Fractal Dimension of Cellulose Powders Analyzed by Multilayer BET Adsorption of Water and Nitrogen

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The aim of this study was to show that multilayer fractal Brunauer−Emmett−Teller (mfBET) theory can be used as a tool to obtain information about the distribution of water in cellulose powder particles of varying crystallinity. Microcrystalline cellulose, agglomerated micronized cellulose, low-crystallinity cellulose, and cellulose powders from green and brown algae were characterized by scanning electron microscopy and mfBET analysis on water and nitrogen adsorption isotherms. The distribution of water in the cellulose materials was found to be characterized by a fractal dimension smaller than 1.5 for all powders. The results showed that for highly crystalline cellulose materials, such as *Cladophora* cellulose, the cellulose−water interactions take place mainly on cellulose fibril surfaces adjacent to open pores without causing any significant swelling of the material. For less ordered celluloses the water interaction was found to take place inside the bulk material and the water uptake process caused the pore volume to swell between 1 and 2 orders in magnitude. For the *Cladophora* cellulose, the thickness of the adsorbed water layer at the outer cut off of the fractal region was found to coincide very well with the average pore size obtained from nitrogen adsorption measurements. The multilayer fractal BET analysis on nitrogen adsorption isotherms showed that the particles could be characterized by fractal dimensions between 2.13 and 2.50. We conclude that water adsorption has the ability to alter the structure of the studied material and reveal a sorption-induced, "apparent" fractal structure over a relatively narrow length scale interval, while nitrogen adsorption probes the substrate morphology over a wide range of length scales and reveals the "true" fractal structure.

1. Introduction

The concept of a fractal dimension has been applied in most areas of science since Mandelbrot[1] introduced "fractal geometry" as a unifying description of natural phenomena that are not uniform but still obey simple power laws of the form

$$M \propto L^D \tag{1}$$

with noninteger dimensions D. Here M denotes a quantity that is a function of length scale L.

In the field of pharmaceutical materials science the fractal concept has been frequently used during the latest decade[2−5] to analyze everything from dissolution kinetics,[6−9] drug transport,[10,11] matrix structures,[12,13] and tablet compaction[14] to the roughness of pharmaceutical particles.[15−23]

The common denominator for most studies that have been performed on pharmaceutical particles is that some kind of imaging technique, like optical microscopy, atomic force microscopy (AFM), or scanning electron microscopy (SEM), has been used to obtain a picture from which the fractal dimension can be extracted. However, when sorption phenomena are investigated, as for the formulation of liquid drugs onto solid carriers[24] or production of ordered mixtures of drugs and carriers,[25] it is the distribution of available regions for interaction between the drug and the carrier that is the important property of the carrier material and not the actual surface structure of the carrier particle.

The interaction of water with tablet excipient particles is a process of crucial importance for, among others, the process of drug delivery. For this process it has earlier been found that the actual surface topography reveals very little about how water molecules are distributed in the particles.[26,27]

In this paper we aim to show that multilayer fractal Brunauer−Emmett−Teller (mfBET) theory[28] is a versatile tool to extract information about the distribution of water in cellulose powder particles of identical chemical nature but of various crystallinity and origins.[27]

2. Materials and Methods

2.1. Materials. The preparation procedure of the materials under study in this work as well as the crystallinity index (CI) determination is thoroughly described in ref 27. Briefly, five different types of cellulose were studied: microcrystalline cellulose (MCC; Avicel PH 102, FMC, Ireland) with a CI of 82.2, agglomerated micronized cellulose (AMC) with a CI of 69.1, low-crystallinity cellulose (LCC) with a CI of 45.0, brown algae cellulose (Algiflor, Danisco, France) with a CI of 81.7, and green algae cellulose (*Cladophora glomerata* harvested from the Baltic Sea) with a CI of 95.2.

