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Determination of the expansion characteristics of porous cellulose matrices by image analysis

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Abstract

A method for the precise determination of the swelling properties of a new type of highly porous cellulose beads by comparing the projected areas of individual matrices in the dry and wet states is described and its importance for the pharmaceutical applications of the matrices is discussed. Matrices prepared from four different types of cellulose and of different manufacture are compared. The method is shown to be sufficiently sensitive and precise to detect differences in expanding behaviour due to the raw materials, manufacturing parameters and even batch-to-batch variation. All the matrices examined expand appreciably in water, most of that expansion taking place within minutes of immersion. The degree of expansion observed suggests that both swelling of the cellulose fibres and relaxation of the matrix structure are taking place.

Keywords: Spherical matrix; Image analysis; Porous cellulose bead; Expansion in water

1. Introduction

Cellulose, in various forms, is commonly used as a pharmaceutical excipient finding many different applications. One recent application (Davidson et al., 1993a) is based on the manufacture of beads from fibrous cellulose prior to their loading with drug substances. The loading may even be accomplished as part of the drug manufacturing process, from polar as well as non-polar solvents. This method may bring benefits in process streamlining, handling safety, cost reduction, and ease of further processing. The authors also suggest that as well as functioning as inert drug carriers these cellulose matrices can be useful in the control of drug release. This control may be brought about by adding diffusion retarding agents, applying a coating layer, or relying on the matrix effect of the beads themselves. Particularly in the latter case the porosity of the beads would be of considerable importance. This porosity, whether regarded as a total voidage or as a pore size distribution, is dependent on the raw material employed and on the manufacturing parameters, (Davidson et al., 1993b). Cellulose is known to swell in polar solvents such as water which may alter the pore size or the total voidage of the matrices and thus influence both the drug loading from aqueous solutions and subsequent drug re-

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lease. Furthermore, a substantial dimensional change would impose severe strain on a coating layer, as has been demonstrated in similar cases (Gazzaniga et al., 1988). The swelling of different pharmaceutical formulations has been the concern of other authors and one can find several attempts to quantify the process. For example, in the case of large tablet-type matrices, manual measurement with a dial gauge has been used (Wan et al., 1993). In the case of small chitosan matrices, the swelling has been calculated by estimating their equilibrium fluid content (Chithambara Thanoo et al., 1992). Some authors do not attempt to directly quantify the degree of swelling, but rather describe its effect upon the drug release behaviour of swellable or non-swellable matrices (Akbuga et al., 1993; Gazzaniga et al., 1993). A video recording technique has also been employed for excipient powders (Prasad et al., 1987; Wan et al., 1990), requiring the manual tracing of particle contours from a monitor screen for further processing. None of these approaches were thought to be satisfactory in our particular circumstances. Image analysis is a technique capable of considerable accuracy in measuring particle size, and has been suggested as an optimal method for narrow size distributions, (Kanerva et al., 1993). By adapting the procedure to measure changes in size a method suitable for the determination of the degree of expansion of porous cellulose matrices in water was developed and the results obtained are presented and discussed.

2. Materials and methods

The method chosen allows the measurement of the projected areas of individual matrices under dry and wet conditions, using a direct image analysis technique, each matrix being its own control.

2.1. Materials

The matrices were prepared according to a previously published method (Davidson et al., 1993a) from two types of fibrous cellulose, CEPO S-10 and S-20 (Svenska Trämjölsfabrikerna, Sweden) and from two common pharmaceutical grades, Avicel PH101 (FMC Corp., DE, U.S.A.) and Solka-Floc BW20 (Edward Mendell Co. Inc., NY, U.S.A.).

The batches examined and their composition are listed in Table 1.

