ELSEVIER

International Journal of Pharmaceutics 122 (1995) 49-56

international journal of pharmaceutics

Pore swelling in beads made of cellulose fibres and fibre fragments

Ragnar Ek [a,*], Helena Lennholm [b], Ricardo Davidson [c], Christer Nyström [a], Gert Ragnarsson [c]

[a] *Department of Pharmacy, Uppsala University, S-751 23 Uppsala, Sweden*
[b] *Swedish Pulp and Paper Research Institute (STFI), Box 5604, S-114 86 Stockholm, Sweden*
[c] *Pharmacia AB, S-112 87 Stockholm, Sweden*

Received 27 June 1994; revised 12 January 1995; accepted 24 January 1995

Abstract

The swelling of a new pharmaceutical excipient consisting of highly porous cellulose beads has been studied. Different degrees of swelling were produced by absorption of water and cyclohexane, two liquids with different 'swelling capacity'. The pore size in cellulose beads with different porosities was investigated using the spin echo NMR technique and found to increase due to swelling. The crystallinity of dry and wet cellulose fibres was investigated using ^{13}C CP/MAS NMR. A basic application of the beads is to use them as well-defined drug carrier particles. The beads can be loaded with drugs by a sorption process from water or organic solvents. It was concluded that it is beneficial to load the beads using drug solutions containing a cellulose swelling liquid.

Keywords: Porous cellulose bead; ^{13}C CP/MAS NMR; Crystallinity; Pore size; Spin echo NMR; Swelling; Tortuosity

1. Introduction

Pellet preparations for sustained drug release can be manufactured by absorption of a drug solution into porous beads followed by evaporation of the solvent. The process of loading empty beads with drug, instead of granulation, has the advantage that empty beads can be fractionated into a desirable size range before loading. The amount of waste material can thus be minimised. Cellulose beads can be made from microcrystalline cellulose (Newton et al., 1992), cellulose fibre fragments (Davidson et al., 1993) or from regenerated cellulose (Loth and Fanter, 1993). The amount of drug that it is possible to load into a bead is proportional to the pore volume and for efficient drug loading into the porous cellulose beads it is essential to start with a high porosity. The question of which type of solvent should be used (a swelling or non-swelling liquid) when a drug is absorbed into the beads has been raised.

Porous cellulose beads are considered to consist of a three-dimensional skeletal fibre system. Thus, liquid can be taken up both in the pores between fibres and in the solid fibre matrix itself. The swelling of cellulose fibres (Hermans, 1949;

---

[*] Corresponding author.

SSDI 0378-5173(95)00034-8

Stone and Scallan, 1968), paper products (Yamauchi et al., 1979; Corte, 1982; Bristow, 1986) and hydrogels (Westman and Lindström, 1981; Peppas and Khare, 1993) has been extensively studied. Cellulose can be swollen by intracrystalline swelling agents (penetration between but not within crystalline zones) or by intracrystalline swelling agents (penetration within crystalline zones). Since the bead structure is lost in the case of intracrystalline swelling, only intercrystalline swelling is considered in this work.

Microscopy techniques have been used to study the expansion of beads due to swelling (Davidson et al., 1994; Kleinebudde, 1994a,b), however, such methods cannot be used to establish changes in the pore size within the beads. The common method for determining pore size in porous solids is mercury intrusion. This approach involves surrounding the sample with mercury and monitoring the intrusion into the sample as the external pressure is increased. The method is, however, incapable of characterising wet swollen cellulose when the voids are already filled with another liquid. In methods based on liquid flow through (Corte, 1982) it is difficult to discriminate between pores within and voids between the cellulose beads.