2.2. Methods.

2.2.1. Scanning Electron Microscopy. Micrographs of each sample were taken (Leo Gemini 1550 FEG SEM, U.K.). The samples of each powder were mounted onto double-sided sticky

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Fractal Dimension of Cellulose Powders by BET

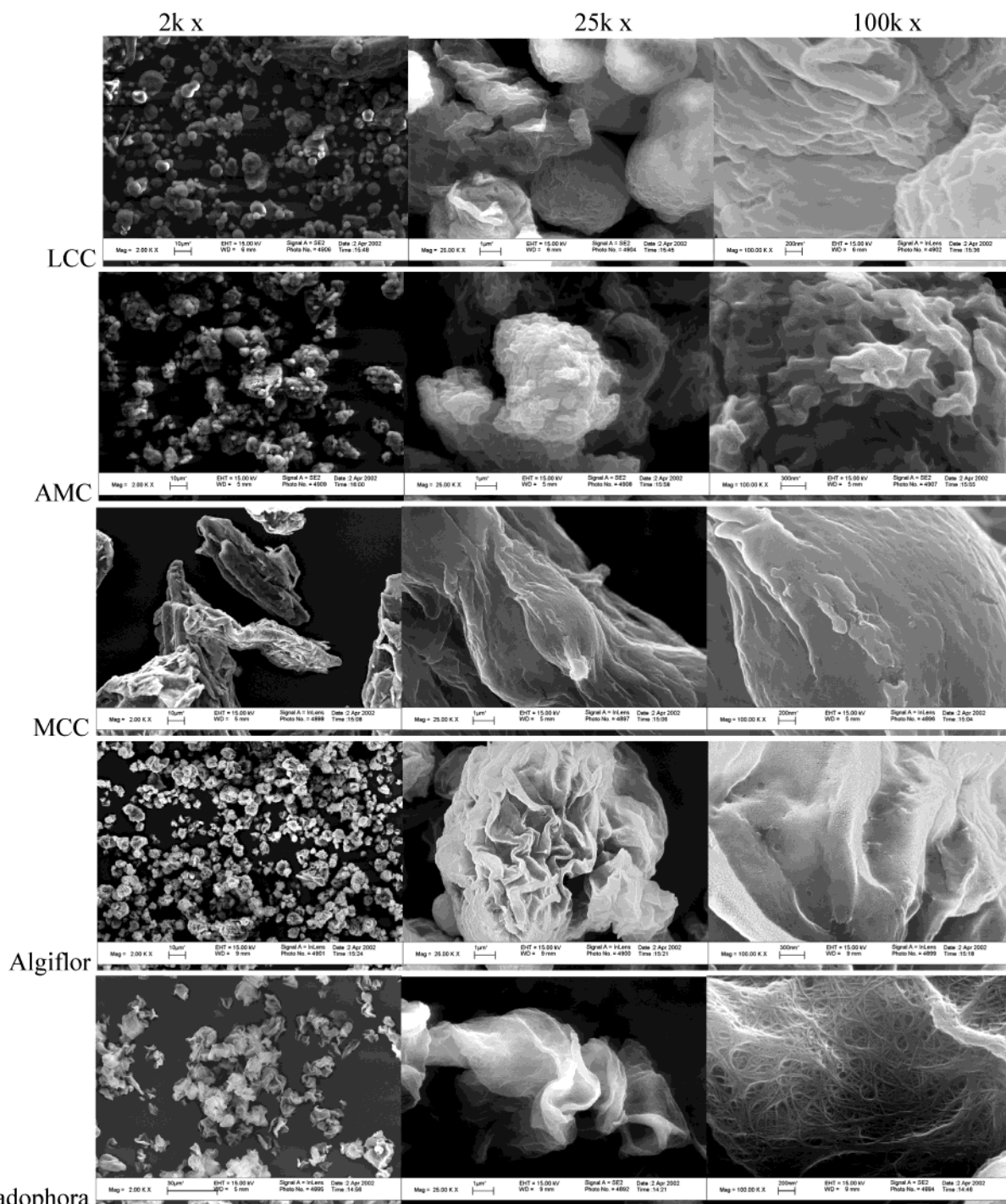*J. Phys. Chem. B, Vol. 107, No. 51, 2003* **14379**

Figure 1. SEM micrographs showing the different cellulose powders at three different magnifications.

tape over aluminum stubs and coated with gold under vacuum prior to the studies.

2.2.2. Water Adsorption. The water content was measured gravimetrically after samples had been stored for at least 48 h at 25 °C over saturated salt solutions of LiCl, CH_3COOK, K_2CO_3, NaBr, NaCl, and KNO_3, corresponding to 11%, 25%, 40%, 63%, 75%, and 96% relative humidity (RH), respectively. Prior to the measurements, the samples were stored over P_2O_5 (0% RH) for 10 days.