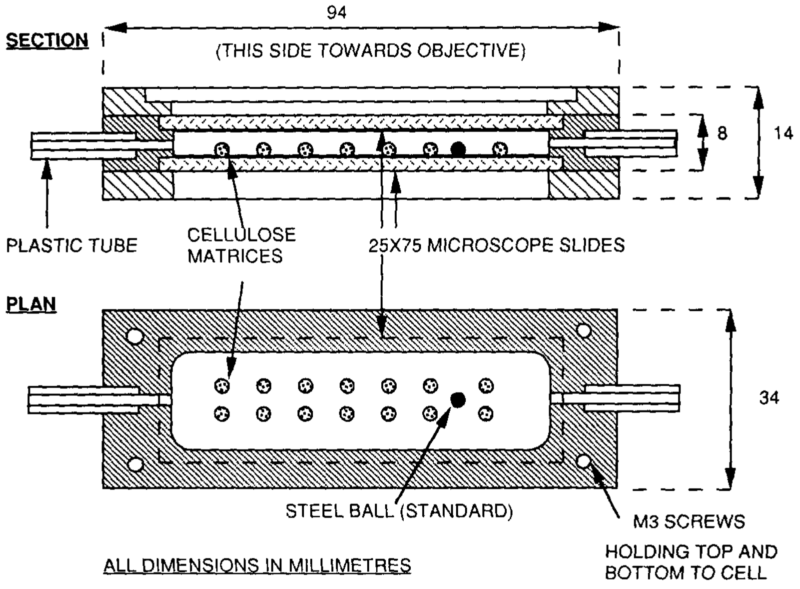

Fig. 1. Bead expansion cell.

Table 1
Batches examined and their respective composition (water content of original mass in g per g dry cellulose)

Batch no.	Raw material	Water (g)	Comments
007 and 009	CEPO S-20	3.125	'standard'
018	CEPO S-20	2.125	low water
042	CEPO S-20	4.375	high water
022	CEPO S-10	3.125	long fibre
028	Avicel	1.30	microcrystalline cellulose
033	Solka-Floc	2.50	powdered cellulose

2.2. Apparatus

A chamber was constructed from aluminium (Fig. 1), allowing the matrices to be exposed to fluids and simultaneously observed under the microscope. Small plastic cocks were fitted to each of the two plastic tubes in order to fill and close the cell. The cell top has a step milled around the aperture to clear the microscope objectives. The matrices were fixed to the lower slide with very small drops of commercial epoxy resin, applied with a fine needle, and cured at 50°C for 1 h. A standard, in the shape of a 0.6–1.0 mm diameter steel sphere was also cemented to the slide. The slide carrying the matrices was fixed to the chamber by the mounting plate and sealed with a commercial brand of liquid gasket compound resistant to water and hydrocarbons. The matrices were then observed individually at the highest practical magnification and an image analysis sequence carried out. The microscope employed was a Leitz Aristomet (Leica GmbH, Wetzlar, Germany) fitted with 2.5 × and 5 × PL-Fluotar objectives. The video camera system was an MTI CCD 72 (Dage-MTI, Michigan City, IN, U.S.A.), the computer was a Macintosh II fx, and the software was Neotech Image Grabber version 2.03 and Graftek Optilab™ version 1.4.2.

2.3. Calibration

As the matrices could expand assymmetrically, the increase in projected area was selected as being the most representative parameter of the size increase. The projected area of each matrix in pixels was taken and used for the comparisons, any absolute measurement required being obtained by comparison to the standard steel sphere. The dimensions of the standard sphere were determined optically using the scale in the microscope as well as mechanically with a micrometer screw gauge. A preliminary system validation was carried out using a standard sphere and dry cellulose matrices.

2.4. Measurement procedure

During the measurements the microscope parameters were kept constant for every run. The camera control box and converter were left on automatic for the exposure parameters, this providing the best all-round combination. Each image was focussed individually on the screen using the real-time focussing facility in the Image Grabber program.

Each matrix was measured once during each measuring run, recording the projected area. The standard sphere was measured at least three times at each of the two magnifications employed, and the mean of the readings taken. The scatter of these readings provided an internal method control.

The projected areas (in pixels) in the dry state were recorded as the control situation. Gas-free distilled water was then gradually introduced into the cell until it was full. The projected areas were determined again, noting the time (to the nearest minute) between the first contact with water and the moment the respective image was 'grabbed'. This time was used to calculate the mean immersion time. The increment in area between the dry and wet situations for each matrix was calculated as a percentage and corrected by subtracting the increment observed on the steel sphere projected area at that particular magnification. The corrected projected area changes were then used to calculate means for each batch and particle size combination at a given time of immersion, and these are the results presented in the tables and figures.

The initial readings were taken typically 30 min to 2 h after wetting. Later readings were taken at 24 h, 48 h and 5 days. It soon became evident that most of the expansion was taking place very soon, and after 48 h all the different batches had reached an acceptable steady state, therefore 48 h was taken as the expansion time for comparison between different matrix types.

