Phosphoric acid mediated depolymerization and decrystallization of cellulose: preparation of low crystallinity cellulose—a new pharmaceutical excipient

S. Wei[a], V. Kumar[b], G.S. Banker[b],*

[a]R.W. Johnson Pharmaceutical Research Institute, Johnson and Johnson Co., P.O. Box 300, Raritan, NJ 08869, USA
[b]Division of Pharmaceutics, College of Pharmacy, The University of Iowa, Iowa City, IA 52242, USA

Abstract

The reactions of cellulose with phosphoric acid under different temperature conditions were investigated to prepare a new class of cellulose excipients which have controlled, low degrees of crystallinity and reduced levels of polymerization. The results showed the depolymerization of cellulose by phosphoric acid to be a first order reaction with rate constant values corresponding to 4.79×10^{-3} and 0.314 per hour at 25 and 55°C (after 1 h pretreatment at 22°C), respectively. Products prepared from reactions at 25, 30, 35, 45, and 55°C for 216, 120, 72, 15, and 4.5 h, respectively, exhibited degrees of polymerization values ranging from 64 to 88. The degree of crystallinity of the products prepared at 25, 30, 35, and 45°C ranged from 32 to 45%, whereas that of the product isolated at 55°C was 80%. The activation energy, calculated using the Arrhenius relationship, was 25.3 kcal/mol. A temperature sequencing method, wherein the cellulose is treated at room temperature (22–25°C) for 1–14 h, and then at 50°C for 2–10.5 h, resulted in the preparation of low crystalline cellulose materials with degree of crystallinity and degree of polymerization values ranging between 19–43% and 45–138, respectively.

1. Introduction

The hydrolysis of cellulose by mineral acids has been extensively investigated to prepare micro- crystalline cellulose (MCC)—the most commonly and widely used direct compression excipient in tabletting (Battista, 1961, 1975; Von Engelbert Graf, 1978). MCC is currently marketed world- wide under the trade names Avicel® (FMC, USA), Emcocel (Edward Mendell, USA), Ex-cel (Cellulose Products of India, India), Indocel-80

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* Corresponding author.

(Neelkanth Chemicals, India), MC NF XV type 101 (Ming Tai, Taiwan), Microcel MC-201 (Trinca Industria e Comercio, Brazil), Unimac MG-100 (Unitika Rayon, Japan), Dynacel (Cellupharm, Sweden), Serva® (Serva Fein-biochimica, Heidelberg, Germany), Sanaq® (Pharma Trans Sanaq AG, Switzerland), and Heweten® (Rettenmaier and Sons, Ellwangen-Holzmuhle, Germany). MCC is characterized by a high degree of crystallinity. The crystallinity values typically range between 55% and 80% (as determined by the powder X-ray diffraction method), depending on the origin of the cellulosic source, processing variables, such as reaction temperature and duration, mechanical agitation of the slurry, and drying conditions (Doelker et al., 1987; Landin et al., 1993a,b).

Low crystallinity celluloses (LCC) are materials that have a substantially reduced degree of crystallinity, typically ranging between 15 and 45%. LCC can be prepared either by mechanical disintegration of the cellulosic source (dry or wet milling) (Blaschek, 1990; Doelker et al., 1987; Voigt and Bornschein, 1987) or from a chemical reaction between cellulose and concentrated mineral acids (e.g. 37–42% concentrated hydrochloric acid at 30–50°C, 65–75% sulfuric acid at 35–45°C for 10 min, and a mixture of hydrochloric and sulfuric acid or phosphoric acid at < 50°C) (Greidinger et al., 1968; International Cellulose Company, 1916). Compared to native and regenerated cellulose, low crystallinity cellulose shows improved dispersibility in water, increased compatibility with materials such as starches, proteins, and lipids, and is useful as an excipient in the preparation of tablets and confectionery products (Sachetto et al., 1982).

The use of phosphoric acid to prepare an amorphous cellulose suitable as a source for glucose, or as a substrate for microbial production of antibiotics and other metabolites, single cell proteins and industrial alcohol, has been investigated by Bellamy and Holub (Bellamy and Holub, 1977). Whitmore and Atalla (Whitmore and Atalla, 1985) used phosphoric acid for the regeneration of cellulose I. Studies show that cellulose swells rapidly in 71–80% phosphoric acid solutions. At higher phosphoric acid concentrations, the disso-

lution of cellulose occurs (Hudson and Cuculo, 1980). Warwicker (Warwicker, 1971) reported that at a phosphoric acid concentration of 81% or less, cellulose undergoes an interfibrillar swelling, whereas at a concentration of 90% the crystallinity of cellulose is affected. The dissolution of cellulose has been reported to be incomplete in solutions containing 81–85% and 92–97% phosphoric acid (Hudson and Cuculo, 1980). Ekenstam et al. (Ekenstam, 1942) and Danilove et al. (Danilove and Gintse, 1956) reported that the dissolution of cellulose in phosphoric acid increases with increasing temperature.