2.2.3. Nitrogen Adsorption. The N_2 adsorption of the samples was measured on an ASAP 2010 instrument (Micrometrics) at a temperature of 77.35 K.

2.2.4. Multilayer Fractal BET Theory. The mfBET theory, developed by Pfeifer et al.,[28] is a generalization of the work of

Brunauer, Emmett, and Teller[29] and it gives the number of adsorbed molecules N as

$$N = N_m \frac{(D-1)}{(1-n_{max}^{1-D})} \int_1^{n_{max}} n^{1-D} f_n(x) \, dn \qquad (2a)$$

where

$$f_n(x) = \frac{cx[1-(n+1)x^n + nx^{n+1}]}{(1-x)[1+(c-1)x-cx^{n+1}]} \qquad (2b)$$

In the above equations, D is the fractal dimension of the distribution of sites at which the molecules are adsorbed, and
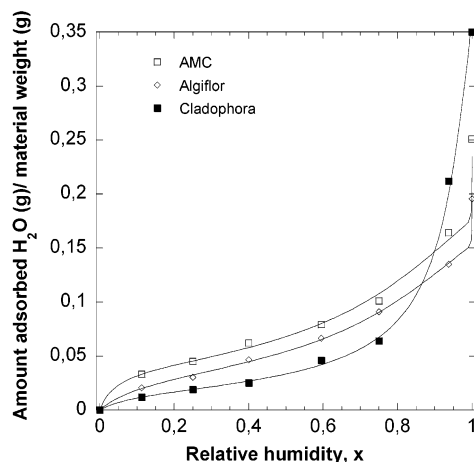
14380 *J. Phys. Chem. B, Vol. 107, No. 51, 2003*

Strømme et al.

Figure 2. Water adsorption isotherms on three different cellulose powders (separate markers) together with fits to eq 2 (continuous lines).

N_m is the number of molecules in a monolayer. Further, n_{max} represents the number of adsorbed layers corresponding to the cutoff of the fractal range. The adsorption strength, determined by the heats of adsorption and condensation, is denoted c, and the symbol for the relative partial pressure of the molecules to be adsorbed is x. It should be noted that this version of the mfBET theory assumes that the dimension of the embedding space of the material under study is 3 and that the topological dimension is 1, i.e., that the material is a fractal aggregate, which is true for almost all experimentally known mass fractals.[28] This means that the D value in eq 2 theoretically can take any value between 1 and 3. The parameters D, N_m, n_{max}, and c are obtained by fitting adsorption isotherms of the types described in sections 2.2.2 and 2.2.3 to eq 2.

For celluloses, known to consist of microfibrils, the *mass fractal* hypothesis underlying the fractal BET theory is expected to be well satisfied. Surface fractals, on the other hand, are more appropriately investigated by using the Frenkel−Halsey−Hill (FHH) theory.[30]

3. Results and Discussions

3.1. SEM Micrographs. Figure 1 shows micrographs of the powder particles taken at three different magnifications. From the 2K× magnifications it is seen that the size of the particles range from less than 10 μm (Algiflor) to ∼100 μm (MCC). The surface structure of the particles on length scales of ∼200 nm, as seen in the 100K× magnifications, differs among the particles. In this large magnification it is the appearance of the *Cladophora* particles that diverges most from the rest of the particles, which all have a more or less smooth−although wavy, laminar, or slightly grooved−structure.[27] For the *Cladophora* particles, distinct filaments with a diameter of about 10−30 nm are clearly visible. The observed filament diameter coincides very well with literature values obtained by nuclear magnetic resonance (NMR) measurements[31,32] and AFM.[31,32] From the 100K× magnification on the *Cladophora* particle we can also guess a very porous structure where the largest pores visible seem to have a diameter of ∼100 nm.

