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Evaluation of cellulose II powders as a potential multifunctional excipient in tablet formulations

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Abstract

The use of UICEL-A/102 and UICEL-XL, the cellulose II powders, as a multifunctional direct compression excipient in the design of tablets containing hydrochlorothiazide (HCTZ) or ibuprofen (IBU), the model low and high dose drugs, respectively, has been reported. Commercial Oretic® and Advil® tablets containing HCTZ and IBU, respectively, and tablets made using Avicel® PH-102—the most commonly and widely used commercial direct compression excipient, were used in the study for comparison purposes. Tablets were made by first blending drug with the excipient and then with stearic acid, a lubricant, in a V-blender, followed by compressing into a tablet on a hydraulic press using 105 MPa of compression pressure and a dwell time of 30 s. The crushing strengths of HCTZ tablets decreased in the order Avicel® PH-102 > UICEL-XL, UICEL-A/102 > Oretic® and of IBU tablets in the order Avicel® PH-102 ≥ UICEL-XL ≃ UICEL-A/102 > Advil®. The friability values for all tablets were well below the maximum 1% USP tolerance limit. UICEL-A/102 and UICEL-XL tablets containing HCTZ disintegrated rapidly (<25 s). Oretic® tablets disintegrated in about 60 s, while Avicel® PH-102 tablets remained intact during 1 h test period. The IBU tablets made using UICEL-A/102 disintegrated the fastest, UICEL-XL and Advil® tablets the next, and Avicel® PH-102 tablets remained intact. All tablets, except for those of Avicel® PH-102, conformed to the USP drug release requirements. These results conclusively show that UICEL-A/102 and UICEL-XL have the potential to be used as filler, binder, and disintegrant, all-in-one, in the design of tablets containing either a low dose or high dose drug by the direct compression method.

Keywords: Cellulose II powders; Tablet excipients; Direct compression excipients; Multifunctional tableting agents; Ibuprofen; Hydrochlorothiazide

1. Introduction

Solid dosage forms are defined as drug delivery systems presented as solid-dose units (Marshall and Rudnic, 1990). Tablets and capsules are the most popular and preferred drug delivery vehicles because they can be accurately dosed, easily manufactured and packaged on a large scale, have good physical and chemical stability, and can contribute to good patient compliance given their ease of administration (Joshi and Duriez, 2004; Marshall and Rudnic, 1990).

The types of components in a tablet dosage formulation typically used include the drug, a diluent, a binder, a lubricant, a disintegrant, and a glidant. A diluent is used to increase the bulk of the tablet, a binder is employed to add cohesiveness to the powder bed, and a lubricant helps to reduce the friction between the powder bed and the die wall during compression and ejection by interposing a film of low shear strength between them. A disintegrant facilitates the breakup of the tablet after administration, and finally, a glidant is added to improve the flow characteristics by modifying the interaction between particles (Peck et al., 1989). Most lubricants also act as anti-adherents, which prevent sticking of the powder to the punches and die.

Currently, microcrystalline cellulose is perhaps the most commonly used direct compression excipient. It primarily functions as a binder/filler. Currently, cross-linked sodium carboxymethylcellulose, marketed under the trade name Ac-Di-Sol® (FMC Bio-Polymer, Philadelphia, PA), is the only cellulose based disintegrant commercially available. We have recently prepared and characterized cellulose II powders, which can be compressed into a rapidly disintegrating compact, without the need of a disintegrant (Reus-Medina, 2005; Reus-Medina et al., 2004; Kumar et al., 2002). In the present paper, we report, for the first time, the use of cellulose II powders as a multifunctional excipient in tablet formulations of low and high dose

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model drugs, (hydrochlorothiazide and ibuprofen, respectively), by direct compression. The use of direct compression for making tablets has steadily increased over the years because of its ease of manufacture and lower cost.

2. Experimental

2.1. Materials

Avicel® PH-102 was received from FMC Corporation (Philadelphia, PA). Hydrochlorothiazide and ibuprofen were purchased from Spectrum (New Brunswick, NJ). Stearic acid was acquired from Mallinckrodt Specialty Chemicals Co. (St Louis, MO). All other chemicals were of analytical grade. UICEL-A/102 and UICEL-XL were prepared as described earlier (Reus-Medina, 2005; Reus-Medina et al., 2004).

