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Evaluation of the disintegration properties of microcrystalline cellulose II and commercial disintegrants

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This study was conducted to assess the disintegration properties of cellulose II excipients named as spray-dried cellulose II (SDCII) and non spray-dried cellulose II (MCCII) in comparison with commercial disintegrants. Swelling and water sorption characteristics were determined by conventional methods. The swelling values, water uptake and percentage of compact volume expansion all suggested that SDCII and MCCII compacts disintegrate by a wicking mechanism similar to that of Polyplasdone-XL, whereas a swelling mechanism dominates for Primojel and Ac-Di-Sol. With commercial binders, SDCII, MCCII and Polyplasdone-XL produced strong, but fast disintegrating tablets. At high levels, their performance as a disintegrant was superior compared to Primojel and Ac-Di-Sol. Disintegration times of the pure excipients revealed SDCII and MCCII to be comparable to Polyplasdone-XL, but faster than Primojel and Ac-Di-Sol. Ibuprofen tablets prepared using disintegrants at all levels released 80% of the drug within 60 min. SDCII and MCCII offer potential for use as a disintegrant in the design and development of solid dosage forms.

1. Introduction

Disintegrants are agents that promote disintegration of tablets into primary particles when placed in an aqueous environment. The selection of a disintegrant is important, especially for poorly soluble drugs, as the tablet disintegration could determine drug availability for dissolution and, subsequently, absorption (Kottke and Rudnic 2002; Shangraw et al. 1980; Niazi 2002).

Traditionally, starch and free carboxymethylcellulose have been used as disintegrants. In the 1980 s, new disintegrants, based on crosslinked sodium carboxymethylcellulose (Ac-Di-Sol), sodium starch glycolate (Primojel), and polyvinyl pyrrolidone (Polyplasdone-XL), became commercially available. These agents, commonly called superdisintegrants, trigger compact disintegration within few seconds of coming in contact with an aqueous environment and, hence, are ideally suited to formulate compacts to deliver drugs in the upper part of the gastrointestinal (GI) tract preferably, in the stomach (Bhargara et al. 1991; Massimo et al. 2000). The mechanisms by which these superdisintegrants appear to work involve water uptake through wicking, heat of wetting, shape deformation, swelling, and/or particle repulsion (Zhao and Ausburger 2005).

Microcrystalline cellulose II (MCCII) as obtained by mercerization of cotton linter followed by regeneration with ethanol and further washing was introduced as a new excipient for direct compression and named as UICEL (Kumar et al. 2002). It is denser, but less crystalline and ductile than Avicel PH-102. MCCII can also be obtained from Avicel PH-102 rendering a powder with a lower porosity, higher elastic recovery, better flow and fast disintegration (Reus et al. 2004). Compacts made from this material and hydrochlorothiazide or ibuprofen showed faster release than compacts formulated with Avicel PH-102 (Reus and Kumar 2006). Further, spray drying of MCCII produced from cotton linters rendered a product denominated as SDCII with better flow due to the formation of rounded and semispherical particles (Rojas and Kumar 2011). Studies demonstrated that independent of the manufacturing process, MCCII always shows a low degree of polymerization, fast disintegration and less compressibility than Avicel products (Rojas et al. 2011). For all the above reasons, it is worthwhile to study the superior disintegration properties of MCCII as produced or its spray-dried form and assess their performance in formulations with other excipients (USP/NF 2009). In this study, we investigated the disintegration properties of MCCII and compared these results with those of commercially available superdisintegrants, such as, Ac-Di-Sol, Primojel and Polyplasdone-XL.

2. Investigations, results and discussion

2.1. Powder properties

Figure. 1 shows the morphological features of the materials. SDCII was composed of oblong, rounded and smooth particles, while MCCII consisted of fibrous particles with smooth striated surface and truncated ends. Polyplasdone-XL was formed by highly porous and irregularly-shaped particles. A more detailed image of the pores shows an intricate fused net-like shape resembling a sponge. Primojel is formed primary by spherical and semispherical particles and its surface is partially covered with tiny clusters. Since Ac-Di-Sol is a cellulose derivative, it also shows a fibrous shape similar to that shown by the cellulose II