Because phosphoric acid is non-corrosive, non-toxic, and safer to use, (compared to other inorganic mineral acids), its reactions with cellulose were investigated at different temperatures. The objective of the study was the development of a method to prepare controlled low crystallinity cellulose materials and to explore their applications as excipients for pharmaceutical, cosmetic and other related applications. In this paper, the depolymerization kinetics of the cellulose-phosphoric acid reaction system and the preparation and characterization of low crystallinity cellulose, are presented.

2. Materials and methods

2.1. Materials

Cotton linters, in the sheet and pulp forms, were obtained from Southern Cellulose Products, Inc., Chattanooga, TN. Cupriethylenediamine hydroxide (1.0 M solution; cuen) was received from G. Frederick Smith Chemical, Powell, OH. Phosphoric acid (conc. ⩾ 85%) was NF grade, and used as received from Fisher Scientific, Pittsburgh, PA. The Ubbelohde capillary viscometer was from industrial research glassware, Union, NJ.

2.2. Reaction of phosphoric acid with cellulose

(1) Cotton linter (200 g) was suspended in 1000 ml of ⩾ 85% phosphoric acid. The mixture was allowed to react at 25, 30, 35, 45, and 55°C for

different periods of time, with occasional stirring using a glass rod. The cellulose underwent appreciable swelling initially and subsequently dissolved in the acid. The resulting light creamy gel was then poured into water with vigorous stirring. The white precipitate that formed was collected using a Whatman 113 filter paper. The solid obtained was first washed with water until neutrality and then dehydrated using a water-miscible organic solvent, e.g., acetone, isopropanol, n-butanol. The resulting anhydrous powder was either dried at ambient conditions overnight or at 75°C for 4 h. Following drying, the powders were ground to reduce particle size. The dry powder obtained was passed through a No. 120 sieve (125 μm).

(2) Two hundred grams of cotton linter and 1000 ml of 86% phosphoric acid were first reacted at 22°C for 1–14 h and then heated at 50°C for 2–10.5 h. The reaction was terminated by dilution with water and, subsequently, worked-up as described above.

2.3. Characterization methods

2.3.1. Infrared spectroscopy
The Fourier-transform infrared (FT-IR) spectra were recorded as potassium bromide pellets on a Nicolet 5DXC infrared spectrophotometer.

2.3.2. Electron spectroscopy for chemical analysis (ESCA)
ESCA was performed on a Perkin Elmer Model PHI 555 spectrometer, equipped with PHI 555/ ESCA/SAM software for calculating surface composition. The pressure of the analysis chamber was 1×10^{-10} torr.

2.3.3. Degree of polymerization, DP
The degree of polymerization was determined from viscosity, η, measurements at 25 ± 0.5°C using the Ubbelohde capillary viscometer, according to the equation (ASTM, 1965; Craig and Henderson, 1956):

$$DP = 190 \, (\eta)$$

where (η) is the intrinsic viscosity calculated from the plot between (ln $\eta_{rel}/C)_{c \to 0}$ and C or $(\eta_{sp}/C)_{c \to 0}$ and C, where C is the concentration in g/100 ml.

The relative viscosity (η_{rel}) is calculated by dividing the viscosity of the sample by the viscosity of the solvent (Cuen), and η_{sp} is the specific viscosity obtained by subtracting 1 from the relative viscosity value.

The viscosity measurement was performed as follows: a cellulose sample (0.90–1.00 g on a dry weight basis) was weighed and suspended in 25 ml water in a 125 ml Erlenmeyer flask. The suspension was flushed with nitrogen to remove entrapped air from the sample. While nitrogen was being passed, 25 ml of 1.0 M cuen solution was added. Flushing of the suspension with nitrogen was continued for an additional 2 min. The Erlenmeyer flask was then stoppered and shaken with a wrist Action® shaker (Model 75, Burrell, Pittsburgh, PA) at room temperature for 30 min. The resulting cellulose solution was equilibrated at 25 ± 0.5°C. Following equilibration, the Ubbelohde capillary viscometer was filled with the cellulose solution between the marks in the reservoir, and held vertically in the water bath. While closing the side arm, suction was applied to the capillary tube to draw the solution into the upper bulb. The side arm was opened and the efflux time of the solution between the two marks was measured. The same procedure was employed to measure the efflux time of 0.5 M cuen solution (used as a blank). The relative viscosity (η_{rel}) was calculated using the relationship: $\eta_{rel} = $ efflux time$_{(sample)}/$ efflux time$_{(solvent)}$.

