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Prediction of drug release by characterisation of the tortuosity in porous cellulose beads using a spin echo NMR technique

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Abstract

The tortuosity of pores in cellulose beads has been estimated using a spin echo NMR technique and by direct release measurements. The tortuosity determined with NMR was slightly higher ($\tau = 2.7$) than the values obtained from direct release measurements ($\tau = 1.6$–2.4). The deviations are explained in terms of unfulfilled prerequisites for the models describing the dissolution process. Another explanation may be differences in drug loading and pore structure in the outer and inner layer of the porous cellulose beads. The NMR measurements are described in detail and special problems occurring when applying this technique are discussed. In this work it is shown to be possible to predict drug release from structural data of porous cellulose beads.

Keywords: Diffusion; Drug release; NMR; Porous cellulose matrix; Tortuosity

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1. Introduction

The traditional method of investigating drug release from granules is to measure the drug dissolution and calculate a diffusion coefficient from release models (Desai et al., 1966; Farhadieh et al., 1971; Foster and Parrott, 1990). From the diffusion coefficient a value of the tortuosity of the pores in the granules can be calculated. In this work we wished to do the reverse; to predict drug release from measurements of the tortuosity of the pores in granules. To enable this a method of estimating the diffusion coefficient within the granules must be found.

An early attempt to estimate water and drug diffusion in polymeric membranes was made with the spin echo NMR technique (Persson et al., 1981). Three major difficulties were identified. Firstly, the signal broadening occurring in heterogeneous systems resulted in overlapping peaks in the NMR spectra. Both water and drug diffusion contributed to the estimated diffusion coefficient. Secondly, the resulting spin echo amplitudes $A(g)$ did not form a straight line, as they do in homogeneous solutions, when the spin echo amplitudes $A(g)$ were plotted vs squared gradient strength

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g^2. The span between the lowest and highest diffusion coefficient possibly obtainable was almost a decade. Finally, the diffusion coefficient decreased with the time during which diffusion was studied.

Recently, the spin echo NMR technique has been used to estimate pore sizes and tortuosity in porous cellulose beads (Ek et al., 1994a,b). The problem of signal broadening was avoided by characterizing the structure from water self-diffusion in the absence of drug substance. By using only the initial parts of the spin echo data, it was possible to eliminate the problem of a variable diffusion coefficient. Finally, it was shown to be possible to reach a steady-state level in the diffusion coefficient by prolonging the diffusion time sufficiently.

Thus, the purpose of this work was to examine whether it is possible to predict the drug release from cellulose beads from a knowledge of the pore structure (porosity and tortuosity).

2. Experimental

2.1. Porous cellulose beads

The physicochemical data of the different drug substances and the loaded beads are summarised in Table 1. The drugs loaded into the porous cellulose beads where NAC (*N*-acetyl-L-cysteine), terodiline (*N-tert*-butyl-1-methyl-3,3-diphenylpropylamine) and ISDN (isosorbide dinitrate) as obtained from Pharmacia AB, Sweden.

2.2. Drug release

The drug dissolution tests were performed according to the paddle method (US Pharmacopeia, 1990) in 0.1 M HCl at 50 rpm.

2.3. NMR measurements

2.3.1. Equipment

The experiments were performed on a Bruker MSL NMR Spectrometer equipped with a 4.7 T superconducting magnet operating at 200 MHz for ^{1}H-NMR. A Bruker imaging probe with a 10 mm RF insert was used and the gradient coil was driven by a stereo power amplifier from NAD Electronics Inc., Boston (model 2200).

2.3.2. Pulse program

The experiment started with a 90° RF pulse followed by a 180° RF pulse after a time t and finally, echo detection after $2t$. Magnetic field gradient pulses of strength g and duration δ were applied 1 ms after the 90 and 180° pulses. In the experiments, the time during which the gradient was applied increased between each spin echo experiment. The time delay between each experiment was 10 s for pure water and 2 s for 2 mM $CuSO_4$. The diffusion time $(t - \delta/3)$ was approximated by t since $t \gg \delta$. Between each experiment the gradient duration was increased in regular steps. To maintain a high signal-to-noise ratio at long diffusion times ($t \geq 0.03$ s), a stimulated echo pulse program was used where the

Table 1
Physicochemical data for drug substances and loaded cellulose beads

Substance	Solubility C_s (mg/ml)	Bead loading		
		Drug solute [a]	Drug fraction	
			% (w/w)	C_0 (mg/ml)
Isosorbide dinitrate	1.24 [b]	acetone	29	334
Terodiline	28 [c]	dichloromethane	21	217
N-Acetyl-L-cysteine	220 [d]	water	36	459

The empty beads had a porosity of 52% v/v and sieve size of 1.0–1.4 mm.

