

# Effect of the Agitation Rate on the Generation of Low-Crystallinity Cellulose from Phosphoric Acid

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**ABSTRACT:** Changes in the basic powder properties of low-crystallinity powder cellulose (LCPC) as a function of the agitation rate used during its generation from phosphoric acid were investigated. We reacted cotton linter with phosphoric acid (85% w/v) at room temperature for an hour and then at 50°C for 3 h to produce the LCPC solution. The latter was slowly added to water (ca. 10 times the volume of phosphoric acid used) at a constant agitation rate of 700, 2000, or 4000 rpm. LCPC powder thus formed was collected by filtration, washed with water and acetone, and dried at 30°C. Scanning electron micrographs showed the three products to be highly aggregated in structure. The crystallinities of LCPC prepared at 700, 2000, and 4000 rpm were 39, 31, and 24%, respectively. The crystalline component of LCPC produced at 700 and 2000 rpm contained both cellulose II (major component) and cellulose I (minor component), whereas LCPC generated at 4000 rpm belonged to the cellulose II crystal lattice. The porosity and true, bulk, and tap densities of LCPC made at 4000 rpm were 88.55% and 1.435, 0.138, and 0.164 g/cc, respectively. The corresponding values for LCPC made at 700 and 2000 rpm were 60.30% and 1.452, 0.541, and 0.576 g/cc and 54.49% and 1.465, 0.583, and 0.667 g/cc, respectively. Avicel® PH-101, in contrast, had a degree of crystallinity of 89% and a true density value of 1.577 g/cc. The porosity, bulk density, and tap density values were intermediate to those of LCPC made at 4000 rpm and 700 or 2000 rpm. © 2001 John Wiley & Sons, Inc. *J Appl Polym Sci* 82: 2624–2628, 2001

**Key words:** low-crystallinity cellulose; cellulose polymorphs; direct-compression cellulose excipient; microcrystalline cellulose; hydrocellulose; tableting excipient

## INTRODUCTION

Low-crystallinity powder celluloses (LCPCs) are materials that show a substantially reduced degree of crystallinity, typically ranging from 15 to 45%. They can be prepared by either the mechanical disintegration (wet or dry milling) or chemical hydrolysis of cellulose. The latter involves the

treatment of cotton linter with a concentrated mineral acid under controlled conditions (e.g., 30–40% concentrated HCl at 30–50°C<sup>1</sup> or concentrated H<sub>3</sub>PO<sub>4</sub> first at ambient temperature for 1–4 h and then at 50°C for 2.5–10 h<sup>2–4</sup>). The reaction mechanism is widely believed to involve the simultaneous decrystallization and depolymerization of cellulose. Compared with microcrystalline cellulose, which is prepared by the reaction of cellulose with a dilute mineral acid and perhaps is the most commonly and widely used direct-compression excipient today, phosphoric acid-derived LCPC has been shown to exhibit superior tableting properties.<sup>2,3</sup> This has been attributed to the lower degree of crystallin-

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ity, which causes more hydroxyl groups to be available for interactions during compression.

The phosphoric acid-mediated preparation of LCPC from cellulose involves an initial decrystallization and depolymerization reaction followed by a regeneration step.<sup>2-4</sup> Whitmore and Atalla<sup>5</sup> showed that, depending on the age of the phosphoric acid solution, the length of the regeneration time, the temperature of the regeneration medium, and the nature of the regeneration medium, nuclei of different cellulose forms can simultaneously form during cellulose regeneration. They reported that, in water and at room temperature, the regeneration of cellulose results in the formation of cellulose II and amorphous cellulose as predominant polymorphs and cellulose I as a minor component. Structurally, cellulose I contains cellulose chains in a parallel up manner and shows X-ray diffraction (XRD) peaks at  $2\theta = 14.8, 16.3, \text{ and } 22.6^\circ$  due to  $\bar{1}10, 110, \text{ and } 200^6$  (or  $101, 10\bar{1}, \text{ and } 002^7$ ) reflections, respectively. A shoulder at  $2\theta = 20.4^\circ$  due to 012 or 021 reflection has also been noted in certain cellulose I materials.<sup>7,8</sup> In cellulose II, the cellulose chains are arranged in an antiparallel manner, and the corresponding reflections appear at about  $2\theta = 12.0\text{--}12.3, 19.8\text{--}20.0, \text{ and } 21.8\text{--}22.0^\circ$ .<sup>6,7</sup>

