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Particle analysis of microcrystalline cellulose: Differentiation between individual particles and their agglomerates

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Abstract

The presence of two types of particles, the individual particles and their agglomerates, complicates the characterization of the particle size and the external surface area in the microcrystalline cellulose powders. During characterization, different degrees of de-agglomerations may be applied with varying size and surface areas as a result. The crystallinity of the cellulose particles were characterized by a crystallinity index, using the solid state NMR technique. Methods for the characterization of particle size, surface, shape of individual particles and their agglomerates were examined and recommendations of suitable methods are given. Individual particles were separated from agglomerates by ultrasonic treatment of a water suspension of agglomerates. Photoextinction measurements on sonicated water suspensions were used in the characterization of size and surface area of individual particles. The size of the agglomerates were estimated by dry sieving and the external surface area of the agglomerates with photoextinction measurements on cyclohexane suspensions not treated with ultrasonic energy.

Key words: Agglomerate; Crystallinity; Microcrystalline cellulose; Individual particle; Particle size; Particle shape; Particle surface; Solid-state NMR

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1. Introduction

Microcrystalline cellulose is most commonly used as an excipient in the pharmaceutical industry due to several advantages of the cellulose material. The substance is reported to be white, tasteless, stable, biocompatible and it shows good compaction behaviour with drugs. Microcrystalline cellulose is prepared from dissolving pulp of high purity. The native cellulose chain is built up of D-glucopyranose units joined by β-1,4-linkages, chains ranging up to several thousand units, the exact number depending on the source of the cellulose fibres. The cellulose materials consist of amorphous cellulose areas, in addition to well ordered crystalline regions. During the manufacture of microcrystalline cellulose, accessible amorphous cellulose areas are hydrolysed away and the chain length, measured as the degree of polymerization of the cellulose, falls to level off at degree of polymerization value around some hundreds. The characteristic levelling-off lengths of the microcrystals in different cellulose raw

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materials have been reported in the literature (Battista, 1965). When the fibrous structures are broken down, the resulting cellulose particles are washed and spray dried into a cellulose powder (Battista, 1950, 1964, 1971). Today the product is marketed by several different suppliers (Doelker et al., 1987a).

In spite of widespread use, the physical character of the microcrystalline cellulose particle is not well understood, especially concerning the dimensions and surface area of the particles. For example, different values of the median Stokes particle diameter in Avicel PH 101 have been reported in the literature; 46–54 μm (Nyström et al., 1977) and 23 μm (Ahlneck and Alderborn, 1988). In a review, Zografi et al. (1984) also found several inconsistencies and uncertainties for the specific surface area. One possible reason for the wide range of particle sizes and surface areas reported in the literature may be that the particles in Avicel PH 101 are agglomerates of smaller individual particles. Individual particles are units of matter whose size and shape depend on the forces of cohesion and are to be distinguished from the agglomerates formed as larger groups of individual particles (Herdan, 1960). The formation of such larger agglomerates is obviously facilitated by the spray drying step in the manufacturing process. During characterization, different degrees of de-agglomerations may be applied with varying size and surface areas as a result.

Investigations using X-ray diffraction and infrared spectroscopy to characterize the crystallinity of cellulose are available (Hermans, 1950; Landin et al., 1993; Rowe et al., 1994). Studies of the crystalline components and the microstructure in native celluloses using solid-state NMR techniques have been reported (Horii et al., 1987; VanderHart and Atalla, 1984). However, there appear to be no published investigations using solid-state NMR to measure a crystallinity index of microcrystalline celluloses intended for pharmaceutical use. The advantage of using solid-state NMR instead of X-ray methods is the possibility of studying polymorphism of the cellulose material (Sugiyama et al., 1991).

The purpose of this paper was to treat and to characterize microcrystalline celluloses in different ways to establish if there were reasons for describing the microcrystalline celluloses to be agglomerates of smaller individual particles and to demonstrate suitable measuring techniques. Three different celluloses, Avicel PH 101, Avicel PH 102 and Dynacel, were examined. The characterization of these microcrystalline cellulose powders includes some solid-state properties as well as size, surface area and shape measures of both individual particles and their agglomerates.

