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Characterisation of instantaneous water absorption properties of pharmaceutical excipients

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Abstract

Powders absorb water by both capillary imbibition and swelling. The capillary process is almost instantaneous but swelling occurs over a period of time. An isothermal transient ionic current technique was used in this study to characterise the instantaneous absorption properties (rate and capacity) of a few selected pharmaceutical excipients. The results indicate that the instantaneous and long term water absorption properties of pharmaceutical powders can differ considerably. The rate of instantaneous water absorption appears to correlate with the total surface area while the absorption capacity correlates more with the porosity of the powder. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Water absorption; Rate; Capacity; Pharmaceutical powders

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1. Introduction

The absorption of water into particles and compacts determines the performance of many pharmaceutical products. For example, the absorption of water into tablets is necessary for the drug to be released. Tablets will consequently often contain a tiny amount of disintegrant which disrupts the tablet by swelling during absorption of water. A relatively new pharmaceutical field in which water absorption is important involves the nasal administration of drugs. This route of administration seems to be an increasingly attractive alternative for both topical and systemic drug delivery (Davis, 1999). It has been reported that drug absorption through the nasal mucosa can be enhanced by administering a dry powder together with the drug (Nagai et al., 1984). The theory is that when liquid is absorbed from the nasal epithelia cells into the accompanying powder, the

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subsequent dehydration and shrinkage of the cells may cause the tight junctions between the cells to open, thus promoting drug absorption (Edman and Björk, 1992; Björk et al., 1995).

The instantaneous absorption properties of a pharmaceutical powder used as a drug absorption enhancer for administration by the nasal route could thus be very important. In order to enhance the absorption of the drug, the powder must be able to absorb liquid from the cells *rapidly*. If the process of absorption is too slow, the loss of water from the cells could be compensated for by replacement from underlying tissues, and the desirable opening of the tight junctions will not be achieved. Therefore, a powder which has a good long term absorptive capacity will not necessarily be a suitable drug absorption enhancer. It appears likely that both the capacity and rate of instantaneous absorption are crucial characteristics for the ideal drug absorption enhancer.

It has been reported recently that cellulose agglomerates are able to absorb substantial amounts of water in less than a second (Strømme Mattsson et al., 2000). In contrast, the European Pharmacopoeia recommends that water absorption is measured over a period of 4 h (European Pharmacopoeia, 1997).

Our hypothesis is that liquid absorption in pharmaceutical powders can occur in two phases, almost instantaneous and long term, and that the characteristics of these phases differ widely from each other. We also suspect that the instantaneous absorption properties can differ considerably among different powders.

There are currently no records of investigations into the instantaneous absorption properties of powdered materials. This is probably because no technique for measuring these fast processes has been available. As mentioned above, the pharmaceutical method used to characterise the liquid absorption of powders relies on an absorption time of 4 h (European Pharmacopoeia, 1997).

The purpose of this work was to investigate the instantaneous absorption properties of different pharmaceutical powders using a new method, and to indicate the relationship between these absorption properties and the structure of the absorbing particles.

2. Materials

Two types of cellulose powders were used: microcrystalline cellulose (Avicel PH 102, lot number 7741, FMC, USA) and algae cellulose powder (Ek et al., 1998). A highly swelling powder was obtained by using a tablet disintegrant, crosslinked carboxyl methyl cellulose sodium (Ac-Di-Sol, lot number T645, type SD-711, FMC, USA). We also used degradable starch microspheres (Spherex, Pharmacia AB, Sweden).

3. Methods

3.1. Material preparations

3.1.1. Micronised cellulose

Avicel PH 102 containing 50 wt.% distilled water was milled for about 4 h in a mortar mill (Mortar Grinder KM1, Retsch AG, Germany).

3.1.2. Cellulose and algae agglomerates

The cellulose agglomerates were prepared by spray drying (Minor type 53, A/S Niro Atomizer, Denmark) a water suspension of microcrystalline cellulose. The entering air flow was kept at a temperature of 200–225°C while the leaving air flow was regulated to a temperature of 75–85°C. The agglomerates were then washed several times with distilled water and finally with 95 wt.% ethanol. The algae agglomerates were prepared in the same way.