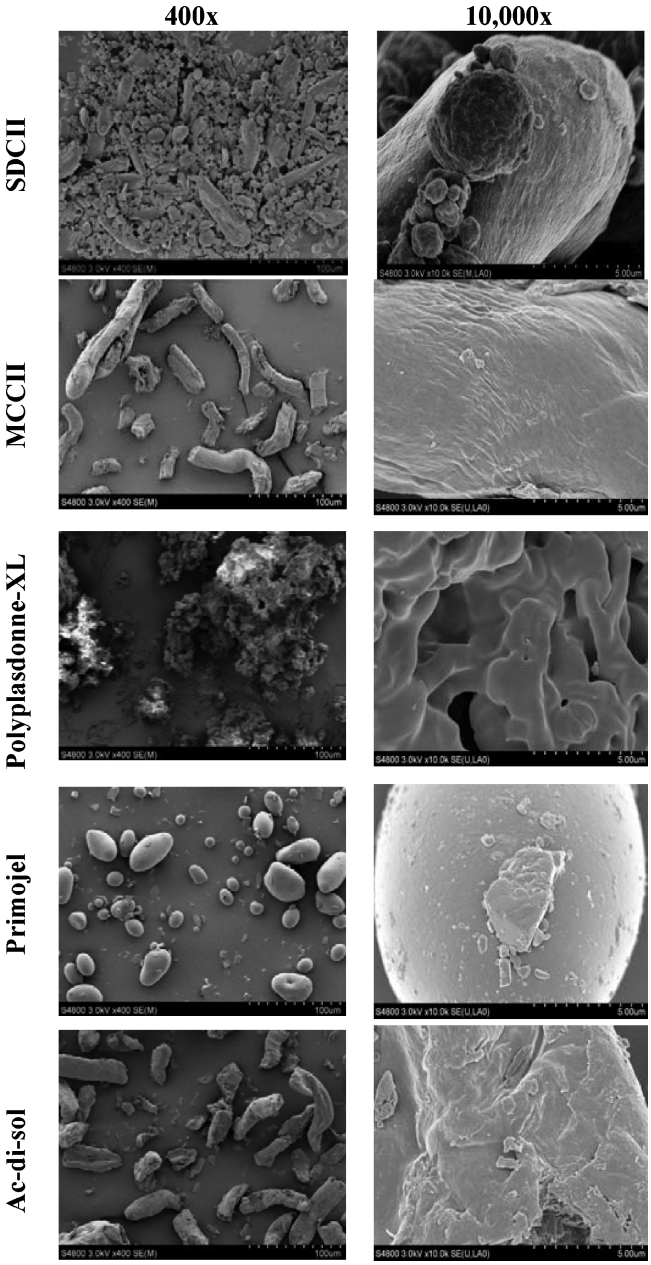

Fig. 1: SEM images showing the morphology of the disintegrants.

materials. In this case, the surface is highly irregular showing protrusions and cavities.

The selected properties of cellulose II materials and commercial disintegrants are listed in Table 1. SDCII particles, as produced, had a geometric mean size of 67.7 μm and appear to be more packed than MCCII. This might be due to the more rounded and elongate shape and smaller particle size than MCCII (D_{geom} = 89.9 μm). This indicates that the process of homogenization and spray drying reduced slightly the particle size of MCCII. Polyplasdone-XL particles had a geometric mean diameter of 160.8 μm, whereas Primojel and Ac-Di-Sol were smaller in size (40.4 and 28 μm) respectively. The moisture content of SDCII, and MCCII was about 4.1 and 3.6%, respectively. Polyplasdone-XL, Primojel and Ac-Di-Sol all contained a moisture content below the upper limit specified in the USP monographs.

The swelling value determined as a function of time for each material is shown in Fig. 2. It describes the ability of the powder to increase in size/volume due to water uptake of the particles. Results confirmed that Primojel was the largest swelling

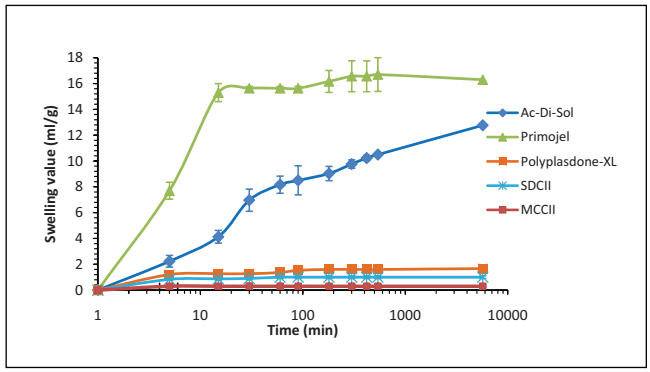

Fig. 2: Swelling values of the disintegrants

material, followed by Ac-Di-Sol (swelling values: 16.7 and 12.8 ml/g, respectively). On the contrary, MCCII, SDCII and Polyplasdone-XL had the lowest swelling values (0.3 ml/g, 1.0 ml/g and 1.7 ml/g, respectively). Water uptake is shown in Fig. 3, and followed a similar trend as observed for swelling value: Primojel ≥ Ac-Di-Sol > Polyplasdone-XL > SDCII > MCCII. Primojel, Ac-Di-Sol, MCCII and SDCII took about 60–70 s to attain the maximum water uptake value, whereas for Polyplasdone-XL the time to peak the water uptake was 40 s. Highly swelling materials such as Primojel and Polyplasdone-XL showed the largest water uptake indicating that water penetration by swelling prevails over water wicking to cause a fast gain in mass. Thus, it is possible that formation of capillaries in MCCII, SDCII and Polyplasdone-XL draw water into the particles at a small magnitude since their swelling values were the lowest. A high powder porosity is not always a condition for the rapid water uptake since Primojel and Ac-Di-Sol had ~47% and 71% porosity values, respectively, and both had high water uptake and swelling values.

