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Compression, Compaction, and Disintegration Properties of Low Crystallinity Celluloses Produced Using Different Agitation Rates During their Regeneration from Phosphoric Acid Solutions

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ABSTRACT The tabletting characteristics of low crystallinity celluloses (LCPC)-LCPC-700, LCPC-2000, and LCPC-4000-prepared using agitation rates of 700, 2000, and 4000 rpm, respectively, during their regeneration from phosphoric acid, were evaluated and compared with those of Avicel PH-102 and Avicel PH-302. The mean deformation pressure values calculated from the linear region of the Athy-Heckel curves indicated LCPC-4000 to be the most ductile material. The area under the Athy-Heckel curve for LCPC-4000 was 330 MPa, whereas LCPC-700 and LCPC-2000 showed a corresponding value similar to that of Avicel PH-102 and Avicel PH-302 (192-232 MPa). The tensile strength of LCPC and Avicel compacts increased linearly with increasing applied pressures. A comparison of the area under the tensile strength-compression pressure curves indicated that LCPC-4000 formed the strongest tablets. The strengths of LCPC-700 and LCPC-2000 compacts, in contrast, were slightly lower than that of Avicel PH-302 and Avicel PH-102, respectively. The compacts of both LCPC-4000 and Avicel PH-102 were intact in water for 6 hours, whereas LCPC-2000 and Avicel PH-302 compacts disintegrated in 4 minutes and 2 minutes, respectively. In conclusion, LCPC-4000 was the most ductile material and exhibited the highest compression and compaction characteristics. The corresponding properties of LCPC-700 and LCPC-2000, in contrast, were comparable to that of Avicel PH-102 or Avicel PH-302.

KeyWords: Low crystallinity cellulose, Microcrystalline cellulose, Direct compression cellulose excipients, Compression and compaction characteristics

INTRODUCTION

Low crystallinity cellulose (LCPC) is a direct compression excipient prepared by reacting cellulose with 85% weight/weight phosphoric acid, first at room temperature for 1 hour, then at 50°C until a viscous opalescent solution is formed. The latter is poured into water to produce a fine powder of LCPC [1-3]. The powder properties of LCPC vary significantly depending on the agitation rate employed during its regeneration from phosphoric acid [4]. The use of a very high agitation rate (4000 rpm) during this step produces LCPC with approximately 85% porosity and an approximately 23% degree of crystallinity. At low agitation rates (700 and 2000 rpm), the products produced were less porous (55%-60%) and exhibited higher degrees of crystallinity (40%-56%). In addition, LCPC generated at 4000 rpm contained the cellulose II lattice exclusively, whereas products made at 700 and 2000 rpm displayed diffraction patterns characteristic of both cellulose I and cellulose II polymorphs. The proportion of cellulose I in the product was shown to increase with decreasing agitation rate.

This article evaluates the compression and compaction characteristics of LCPC products produced using agitation rates of 700, 2000, and 4000 rpm, hereinafter referred to as LCPC-700, LCPC-2000, and LCPC-4000, and those of commercial microcrystalline cellulose products, namely, Avicel PH-102 and Avicel PH-302 (FMC Corporation, Philadelphia, PA). Microcrystalline cellulose (MCC) is the common name used for highly crystalline cellulose aggregates produced by treating a cellulose material with a dilute

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mineral acid, usually hydrochloric acid. MCC is currently regarded as the best direct compression tabletting excipient. It is commercially available in several different grades under various trade names. Studies show that different brands of MCC possess different physicochemical and mechanical properties and hence differ in their performance as a tabletting agent [5-9].

EXPERIMENTAL

Materials

Avicel PH-102 and Avicel PH-302 were received from FMC Corporation. Cotton linter (Grade R270), the starting cellulose source, was obtained from Southern Cellulose Products, Inc (Chattanooga, TN). Phosphoric acid (85% wt/wt; food grade, lot number TO 8450-061794) and acetone USP-NF (lot number 970721) were from Monsanto Pharmaceutical Ingredients (St Louis, MO) and Van Waters and Rogers Inc (Summit, IL), respectively.