3.2. Powder and particle characterisation

3.2.1. Bulk density

The bulk densities of the powdered materials were obtained by placing a carefully measured amount of powder (15–20 ml) into a 25 ml graded glass container and then weighing the material. The bulk densities were measured after zero and 200 taps to the glass, and are denoted ρ_b and ρ_t, respectively. The tapping frequency was 1 Hz.

3.2.2. Flowability

The ease of flow, or flowability, of the powders was characterised by using the Hausner ratio, $\frac{\rho_t}{\rho_b}$.

3.2.3. Particle density

The particle densities were obtained with a gas (He) pycnometer (Accu Pyc Micrometrics 1330 USA). The apparatus was set to perform 99 washes and 10 runs. The average of two or three determinations was calculated and the relative standard deviation was found to be below 0.2%.

3.2.4. Porosity

The porosity (ε) of the powders was calculated, by using the untapped bulk density (ρ_b) and the particle density (ρ_p) of the powders, as $\varepsilon = 1 - \frac{\rho_b}{\rho_p}$.

3.2.5. Total surface area

The total surface area of the powdered materials was measured as the BET (N_2) surface area (ASAP 2000, Micromeritics Instrument Corporation, USA).

3.2.6. Particle size

The particle diameters were measured by light diffraction (Laser Diffraction, Sizing 230, Coulter Corporation, USA) with the particles suspended in water and again in cyclohexane (extra pure, Kebo Laboratory, Sweden). Water was used because it is the absorbed medium in this study, although it is known to interact with cellulose (Ek et al. 1994). Cyclohexane does not interact with cellulose-based excipients and was used to obtain the correct estimate of the particle size in the unswelled state (Ek et al. 1994).

When measuring the particle size of cellulose materials, the absorption coefficient was set to zero and the refractive index was set equal to that of cotton, viz. 1.576 (Meredith, 1946). When the refractive index was unknown, Fraunhofer diffraction was used. The particle size of micronised cellulose could not be determined using the Laser Diffraction instrument because clusters of particles were produced as the suspensions were prepared.

3.3. Water absorption characterisation

3.3.1. Long term absorption

The long term absorption properties were measured by studying the swelling of the materials. The volume occupied by the powder before and after swelling was measured (European Pharmacopoeia, 1997). The powder (1.0 g) was placed into a 25 ml measuring glass graded in 0.5 ml divisions and the dry powder volume was noted. The powder was then moistened with 1.0 ml 95 wt.% ethanol and 25 ml distilled water or salt solution (0.9 wt.% NaCl) was added. The glass was shaken vigorously every ten minutes for 1 h and was then allowed to stand for 3 h. Ninety minutes after the beginning of the test, any liquid retained among the powder particles was released by rotating the glass cylinder about a vertical axis. Three tests were carried out at the same time and the ratio of the wet to dry mass of material was calculated as the average value obtained from these tests.

3.3.2. Instantaneous absorption

The instantaneous absorption properties of the materials analysed in this project were measured by a method based on the isothermal transient ionic current (ITIC) technique. The experimental set-up consisted of a liquid container, a powder application device and two electrodes (Strømme Mattsson et al., 2000). The liquid container was filled with 50 μl of water. To reduce surface tension and ensure a planar liquid film, 0.05 wt.% poly Tween 80 batum was added to the water. In addition, the water contained 0.9 wt.% NaCl to approximate the salinity of the epithelia cells in the nasal mucosa (Eichner et al., 1983). A constant potential of 1 V was then applied across the cell and the current through the cell was measured. About 20 s after the potential was applied across the water container, the powder was dropped from the powder application device onto the liquid film. The amount of powder used in each experiment was in the order of 10–50 mg.

With the experimental conditions used in this work, the absorption capacity and rate are obtained from

Table 1
Physical properties of the powders

Material	Bulk density untapped (kg/m^3)	Flowability Hausner ratio (−)	Particle density (kg/m^3)	Porosity (−)	Surface area (m^2/g)	Particle size cyclohexane (μm)	Particle size water (μm)
Avicel PH 102	300	1.36	1576	0.81	1.23	111	139
Micronised cellulose	500	1.25	1463	0.66	1.07	–	–
Cellulose agglomerates	420	1.20	1525	0.72	3.07	37	50
Spherex	560	1.36	1432	0.61	0.32	19	45
Ac-Di-Sol	450	1.38	1590	0.72	0.85	44	78
Algae agglomerates	250	1.43	1560	0.84	1.75	55	77

$$\text{absorption capacity} = K \cdot \frac{\Delta I \rho_b}{m_{\text{powder}}} \tag{1}$$

and

$$\text{absorption rate} = K \cdot \frac{dI}{dt} \cdot \frac{\rho_b}{m_{\text{powder}}}, \tag{2}$$

respectively. In these equations, the constant $K = 2.77 \cdot 10^{-4}$ m^3 A^{-1}. ΔI is the magnitude of the drop in current and dI/dt is the time derivative of the current in the absorption step. The powder mass is denoted m_{powder}.