[a] Solute during drug loading of the beads.

[b] In water at 37° C (Lagerkvist, P., unpublished data, 1994; Bofors Explosives AB).

[c] In water, measured at 37° C.

[d] In water, at 25° C (Bonanomi and Gassaniga, 1980).

180° pulse was divided into two 90° pulses (Tanner, 1970).

2.3.3. Spin echo data evaluation

By plotting ln $A(\delta)$ vs the squared gradient duration δ^2, it is possible to calculate the apparent diffusion coefficient (Stejskal and Tanner, 1965):

$$\frac{A(\delta)}{A(0)} = \exp\left(-\frac{2t}{T_2} - (\gamma g \delta)^2 D(t)\left(t - \frac{\delta}{3}\right)\right) \quad (1)$$

where δ is the gradient duration time, γ the magnetogyric ratio and g the gradient strength. The initial decrease of the spin echo amplitudes forming a straight line (slope $= (\gamma g)^2 t D(t)$) was analysed (Ek et al., 1994a).

2.3.4. Calibration

The field gradients were calibrated against pure water at 25° C containing 2 mM $CuSO_4$. The diffusion coefficient of water was taken to be equal to 2.3×10^{-9} m^2/s (Callaghan et al., 1983).

2.3.5. Sample preparation

Pure water and water containing 2 mM $CuSO_4$ were added to the porous cellulose beads. The addition of $CuSO_4$ shortens the NMR relaxation time and allows a higher repetition rate in the experiments. Up to diffusion times ≤ 0.2 s the beads contained water with 2 mM $CuSO_4$. At longer diffusion times pure distilled water was used. The beads (dryness 50%) were still free flowing after water addition, indicating that no access water was present on the bead surface.

3. Results

3.1. NMR technique

In solution, the technique is straightforward (Stilbs, 1987), however, diffusion in heterogeneous systems has been less thoroughly investigated. Therefore, a number of experiments were performed on the applicability of the technique to our system.

3.1.1. Independence of the applied gradient

The apparent diffusion coefficient obtained must be independent of gradient strength. On a sample of porous cellulose beads containing water, the apparent diffusion coefficient was calculated from sets of experiments with different gradient strengths. In the experiments the attempt was made to attain a relative standard deviation of diffusion coefficients below 5%. The uncertainty in a given experiment of course depends on the signal-to-noise ratio, which in turn depends on the porosity (amount of liquid in beads), diffusion time, gradient strength and duration. To reach the desired accuracy, a different number of spin echo experiments was employed (Ek et al., 1994a). An example is shown in Fig. 1. The conclusion was drawn that the results are independent of the applied gradient strength.

3.1.2. Measurement range

From the apparent diffusion coefficients, $D(t)$, at different diffusion times, t, it is possible to calculate an average diffusion distance, x_{rms}, for

