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In vitro drug release from porous cellulose matrices

T. Gren[a,*], C. Bjerre[b], O. Camber[b], G. Ragnarsson[1b]

[a] *Pharmacia and Upjohn, S-751 82 Uppsala, Sweden*
[b] *Pharmacia and Upjohn, S-112 87 Stockholm, Sweden*

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Abstract

Drugs of different solubilities were incorporated into porous cellulose matrices (PCMs) by solvent evaporation. The rate of release of the drugs from the PCMs was found to decrease with increasing drug concentration and decreasing drug solubility. At low or moderate drug concentrations, the release rate remained moderately high except for drugs of very low solubility. The mechanisms controlling release rate appeared to include diffusion within the matrix but may be more complex.

Keywords: Drug release; Inert matrix; In vitro dissolution; Multiple units; Porous cellulose matrices

1. Introduction

Porous cellulose matrices (PCMs) are spherical cellulose particles with a high porosity (typically 50–70%). Studies have shown these particles to be potential multiple unit drug carriers (Björk and Nyqvist, 1991; Davidson et al., 1993).

PCMs into which drugs have been incorporated may be used for several purposes in drug formulation, including reduction of dusting, improvement of flowability, direct compression or modified release. Drug release from PCMs may be modified either by coating or by incorporation of release-modifying agents.

The mechanisms of drug release from PCMs are important for several reasons:

1) These mechanisms will determine the release characteristics if the system is used as an uncoated carrier system;

2) If the system is coated to form a controlled-release system, drug release from the PCMs could influence the total release rate. This may complicate control of the release rate or have unfavourable effects on the release profile (e.g. cause deviations from zero-order release kinetics);

* Corresponding author. Temporary address: Department of Pharmaceutics, Uppsala University, S-751 23 Uppsala, Sweden.

[1] Present address: Astra Draco AB, Box 34, S-221 00 Lund, Sweden.

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3) Improved understanding of drug release from PCMs will make it easier to understand the mechanisms of release from more complex systems, such as those with additional release modifiers incorporated together with the drug in order to adjust the release rate or other release characteristics.

The release of drugs from PCMs has been correlated with diffusion characteristics obtained using spin echo nuclear magnetic resonance techniques (Ek et al., 1995), although the experimental data in this study were too limited to allow conclusions regarding release mechanisms.

It has been shown that spherical granules of microcrystalline cellulose and drug substances manufactured by extrusion/spheronisation act as an extended release system of the inert granular matrix type (O'Connor and Schwarz, 1993). Drug release from PCMs may follow a similar pattern.

However, we may expect large differences in porosity, pore size distribution and pore structure between drug-loaded PCMs and cellulose granules manufactured by extrusion/spheronisation. This is obvious if the manufacturing processes for PCMs and extruded granules are considered. In contrast to the extruded granules, PCMs have a fixed initial void volume which is gradually filled with drug. The corresponding void space in extruded/spheronised granules is to a large extent created when the drug and other soluble substances are dissolved out. These differences between drug-loaded PCMs and extruded granules will be accentuated when low or moderate amounts of drug are incorporated into the PCMs. Differences in porosity may result in different mechanisms controlling drug release. If the porosity is sufficiently high, diffusion in the matrix will not be rate limiting and the release will be controlled by dissolution only.

The aim of this study was to investigate the in vitro release of drugs with different aqueous solubilities from PCMs.

2. Experimental

2.1. Materials

PCMs were manufactured from cellulose using a special process involving mechanical treatment in the presence of water (Ek et al., 1991). The size fractions 0.5–0.71 mm, 0.71–1.0 mm and > 1.4 mm were obtained by sieving.

Two drugs with different aqueous solubilities were chosen as main model substances: oxazepam (F.I.S., Italy) and paracetamol (Mallinckrodt, USA). In order to study the effect of solubility in more detail four additional substances were used: caffeine (Boehringer-Ingelheim, Germany), indomethacin (Sigma, USA), propiomazine maleate (Sanofi, France) and theophylline (Boehringer-Ingelheim, Germany).

