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Cross-linked cellulose as a tablet excipient: A binding/disintegrating agent

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Abstract

The properties of a new tablet binding/disintegrating agent, cross-linked cellulose (CLC), were evaluated in comparison with other binding/disintegrating agents widely used in tablet manufacture such as Avicel PH101® and Avicel PH102®, as well as with superdisintegrants known for their high efficiency such as Ac-Di-Sol™ and Explotab®. CLC-C25 was obtained by a simple reaction of cellulose with epichlorohydrin in a strongly basic medium. The granule swelling power, and the rate and amount of water uptake of tablets were determined. The influence of different fillers was evaluated by measuring the disintegration time and the crushing strength of the tablets. The effect of CLC-C25 concentration on the physical properties of direct compressed tablets was also studied. CLC-C25 demonstrated good binding/disintegrating properties. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Cross-linked cellulose; Binder, Disintegrant; Tablet hardness; Disintegration time; Polymer

1. Introduction

In the preparation of a tablet from a drug as a dosage form, pharmaceutical ingredients are required: fillers are added to increase bulk to the formulation, and lubricants, to reduce friction during the tableting process. Some pharmaceutical ingredients require a binder for tableting. This provides the cohesiveness necessary for bonding together ingredient granules under compression. The quantity used must be carefully regulated, since the tablet must disintegrate after administration to liberate the drug. Disintegrants are usually added for the purpose of causing the compressed tablet to break apart when placed in an aqueous medium. Some excipients, such as Avicel PH101® and Avicel PH102®, demonstrate both properties, being disintegrants and binders (Lieberman et al., 1989). For a successful formulation, equilibrium between binder and disintegrant concentrations must be reached for the ingredient granules to be

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easily compressed, to form a tablet and finally disintegrate after reaching an aqueous medium.

The solubility of the filler in a formulation affects both the rate and mechanism of tablet disintegration. Water-soluble fillers tend to dissolve rather than disintegrate, while insoluble fillers produce rapid disintegration. It has been shown that superdisintegrants have a greater effect on disintegration time in an insoluble system than in a soluble or partially soluble system (Bathia et al., 1978; Cartilier et al., 1987; Sheen and Kim, 1989; Johnson et al., 1991).

Cellulose is a polymer of D-glucose in which the individual units are linked by β-glucosidic bonds from the anomeric carbon of one unit to the C-4 hydroxyl of the next unit. It is a linear polysaccharide, the isolated form containing an average of 3000 units per chain, corresponding to an average molecular weight of about 500000. It is a natural polysaccharide, where hydroxyl groups of each glucose have different reactivities: the C-6 OH group (OH^1) is the most reactive (primary carbon), the C-2 OH group is less reactive (OH^2) and the C-3 OH group (OH^3) is the weakest for the 'bent' conformation with reasonable distance which allows the formation of a hydrogen bond between C-3 OH and the neighboring oxygen molecule (Fig. 1) (Champetier, 1933; Walton and Blackwell, 1973; Streitweiser and Heathcok, 1985).

Cross-linked cellulose (CLC) (Fig. 2) was prepared by cellulose treatment with epichlorohydrin in a strongly basic medium at 60–65°C (Encyclopedia of Polymer Science and Engineering, 1985).In this way, two neighboring cellulose chains are attached to form a network which binding and disintegrating properties are a function of the cross-linking degree (CLD). The studied polymer will be hereinafter referred as CLC-C25, where CLC means cross-linked cellulose, C is the type of cellulose used (microcrystalline) and 25 represents the degree of cross-linking expressed as the ratio: g of epichlorohydrin/100 g of cellulose. CLC-C25 was proven to have better disintegrating properties of those of superdisintegrants known for their high efficiency (Ac-Di-Sol™ and Explotab®), and good binding properties in comparaison to Avicel PH101 and Avicel PH102.

This paper presents facts and experimental results on the use of CLC-C25 as a binding/disintegrating agent.