The aim of this study was to determine whether the size of the pores increases or decreases due to swelling using the spin echo NMR technique (Stilbs, 1987). The spin echo NMR technique has been used to study pore size in porous cellulose beads (Ek et al., 1994) filled with cyclohexane (a non-swelling liquid). Together with the same type of measurements on beads filled with water (a swelling liquid) information about alteration in pore size due to swelling was obtained. The work is divided into two parts. In the first section the spin echo NMR technique was used to characterise void size and tortuosity in a sedimented bed of swollen fine particulate cellulose beads (sizes between 10 and 50 μm). In the second part the pore size were characterised in coarse cellulose beads ($\varnothing = 0.7$–0.8 mm) with different porosities, exposed to a swelling (water) and a non-swelling (cyclohexane) liquid (Porter and Orr, 1965). Since the crystallinity of the cellulose is related to the degree of swelling a crystallinity index of the cellulose fibres was also measured at different levels of water content, using the ^{13}C CP/MAS NMR technique.

2. Experimental

2.1. Materials

2.1.1. Fine particulate cellulose beads (10–50 μm)

The cellulose beads were manufactured by hydrolysing and grinding microcrystalline cellulose (Avicel PH 101, FMC, USA) into a cellulose suspension ($\approx 8\%$ dry matter content) subsequently spray dried. The possibility of obtaining small cellulose granules from spray drying a hydrolysed cellulose suspension has previously been described by Battista (1971). The resulting spray dried beads were sized through a 0.13 mm screen to remove a small amount of larger cellulose lumps. Samples were prepared by exposing the dry beads (105° C, 3 h) to pure water for 24 h after which the excess water over the sediment bead bed was sucked off. The resulting solid fraction in the bed of porous cellulose beads was $\phi_{PCB} = 0.45$ and subsequently a bed porosity of $\epsilon = 0.55$ was assumed. The particle size distribution of the swollen porous cellulose was determined by microscopic estimation (British Standard, 1963) and is presented in Fig. 1.

2.1.2. Coarse cellulose beads (0.7–0.8 mm)

Four batches of coarse, porous cellulose beads were manufactured by a cyclone rolling method (Ek et al., 1991) from microcrystalline cellulose (Avicel PH 101, FMC, USA) and powdered celluloses (CEPO S10 and S20, Svenska Trämjölsfabrikerna, Sweden and Solka Floc BW 20, Mendel, USA). After granulation and drying the beads were fractionated between sieves with openings of 0.7 and 0.8 mm. Dry (105° C, 3 h) beads were exposed to a swelling (water) and a non-swelling (cyclohexane) liquid (Porter and Orr, 1965). An excess of liquid was added to the beads and the samples were left in an evacuated desiccator for at least 24 h. Thereafter, the excess liquid was first aspirated off and then evaporated off under vacuum. The evaporation process was

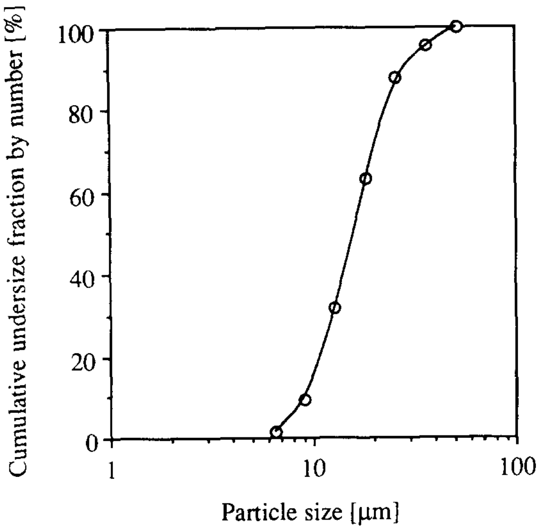

Fig. 1. Diameter of water wet porous cellulose beads, fraction by number, estimated by microscope (British Standard 3406, 1963).

stopped when the beads became free flowing, indicating that no liquid was present on the surface of the beads.

2.2. Methods

2.2.1. Spin echo NMR

The spin echo NMR 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). The experiments were carried out by varying the gradient duration and keeping the gradient strength constant. Only spin echoes forming a straight line, when plotted as spin echo amplitudes vs the squared gradient duration, were used in the evaluation. At diffusion times $t \geq 0.03$ ms a pulse program with stimulated echo (Tanner, 1970) was used. The field gradients were calibrated against cyclohexane and distilled water containing 2 mM $CuSO_4$. The reference values of the diffusion coefficients at 25° C were 2.3×10^{-9} m^2/s for water (Callaghan et al., 1983) and 1.5×10^{-9} m^2/s for cyclohexane (Mills, 1965).