2. Materials and methods

2.1. Cellulose samples

The microcrystalline cellulose (Avicel PH 101, Avicel PH 102 and Dynacel) is manufactured by hydrolysing a dissolving pulp of high purity into fibre fragments, which agglomerate into a powder in the spray dryer consisting of both individual particles and their agglomerates (Fig. 1). The amorphous and crystalline cellulose samples were used as reference substances for the NMR spectra.

2.1.1. Avicel PH 101

Avicel PH 101 (lot 6153, 4.5% moisture) was obtained from FMC, Ireland.

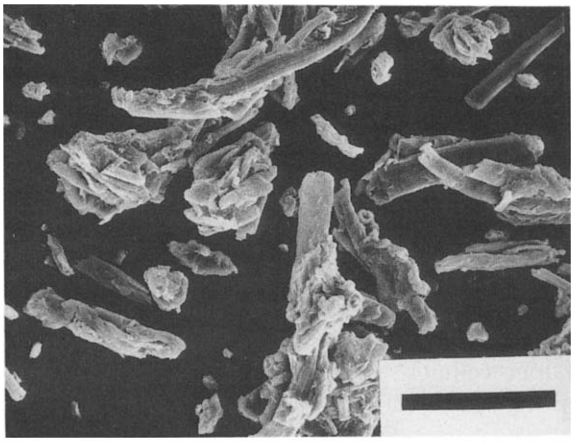

Fig. 1. Scanning electron microscope photograph of microcrystalline cellulose particles in Dynacel. Scale bar equal to 100 μm.

2.1.2. Avicel PH 102

Avicel PH 102 (lot 7004, 4.3% moisture) was obtained from FMC, Ireland.

2.1.3. Dynacel

Dynacel (lot 180, 4.9% moisture) was obtained from Cellupharm, Sweden. In order to obtain a direct measure of individual particles before the spray drying step, a suspension sample was also prepared. This was collected from the Cellupharm pilot plant. The feed into the spray dryer was a suspension of 15.4% hydrolysed hardwood sulphate pulp (Acetacraft from International Paper, U.S.A.).

2.1.4. Amorphous cellulose

The amorphous cellulose was obtained by immersing 50 g air-dried cellulose pulp (Acetacraft, International Paper, U.S.A.) in 1 kg 70% aqueous $ZnCl_2$ solution. After 1 h, water was added and the cellulose pulp was washed clean until the conductivity of the wash water fell below 10 mSi. This method of preparing amorphous cellulose has previously been used (Patil et al., 1965; Pandy and Nair, 1976).

2.1.5. Crystalline cellulose

Valonia ventricosa cellulose algae were used as an example of a highly crystalline cellulose structure. The cellulose sample was provided by Jerry Stålberg, Department of Microbiology, Uppsala University. The sample was prepared by boiling algal cell walls in 1% NaOH solution in 6 h. The cellulose suspension was rinsed with 0.05 N HCl and freezed dried.

2.2. Characterization of solid-state properties

2.2.1. Crystallinity

The crystallinity of the celluloses was determined from the solid-state ^{13}C CP/MAS NMR spectra. The measurements were performed on a Bruker AMX 300 spectrometer operating at 75.48 MHz with 5 kHz spinning using a double air bearing probe and ZrO_2 rotors. The instrumental parameters were; 0.8 ms contact time, 2048 data points filled to 4096 K. The chemical shift scale was referenced to the carbonyl in glycine located at 176.03 ppm. The number of scans on each spectrum was 2000. Measurements were made on damp cellulose samples at about 50% moisture content. The crystallinity of the cellulose material was calculated as a crystallinity index obtained by dividing the intensity of the crystalline C4 peak by the sum of the crystalline and amorphous C4 intensities. The crystalline peak was located at 89 ppm and the amorphous peak at 84 ppm.

