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Porous cellulose matrices containing lipophilic release modifiers—a potential oral extended-release system

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Abstract

A multiple-unit extended-release matrix preparation was prepared by the incorporation of a hydrophilic drug (paracetamol) and lipophilic release modifiers (cetyl alcohol and paraffin) into porous cellulose matrices. The incorporation was performed using a one-step melt method. The in vitro drug release could be extended up to at least 16 h. The release rate could be controlled by varying the ratio of cetyl alcohol to paraffin. The porosity of the matrix during release increased to a larger extent than explainable by dissolution of the drug substance. This increase in porosity appears to be caused by swelling of the cellulose in combination with some erosion of the matrix material.

Keywords: Extended release; Matrix; Melt; Multiple unit; Porous cellulose matrices; Porosity

1. Introduction

Porous cellulose matrices (PCMs) hold a potential for use as multiple-unit drug carriers (Björk and Nyqvist 1991; Ek et al., 1991, 1995; Davidson et al., 1993; Davidson, 1996). Incorporation of drugs into PCMs may retard drug release but usually not to an extent sufficient for extended-release purposes (Gren et al., 1996). One method of extending drug release is by coating drug-loaded porous matrices with a release-controlling membrane (Davidson, 1996). The drug release rate from PCMs may also be modified by incorporation of release-modifying substances together with the drug into the pores of the cellulose matrix.

One possibility for a release-modifying substance would be a thermoplastic material, which could be incorporated by melting without excessive energy input or organic solvents. If the drug could be suspended in the melt, it would be possible to produce extended-release pellets by a one-step process. Lipids may be suitable in this way as release modifiers for incorporation into PCMs, since they often have low melting points, are non-toxic and relatively inexpensive and have a broad range of physico-chemical properties. Lipids may be classified on the basis of their interactions with water into nonpolar lipids (e.g. aliphatic hydrocarbons) and polar lipids (Small, 1986). Polar lipids can be further subdivided into different classes: (I) insoluble nonswelling am-

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phiphilic lipids, (II) insoluble swelling amphiphilic lipids and (III) soluble amphiphilic lipids. The release rate from lipophilic matrices can be controlled by the use of a mixture of a nonpolar with a polar lipid or of two polar lipids from different classes (Thomsen, 1992; Adeyeye and Price, 1994; Thomsen et al., 1994).

If drug particles are uniformly distributed in a lipophilic matrix which is not changed during release (e.g. by swelling or erosion), the system can be described as an inert granular matrix. A frequently cited description of drug release from an inert granular matrix is summarised in Eq. (1) which was developed by Higuchi (1963):

$$Q = \sqrt{\frac{D\varepsilon}{\tau}(2A - \varepsilon C_s)C_s t} \quad (1)$$

where Q is the amount of drug released at time t per unit surface area of the matrix, D is the diffusion coefficient of the drug in the release medium, ε is the porosity when all of the drug is dissolved, A is the concentration of drug in the matrix, C_s is the solubility of the drug and τ is the tortuosity. It is assumed that the drug particles are relatively small compared to the distance of diffusion and that they are homogeneously distributed throughout the matrix. For the equation to be valid, A must be greater than εC_s by a factor of 3 or 4. This equation was developed for a planar system. However, Higuchi (1963) showed that the deviations between Eq. (1) and a more complex equation describing the release from a sphere is small when $< 50\%$ of the drug has been released. Hence, for simplicity, Eq. (1) will be used when discussing the effects of porosity and matrix surface area although this is valid only at an early stage of the release process.

For release of the first 60% of drug from polymeric systems, Ritger and Peppas (1987) have suggested the following equation:

$$M = kt^n \quad (2)$$

where k is a constant and n is an exponent. The value of n characterises the mechanism of release. If drug release is controlled solely by Fickian diffusion from a matrix, the value of n will be equal to 0.5 for a planar slab and Eq. (2) is in agreement with Eq. (1). For a sphere, n will be equal to 0.43 for Fickian release. As can be seen from Eq. (1), a drawback of this type of release control is that the release rate is not constant but decreases with time. However for a number of drugs with relatively large therapeutic indices this would probably not be a major disadvantage.

The aim of this study was to investigate whether drug release from PCMs can be controlled by incorporation of lipophilic release modifiers together with the drug substance.

2. Materials and methods

2.1. Materials

Paracetamol (Hoechst, Germany) was chosen as a model drug since it has rather high aqueous solubility, is relatively stable and non-toxic and can easily be analysed spectrophotometrically. Three different size fractions were obtained by micronisation in a pin disc mill (Alpine, Germany) and air classification (100 MZR, Alpine, Germany)

Cetyl alcohol (Bionord AB, Sweden) and hard paraffin (BP) with a congealing interval of 52–54(C (MB Sveda, Sweden) were used as release modifiers, representing polar (class I) and nonpolar lipids respectively (Small, 1986).

2.2. Preparation and loading of PCMs

PCMs were manufactured from powdered cellulose (Sanacel 90, Cellulose Füllstoff Fabrik, Germany) using a specific process involving mechanical treatment in the presence of water (Björk et al., 1994). The size fractions 0.5–0.71, 0.71–1.17 and 1.17–1.4 mm were obtained by sieving.