Recently, it was reported that the crystalline component of LCPC, prepared from cellulose by treatment with phosphoric acid first at room temperature for an hour and then at  $50^\circ\text{C}$  for 3–4 h, contained both cellulose II and cellulose I polymorphs; the former being the major component.<sup>9</sup> Powdered celluloses (e.g., Solka Floc BW-100) and microcrystalline celluloses (e.g., Avicel® PH-101 and Avicel® PH-102), in contrast, were determined to exclusively contain the cellulose I lattice.<sup>9</sup> In this article, we report the changes in crystallinity, crystal polymorphs, and other basic powder properties of LCPC as a function of the agitation rate during its generation from phosphoric acid. The goal of this study was to identify agitation rates that would allow the manufacture of LCPC with reproducible physicochemical properties for use as a direct-compression excipient in the development of solid, oral-dosage forms.

## EXPERIMENTAL

### Materials

The chief raw materials employed in the preparation of LCPC included cotton linter sheets (grade R270, Southern Cellulose Products, Inc.,

Chattanooga, TN), phosphoric acid (85% w/w, food-grade, lot no. TO 8450-061794, Monsanto Pharmaceutical Ingredients, St. Louis, MO), and acetone USP/NF (United States Pharmacopeia/National Formulary; lot no. 970721, Van Waters and Rogers Inc., Summit, IL). Avicel® PH-101 (lot no. 1430) was received from FMC Corp. (Princeton, NJ).

### Preparation of Low-Crystallinity Cellulose

Cotton linter (500 g) was reacted with 85% (w/v) phosphoric acid (5 L) first for an hour at room temperature and then at  $55^\circ\text{C}$  for 3–4 h, according to the method of Wei.<sup>3</sup> The resulting opalescent, viscous solution was poured slowly into distilled water, about 10 times the volume of the phosphoric acid used in the preparation, in a 10-gallon cylindrical glass tank at a constant agitation rate (700, 2000, or 4000 rpm). The agitation was controlled with a mechanical stirrer, equipped with a stainless steel shaft with a three-blade, 4.5-cm-diameter impeller and set vertically in the tank. The shaft was set vertically. An immediate precipitation of a white solid occurred. The agitation was continued for an hour. The suspension was allowed to stand at room temperature over night and then filtered under vacuum. The solid was washed with distilled water until the filtrate, or the supernatant of the LCPC slurry in water, showed no phosphate ions and had a pH of 5. The former was monitored by the silver nitrate test. To 2 mL of the filtrate or supernatant, a solution of concentrated ammonium hydroxide was added dropwise with constant stirring until the mixture was alkaline, and then two drops of 0.1N silver nitrate were added. A yellow precipitate of silver phosphate was immediately formed if the phosphate ions were in the test solution. We then suspended and stirred the acid-freed precipitate in acetone NF to remove the residual-free water. Typically, we used three such washings with 10 times the volume of the product to ensure the maximum removal of water. The dehydrated cake of LCPC was passed through an oscillating particle sizer (Erweka AR 400, Heusenstamm, Ottostr, Germany) equipped with a 40# sieve (U.S. standard sieve;  $420\text{-}\mu\text{m}$  pore size). The product was air-dried at  $30^\circ\text{C}$  in a convection oven for 4 h.

### Characterization Methods

#### Volatile Content

The amount of volatile content present in the sample was determined by thermogravimetric

analysis. The sample was heated between 25 and 225°C at a rate of 10°C/min on a PerkinElmer series 7 thermal analyzer (Norwalk, CT). The weight loss observed between 25 and 150°C was used to calculate the volatile content.

### **Bulk and Tap Densities**

A known quantity of each sample (25 g) was poured through a funnel into a 100-mL tared graduate cylinder. We then lightly tapped the cylinder twice to collect all the powder sticking on the wall of the cylinder. The volume was then read directly from the cylinder and used to calculate the bulk density. For tap density, we tapped the cylinder 50 times from a height of 2.5 cm on a wooden bench top to attain a constant volume reading from the cylinder.

### **True Density**

The true density of powders, dried at room temperature under vacuum (10 mmHg), was determined with a Quantachrome helium pycnometer (Syosset, NY). The reference volume and cell volume were calibrated before each determination with two solid, stainless steel spheres with a volume of 2.145 cc. The true density was calculated with the equation  $\rho_{\text{true}} = W/V_p$ , where  $\rho_{\text{true}}$ ,  $W$ , and  $V_p$  are the true density, weight of the sample, and true volume of the powder, respectively.