2. Materials and methods

2.1. Materials

Avicel PH101® and Avicel PH102® (FMC Corperation, Avicel sales, Philadelphia, PA), Spray-dried lactose® (Mallinckrodt Chemicals, Toronto), Lactose 100 mesh® (Mallinckrodt), dicalcium phosphate known as Emcompress® (Mendell, New York), cross-linked car-

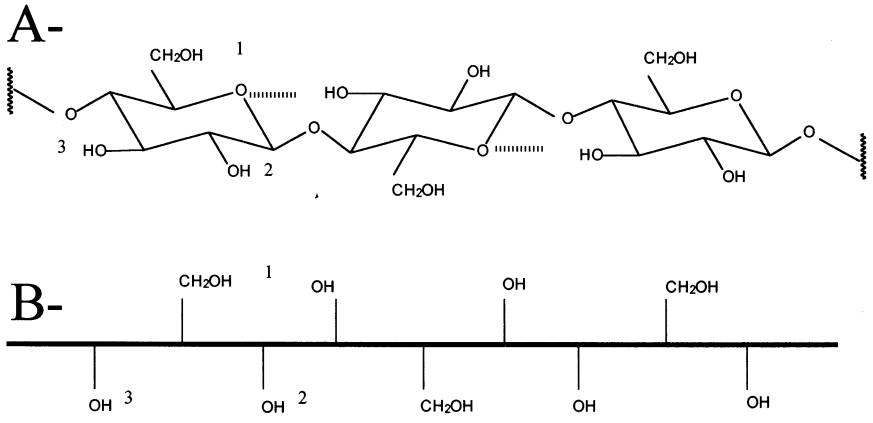

Fig. 1. Cellulose: (A) Conventional 3-D structure (B) Conventional 2-D structure.

boxymethylcellulose, Ac-Di-Sol™, (FMC, Food and Pharmaceutical Products division, Philidelphia, PA), sodium starch glycolate, Explotab® (FMC) magnesium stearate (Sigma, St. Louis, MO), epichlorohydrin (Sigma) and acetaminophen (Mallinckrodt).

2.2. CLC synthesis

20 ml of NaOH 1N was added to 15 g of cellulose. The system was homogenized for 10 min on ice ($T < 5$°C). For the synthesis of CLC-C25, 3.2 ml of epichlorohydrin were added gradually and homogenization continued for another 15 min. The milky solution obtained was then heated gradually to 60–65°C. Once system temperature reached 50°C, the milky solution changed to a yellowish color. The system was heated for 1.5 h at 60–65°C. The CLC-C25 gel was then neutralized with distilled water and washed twice through a Büchner funnel with a solution of 85/15 acetone/water and finally twice more with 100% acetone. The resulting solid gel was exposed overnight to air.

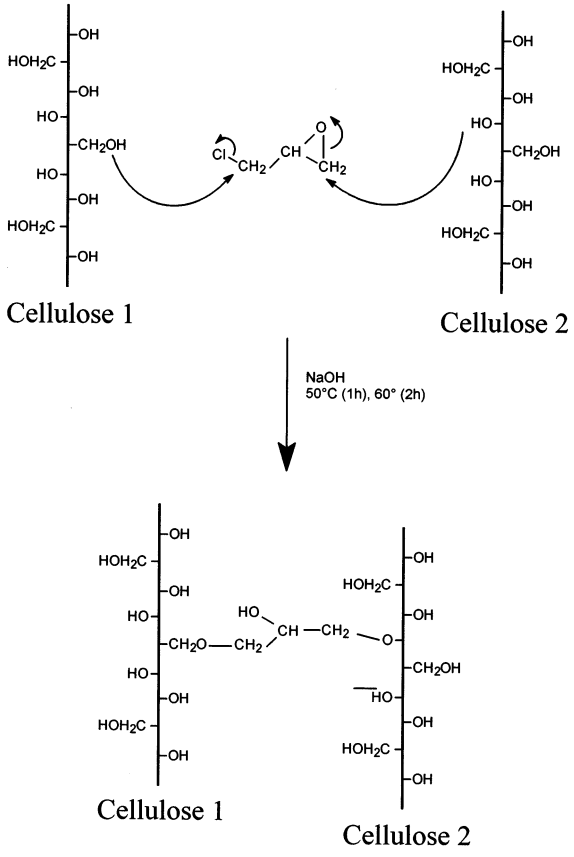

Fig. 2. Synthesis of cross-linked cellulose.

2.3. Surface morphology

The surface morphology of Avicel PH101® and CLC-C25 particles was observed by scanning electron microscopy (SEM-Jeol, JSM 840, Jeol, Tokyo) (Cartilier and Tawashi, 1993).

