drug remaining vs time), and the Higuchi model (cumulative percentage of drug released vs square root of time) in order to determine the mechanism of drug release. Thus the mathematical models tested were (Richards, 1972b; Higuchi, 1963):

Table 3: Values of release rate constants of the granules based on the first order release and Higuchi models

Conc of wax material (%w/w)	Rate constants for the types of granulations		
	Goat wax	Carnuba wax	Glyceryl monosterate
First order model	h^{-1}	h^{-1}	h^{-1}
0	1.95±0.02	1.95±0.02	1.95±0.02
10	0.22±0.004	0.30±0.0001	0.50±0.001
20	0.13±0.001	0.12±0.003	0.13±0.002
25	0.11±0.003	0.12±0.003	0.10±0.002
30	0.09±0.004	0.13±0.004	0.09±0.003
40	0.08±0.001	0.10±0.002	0.09±0.002
Higuchi model	$\%h^{-1/2}$	$\%h^{-1/2}$	$\%h^{-1/2}$
0	60±2.4	60±2.4	60±2.4
10	28±1.6	36±2.1	42±1.5
20	28±1.2	28±1.4	25±1.8
25	29±1.5	29±1.3	26±1.5
30	27±1.8	30±1.1	25±1.4
40	26±1.2	27±1.3	26±1.7

Note: 0% wax refers to the conventional granules.

Zero order equation: $m = k_0 t$ (1)
First order equation: $\log m_1 = \log m_0 - 0.43 k_1 t$ (2)
Higuchi equation: $m = k_2 t^{1/2}$ (3)

where m is the percentage (%) amount of drug released in time, t; m_1 is the residual amount (%) of drug in time, t, m_0 is the initial amount of drug (100%) at the beginning of the first order release, and k_0, k_1 and k_2 are the release rate constants for the zero order, first order and the Higuchi release model, respectively.

RESULTS AND DISCUSSION

Packing and flow properties

The tapped density and compressibility index values of the granules are presented in table 1. The density increased as the proportion of wax in the granules increased but the compressibility index (measure of ease of compaction of the granules upon tapping) decreased correspondingly. This observation is attributable to the sticky nature of the waxes, resulting in interparticle cohesion. This effect was more severe with the goat wax and the glyceryl monosterate granulations, which did not flow at all during measurement of angle of repose. Systems granulated with carnuba wax were less sticky; hence some degree of flowability was achieved (table 1). The increase in the angle of repose with increase in the carnuba wax implies that flowability decreased. This consideration is important when the wax granulations are to be compressed to tablets or filled into capsules as multi-unit dosage forms (i.e. containing particles of different release profiles in one dose). This problem can be overcome by admixing the wax-granulations with granules of excipients such as α-cellulose, microcrystalline cellulose or lactose prior to tableting or encapulation. This aspect will be investigated in further studies.

Drug release profiles of the granules

The drug release profiles of the granules are presented in Fig 1. With all three waxes the release rates were markedly retarded after melt granulation particularly when the wax content in the granules was ≥ 20%w/w. For instance, with the convectional granules (made with 20%w/v starch mucilage), maximal drug release was achieved in the first one hour but after melt granulation with any of the waxes (20%w/w) maximal release was now achieved in 8h. These results showed that these systems are applicable for prolonged release formulations.

Drug release mechanisms

Knowledge of the drug release kinetics will provide understanding of the drug release mechanism, as well as provide a basis for predicting release profiles from the systems studied. Three mathematical models for drug release were considered, namely: zero order, first order and the Higuchi square root of time plots. Values of the linear regression coefficients (R^2) are presented in table 2. At the wax concentrations (0 to 40%w/w) in the goat wax granulations the corresponding R^2 values were 0.6850 to 0.8855 (zero order), 0.8886 to 0.9879 (first order), 0.8081 to