2.2. Methods

2.2.1. Incorporation of drugs into PCMs

Different amounts of the drugs were incorporated into the PCMs (Table 1). Drug concentration and PCM particle size were varied only for oxazepam and paracetamol. The drug was dissolved in water (caffeine, paracetamol and propiomazine maleate) or 95% ethanol (indomethacin, oxazepam and theophylline) according to its solubility. The PCMs were then dispersed in the solution and the solvent was evaporated. When ethanol was used, water was added when most of the ethanol was evaporated. Most of the solvent was evaporated before the final freeze drying. It has been shown in preliminary studies that freeze drying as the final step promotes a homogenous drug distribution.

2.2.2. Characterisation of empty PCMs

2.2.2.1. Particle size and shape. Particle size and shape were characterised using image analysis for all size fractions of PCMs. 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 or more particles. The arithmetic means were then calculated. A macro lens (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

Table 1
Manufactured batches of drug-loaded PCMs

Drug	Drug concentration (% w/w)	Size fraction of PCMs (mm)	Solvent for incorporation
Paracetamol	1.9	0.71–1.0	Distilled water
Paracetamol	4.1	0.71–1.0	Distilled water
Paracetamol	9.5	0.71–1.0	Distilled water
Paracetamol	4.8	>1.4	Distilled water
Paracetamol	4.1	0.50–0.71	Distilled water
Oxazepam	1.2	0.71–1.0	Ethanol (95%)
Oxazepam	3.1	0.71–1.0	Ethanol (95%)
Oxazepam	3.7	0.71–1.0	Ethanol (95%)
Oxazepam	4.2	>1.4	Ethanol (95%)
Oxazepam	3.9	0.50–0.71	Ethanol (95%)
Caffeine	4.6	0.71–1.0	Distilled water
Theophylline	4.1	0.71–1.0	Ethanol (95%)
Indomethacin	4.9	0.71–1.0	Ethanol (95%)
Propiomazine maleate	4.2	0.71–1.0	Distilled water

and Graftek Optilab™ version 1.4.2.

2.2.2.2. Density. The true density of the PCMs was determined using helium pycnometry (Accu Pyc 1330, Micromeritics, USA) ($n = 10$).

2.2.2.3. Porosity. The intraparticular porosity and pore size distributions of the different size fractions of PCMs were measured ($n = 2$) by mercury intrusion porosimetry (Accupore II 9220, Micromeritics, USA) assuming a contact angle of 130°.

2.2.3. Characterisation of drug-loaded PCMs

2.2.3.1. Assay of drug content. The amounts of drug incorporated into PCMs were assayed spectrophotometrically after extraction in 95% ethanol or distilled water ($n \geq 2$).

2.2.3.2. In vitro drug release. The release rates were determined according to USP method II (paddle) in phosphate buffer (pH 6.8) at 37°C ($n = 6$). The rotation speed was 100 rpm. The amount of PCMs was adjusted in order to maintain sink conditions during the entire release and in order to obtain optimal analytical sensitivity. The initial release rates were calculated by linear regression using the initial part of the release profile.

2.2.3.3. Solubility of drug substances. The solubilities of the different drugs in 37°C phosphate buffer (pH 6.8) were determined ($n = 2$). Excess of the drugs was suspended in phosphate buffer. The suspensions were magnetically stirred for 24 h at 37°C and centrifuged. The supernatant was then filtered through a 0.22-μm membrane filter. The centrifuge vials and the filtering equipment were carefully conditioned to 37°C. The drug concentration in the filtered supernatant was determined spectrophotometrically.

3. Results and discussion

3.1. Characterisation of unloaded PCMs

The mean diameters and circularity factors for each size fraction are listed in Table 2. All size fractions had circularity factors close to 1, indicating a shape close to spherical, which was confirmed by visual inspection. The decreasing circularity factor with increasing size was probably due to the measurement technology. The larger the particles the more easily are irregulari-

Table 2
Mean particle characteristics of PCMs (standard deviations within brackets)

Size fraction (mm)	Diameter (mm)[a]	Circularity factor[b]	Porosity (%)	True density (g/cm^3)	Specific surface area[c] (cm^{-1})
0.50–0.7	0.599 (0.082)	1.0 (0.084)	53	1.55	96.4
0.71–1.0	0.873 (0.113)	0.99 (0.062)	55	1.55	66.5
>1.4	1.49 (0.145)	0.95 (0.076)	58	1.55	39.4

[a] Projected area diameter.
[b] Perimeter of area equivalent circle/actual perimeter (Allen, 1975).
[c] Σ surface of measured particles/Σ volume of measured particles, assuming that all particles are perfect spheres.

ties detected by the image analysis system. The standard deviations of both diameters and circularity factors were small. The influence of the sampling procedure should thus be small when withdrawing samples for in vitro release rate determinations, and calculations of release rate per unit surface area should be reasonably accurate.