2.4. Particle size analysis

Granulometric analysis of Avicel PH101® and CLC-C25 particles was done on a light microscope (Nikkon type 104, Labophot 2) in conjunction with a camera system (Dage, Mit 81) connected to a Macintosh Quadra 900 computer system. Image Grabber™ 2.1 (Neotech™) and Ultimage™ / × 1.41 (Graftek) computer programs were used for digitizing and analyzing particle images. Approximately 20 particles were analyzed under different magnifications in methanol 95% for better dispersion.

The following parameters were calculated; (1) projected surface area diameter (μm), which is equal to the diameter of the disk with the same area as the particle; (2) area (μm^2); (3) elongation factor, which is equal to the ratio of max intercept over mean perpendicular intercept. The more elongated the shape of an object, the higher its elongation factor; (4) Heywood circularity factor, which is equal to the ratio of particle diameter over perimeter of the circle with the same area as the particle. The closer is the shape of an object to a disk, the closer the Heywood circularity factor is to 1 (Ultimage™ / × 1.41).

2.5. Swelling capacity of powder bed

A total of 5 g of Avicel PH101®, Avicel PH102® and CLC-C25 powder was dispersed in distilled water and liquid paraffin. The dispersed systems were centrifuged for 3 h at 3500 rpm (Centra-8R Centrifuge, IEC Division of Damon).

Table 1
Tablet composition

Filler	Disintegrant (%)	Binder/disintegrant (%)	Mg stearate
Emcompress®	Explotab® (2, 3, 5, 10, 15 & 20)	—	0.5
	Ac-Di-Sol® (2, 3, 5, 10, 15 & 20)	—	0.5
	—	CLC-C25 (2, 3, 5, 10, 15 & 20)	0.5
	—	Avicel PH101® (2, 3, 5, 10, 15 & 20)	0.5
	—	Avicel PH102® (2, 3, 5, 10, 15 & 20)	0.5
Lactose 100 mesh®	Explotab® (2, 3, 5, 10, 15 & 20)	—	0.5
	Ac-Di-Sol® (2, 3, 5, 10, 15 & 20)	—	0.5
	—	CLC-C25 (2, 3, 5, 10, 15 & 20)	0.5
	—	Avicel PH101® (2, 3, 5, 10, 15 & 20)	0.5
	—	Avicel PH102® (2, 3, 5, 10, 15 & 20)	0.5
Spray-dried lactose®	Explotab® (2, 3, 5, 10, 15 & 20)	—	0.5
	Ac-Di-Sol® (2, 3, 5, 10, 15 & 20)	—	0.5
	—	CLC-C25 (2, 3, 5, 10, 15 & 20)	0.5
	—	Avicel PH101® (2, 3, 5, 10, 15 & 20)	0.5
	—	Avicel PH102®(2, 3, 5, 10, 15 & 20)	0.5

Precipitated volumes of powder (in water and in liquid paraffin) were recorded and the ratio of $V_{H_2O})/V_{paraffine}$ was defined as the swelling capacity of the powder bed (Cartilier et al., 1987). A single measurement was taken for each sample.

2.6. Preparation of tablets

Different lots of tablets were prepared with different fillers, as described in Table 1, on a hydraulic 30-ton press (C-30 Research & Industrial Instruments, London).

Tablets weighing 500 mg each could include in their composition a filler as Emcompress®, Spray-dried lactose®, or Lactose 100 mesh®, various concentrations of binder/disintegrant (Avicel PH101® and Avicel PH102®), or different disintegrating agents (Ac-Di-Sol™ or Explotab®), and 0.5% of magnesium stearate used as a lubricant.

2.7. Water penetration into tablets

The method adopted to measure the rate of water penetration into tablets was similar to that described by several investigators (Van Kamp et al., 1986; Sheen and Kim, 1989; Pourkavoos and Peck, 1993). The apparatus consisted of a fritted glass disk filter (Pyrex, n° 36060, 15 ml, ASTM 40–60) connected to a 2 ml pipette (0.01 ml divisions) via tygon tubing. The filter and the pipette were in a vertical position. The assembly was filled with distilled water and adjusted to zero reading on the pipette. The tablet was placed in direct contact with the moist fritted glass disk, so water could draw into the tablet through it. Water uptake was recorded as the change in water level in the pipette versus time at room temperature. Three measurements were taken for each excipient. Tablets weighing 500 mg each, compressed on a hydraulic press at 2 ton/cm^2 compression force, were studied. They contained 100% of the excipients studied, CLC-C25, Avicel PH101® and Avicel PH102®.