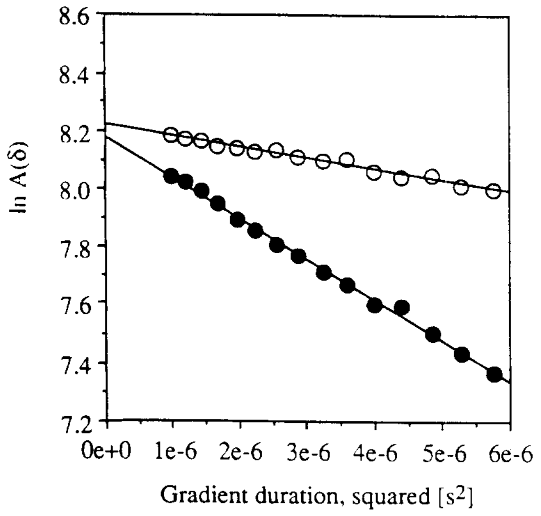

Fig. 1. Spin echo amplitudes of water within porous cellulose beads as a function of the squared gradient durations ($\delta = 1$, 1.1,...2.4 ms) at two different gradient strengths ($g = 72.8$, 146 mT/m) at a diffusion time of 100 ms. (○) $g = 72.8$ mT/m, line slope 3.9×10^4, $D(t) = 10 \times 10^{-10}$ m^2/s. (●) $g = 146$ mT/m, line slope 1.4×10^5, $D(t) = 9.1 \times 10^{-10}$ m^2/s.

the molecules during the diffusion time (Atkins, 1994):

$$x_{\mathrm{rms}} = \sqrt{2D(t)t} \qquad (2)$$

The practical limit of the available diffusion times is from a few milliseconds to some seconds. This corresponds to a possible diffusion distance in the order of 1–100 μm. If the structure contains larger pores it will not be possible to measure the effective diffusion coefficient.

3.2. *Tortuosity and porosity of porous cellulose beads*

The preformed porous cellulose beads can be filled with any drug. The interaction with the cellulose will be purely mechanical, since it is possible to neglect chemical interactions between drug molecules and solid surfaces. This is because the amount of small organic molecules (Larsson and Stenius, 1987) and drugs (Nyqvist et al., 1978) interacting with the surfaces of microcrystalline cellulose is of the order of 10^{-6} mol/g cellulose. This is much smaller than the common drug loading typical for porous cellulose beads, 10^{-2} mol/g cellulose. In these cases it is possible to express the relative diffusion coefficient $D(\infty)/D(0)$ as a function of porosity ϵ and tortuosity τ (Higuchi, 1963; Takenaka et al., 1979):

$$\frac{D(\infty)}{D(0)} = \frac{\epsilon}{\tau} \qquad (3)$$

3.2.1. *Tortuosity*

When the diffusion time in the spin echo NMR experiment increases the fraction of molecules that have reached an obstruction and have been hindered in their diffusion movements increases. The apparent diffusion coefficient decreases with increasing diffusion time. At long diffusion times most molecules have had the time to meet restrictions and the apparent diffusion coefficient levels out to an effective diffusion coefficient. In models of drug release the effective diffusion coefficient is a highly desirable parameter.

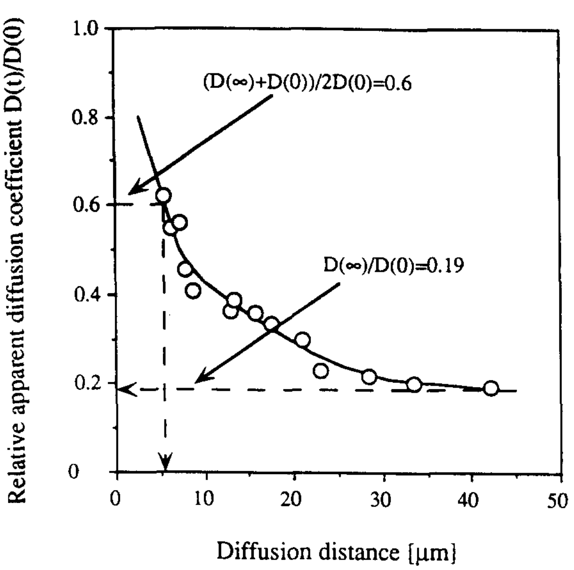

Fig. 2. Relative apparent diffusion coefficients for water in cellulose beads plotted vs the diffusion distances measured using the spin echo NMR technique and diffusion times between 0.01 and 2 s. The diffusion times have been transformed into diffusion distances using Eq. 2. The levelling off value is indicated as a straight line.

For water diffusing in porous cellulose beads the apparent diffusion coefficient levels off to an almost constant value after a diffusion distance of 30–40 μm (Fig. 2). Knowing $D(\infty)/D(0) = 0.19$ and 52 vol.% porosity, a tortuosity $\tau = 2.7$ was subsequently calculated from Eq. 3.