### **Porosity**

The porosity of the test powders was determined with the equation  $\epsilon = (1 - \rho_{\text{tap}}/\rho_{\text{true}}) 100$ , where  $\epsilon$ ,  $\rho_{\text{tap}}$ , and  $\rho_{\text{true}}$  are the porosity, tap density, and true density of the powder, respectively.

### **Powder XRD Analysis**

The XRD measurements on LCPC and Avicel® PH-101 powders were performed on a Philips PW 1710 powder X-ray diffractometer (Mount Vernon, NY) over an angular range of  $2\theta = 10\text{--}30^\circ$  with monochromatic Cu K $\alpha$  X-rays (40 kV, 30 mA,  $\alpha_1 = 1.54060 \text{ \AA}$ ,  $\alpha_2 = 1.54438 \text{ \AA}$ ). The step width was kept at  $2\theta = 0.02^\circ$ , and the time constant was maintained at 1 s per step. The area under the crystalline reflections of the entire diffraction pattern was calculated with Philips APD software, version 2. The crystallinity of samples was determined by integration of the peaks due to crystalline reflections and was expressed as the percentage ratio of the integrated intensities of the sam-

ples to that of hydrocellulose. The latter was prepared from cellulose by treatment with 2.5*N* HCl at the boiling point for 30 min.<sup>10</sup> The use of hydrocellulose as the 100% crystalline reference was validated as reported earlier.<sup>9</sup> The powder weight was kept constant at 400 mg for all the samples in this study.

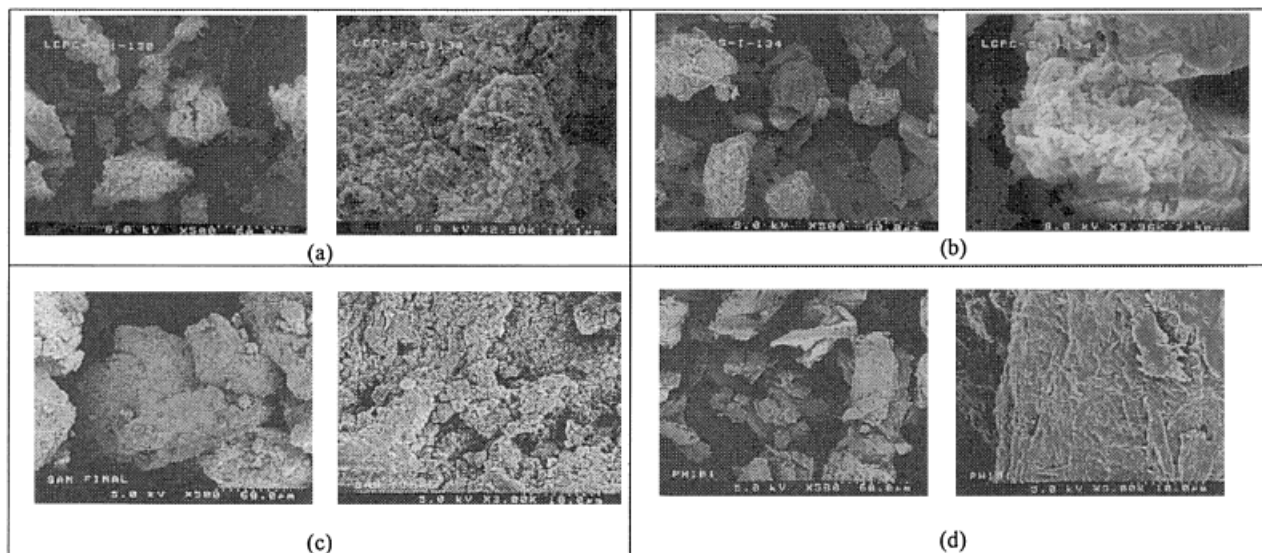
### **Scanning Electron Microscopy (SEM)**

The samples were loaded on a stub covered with liquid graphite and then coated with gold; this was followed by a layer of carbon for 4 min in an Emitech K550 coater (Ashford, Kent, UK). SEM photographs were then taken on a Hitachi S-4000 scanning electron microscope (Tokyo, Japan) with Polaroid films.