As expected, there was no variation in density between different size fractions of PCMs (Table 2). The porosities of the different batches are listed in Table 2. The porosities and pore size distributions were in agreement with earlier measurements for PCMs (Ek et al., 1994).

3.2. Characterisation of drug-loaded PCMs

The contents of drug in the different batches of PCMs are listed in Table 1. The results show that the drug content can be controlled by adjusting the concentration and volume of the drug solution. However, it was difficult to obtain a higher drug content of oxazepam than approximately 4% (w/w) when using the described loading technique, because of the low solubility of this drug in the solvents.

3.3. Characterisation of in vitro drug release

Three possible types of release, with varying importance of dissolution and diffusion as release controlling mechanisms, are discussed.

3.3.1. Type 1 (dissolution control)

If the transport of dissolved drug from the matrix is faster than the dissolution rate, then the concentration of drug dissolved in the liquid in the matrix voids will be much smaller than the solubility of the drug. That is, sink conditions will be valid within the matrix. The release rate will then be controlled entirely by the dissolution process.

The release rate will be proportional to the surface area of the drug. The drug surface area available for dissolution will decrease during the dissolution process. The release kinetics will depend on the rate of drug surface area decrease. An equation for the release due to dissolution was developed by Hixon and Crowell (1931). However, this equation is based on the assumption that the shape of the dissolving particles are constant, which is true for spherical particles in suspension but is not very likely for drug particles, of unknown shape, inside a porous matrix.

3.3.2. Type 2 (diffusion control)

If the transport of dissolved drug is not sufficiently fast to achieve sink conditions within the matrix voids, the release rate will be controlled by both the solubility of the drug and diffusion of the drug within the matrix. Type 2 release control is often referred to as 'diffusion control' in the literature since the effect of solubility is implicit. A number of equations have been derived for this type of release control. One of the most frequently used is Eq. (1), which was derived for a granular inert matrix by Higuchi (1963).

$$Q = \left(\frac{D\varepsilon}{\tau} (2A - \varepsilon C_s) C_s t \right)^{1/2}, \quad (1)$$

where Q is the amount 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 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 three or four. This equation was developed for a planar system. However, Higuchi (1963) has shown that the deviations between Eq. (1) and a more complex equation, describing the release from a sphere, is small when more than 50% of the drug has been released. Hence, for simplicity, Eq. (1) will be used when discussing initial release rates.

Eq. (1) can also be written as

$$100 - m = k_1 t^{0.5}, \quad (2)$$

where k_1 is a constant.

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

$$100 - m = k_2 t^n, \quad (3)$$

where k_2 is a kinetic constant characteristic 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 that contains undissolved drug, the value of n will be equal to 0.5 for a planar slab and Eq. (3) is in agreement with Eqs. (1) and (2). For a sphere, n will be equal to 0.43 for Fickian release.

3.3.3. Type 3 (pure diffusion control)

When all the drug is dissolved in the release medium within the matrix voids, the drug release rate will be unaffected by the solubility and entirely controlled by diffusion from the matrix.

The release of a dissolved substance from a sphere has been described by Baker and Lonsdale (1974). The equation for the final part of the release is

$$M(t)/M(0) > 0.6,$$

$$M(t)/M(0) = 1 - (6/\pi^2) \exp(-\pi^2 Dt/r^2), \quad (4)$$

where $M(t)/M(0)$ is the relative amount of released drug and r is the radius of the sphere. Eq. (4) is valid for a homogeneous matrix but can be adapted for a granular matrix by including the porosity and tortuosity in the equation. As can be seen, Eq. (4) is analogous to a first order equation

$$\ln m = -bt + a, \quad (5)$$

where a and b are constants.