3.2.2. *Pore size*

The pore radius has been shown to correlate with the diffusion distance where $D(t) = (D(\infty) + D(0))/2$ (Ek et al., 1994a). In our sample this diffusion distance is of the order of 5 μm (Fig. 2) which provides an estimate of the average pore size in the cellulose beads.

3.3. *Direct measurements of drug release (dissolution testing)*

The drug release from a diffusion-controlled monolithic device can be divided into two phases, the initial phase when drug is present both in solution and in the solid phase and in a final part

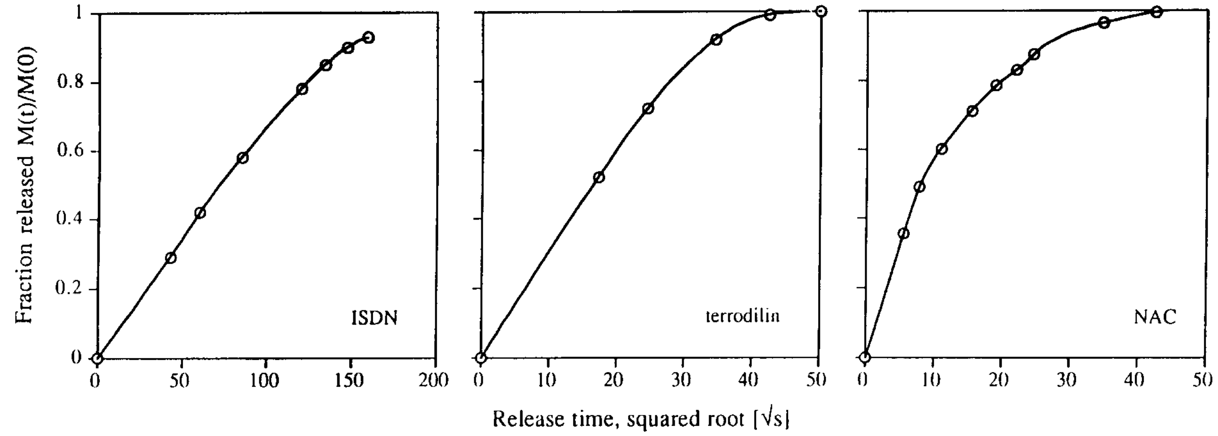

Fig. 3. Fraction released drug (ISDN, terodiline and NAC) from in vitro dissolution tests plotted vs the squared root release time. The initial drug release rate has been plotted as a straight dotted line. Slope in Table 2, Eq. 5.

when all solid drug is dissolved (Baker and Lonsdale, 1974; Langer, 1980).

During the initial phase when drug is present both as solid material and in solution (Higuchi, 1961, 1963), the release of drug from a planar system follows:

$$Q=\sqrt{D(\infty)C_s(2C_0-\epsilon C_s)t} \qquad (4)$$

where Q is the amount of drug released per unit area during the release time t, $D(\infty)$ the effective diffusion coefficient, C_s is the solubility of the drug and C_0 is the actual bead loading of drug in the porous cellulose beads. The porosity ϵ refers to the porosity of the leached portion of the cellulose granules, i.e., pores without drugs. Due to the lack of better estimates, we have used the porosity of the dry unloaded cellulose beads in this work. The real porosity value will be different due to swelling of the cellulose beads and due to the volume of included but still undissolved drug. That is, the porosity will change during the dissolution process.

Eq. 4 was developed for planar systems and extended to spherical pellets (Higuchi, 1963) but it was concluded that the calculation starts to diverge significantly beyond the first 50% release and hence it is possible to use Eq. 4 in the initial phases of drug release. Eq. 4 can be transformed

Table 2
Calculations of tortuosity values from direct drug release measurements (slopes in Fig. 6–8 using Eq. 3 and 5)

Substance	Line slope [a] in Fig. 6–8	$D(\infty)$ [a]	$D(0)$ [b]	Tortuosity [c]
Isosorbide dinitrate	6.8×10^{-3}	2.5×10^{-10}	9.3×10^{-10}	1.9
Terodiline	2.9×10^{-2}	1.4×10^{-10}	6.2×10^{-10}	2.4
N-Acetyl-*l*-cysteine	6.2×10^{-2}	1.8×10^{-10}	5.6×10^{-10}	1.6

[a] Eq. 5: line slope = $\frac{3}{rC_0}\sqrt{D(\infty)C_s(2C_0-\epsilon C_s)}$; data from Table 1.