2.2.2. Estimations of pore and void sizes

Structures can be identified from diffusion studies since, at short diffusion times, only a fraction of the diffusing molecules have had the time to interact with solid surfaces. As the diffusion times increase, restrictions in the structure are reached by the diffusing molecules and the diffusion rate decreases. The apparent diffusion coefficient $D(t)$ initially equal to the free diffusion coefficient $D(0)$ in bulk solutions gradually approaches an effective diffusion coefficient $D(\infty)$ at sufficiently long diffusion times.

The spin echo NMR technique measures an apparent diffusion coefficient during a given diffusion time t. To obtain a rapid estimate of the typical pore/void size, the relative apparent diffusion coefficient $D(t)/D(0)$ was plotted against the diffusion distance x_{rms}. The diffusion distance x_{rms} was calculated using (Atkins, 1994):

$$x_{\mathrm{rms}} = \sqrt{2D(t)t} \qquad (1)$$

A detailed description of pore size estimations from diffusion studies using the spin echo NMR technique is available (Ek et al., 1994).

2.2.3. Estimation of tortuosity in a sedimented bed of fine particulate cellulose beads

From knowledge of the porosity ϵ, the free $D(0)$ and effective $D(\infty)$ diffusion coefficients it is also possible to calculate the bead bed tortuosity τ (Higuchi, 1963; Takenaka et al., 1979):

$$D(\infty) = \frac{\epsilon}{\tau} \cdot D(0) \qquad (2)$$

The effective diffusion coefficient is obtained by extending the diffusion times over such a long period that the apparent diffusion coefficient becomes constant.

2.2.4. Mercury intrusion

Pore volumes and pore size distributions of the coarse porous cellulose beads were determined using a mercury porosimeter (Pore Sizer 9305, Micromeritics, USA). The values used for mercury surface tension and contact angle were 485 mN/m and 130°, respectively. The applied pressure varied between 3.45×10^{-3} and 103 MPa. The sample weight was about 0.25 g. For the calculations of total pore volume, pores larger than 25 μm have been ignored to eliminate the influence of voids between beads.

2.2.5. Crystallinity of the cellulose material

The crystallinity of the cellulose fibre and fibre fragments used in the bead granulation was determined using the ^{13}C CP/MAS NMR technique. The NMR measurements were performed on a Bruker AMX NMR spectrometer operating at 75.47 MHz for ^{13}C-NMR. Instrumental parameters were: 0.8 ms contact time, 2K data points filled to 4K, 5 kHz spinning using a double air bearing probe and ZrO_2 rotors. The chemical shift scale was referenced to the carbonyl in glycine located at 176.03 ppm. The number of scans on each spectrum was equal to 2000.

It has been shown that there is a linear relationship between crystallinity determined by X-ray diffraction and ^{13}C CP/MAS NMR (Teeäär et al., 1987). The latter authors estimated the crystallinity as a crystallinity index I_{cr}, defined as the ratio of the spectral intensity at 89 ppm to the total intensity of the C4 carbon signals at 89 (I_{89}) and 84 (I_{84}) ppm by fitting combinations of Gaussian and Lorenzian functions to the signals:

$$I_{cr} = \frac{I_{89}}{I_{89} + I_{84}} \tag{3}$$

The same formula using the peak intensity at 84 and 89 ppm was used in this work.

The cellulose samples were obtained by storing the cellulose fibres for 2 days over phosphorus pentoxide and then adding cyclohexane, equilibrating the fibres with air at 50% RH 20° C and mixing the dry fibres and pure distilled water in equal amounts.