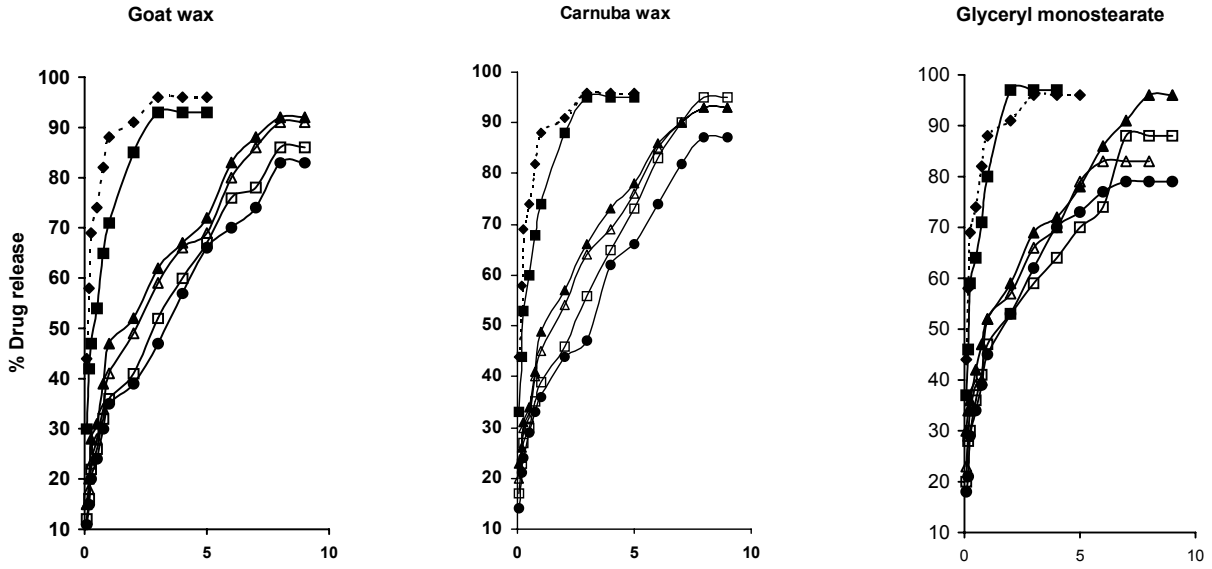

Fig. 1: Drug release profiles of the granules; conventional granules (broken lines…♦…) and the melt granules of varying wax content: 10% (■), 20% (▲), 25% (△), 30% (□) and 40% (•).

0.9959 (Higuchi). The pattern was the same for the carnuba wax and the glyceryl monostearate granulations (table 2), indicating that linearity of the plots increased generally as the wax content in the granules increased. At zero percent wax (i.e. the conventional granules) the R^2 values were generally low, indicating that the drug release profile did not follow any of the three tested models. However, R^2 values for the conventional granulation increased to ≥0.95 when the data were plotted on the basis of an initial zero order (first 55% release), followed by a first order profile for the remaining 45%. Eichie and Okor (2002) reported a similar biphasic release profile for aspirin crystals. Release from such systems follows a dissolution-controlled mechanism whereby the surface of the particle is gradually eroded by the leaching fluid. Compared with the zero order release profile, there was greater linearity (R^2 values > 0.95) for the melt granulations when the release data were plotted either on the basis of the first order kinetic or the Higuchi model (table 2), which shows that the release data appropriately fit into these two models (i.e. the first order and the Higuchi equations). The photomicrographs (fig 2) of the goat wax granulations and that of the acetaminophen powder alone showed that the drug particles were initially discrete before granulation but were embedded in the wax continuum in the melt granulations. Drug release from this type of structure will be diffusion controlled, characterized by a receding zone of diffusion layer (i.e. a Higuchi model). Also, the release will be determined by the residual amount of drug in the wax continuum, which explains the high linearity when the data were plotted according to the first order kinetic. Thus, the analysis showed that drug release from the melt granulations was by a diffusion mechanism, whereas the release from the convectional granulation was by a dissolution (erosion) mechanism. Since the lipid phase is not porous a partition mechanism is expected whereby the disperse drug particles will partition into the lipid phase followed by diffusion through it.