[b] Diffusion coefficient in water solution. NMR measurements in D_2O. The diffusion coefficient was assumed to be 20% higher in H_2O (Callaghan et al., 1983). Due to difficulties in handling the explosive isosorbide dinitrate, the diffusion coefficient was calculated (Perry and Chilton, 1974).

[c] Eq. 3: $D(\infty)=\frac{\epsilon}{\tau}\cdot D(0)$

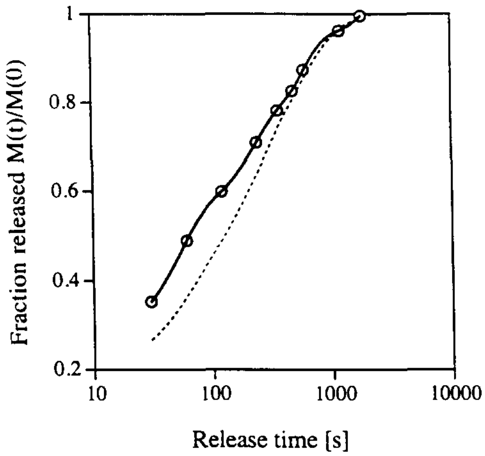

Fig. 4. Fraction released drug (NAC) but plotted against the release time. The dotted line represents drug release predicted from Eq. 6 and 7 and a tortuosity of $\tau = 2.7$.

to describe the amount of drug released $M(t)$ at time t relative to the total loading $M(0)$ by inserting the external area $a = 4\pi r^2$ and

$$M(0) = V\cdot C_0 = \frac{4\pi r^3}{3} C_0$$

where V is the volume of one bead and r denotes the radius of the beads.

$$\frac{M(t)}{M(0)} = \frac{Q\cdot a}{V\cdot C_0} = \frac{3}{r\cdot C_0}\sqrt{D(\infty)C_s(2C_0-\epsilon C_s)t} \qquad (5)$$

On this basis, the in vitro drug release from porous cellulose beads plotted vs the square root of time is shown in Fig. 3. From the slope of the line during the initial phase of drug release the tortuosity was calculated and subsequently summarized in Table 2. One limitation in Eq. 4 and 5 is that the drug loading C_0 should exceed ϵC_s by a factor of 3–4. This is not fulfilled for the beads with *N*-acetyl-L-cysteine granules. In this case, the drug release is better described by Eq. 6 and 7 and in Fig. 4 the direct measurements are plotted together with calculations using a tortuosity of 2.7 (NMR value).

The equations describing the release of dissolved drug from a sphere can be written in two parts (Crank, 1956) – the initial part of drug release:

$$\frac{M(t)}{M(0)} < 0.4,\quad \frac{M(t)}{M(0)} = 6\sqrt{\frac{D(\infty)t}{r^2\pi}} - \frac{3D(\infty)t}{r^2} \qquad (6)$$

and the final part of drug release:

$$\frac{M(t)}{M(0)} > 0.6,\quad \frac{M(t)}{M(0)} = 1 - \frac{6}{\pi^2}\exp\left(-\frac{\pi^2 D(\infty)t}{r^2}\right) \qquad (7)$$

3.4. Predictions of drug release

By inserting the tortuosity value (the effective diffusion coefficient) obtained from the NMR measurements on unloaded beads into Eq. 5–7 it was possible to calculate the times for given fractions of drugs with different solubility to be released. In Table 3 these values are compared with drug release times obtained from direct experiments.

Table 3
Comparison of directly measured and predicted (NMR) drug release data

Drug loaded	Time for fraction release (h)					
	50%			90 %		
	Predicted	Measured	Pred./meas.	Predicted	Measured	Pred./meas.
Isosorbide dinitrate [a]	2.1	1.5	1.40	6.9	6.0	1.15
Terodiline [a]	0.095	0.068	1.38	0.31	0.23	1.30
N-Acetyl-L-cysteine [b]	0.038	0.018	2.11	0.24	0.22	1.09

[a] Predicted from Eq. 5.
[b] Predicted from Eq. 6 and 7.