The drug was dry mixed with the lipid, using a mortar and pestle. The drug–lipid mixture was then melted over a water bath and the drug was dispersed in the melt. PCMs were added and the mixture was allowed to cool during stirring. Agglomerates were then separated by gentle shaking. Eventually the pellets were sieved to remove any remaining agglomerates. Pellets were also prepared in this manner without any drug in order to study erosion and water penetration behaviour of

the excipients. Lipid–drug particles without any cellulose were also prepared as a control by extruding a partially congealed suspension of drug in lipid through a 1 mm sieve. The fraction 0.71–1.17 mm was then obtained by sieving. The different formulations are shown in Table 1. The batch size was 50 g.

2.3. Particle size and shape

Particle size and shape for the pellets were characterised using image analysis. The spherical diameter equivalent to the projected surface area and the circularity factor (Allen, 1975) for the projection of each particle were calculated for 300 particles. The arithmetic means were then calculated. A macro lens (Micro-Nikkor, 55 mm, 1:2.8, Nikon, Japan), a video camera MTI CCD 72 (Dage-MTI, USA) and a computer Macintosh II fx were used. The software was Neotech Image Grabber version 2.03 and Graftek Optilab™ version 1.4.2.

The surface equivalent diameter (d_s) of the different size fractions of paracetamol was determined by dynamic air permeametry, in a Blaine apparatus at a porosity of 65%. This porosity was chosen because the measured surface areas were independent of porosity around this value. Calculations were made using an equation including terms for both viscous and molecular flow as described by Alderborn et al. (1985).

2.4. Porosity

Porosity and pore size distributions of some of the prepared batches of pellets were measured ($n = 2$) by mercury intrusion porosimetry (Accupore II 9220, Micromeritics, USA) assuming circular pore openings, a surface tension for mercury of 485 mN/m and a contact angle between mercury and the solid of 130°. The porosity of drug depleted pellets was also determined. The effective particle density (British Standard, 1958) was cal-

Table 1
Prepared granules and results from linear regression of ln (released drug) vs. ln(time) for < 60% drug released for studied granules[a]

Lipid composition (paraffin–cetyl alcohol)	Paracetamol content (% w/w)	Granule particle size (mm)	Drug particle size (μm)	Slope[b] (n)	R^2
1:0	2.5	0.7–1.2	2.2	0.60 ($\pm$0.22)[c]	0.986
1:1	2.5	0.7–1.2	2.2	0.60 ($\pm$0.08)[d]	0.978
1:2	2.5	0.7–1.2	2.2	0.43 ($\pm$0.03)	0.993
1:3	2.5	0.7–1.2	2.2	0.42 ($\pm$0.07)	0.988
0:1	2.5	0.7–1.2	2.2	–[e]	–
1:2 (40% Lipid)	2.5	0.7–1.2	2.2	–[e]	–
1:2 (37% Lipid)	2.5	0.7–1.2	2.2	–[e]	–
1:2 (No cellulose)	2.5	0.7–1.2	2.2	0.60 ($\pm$0.02)	0.998
1:2	2.5	0.5–0.7	2.2	0.33 ($\pm$0.04)	0.995
1:2	2.5	1.2–1.4	2.2	0.48 ($\pm$0.03)	0.993
1:2	2.5	0.7–1.2	3.4	0.36 ($\pm$0.03)	0.993
1:2	2.5	0.7–1.2	8.4	0.20 ($\pm$0.02)	0.993
1:2	1	0.7–1.2	2.2	0.50 ($\pm$0.08)	0.959
1:2	5	0.7–1.2	2.2	0.46 ($\pm$0.25)	0.998
1:0	0	0.7–1.2	2.2	–	–
1:2	0	0.7–1.2	2.2	–	–
1:2 (No cellulose)	0	0.7–1.2	2.2	–	–
0:1	0	0.7–1.2	2.2	–	–

[a] Lipid concentration is 43% (w/w) unless otherwise indicated. (95% confidence limits are shown within brackets).
[b] The exponent n in 2 is a characteristic of the curvature of the release profile. If $n = 1$, the release rate is constant with time and if $n = 0.5$, the amount released is proportional to the square root of time.
[c] Evaluated for < 7% released drug.
[d] Evaluated for < 25% released drug.
[e] Release too rapid to allow calculations for < 60% released.

culated from mercury intrusion data. The apparent particle density of the PCMs was determined by helium pycnometry (Accu Pyc 1330, Micromeritics, USA) ($n = 2 \times 10$). The intraparticulate porosity was then calculated from the effective particle density and the apparent particle density.

2.5. In vitro drug release

The release rates were determined according to USP method I (basket) in deionised water, at 37°C ($n = 6$). The amount released was detected spectrophotometrically ($\lambda = 244$ nm). The amount of pellets was adjusted in order to maintain sink conditions during the entire release and to obtain optimal analytical sensitivity. To investigate the effect of agitation, pH and surfactants, these conditions were also varied.