3.2. Adsorption Isotherms. The adsorption experiments were repeated three times for each type of material and the obtained isotherms were found to be highly reproducible. Figures 2 and 3 show a selection of water and nitrogen adsorption isotherms, respectively, together with fits to eq 2. The mfBET theory very well describes both water and nitrogen adsorption isotherms over the whole experimental range. The fitting parameters for water
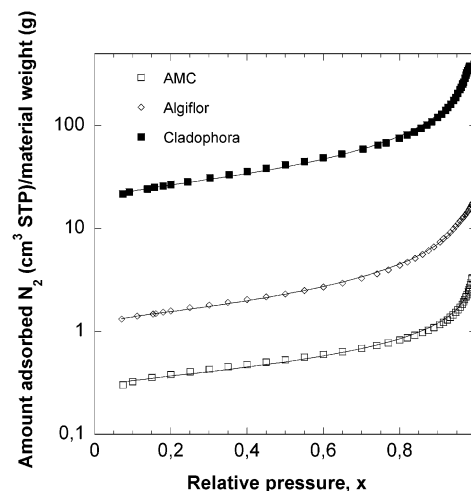

Figure 3. Nitrogen adsorption isotherms on three different cellulose powders (separate markers) together with fits to eq 2 (continuous lines). Note that the vertical axis is logarithmic.

TABLE 1: Characteristics of Cellulose Powders Obtained by mfBET Analysis on *Water* Adsorption Isotherms[a]

	pore volume (cm³/g)	D	N_m (mg/g)	c	n_{max}	outer cutoff ξ (nm)
LCC	0.28 (35)	1.46 (3)	34.4 (8)	10 (21)	12 (16)	3.7
AMC	0.25 (4)	1.39 (2)	19.6 (6)	24 (26)	17 (12)	5.3
Algiflor	0.20 (11)	1.32 (2)	19.8 (5)	9.0 (17)	18 (5)	5.6
MCC	0.20 (3)	1.43 (3)	16.8 (6)	13 (22)	15 (13)	4.7
Cladophora	0.35 (22)	1.09 (2)	11.7 (4)	10 (16)	78 (6)	24

[a] The values are given as averages over three measurements. The numbers within parentheses are absolute deviations in percent.

and nitrogen adsorption are displayed in Tables 1 and 2, respectively, together with the total pore volumes occupied by the probing molecule. For water this value is obtained from the amount adsorbed water at ∼100% relative humidity, while for nitrogen the values refer to relative pressures around 98%. In Table 2, the sizes of the largest pore filled with nitrogen at high pressure are also given. These values are calculated from the Kelvin equation[33] by the ASAP 2010 V4 software. It is worth noticing that the largest pore size sensed by the nitrogen adsorption process coincides very well with that observed in the 100K× magnification SEM micrograph of *Cladophora*. It should also be noticed that the N_m unit of water adsorption is in milligrams of adsorbed water per gram of material, while for nitrogen it is the volume adsorbed in units of cubic centimeters at saturation pressure per gram of material, as obtained from the ASAP 2010 V4 software. The N_m values presented here are not to be confused with those used for the determination of the classical BET surface area, where a nonfractal sample is assumed. From the number of adsorbed layers, n_{max}, an outer cutoff ξ of the fractal region probed by the two different types of molecules under study can be estimated from

$$\xi = n_{max} t \qquad (3)$$

where t is the thickness of an adsorbed monolayer. This thickness, calculated as (number of molecules per volume of bulk liquid)$^{-1/3}$, is 3.10 and 3.34 Å for water and nitrogen, respectively. The calculated ξ values are displayed in the tables.

As is seen from Tables 1 and 2, the fractal parameters from water and nitrogen adsorption differ significantly. The analysis of this difference will be carried out in the following sections.

Fractal Dimension of Cellulose Powders by BET

J. Phys. Chem. B, Vol. 107, No. 51, 2003 **14381**

TABLE 2: Characteristics of Cellulose Powders Obtained by mfBET Analysis on *Nitrogen* Adsorption Isotherms[a]

	pore volume[b] (cm^3/g)	DLP[c] (nm)	D	N_m (cm^3 STP/g)	c	n_{max}	outer cutoff ξ (nm)
LCC	0.0016[d] (34)	142[d] (5)	2.30 (7)	0.022 (10)	189 (21)	910 (11)	304
AMC	0.0044[e] (23)	137[e] (3)	2.50 (3)	0.111 (2)	321 (18)	335 (7)	112
Algiflor	0.0250[f] (1)	138[f] (11)	2.17 (2)	0.323 (2)	82 (20)	226 (3)	76
MCC	0.00304[g] (5)	142[g] (2)	2.41 (4)	0.0530 (3)	234 (22)	646 (5)	216
Cladophora	0.554[h] (1)	98.1[h] (6)	2.13 (2)	4.66 (5)	130 (6)	482 (2)	161