2.3.4. Degree of crystallinity
The crystallinity index was determined and computed on a Siemen D500 powder X-ray diffractometer, equipped with a monochromatic CuK$_x$ radiation, and Rigaku V2.4 X-ray diffraction software (Rigaku/USA, Danvers, MA). The sample was scanned over 5–30° 2θ range with a scanning rate of 0.05° 2θ per second. Hydrocellulose, a highly crystalline cellulose, prepared using 2.5 N HCL solution at boiling temperature for 30 min, was used as a 100% crystalline standard. The diffuse halo due to the amorphous regions of the cellulose was subtracted, and the resulting diffraction peaks were integrated and used to calculate the percentage crystallinity (% DC) by the equation (Wei, 1991):

$$DC\% = \frac{(\int I_c \, d\theta)_x}{(\int I_c \, d\theta)_{100s}} \times 100$$

where I_c is the intensity of the diffracted X-ray radiation at an angle θ. Subscripts X and 100s denote the sample and the 100% crystalline standard, respectively.

3. Results and discussion

Cellulose, in the presence of acids, is known to undergo hydrolysis (depolymerization), producing hydrocelluloses, soluble polysaccharides, oligosaccharides, and/or glucose as products (Fan et al., 1987). The extent and the rate of hydrolysis depend on the acid concentration, the reaction temperature, and the treatment duration. Studies show that in dilute acids only the amorphous regions of the cellulose are hydrolyzed, producing small chains of a highly crystalline product (hydrocellulose). In concentrated acids, on the contrary, cellulose undergoes an initial decrystallization/swelling step, followed by its dissolution and hydrolysis. The decrystallization and dissolution of cellulose in acids occur as a result of the formation of cellulose-acid complexes. The hydrolysis mechanism, in general, irrespective of the acid concentrations, involves an initial rapid protonation of the anhydroglycosidic ether oxygen atom (and/or β-D-glucopyranose ring oxygen atom), followed by a charge-transfer step producing a carbonium ion, and subsequently, the slow splitting of the glycosidic bond induced by the addition of a water molecule. Under homogeneous conditions, the depolymerization reaction has been reported to follow first-order kinetics with the rate-limiting step being the splitting of glycosidic bonds (Fan et al., 1987). This can be expressed by the equation:

$$- dDP/dt = kDP$$

Integration and subsequent rearrangement yield:

$$\log DP = \log DP_o - k \, t/2.303$$

where k is the depolymerization rate constant and t is the reaction time.

The results of the hydrolysis of cellulose with phosphoric acid at 25 and 50°C (after 1 h and 14 h pretreatment at 22°C) are depicted in Fig. 1. The linear relationship between $\log DP$ and t shows that the depolymerization of cellulose by phosphoric acid follows first-order reaction kinetics. The rate constant values calculated from the slopes correspond to 4.79×10^{-3} per hour at 25°C and 0.314 per hour at 50°C, indicating about a 65-fold increase in the reaction rate at 55°C compared to that at 25°C. Further evidence for this increase in the depolymerization rates with an increase in temperature was obtained by reacting cellulose with phosphoric acid at 25, 30, 35, 45, and 55°C for 216, 120, 72, 15, and 4.5 h, respectively. All products exhibited degree of polymerization values between 66 and 88.

The activation energy, Ea, of the reaction was calculated using the Arrhenius equation:

$$k = A \, e^{(-Ea/RT)}$$

where k is the rate constant, A is a constant known as the frequency factor, R is the gas constant (1.987 cal/°C), and T is the absolute temperature (°K). Since at a given temperature the time interval, t, is inversely proportional to the rate constant, the Arrhenius equation can be expressed as:
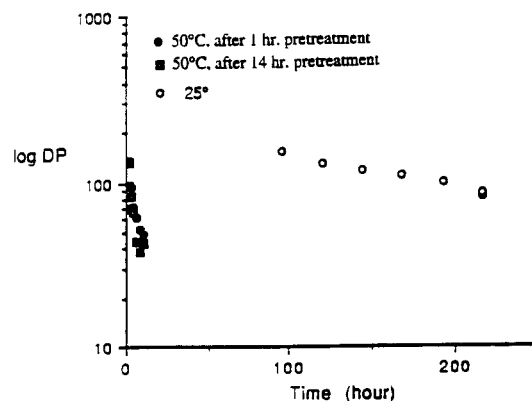
$$1/t = A \, e^{(-Ea/RT)}$$