Oretic® (25 mg tablets, Abbott Laboratories, North Chicago, IL) and Advil® (200 mg coated tablets, Wyeth, Madison, NJ) containing HCTZ and IBU formulations, respectively, were purchased from a local drug store and used as the reference standards to determine the performance of cellulose excipients used in the study.

2.2. Methods

2.2.1. Preparation of model hydrochlorothiazide (HCTZ) and ibuprofen (IBU) tablets

The compositions of tablet formulations tested are presented in Table 1. Appropriate amounts of drug and UICEL-A/102, UICEL-XL or Avicel® PH-102, equivalent to produce 100 tablets, were accurately weighed and mixed in a V-blender for 30 min. The stearic acid (1%) was then added and blended for 5 min. The tablets were compressed on a Carver Press (Fred S. Carver Inc., Summit, NJ) using an 11 or a 13 mm flat-faced set of punches and die. The compression pressure and dwell time used were 105 MPa and 30 s, respectively.

2.2.2. Tablet characterization

Crushing strength, friability, weight, thickness, drug content, dissolution time and disintegration time of the tablets were determined 48 h after manufacture. Crushing strengths were determined using a Dr. SCHLEUNIGER® Pharmatron tablet hardness tester (Schleuniger Model 8, Manchester, NH). The disintegration test was performed according to the United States Pharmacopoeia 27/National Formulary 22 (USP, 2003) in water at 37 °C using Erweka GmbH apparatus (type 712, Erweka, Offenbach, Germany). The friability test was conducted according to the United States Pharmacopoeia 27/National Formulary 22 (USP, 2003) Erweka friability method using a Friabilator apparatus (model 45-1000, Erweka, Cary, NC).

Table 1
Compositions of model hydrochlorothiazide and ibuprofen tablet formulations

Ingredients	HCTZ formulation	IBU formulation
Drug (mg)	25	300
Cellulose excipient[a] (mg)	272	195
Stearic acid (mg)	3	5
Tablet weight (mg)	300[b]	500[c]

[a] UICEL-A/102, UICEL-XL and Avicel® PH-102.
[b] Tablet diameter was 11 mm.
[c] Tablet diameter was 13 mm.

2.2.3. Drug content determination

For both HCTZ and IBU, a fully automated Shimadzu HPCL system (Shimadzu Corporation, Kyoto, Japan), equipped with a pump (model LC-10AS), a system controller (model SCL-10A), an auto injector (model SIL-10A), an UV–vis spectrophotometric detector (model SPD-10A) and a data processor/recorder (model C-R5A), was used. The system suitability was tested prior to performing analysis. Replicate injections of the standard preparations of HCTZ (concentration = 0.15 mg/mL) and IBU (concentration = 0.12 mg/mL) were made and the relative standard deviation (R.S.D.) for six replicated injections were performed. The R.S.D. was always 2% or less, which meets the USP requirement. The injection volume for standard and test samples was 20 μL. All samples were filtered through a 0.45 μm nylon membrane (Chrom Tech. Inc., Apple Valley, MN) prior to injection.

The analysis of HCTZ tablets was performed on a Supelco C18 (5 μm, 15 mm × 4.6 mm, Supelco, Bellefonte, PA) reversed-phase analytical column using a mobile phase consisting of a 9:1 (v/v) ratio of 0.1 M monobasic sodium phosphate and acetonitrile, adjusted to pH 3.0 ± 0.1 with an acid. The mobile phase was filtered through 0.45 μm nylon filter membrane (Chrom Tech. Inc., Apple Valley, MN) and degassed under vacuum using a Bransonic Ultrasonic cleaner (model 3200, Bransonic Ultrasonic Corporation, Danbury, CT) for 15 min before use. The flow rate was 2 mL/min and the effluent was detected at 254 nm. The drug concentration in the test samples were calculated using the calibration curve method; the concentration of standard solutions ranged from 0.05 to 0.25 mg/mL.