3. Results and discussion

Special problems appear when the spin echo NMR method is applied for structure characterisations between permeable membranes (Von Meerwall and Ferguson, 1981). Since cellulose is to some extent permeable to water but not to cyclohexane, the experimental work was divided into two parts. In the first section the technique was tested. The void sizes and the effective diffusion coefficient for water in a sedimented bead of cellulose beads, ∅ = 10–50 μm were compared to theoretical estimations and data reported in the literature. In the second part the method was used to characterise the pores in cellulose beads of different porosities, ∅ = 0.7–0.8 mm, in the dry and swollen states.

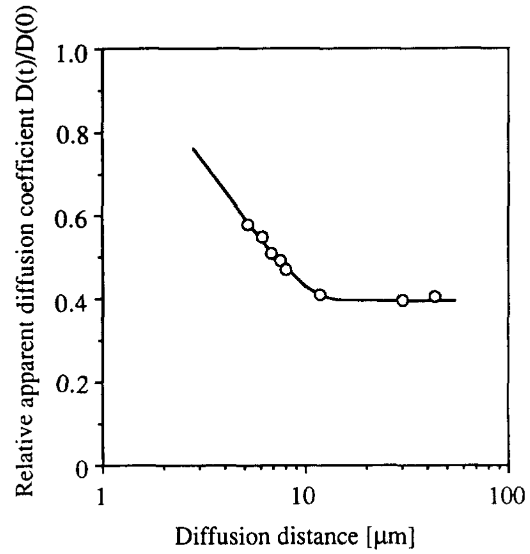

Fig. 2. Water diffusion in a bed of porous cellulose beads, bed porosity $\epsilon = 55\%$ w/w, with the size distribution shown in Fig. 1. Relative apparent diffusion coefficient measured at different diffusion times and plotted against diffusion distance (Eq. 1).

3.1. Void size and tortuosity of a fine particulate cellulose bead bed

In this system, a sedimented bead bed, all beads are covered with water. The apparent diffusion coefficient for water in the bed reaches half-reduction $(D(0) + D(\infty)/2D(0) = 0.7)$ at a typical diffusion distance equal to 3–4 μm (Fig. 2). The shortest diffusion time it was possible to use in the NMR experiments was 10 ms, corresponding to a diffusion distance of the order of some micrometres. The method is not exclusive for voids between beads, small pores between and within cellulose particles in fact also contributing to the typical diffusion distance. The sizes of these pores are of the order of some nanometres (Stone and Scallan, 1968). If it had been possible to follow the apparent diffusion coefficients down to very small diffusion distances, the technique would probably have revealed the size of the pores within the fibre fragments, probably by a bimodal appearance of the curve in Fig. 2.

It is also possible to estimate the void dimensions d, from knowledge of the sphere diameter d_p and the bed porosity ϵ, using Eq. 3 (Graton and Fraser, 1935):

$$d = \frac{1}{6}\left(\frac{\epsilon}{1-\epsilon}\right)d_p \qquad (4)$$

and use this estimation as a check of the validity of the NMR technique. By assuming the liquid fraction in the bead to be equal to the bed porosity ($\epsilon = 0.55\%$) and a particle diameter between $d_p = 10$ and 50 μm (Fig. 1), the void radius falls into the range between 1 and 5 μm (compared to 3-4 μm from the NMR measurements).

Another check of the method can be made from the estimation of the effective diffusion coefficient. The limits of the ratio between the effective $D(\infty)$ and the free diffusion coefficient $D(0)$ in a bed of beads with porosity ϵ is given by (Van Brakel and Heertjes, 1974):

$$0.5\epsilon < \frac{D(\infty)}{D(0)} < 0.8\epsilon \qquad (5)$$

This gives a range of relative effective diffusion coefficients (bed porosity $\epsilon = 0.55$) between 0.28 and 0.44. The NMR estimated relative effective diffusion coefficient falls within this region, $D(\infty)/D(0) = 0.4$ (Fig. 2). The calculated bead bed tortuosity (Eq. 2) is 1.4. A straight channel will have a tortuosity of 1, whereas a spherical glass bead bed column will have a value of 2-3 (Desai et al., 1966). The low tortuosity value of the porous bead bed perhaps indicates some diffusion also through the cellulose beads.