## **RESULTS AND DISCUSSION**

SEM photographs of LCPCs prepared at 700, 2000, and 4000 rpm (hereafter called LCPC-700, LCPC-2000, and LCPC-4000) and Avicel® PH-101 are shown in Figure 1. Regardless of the agitation rate used, the three LCPC products showed aggregated structures. The primary particles forming the aggregates of LCPC-4000 appear much smaller than those of LCPC-700 or LCPC-2000 aggregates. Also, the boundaries of the primary particles in LCPC-4000 are more distinct than those in LCPC-700 or LCPC-2000. This difference in the size and morphology of the primary particles suggests that at 4000 rpm the phosphoric acid solution, when added to water, readily disperses as fine droplets and, subsequently, precipitates to produce the LCPC powder. The vigorous agitation at 4000 rpm not only reduces the aggregation of primary particles but also facilitates the breakup of aggregates that have formed. Avicel® PH-101, in contrast, appears as flakes consisting of coalesced microfibrils.

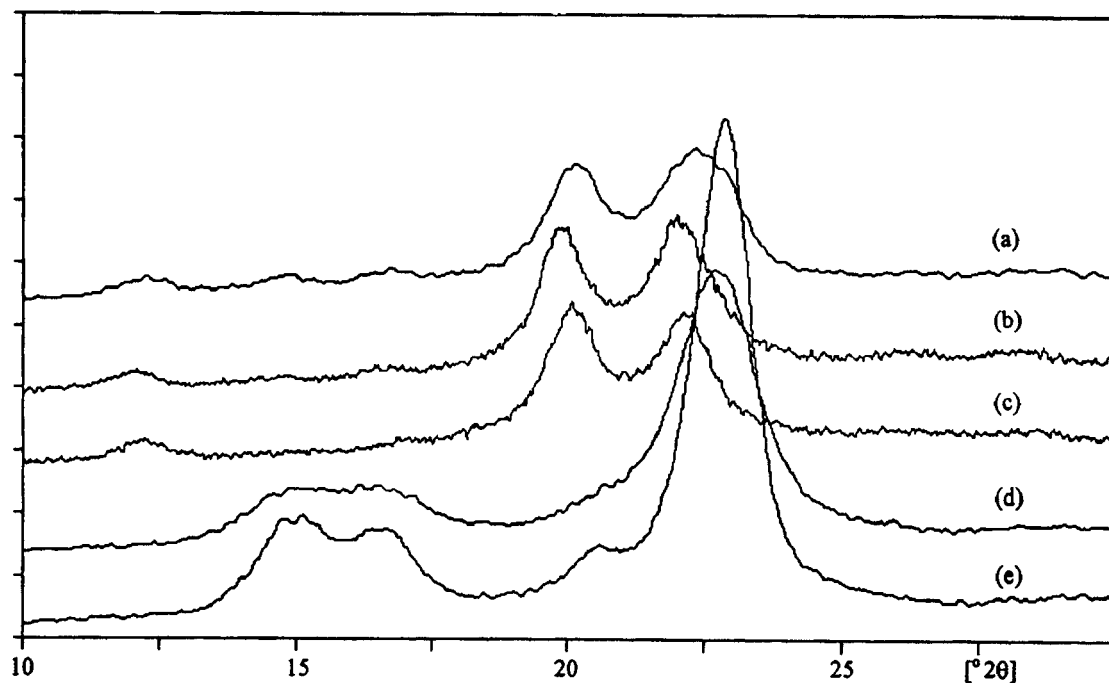
The XRD patterns of LCPC prepared at different agitation rates and of hydrocellulose and Avicel® PH-101 are shown in Figure 2. Avicel® PH-101 [Fig. 2(d)] and hydrocellulose [Fig. 2(e)] show diffraction profiles similar to that of the cellulose I lattice, whereas LCPC-4000 [Fig. 2(c)] exhibits peaks that are characteristic of the cellulose II lattices, as reported earlier.<sup>6</sup> The XRD patterns of LCPC-700 [Fig. 2(a)] and LCPC-2000 [Fig. 2(b)], in contrast, show diffraction peaks due to both cellulose I and cellulose II polymorphs. A comparison of the peak intensities indicates that the



**Figure 1** SEM photographs of (a) LCPC-4000, (b) LCPC-2000, (c) LCPC-700, and (d) Avicel® PH-101.

proportion of cellulose I is slightly higher in LCPC-700 than in LCPC-2000. These results suggest that at lower agitation rates (700 and 2000 rpm), the generation of LCPC produces a mixture of cellulose II and cellulose I, whereas the highest agitation rate used (4000 rpm) favors the formation of cellulose II exclusively.