Some batches were also exposed to cyclohexane, selected as a typical non-polar (and therefore non-swelling) solvent. The cell was emptied, the matrix slide detached and dried at 80°C for 2 h, these drying conditions being the same as those employed during the manufacture of the beads. The cell was reassembled and a fresh control run carried out. Following this cyclohexane was introduced into the cell and 24 h later bead measurements were carried out.

2.5. Statistical processing

Statistical significance was estimated by the Student-Fisher method as this was considered a suitable method for comparing two small groups of similar data. Levels of significance with a P' greater than 0.05 were considered not significant ($P' = 2P$). The formula employed for the calculation of the t factor included an estimate of the pooled variance as follows:

$$t = \frac{(M_1 - M_2)}{\sqrt{\dfrac{(V_1 + V_2)}{(n_1 + n_2 - 2)}}} \times \frac{1}{\sqrt{\left(\dfrac{1}{n_1} + \dfrac{1}{n_2}\right)}}$$

where M, V and n are respectively the means, variances and population size for each of the pairs of data being compared, and t denotes Student's factor. The tables employed were the Documenta Geigy (p. 32 and 33).

3. Method testing procedure

The results of the method testing procedure are presented in Table 2. These results show that with the standard sphere (1.0 mm diameter) relative standard deviations of about 0.07% (2.5 × objective) and 0.04% (5 × objective) are obtained for a run of six consecutive independently focussed images; this scatter can be considered typical. Logically, as the magnification decreases so the relative standard deviation increases, however, the relationship is not linear. The lower magnification objective has a greater depth of field and is therefore more tolerant of slight focussing errors.

The measurements carried out on the cellulose matrices in the dry condition revealed that even better precision was possible than with the steel standard, around 0.022% (5 ×) and 0.023% (2.5 ×) relative standard deviation for six consecutive independent images, also very little difference in precision was observed for the two magnifications employed. This was attributed to the increased ease of focussing on exactly the same plane for consecutive images, provided by the surface irregularities present on the cellulose matrices. During the experiments, as a matter of routine, focussing was generally carried out on the top right-hand edge of the matrix or on the top centre, according to whichever gave the best

Table 2
Results from the method testing procedure

Subject	Objective	Number of images	Mean P.A. (pixels)	S.D. (pixels)	Relative S.D. (%)
009 no. 14 > 0.8 mm diameter	5 ×	6	135509.8	29.755	0.0220
009 no. 14 > 0.8 mm diameter	2.5 × central	6	33674.7	7.8655	0.0234
009 no. 14 > 0.8 mm diameter	2.5 × peripheral	6	33588.5	44.590	0.1328
009 no. 28 > 1.6 mm diameter	2.5 ×	6	111143.0	19.068	0.0172
1 mm diameter steel standard	2.5 ×	6	42570.8	28.937	0.0680
1 mm diameter steel standard	5 ×	6	171666.7	74.830	0.0436

The first four subjects are cellulose matrices in the dry state identified by the batch number, position number and the nominal diameter. The last two subjects are the same individual steel standard sphere.

overall sharpness. Therefore, the precision obtained for the cellulose matrices during these preliminary trials illustrates the capabilities of the method, but is actually misleading and the precision obtained for the steel sphere is regarded as the best that can be systematically obtained.

Two series of images of the same cellulose matrix were obtained, one with the object placed centrally in the image frame and one with the object placed close to the periphery. The means were compared statistically, and were found to be significantly different ($P' \leq 0.001$). This can partly be explained in optical terms, however, it is of no practical significance as the images would normally be centered, and the statistical significance is due to the very low variances observed. The means differed by only 0.25%.

