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Evaluation of microcrystalline cellulose II (MCCII) as an alternative extrusion-spheronization aid

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Microcrystalline cellulose II (MCCII) is a different allomorph of MCC that can be used as a filler and a disintegrant for direct compression. MCCII was studied as new pelletization aid with the aim to prepare pellets with a faster drug release than MCCI-based pellets. MCCII-based pellets showed an immediate diphenydramine·HCl release profile comparable to that of Benadryl® and a faster griseofulvin release than MCCI-based pellets. MCCII offers potential to use as an alternative pelletization aid.

1. Introduction

Spheronization is a technique used to transform fine powders and granulates of bulk drugs or excipients into spherical or semi-spherical pellets with a mean size between 0.5 and 2 mm. This technique could potentially incorporate high drug loads rendering a narrow size distribution, high density, low friability, good flow properties and cost effectiveness (Sinh et al. 2009). Pellets provide a reproducible drug blood levels, improved bioavailability, and a low risk of side effects by preventing dose dumping. Further, pellets with similar densities and particle sizes show a lesser tendency toward segregation improving content uniformity (Hileman et al. 1997; Cosijns et al. 2009).

To date, microcrystalline cellulose I (MCCI) is the most frequently used excipient for the production of pellets by extrusion-spheronization. However, MCCI-based pellets of low soluble drugs show a tendency to have a prolonged drug release profile due to the lack of disintegration (Verheyen et al. 2009). Alternative substitutes of MCC (e.g. crospovidone, chitosan, carrageenan, starch, glycerides, cylodextrins and pectinic acid) suffer from ionic charge, an inadequate pellet shape, flexibility, a low drug load capacity, insufficient mechanical strength and water holding capacity (Verheyen et al. 2009).

MCCII was introduced by Kumar and collaborators as a new pharmaceutical excipient for direct compression (Kumar 2002; Reus 2004). MCCII is characterized for rendering compacts with a rapid disintegration which is independent of the compact porosity (Reus 2006). Recent studies demonstrated that the polymorphic form of cellulose affect the release rate of low water soluble drugs such as chloramphenicol (Krueger 2010). The purpose of this study was to evaluate the spheronization characteristics of MCCII compared to MCCI excipients such as Avicel PH-101 and Prosolv®SMCC50 using diphenydramine. HCl and griseofulvin as model drugs.

2. Investigations, results and discussion

The Table shows the resulting pellet properties for the two types of drugs. Independent of the drug used, porosity, bulk density and moisture content for all pellets were comparable. The excipient:griseofulvin ratio was 1:2 since none of the excipients was able to render a higher drug load without producing friable pellets. All capsules showed a good uniformity of dosage indicating a homogeneous distribution of the drugs within the beads and per capsule. Further, all beads had a moisture content below 5% which is acceptable for cellulosic materials. Even though values of true density were slightly higher for pellets made of Prosolv® SMCC50, values of porosity remained virtually unchanged and low. Further, pellets presented a Carr's index between 5–15% indicating excellent flow which is typical for pellets. Researchers have reported similar findings when MCCI is used as the spheronization aid (Durgapal et al. 2010; Ghebre-Sellassie 2003). This behavior is due to the combined effect of increased bulk density, spherical shape, high particle size and narrow particle size distribution. Pellets composed of Prosolv® SMCC50 exhibited a slightly lower diameter, probably due to the presence of SiO_2, which may cause a low affinity of cellulose for water hindering the water uptake needed for the extrudate to grow and transform into a pellet.

Figure 1 shows the release profiles of diphenhydramine.HCl capsules. MCCII and Benadryl® capsules presented a comparable fast release ($F_2 = 62.8$). MCCI pellets had a slower release than MCCII and Benadryl® capsules. This product showed a fast release due to the formulation process which involves a physical mixture of water soluble powdered excipients and a hydrophilic drug. Conversely, pellets containing Prosolv® SMCC50 presented the slowest release, but were able to release at least 80% of the drug within 30 min. The high solubility of the drug (100 mg/ml) appears to be responsible for the fast diffusion and release from the pellets.

Figure 2 shows the griseofulvin release results of griseofulvin capsules. Grisactin® presented the fastest release profile and released about 87% of the drug within 30 min. This formulation does not include pelletization, but a powder mixture of the drug, lactose and sodium lauryl sulfate (surfactant) which eases drug release. However, none of the excipients used rendered pellets with release properties of griseofulvin close to that of

Table: Pellet properties of materials containing cellulosic excipients and diphenhydramine.HCl or griseofulvin

Test	Diphenhydramine.HCl		
	Avicel	MCCII	Prosolv® SMCC50
Uniformity of dose (capsule)(%), n = 10	103.6 (1.3)	108.9 (3.2)	108.5 (1.2)
Uniformity of dose (powder)(%), n = 3	103.5 (4.2)	109 (9.5)	103.4 (6.6)
True density (g/cc), n = 3	1.47 (0.1)	1.47 (0.1)	1.50 (0.0)
Porosity, n = 1	0.52	0.52	0.53
Bulk density (g/cc), n = 1	0.71	0.70	0.70
Tap density (g/cc), n = 1	0.79	0.76	0.82
Carr's index (%), n = 1	9.1	7.9	14.7
Moisture content (%), n = 2	3.7 (1.0)	3.2 (1.0)	3.2 (0.2)
Geometric mean (μm) (standard error)	1179 (89)	1193 (63)	991 (78)
F_2	46.1	62.8	24.5
	Griseofulvin		
Uniformity of dose (capsule)(%), n = 10	102.8 (1.3)	104 (2.9)	101.4 (1.7)
Uniformity of dose (powder)(%), n = 5	113 (0.4)	105 (1.4)	116 (0.2)
True density (g/cc), n = 3	1.50 (0.1)	1.49 (0.1)	1.54 (0.0)
Porosity, n = 1	0.53	0.54	0.55
Bulk density (g/cc), n = 1	0.70	0.69	0.69
Tap density (g/cc), n = 1	0.74	0.81	0.74
Carr's index (%), n = 1	5.0	15.1	6.1
Moisture content (%), n = 2	2.9 (0.5)	2.7 (0.5)	3.2 (0.4)
Geometric mean (μm) (standard error)	1021 (109)	1229 (49)	960 (96)
F_2	8.3	14.4	8.5