2.6. Characterisation of water uptake and erosion

An estimation of the effects of water uptake and erosion on the release of drug was made by gravimetric estimation of the amount of water absorbed and loss on drying (Sutananta et al., 1995). This was done by placing PCMs containing different lipids but no drug in the dissolution test apparatus and analysing the samples ($n = 6$) after 1, 6 and 16 h. The percentage matrix erosion was calculated according to Eq. (3):

$$\text{Weight loss } (\%) = \left(\frac{W_{\text{initial}} - W_{\text{dried}}}{W_{\text{initial}}} \right) \times 100 \qquad (3)$$

where W_{initial} is the weight of the sample before the test and W_{dried} is the weight after the dissolution test and dried to a constant weight at 35–40°C. The percentage water uptake was calculated according to Eq. (4):

$$\text{Water uptake } (\%) = \left(\frac{W_{\text{wet}} - W_{\text{dried}} - W_0}{W_{\text{dried}}} \right) \times 100 \qquad (4)$$

Where W_{wet} is the wet weight of the sample after dissolution. (W_{wet} was obtained by taking the sample in the basket from the dissolution apparatus and removing excess water by gentle shaking. The sample was allowed to stand for 6 minutes at room temperature before weighing. The dry weight of the basket was then subtracted.) W_0 is the average weight of water adsorbed onto the basket ($n = 6$) and was introduced into the formula since this was not negligible compared with ($W_{\text{wet}} - W_{\text{dried}}$). Statistical evaluation of the water uptake and erosion data was performed using the In Stat 2.02 software (Graph Pad, USA).

3. Results and discussion

3.1. General effects of lipid incorporation

The molten lipids, including the micronised drug, penetrated rapidly into the pores of the PCMs, forming free-flowing pellets after cooling. Paracetamol added to the melt formed a milky suspension, indicating that the drug was not dissolved in the lipids. Image analysis revealed that the loaded PCMs were still spheroidal particles with approximately the same diameter as before loading (Table 2). Scanning electron microscope photographs showed that the surface of the particles changed from a fibrous structure with many pores to a smoother less porous structure (Fig. 1).

The release rate increased as the amount of incorporated lipid decreased (Fig. 2). This may have been caused by an increase in the initial porosity when the amount of lipid is decreased. At the highest lipid concentration, 43% (w/w) (or 45.5% for pellets without drug), the volume of the paracetamol and lipid mixture constitutes 51–55% of the pellet volume (calculated from density values obtained by helium pycnometry). This corresponds approximately to the porosity of the PCMs (54%). Consequently, the porosity was low for all tested systems where a concentration of 43% lipid was used (Table 3). When the concentration of lipid is decreased, the porosity will increase. According to Eq. (1), the release rate decreases with decreasing porosity (ε) of the portion of the matrix without drug. The value of ε is equal to the sum of the initial matrix porosity and the porosity developed during drug release. The presence of hydrophilic cellulose surfaces in the matrix will probably cause rapid penetration of water into all pores, accentuating the effect of an

Table 2
Particle characteristics for pure PCMs and PCMs incorporating 2.5% (w/w) paracetamol and 43% (w/w) lipid, before and after the in vitro dissolution test[a]

Lipid composition (paraffin–cetyl alcohol)	Size fraction (mm)	Before the dissolution test			After the dissolution test		
		Particle diameter[b] (mm)	Circularity factor[c] (−)	Specific surface area[d] (cm^{-1})	Particle diameter[b] (mm)	Circularity factor[c] (−)	Specific surface area[d] (cm^{-1})
Pure PCMs	0.5–0.7	0.52 (0.08)	0.97 (0.10)	110	–	–	–
Pure PCMs	0.7–1.2	0.76 (0.14)	0.98 (0.07)	74.0	0.82 (0.12)	0.99 (0.06)	70.1
Pure PCMs	1.2–1.4	1.12 (0.15)	1.0 (0.07)	51.7	–	–	–
1:2	0.5–0.7	0.46 (0.14)	0.93 (0.11)	109	0.58 (0.08)	0.97 (0.09)	101
1:2	0.7–1.2	0.83 (0.24)	0.99 (0.08)	62.3	0.86 (0.12)	1.0 (0.07)	67.4
1:2	1.2–1.4	1.08 (0.17)	1.0 (0.07)	53.6	1.35 (0.13)	1.0 (0.04)	43.7
1:0	0.7–1.2	0.69 (0.15)	0.99 (0.12)	79.7	0.80 (0.15)	1.0 (0.10)	69.9
0:1	0.7–1.2	0.80 (0.14)	0.99 (0.06)	70.7	0.90 (0.12)	1.0 (0.09)	64.5

[a] After 24 h in USP I (basket), 100 rpm, in deionosed water. S.D.s within brackets, $n \geq 300$.
[b] Arithmetic mean by number.
[c] Perimeter of area equivalent circle/actual perimeter (Allen, 1975).
[d] Σ surface of measured particle/Σ volume of measured particles, assuming that all particles are perfect spheres.