The conclusion of these tests was that the system is capable of a very high degree of accuracy but requires considerable operator care. With the cellulose matrices this accuracy is not as easy to achieve systematically as with the standards mainly because the beads are not perfect spheres. The projected plane is not regular and it cannot coincide in its entirety with the plane of focus of the objective, therefore images of the same bead taken at different times will have slightly different focus which will introduce a small error. If the focus is always adjusted to the same part of the bead then this error is reduced. The system is at its most accurate when the tonal scale is compressed, i.e., with a sharp black and white image that has no ambiguous gray shades. This does not often occur, and in order to reduce the scale of gray shades in a reproducible way, the same numerical value for threshold must be set for every reading. Any variation in the processor regarding contrast will also affect the result, how-

Table 3
Cellulose matrix expansions after 48 h immersion in water, expressed as the mean percentage increase of the dry projected area (standard deviations and the number of matrices in each class are also given)

Size fraction (mm nominal diameter)		1.6–2.0	1.4–1.6	1.0–1.12	0.9–1.0	0.8–0.9	0.7–0.8	0.5–0.63	Pooled results
Batch 009	mean	10.92	11.20	10.65		10.69		11.07	10.89
standard	S.D.	1.364	1.220	1.719		0.774		1.613	1.364
	n	6	6	9		6		8	35
Batch 007	mean	11.17	9.941	9.905		8.845	9.177	10.06	9.970
standard	S.D.	0.956	0.335	1.322		0.737	0.500	0.908	1.181
	n	6	6	6		9	5	8	40
Batch 042	mean		12.51	12.06			12.15	11.70	12.10
high water	S.D.		1.048	1.127			0.838	1.458	1.103
	n		6	6			6	6	24
Batch 018	mean		12.19	14.55			11.40	9.988	12.37
low water	S.D.		1.736	3.641			1.935	0.264	2.781
	n		6	6			5	3	20
Batch 022	mean		6.835	8.157			7.219	8.264	7.707
logn fibre	S.D.		1.642	1.068			0.887	1.182	1.246
	n		6	11			12	11	40
Batch 028	mean		18.19		19.66		19.13	16.95	18.22
Avicel	S.D.		1.662		1.729		1.282	1.439	1.824
	n		5		6		6	11	28
Batch 033	mean		11.90	10.37			9.984	11.15	11.00
Solka-floc	S.D.		1.652	1.044			0.995	1.785	1.608
	n		6	5			4	12	27

ever, there was never any evidence of this occurring.

4. Results and discussion

Although the method employed in this work can be described as satisfactory, some aspects merit a more detailed discussion.

During the filling of the cell with water some air bubbles would form on or close to the matrices and had to be dislodged by tapping the cell otherwise they would interfere with the projected area determinations. This occasionally led to matrices coming adrift from the glass slide. Examination of the attachment sites often showed the remains of a few fibres of cellulose imbedded in the resin, and leads us to believe that very little resin is actually taken up into the matrix. Therefore, we do not expect a significant effect of the attachment sites upon the overall expansion capacity of the matrices. This bubble formation was also the main impediment to immediate expansion readings.

The overall expansion results obtained are presented in Table 3 as the mean projected area increase for a given number of individual matrices, with the respective standard deviation. The smallest expansions, in the 6–8.5% range, were seen with long fibre cellulose (batch 022) and the greatest expansion was observed with microcrystalline cellulose (batch 028). In all cases, most of the expansion took place within a few minutes. Some fractions exhibit a trend to continue to expand even after 5 days immersion, although the differences between 2 and 5 days were not significant. A statistical analysis of the pooled results presented in Table 3 revealed that all permutations were significantly different ($P' \le 0.001$), except batch 009 compared with batch 033 ($P' \le 0.20$), and batch 042 compared with batch 018 ($P' \le 0.10$). All comparisons were made at 48 h exposure to water, and are presented in Tables 4, 5 and 6.

4.1. Effect of exposure to cyclohexane

Cyclohexane did not produce any significant change in the projected area of the matrices. This is as expected, and in agreement with observations by other authors on cotton fibres (Porter et al., 1965).

4.2. Comparison between two batches made to the same specification

The following size fractions showed significant differences between batches 007 and 009: 0.8–0.9 mm diameter ($P' \le 0.001$) and 1.4–1.6 mm diameter ($P' \le 0.05$). These differences are considered to be due to small batch-to-batch variations, as these batches were made in the same way from the same material (CEPO S-20) and are supposedly identical. It should, however, be noted that both these batches produced mean expansions with rather small standard deviations giving statistically significant differences between means that are actually very similar. The small scatter of the results indicates a good homogeneity of the sample and satisfactory method performance. The various comparisons and their statistical significance are presented in Table 4.

The pooled results (Table 3) also reveal a statistically significant difference ($P' \le 0.001$) between these two batches.