2.8. Disintegration of tablets

Disintegrating time was measured in distilled water at 37 ± 1°C, pH 6.5, according to the method described by the US Pharmacopoeia USP XXIII〈2040〉Disintegration and Dissolution of Nutritional Supplements, using a tablet disintegration tester apparatus (Vanderkamp Tablet Disintegration Tester, Van-Kel Industries , NJ). The tablets were considered completely disintegrated

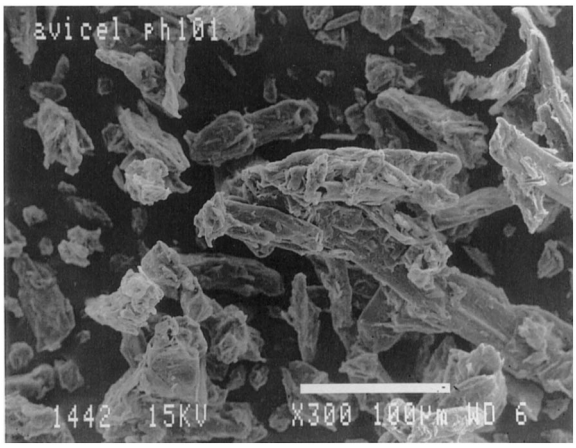

Fig. 3. Photomicrograph of Avicel PH101® (× 300).

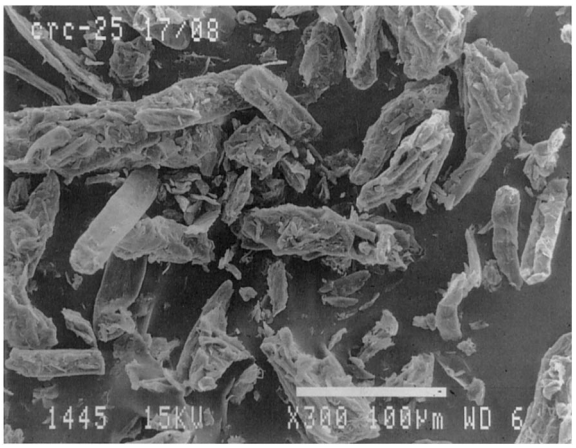

Fig. 4. Photomicrograph of CLC-C25 (× 300).

when all particles passed through the wire mesh; tablets with a surface erosion disintegration pattern retained their shape and only reduced their size with time.

Three measurements were taken for each tablet formulation. Mean values and standard deviations were calculated.

2.9. Tablets hardness

Crushing strength of the tablets was estimated on the Amtrex Schleuniger-4M tablet hardness tester (Vector Corporation, Iowa). Three tablets from each formulation were used in each determination and the mean values expressed in kg force.

3. Results and discussion

3.1. Surface morphology

According to scanning electron photomicrographs, Avicel PH101® consisted of relatively large and iregular particles, among which were numerous smaller more regularly shaped particles (Fig. 3). The structure of CLC-C25 particles consisted mainly of large and roughly more elongated particles, among which were fewer small particles (Fig. 4).

3.2. Particle size analysis

Table 2 gives the parameters related to the size and shape of cellulose particles before (Avicel PH101®) and after (CLC-C25) the cross-linking reaction. Because cellulose chains cannot realign themselves when cross-linked, the chains extensibility of cross-linked cellulose is reduced. This is generally observed as an increase in the elongation factor since cross-linked cellulose chains are brought closer to each other in a parallel way. As seen on the scanning electron photomicrographs, CLC-C25 particles are more elongated and have a bigger projected surface area diameter which is equal to the diameter of the disk with the same area as the particle. This leads to an increase in the Heywood factor which describes the circularity of the particle: the closer the shape of an object to a disk, the closer the Heywood factor is to 1.

3.3. Swelling capacity of powder bed by water penetration

According to Table 3, the results obtained show that Avicel PH101®, Avicel PH102® and CLC-C25 promoted no swelling since their swelling capacity ratio was approximately equal to 1. This proves the fact that CLC-C25 does

not disintegrate the tablet by swelling mecanism but by adsorption of water molecules, filling the void space and exercing an opposite force to those keeping the chains together.