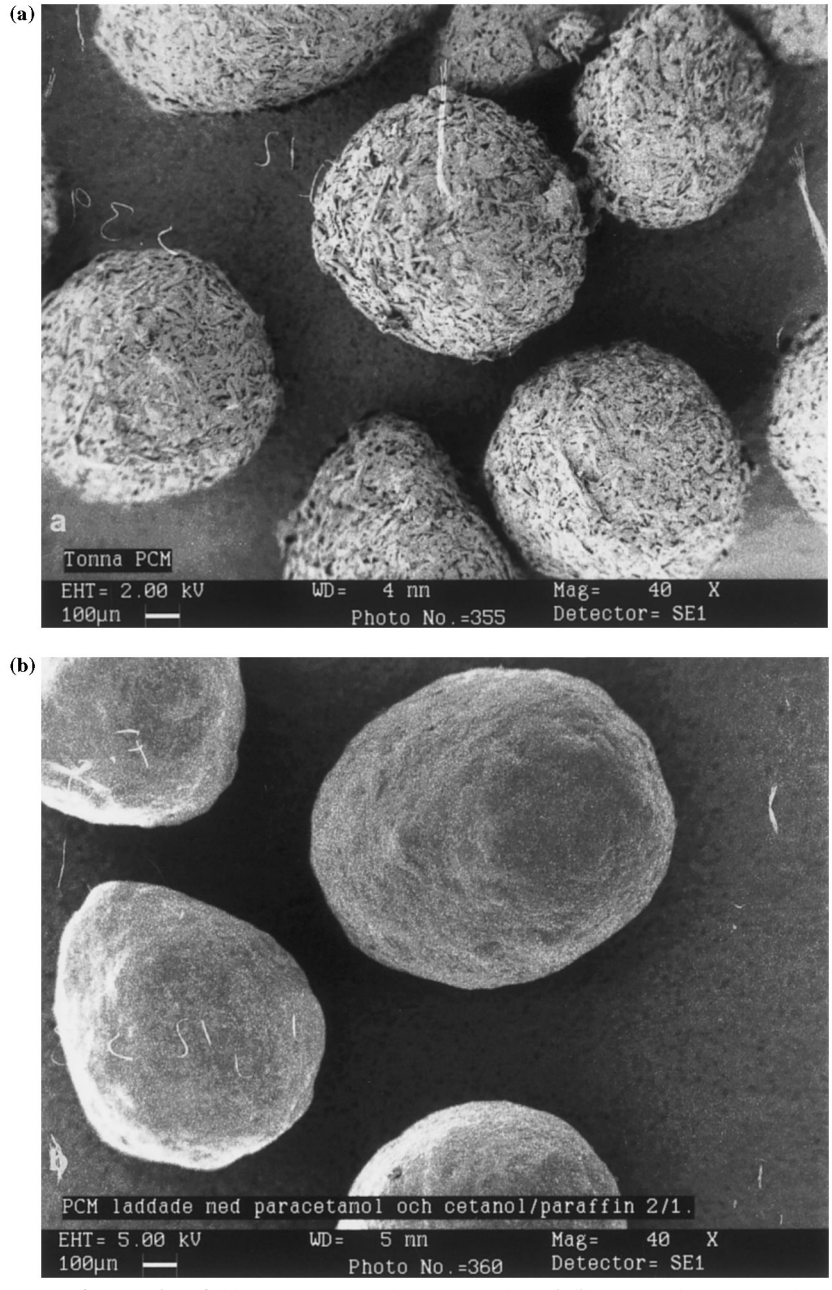

Fig. 1. Scanning electron micrographs of (a) empty PCMs (0.7–1.2 mm) and (b) PCMs (0.7–1.2 mm) containing 2.5% (w/w) paracetamol ($d_s = 2.2$ μm) and 43% (w/w) lipid (paraffin–cetyl alcohol 1:2). Scale bars are 100 μm.

initially high porosity on the release rate. Hence, it is important to fill all voids in the PCMs completely, if maximum extension of the drug release is desired.

3.2. The effect of lipid composition

Fig. 3 shows the release rate from PCMs with varying lipid composition. It is clear that the

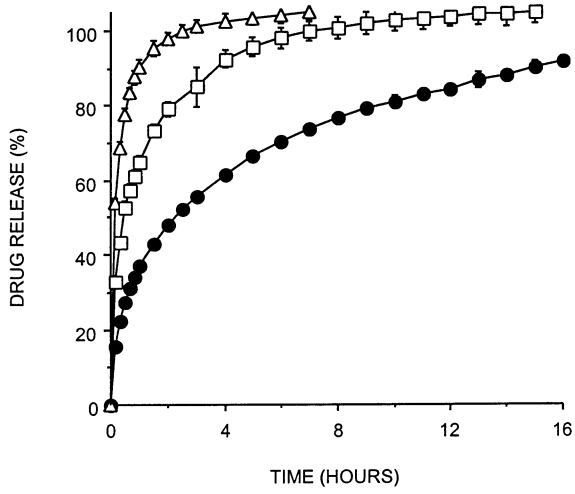

Fig. 2. Relative amount of released drug vs. time for PCMs (0.7–1.2 mm) containing 2.5% (w/w) paracetamol ($d_s = 2.2$ μm) and various concentration of lipid (paraffin–cetyl alcohol 1:2): (●) 43% (w/w) lipid, (□) 40% (w/w) lipid, and (△), 37% (w/w) lipid. Error bars show 95% confidence limits for the mean and are within symbols if excluded.