LCPC-700, LCPC-2000, and LCPC-4000 (degree of crystallinity 50.42%, 31.17%, and 23.78%, respectively), were prepared on a 500 g scale according to the literature method [2], with minor modifications. Briefly, a mixture of cotton linter sheet, broken into small pieces, and phosphoric acid (taken in a 1:10 wt/vol ratio) was allowed to stand at room temperature for an hour and then heated at 55oC for 3 to 4 hours. The resulting opalescent viscous solution was poured slowly into room temperature distilled water (employed at about 10 times the volume of the phosphoric acid used) at a constant agitation rate of 700, 2000, or 4000 rpm. An immediate precipitation of a white solid occurred. The agitation was continued for an hour and the mixture was then allowed to stand overnight at room temperature. The white solid that settled was collected by filtration and washed first with water to a near-neutral pH and then with acetone. The dehydrated cake of LCPC was passed through an oscillating particle sizer (Erweka AR 400, Heusenstamm, Ottostr 20-22, Germany), equipped with a 40# sieve (US standard sieve; pore size 420 μm), and then dried at 30°C in a convection oven for 4 hours.

Preparation of Compacts

All materials used were fractionated using a Cenco-Meinzer sieve shaker (Central Scientific Co., Chicago, IL). The fraction that contained particles ranging in size between 140 mesh and 200 mesh, corresponding to an average particle size of about 90 μm, was used in the study. Compacts, each weighing about 500 mg, were prepared on a Carver hydraulic press (Fred S. Carver Inc., Menomonee Falls, WI) at different compression pressures, ranging from 8 MPa to 106 MPa, using a 13-mm diameter die and flat-faced punches and a dwell time of 30 seconds.

Characterization of Compacts

The thickness and diameter of the tablets were measured with a screw gauge micrometer that had a 0 to 25 mm scale and was capable of differentiating up to 0.01 mm. The tablet thickness is expressed as averages of 5 measurements made at 5 different points between the 2 surfaces of the compact.

The volume of the compact at a given pressure was calculated according to the equation: $V = \pi r^2 h$, where V is the volume, r is the radius, and h is the thickness of the compact.

The true density of the cellulose excipients was determined using a Quantachrome Model MPY-2 helium displacement pyknometer (Quantachrome Corporation, Syosset, NY). The pyknometer was calibrated before use. All samples were dried at room temperature under reduced pressure for 24 hours before being analyzed.

The apparent density (ρ_{app}) of the compact was calculated from the ratio of the tablet mass to the volume of the compact.

The porosity of the compacts was calculated using the relationship $\varepsilon = (1-\rho_{app}/\rho_{true})$, where ε is the porosity of the compacts, ρ_{app} is the apparent density of the compact, and ρ_{true} is the true density of the particles. The ratio of ρ_{app}/ρ_{true} is a measure of the relative density or the solid fraction of the compact.

The Carr's "percent compressibility" [10] and the Hausner ratio [11] were calculated using the equation $([\rho_{tap}-\rho_{bul}]/\rho_{tap}) \times 100$ and ρ_{tap}/ρ_{bulk}, respectively. The bulk and tap densities were determined as follows: A known quantity of each sample (25 g) was poured through a funnel into a 100-mL tarred graduated cylinder. The cylinder was then lightly tapped 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, the cylinder was tapped from a height of 2.5 cm 50 times on a wooden bench top to attain a constant volume reading from the cylinder.

Athy-Heckel Analysis

Compacts having a 13-mm diameter were prepared as described above at compression forces from 330 lb to 4000 lb, corresponding to the compression pressures of 8 MPa to 106 MPa, respectively. The Athy-Heckel plots were constructed by plotting the natural log of the inverse of the compact porosity against the respective compression pressures. The regression analysis was performed on the linear portion of the curve. The slope values obtained were converted to mean deformation pressures (P_y) using the relationship: P_y = 1/slope. The area under the Athy-Heckel curve (AUHC) was calculated by the trapezoidal method, and used to express the extent of volume reduction (ie, compressibility) that the material had undergone during the entire compression pressure range.