3.4. Water uptake of tablets

Water uptake by Avicel PH101®, Avicel PH102® and CLC-C25 is presented in Table 3. Avicel PH101® and CLC-C25 had approximately the same rate of water penetration. One can assume that the density of the powder affected the water penetration rate, i.e. by the presence of fine particles and porosity of the tablet (Wan and Choong, 1986).

3.5. Disintegrating properties

The results of the disintegration study are shown in Figs. 5–7. According to these data, CLC-C25 appears to be an interesting disintegrant. Its disintegrating properties are compared to those of superdisintegrants, without being affected by the solubility of the filler used in the formulation, as in the case of the superdisintegrants.Tablets containing Emcompress® as unsoluble filler (Fig. 5) clearly proved the high efficiency of CLC-C25 as a disintegrant used at levels 10–20%, with an approximate disintegration time three to five times less than those of Explotab® and Ac-Di-Sol™ (Table 4). Fig. 5 also shows that an increase in the studied excipients concentration, increases the disintegration time except for CLC-C25, where at levels 10–20% it disintegrates the tablets three to five times faster than the studied disintegrants.

Tablets containing Lactose 100 mesh® as soluble filler also proved the high ability of CLC-C25 as a disintegrant used at levels 10–20% when compared to the superdisintegrants Explotab® and Ac-Di-Sol™, and to the binding/disintegrating agents Avicel PH101® and Avicel PH102® (Fig. 6). Lactose 100 mesh® tablets show the same effect of the excipient concentration on the disintegration time as in Emcompress® tablets. On the other hand, Lactose 100 mesh® tablets took longer to disintegrate than Emcompress® tablets. One can deduce the effect of the filler solubility on the disintegration time of the tablet: the more soluble is the filler, the longer is the disintegration of the tablet.

Tablets containing Spray-dried lactose® as highly soluble filler show a significant increase in disintegration time (Fig. 7). Although it takes twice the time for CLC-C25 to disintegrate Spray-dried lactose® tablets compared to the superdisintegrants Explotab® and Ac-Di-Sol™, CLC-C25 can still be considered an excellent disintegrant (Table 4).

A comparison of Figs. 5–7 illustrates that tablets containing soluble fillers, such as Lactose 100 mesh®, and Spray-dried lactose® take longer

Table 2
Particle size analysis parameters (magnification × 40)

Excipient	Diameter (μm)	Area $\times 10^2$ (μm^2)	Elongation	Heywood factor $\times 10^{-1}$
Avicel PH101®	45 ± 9	22.0 ± 7.9	2.8 ± 0.2	12.5 ± 0.6
CLC-C25	50 ± 6	20.7 ± 4.3	3.6 ± 0.3	17.9 ± 1.9

Table 3
Swelling and water uptake of excipients

Excipient	Swelling capacity $V_{H_2O}/V_{paraffin}$	Initial water uptake[1] $\times 10^{-3}$ (ml/s) W_i	Saturation volume (ml) S_v
Avicel PH101®	0.95	5.9 ± 0.4	0.40 ± 0.01
Avicel PH102®	0.95	1.8 ± 0.1	0.27 ± 0.01
CLC-C25	0.92	3.5 ± 0.2	0.44 ± 0.01

[1] Initial water uptake rate is the slope of the linear part of volume uptake (ml) versus time (s).

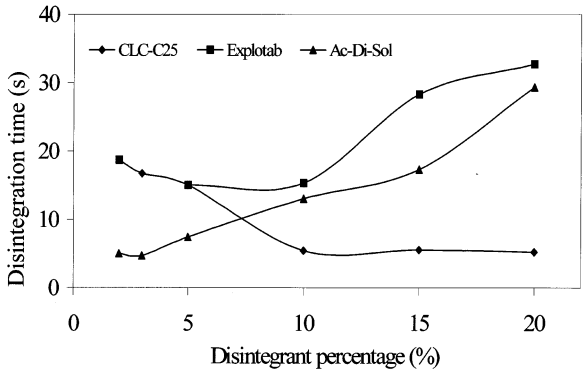

Fig. 5. Disintegration test for tablets containing Emcompress® as a filler.