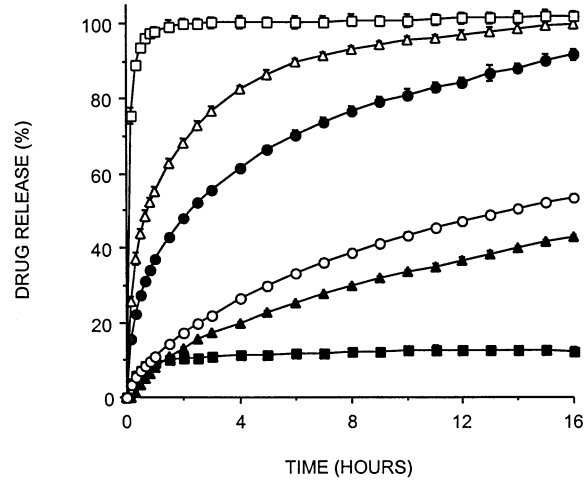

Fig. 3. Relative amount of released drug vs. time for pellets (0.7–1.2 mm) containing 2.5% (w/w) paracetamol ($d_s = 2.2$ μm) and 43% (w/w) lipid of differing composition: (▲) paraffin–cetyl alcohol 1:1, (●) paraffin–cetyl alcohol 1:2, (△) paraffin–cetyl alcohol 1:3, (□) pure cetyl alcohol, (■) pure paraffin, and (○) reference pellets without cellulose, 97.5% lipid (paraffin–cetyl alcohol 1:2). Error bars as in Fig. 2.

release rate could be controlled by varying the proportion of cetyl alcohol to paraffin. Increasing the proportion of the more amphiphilic cetyl alcohol increases the release rate, while pure paraffin results in slow incomplete drug release. The faster release rate when cetyl alcohol is present could be because the more hydrophilic cetyl alcohol allows more rapid penetration of water into the matrix and/or more matrix erosion. It is also clear from Fig. 3 that release is slower from particles without cellulose than for PCM pellets with the same lipid composition. It seems to be possible to extend the release rate over at least 16 h. Variations in the release profiles were very small for all batches, as evident from the 95% confidence limits, which are within the symbols for most batches.

Table 3
Mercury porosimetry data for granules before and after the in vitro dissolution test

Lipid composition (paraffin–cetyl alcohol)	Paracetamol content (% w/w)	Lipid content (% w/w)	Initial porosity[a] (%)	Porosity after the dissolution test (%)	Median pore diameter after the dissolution test (μm)
Pure PCMs	0	0	54	–	4.2[b]
1:0	0	45.5	–0.2	4.3	1.1
1:2	0	45.5	2.4	22	3.6
0:1	0	45.5	0.2	25	5.7
1:0	2.5	43	0.0	4.2	0.1
1.2	2.5	43	−0.1	40	0.9
0:1	2.5	43	−1.0	32	5.5

[a] Calculated from granule density measured by mercury porosimetry and apparent density by helium pycnometry.
[b] Measured before in vitro dissolution.

3.3. The effect of in vitro dissolution test conditions

The drug release was not influenced by variation of pH from 1.2 (hydrochloric acid buffer) to 6.8 (phosphate buffer) (Fig. 4). However, the release was somewhat faster in pure water than in the buffers used, indicating that the ion strength of the release medium had a moderate effect. An increase in the rotation speed of the basket from 100 to 200 rpm had only a small effect on the release rate. This is expected because transport in the stagnant diffusion layer surrounding the pellets should be fast when compared with the rate of transport within the matrix, since diffusion inside the matrix is limited by the porosity and tortuosity of the matrix and since the distance of diffusion is greater. The addition of 0.01% Tween 80 to the medium also had only a limited effect on the release rate, suggesting that wetting the pellets is not rate-limiting. This may indicate that the lipophilic nature of the lipids is counteracted by the more hydrophilic cellulose and paracetamol.

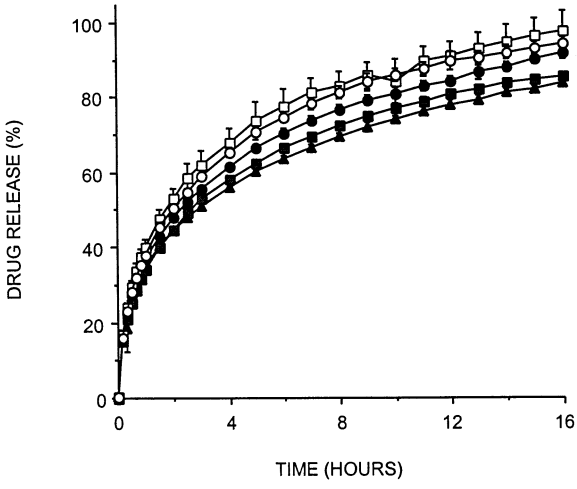

Fig. 4. Relative amount of released drug vs. time for PCMs (0.7–1.2 mm) containing 2.5% (w/w) paracetamol ($d_s = 2.2$ μm) and 43% (w/w) lipid (paraffin–cetyl alcohol 1:2): (▲) pH 6.8, rotation speed 100 rpm; (●) deionized water, rotation speed 100 rpm; (□) 0.01% Tween 80 rotation speed 100 rpm; (■) pH 1.2, rotation speed 100 rpm; and (○) deionised water, rotation speed 200 rpm. Error bars as in Fig. 2.

3.4. Evaluation of swelling and erosion of the matrix

The value of the exponent n in Eq. (2) was calculated by linear regression of ln (relative amount released) versus ln (time) for $< 60\%$ drug released (Table 1). It was found that in many batches n differed significantly from 0.43, indicating that the drug release is controlled by additional mechanisms apart from pure diffusion from a homogeneous granular matrix. Such additional mechanisms could include matrix erosion, swelling of the matrix, and heterogeneous distribution of the drug in the matrices. The decrease of n with decreasing pellet size and with decreasing drug particle size is difficult to explain for an ideal diffusion-controlled matrix and supports the assumption that additional mechanisms exist.