2.2. *Compact disintegration behavior*

The correlation between crushing strength and disintegration time is depicted in Fig. 4. SDCII, MCCII and Polyplasdone-XL formed the fastest disintegrating compacts. In addition, Primojel was less compactable than Ac-Di-Sol. Considering the water uptake results and swelling values for Primojel and Ac-Di-Sol, it appears that their slow disintegration time could be due to their higher swelling propensity. From the results, it is clear that, MCCII, SDCII and Polyplasdone-XL formed the strongest and the fastest disintegrating tablets. As reported earlier, in the case of Polyplasdone-XL, the higher powder and compact porosity and irregular particle morphology contribute to the quick

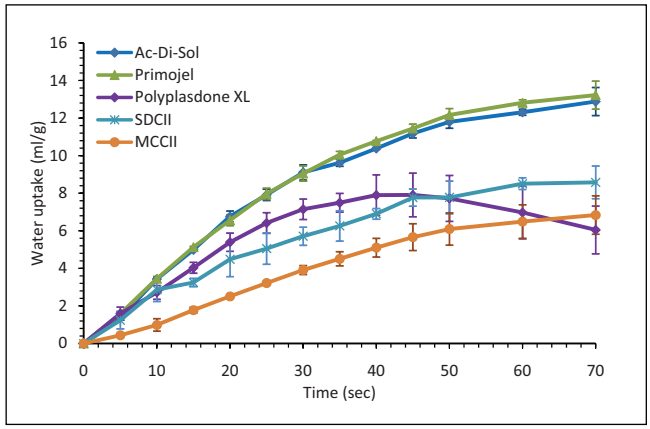

Fig. 3: Water uptake rates of the disintegrants

Table 1: Powder and tableting properties

	D_{geom} SE[b] (μm)	Moisture content (%)[a]	Porosity (%)	Water sorption ratio[a]	Compact volume expansion[a] (%)
SDCII	67.7 ± 4.1	4.1 ± 0.4	64.0	2.3 ± 0.5	2.9 ± 0.5
MCCII	89.9 ± 5.0	3.6 ± 0.4	76.0	1.6 ± 01	2.6 ± 0.1
Polyplasdone-XL	160.8 ± 4.6	4.9 ± 0.1	82.0	4.8 ± 0.1	8.1 ± 1.8
Ac-Di-Sol	28 ± 2.1	6.4 ± 0.3	71.0	6.6 ± 0.5	8.8 ± 0.5
Primojel	40.4 ± 3.4	7.4 ± 0.6	47.0	10.4 ± 0.3	13.5 ± 2.9
p-value	0.00	0.00	N.A.	0.00	0.00

[a] n = 3,
[b] SE = standard error

water wicking action, leading to increased hydrostatic pressure and, consequently, a fast disintegration of the tablets (Gonnissen et al. 2008). These results agreed with the water sorption ratio values shown in Table 1. For this reason, highly swelling materials such as Primojel and Ac-Di-Sol showed the highest values (10.4 and 6.6, respectively), whereas water wicking materials such as Polyplasdone-XL, SDCII and MCCII showed the lowest values (4.8, 2.3 and 1.6, respectively). During this test, Primojel and Ac-Di-Sol compacts presented the highest percentage in volume expansion (13.5% and 8.8%, respectively) compared to Polyplasdone-XL, SDCII and MCCII (8.1, 2.9 and 2.7%, respectively).

In order to compare the performance of SDCII against commercial disintegrants, tablets of A-TAB, mannitol, Fast Flo 316, Avicel PH-102 and Starch 1500 containing 0, 2.5, 5, 10 and 20% of the test disintegrant and 0.5% magnesium stearate were evaluated. The change in compact disintegration time as a function of disintegrant level is shown in Fig. 5. In the absence of the disintegrant, compact disintegration varied as: Avicel PH-102 (1902 s) > Starch 1500 (510 s) > mannitol (346 s) > A-TAB (344 s) > Fast Flo 316 (36 s), respectively. Mannitol and Fast Flo 316 compacts disintegrate by slow dissolution, Avicel PH-102 by fragmentation, A-TAB mainly by erosion and Starch 1500 by swelling and dissolution. Except when Starch 1500 and Fast Flow 316 are used as diluents, the addition from 2.5-5% of disintegrant caused a major decrease in disintegration time. Further increase in the disintegrant level did not reduce disintegration times. On the contrary, for highly swelling materials such as Ac-Di-Sol and Primojel, levels higher than 5% delayed disintegration times, irrespective of the diluent employed. This behavior has been previously reported (El-Barhouthi et al. 2008; Mattson et al. 2001). This is explained by the formation of a viscose gel around the compacts due to water uptake retained in its tridimensional network hindering the erosion/dissolution of the compacts.