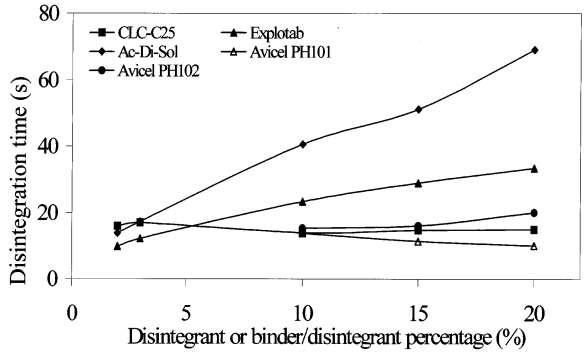

Fig. 6. Disintegration test for tablets containing Lactose 100 mesh® as a filler.

to disintegrate. Knowing that Emcompress® is insoluble in water, therefore, the matrix can be easily and quickly broken up with no increase in the void space, allowing the disintegrant to absorb water fast into the tablet, thus speeding up the disintegration process. As for Spray-dried lactose®, it dissolves faster than Lactose 100 mesh®, leading to a disintegration time of tablets in min. Since lactose is water-soluble, it dissolves and increases the void space of the tablet, then it becomes more difficult for the disintegrant to push against the insoluble remaining matrix; but CLC-C25 draws more water to saturate the increased void space, in order to exert the necessary pressure to brake apart the granules, thus increasing tablet disintegration time.

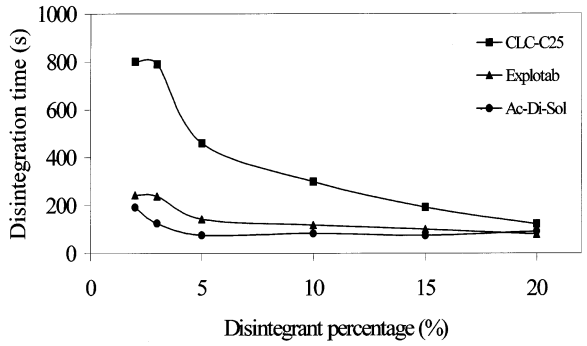

Fig. 7. Disintegration test for tablets containing Spray-dried lactose® as a filler.

The mechanism of disintegration consequently appears to be governed first by the capillarity, then by the mechanical phenomenon, the breaking up of interparticulate bonds.

In other terms, tablet disintegration depends on solubility of the filler and/or any formulated ingredient as well as the water uptake of the disintegrating agent.

To observe this phenomenon, we studied the disintegration of tablets containing Emcompress® as insoluble filler with various percentages of diltiazem HCl salt as a soluble drug (Fig. 8). Raising the concentration of the soluble drug increased disintegration time by increasing the void space in the tablet so that more water volume was required to fulfill this function.

3.6. Binding properties

The results shown in Figs. 9–11 and Table 5 prove that CLC-C25 can be used as an excellent tablet binder.

Hardness of the tablets containing Emcompress® as insoluble filler increased when excipient concentration increased (10–20%); CLC-C25 tablets were the hardest when used at levels 10–20% compared to Avicel PH101® and Avicel PH102® while tablet hardness with Explotab® and Ac-Di-Sol™ decreased when their concentration increased (Fig. 9).

Tablets containing Lactose 100 mesh® as soluble filler also showed the efficiency of CLC-C25 as a binder (Fig. 10). CLC-C25 tablets were the hardest.

Table 4
Disintegration test for tablets containing a filler, various percentages of disintegrant or binder/disintegrant and 0.5% of magnesium stearate