4. Results

4.1. Powder and particle characterisation

The physical data relating to the powders and particles, shown in Fig. 1, are presented in Table 1. The bulk densities ρ_b of the powdered materials varied between 250 and 560 kg/m^3. All powders had relatively good flowability, although the cellulose agglomerates were best (Hausner ratio 1.20) and the algae agglomerates were poorest (Hausner ratio 1.43) in this respect. The porosities of the powders varied between 0.61 and 0.84. The surface areas differed considerably: cellulose agglomerates (3.07 m^2/g) had the largest surface area and Spherex (0.32 m^2/g) had the smallest. The surface area of the micronised cellulose (1.07 m^2/g) was less than that of both Avicel PH 102 (1.23 m^2/g) and the cellulose agglomerates despite the smaller particle size of micronised cellulose. The particle diameters were larger when measured by Laser diffraction in water than when measured in cyclohexane because of swelling.

4.2. Water absorption characterisation

4.2.1. Long term absorption

The long term absorption capacities of the powders, obtained by measuring swelling in distilled water and in saline solution, are listed in Table 2. The reader should note that the swelling index according to the European Pharmacopoeia (1997) is given in units of ml water/g material. In this work we choose to express it in kg water/kg material instead. The order of magnitude of the absorption capacities was the same in the two experiments (water and saline). The long term capacity was substantially greater for Spherex and Ac-Di-Sol than for the other analysed materials.

4.2.2. Instantaneous absorption

Fig. 2 shows examples of the current–response curves of the studied materials obtained by the ITIC technique. When the powder was applied onto the liquid film, the slope of the current versus time curve varied with the powder used. A straight line was fitted to the current–response data at the water absorption step and the instan-

Table 2
Water absorption properties of the investigated materials

Materials	Instantaneous absorption[a]				Long term absorption	
	Capacity (kg/kg)	St. dev. (%)	Rate (kg/kg per s)	St. dev. (%)	Capacity	
					(kg/kg)[b]	(kg/kg)[c]
Avicel PH 102	0.45	4	0.64	2	1.00	1.25
Micronised cellulose	0.17	16	0.70	12	0.83	1.20
Cellulose agglomerates	0.27	10	0.90	9	1.97	2.25
Spherex	0.43	13	0.042	12	9.33	7.78
Ac-Di-Sol	0.30	13	0.10	9	10.50	9.75
Algae agglomerates	0.43	10	1.55	8	2.13	1.67

[a] The given capacities and rates are averages over ca. ten measurements.

[b] Swelling after 4 h in distilled water.

[c] Swelling after 4 h in water containing 0.9 wt.% NaCl.