Tensile Strength Measurements

The tensile strength of the compacts was determined using the Qtest I™ (MTS, Cary, NC) universal tester, according to the method developed by Ramsey [12]. The crosshead speed (ie, the rate of load application) was maintained constant at 11 lb per second. The peak load required to cause diametrical splitting of the tablet was then used to calculate the tensile strength according to the equation $\sigma o = 2P/\pi Dt$, where $\sigma 0$ is the maximum radial tensile strength, P is the applied load, D is the diameter of the compact, and t is the compact thickness [13]. The tensile strength values were then plotted against the respective compression pressures. The area under the tensile strength versus compression pressure curves (AUTSC) was calculated by the trapezoidal method. This is a measure of the compactibility of the material (ie, strength of the tablets) [14]. Tensile strength measurements were made on 10 compacts prepared at each compression pressure between 8 MPa and 107 MPa. Thus, the compactibility value reported is an average of areas of 10 tensile strength versus compression pressure curves.

Disintegration Studies

The disintegration test was performed in water at 37°C using an Erweka GmbH apparatus (type 712, Erweka, Offenbach, Germany). The disintegration times reported are averages of 6 determinations.

RESULTS AND DISCUSSION

The selected powder properties of LCPC and Avicel products used in this study are presented in Table 1 [4]. LCPC-4000 had the highest porosity and showed the lowest degree of crystallinity, true density, tap density, and bulk density values. LCPC-700 and LCPC-2000, in contrast, were the densest materials, with degree of crystallinity, true density, and porosity values between those of LCPC-4000 and Avicel PH-102 and Avicel PH-302 products. The viscosity-average molecular weights of LCPC-700, LCPC-2000, and LCPC-4000 were nearly the same, corresponding to a value of 5760. The corresponding value for Avicel PH-102 and Avicel PH-302, in contrast, was 19 764 and 31 428, respectively. The moisture content in the LCPC products varied between 4.5% and 7.0%, about 2 to 3 times higher than that observed for Avicel products. This is attributed to the lower degrees of crystallinity of the LCPC products, which causes more hydroxyl groups to be accessible for interaction with water molecules.

The Hausner ratio [11] and the Carr index [10], which are measures of interparticle friction and the potential powder arch or bridge strength and stability, respectively, have been widely used to estimate the flow properties of powders. According to Wells [15], a Hausner ratio value of less than 1.20 is indicative of

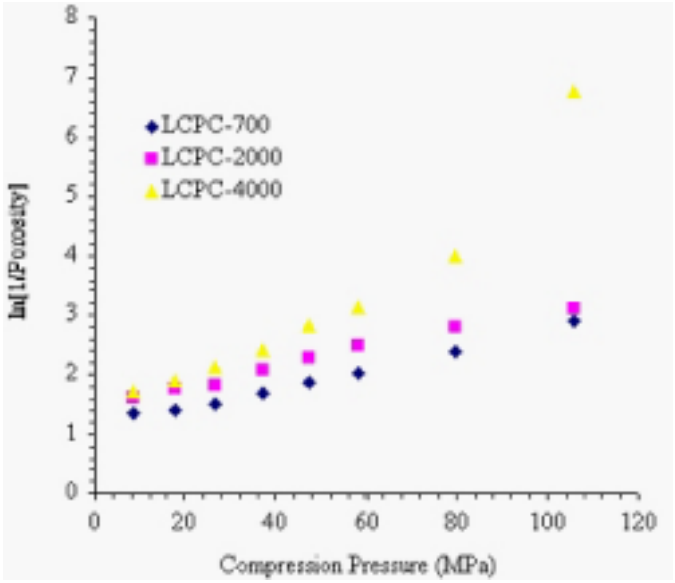
Table 1. Powder Properties of Cellulose Excipients

Product	Crystallinity % (n = 3)	DP	Carr's Value	Hausner Ratio	Density (g/cc)			Porosity	Moisture
					True (n=3)	Bulk (n=6)	Tap (n=6)	%	%(n=3)
LCPC-4000*	23.78 (0.76)	34	15.83	1.19	1.435 (0.005)	0.138 (0.003)	0.164 (0.003)	88.55	7.11 (0.21)
LCPC-2000*	31.17 (1.76)	35	12.59	1.14	1.465 (0.003)	0.583 (0.023)	0.667 (0.015)	54.49	7.12 (0.24)
LCPC-700*	39.00 (0.57)	35	6.08	1.06	1.452 (0.031)	0.541 (0.015)	0.576 (0.008)	60.30	4.52 (0.06)
Avicel PH-102	84.51 (2.75)	194	7.97	1.08	1.526 (0.005)	0.254 (0.014)	0.276 (0.010)	81.93	2.08 (0.08)
Avicel PH-302	74.38 (2.75)	122	16.06	1.19	1.519 (0.004)	0.413 (0.005)	0.492 (0.006)	67.62	3.47 (0.03)