Since the agreement between the two methods is reasonable for the voids between the beads

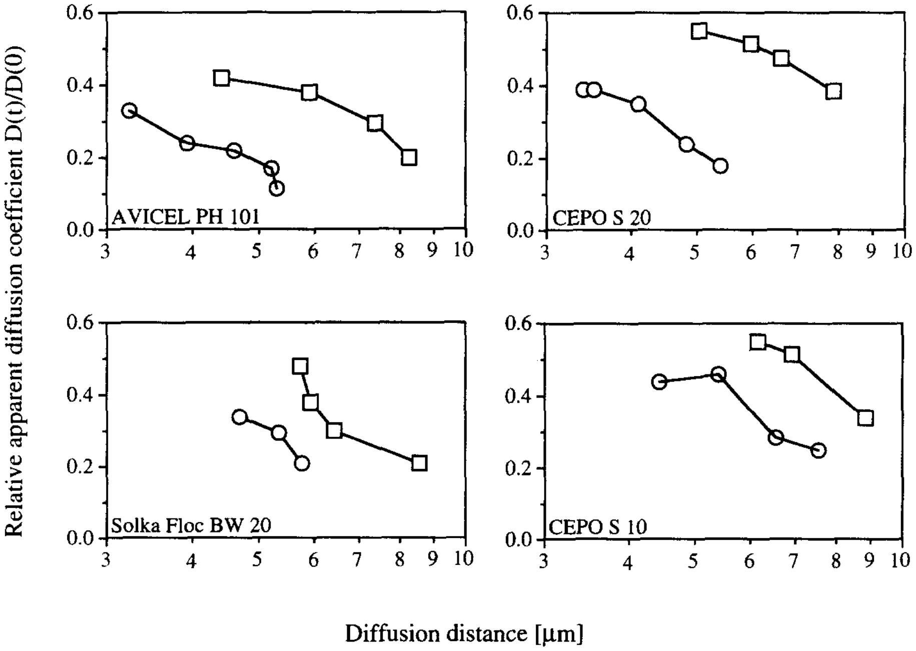

Fig. 3. Relative apparent diffusion coefficient vs diffusion distance in porous cellulose beads. (○) Beads filled with cyclohexane; (□) beads filled with water.

(3–4 μm from spin echo NMR and 1–5 μm from particle sizes) and the relative effective diffusion coefficient falls within the reported range ($D(\infty)/D(0) = 0.4$ from spin echo NMR with 0.28–0.44 as the reported range) the conclusion was drawn that the NMR technique is also valid for estimations of pore sizes within beads for water wet systems.

3.2. Pore characterization of coarse particulate cellulose beads

Correct filling of the pores within the cellulose beads is important in the NMR technique, since liquid on the surface or unfilled pores will give incorrect size estimates. This experimental difficulty is also an advantage for the NMR technique compared with the mercury intrusion method, since any influence of voids between beads can be neglected by correct filling. This can be a problem with the mercury intrusion technique. The diffusion distances in beads filled with cyclohexane showed fair agreement with estimations of the pore radius on dry beads using mercury porosimetry (Fig. 3 and Table 1). An exact agreement between the two methods should not be expected since the mercury method characterises the pore openings and the characteristic diffusion length from NMR measurements is a measure of the pore size in the cellulose beads. There is a deviation between mercury intrusion and NMR estimated pore size for low porosity beads (Table 1). An exact agreement between the two methods should not be expected, since the mercury method characterises the pore openings and the characteristic diffusion length is a measure of pore sizes within the cellulose beads. The lower value of pore diameter obtained by the mercury method for the low porosity beads might be attributed to especially large structural differences between pore size and the corresponding pore openings (Davidson et al., 1993). Another factor is the pressure difference between the beads (6.9 MPa on high porosity beads and 103 MPa on low porosity beads). In our opinion the NMR method gives a more correct picture of the pore size.