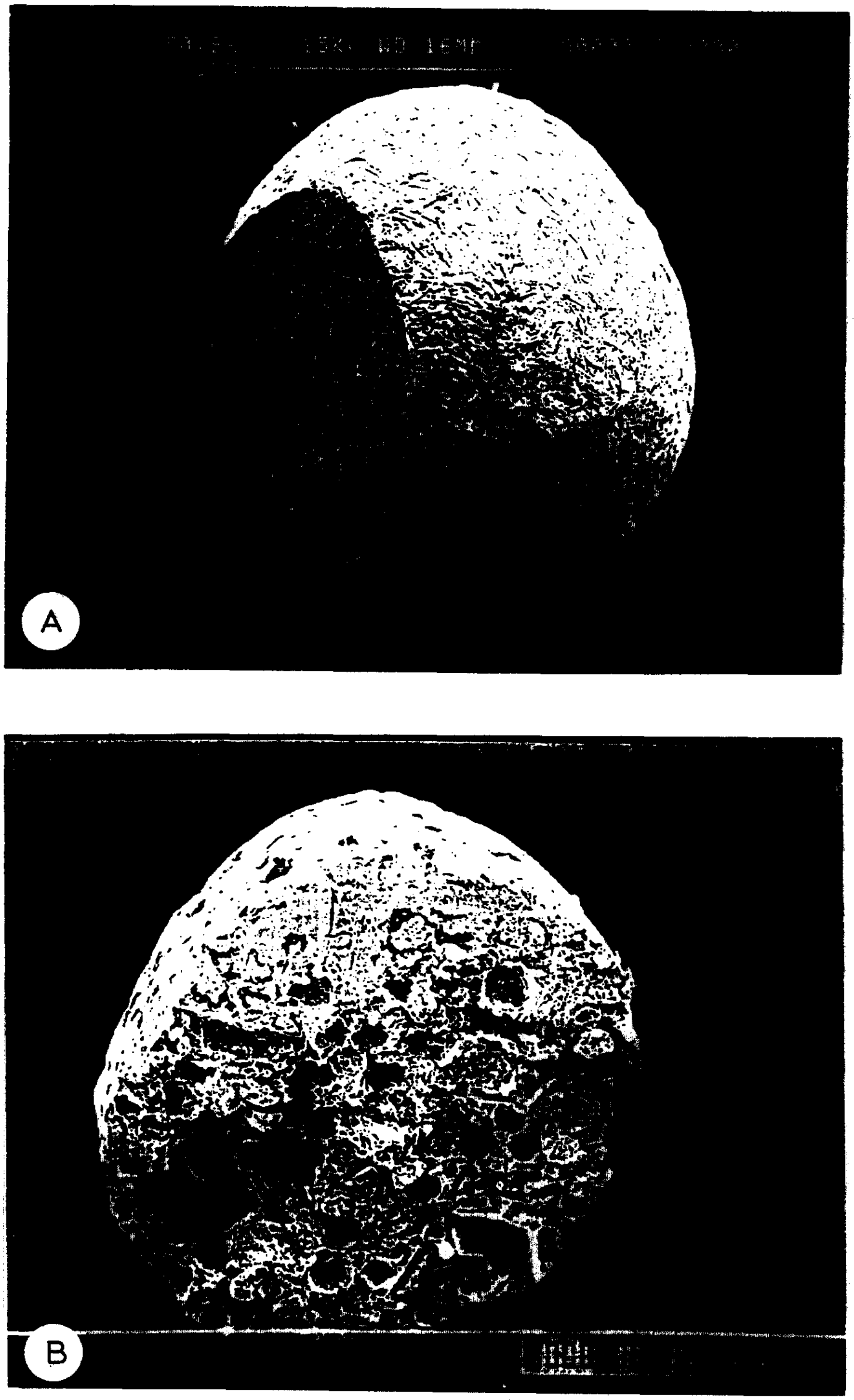

Fig. 5. Cutted cellulose beads without drug. The beads in panel a were manufactured by cyclone rolling (Ek et al., 1991) and those in panel b by leaching the drug from beads formed by extrudation/spheronization (Deasy, 1984). The diameters of both beads are approx. 1 mm.