Fast Flow 316 *per se* showed a fast disintegration, and hence there is no need for a disintegrant when it is used in a formulation.

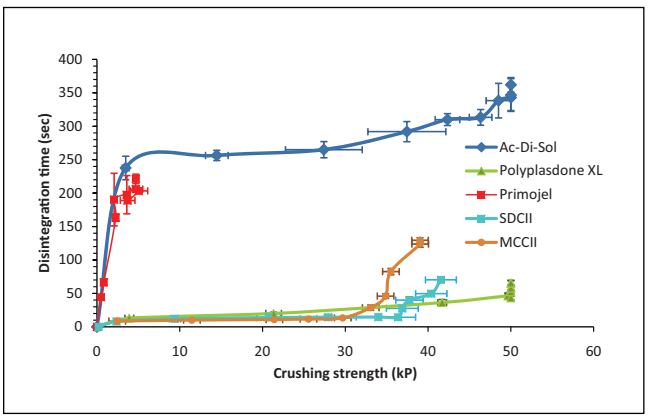

Fig. 4: Correlation between crushing strength and disintegration time

Likewise, Starch 1500 showed virtually no improvement when formulated with highly swelling disintegrants since this property is usually enhanced. Disintegration time for this material is only reduced by half when formulated with ~20% of water wicking disintegrants.

MCCII and SDCII were very effective as disintegrants at levels from 2.5 to 5% when A-TAB and mannitol are used as diluents. Polyplasdone-XL was very effective when formulated with A-TAB, mannitol and Avicel PH-102 at levels from 2.5 to 5%. Similarly, highly swelling materials such as Ac-Di-Sol and Primojel are effective only when formulated with A-TAB, mannitol and Avicel PH-102. In terms of the minimal disintegrant level which highly reduced disintegration time, the best disintegrant that worked for strong non-soluble binders such as Avicel PH-102 was Primojel at a 2.5% level which showed a disintegration time of ~60 s. For slowly eroding and fragmenting materials such as A-TAB, either, Ac-Di-Sol, Primojel or Polyplasdone-XL worked fine as disintegrant at a 2.5% level. As mentioned previously, for fast dissolving diluents such as Fast Flow 316, there is no need for using any disintegrant at any level. On the contrary, if highly swelling materials are employed, disintegration times are lingered. For slow dissolving materials such as mannitol Polyplasdone-XL was the best disintegrant at a 2.5% level since it has a large water wicking action combined with a moderate swelling easing dissolution. For highly swelling diluents such as Starch 1500, water wicking agents such as SDCII and Polyplasdone-XL were the best disintegrants.

For all the water wicking disintegrants, levels from 5–20% did not caused a major reduction in disintegration times, except when the combination of MCCII/SDCII and Avicel PH-102 are used. Conversely, in highly swelling materials such as Ac-Di-Sol and Primojel increasing disintegrant levels from 5–20% led to delay in disintegration times.

To further investigate the use of SDCII and MCCII as disintegrants, tablets containing Avicel PH-102, ibuprofen, disintegrant and magnesium stearate at a 54.5:4 0.0:5.0:0.5, 49.5:40.0:10.0:0.5, 39.5:4 0.0:20.0:0.5, and 59.8:40.0: 0.0:0.5 weight ratios were made and their friability, crushing strength and disintegration time were determined (Table 2). All compacts showed a decrease in disintegration time with increasing levels of disintegrant except for Primojel at a 20% level. As seen before, the gel formation caused a delay in compact disintegration. Since all compacts contained Avicel PH-102, their friability value was well below the maximum 1% limit set by the USP. Further, the increase in the SDCII and Polyplasdone-XL level from 10% to 20% caused a decrease in the friability value due to the contribution of the binding properties of these materials on the overall compact strength. Friability values of SDCII were better than those of MCCII since the former is a better binder. At high levels, poorly compactable disintegrants such as Primojel showed the highest friability.