2.2.2. Apparent particle density

The apparent particle density, defined as the mass of a particle divided by the volume of the particle excluding open pores but including closed pores (British Standard, 1958), was measured using a gas comparison pycnometer (Beckman, U.S.A., pycnometer model 930). The average of three determinations, using air as the gas, was calculated and the relative standard deviation was found to be below 0.67%.

2.2.3. Water sorption

Cellulose samples of, approx. 1-2 g, were stored for 10 days over phosphorus pentoxide and carefully weighed before and after being equilibrated in different desiccators containing saturated salt solutions at 20°C. The saturated salt solutions were $MgCl_2$, NaBr, NaCl, KCl and KNO_3, resulting in relative humidities of 33, 57, 75, 84 and 94%, respectively (Nyqvist, 1983).

2.3. Characterization of particle properties

The microcrystalline cellulose particles were characterised by size, shape and external surface area. The characteristics were estimated by several methods utilizing different degrees of de-agglomeration.

2.3.1. Particle size

2.3.1.1. Individual particles. The individual particles were obtained by ultrasonic treatment of a cellulose powder in a water suspension for 15 min. The particle sizes were characterized by sedimentation analysis of approx. 0.3 g cellulose with a wide-angle scanning photo sedimentometer (WASP, Microscal Ltd, U.K.). The concentration was followed during settlement by photoextinction measurements and the median Stokes diameter by weight was calculated (Allen, 1968/9). The harmonic means by weight d_h were calculated from Eq. 1:

$$d_h = \frac{1}{\sum_0^n \left(\frac{w_i}{d_i}\right)} \tag{1}$$

where w_i is the weight fraction retaining in each class size and d_i denotes the median class size. The average of three determinations was calculated and the relative standard deviation was 13%.

2.3.1.2. Agglomerates. Dry powder, approx. 0.5 g dry cellulose, was fractionated by gentle hand sieving (precision sieves with circular openings, Veco, The Netherlands) for 5 min, using sieves 45, 65, 90, 130 and 180 μm. The median values by weight and subsequently also the harmonic means by weight were calculated from sieve data. The class middle was the average of the lower and upper sieve opening diameter.

2.3.2. Particle surface area

2.3.2.1. Individual particles. Microcrystalline cellulose, approx. 0.01 g, was dispersed in 50 ml water by ultrasonic treatment for 15 min. The surface of the cellulose particles was calculated from the amount of transmitted light (Rose Photometer, Evans Electroselenium Ltd) by applying Lambert-Beers law (Alderborn and Nyström, 1993). The average of three determinations was calculated and the relative standard deviation found to be 5%.

2.3.2.2. Agglomerates. Light extinction: In the photometric method microcrystalline cellulose powder, approx. 0.01 g, was suspended in 50 ml cyclohexane and treated gently. The surface of the cellulose particles was calculated from the amount of transmitted light (Rose Photometer, Evans Electroselenium Ltd) by applying Lambert Beers law. The average of three determinations was calculated and the relative standard deviation found to be 5%.

Air permeability-powder bed: The particle sizes were estimated from permeability measurements on a cellulose powder bed with a height of 10–20 cm located in a tube with a diameter of 1 cm (Eriksson et al., 1990). The density of the agglomerates was assumed to be equal to the density of microcrystalline cellulose, i.e., 1.57 g/cm^3. The average of three determinations was calculated and the relative standard deviation found to be 0.6%.

Air permeability-compact: In the Fisher Subsieve Sizer method, described by e.g. Kaye (1967), air flow resistance in a slightly compacted plug containing 1.52 g air dried cellulose was measured. The average of three determinations where the plugs were pressed between 35 and 100 kPa was calculated. The relative standard deviation of the measurements was estimated to be 3%.