3.3.4. Release kinetics

It was found that the release data for all drugs except oxazepam and theophylline yielded approximately straight lines when plotted according to first-order kinetics (Eq. (5)) (Fig. 1). Hence, first-order release constants may be used for comparison of release rates. The adherence of release

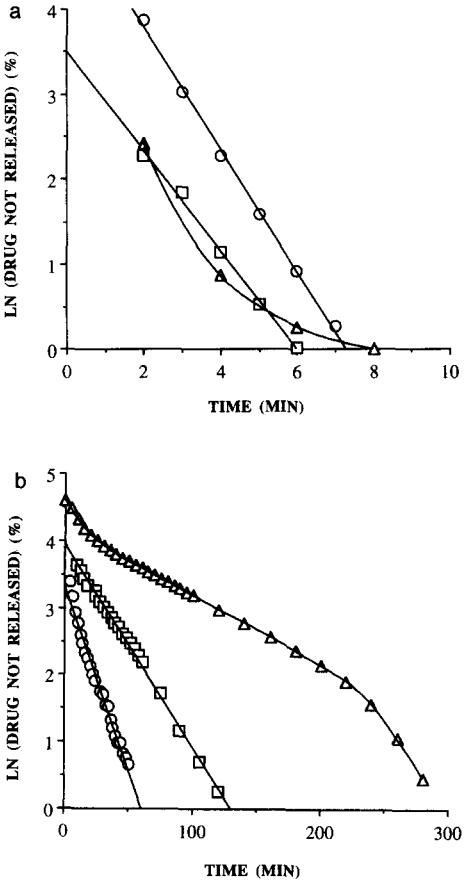

Fig. 1. Ln (drug not released) vs. time for PCMs (0.71–1.0 mm) containing approximately 4% drug. (a) —○—, paracetamol; —□—, caffine; —△— theophylline. (b) —○—, propiomazine maleate; —□—, indomethacin; —△—, oxazepam.

Table 3
Linear regression of ln (100 − m) versus ln t (95% confidence intervals within brackets)

Drug	Drug concentration (% w/w)	Size (mm)	Y intercept	Slope (n)	r^2
Oxazepam	3.9	0.50–0.71	1.08 (±0.20)	0.77 (±0.06)	0.990
Oxazepam	3.7	0.71–1.0	1.67 (±0.35)	0.65 (±0.11)	0.960
Oxazepam	4.2	>1.4	1.58 (±0.38)	0.70 (±0.13)	0.968

data to Eq. (5) may be due to Type 3 release during the final release phase, for the more soluble drugs. For indomethacin and oxazepam a Type 3 mechanism is not probable, since their solubilities are very low. It should be emphasised that the release rates for all drugs, except oxazepam, are so rapid that only few data points for more than 60% of drug was recorded. Hence, the observed fit to Eq. (5) may be valid only for the final phase of drug release.

For oxazepam, the earlier phase of drug release (< 60% drug released) was investigated. The value of n in Eq. (3) was evaluated by linear regression of a plot of ln m versus ln t up to $m = 60\%$ (Table 3). Unfortunately, this evaluation was possible only for the highest concentration of oxazepam, since the release rate was too rapid to give a sufficient number of data points ($m < 60\%$) for lower drug concentrations. The slope (n) varied from 0.65 to 0.77 indicating that the release is not controlled by Fickian diffusion.

3.3.5. Effect of drug solubility

The initial drug release rate tended to increase with increasing solubility of the incorporated drug (Fig. 2). This is expected since the solubility of the drug will affect the release rate both in Type 1 and Type 2 control.

According to the Noyes–Whitney equation (Noyes and Whitney, 1897), the release rate will be directly proportional to the solubility of the drug if sink conditions are assumed and the release is controlled solely by dissolution (Type 1).

If drug release is controlled by diffusion (Type 2), the influence of drug solubility is described by Eq. (1).