Fig. 1. Hydrolysis of cellulose with time in phosphoric acid at 25°C and 50°C (following 1 h and 14 h of pretreatment/swelling at 22°C).
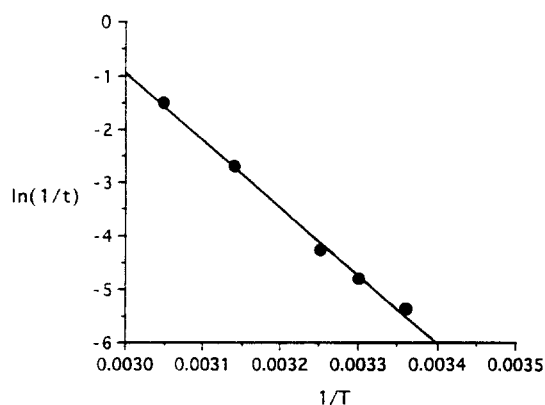
Fig. 2. Arrhenius relationship for cellulose depolymerization

or

$$\ln 1/t = \ln A - Ea/RT$$

The values of $\ln 1/t$ versus $1/T$ for the phosphoric acid reactions are plotted in Fig. 2. The activation energy calculated from the slope corresponds to a value of 25.2 kcal/mol, about 5–10 kcal/mol higher than the values reported for simple hydrolysis reactions (Labuza, 1984). The higher activation energy in the case of cellulose may be attributed to its supramolecular structure, which impedes the penetration of reagent to the reaction sites, and hence, requires more energy.

The degree of crystallinity of cellulose depends on the extent of inter- and intra-chain hydrogen bondings. The powder X-ray diffraction patterns of low crystallinity cellulose, 100% crystalline hydrocellulose, and Avicel® PH-101 are shown in Fig. 3. The reactions at 50°C for 13.5 h (followed by 10.5 h at 22.5°C) and at 55°C for 4.5 h, produced highly crystallinity products (degree of crystallinity values were 78 and 80%, respectively). All other reactions that involved pretreatment (swelling) at room temperature for 1–14 h prior to the hydrolysis reaction at 50°C for different periods of time, yielded products with degree of crystallinity values ranging between 17 and 40% (Fig. 4). The degree of crystallinity of products prepared at 25, 30, 35, and 45°C for 216, 120, 72, 15, and 4.5 h, respectively, were between 32 and 45. These results suggest that at room temperature decrystallization/swelling of the cellulose pre-

cedes the hydrolysis reaction, whereas at elevated temperatures ($\geqslant 50°C$) the hydrolysis of the amorphous regions of cellulose is the predominant reaction. The latter results in the formation of cellulose crystallites, which retard further hydrolysis by the phosphoric acid, and are regenerated when the reaction is quenched with water. The degree of crystallinity of Avicel® PH-101 was determined to be 80%.

The effect of room temperature swelling time on the degree of crystallinity and degree of polymerization is depicted in Figs. 4 and 5, respectively. It is obvious from the data plotted in these figures that there is little difference in either of the two properties after room temperature pretreatment swelling periods of 1 and 14 h. The data in Fig. 4, however, show an increase in the crystallinity of the product, from 14 to 45%, with increasing reaction times at 50°C. The most plausible explanation for this is that as the reaction time increases, the degree of polymerization gradually decreases (Fig. 5), producing progressively shorter chains of cellulose that display relatively stronger interchain hydrogen bonding, and hence, an increase in crystallinity with increasing hydrolysis time.

The yield of LCC ranged between 65 and 95%, decreasing with increasing reaction time. The infrared spectra of all the isolated products were very similar to that of the native cellulose, suggesting no change in the functional groups as a result of the reaction with phosphoric acid. ESCA analysis of LCC showed no peaks in the region 128–146 eV, characteristics of the 2 p electron of phosphorous, ruling out the possibility of the presence of any phosphorous substituted cellulose derivatives in the product.