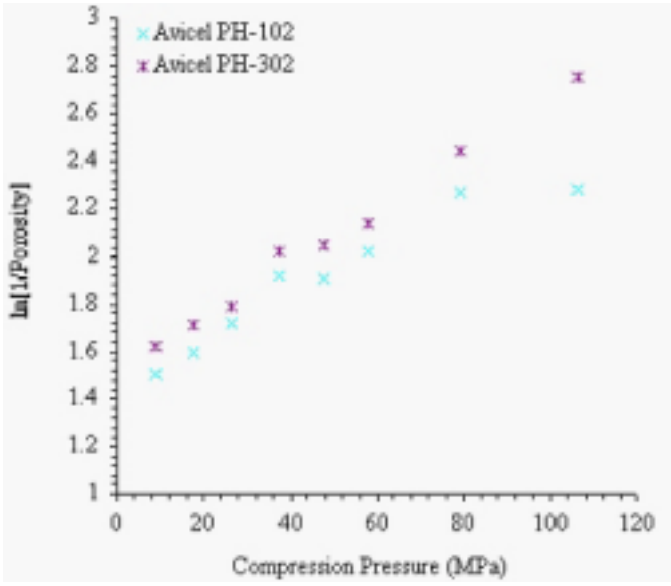
* Data from Kumar V, Kothari SH, Banker GS. Effect of agitation rate on the generation of low crystallinity cellulose from phosphoric acid. J Appl Polym Sci. 2001;in press.

good flowability of the material, whereas a value of 1.5 or higher suggests a poor flow display by the material. The Carr index is also called "percent compressibility." According to Carr [10], a value between 5 and 15, 12 and 16, 18 and 21, and 23 and 28 indicates excellent, good, fair, and poor flow properties of the material, respectively. The Hausner ratio and Carr's index values listed in Table 1 for LCPC and Avicel products used in this study suggest that they all possess good flow properties. These data also indicate that the flow behavior of LCPC-700 and LCPC-4000 is comparable to that of LCPC-102 and Avicel PH-302, respectively, whereas LCPC-2000 possesses flow properties intermediate to those of LCPC and the Avicel products. Among the LCPC products, the Carr index and the Hausner ratio values decreased in the order: LCPC-4000 > LCPC-2000 > LCPC-700. This suggests that the increased agitation rates during the regeneration step from phosphoric acid adversely affected the flow properties of LCPC powders. The relatively higher tap densities of LCPC-700 and LCPC-2000, compared with those of Avicel PH-102 or Avicel PH-302, should be advantageous in tabletting because the volume of die-fill would be correspondingly reduced. This property, plus the good to excellent flow properties of LCPC-700 and LCPC-2000, should also maintain good weight uniformity and content uniformity of the corresponding compressed tablets.

The Athy-Heckel analysis is routinely performed to study the effect of applied pressure on the relative density of a powder bed during compaction and to determine the deformation mechanism of particles forming the compacts [5,16,17]. The Athy-Heckel plots for the LCPC and the Avicel products used in this study are shown in Figure 1. Table 2 lists the compression pressure range over which the regression analysis was performed, the regression analysis results, mean deformation pressure values, and the areas under the Athy-Heckel curves.