4. Discussion

The process of loading empty beads with drug, instead of conventional pelletization techniques (Gamlen, 1985; Ghebre-Sellassie, 1989), has the advantage the beads can be fractionated into a desirable size range before loading (Ek et al., 1991; Davidson et al., 1993). Another possible advantage with preformed beads is that it might be possible to predict the drug release from physicochemical data of the drug, matrix loading and knowledge about matrix structure. Predictions of drug release are compared with direct measurements from drug-loaded porous cellulose beads (Table 3). From these data, it seems possible to predict drug release from preformed porous cellulose beads with knowledge about the pore structure. This is because the pore structure of these pellets is independent of both the drug compound and process variables involved during the actual processing of the granules. When drug and excipients are granulated together the pore system formed varies from formulation to formulation and from drug to drug. An example of the two types of beads is shown in Fig. 5.

The tortuosity values calculated from in vitro drug release ($\tau = 1.6, 1.9, 2.4$; Table 2), however, are lower than that obtained from the NMR estimation ($\tau = 2.7$). Thus, the predicted time for a specified drug release fraction will be slightly longer than found in the indirect drug release test (Table 3). There might be several reasons for this discrepancy.

Firstly, it could be questioned whether the assumptions made in deriving the Higuchi equation (Higuchi, 1961, 1963) are fulfilled. The value of the porosity is then of special importance. The value used of the porosity is obtained from mercury intrusion on dry beads, at the same time as it is known that the pore sizes of the beads change due to the swelling of cellulose fibres (Ek et al., 1994b). Another aspect regarding the porosity is that the drug release process might not proceed via a clear moving front as assumed in the derivation of the equations.

Secondly, there might be differences in drug loading and pore structure in the outer and inner layers of the porous cellulose beads. The NMR method estimates the tortuosity in the entire bulk of the bead while the direct drug dissolution test mainly considers the dissolution of drug from the outer parts of the porous cellulose beads.

Many of the problems with porosity and uneven drug loading disappear when all drug is dissolved. This is the case in the final stages of *N*-acetyl-L-cysteine release (Fig. 4), where the predictions from Eq. 6 and 7 and direct measurements of drug release coincide.

5. Conclusions

The spin echo NMR technique can be used to estimate the tortuosity of porous structures from water self-diffusion studies. Knowing the tortuosity it has been shown to be possible to predict drug release from porous cellulose beads. Therefore, without any direct drug release experiments, one can conclude whether the drug is sufficiently sustained by the cellulose matrix itself or if film coating might be necessary.

A basic application of the beads is to use them as well-defined drug carrier particles. It has been shown that sparingly soluble drugs are sustained by the cellulose matrix itself while for highly soluble drugs, film coating might be necessary for sustained release. To some extent it might be possible to regulate the drug release rate by varying the porosity, particle size or loading of the drug-loaded beads.

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Glossary

Symbol	Meaning
a	external surface area of beads [m^2]
$A(\delta)$	spin echo amplitude at gradient duration δ [–]
$A(0)$	spin echo amplitude without gradient [–]
C_0	drug loading in beads [$\mathrm{kg/m}^3$]
C_s	concentration of saturated solution [$\mathrm{kg/m}^3$]
$D(0)$	diffusion coefficient in homogeneous solutions [m^2/s]
$D(t)$	apparent diffusion coefficient at diffusion time t [m^2/s]
$D(\infty)$	effective diffusion coefficient [m^2/s]
g	gradient strength [T/m]
$M(0)$	total drug loading in beads [kg]
$M(t)$	amount of drug released during release time t [kg]
Q	amount of drug released per unit area during time t [$\mathrm{kg/m}^2$]
r	bead radius [m]
t	release or diffusion time [s]
T_2	magnetic relaxation time [s]
V	bead volume [m^3]
x_{rms}	average diffusion distance [m]
ϵ	bead porosity [–]
δ	gradient duration [s]
γ	magnetogyric ratio of protons, 2.68×10^8 [$\mathrm{rad\ s^{-1}\ T^{-1}}$]
τ	tortuosity defined by Eq. 3 [–]

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