The degree of crystallinity and other basic powder properties of LCPC and Avicel® PH-101 are presented in Table I. As is evident, the crystallinity of LCPC decreased with increasing agitation rate. It appears that with increasing agitation rate, fewer and fewer molecules of cellulose are able to align in a parallel up or



**Figure 2** Powder X-ray diffraction patterns of (a) LCPC-700, (b) LCPC-2000, (c) LCPC-4000, (d) Avicel® PH-101, and (e) hydrocellulose.

**Table I Physicochemical Properties of Low Crystallinity Cellulose (LCPC) and Avicel PH-101**

Cellulose Excipient	Crystallinity % ( <i>n</i> = 3)	DP	Density (g/cc)			Porosity %	Moisture % ( <i>n</i> = 3)
			True ( <i>n</i> = 3)	Bulk ( <i>n</i> = 6)	Tap ( <i>n</i> = 6)		
LCPC-4000 <sup>a</sup>	23.78 (0.76)	34	1.435 (0.005)	0.138 (0.003)	0.164 (0.003)	88.55	7.11 (0.21)
LCPC-2000 <sup>a</sup>	31.17 (1.76)	35	1.465 (0.003)	0.583 (0.023)	0.667 (0.015)	54.49	7.12 (0.24)
LCPC-700 <sup>a</sup>	39.00 (0.57)	35	1.452 (0.031)	0.541 (0.015)	0.576 (0.008)	60.30	4.52 (0.06)
Avicel® PH 101	72.23 (2.67)	207	1.577 (0.005)	0.315 (0.014)	0.410 (0.010)	74.00	5.20 (0.09)

<sup>a</sup> 700, 2000, and 4000 represent the agitation rate (in r.p.m.) used.

down orientation and form hydrogen bonding to produce the ordered regions. Compared with LCPC, Avicel® PH-101 is a highly crystalline material. This difference in the crystallinities of Avicel® and LCPC is due to the difference in their methods of preparation. The manufacture of Avicel® involves the hydrolysis of amorphous regions of cellulose only, whereas for LCPC, either the decrystallization and hydrolysis of cellulose occur simultaneously or decrystallization precedes depolymerization.

As is evident from the data in Table I, the porosity, bulk density, and tap density of LCPC were little affected when the agitation rate was increased from 700 to 2000 rpm. However, a further increase in the agitation rate to 4000 rpm increased the porosity of LCPC about 1.5–1.7 times, whereas the bulk and tap densities decreased by a factor of 4 compared with the values obtained for LCPC-700 and LCPC-2000. This suggests that the agitation rate of 4000 rpm produces sufficient turbulence in the solution to keep the primary particles constantly moving, thereby preventing aggregation and, consequently, coalescence of particles. The true density values of LCPC-700, LCPC-2000, and LCPC-4000 were nearly the same, suggesting that the increase in the agitation rate during the regeneration step did not degrade LCPC further. Avicel® PH-101, in contrast, exhibited porosity, tap density, and bulk density values that were intermediate to those of LCPC-4000 and LCPC-700 or LCPC-2000.

The leveling-off degree of polymerization (DP) of LCPC was 34–35, whereas that of Avicel® PH-101 was 207. This difference in the DP is attributed to the difference in the manufacture of the two materials. As noted previously, Avicel® PH-101 is reportedly prepared with a dilute mineral acid that hydrolyzes only the amorphous regions of the cellulose source, whereas the preparation of LCPC involves decrystallization and depolymerization.

## CONCLUSION

From the results presented, it can be concluded that the degree of crystallinity of LCPC decreases with an increase in the agitation rate during its generation from phosphoric acid. The porosity, tap density, and bulk density of LCPC were more affected at a high agitation rate (4000 rpm) than at low agitation rates (700 and 2000 rpm). At 4000 rpm, the phosphoric acid solution of LCPC produced a highly porous (and, therefore, less dense) and low-crystallinity material. The crystalline lattice of this material contains the cellulose II lattice exclusively.

Because the nature and extent of hydrogen bonding varies with the crystallinity and crystal polymorphs of cellulose, future studies in this field will deal with investigations of the tableting mechanism(s) (i.e., compaction and compression properties) of LCPC and commercial microcrystalline and powder celluloses.

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