2.3.3. Particle shape

The shape of the individual particle and the agglomerate was calculated according to Eq. 2 as a surface to volume shape factor α_{sv} (Heywood, 1954):

$$\alpha_{sv} = S_w \rho_s d_h \tag{2}$$

The value of α_{sv} ranges from 6 (spheres) and higher. The cellulose particles were characterized by the external surface area per unit weight S_w, the density of the cellulose ρ_s, and the harmonic diameter by weight d_h. The volume to shape factor α_{sv} was calculated according to Eq. 1 and 2.

3. Results and discussion

3.1. Solid-state properties

The typical solid-state ^{13}C-NMR spectra of cellulose samples are shown in Fig. 2. With reference to the microcrystalline cellulose the spectrum of *V. ventricosa*, one of the most crystalline cellulose known, is presented together with those of amorphous cellulose material. The peaks from

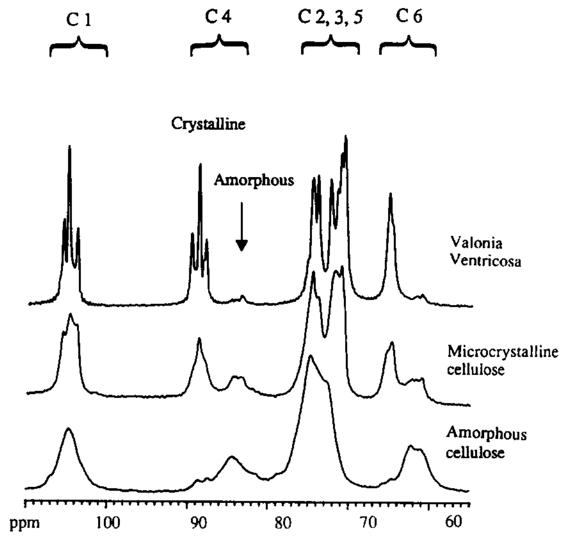

Fig. 2. Solid-state NMR spectra of cellulose powders of different crystallinity. The crystallinity index of the highly crystalline cellulose *Valonia ventricosa* was 94%, for the microcrystalline cellulose (Avicel PH 101) 74% and for amorphous cellulose 25%. The solid-state NMR measurements were performed on cellulose samples containing 50% water by weight.

left to right are assigned to the carbons in the anhydroglucose units (Fig. 2).

It has been shown that there is a linear relationship between crystallinity determined by X-ray diffraction and solid-state ^{13}C-NMR (Teeäär et al., 1987). We have found that the three microcrystalline celluloses all had a crystallinity index at about 73–74% which falls into the crystallinity range, 63–78% for Avicel PH 101, determined by X-ray diffraction (Doelker et al., 1987).

There are difficulties in characterization of the density of cellulose fibres (Hermans and Vermaas, 1946; Khan et al., 1988). The density of the cellulose fibres depends on the moisture content and different abilities of the surrounding media to penetrate the pores in the cellulose fibre surface. The influence of the water content on the density is small when the moisture content is below 5% (Hermans, 1949) and the densities of the microcrystalline celluloses were all equal to 1.57 g/cm^3.

Dynacel had the lowest level of water sorption of all the samples tested (Table 1). Since water cannot enter cellulose crystals and there is no difference in crystallinity, it is possible that the Dynacel powder has a somewhat smaller total surface area than the Avicel powders.

Table 1
Water sorption at 20°C by the microcrystalline celluloses at different air humidities

	Relative air humidity [a]					
	33%	57%	75%	84%	94%	100%
Avicel PH 101	2.77	6.18	8.13	10.3	13.0	21.8
Avicel PH 102	2.75	6.07	8.05	10.2	12.9	21.2
Dynacel	2.72	5.07	7.19	9.04	11.8	19.6

[a] Humidity in air above saturated water solutions of the following salts (Nyqvist, 1978): $MgCl_2$ (33%), NaBr (57%), NaCl (75%), KCl (84%), KNO_3 (94%).