If $2A \gg \varepsilon C_s$, Eq. (1) can be simplified into

$$Q = \left(\frac{2D\varepsilon A C_s t}{\tau}\right)^{1/2} \tag{6}$$

and

$$\frac{dQ}{dt} = \left(\frac{D\varepsilon A C_s}{2t\tau}\right)^{1/2}. \tag{7}$$

It is seen from Eq. (7) that the release rate in a matrix system where drug release is controlled by diffusion (Type 2) will be proportional to the square root of the solubility. Hence the effect of solubility on release rate could be expressed as

$$\frac{dQ}{dt} = k_3 C_s^z, \tag{8}$$

where k_3 is a constant and the exponent z will be equal to 1 for release controlled by dissolution (Type 1) and 0.5 for release of the Higuchi type (Type 2). A linear regression of a plot of ln (initial release rate) versus ln (solubility) yielded a fairly straight line ($r^2 = 0.93$) with a slope (z) of 0.37 with a 95% confidence interval ranging from 0.23 to 0.51. This suggests that drug release is generally controlled by diffusion (Type 2) from the matrix rather than by simple dissolution (Type 1).

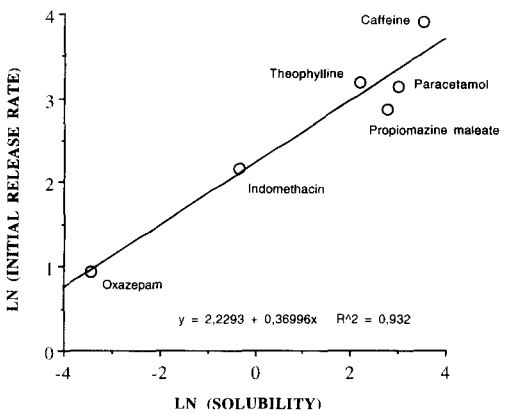

Fig. 2. Ln (initial drug release rate) vs. ln (solubility) for approximately 4% drug incorporated into PCMs (0.71–1.0 mm).

Table 4
First-order release constants for approx. 4% drug incorporated in PCMs 0.71–1.0 mm (95% confidence intervals within brackets)

Drug	Solubility[a] (mg/ml)	b (min^{-1})
Caffeine	34	0.54 ($\pm$0.08)
Paracetamol	20	0.59 ($\pm$0.07)
Propiomazine maelate	16	0.055 ($\pm$0.003)
Theophylline[b]	9.0	0.39 ($\pm$0.45)
Indomethacin	0.70	0.030 ($\pm$0.007)
Oxazepam[b]	0.032	0.012 ($\pm$0.007)

[a] Solubility at pH 6.8, 37°C.
[b] A plot according to Eq. (5) is not linear for these substances.

It should be pointed out that the release rate could also be affected by differences in crystal form caused by the incorporation method, distribution of drug particles and drug particle size. The release controlling mechanism may also differ between drugs of different solubility. Hence it is not surprising that a perfect correlation between solubility and release rate was not found (Fig. 2).

A slightly different situation appears when comparing release rates during the last stages of release. The rank order of drug release rate (expressed as first-order release constants) corresponded to solubility only for less soluble drugs (Table 4). First-order release constants of caffeine and paracetamol have approximately the same value. The release rate of propiomazine maleate, the solubility of which is of the same order of magnitude, is much slower. This may be due to the fact that the release rate of more soluble drugs during the final phase is controlled by the diffusion of completely dissolved substance from the cellulose matrix (Type 3). Consequently, the release rate is controlled by the diffusion coefficient rather than the solubility.

3.3.6. *Effect of drug concentration*

The relative in vitro release rate (i.e. the ratio of amount released to the total amount per unit time) of both paracetamol and oxazepam, with the exception of paracetamol 4.1%, decreased with increasing drug concentration in the PCMs (Figs. 3 and 4). This decrease in relative release

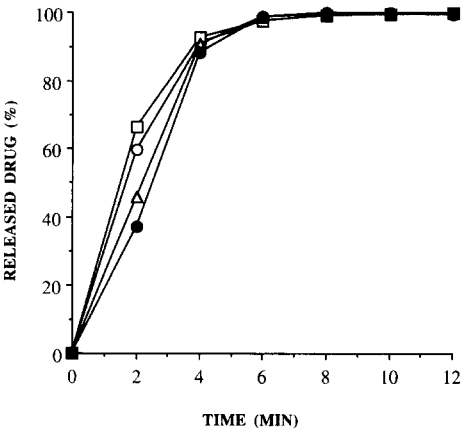

Fig. 3. Relative amount of released drug vs. time for different concentrations of paracetamol incorporated into PCMs (0.71–1.0 mm): —○—, 1.9%; —□—, 4.1%; —△—, 9.5%; —●—, 25%.

rate could be explained by Eq. (1) for a diffusion controlled matrix system (Type 2) if it is considered that Q is the absolute amount released per unit surface area.