4.3. Comparison between different size fractions in standard batches

The differences between the various matrix size fractions within the same batch were in some cases significant. The two batches considered as standard (007 and 009) were examined in more detail, the statistical significance results are pre-

Table 4

Values of P' for comparisons of bead expansions for batches 007 and 009, given as the upper limit to the nearest 0.1 unit above 0.05 (values smaller than 0.05 are in bold script; underlined values are those that represent significatn differences between the same size fractions in the two batches)

	009/1.6	009/1.4	009/1.0	009/0.8	009/0.5
007/1.6	0.80	0.90	0.60	0.40	0.90
007/1.4	0.20	**0.05**	0.40	0.10	0.20
007/1.0	0.30	0.20	0.40	0.30	0.20
007/0.8	**0.01**	**0.001**	**0.02**	**0.001**	**0.01**
007/0.5	0.20	0.10	0.50	0.20	0.20

sented in Table 5. Batch 007 revealed several significant differences between size fractions, mainly associated with the larger fractions. Batch 009 showed uniform expansion behaviour in all size fractions. This difference between two standard batches implies that there are process variables which have not yet been identified. It may be significant that batch 042 (high water) also demonstrates this uniformity of behaviour between different size fractions.

4.4. Comparison between different amounts of water in manufacture

Batches 018 (low water), 042 (high water) and 007 (standard) were compared and the statistically significant differences are presented in Table 6 (a). Both non-standard batches showed greater expansions than batch 007. The differences between the expansions of batches 042 and 018 were not statistically significant either as pooled results or as individual size fractions. Batch 018 suffered considerable splitting of the beads during expansion. One could suggest that with lower proportions of water in the mass the fibres are not able to move around and intertwine to the same extent during the manufacturing process which includes a rolling phase in a cyclone. This would result in a less ordered structure with poorer mechanical properties and a relatively high voidage.

Table 5
Statistical significance of differences in projected area expansions for different size fractions in each of the two standard batches (significant differences ($P' \le 0.05$) are in **bold** script)

Diameter (mm)	1.6–2.0	1.4–1.6	1.0–1.2	0.8–0.9	0.71–0.8
Batch 007					
1.4–1.6	**0.02**	–	–	–	–
1.0–1.12	0.10	0.95	–	–	–
0.8–0.9	**0.001**	**0.005**	0.10	–	–
0.71–0.8	**0.005**	**0.02**	0.30	0.40	–
0.5–0.63	**0.05**	0.80	0.90	**0.01**	0.10
Batch 009					
1.4–1.6	0.80	–	–	–	
1.0–1.12	0.80	0.60	–	–	
0.8–0.9	0.80	0.50	0.975	–	
0.5–0.63	0.90	0.90	0.70	0.70	

Table 6
Statistically significant differences in expansion due to changes in composition of the porous cellulose matrices

Batch	Size fraction (mm diameter)	Significance
(a) Different % of water in manufacture		
018 ≠ 007	0.71–0.8	$P' \le 0.05$
018 ≠ 007	1.0 –1.12	$P' \le 0.02$
018 ≠ 007	1.4 –1.6	$P' \le 0.01$
042 ≠ 007	0.5 –0.63	$P' \le 0.05$
042 ≠ 007	0.71–0.8	$P' \le 0.001$
042 ≠ 007	1.0 –1.12	$P' \le 0.02$
042 ≠ 007	1.4 –1.6	$P' \le 0.001$
(b) Different cellulose types		
028 ≠ 007	all size fractions	$P' \le 0.001$
028 ≠ 022	all size fractions	$P' \le 0.001$
028 ≠ 033	all size fractions	$P' \le 0.001$
022 ≠ 007	1.4 –1.6	$P' \le 0.01$
022 ≠ 007	1.0 –1.12	$P' \le 0.01$
022 ≠ 007	0.5 –0.63	$P' \le 0.01$
022 ≠ 077	0.71–0.8	$P' \le 0.001$

4.5. Comparison between cellulose types

Batches 007 (standard), 022 (long fibre), 028 (Avicel), and 033 (Solka-Floc) were compared and the results are presented in Table 6 (b).