Filler	Disintegrant (%)	Disintegration time (s)				
		CLC-C25	Explotab®	Ac-Di-Sol™	Avicel PH101®	Avicel PH102®
Emcompress®	2	18.7 ± 0.7 Agg.	18.7 ± 0.7	5.0 ± 0.1	—	—
	3	16.7 ± 0.7 Agg.	10.3 ± 0.3	4.7 ± 0.3	—	—
	5	15.0 ± 0.6	15.0 ± 0.9	7.4 ± 0.2	266 ± 8 Agg.	>1200
	10	5.4 ± 0.2	15.3 ± 0.3	13.0 ± 0.9	177 ± 3 Agg.	>1200
	15	5.5 ± 0.2	28.3 ± 1.9	17.3 ± 1.2	121 ± 1 Agg.	>1200
	20	5.2 ± 0.3	32.7 ± 1.8	29.3 ± 0.3	72 ± 6 Agg.	>1200
Lactose 100 mesh®	2	15.9 ± 0.2	9.8 ± 0.1	13.8 ± 0.2	—	—
	3	16.9 ± 0.5	12.2 ± 0.2	17.2 ± 0.8	—	—
	5	16.1 ± 0.1	15.6 ± 0.7	24.8 ± 0.9	16.0 ± 0.5	39.7 ± 0.3
	10	13.9 ± 0.4	23.3 ± 0.9	40.5 ± 1.6	13.7 ± 1.2	15.3 ± 0.7
	15	14.6 ± 0.2	28.9 ± 0.9	51.1 ± 1.6	11.3 ± 0.3	16.0 ± 0.5
	20	14.9 ± 0.2	33.3 ± 0.7	69.0 ± 2.4	10.0 ± 0.5	20.0 ± 0.9
Spray-dried lactose®	2	800 ± 29	243 ± 7	192 ± 6	—	—
	3	790 ± 22	238 ± 3	125 ± 12	—	—
	5	460 ± 16	142 ± 6	75 ± 8	>1080	>1200
	10	299 ± 14	117 ± 9	83 ± 6	>1080	>1200
	15	192 ± 5	100 ± 6	74 ± 4	>1080	>1200
	20	122 ± 9	80 ± 2	92 ± 3	>1080	>1200

Tablets containing Spray-dried lactose® as highly soluble filler were the hardest. As seen in Fig. 11, CLC-C25 tablets were as hard as Avicel PH101® tablets. The hardness of Avicel PH102® tablets was somehow stable. Explotab® and Ac-Di-Sol™ tablets presented a slight decrease in the crushing strength as their concentration increases.

Tablet hardness was function of the filler morphology. Lactose 100 mesh® is consisted of large and regularly shaped particles, but Spray-dried lactose® particles are mainly large and roughly spherical porous agglomerates. Tablets made with the last filler are the hardest, but CLC-C25 powder seemed to be (independent of the type of the filler used) even better binding material than microcrystalline cellulose PH101 and PH102, which itself has been recognized as a superior binding agents for direct compression.

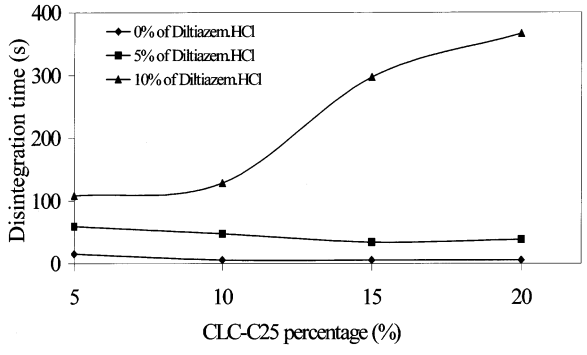

Fig. 8. Effect of a soluble drug, Diltiazem HCl, on Emcompress® tablet disintegration.

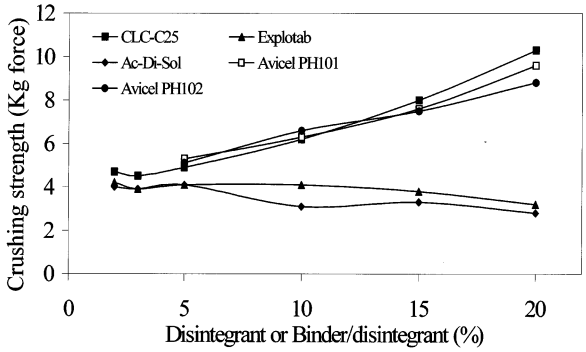

Fig. 9. Hardness test for tablets containing Emcompress® as a filler.

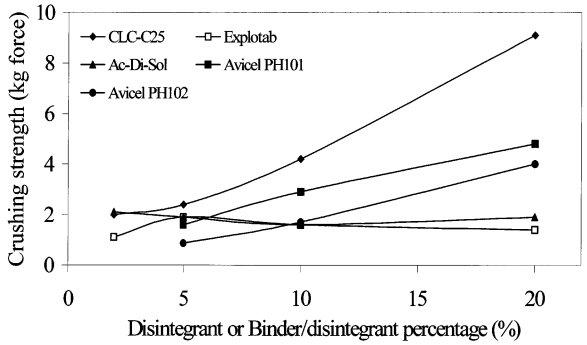

Fig. 10. Hardness test for tablets containing Lactose 100 mesh® as a filler.