For IBU tablets, the drug content was determined using the same conditions as reported by Kumar et al. (2001). Briefly, the mobile phase consisted of a 4:6 (v/v) ratio of 0.01 M potassium monophosphate solution and acetonitrile. It was filtered through 0.45 μm nylon filter membrane (Chrom Tech. Inc., Apple Valley, MN) and degassed under vacuum using a Bransonic Ultrasonic cleaner (model 3200, Bransonic Ultrasonic Corporation, Danbury, CT) for 15 min before use. The flow rate was 1 mL/min and the effluent was detected at 220 nm. The drug concentration in the test samples were calculated using the calibration curve constructed using standard solutions ranging in concentration from 0.05 to 0.20 mg/mL.

2.2.4. Dissolution studies

The dissolution tests were performed using a Pharma Test dissolution apparatus (Scientific Instruments and Technology Corporation, Piscataway, NJ) according to the procedures described in the United States Pharmacopoeia 27/National Formulary 22 (USP 27/NF 22) monographs for HCTZ and IBU tablets (USP, 2003). Table 2 lists the test conditions and the drug dissolution specifications employed in the study. The HCTZ released in the medium was analyzed spectrophotometrically by measuring the

Table 2
Dissolution conditions used for HCTZ and IBU tablets

Ingredients	HCTZ tablets	IBU tablets
Apparatus type	I	II
Dissolution medium (volume)	0.01 N HCl (900 mL)	pH 7.4 phosphate buffer (900 mL)
Agitation rate (rpm)	100	50
Temperature (°C)	37	37
"Q" value[a]	Not less than 60% in 60 min	Not less than 80% in 60 min
Acceptance criterion specified (stage S1)	Not less than $Q+5\%$ in 60 min	Not less than $Q+5\%$ in 60 min

[a] Amount of dissolved active ingredient expressed as a percentage of the labeled content.

absorbance at 272 nm employing a UV–vis spectrophotometer (HP 8453, Hewlett Packard, Scientific Institution Division, Palo Alto, CA) and quantitated by the calibration curve method; the concentration of standard solutions used ranged from 0.01 to 0.06 mg/mL.

For IBU, the concentration in the dissolution medium was determined by measuring the UV absorbance at 221 nm and employing the calibration curve constructed using standard solutions ranging in concentration from 0.006 to 0.035 mg/mL.

3. Results and discussion

3.1. HCTZ tablets

Table 3 presents the drug content, tablet thickness, and tablet friability test results for the HCTZ tablets made using UICEL-A/102, UICEL-XL, and Avicel® PH-102, separately, as a direct compression excipient and for the commercial HCTZ tablet product, Oretic®. The average amounts of HCTZ determined in UICEL-A/102 and UICEL-XL tablets were 101.2% and 97.4%, respectively. Avicel® PH-102 tablets had an average drug content of 111.8%. The average HCTZ amount in Oretic® was 99.5%. The higher drug content observed in the case of Avicel® PH-102 tablets, compared to the USP upper potent limit of 110%, could be due to poor flow of the Avicel® PH-102 powder, resulting in less efficient mixing. The higher standard deviation obtained for the drug content in the Avicel® PH-102 tablets, compared to the values for other tablet formulations, supports this. The thickness of Avicel® PH-102 tablets was about 2.22 mm, while tablets of UICEL-A/102 and UICEL-XL had a value of about 2.32 mm. Oretic® tablets, in contrast, were about 3.32 mm in thickness. The higher thickness value observed for tablets made using UICEL-A/102 and UICEL-XL, compared to that of Avicel® PH-102 tablets, is due to greater elasticity of these materials (Reus-Medina, 2005; Reus-Medina et al., 2004).

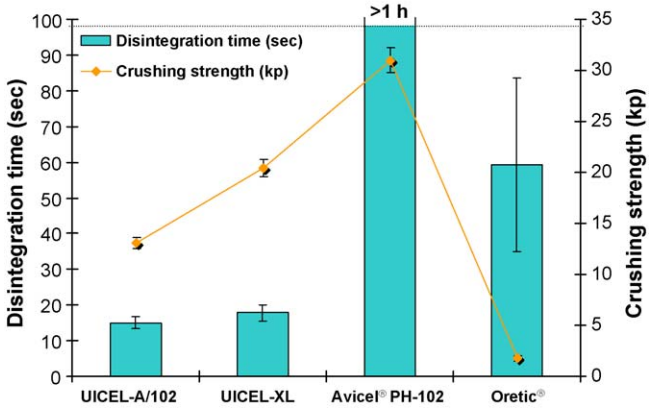

Fig. 1. Crushing strength and disintegration times of HCTZ tablets.