The effect of drug concentration could also be a consequence of a possibly increased drug crystal size with increasing drug concentration in the PCMs. This will cause a decrease in specific surface area available for dissolution when higher amounts of drug are incorporated into the PCMs. Hence, the effect of drug concentration could also

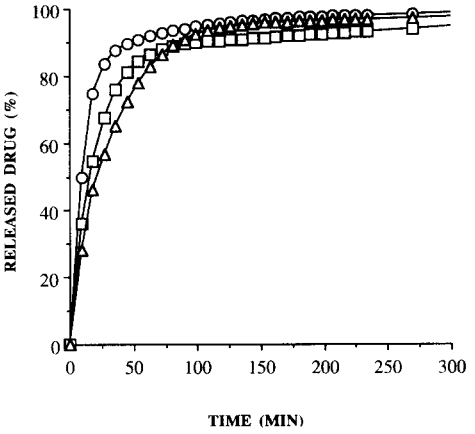

Fig. 4. Relative amount of released drug vs. time for different concentrations of oxazepam incorporated into PCMs (0.71–1.0 mm): —○—, 1.2%; —□—, 3.1%; —△—, 3.7%.

Table 5
First-order release constants for paracetamol in PCMs 0.71–1.0 mm (95% confidence intervals within brackets)

Drug content (% w/w)	b (min^{-1})
1.9	0.54 (±0.12)
4.1	0.59 (±0.07)
9.5	0.61 (±0.19)
25	0.98 (±0.05)

be explained for a release controlled by dissolution (Type 1).

First-order rate constants varied very little between different loading concentrations in the final stages of paracetamol release, except for the highest concentration (25%) (Table 5). This is in accordance with the earlier assumption that the release rate of paracetamol during the final stage is controlled by diffusion of completely dissolved drug from the spheres (Type 3).

3.3.7. *Effect of particle size of PCMs*

A release rate controlled by diffusion (Type 2 or 3) will increase with decreasing PCM particle size since the outer surface area of the matrix will increase and the diffusion paths will be shorter. This is obvious from Eq. (1) since Q is the amount released per unit surface area. However, a release rate controlled by dissolution (Type 1) will be proportional to the surface area of drug available for dissolution but independent of the surface area of the PCMs.

Increasing the particle size of the PCMs led to a decrease in release rate for paracetamol. The release rate appeared to be proportional to the outer surface area of the PCMs (Table 6). This

Table 6
First-order release constants and specific surface area for PCMs of different size containing approx. 4% paracetamol (95% confidence intervals within brackets)

Particle diameter (mm)	b (min^{-1})	S_v (cm^{-1})	b/S_v (cm/min)
0.50–0.71	1.0 (±0.30)	96.4	0.010
0.71–1.00	0.59 (±0.07)	66.5	0.0089
>1.4	0.38 (±0.04)	39.4	0.0096

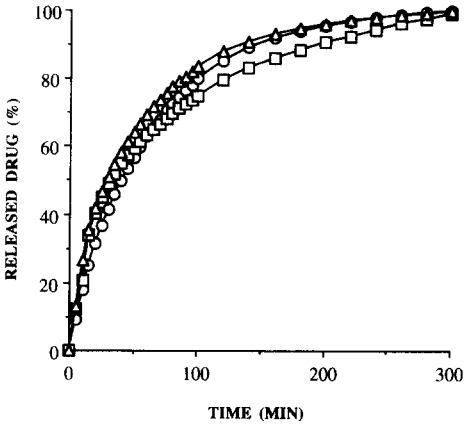

Fig. 5. Relative amount of released drug vs. time for approximately 4% oxazepam incorporated into PCMs of different diameter: —○—, 0.5–0.71 mm; —□—, 0.71–1.00 mm; —△—, >1.4 mm.

clearly indicates that the release of paracetamol is controlled by diffusion (Type 2 or 3).