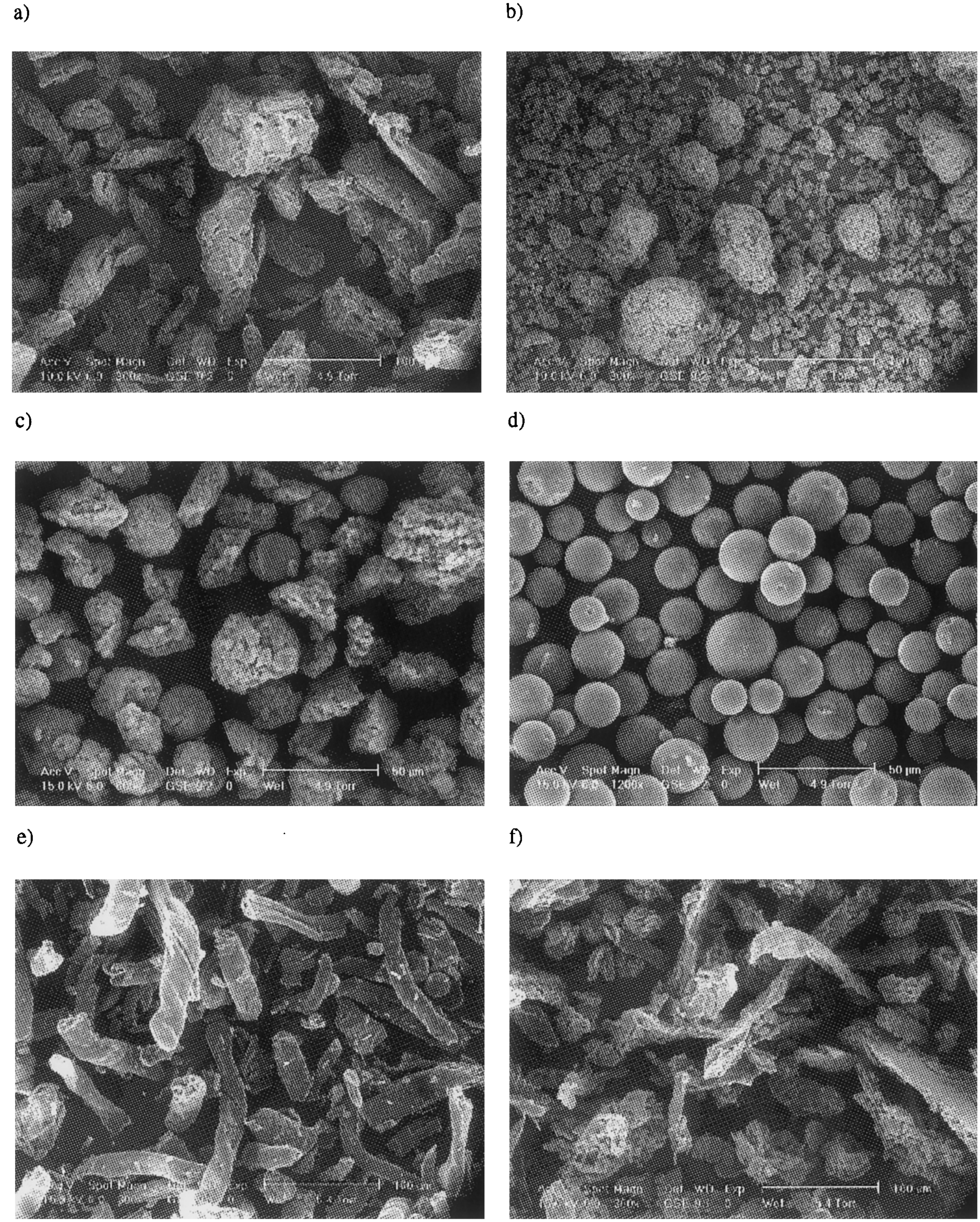

Fig. 1. Environmental scanning electron microscope micrographs of (a) Avicel PH 102, (b) micronised cellulose, (c) cellulose agglomerates, (d) Spherex, (e) Ac-Di-Sol and (f) algae agglomerates.