[a] The values are given as averages over three measurements. The numbers within parentheses are absolute deviations in percent. [b] Pore volume refers to the total volume of pores filled with nitrogen at the relative partial pressures indicated. [c] DLP refers to the diameter of the largest pore that is filled with nitrogen at the listed pressures. The pore volumes and DLPs are obtained from the ASAP 2010 V4 software. [d] Relative partial pressure 0.9861. [e] Relative partial pressure 0.9857. [f] Relative partial pressure 0.9858. [g] Relative partial pressure 0.9862. [h] Relative partial pressure 0.9799.

The conclusion, in a nutshell, will be that water adsorption may alter the structure of the studied material and accordingly reveal a sorption-induced, "apparent" fractal structure, at length scales from 10^{-1} nm to 10^{0}–10^1 nm. By contrast, nitrogen adsorption does not alter the morphology of the material; it probes the substrate morphology over a much wider range of length scales and reveals the "true" fractal structure, at length scales up to 10^2–10^3 nm.

3.2.1. Water Adsorption. We now discuss the physical interpretation of the fitting parameters. For the water adsorption process we find that the characteristic fractal dimension for the various cellulose powders is between 1.09 and 1.46.

In an earlier published model describing water−cellulose interactions it has been shown that,[34] at low humidities, water molecules bind to anhydroglucose units in amorphous regions of the cellulose with a stoichiometry of one water molecule per anhydroglucose unit, and at higher humidities, additional water binds to the water molecules already bound to these units. The last step may require the breaking up of polymer−polymer hydrogen bonds in the cellulose.

From Table 1 we see that n_{max} is between 12 and 18 for all types of cellulose particles under study, corresponding to a water layer thickness of ∼4−5 nm, except from the *Cladophora* cellulose that has a n_{max} value of 78 and, therefore, a ξ value of 24 nm. *Cladophora* has the highest crystallinity index among the powders, above 95%. Thus, it is very likely that the regions available for water interactions in this material are located mainly on microfibrils neighboring open pores, in contrast to the less ordered powders, where such sites to a greater extent also are available in the bulk of the material. This interpretation is in line with the values of D in Table 1. For *Cladophora D* is close to unity, which shows that the available regions for water molecules in the *Cladophora* are not distributed uniformly throughout the material but rather restricted to surfaces of fibrils alongside quasi-linear pores. For the other materials, D is significantly higher, which suggests a more space-filling distribution of activities. This may also explain the relatively large difference in n_{max} between the *Cladophora* and the other materials: When water is bound to fibrils bordering open pores in the *Cladophora* cellulose, the process of binding additional water molecules to the already bound molecules does not require the breaking up of polymer−polymer hydrogen bonds. Hence, new water molecules can bind to other water molecules more or less unhindered. In this manner the pore size sets an upper limit to how many layers of water can be adsorbed. In this context it is appropriate to mention that, while the *largest* pore size sensed by the nitrogen adsorption process was found to be 98 nm for the *Cladophora* (cf. Table 2), the *average* pore diameter, given by the ASAP 2010 V4 software, was found to be ∼23 nm, which is in very close agreement with the ξ value of 24 nm obtained from the H$_2$O mfBET fit (cf. Table 1). The fact that the pore volume probed by water (Table 1) and nitrogen

(Table 2) adsorption are of the same order of magnitude supports the above analysis: In the highly crystalline *Cladophora* cellulose, water is attached to fibrils adjacent to open pores in the material without causing any significant swelling of the material.

For the less ordered celluloses, the volumes occupied by water molecules (Table 1) are between 1 and 2 orders in magnitude larger than the corresponding volumes for nitrogen adsorption (Table 2). This shows that the accommodation of water in these materials induces swelling of the material, which is supported by earlier NMR studies on microcrystalline cellulose.[35] Thus the distance, after swelling, between neighboring cellulose chains is a measure of how many layers of water can be accommodated in the structure. From Table 1 we find this distance to be ∼4−5 nm, which actually is of the same order of magnitude as the width of the microfibrils of land plant cellulose.[31]

3.2.2. Nitrogen Adsorption. The characteristic fractal dimension sensed by nitrogen adsorption onto the various cellulose powders is found to be between 2.13 (*Cladophora*) and 2.50 (AMC), Table 2. Interestingly, the fractal dimensions of the powders obtained from algae are significantly lower than the others. From the ξ values in Table 2 we find that the fractal region probed by nitrogen adsorption for the studied powders is located at length scales smaller than a hundredth of the particle size. This means that the SEM pictures of highest magnification in Figure 1 can provide us with information only about the features around the outer cutoff and not about the fractal region located at smaller length scales. We also notice that all ξ values in Table 2 are of the same order of magnitude as the values of the largest pore sizes (DLP), obtained from the Kelvin equation.