Figure. 6 compares the release profiles of ibuprofen tablets. According to the USP monograph, ibuprofen compacts must release 80% of the drug within 60 min. All tablets containing

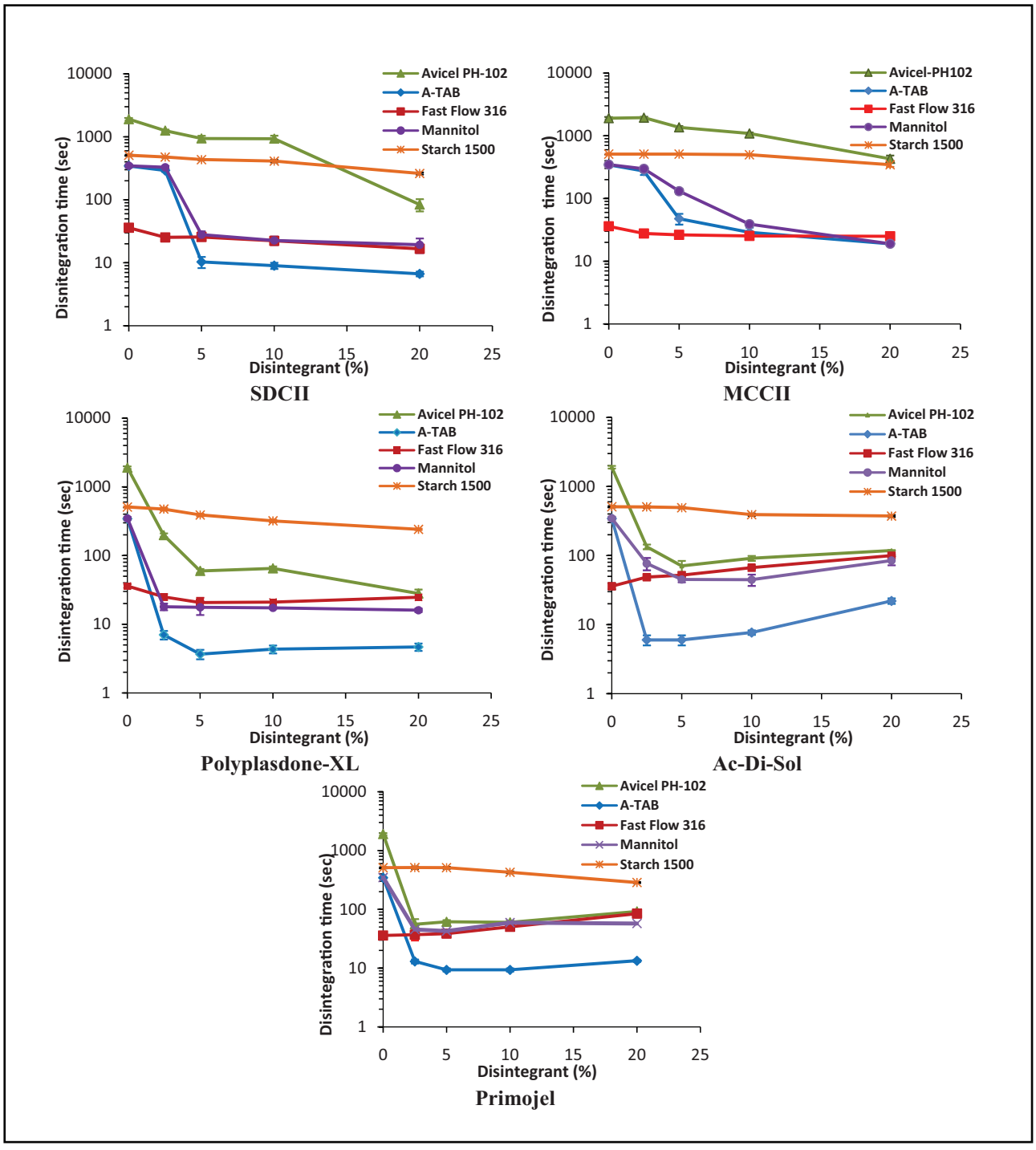

Fig. 5: Effect of different amounts of disintegrants on disintegration time for tablets of some commonly used binders

disintegrant met the USP requirement and some disintegrants showed a faster ibuprofen release than Advil® compacts. As seen previously, for Avicel PH-102, the best disintegrant at the 2.5, 5 and 10% levels was Primojel, whereas at the 20% the best one was Polyplasdone-XL. The amount of drug released after 5 min can be used to compare the efficacy of the disintegrants. Thus, at the 5% disintegrant level, Ac-Di-Sol provided the fastest release, followed by Primojel and Polyplasdone-XL and MCCII in equal magnitude. In the release profiles containing a 10% level of disintegrant, Polyplasdone-XL and Ac-Di-Sol showed the fastest release followed closely by Primojel. Further, at the 20% level of disintegrant, Polyplasdone-XL and Primojel were comparable and the fastest, followed by SDCII. Further, compacts without disintegrant released the drug slowly, barely meeting the USP criteria. The above results indicate that SDCII and MCCII work better as disintegrant at levels $\geq$ than 10%. It must be emphasized that not always disintegration times can be used to predict which disintegrant might work the best for a drug release due to the differences with the physicochemical properties of such drug.