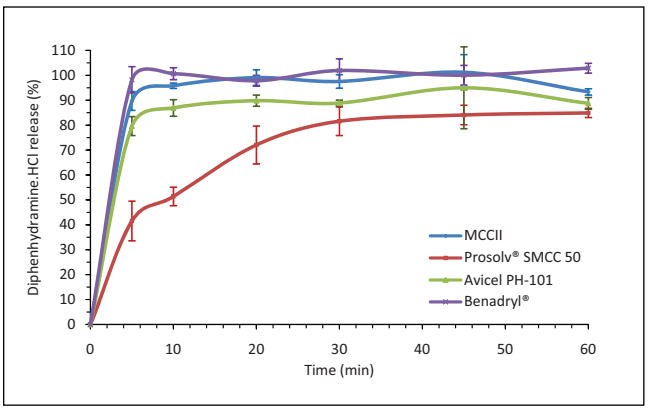

Fig. 1: Dissolution profiles of diphenydramine. HCl pellets

Grisactin®. Moreover, MCCI pellets had comparable and very slow release profiles. Since their pellets were intact after the test, it is plausible that MCCI functions as a porous matrix which regulates the diffusion of the drug towards the medium. MCCII, on the other hand, exhibited a faster release due to the formation of cracks in the pellets which eased the release of griseofulvin. The combined effect of the poor aqueous solubility of griseofulvin (0.05 mM) and the matrix dissolution behavior of MCCI materials contributed to the slow diffusion and further release of this drug.

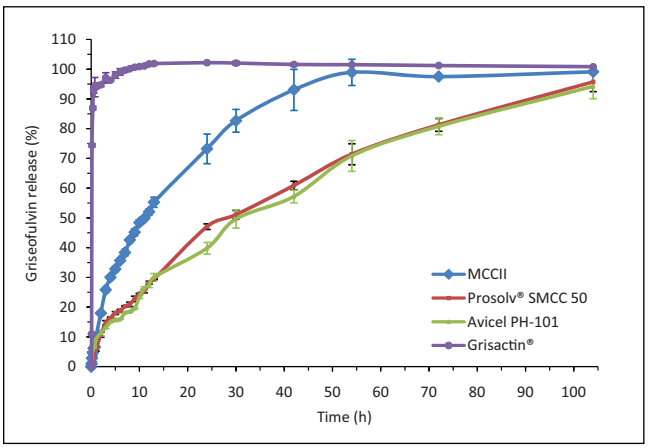

Fig. 2: Dissolution profiles of griseofulvin pellets

Extrusion-spheronization of diphenhydramine.HCl and griseofulvin rendered pellets of a narrow particle size distribution, high density, low porosity and excellent flow. MCCII-based pellets showed comparable release profiles of diphenydramine. HCl to that of Benadryl®, and a faster griseofulvin release than those of MCCI-based pellets.

3. Experimental

MCCII was obtained from cotton linters as reported previously (Rojas and Kumar 2011). Approximately 13 g of MCCII, Avicel PH-101, or Prosolv® SMCC50 and 6.5 g griseofulvin were mixed using a V-blender (Model LB429, The Petterson Kelley Co. East Stroudsburg, PA) for 30 min. Distilled water was sprayed and mixed to make a wet mass containing ~45% moisture content. The wet mass was passed through an Erweka oscillating granulator (Model AR400, Chemical and Pharmaceutical Industry, Inc., New York, NY), equipped with a 425 μm screen. The granules thus obtained were put in the spheronizer chamber (G.B. Caleva LTD, Model SPH120, Dorset, England) and subjected to spheronization at 2000 r.p.m. from 5 to 10 min. Beads were dried at room temperature until reaching a moisture content of less than 5%. Gelatin capsules (size zero) were filled manually with ~380 mg of beads (125 mg of griseofulvin). The above procedure was repeated to prepare excipient-diphenhydramine. HCl beads except that the ratio of excipient:drug was 1:5 (5 g of drug and 25 g of excipient) and a size 3 gelatin capsules were used and filled with ~150 mg of powder, equivalent to 25 mg of diphenhydramine. HCl. The bulk, tap and true densities, Carr's index, porosity, particle size and moisture content were conducted as described previously (Rojas et al, 2011). A VanKel friabilator apparatus was employed for the friability test (Model 45-1000, Erweka, Cary, NC) performed according to the method of Agrawal et al. (2004).

Griseofulvin was used for the *in vitro* dissolution studies. Capsules containing pellets were analyzed according to the USP/NF (28/23) UV method (USP 28/NF23). The *in vitro* release profiles of marketed diphenydramine. HCl and griseofulvin capsules were compared to those

exhibited by the test excipients using the similarity factor given by the equation:

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{N} \right) \sum_{n=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (1)$$

where N is the number of time points, R_t and T_t are the reference and test profiles at the same time point t, respectively. If f_2 falls between 50 and 100, the two samples have similar drug release profiles.

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