By adding water and thus swelling the structure of the porous cellulose beads, it was found that the pore sizes in the beads increased (Fig. 3). We have tried to evaluate the pore size in the beads, by calculating the diffusion distances where $D(t)/D(0) = 0.5$ (Table 1). The pore sizes in the beads appear to be almost doubled in water swollen beads. It has been shown that pore expansion also occurs in paper products when water is absorbed (Bristow, 1971; Hoyland, 1978; Salmen and Fellers, 1989). In this respect it appears that the beads show similarities in swelling behaviour with paper products.

3.3. Crystallinity index of cellulose fibres at different degrees of water interaction

The native cellulose fibres used in the production of cellulose beads are in the cellulose I form (VanderHart and Atalla, 1984) (Fig. 4). The crys-

Table 1

Estimations of pore size in porous cellulose beads, mercury intrusion (unswollen beads) and spin echo NMR technique (unswollen and swollen beads)

Cellulose material	Mercury intrusion [a]			NMR diffusion lengths [b]	
	Porosity		Pore radius (μm)	Unswollen [c] (μm)	Swollen [d] (μm)
	(ml/g)	(% v/v)			
Avicel PH 101	0.18	21	0.3–0.4	2–3	3–4
Solka Floc BW 20	0.79	55	2–3	3–4	5–6
CEPO S10	0.93	59	4–6	4–5	6–7
CEPO S20	0.62	50	2–3	3–4	5–6

[a] Total absorbed volume mercury for pores larger than 25 μm.

[b] Rough estimate of the diffusion length x_{rms} from Fig. 3, where the relative apparent diffusion coefficient is $D(t)/D(0) = 0.5$.

[c] Pores filled with cyclohexane.

[d] Pores filled with water.

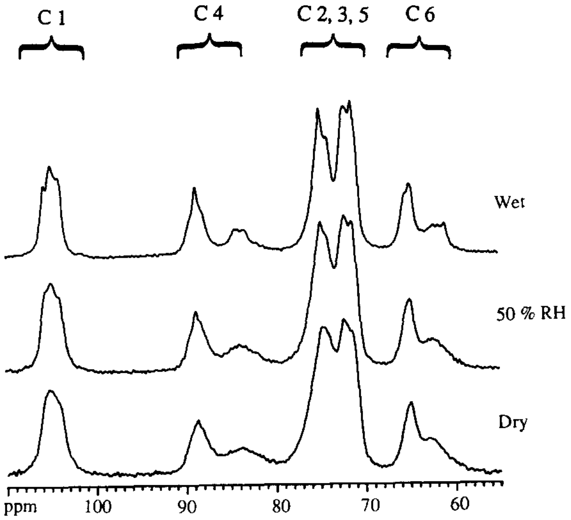

Fig. 4. ^{13}C CP/MAS NMR spectra for Avicel PH 101 of different moisture contents. The peaks from left to right are assigned to the carbons in the anhydroglucose units as, C1, C4 crystalline, C4 amorphous, a cluster of C2, C3, C5 and finally C6 crystalline and C6 amorphous (VanderHart and Atalla, 1984). The index of crystallinity in Table 2 was obtained by dividing the C4 crystalline amplitude at 84 ppm by the total C4 resonances (amplitudes at 84 and 89 ppm) (Eq. 3).

tallinity index is probably equal in the fibres and beads, since the beads are formed without milling or chemical treatment of the cellulose fibres. The results indicate that the crystallinity index of the cellulose powders (CEPO and Solka Floc) is lower than for microcrystalline cellulose (Avicel PH 101), Table 2. The variation between the three different cellulose powders (CEPO and Solka Floc) is, however, small and can at this stage not be distinguished from reported batch variations (Rowe et al., 1994).

Table 2
Crystallinity index of cellulose fiber raw materials

Cellulose powder	Dry [a] (–)	50% RH [b] (–)	Wet [c] (–)
Avicel PH 101	0.68	0.69	0.74
Solka Floc BW 20	0.64	0.65	0.68
CEPO S10	0.55	0.58	0.64
CEPO S20	0.60	0.62	0.65

[a] Cellulose fibres, bone dry, obtained by 2 days drying over phosphorus pentoxide, soaked with cyclohexane.
[b] Cellulose fibres in equilibrium with air, 50% RH, 20° C.
[c] Cellulose fibres with 50% dry solids.