The three tablet formulations as well as the commercial Oretic® tablets passed the USP friability test, showing the percentage friability value well below the 1% upper level of acceptability for pharmaceutical tablets (USP, 2003).

Fig. 1 displays the crushing strengths and disintegration times for the tested tablet formulations. UICEL-A/102 and UICEL-XL tablets disintegrated within 25 s, while Oretic® tablets took about 60 min to disintegrate. Avicel® PH-102 tablets, in contrast, remained intact during the test period of 1 h. The crushing strengths of the tablets decreased in the order: Avicel® PH-102 > UICEL-XL > UICEL-A/102 > Oretic®. For Avicel® PH-102, UICEL-XL, and UICEL-A/102 tablets, the crushing strength results are in good agreement with the friability test results (Table 3). Oretic® tablets had the lowest crushing strength but showed the least tendency to chip off during the friability

Table 3
Drug content, friability and thickness results of HCTZ tablet formulations

Tablet	Average drug content, % (S.D.)[a]	Friability (%)	Average thickness, mm (S.D.)[b]
UICEL-XL	97.4 (2.3)	0.07	2.33 (0.02)
UICEL-A/102	101.2 (1.1)	0.23	2.31 (0.02)
Avicel® PH-102	111.8 (3.0)	0.02	2.22 (0.02)
Oretic®	99.5[c] (1.8)	0.01	3.32 (0.03)

[a] Standard deviation; $n=3$.
[b] Standard deviation; $n=10$.
[c] Percentage of the labeled amount.

Table 4
Assay content, friability and thickness results of IBU formulations

Tablet	Average drug content, % (S.D.)[a]	Friability (%)	Average thickness, mm (S.D.)[b]
UICEL-XL	101.1 (2.8)	0.48	3.10 (0.03)
UICEL-A/102	101.2 (3.1)	0.46	3.15(0.05)
Avicel® PH-102	99.5 (0.8)	0.24	3.09 (0.03)
Advil®	100.0[c] (1.3)	0.11	6.24 (0.04)

[a] Standard deviation; $n = 3$.
[b] Standard deviation; $n = 10$.
[c] Percentage of the labeled amount.

test. This could be attributed to the wet granulation method used in their manufacture (USP, 2003).

Fig. 2 presents the HCTZ release profile from the different tablet formulations. UICEL-A/102 and UICEL-XL tablets released 85–90% of the drug in 15 min while about 80% of HCTZ was released from Oretic® tablets within the same time-period. At 30 min, 100% of the drug was released from UICEL-A/102, UICEL-XL and Oretic® tablet formulations. Avicel® PH-102 tablets, in contrast, released only 23% HCTZ in 60 min. The drug release tolerance specified in the USP monographs for HCTZ tablets is that not less than 60% of the labeled amount must be dissolved in 60 min (USP, 2003).

The faster drug release from UICEL-A/102, UICEL-XL, and Oretic® tablets is due to their rapid disintegration. These results illustrate that the rapid disintegration property of cellulose II promotes the complete dissolution of the drug within 60 min.

3.2. IBU tablets

The drug content, friability and thickness results for the UICEL-A/100, UICEL-XL, and Avicel® PH-102-based IBU tablets and for the commercial Advil® tablets are presented in Table 4. The thickness of Advil® tablets was about twice that of those made using UICEL-A/102, UICEL-XL or Avicel® PH-102. All tablets showed friability values well below the 1% tolerance limit set by USP for pharmaceutical tablets (USP, 2003).

The crushing strengths and the disintegration times of the tablets are displayed in Fig. 3. Interestingly, UICEL-A/102, UICEL-XL, and Avicel® PH-102 tablets all had comparable crushing strengths, but they significantly differed in their disintegration times. UICEL-A/102 tablets disintegrated in about 70 s, whereas UICEL-XL tablets had a disintegration time of 6–7 min. Avicel® PH-102-based IBU tablets did not disintegrate during the test period. Advil® tablets showed the lowest crushing strength value but disintegrated in about the same time-period as UICEL-XL tablets.