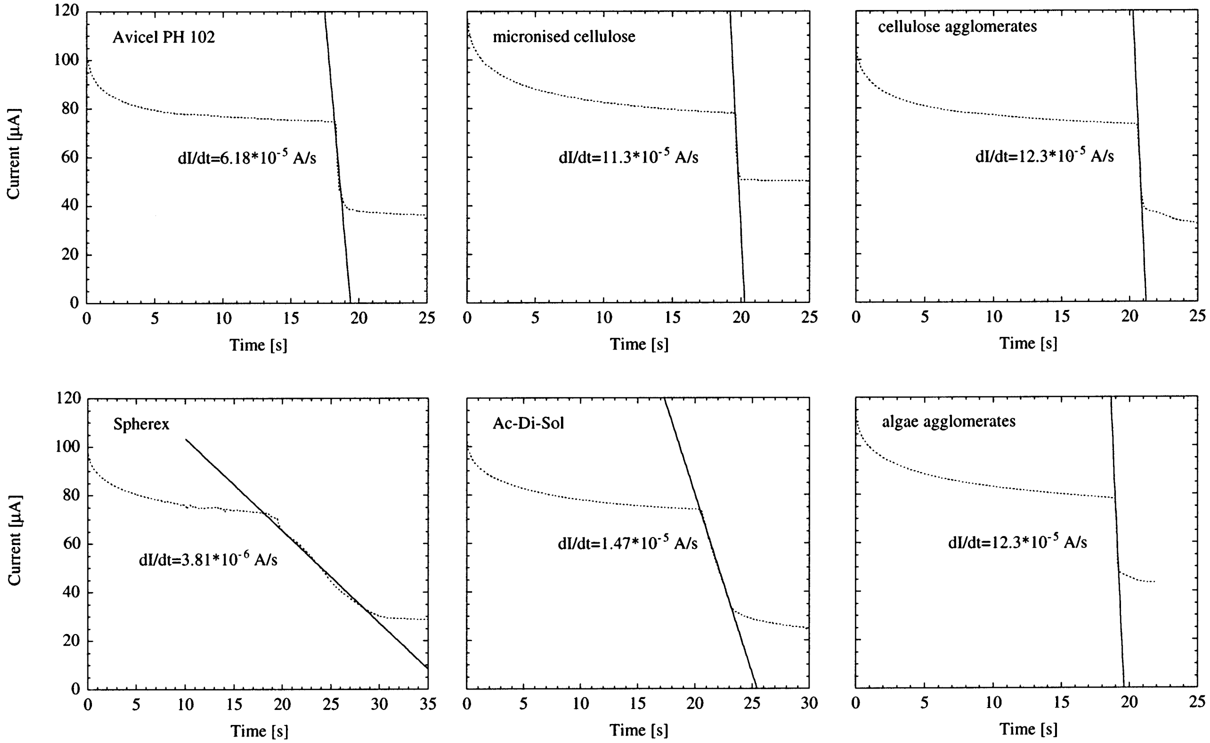

Fig. 2. Current–response data for Avicel PH 102, micronised cellulose, cellulose agglomerates, Spherex, Ac-Di-Sol and algae agglomerates when added to a container of NaCl solution. The solid lines depict the closest linear fit to the region of almost instantaneous water absorption. The slopes of these linear regions are given in the figures.

taneous absorption rate was calculated from its slope. The instantaneous absorption capacity was obtained from the total current decay in the absorption step. It should be noted that the ranking of powders by rate and capacity cannot be immediately deduced from the derivative of the current–response curves and the magnitude of the drop in current in the absorption region of the curves, respectively. The instantaneous absorption rate and capacity can only be obtained after these factors are divided by the powder mass (see Eq. (1) and (2)).

The instantaneous absorption properties of the analysed powders shown in Table 2 are averages of about 10 measurements. The absorption capacities of the studied powders were all within the same order of magnitude. However, the instantaneous absorption capacities differed considerably from the absorption capacities obtained after 4 h of swelling. Algae agglomerates had the highest instantaneous absorption rate (1.55 kg water/kg material/s) of the analysed materials while Spherex had the lowest (0.042 kg water/kg material/s).

5. Discussion

It is important that the powders to be analysed flow easily (have high flowability), because the desired dispersal is then more easily obtained as the powders sift down towards the water surface. All powders analysed in this project flowed relatively well (Hausner ratio ≤ 1.4), which facilitated the measurements and ensured good dispersal. A Hausner ratio close to 1 indicates liquid-like flowability while a higher ratio signifies poorer flowability.

It can be seen from Table 2 that the instantaneous absorption capacities differed considerably from the absorption capacities obtained after 4 h of swelling. At the beginning of the water absorption process (measured by ITIC), water enters the pores within the particles as well as those between the particles, and the swelling process begins. This capillary absorption is rapid and proceeds within seconds. The long term swelling occurs as a result of gelling, a slow process that may be retarded by closing of pores due to swelling of the material. It should be noted, however, that pores are not closed during swelling in all materials; a pore-opening process has been reported for cellulose agglomerates (Ek et al., 1995).

If the instantaneous water absorption capacity is plotted versus the porosity of the powder, Fig. 3a, it is apparent that these two parameters correlate. Powders with high porosity seem to absorb more water in the initial stages than powders with lower porosity. This is consistent with the idea that the initial water absorption is a capillary process which will thus depend on the porosity of the powder. Spherex is an exception to this rule, but it should be noted that Spherex is a starch while the five other materials are based on cellulose. It is also apparent (Fig. 3b) that the instantaneous absorption capacity does not correlate with the BET surface area.