Intraparticulate porosity data offer an explanation for the increase in the rate of drug release when the ratio of cetyl alcohol to paraffin is increased (Table 3). The porosity before drug release is close to zero for all batches. The small negative values observed for some batches are probably due to the difficulty of measuring very low porosities. At low porosities the effective particle density will approach the apparent density. A slight overestimation of the former will then give a negative porosity value. In any case it is clear that the lipid and drug mixture has filled most of the pores in the PCMs. After the in vitro dissolution test the porosity increased far more than could be explained by the dissolution of drug. The porosity also increased markedly when no drug was present. This increase in porosity could be explained by erosion of lipids from the matrix or by formation of cracks and voids caused by the swelling of the cellulose matrix. The higher increase in porosity seen when cetyl alcohol was present in the matrix probably occurred because this substance is more hydrophilic than paraffin. The more hydrophilic nature of cetyl alcohol could increase the porosity both by increased erosion and increased swelling of the cellulose. Since the aqueous solubility of cetyl alcohol is likely to be higher it will increase the solubility of the release modifier. Further, its more hydrophilic nature could also allow more penetration of water

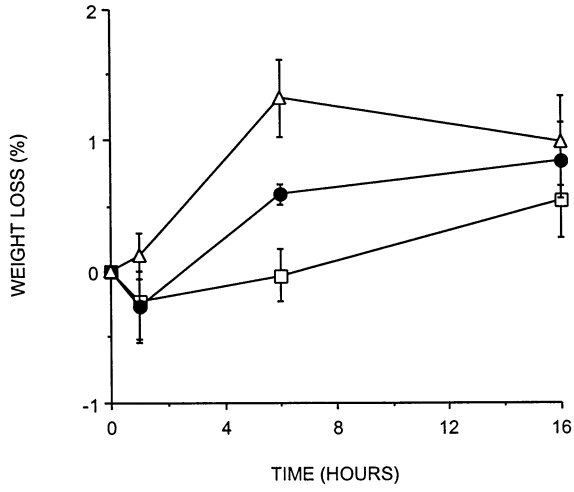

Fig. 5. Weight loss (%) vs. time for lipid-PCMs (0.7–1.2 mm) without drug and 45.5% (w/w) lipid: (□) pure paraffin, (●) paraffin–cetyl alcohol 1:2, and (△) pure cetyl alcohol. Error bars as in Fig. 2.

into the pellets and consequently more swelling of the cellulose.

The small increase in porosity seen when paraffin alone was incorporated into the matrices could hardly have been caused by dissolution of the insoluble paraffin. A more probable explanation is that cracks were formed in the matrix when the cellulose swelled in the presence of water. Davidson et al. (1994) showed that empty PCMs expand in water. It should also be noted that the particle diameter of both empty PCMs and PCMs containing the drug–lipid mixture increased after the dissolution test (Table 2).

The presence of limited matrix erosion is supported by the gravimetric studies (Fig. 5). It should be emphasised that the term matrix erosion, in this case, refers to erosion from within the matrices resulting in a higher porosity, since it can be seen from the image analysis data (Table 2) that the particle size does not decrease (but increases) after the in vitro dissolution test. The amount of erosion appears greater and the rate is faster when the ratio of cetyl alcohol to paraffin is increased. It was noted that the matrix erosion measured by the gravimetric method ($<1.5\%$) could not have been solely responsible for the increase in porosity seen after drug dissolution (4–40%). It is possible that some water was bonded to the cellulose and not released during drying. This could have resulted in underestimation of the amount of matrix erosion. It should also be noted that matrix erosion is expressed as percent by weight while porosity, for obvious reasons, is expressed as percent by volume. However, this is insufficient to explain the total difference seen between weight loss and increased porosity. It is more likely that most of the increase in porosity is due to an increase in particle size caused by swelling of the cellulose matrix rather than erosion of the lipid matrix material. This theory is supported by the increase in particle diameter seen after the in vitro dissolution test (Table 2).This increase in particle diameter obviously corresponds to a more pronounced increase in PCM particle volume after dissolution testing. The mean volume increase after dissolution testing for loaded PCMs in Table 2 is 60%, which alone could account for a porosity of 38%. It should be remembered that both porosity and particle diameters after the dissolution test were measured on dried beads. Hence, shrinkage during drying may affect these data. Decrease in particle size after drying swollen unloaded PCMs has been demonstrated by Davidson et al. (1994). This means that the porosity seen in the dried pellets might not necessarily represent water-filled voids during release. The voids may be filled to some extent with swollen cellulose. The estimation of erosion from pellets without cellulose was affected by attrition of material from the surface. This was probably due to the rough surface structure of these pellets caused by the different preparation processes and not due to the absence of cellulose itself. Hence, no matrix erosion data for pellets without cellulose are shown in Fig. 5.