3.2. Particulate properties

3.2.1. Differentiating between individual particles and their agglomerates

Before measuring the size, surface and shape of the particles in cellulose it is necessary to differentiate between individual particles and their agglomerates. Individual particles were obtained by disintegration of agglomerates by ultrasonic treatment of a water suspension of cellulose particles. In Fig. 3, the surface development is shown as a function of treatment time in the

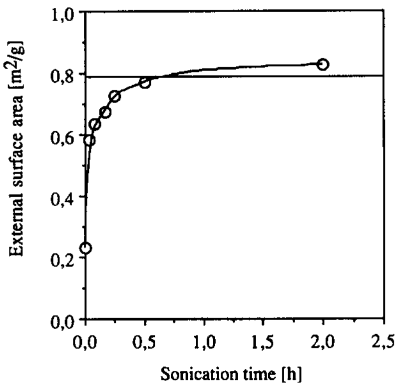

Fig. 3. External surface area per weight increase of a water suspension of microcrystalline cellulose (Dynacel) given ultrasonic treatment. The straight line indicating the surface area of individual particles before agglomeration in the spray drier, based on a sample taken from the production line (Cellupharm AB, Sweden).

Table 2
External surface area of agglomerates of microcrystalline cellulose powders estimated by different methods

Material	Light extinction cyclohexane suspension (m^2/g)	Light extinction water suspension (m^2/g)	Air permeability powder bed [a] (m^2/g)	Air permeability compact [b] (m^2/g)
Avicel PH 101	0.111	0.192	0.214	0.346
Avicel PH 102	0.076	0.162	0.164	0.288
Dynacel	0.127	0.190	0.253	0.339

[a] Air permeability of an uncompressed cellulose powder bed using the method described by (Eriksson et al., 1990).
[b] Air permeability of a slightly compacted cellulose plug using Fisher Subsieve Sizer (Kaye, 1967).

ultrasonic bath. The external surface area of individual particles obtained from measurements on an undried suspension of hydrolysed cellulose fibre fragments is indicated as a straight line. Apparently, the development of surface area of the cellulose powders levels off at about the same surface area as characterizes the undried cellulose particles. Thus, it seems that by sonication the agglomerates obtained by spray drying break down to the orginal individual particles. However, since the cellulose fibres are known to be broken by ultrasonic treatment (Willems, 1961), the correct dispersion time in the ultrasonic bath is not self-evident. Another complication is that different materials may require different dispersion times. In this work we have sonicated for 15 min, a time equal to the standard time used for dispersion of cellulose particles during hydrolyses of cellulose (Morehead, 1950).

Different methods resulted in different values of the external surface area (Table 2). Methods based on air permeability measurements of a compressed powder plug, e.g., Fisher Subsieve Sizer, should not be used in the characterization of particles containing agglomerates because of the risk of de-agglomeration during compaction. The problem using the method with an uncompressed cellulose powder (Eriksson et al., 1990) is that the porosity of the agglomerate must be known. This porosity is in our case unknown and the calculations for the results presented in Table 2 were made with the assumption that the agglomerates were solid cellulose particles, having a density of 1.57 g/cm^3. Cellulose particles in cyclohexane suspensions show a lower external surface area than the corresponding water suspensions. We beleive that when the cellulose particles are suspended in water, part of the agglomerates disintegrates due to the breaking of hydrogen bonds between fibre fragments in the agglomerates during the swelling process. This is probably not the case in a cyclohexane suspen-

Table 3
Characterization of individual particles and agglomerates in microcrystalline cellulose powders

Material	Type of particle	Mean diameter by weight [a]		External surface area [b] S_w (m^2/g)	Surface to volume shape factor [c] α_{sv} (−)
		Median (μm)	Harmonic d_h (μm)		
Avical PH 101	individual particle	27.6	18.4	0.757	21.9
	agglomerate	102	81.7	0.111	14.2
Avicel PH 102	individual particle	29.4	20.7	0.743	24.1
	agglomerate	120	93.3	0.076	11.1
Dynacel	individual particle	19.8	16.7	0.691	18.1
	agglomerate	81.5	56.9	0.127	11.3

[a] Individual particles, Stokes diameter, in sonicated (15 min) water suspensions. Dry agglomerates characterized by the sieve diameter.
[b] Individual particles, photoextinction measurement in sonicated (15 min) water suspensions, agglomerates in cyclohexane suspension without sonication.
[c] Calculated from Eq. 2, $\alpha_{sv} = S_w \rho_s d_h$.