The greatest expansions took place in batch 028 (Avicel) and the smallest in batch 022 (long fibre), batches 033 (Solka-Floc) and 007 (standard) produced intermediate expansions not significantly different from each other. From Table 1 it can be seen that the different cellulose types require different amounts of water for manufacture of the matrices. However, taking into account the differences induced solely by the manufacturing variables described above, the variations induced by the different raw materials seem to be more important.

CEPO S-10 had the highest degree of polymerization (D.O.P.) value (batch 022), and conversely microcrystalline cellulose had the lowest D.O.P. value. Fig. 2 shows mean 48 h expansions related to the D.O.P. of the raw material; there would seem to be a correlation between these

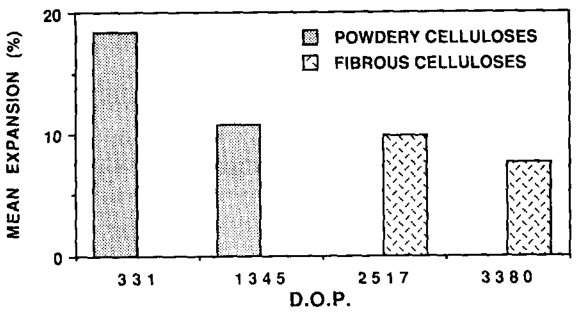

Fig. 2. Histogram representing the mean expansions of cellulose matrices after 48 h in water against the degree of polymerization (D.O.P.) of the raw material.

two parameters but restricted to fibrous celluloses and powdery celluloses separately. Solka-Floc BW20 and Avicel PH101 are considered powdery in this context as the characterization of the fibre dimensions is less clear if the length/width ratio is less than 4, or if there is a significant proportion of particles covering less than 5 pixels in the STFI Fibremaster and SCAN-C18 tests. The swelling in water of Avicel PH-101 (free particles) has been measured by an imaging technique (Wan et al., 1990) and a swelling of 33.58% quoted for the projected area diameter. This includes changes in shape and bulkiness, corresponding to a total projected area change of 78.4%, which is about 3 × the value for the matrices.

Fig. 3 shows the 48 h expansions for the different materials as a function of mean nominal particle size; it would seem that the differences in raw material and matrix porosity are more important than the particle size in determining the expansion.

4.6. Expansion as a function of immersion time

Plotting the expansions against the logarithm of time, as presented in Fig. 4, one can observe that in general expansion is still going on slowly even after 5 days. The rate of expansion seems to be a constant with log[time] for some batches, which may be related to the expansion mechanism. The time-related characteristics of the swelling process have been described previously for paper (Bristow, 1971) and similar results were observed. This author proposes that there are two more or less distinct phenomena taking place, i.e., absorption into the voids and absorption by the fibres. Our results would appear to support this interpretation, as it may explain the very rapid initial expansion as a result of a surface

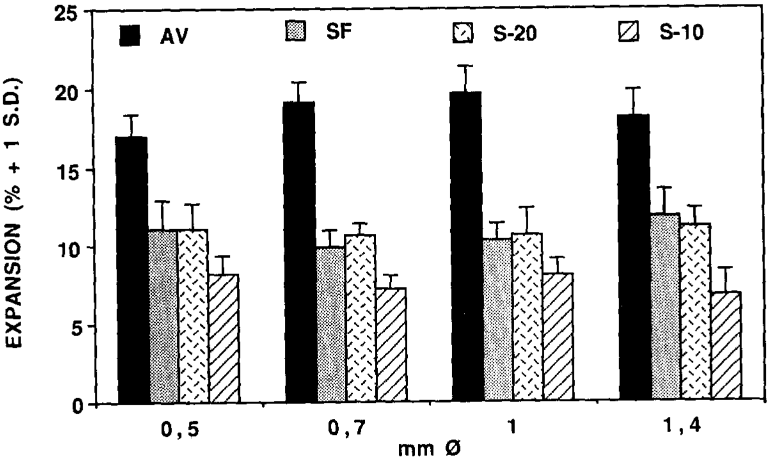

Fig. 3. Histogram plotting the mean expansions of cellulose matrices after 48 h in water against approximate bead diameter, for four different cellulose types: CEPO S-20 (S-20), CEPO S-10 (S-10), Avicel (AV), and Solka-Floc (SF).

effect whilst the longer term expansion would be dependent on the diffusion of water into the relatively dense fibres.