Gravimetric estimation of water uptake into the matrices showed no significant change in the relative amount of water which penetrated the matrices from 1 to 16 h (Fig. 6). Hence, it is assumed that water penetration is a relatively rapid process, occurring mostly during the first hour. The variability of these measurements is quite high but when measurements at different times were pooled it could be shown (by Kruskal–Wallis nonparamatric ANOVA combined with Dunn's

multiple comparisons test) that the uptake of water was significantly higher ($P < 0.05$) when cetyl alcohol was present in the matrix. Water penetration was significantly lower in the pellets without cellulose than in corresponding lipid-loaded PCMs. Thus, most of the water penetration appears to be caused by the cellulose fibres. This may explain why drug release is faster from PCM-pellets than from pellets without cellulose. The water could either be absorbed into the cellulose fibres or present in the pores inside the matrix. The latter probably accounts for most of the water. It should also be remembered that water adsorbed onto the surfaces of the pellets will influence the results of these measurements.

3.5. The effect of particle size of PCM and drug

The drug release rate increased with decreasing particle size of the pellets (Fig. 7). This is in accordance with Eq. (1) since Q is the amount released per unit surface area. It was also found that if the initial release rate was estimated by extrapolation to time zero and these values were plotted versus initial pellet surface area (Table 2) an approximately straight line was obtained (not shown).

When the mean particle size (expressed as surface equivalent diameter, d_s) of the drug was increased from 2.2 to 3.4 μm, the release rate was not affected. However an increase to 8.4 μm had

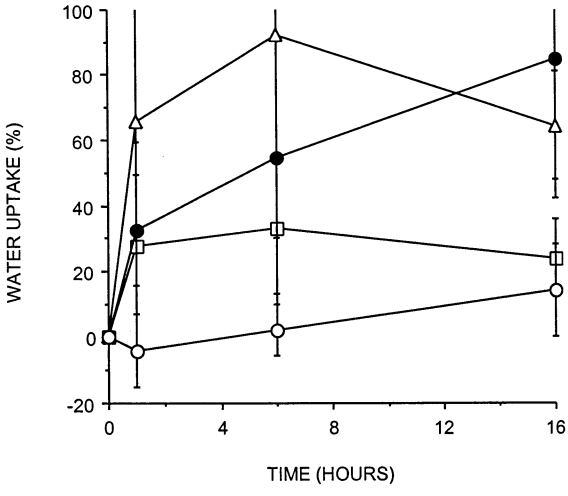

Fig. 6. Water uptake (%) vs. time for pellets (0.7–1.2 mm) without drug: (□) 45.5% (w/w) pure paraffin and PCMs, (●) 45.5% (w/w) paraffin–cetyl alcohol 1:2 and PCMs, (△) 45.5% (w/w) pure cetyl alcohol and PCMs, and (○) reference pellets paraffin–cetyl alcohol 1:2 and no cellulose. Error bars as in Fig. 2.

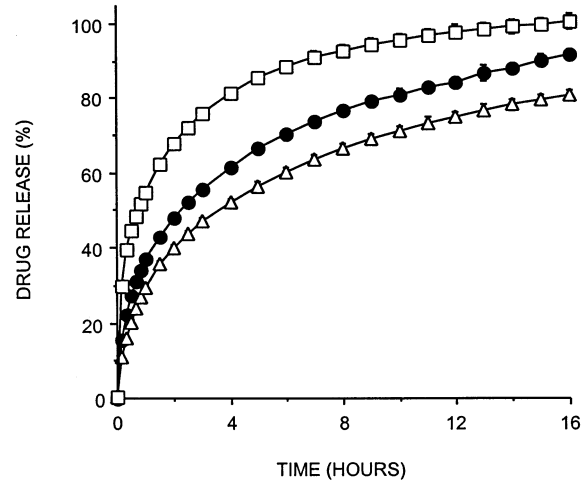

Fig. 7. Relative amount of released drug vs. time for PCMs of different pellets size containing 2.5% (w/w) paracetamol (d_s = 2.2 μm) and 43% (w/w) lipid (paraffin–cetyl alcohol 1:2): (□) 0.5–0.7 mm, (●) 0.7–1.2 mm, and (△) 1.2–1.4 mm. Error bars as in Fig. 2.

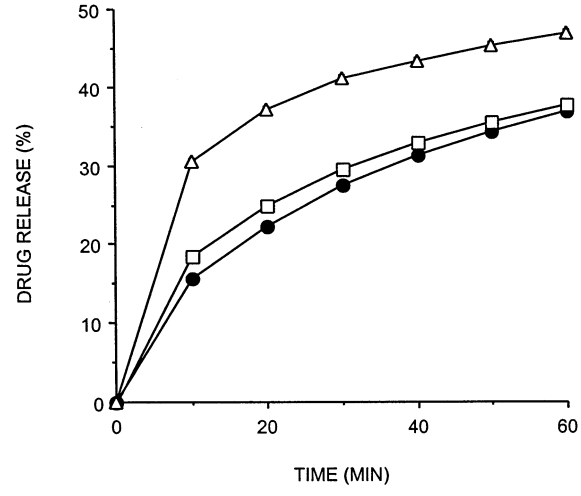

Fig. 8. Relative amount of released drug vs. time for PCMs of different drug particle size containing 2.5% (w/w) paracetamol and 43% (w/w) lipid (paraffin–cetyl alcohol 1:2): (●) 2.2 μm, (□) 3.4 μm, and (△) 8.4 μm. Error bars as in Fig. 2.

a significant effect on the release rate (Fig. 8). The effect of particle size was more marked during the initial phase of drug release. That particle size affects the release rate is not expected for an inert granular matrix as described by Eq. (1), although a similar effect has been observed for theophylline containing spheres of cellulose acetate propionate (Shukla and Price, 1989). However, in that case the size of the drug particles was not negligible compared to the size of the spheres as assumed in Eq. (1). In the present study the particle size of the drug is negligible compared to the size of the spheres and there are other reasons for the effect of drug particle size.