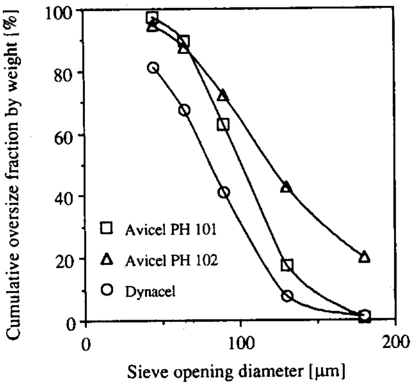

Fig. 4. Cumulative cellulose particle oversize fraction by weight distribution for Avicel PH 101, Avicel PH 102 and Dynacel. Hand sieving of dry powder (precision sieve with circular openings, Veco, The Netherlands).

sion, since cyclohexane is known to produce very low swelling of cellulose (Porter and Orr, 1965).

3.2.2. Particle size

The Stokes diameter was used to obtain size data for individual particles, and the sieve diameter was applied for agglomerates (Table 3). In Table 3 both the median as well as the harmonic means of the particle sizes are given.

The individual particle sizes were about the same for Avicel PH 101 and Avicel PH 102 but smaller for the Dynacel particle. Avicel 102 contained the largest agglomerates and Avicel PH 101 had a narrower distribution than the Avicel PH 102 and Dynacel (Fig. 4). The reason for using dry sieving when characterization of the agglomerate size is that the agglomerate density is an unknown parameter in the Stokes equation.

3.2.3. Particle surface area

We consider photoextinction measurements of a cellulose particle suspension to be the most valid measuring technique for estimating the external surface area. By this technique individual particles can be assessed after sonication of a water-based suspension and agglomerates without sonication in cyclohexane-based suspension.

The external surface area of the individual particles in Avicel PH 101 and Avicel PH 102 were about the same and only slightly smaller for Dynacel (Table 3). The external surfaces of the agglomerates were unequal, the smallest being Avicel PH 102 and the largest Dynacel.

3.2.4. Particle shape

The shape factors calculated as surface to volume factor according to Eq. 2 are presented in Table 3. The individual particle shapes were about the same for the two Avicel qualities but smaller for Dynacel.

The results suggest that the two Avicel qualities (PH 101 and PH 102) are based on individual particles of similar properties.

4. Conclusions

This work shows that it is relevant to classify microcrystalline cellulose particles into two categories, namely, individual particles and agglomerates. Individual particles can be obtained from the agglomerates by sonication of a water suspension of cellulose particles. Individual particles should be characterized with respect to both size and surface area by light extinction in sonicated water suspension. The surface area of the agglomerates should be characterized by light extinction measurements on suspensions based on liquids which do not swell the cellulose particles, e.g., cyclohexane. The particle size of the agglomerates is preferably determined by dry sieving of a gently treated dry powder.

The possibility of characterizing both the individual particles as well as the agglomerates is important in studies of pharmaceutical unit operations. This is because agglomerates tend to disintegrate during treatment and thereby ruin the desired properties of the powder bulk, such as flowability. To preserve the agglomerate during the process of tabletting the powder should be treated gently to minimize creation of individual particles in pharmaceutical unit operations such as blending, classification and drying. In studies of compaction of powders into tablets the size, surface area and shape of the particles are properties of importance. Nevretheless, it should be borne in mind that the relation between individual particles and agglomerates differs in the powder and in the tablet due to the disintegration of agglomerates during the tabletting operation.

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