We have found that it is necessary to assume that the topological dimension, D_{top}, of the materials is unity, to fit the nitrogen adsorption isotherms. This indicates that the fibril network exhibits a fractal structure on length scales below about 100 nm. A nonfractal bulk with a rough fractal surface is excluded, since this case should have $D_{top} = 2$. Our conclusion is in agreement with an earlier study on fine-powdered microcrystalline cellulose,[36] which showed that the fractal dimension obtained by small-angle neutron scattering (SANS) was about 2.2 on length scales between 10 and 100 nm. With the SANS technique it is possible to distinguish a "bulk" fractal structure from a fractal surface roughness,[37] and the results of ref 36 clearly exclude a fractal surface on a nonfractal bulk material.

4. Summary and Conclusion

In this work we have shown that multilayer fractal BET theory can be used to obtain extensive information about the distribution of adsorbed water on cellulose powder particles on nanometer length scales. We have found that this distribution can be characterized by a fractal dimension smaller than 1.5.

The mfBET analysis also indicated that for highly crystalline cellulose materials, such as *Cladophora* cellulose, the cellulose−water interactions take place mainly on fibrils neighboring open pores without causing any significant swelling of the material, while for the less ordered celluloses the adsorbed water is located inside the bulk material and the uptake process causes the pore volume to swell between 1 and 2 orders in magnitude. For the *Cladophora* cellulose we particularly found that the thickness of the adsorbed water layer at the outer cutoff of the fractal region coincided very well with the average pore size obtained from nitrogen adsorption measurements, while for the less ordered celluloses this thickness was found to be of the same size as the width of the cellulose microfibrils.

The "true" topography of the cellulose powder particles was examined by mfBET theoretical analysis of nitrogen adsorption isotherms. This analysis showed that the fractal dimension of the powder particles was between 2.13 and 2.50.

To conclude, our findings suggest that multilayer fractal BET analysis of adsorption isotherms is a versatile tool to obtain extensive information about the distribution of sites available for liquid molecules on particles, something that may prove very useful when developing new carrier materials for, e.g., liquid drugs.

References and Notes

(1) Mandelbrot, B. B. *The Fractal Geometry of Nature*; Freeman: San Francisco, CA, 1982.

(2) Koch, H. P. *Pharmazie* **1993**, *48*, 643−659.

(3) Carstensen, J. T.; Franchini, M. *Drug Dev. Ind. Pharm.* **1993**, *19*, 85−100.

(4) Tawashi, R. *Saudi Pharm. J.* **1997**, *5*, 1−5.

(5) Hickey, A. J.; Concessio, N. M. *Adv. Drug Delivery Rev.* **1997**, *26*, 29−40.

(6) Farin, D.; Avnir, D. *J. Pharm. Sci.* **1992**, *81*, 54−57.

(7) Valsam, G.; Macheras, P. *Eur. J. Pharm. Sci.* **1995**, *3*, 163−169.

(8) Tromelin, A.; Gnanou, J. C.; Andres, C.; Pourcelot, Y.; Chaillot, B. *J. Pharm. Sci.* **1996**, *85*, 924−928.

(9) Tromelin, A.; Hautbout, G.; Pourcelot, Y. *Int. J. Pharm.* **2001**, *224*, 131−140.

(10) Yamane, S.; Takayama, K.; Nagai, T. *J. Controlled Release* **1998**, *50*, 103−109.

(11) Ogihara, T.; Tamai, I.; Tsuji, A. *Pharm. Res.* **1998**, *15*, 620−625.

(12) Fernandez-Hervas, M. J.; Vela, M. T.; Fini, A.; Rabasco, A. M. *Int. J. Pharm.* **1996**, *130*, 115−119.