The effect of drug particle size on release rate may be explained by increased entrapment of drug particles in the pores near the PCM surface with increasing particle size. During the loading process, the molten lipid penetrates the PCMs successively from the surface towards the centre. Dispersed particles which are lager than the pore diameter will then be entrapped in the pores, resulting in a higher concentration of drug particles close to the surface than in the centre of the pellets. Confocal laser fluorescence microscopy of PCMs in which sodium fluoresceine ($d_s = 11$ μm) was incorporated instead of paracetamol demonstrated that a higher concentration of drug particles near the pellet surface is possible. Unfortunately, it was difficult to prepare sodium fluoresceine of a smaller particle size. Therefore, a more thorough study of the effect of particle distribution by confocal laser fluorescence microscopy was not performed. The theory that a less uniform drug distribution is the consequence of increased particle size is supported by the increased curvature of the release profile seen when the drug particle size is increased (Fig. 8), which is also reflected as a decrease in the exponent n in Eq. (2) (Table 1). A higher concentration of drug near the surface than in the centre of the PCM-pellets may also be a contributing explanation for the slower drug release seen from lipid pellets without cellulose, where a more uniform drug distribution is assumed. Hence, it seems to be important to control the drug particle size and the pore diameter when incorporating drugs dispersed as particles in melted release modifiers into PCMs.

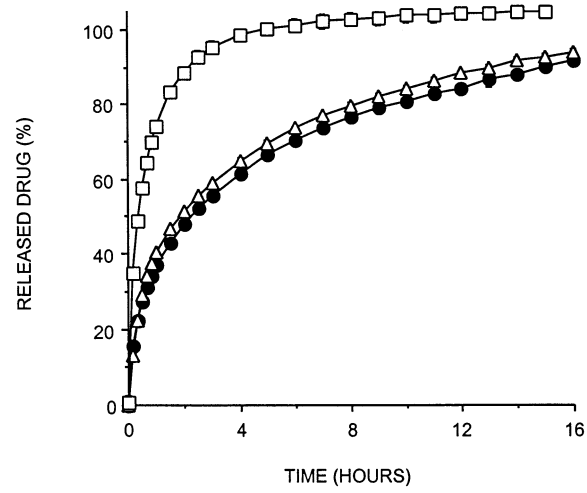

Fig. 9. Relative amount of released drug vs. time for PCMs (0.7–1.2 mm) containing 43% (w/w) lipid (paraffin–cetyl alcohol 1:2)and differing concentrations of paracetamol ($d_s = 2.2$ μm): (△) 1% (w/w), (●) 2.5% (w/w), and (□) 5% (w/w). Error bars as in Fig. 2.

An alternative is to use systems where the drug is soluble in the release modifier. The mechanisms for release control will then of course be different. It has also been shown that the release rate from a solid dispersion may be less stable upon storage if the drug is dispersed on a molecular basis (Sjökvist Saers et al., 1993).

3.6. The effect of drug concentration

The rate drug release was not affected when the drug concentration in the pellets was increased from 1 to 2.5% (Fig. 9). However, an increase in the concentration of incorporated drug to 5% gave a significant increase in release rate. The accelerated drug release with a concentration of 5% may have been caused by increased entrapment of drug particles close to the surface of the PCMs. This could be due to increased viscosity of the drug–lipid dispersion or the formation of more drug agglomerates with increasing drug concentration. Alternatively, a continuous network of paracetamol particles may have been formed at this concentration. The transitions from finite to continuous clusters at a so called percolation threshold is often associated with drastic changes

in properties (Leuenberger et al., 1987). The assumption that a continuous cluster is not formed by paracetamol at a concentration of 2.5% is supported by the incomplete drug release observed when pure paraffin was used as a release modifier.

4. Conclusions

Drug release from PCMs can be extended to at least 16 h by incorporating lipophilic release modifiers together with the drug into the intraparticulate structure of the cellulose matrix. The rate of release could be altered by varying the composition of the release modifier, the concentration of drug and the particle size of the PCMs. Release of the drug appears to be controlled by diffusion from the matrix but is also affected by the distribution of drug in the matrices and an increase in porosity during drug release. This increased porosity, which could only partly be explained by the dissolution of drug, is mainly due to formation of cracks and voids as the cellulose swelled. Erosion of matrix material contributes to a smaller extent to the increase in porosity. The drug and release modifier can be incorporated simultaneously by dispersing the micronised drug into the molten release modifiers. Hence, an extended-release multiple-unit preparation may be prepared from PCMs using a simple, solvent-free, one-step process. The disadvantages of this method include difficulties in incorporating large amounts of drug or drugs of large particle size. It should be pointed out that the preparation of the pellets was performed on a small scale and that the scale up may be difficult. Further, the drug release rate is not constant but decreases with time, as would be expected for a matrix system.

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