2.3. Conclusions

Results showed that alone, SDCII and MCCII are as effective as Polyplasdone-XL, but superior compared to Primojel and Ac-Di-Sol, in their performance as a disintegrant. Compacts of SDCII, MCCII and Polyplasdone-XL disintegrate mainly through a water wicking mechanism, whereas, for Primojel and Ac-Di-Sol a swelling mechanism was predominant. SDCII and

Table 2: Composition and properties of ibuprofen tablets

		Friability[a] (%)	Crushing strength[a] (kP)	Disintegration time[a] (sec)
I. Avicel PH-102:Ibuprofen:magnesium stearate (49.5:40.0:0.5)				
		0.49	20.9 ± 1.3	520.5 ± 33.6
II. Avicel PH-102:Ibuprofen:disintegrant: magnesium stearate (49.5:40.0:5.0:0.5)				
	SDCII	0.39	20.2 ± 0.7	519.8 ± 15.8
	MCCII	0.42	16.0 ± 0.3	456.3 ± 3.2
	Ac-Di-Sol	0.40	21.0 ± 0.8	135.5 ± 8.3
	Polyplasdone-XL	0.46	19.9 ± 1.1	342.3 ± 11.8
	Primojel	0.39	19.6 ± 0.9	105.8 ± 23.2
	p-value	N.A.	0.00	0.00
III. Avicel PH-102:Ibuprofen:disintegrant: magnesium stearate (49.5:40.0:10.0:0.5)				
Disintegrant:	SDCII	0.29	19.3 ± 0.9	450.3 ± 134.1
	MCCII	0.45	16.6 ± 0.2	396.8 ± 25.1
	Ac-Di-Sol	0.32	21.2 ± 1.0	106.3 ± 12.5
	Polyplasdone-XL	0.45	19.2 ± 0.6	275.3 ± 54.2
	Primojel	0.36	17.5 ± 0.8	59.3 ± 3.4
	p-value	N.A.	0.00	0.00
III. Avicel PH-102:Ibuprofen:disintegrant:magnesium stearate (39.5:40.0:20.0:0.5)				
Disintegrant:	SDCII	0.19	19.4 ± 1.1	8.0 ± 0.8
	MCCII	0.55	16.7 ± 0.2	166.0 ± 17.1
	Ac-Di-Sol	0.33	20.9 ± 1.0	89 ± 3.4
	Polyplasdone-XL	0.22	18.9 ± 1.1	8.3 ± 1.0
	Primojel	0.50	15.9 ± 0.5	90.8 ± 4.6
	p-value	N.A.	0.00	0.00

[a] Compacts were made using 120 MPa compression pressure and 30 sec dwell time.

MCCII can be used alone or combined with commercial direct compression binders/diluents to promote compact disintegration

3. Experimental

3.1. Materials

Cotton linter (grade # R270, Southern Cellulose Products, Inc., Chattanooga, Tennessee), Ac-Di-Sol (Sodium carboxymethylcellulose, FMC Biopolymers, Philadelphia, Pennsylvania), Polyplasdone-XL (Crospovidone, International Specialty Products, Wayne, New Jersey), Primojel (Sodium starch glycolate, DMV-Fonterra Excipients, Princeton, New Jersey), Starch 1500 (Colorcon, West Point, Pennsylvania), mannitol (Fisher Scientific, Fair Lawn, New Jersey), A-TAB (anhydrous dibasic calcium phosphate, Rhodia Inc., Cranbury, New Jersey), Avicel PH-102, (microcrystalline cellulose, FMC Corp., New Jersey), Fast Flo 316 (NF Lactose, Foremost, Baraboo, Wisconsin) and ibuprofen (Spectrum Chemicals, New Brunswick, New Jersey) were used as supplied. Magnesium stearate was received from Mallinckrodt Baker (Phillipsburg, New Jersey). All other chemicals were of analytical reagent grade.

3.2. Preparation of unprocessed (MCCII) and spray-dried cellulose II (SDCII)

Cotton linter sheets were cut into small pieces and soaked in 7.5N NaOH (cellulose:NaOH solution 1:6, w/v) for 72 h at room temperature and then hydrolyzed with 1N HCl at 105 °C for 1.5 h with constant stirring. The resulting powder was filtered and extensively washed with water until the filtrate showed the same pH as that of water. The wet cellulose residue (wet cake) thus obtained was dried at room temperature until reaching a moisture content of less than 7%. This material was labeled as MCCII.