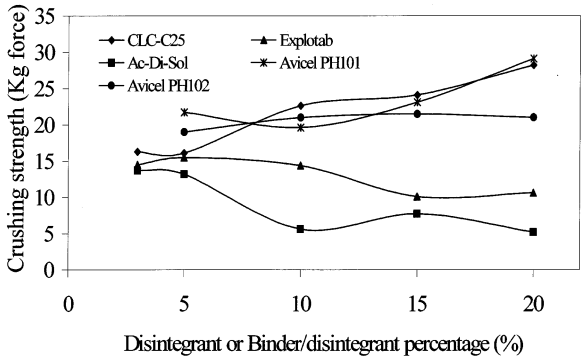

Fig. 11. Hardness test for tablets containing Spray-dried lactose® as a filler.

4. Conclusion

CLC-C25, a new tablet excipient, is essentially water insoluble, but is highly absorbent and provides excellent disintegration and binding properties when used in tablets at levels 10–20%. The mechanism of disintegration appears to be governed first by the capillarity, then by the mechanical phenomenon, the breaking up of interparticulate bonds.

CLC-C25 will make formulation simpler by introducing one double-function excipient instead of two with less probability of incompatibility of the formulative ingredients.

Acknowledgements

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Table 5
Hardness test for tablets containing a filler, various percentages of disintegrant or binder/disintegrant and 0.5% of magnesium stearate

Filler	Disintegrant (%)	Crushing strength (kg force)				
		CLC-C25	Explotab®	Ac-Di-Sol™	Avicel PH101®	Avicel PH102®
Emcompress®	2	4.7 ± 0.1	4.2 ± 0.1	4.3 ± 0.1	—	—
	3	4.5 ± 0.1	3.9 ± 0.1	3.9 ± 0.1	—	—
	5	4.9 ± 0.1	4.1 ± 0.1	4.1 ± 0.1	5.3 ± 0.1	5.1 ± 0.1
	10	6.2 ± 0.3	4.1 ± 0.2	3.1 ± 0.1	6.3 ± 0.1	6.6 ± 0.4
	15	8.0 ± 0.4	3.8 ± 0.3	3.3 ± 0.1	7.6 ± 0.3	7.5 ± 0.1
	20	10.3 ± 0.1	3.2 ± 0.1	2.8 ± 0.1	9.6 ± 0.1	8.8 ± 0.1
Lactose 100 mesh®	2	2.0 ± 0.1	1.1 ± 0.1	2.1 ± 0.4	—	—
	3	2.1 ± 0.1	1.5 ± 0.1	1.2 ± 0.2	—	—
	5	2.4 ± 0.6	1.9 ± 0.4	1.9 ± 0.1	1.6 ± 0.3	0.9 ± 0.1
	10	4.2 ± 0.1	1.6 ± 0.4	1.6 ± 0.1	2.9 ± 0.3	1.7 ± 0.3
	15	6.6 ± 0.5	1.8 ± 0.3	2.2 ± 0.1	3.8 ± 0.1	3.1 ± 0.1
	20	9.1 ± 0.3	1.4 ± 0.1	1.9 ± 0.2	4.8 ± 0.1	4.0 ± 0.1
Spray-dried lactose®	2	21.9 ± 0.9	18.0 ± 0.5	11.8 ± 0.2	—	—
	3	16.3 ± 0.6	14.5 ± 0.3	13.7 ± 0.6	—	—
	5	16.1 ± 2.1	15.5 ± 0.3	13.2 ± 0.2	21.7 ± 0.8	19.0 ± 0.3
	10	22.6 ± 0.2	14.4 ± 0.4	5.6 ± 0.1	19.6 ± 0.8	21.0 ± 0.6
	15	24.1 ± 0.6	10.1 ± 0.3	7.7 ± 0.9	23.1 ± 0.4	21.5 ± 0.6
	20	28.2 ± 0.7	10.6 ± 0.3	5.2 ± 0.4	29.1 ± 0.4	21.0 ± 0.3

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