The crystallinity of the cellulose particles increases when water is added. This phenomenon will be discussed in a later paper (Iversen, personal communication; STFI, Stockholm, 1994).

4. Conclusion

The spin echo NMR technique is a useful tool to characterise the voids between and the pores within swollen cellulose beads. The technique offers special advantages in characterisations of wet systems where mercury intrusion techniques fail, since the pores are already filled with liquid. Using this technique the results indicate that the pore size in cellulose beads increases to almost double when the beads are swollen in water. Since the pore size and therefore probably also the total porosity of the cellulose beads increase due to swelling, loading of beads with drug solutions may best be performed in swollen beads in order to increase the amount of drug incorporated. It is also shown to be possible to estimate the tortuosity in a bed of sedimented cellulose beads.

A conclusion from the crystallinity measurements is that the crystallinity index of cellulose material increases as water is added.

Acknowledgements

The work was partly financed by Nutek (9203530), Sweden. We thank the department of Physical Chemistry, KTH, for assistance with and access to the NMR spectrometer.

References

Atkins, P.W., *Physical Chemistry*. Oxford University Press, Oxford, 1994, p. 855.

Battista, O.A., Microcrystalline cellulose. In Bikales, N.M. and Segal, L., (Eds), *Cellulose and Cellulose Derivatives*, Wiley, New York, Vol. 5, 1971, pp. 1265-1276.

Bristow, J.A., The pore structure and the sorption of liquids.

In Bristow, J.A. and Kolseth, P. (Eds), *Paper Structure and Properties*, Dekker, New York, 1986, pp. 183–201.

Bristow, J.A., The swelling of paper during the sorption of aqueous liquids. *Sven. Papperstidn.*, 74 (1971) 645–652.

British Standard 3406, Methods for determination of particle size of powders: 4. Optical microscope method. British Standard Institute, London, 1963.

Callaghan, P.T., Le Gros, M.A. and Pinder, D.N., The measurements of diffusion using deuterium pulsed field gradient nuclear magnetic resonance. *J. Chem. Phys.*, 79 (1983) 6372–6381.

Corte, H., The porosity of paper. In Rance, H.F. (Ed.), *The Structure and Physical Properties of Paper*, Elsevier, Amsterdam, 1982, pp. 1–70.

Davidson, R., Ek, R. and Ragnarsson, G., Determination of the swelling characteristics of porous cellulose matrices by image analysis. *Int. J. Pharm.*, 112 (1994) 153–163.

Davidson, R., Nyqvist, H. and Ragnarsson, G., Porous cellulose matrices–a novel excipient for the formulation of solid dosage forms. *Int. J. Pharm.*, 100 (1993) 49–54.

Desai, S.J., Singh, P., Simonelli, A.P., Higuchi, W.I., Investigation of factors influencing release of solid drug dispersed in inert matrices: II. Quantitation of procedures. *J. Pharm. Sci.*, 55 (1966) 1224–1229.

Ek, R., Eriksson, K., Nyqvist, H. and Ragnarsson, G., Process for the manufacture of porous cellulose matrices. *International Patent Application WO 91/18590*, 1991.

Ek, R., Henriksson, U., Nyström, C. and Ödberg, L., Pore characterization in cellulose beads from diffusion studies using spin echo NMR technique. *Powder Technol.*, 81 (1994) 279–286.

Graton, L.C. and Fraser, H.J., Systematic packing of spheres – with particular relation to porosity and permeability. *J. Geol.*, 43 (1935) 785–909.

Hermans, P.H., *Physics and Chemistry of Cellulose Fibres*, Elsevier, Amsterdam, 1949.

Higuchi, T.,, Mechanisms of sustained action medication, theoretical analysis of the rate of release of solid drugs dispersed in solid matrises. *J. Pharm. Sci.*, 52 (1963) 1145–1149.