SDCII was prepared as described above except that the wet cake of MCCII was weighed, and suspended in an appropriate volume of distilled water, equivalent to produce ∼3% (w/v) cellulose content in the dispersion, by mixing and passing through a colloid mill (Gifford-wood Co., Hudson, NY) for 10 min. The resulting homogenous aqueous cellulose dispersion was then spray-dried using a Yamato Pulvis spray drier (Model GA-22, Yamato Scientific Co., Tokyo, Japan). The spray drying conditions employed were: inlet air temperature (IT) 195 °C; atomizing air pressure (AA) 1.0 kg-f/cm^2; drying air rate (DA) 0.44 m^3/min; feed spraying rate (FR) 2.0 ml/min, and nozzle diameter (ND) 0.7 mm.

3.3. Powder properties

Particle size distribution was determined on ∼100 g of sample and fractionated for 30 min on a Ro-Tap® sieve shaker (Model, RX29, W.S. Tyler Company, Mentor, OH) using stainless steel 707, 175,150, 125, 105, 75, 53, 45, and 38 μm size sieves. The geometric mean diameter, d_{geom}, and particle size distribution were determined from the log-normal distribution plot constructed between the sieve mean diameter and cumulative percent frequency using the Minitab software (v.15, Minitab Inc, State College, PA). The moisture content was determined by heating the samples of SDCII, MCCII and Polyplasdone-XL at 105 °C for 3 h, Primojel at 130 °C for 90 min, and Ac-Di-Sol at 105 °C for 6 h, in accordance with the USP specifications. Porosity (ε) of the powder was determined from the equation: $\varepsilon = [1-(\rho_{bulk}/\rho_{true})]*100\%$. Where ρ_{bulk} and ρ_{true} are the bulk and true densities of the powder, respectively.

3.4. Swelling value and water uptake analyses

The swelling value is expressed as the ratio of the expanded volume of the powder when sorbs water and the initial sample weight. It was determined as reported previously by Edge et al. (2002). Approximately 500 mg of the powder was vigorously dispersed in a graduate cylinder filled with 10 ml of distilled water at room temperature. The cylinder was placed on a flat surface and the increase in volume was measured with time. The swelling value at each time point was then calculated by dividing the sediment volume by the sample weight.

The water uptake was determined following the procedure of Zhao and Augsburger (2005), with minor modifications. It measures the water sorption of a material upon the addition of water. Briefly, a funnel (diameter 6 cm), attached to a Tygon tubing, was placed on an analytical balance (Model, R200D, Sartorius, Bohemia, NY) held on a tripod stand. The Tygon tubing delivers water into a collecting vessel placed next to the balance. A Whatman filter paper (diameter 90 mm) was wetted with distilled water and placed in the funnel. An accurately weighed sample of the test material (∼ 500 mg) was then added. Ten milliliters (10 ml) of distilled water was then poured into the funnel through the filter paper. The change in weight as a function of time was then recorded. The measurement was stopped when a stable weight reading was observed. The difference of weights, with and without the powder, as a function of time, was taken as the water uptake ability of the powder.

3.5. Excipient morphology

A field emission scanning electron microscope (FE-SEM) (Model 4800, Hitachi, Tokyo, Japan), operating at 3 kV, was used to visualize the surface characteristic of the excipients. The powder was fixed on an aluminum stub using a double-sided adhesive and coated in vacuum with a thin layer of gold/palladium sputtering (3–5 nm) under an argon atmosphere for 4 min at 30 W.