Release rate constants of the various granule formulations

The release rate constants obtained from the first order kinetic and the Higuchi square root of time relationship are presented in table 3 for the various granulations. By comparison with the conventional granulation, the release rate constants dropped remarkably in the melt granulations particularly when the wax content in the granules was up to 20%w/w. For instance, the first order release rate constant for the conventional granules was 1.95± 0.02h^{-1} but dropped to 0.13± 0.001h^{-1} (goat wax granulation), 0.12 ± 0.003h^{-1} (carnuba wax) and 0.13± 0.002h^{-1} (glyceryl monostearate) when the wax content was 20%w/w. Similarly, the Higuchi rate constant dropped from 60 ± 2.4%$h^{-1/2}$ (conventional granulation) to 28 ± 1.2%$h^{-1/2}$ (goat wax), 28 ± 1.4%$h^{-1/2}$ (carnuba wax) and 25 ± 1.8%$h^{-1/2}$ (glyceryl monosterate). These results indicate that all three waxes were equivalent in retarding drug release from the granules.

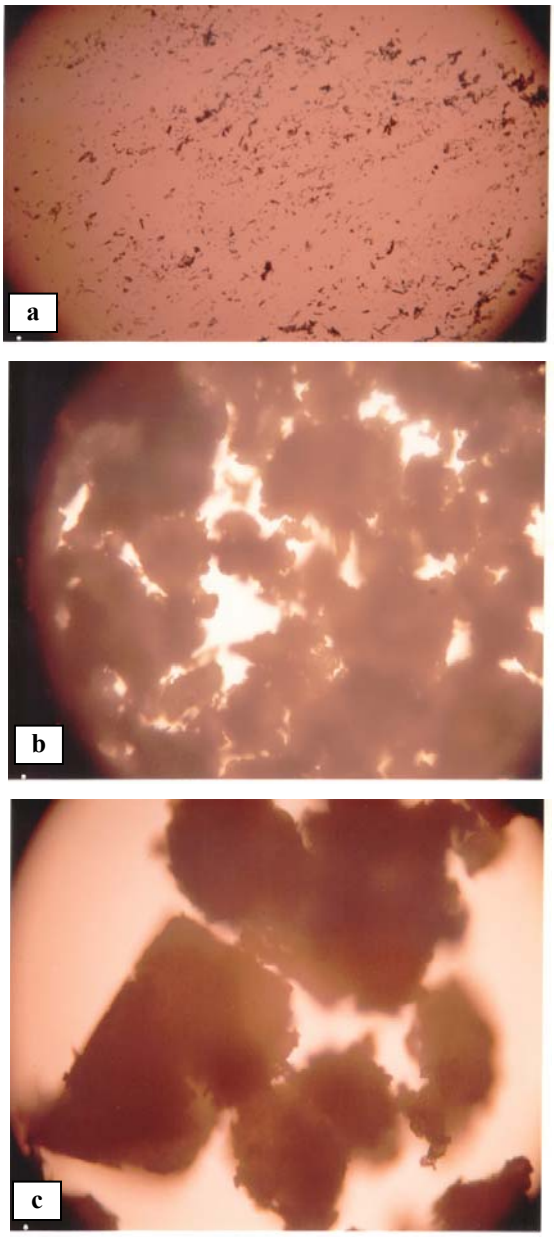

Fig. 2: Photomicrograph (x40) showing the structure of particles in the bulk powder before (a) and after melt granulation with (b) 20%w/w and (c) 40%w/w of goat fat.

CONCLUSION

Melt granulation of drug powder is an approach for retarding drug release from granules. The drug release mechanism is mainly by diffusion through the lipid phase into the external leaching fluid. The study also showed that goat wax, which is cheaply sourced locally, can be substituted for the more expensive carnuba wax and glyceryl monostearate in the melt granulations.

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