(13) Saito, K.; Yamane, S.; Takayama, K.; Nagai, T. *Arch. Pract. Pharm. Yakuzaigaku* **1998**, *58*, 203−212.

(14) Leuenberger, H.; Leu, R.; Bonny, J. D. *Drug Dev. Ind. Pharm.* **1992**, *18*, 723−766.

(15) Fernandez-Hervas, M. J.; Holgado, M. A.; Rabasco, A. M.; Fini, A. *Int. J. Pharm.* **1994**, *108*, 187−194.

(16) Bower, C.; Washington, C.; Purewal, T. S. *Int. J. Pharm.* **1995**, *118*, 229−235.

(17) Holgado, M. A.; Fernandez-Hervas, M. J.; Rabasco, A. M.; Fini, A. *Int. J. Pharm.* **1995**, *120*, 157−167.

(18) Holgado, M. A.; Fernandez-Hervas, M. J.; Fernandez-Arevalo, M.; Rabasco, A. M. *Int. J. Pharm.* **1995**, *121*, 187−193.

(19) Fini, A.; Fazio, G.; Fernandez-Hervas, M. J.; Holgado, M. A.; Rabasco, A. M. *J. Pharm. Sci.* **1996**, *85*, 971−975.

(20) Vertommen, J.; Rombaut, P.; Kinget, R. *Int. J. Pharm.* **1997**, *146*, 21−29.

(21) Holgado, M. A.; Fernandez-Hervas, M. J.; Alvarez-Fuentes, J.; Vela, M. T.; Rabasco, A. M.; Fini, A. *Int. J. Pharm.* **1996**, *142*, 143−151.

(22) Fini, A.; Fernandez-Hervas, M. J.; Holgado, M. A.; Rodriguez, L.; Cavallari, C.; Passerini, N.; Caputo, O. *J. Pharm. Sci.* **1997**, *86*, 1303−1309.

(23) Li, T.; Park, K. *Pharm. Res.* **1998**, *15*, 1222−1232.

(24) Spireas, S. S.; Jarowski, C. I.; Rohera, B. D. *Pharm. Res.* **1992**, *9*, 1351−1358.

(25) Nyström, C.; Westerberg, M. *J. Pharm. Pharmacol.* **1986**, *38*, 161−165.

(26) Ardizzone, S.; Dioguardi, F. S.; Mussini, T.; Mussini, P. R.; Rondinini, S.; Vercelli, B.; Vertova, A. *Cellulose* **1999**, *6*, 57−69.

(27) Mihranyan, A.; Llagostera, A. P.; Karmhag, R.; Strømme, M.; Ek, R. *Int. J. Pharm.* **2003** (in press).

(28) Pfeifer, P.; Obert, M.; Cole, M. W. *Proc. R. Soc. London* **1989**, *A423*, 169−188.

(29) Brunauer, B.; Emmett, P. H.; Teller, E. *J. Am. Chem. Soc.* **1938**, *60*, 309−319.

(30) Pfeifer, P.; Liu, K. Y. *Stud. Surf. Sci. Catal.* **1997**, *104*, 625−677.

(31) Wickholm, K.; Larsson, P. T.; Iversen, T. *Carbohydr. Res.* **1998**, *312*, 123−129.

(32) Ek, R.; Gustafsson, C.; Nutt, A.; Iversen, T.; Nyström, C. *J. Mol. Recognit.* **1998**, *11*, 263−265.

(33) Gregg, S. J.; Sing, K. S. *Adsorption, Surface Area and Porosity*; Academic Press: New York, 1982.

(34) Zografi, G.; Kontny, M. J. *Pharm. Res.* **1986**, *3*, 187−194.

(35) Ek, R.; Lennholm, H.; Davidsson, R.; Nyström, C.; Ragnarsson, G. *Int. J. Pharm.* **1995**, *122*, 49−56.

(36) Sugiyama, M.; Hara, K.; Hiramatsu, N.; Iljima, H. *Jpn. J. Appl. Phys.* **1998**, *37*, L404−L405.

(37) Pfeifer, P. In *Multiple Scattering of Waves in Random Media and Random Rough Surfaces*; Proceedings of the International Symposium, The Pennsylvania State University, State College, PA, 1987; pp 45−49.