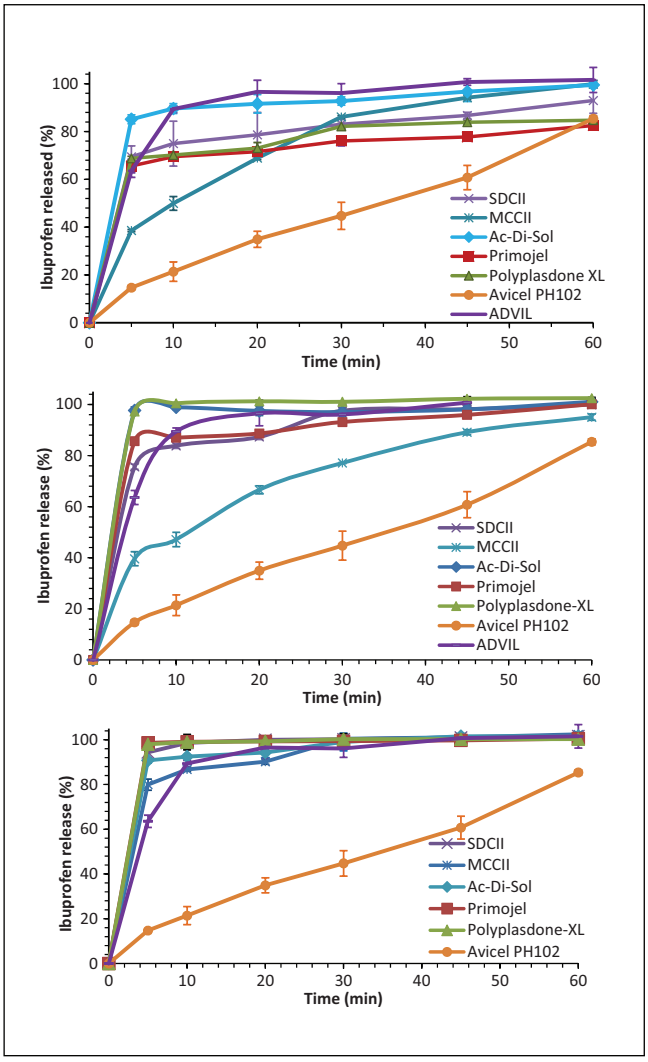

Fig. 6: Dissolution profile of ibuprofen tablets at (A) 5%, (B) 10% and (C) 20% disintegrant levels (See Table 2)

3.6. *Preparation of tablets*

Powder mixtures containing cellulose II materials (or commercial disintegrant) and (i) magnesium stearate (99.5:0.5), (ii) commonly used direct compression excipient (Avicel PH-102, Fast Flo 316, Starch 1500, mannitol or A-TAB) and magnesium stearate (2.5: 97.0:0.5; 5.0: 94.5:0.5; 10.0: 89.5:0.5 and 20.0: 79.5:0.5), or (iii) Avicel PH-102, ibuprofen and magnesium stearate (0.0:59.5:40.0:0.5; 5.0:54.5:40.0:0.5; 10.0:49.5:40.0:0.5, and 20.0:39.5:40.0:0.5) were prepared by mixing in a V-blender (Model LB429, The Petterson Kelley Co. East Stroudsburg, PA) for 30 min. In this direct compression approach the lubricant was added in the beginning to foresee any negative effect on tablet compactibility. Tablets, each weighing 500 mg, were made on a single punch press (Model C, Carver Press, Menomonee Falls, WI) using a 13 mm round, flat-faced punches and die set at 10-260 MPa or 120 MPa and a dwell time of 30 s. The upper punch was equipped with a load cell (Model: LCGD-10 K, Omega Engineering, Inc., Stamford, CT) and a strain gauge meter (Model: DP25B-S, Omega Engineering, Inc., Stamford, CT). Tablets were stored in a desiccator over Drierite® between 15 to 30% RH for 48 h before the analysis. Relative humidity was monitored employing a digital hygro-thermometer (Extech instruments, Waltham, MA).

3.7. *Compact water sorption ratio and volume expansion*

The method of Bi et al. (1999) was employed. This method evaluates the ability of the compact to uptake water. Briefly, on a petri dish which contained a paper and 6 ml of water, a tablet was placed in the center. Once the tablet was completely wetted, the water sorption ratio (WSR) was calculated according to the relationship: $WSR = 100*(W_a - W_b)/W_b$, where W_b and W_a are the weights before and after water sorption, respectively. The percentage of volume expansion was found by replacing the compact weight in the former equation by the compact volumes. Tablets used in the analysis were made on a single punch press (Model C, Carver Press, Menomonee Falls, WI) at 120 MPa compression pressure and a dwell time of 30 s as described above.

3.8. *Tablet disintegration*

The compact disintegration test was performed in distilled water, without discs, at 37 °C according to the USP specifications, employing a Eureka GmbH disintegration apparatus (type 712, Erweka, Offenbach, Germany). Tests were conducted in five replicates.

3.9. *Compact crushing strength*

A Schleuniger Pharmatron 8 M tablet hardness tester (Dr. Scheleuniger Pharmatron Inc., Manchester, NH) was employed. Samples were analyzed in triplicates.

3.10. *Dissolution studies*

The dissolution studies were performed employing a PharmaTest dissolution apparatus (Scientific Instruments and Technology Corp., Piscataway, NJ) in a phosphate buffer at a 7.2 pH, 37 °C and 50 rpm at 5, 10, 20, 30, 45 and 60 min, aliquots (1 ml each) of the dissolution medium were withdrawn, passed through a 0.22 μm membrane filter (Millipore filter corp., Bedford, Mass., USA), and analyzed for ibuprofen content by HPLC using a fully automated Shimadzu system, equipped with a pump (Model LC-10AT), an autoinjector (Model SIL-10A), a system controller (Model SCL-10A), an UV-VIS detector (Model SPD-10A) and a Chromatopac integrator (Model C-R6A). A C_{18} reverse phase analytical column (25 cm × 4.6 mm, 5 μm, Waters, Milford, MA) was employed for the analysis. The mobile phase was a mixture of 60% acetonitrile and 40% water containing 4-chloroacetic acid (4 g), adjusted to a pH of 3.0 with aqueous ammonium hydroxide. The drug was eluted at a flow rate of 2.0 ml/min and the measurements were made at 221 nm. All tablet formulations were analyzed in five replicates.

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