1(A)



1(B)

Figure 1. The Athy-Heckel plots for (A) LCPC and (B) Avicel excipients

Table 2. Mechanical Properties of LCPC and Avicel Products

Athy-Heckel Analysis						
Product	**Compression Pressure**	**R^2**	**Slope**	**Mean Deformation Pressure, Py**	**AUHC**	**AUTSC**
	Range* (MPa)			**(MPa)**	**(MPa)**	**(MPa)2**
LCPC-700 (39)	27-106	0.9991	0.0172	58.12	198.90	512.58
LCPC-2000	27-80	0.9970	0.0167	59.88	232.19	668.97
LCPC-4000	27-80	0.9950	0.0353	28.33	330.00	1362.91
Avicel PH-102	48-80	0.9990	0.0114	86.96	191.57	788.37
Avicel PH-302	48-106	0.9958	0.0125	80.00	210.37	565.33

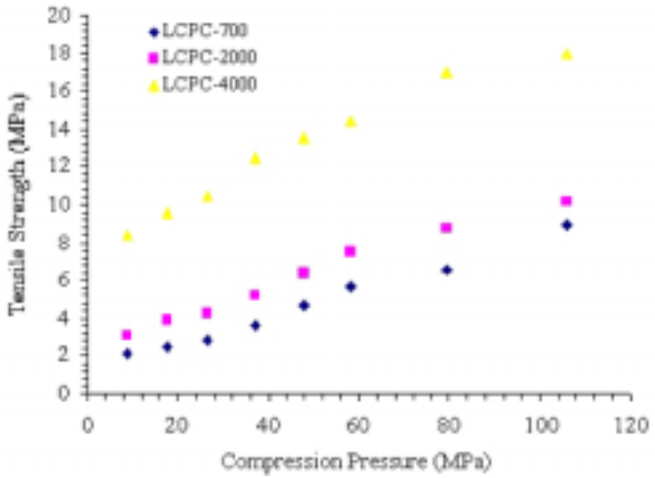
*Used in regression analysis to calculate mean deformation pressures.

R^2 indicates coefficient of determination; AUHC, area under the Athy-Heckel curve; AUTSC, area under the tensile strength versus compression pressure curves.

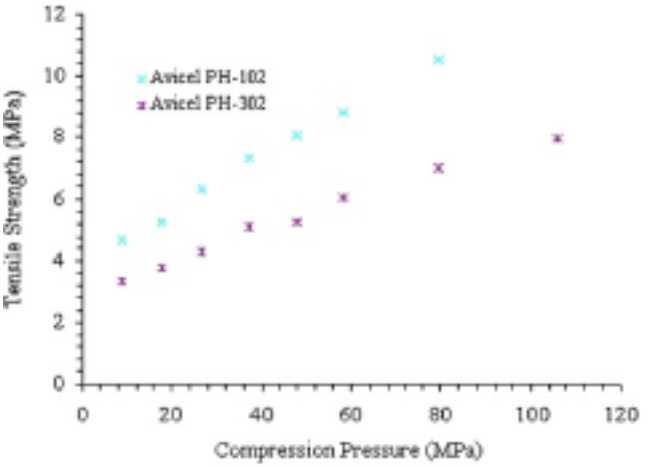
As is evident from Figure 1(A), the Athy-Heckel curves for LCPC-700 and LCPC-2000 were linear over the compression pressure range between 27 MPa and 106 MPa and for LCPC-4000 between 27 MPa and 80 MPa. In the case of Avicel PH-102 and Avicel PH-302 (Figure 1(B)), the Athy-Heckel curves showed 2 linear regions (Avicel PH-102: 8-37 MPa and 47-106 MPa; Avicel PH-302: 8-37 MPa and 47-80 MPa) interrupted by a short plateau (37-47 MPa). The initial region of the Athy-Heckel curve (5-50 MPa) has been used to determine the fragmentation tendencies of the pure substances [18]. A coefficient of determination (R^2) value closed to unity is indicative of plastic deformation, whereas decreasing values suggest fragmentation propensity. Sixsmith [19] and others [20,21] have described that the compression of microcrystalline celluloses lower than 50 MPa corresponds to brittle fracture followed by rebonding by interlocking, hydrogen bonding, or plastic deformation. The R^2 values obtained for the initial linear portion of the Athy-Heckel curves in this study were 0.9907 and 0.9982 for Avicel PH-102 and Avicel PH-302, respectively, suggesting that the former exhibited greater fragmentation. However, because both LCPC and Avicel products exist as aggregates [4], the results suggest that the consolidation of these powders at low compression pressures (below 27 MPa and 37 MPa for LCPC and Avicels, respectively) may have involved both fragmentation of the aggregates as well as plastic deformation of the primary particles.