Hoyland, R.W., Swelling during the penetration of aqueous liquids into paper. In Bolam, F. (Ed.), *Fiber Water Interactions in Papermaking*, Transactions of the 6th Fundamental Research Symposium, Oxford, 1977, Tech. Div. Br. Paper Board Ind. Fed., London, 1978, pp. 557–577.

Kleinebudde, P., Shrinking and swelling properties of pellets containing microcrystalline cellulose and low substituted hydroxypropylcellulose: I. Shrinking properties. *Int. J. Pharm.*, 109 (1994a) 209–219.

Kleinebudde, P., Shrinking and swelling properties of pellets containing microcrystalline cellulose and low substituted hydroxypropylcellulose: II. Swelling properties. *Int. J. Pharm.*, 109 (1994b) 221–227.

Loth, F. and Fanter, C., Perlförmige celluloseprodukte und ihre anwendung als trenn- und trägermaterial. *Das Papier*, 47 (1993) 703–710.

Mills, R., The intradiffusion and derived frictional coefficients for benzene and cyclohexane in their mixtures at 25°. *J. Phys. Chem.*, 69 (1965) 3116–3119.

Newton, J.M., Chow, A.K. and Jeewa, K.B., The effect of excipient source on spherical granules made by extrusion/spheronization. *Pharm. Technol. Int.*, 4 (1992) 52–58.

Peppas, N.A. and Khare, A.R., Preparation, structure and diffusional behavior of hydrogels in controlled release. *Adv. Drug Del. Rev.*, 11 (1993) 1–35.

Porter, B.R. and Orr, R.S., Survey of cotton fiber swelling in various liquids by use of the yarn untwisting test. *Textile Res. J.*, 35 (1965) 159–167.

Rowe, R.C., McKillop, A.G. and Bray, D., The effect of batch and source variation on the crystallinity of microcrystalline cellulose. *Int. J. Pharm.*, 101 (1994) 169–172.

Salmen, L. and Fellers, C., The nature of volume hygroexpansivity of paper. *J. Pulp Paper Sci.*, 15 (1989) J63–J65.

Stilbs, P., Fourier transform pulsed gradient spin echo studies of molecular diffusion. *Prog. NMR Spectrosc.*, 19 (1987) 1.

Stone, J.E. and Scallan, A.M., A structural model for the cell wall of water swollen wood pulp fibres based on their accessibility to macromolecules. *Cellulose Chem. Technol.*, 2 (1968) 343–358.

Takenaka, H., Kawashima, Y. and Lin, S.Y., The effect of wall thickness and amount of hardening agent on the release characteristics of sulfamethoxazole microcapsules prepared by gelatin acacia complex coacervation. *Chem. Pharm. Bull.*, 27 (1979) 3054–3060.

Tanner, J.E., Use of the stimulated echo in NMR diffusion studies, *J. Chem. Phys.*, 52 (1970) 2523.

Teeäär, R., Serimaa, R. and Paakkari, T., Crystallinity of cellulose, as determined by CP/MAS NMR and XRD methods. *Polym. Bull.*, 17 (1987) 231–237.

Van Brakel, J. and Heertjes, P.M., Analysis of diffusion in macroporous media in terms of a porosity, a tortuosity and a constrictivity factor. *Int. J. Heat Mass Transfer.*, 17 (1974) 1093–1103.

VanderHart, D.L. and Atalla, R.H., Studies of microstructure in native celluloses using solid state ^{13}C NMR. *Macromolecules*, 17 (1984) 1465–1472.

Von Meerwall, E. and Ferguson, R.D., Interpreting pulsed-gradient spin-echo diffusion experiments with permeable membranes. *J. Chem. Phys.*, 74 (1981) 6956–6959.

Westman, L. and Lindström, T., Swelling and mechanical properties of cellulose hydrogels: I–IV. *J. Appl. Polym. Sci.*, 26 (1981) 2519–2572.

Yamauchi, T., Murakami, K. and Imamura, R., Development of the pore structure of paper web during consolidation. *J. Jap. Wood Res. Soc.*, 25 (1979) 414–421.