No visible change in shape was observed for the majority of cases over the 5 day period, even surface anomalies remaining unchanged.

4.7. Recovery of the expansion

These porous cellulose matrices would have to be re-dried after drug loading, so their ability to recover from expansion was determined by comparing the projected areas of re-dried matrices with the original dry readings. The results obtained are presented in Table 7, the P' values being obtained by applying expression 599(a), p. 172 of the Documenta Geigy. Very small changes may be explained by differences in the initial moisture content of the beads, however, differ-

Table 7
Recovery of expansion of the matrices on re-drying at 80°C for 2 h

Batch	ΔP.A. (%)	±1 S.D.	n	P'
007 (standard)	0.3836	1.3020	30	≤ 0.2
042 (high water)	−0.0932	0.6998	21	≤ 0.6
018 (low water)	1.296	1.2714	15	**≤ 0.005**
022 (long fibre)	−4.196	0.8982	38	**≤ 0.001**
028 (Avicel)	−1.628	0.8586	28	**≤ 0.001**
033 (Solka-Floc)	−0.9373	0.6749	27	**≤ 0.001**

Results are given as the average percentage change in projected area (P.A.).
Significant differences from 0% ΔP.A. are in **bold** script.

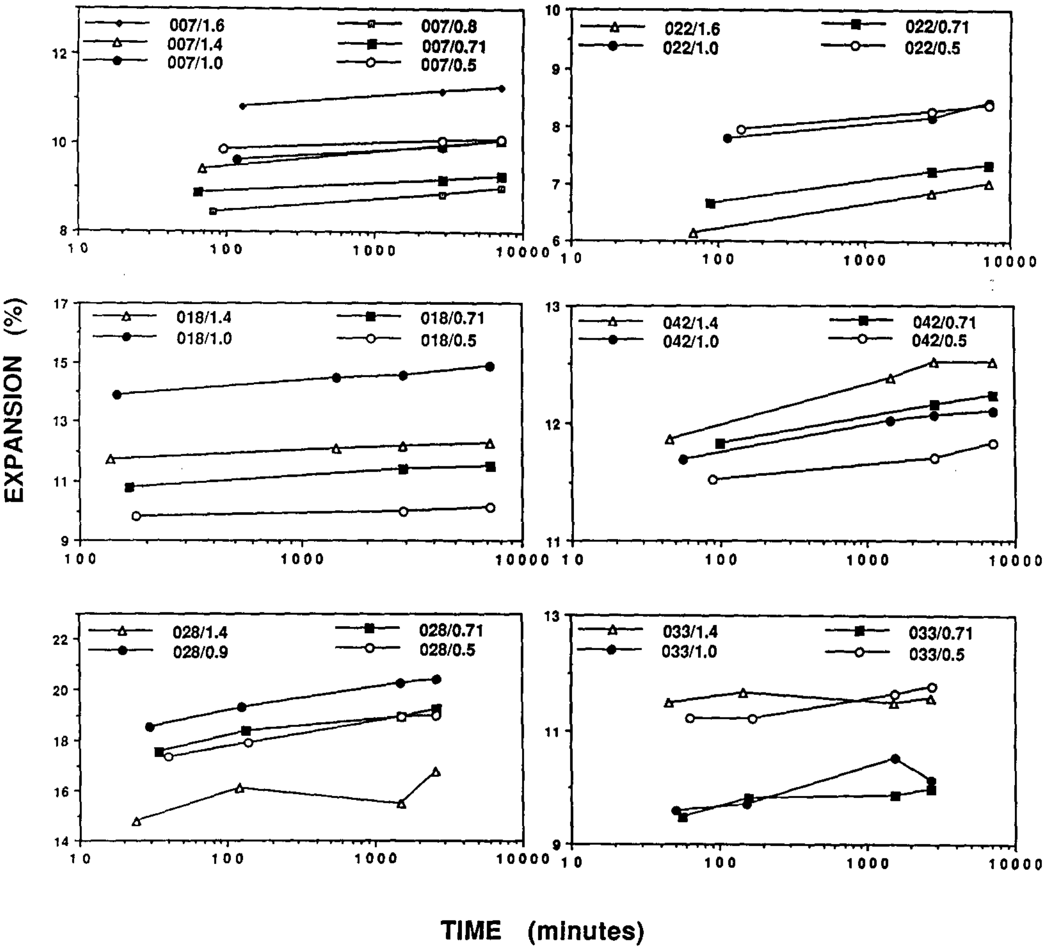

Fig. 4. Graphs representing the percentage projected area increase against log[time] for different matrix batches and size fractions.