At high compression pressures (at or above 27 MPa for LCPC and 47 MPa for Avicels), however, plastic deformation of the primary particles contributed predominantly to the formation of compacts. The mean deformation pressure values calculated from the slope of the linear line constructed over the compression pressure range (Table 2) show that, compared to Avicel PH-102 and Avicel PH-302, LCPC products undergo plastic deformation at a low compression pressure. The greater compressibility of LCPC, compared with Avicel PH-102 and Avicel PH-302, is also evident from the AUHC values (Table 2). From the mean deformation pressure and AUHC results, LCPC-4000 was the most ductile material. The ductilities of LCPC-700 and LCPC-2000 were only slightly higher than that of Avicel PH-102 and Avicel PH-302, respectively. The decreasing AUHC values in the order of LCPC-4000 > LCPC-2000 > LCPC-700 also indicate that the LCPC product produced at a higher agitation rate is more compressible than that made using a lower agitation rate.

The relationship between tensile strengths of LCPC and Avicel compacts and the respective compression pressure is shown in Figure 2. As is evident, only LCPC-4000 showed a linear increase in mean tensile strengths over a whole compression pressures range used in this study. Other materials, in contrast, exhibited the linear relationship only up to 80 MPa. At 106 MPa, all materials, except for Avicel PH-102, showed a small increase in tensile strengths. In the case of Avicel PH-102, no change in the tensile strength was noted. The AUTSC values listed in Table 2, however, clearly show that LCPC-4000 formed the strongest compacts, followed by LCPC-2000, and then by LCPC-700. The strengths of Avicel PH-102 and Avicel PH-302 compacts were slightly higher than those of LCPC-2000 and LCPC-700, respectively.



2(A)



2(B)

Figure 2. The relationship between tensile strength and applied pressures for (A) LCPC and (B) Avicel excipients

Table 3. Tensile Strength and Disintegration of LCPC and Avicel Compacts

Product	Solid Fraction	Tensile Strength	Disintegration Time
		(MPa)	(Seconds)
LCPC-700 (39)	0.945	8.98 ± 0.37	-
LCPC-2000	0.915	7.5 ± 0.19	230 ± 4
LCPC-4000	0.968	16.98 ± 0.57	> 21 600
Avicel PH-102	0.897	10.15 ± 0.26	> 21 600
Avicel PH-302	0.914	7.01 ± 0.13	127 ± 7

The tensile strengths and disintegration times of LCPC and Avicel tablets, compressed to a solid fraction value between 0.90 and 0.95, are presented in Table 3. As noted earlier, LCPC-4000 formed the strongest tablets. The strengths of LCPC-700, LCPC-2000, Avicel PH-102, and Avicel PH-302 also followed the same trend, based on the comparison with AUTSC values. Interestingly, the compacts of the LCPC-4000 were intact in water for more than 6 hours, whereas that of LCPC-2000 showed a disintegration time of about 4 minutes. Avicel PH-102, which exhibited a significantly lower tensile strength value, compared with that of LCPC-4000 compacts, also did not disintegrate during the duration of the test. Avicel PH-302 compacts, in contrast, disintegrated in about 2 minutes. These results suggest that LCPC-4000 and Avicel PH-102 are superior binders compared with LCPC-2000 and Avicel PH-302.

CONCLUSIONS

The results presented show that LCPC produced using an agitation rate of 4000 rpm during its regeneration from phosphoric acid is highly ductile and forms strong tablets that do not disintegrate when placed in water for 6 hours. LCPC produced using an agitation rate of 700 rpm or 2000 rpm showed less ductility; their tablets disintegrated in 3 to 4 minutes. The Carr's percent compressibility and the Hausner ratio values of these materials suggested that their flow property is adversely affected by the agitation rate used during the regeneration step. A comparison of the powder properties, compression behavior, and compactibility of these materials with those of Avicel PH-102 and Avicel PH-302 clearly shows LCPC-4000 to be the most superior binder. LCPC-700 and LCPC-2000, in contrast, showed most properties similar to those of Avicel PH-102 and Avicel PH-302. Further work is needed to establish a correlation between various physicochemical parameters of these 2 different classes of excipients and their tabletting properties.

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