Fig. 4 presents the IBU release profile for all tablet formulations. Advil® and UICEL-XL tablets had a comparable release profile and met the USP requirement of 80% drug release within

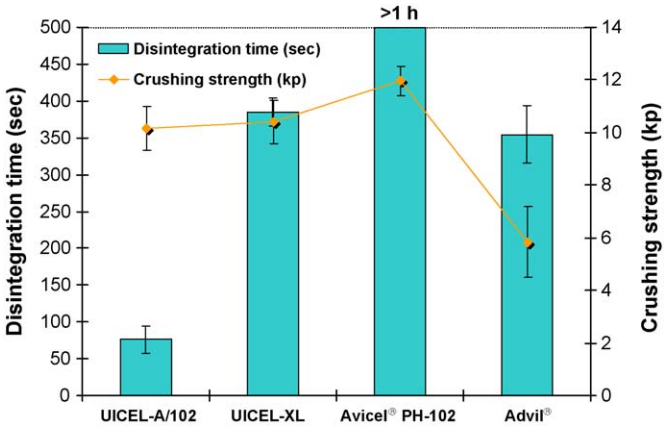

Fig. 3. Crushing strength and disintegration times of IBU tablets.

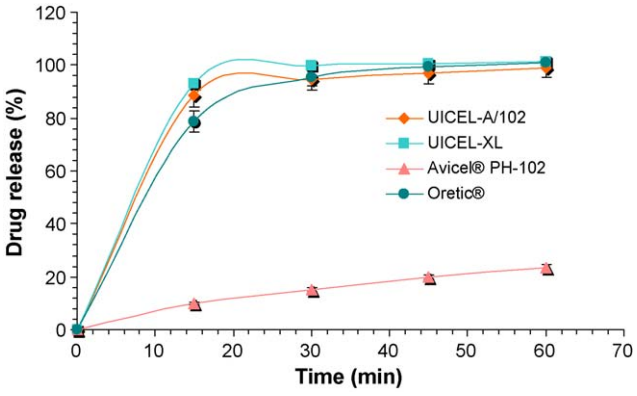

Fig. 2. HCTZ release profile.

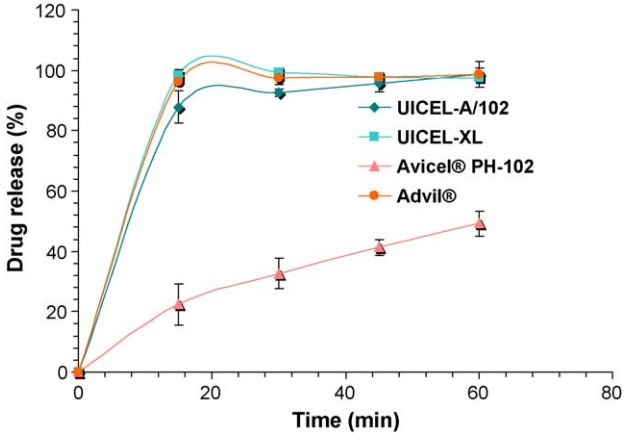

Fig. 4. IBU release profile.

60 min. UICEL-A/102 displayed a slightly slower release profile but met the USP drug release tolerance criterion. Avicel® PH-102 released only about 50% IBU in 60 min.

Interestingly, the crushing strengths of UICEL-A/102 and UICEL-XL tablets were only slightly lower compared to that of Avicel® PH-102, but the disintegration times and dissolution profiles of these products were significantly different. These results further support the premise that the rapid disintegration property of cellulose II causes the drug to release faster from its tablets.

4. Conclusions

For both low- and high-dose drugs, tablets made using UICEL-A/102 and UICEL-XL had adequate crushing strengths and conformed to the USP friability and drug-release requirements. Commercial Oretic® and Advil® tablets, used as reference controls in this study, contained microcrystalline cellulose, in addition to other ingredients, and are manufactured using the wet granulation method. Avicel® PH-102-based tablets, used for comparison purposes, had adequate crushing strength and met the USP friability tolerance limit but failed to pass the USP dissolution test criteria for both drugs. The results of this study unambiguously show that UICEL-A/102 and UICEL-XL, both of which contain the cellulose II powder, offer potential to be used as filler, binder, and disintegrate, all-in-one, in the design and development of tablets containing low dose or high dose drugs by direct compression.

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