A variety of chemicals, e.g., zinc chloride, calcium thiocyanate, lithium chloride, ethylenediamine have been extensively used to prepare low crystallinity or amorphous cellulose. However, none of these reagents proved to be advantageous in this study in producing LCC materials with the desired reduced crystallinity and degree of polymerization values. Phosphoric acid is unique in that it serves both as a decrystallization and depolymerization agent. Of the various reactions described in this paper, the temperature sequenc-
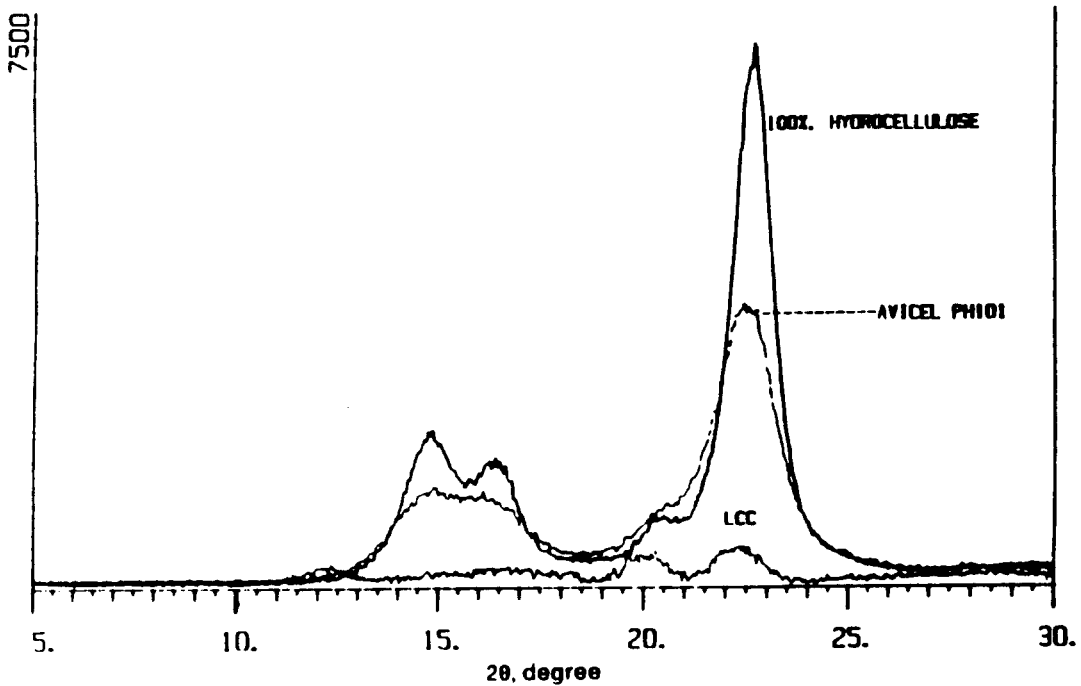
Fig. 3. The powder X-ray diffraction patterns of low crystallinity cellulose, hydrocellulose, and Avicel PH-101.

ing approach, which involved the treatment of cellulose at room temperature for 1 h and then at 50°C for 3 h, is of potential commercial interest as it allows the manufacture of LCC in 2–10.5 h, depending on the degree of polymerization and degree of crystallinity values desired. The room temperature reaction, on the contrary, takes 10–20 times longer to produce the product with the

Fig. 5. Effect of the duration of swelling at room temperature on the hydrolysis of cellulose at 50°C.

same degree of polymerization and crystallinity values.

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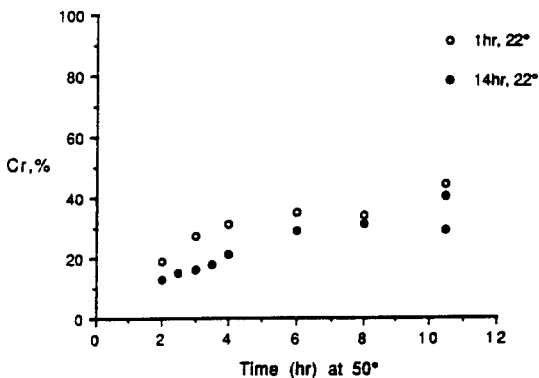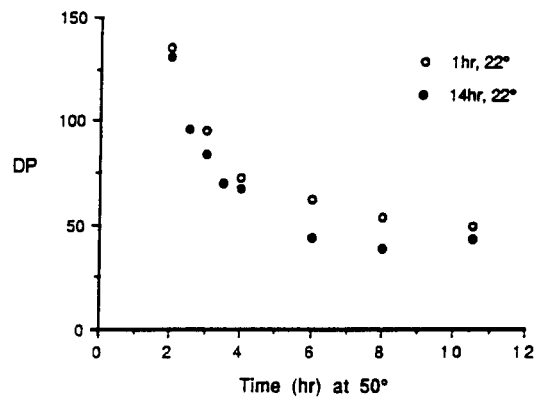

Fig. 4. Effect of the duration of swelling at room temperature on the crystallinity of cellulose isolated after heating at 50°C for different periods of time.

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