The size of the PCMs did not appear to affect the release rate of oxazepam (Fig. 5). (Release profiles, instead of first-order constants, are shown, since the fit of oxazepam release to Eq. (5) was poor). The reason for the differences between oxazepam and paracetamol could be that hindrance due to diffusion in the matrix is of greater importance for the more rapidly dissolving paracetamol. For oxazepam, the dissolution process is slower and may therefore control the overall release rate (Type 1).

3.3.8. *Effect of crushing the PCMs*

The in vitro release rate of oxazepam and paracetamol increased after gently grinding the PCMs in a mortar (Fig. 6). This could be explained either by shorter diffusion distances or by an increased drug surface area. In any case, Fig. 6 clearly demonstrates that the incorporation of drug into PCMs may cause a significant decrease in release rate, caused by either hindered diffusion or slow dissolution due to large drug particle size.

3.3.9. *Release mechanism*

The kinetics of oxazepam release during the early phase (<60% released) indicates a non-Fickian release. Evaluation of the final phase of

release of the more soluble drugs indicates a control purely by diffusion (Type 3).

The effect of solubility indicates that the initial phase of drug release is controlled by diffusion from the matrix (Type 2). The importance of diffusion (Type 2) is not contradicted by the effect of drug concentration on release rate. Further, the influence of PCM particle size on release rate indicates that release is controlled by diffusion from the matrix (Type 2 or 3) for paracetamol but not for oxazepam, which may be controlled by dissolution (Type 1).

Consequently, diffusion in the matrix appears to be an important factor controlling the drug release rate. Pure diffusion (Type 3) may control release of highly soluble substances during the final phase. For drugs of lower solubility and at earlier phases, undissolved drug will be present and the release will be controlled by a Type 2 mechanism. For drugs of very low solubility such as oxazepam, the importance of diffusion in the matrix decreases and the release may approach dissolution (Type 1) control.

Drug release may also be influenced by phenomena other than dissolution and diffusion, such as:

Erosion of the matrix. PCMs have been reported to be robust in water for up to 5 days (Davidson et al., 1994) and the PCMs were judged to be intact when visually inspected after drug release. However attrition of small fragments could be difficult to detect but could still significantly affect the release rate.

Changes in the structure of the cellulose matrix. PCMs have been shown to swell in water (Davidson et al., 1994). This will cause changes in the porosity and hence affect the release rate. For some drugs, affinity for cellulose could also contribute to the release-retarding effect, if the drug loading is low.

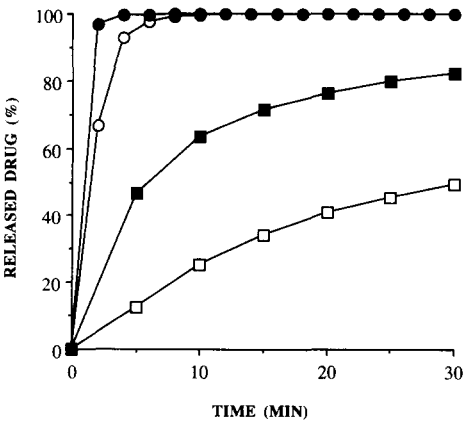

Fig. 6. Relative amount of released drug vs. time for PCMs (0.71–1.0 mm) —○—, 4.1% paracetamol whole PCMs; —●—, 4.1% paracetamol crushed PCMs; —□—, 3.7% oxazepam whole PCMs; —■—, 3.7% oxazepam crushed PCMs.

4. Conclusions

The in vitro drug release rate from PCMs decreased with increasing drug concentration and decreasing solubility of the drug. The incorporation of a substance into PCMs may retard its release. However, at low or moderate drug concentrations the release rate is still fairly high, except for drugs of very low solubility. Consequently the retardation of release by the cellulose matrix will in general not cause any problems if PCMs are used as drug carriers for instant release or for subsequent extended release coating. If PCMs are used as extended release matrices without coating, it is necessary to incorporate release modifying substances (e.g. lipids or polymers).

First-order kinetics was useful in order to describe the final phase of the release of the more soluble drugs, except theophylline. The mechanisms controlling release rate appear to include diffusion, but may be complex and vary depending on factors such as drug substance and drug concentration. The release of drugs of very low solubility may be controlled by dissolution.

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