ences above about 1% must be due to other causes. Batch 022 was re-measured after exposure to room conditions for about 1 year, and the average increase in projected area was 0.226%, not statistically significant. This shows that the relatively stable conditions found indoors cannot account for more than the smallest changes. The small permanent expansion seen with batch 018 (low water) is important as it supports the suggestion that these beads are structurally more unstable. The considerable contractions seen with batches 022 (long fibre) and 028 (Avicel) are more difficult to explain. The small contraction observed with batch 033 (Solka-Floc) is statistically significant and may be related to the small particle nature of the raw material. The matrices from batches 007 (standard) and 042 (high water) recover their original size, indicating that no substantial permanent deformation took place.

4.8. Comparison between total voidage and maximum expansion

In Table 8 we present some results of mercury porosimetry readings representing total voidage volume for nominal pore sizes from about 50 to 2 μm. The lower limit was selected as the porosity below 2 μm is small and almost identical for all samples, probably corresponding to pores in the fibres themselves. The upper limit was selected in order to exclude the bulk of the interparticulate spaces. Fig. 5 demonstrates a graph of the volume expansion at 48 h, calculated from the projected area expansion, against the porosity. A correlation between expansion and matrix porosity is apparent.

Table 8
Total voidage readings obtained by mercury porosimetry for matrices of size fraction 0.71–0.9 mm diameter (voidage for pores ≈ 2–50 μm diameter)

Batch	Voidage (cm^3/g)	Expansion (% volume)
009 (standard)	0.635	16.46
022 (long fibre)	0.784	11.02
028 (Avicel)	0.048	30.03
033 (Solka-Floc)	0.778	15.34

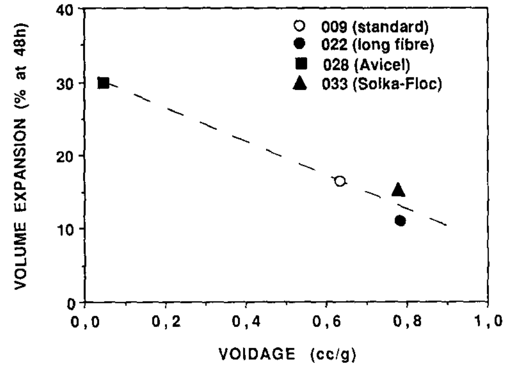

Fig. 5. Graph representing the volume increase (% of dry state) of matrices against matrix porosity (voidage, pores 2–50 μm diameter) determined by mercury penetrometry.

Paper can be considered as a material with some similarities to porous cellulose matrices from a micro-structural point of view, and has been quite extensively studied regarding its expansion characteristics. The swelling of freely dried papers has been described (Salmén, 1993) also showing a correlation between density and volume expansivity.

5. Conclusions

Regarding the technique employed in this work, one can conclude that in terms of precision it is entirely satisfactory exceeding by a large margin the smallest differences detectable by simple microscopic examination against a scale.

The results themselves demonstrate that all the matrices examined expand considerably when exposed to water. This expansion takes place relatively quickly and therefore should be taken into account when considering the required elasticity of any film coating applied to the matrices (Gazzaniga et al., 1988). In most cases the matrices were robust enough to withstand exposure to water for 5 days, suggesting that drug loading from an aqueous solution would be a practical proposition. The recovery data indicate that no significant permanent alteration of the structure has taken place with the expansion. However, the matrices manufactured employing less water in the initial mass are not as robust. Matrix manufacturing optimization should therefore include the determination of the resistance of the matrices to water.

In contrast to water, a non-polar solvent such as cyclohexane produced no significant expansion. This difference should be considered when selecting a suitable medium for the incorporation of drugs into these matrices.

Finally, these results reflect changes in the external dimensions of the beads. We cannot determine exactly to what extent these changes are due to the swelling of the cellulose substance or to the increase in the voidage of the system. The present data are indicative of the latter mechanism, and further research is ongoing in this context, as the voidage of these porous cellulose matrices is one of the fundamental properties for their pharmaceutical application.

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