There was high variability in the instantaneous absorption rates of the analysed materials. As shown in Fig. 3c and d, the instantaneous absorp-

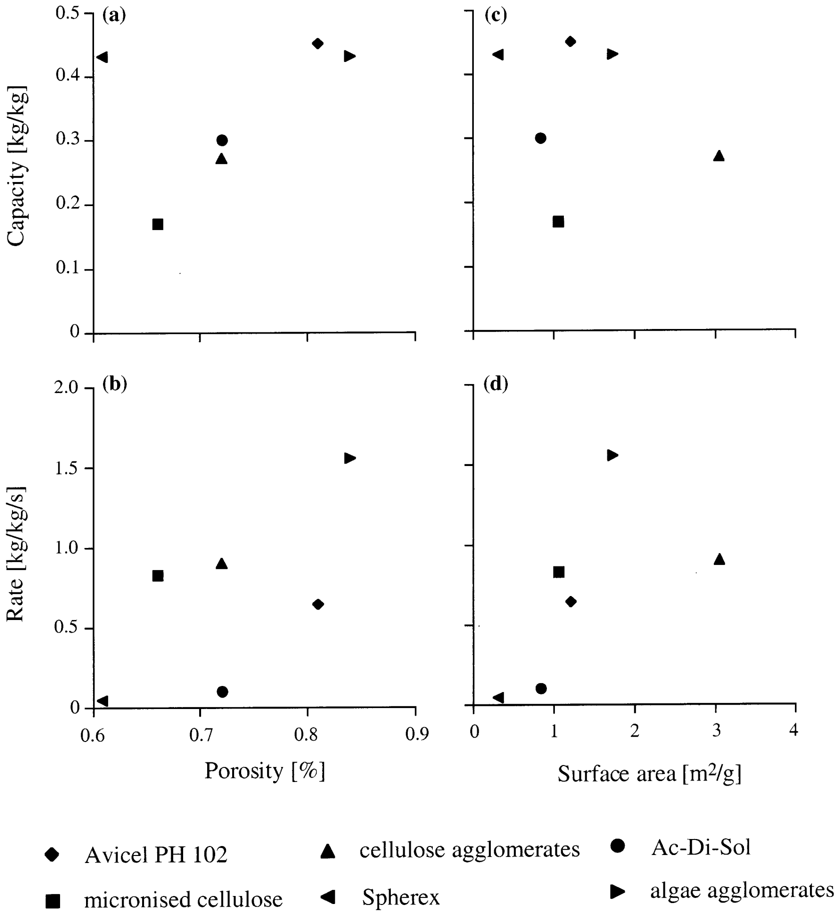

Fig. 3. Instantaneous absorption capacity (a and b) and rate (c and d), as obtained from the ITIC technique, plotted versus porosity and BET surface area for the powders.

tion rate shows a stronger correlation with the surface area of the material than with the porosity. The initial absorption of water takes place over the whole available surface area, involving both the surfaces of pores inside the particles and the outer surface area of the particles. Since absorption is initiated close to these surfaces, it is logical that the absorption rate should correlate with the BET surface area.

Algae cellulose has been included in this study because of the high surface area of the algae cellulose powder (64 m^2/g), as previously reported (Ek et al., 1998). But the grinding process used in the preparation of the material in this study seems to have closed many of the pores, thus decreasing the surface area (1.75 m^2/g). It is apparent that some pores were also closed in microcrystalline cellulose, since grinding of Avicel into micronised cellulose decreased the surface area from 1.23 to 1.07 m^2/g.

Why, then, is the absorption rate so important when a poor rate could be compensated for by increasing the amount of powder? If the volume of powder is more or less unrestricted, the rate may well not be crucial. However, when drugs are administered nasally, the powder volume is restricted to the small amount required to cover the nasal mucosa surface. In this case, the rate of absorption of water by the powder excipient is crucial to the subsequent absorption of drug through the mucosa.

6. Summary and concluding remarks

These results indicate that pharmaceutical powders can posses instantaneous water absorption properties that differ greatly from their long term absorption properties. It also appears that the instantaneous absorption properties can vary to a large extent between different powders. The rate, in particular, of instantaneous absorption varied considerably among the materials analysed. While it seems likely that the instantaneous absorption properties of a powder to be used as a drug enhancer are crucial to the enhancement of drug absorption, further study of the absorption properties of drug enhancers is required. The ITIC technique appears suitable for this task.

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