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RESEARCH ARTICLE

Evaluation of Ceolus™ microcrystalline cellulose grades for the direct compression of enteric-coated pellets

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Abstract

The preparation of multiparticulate tablets by direct compression of functionally coated pellets is technologically challenging. The objective was to investigate the influence of different grades of microcrystalline cellulose (Ceolus™ UF-711, PH-102, PH-200 and KG-802) as fillers on the properties of blends and tablets containing enteric pellets. Celphere™ spheres were drug-layered and then functionally coated with Eudragit® L 30 D-55/FS 30D dispersion. Tablets loaded with 50% pellets were prepared using pure or binary blends of microcrystalline cellulose fillers. The influence of the filler on the blend flow, segregation tendency, tablet hardness and enteric release properties were studied using a mixture design, and the optimum filler composition was determined. Rapidly disintegrating tablets, which yielded a drug release of less than 10% after 2 hours in acidic medium, could be successfully prepared. The blend composition had a significant effect on the flowability, but less on the tablet hardness which was influenced by the selection of lubricant. Blends containing celluloses with low bulk densities exhibited a reduced tendency to segregate. Pellet distribution uniformity was further improved when using Ceolus™ UF-711 blended with a high-density grade. As a conclusion, multiparticulate tablets containing enteric pellets with preserved delayed-release properties were successfully prepared using Ceolus™ microcrystalline celluloses as tableting excipients. The optimized filler blend for the direct compression of 50% enteric pellets into tablets contained Ceolus™ UF-711 as main component in combination with Ceolus™ PH-200.

Keywords: Multiparticulate tablets, pellets, microcrystalline cellulose, Ceolus, eudragit, delayed release, segregation, blend uniformity

Introduction

Controlled or modified release dosage forms provide advantages over conventional immediate release systems with respect to pharmacokinetic properties and patient compliance. Oral delivery systems, which delay drug release to the small intestine or colon are indicated, when the active pharmaceutical ingredient (API) exhibits regional instabilities, is irritating to the stomach mucosa or has a narrow window of absorption. Multiple-unit systems with modified-release properties like coated pellets are preferred over monolithic systems, since the gastric residence time is less variable and food-dependent[1]. Additional benefits of pellets include a potentially enhanced and less variable API absorption due to the more uniform pellet distribution in the intestine, enhanced safety due to elimination of dose dumping, and increased formulation flexibility[2].

With regard to the final drug product, monolithic systems remain the dosage form of choice to provide the patient with an accurately dosed and conveniently administrable medication. Most popularly, functionally coated pellets are converted into monolithic systems by filling them into hard shell capsule or compression into tablets. Tableting yields benefits over capsule-filling with respect to costs, use of standard equipment, production throughputs, stability and susceptibility to tampering[3].

However, the tableting of functionally coated pellets is technologically challenging. During compression, the

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release-controlling film coating may be damaged due to pellet deformation and fragmentation, resulting in a loss of the modified-release properties. Furthermore, multiparticulate tablets exhibit low mechanical strength as hardness decreases and friability increases as a function of the pellet loading[4,5]. High proportions of tableting excipients are necessary to cushion the pellets during compaction and provide sufficient tablet strength, hence limiting the amount of pellets that can be loaded into the tablet. Furthermore, differences in particle size, density and flow properties between pellets and powdered tableting excipients promote blend segregation and failure of tablet content uniformity during tablet compression[6].

Microcrystalline cellulose (MCC) is still the excipient of choice for direct compression applications due to its favorable physical properties[7]. Attributed to its good plastic deformability, tablets of high strength can be obtained at low compaction forces, which is favorable for pellet integrity[8]. Different MCC grades varying in bulk density, particle size and shape, powder flow and compactibility are available. Products with low bulk densities including Ceolus™ KG-802 or KG-1000 exhibit large length-to-diameter ratios and excellent plastic deformability, but powder flow may be compromised. On the other hand, more spherical MCC grades with higher bulk densities grades including Ceolus™ PH-101, PH-102 and PH-200 show superior flow, but higher compaction forces are required to produce tablets of high strength. Ceolus™ UF-711, a recently developed MCC grade, exhibits a unique morphology of aggregated, oblong rods forming comparatively round particles of high porosity promoting flowability, while maintaining high compactibility.

The objective of this study was to investigate the properties of Ceolus™ microcrystalline celluloses as filler excipients for the direct compression of enteric-coated pellets. Applying a mixture design of experiment, the influence of four MCC grades on blend flowability and segregation tendency and on tablet hardness and delayed-release characteristics was studied. Based on these criteria, the optimum filler composition for tablets containing 50% enteric pellets was determined.

Materials and methods

Materials

Anhydrous theophylline, glyceryl monostearate, magnesium stearate, stearic acid and Tween® 80 were purchased from Spectrum Chemicals (Gardena, CA). Microcrystalline cellulose spheres (Celphere™ CP-305), microcrystalline cellulose fillers (Ceolus™ UF-711, KG-802, PH-102, PH-200) and croscarmellose sodium (Kiccolate™ ND-2HS) were kindly provided by Asahi Kasei America Inc. (New York, NY). Poly(methacylic acid-co-ethyl acrylate) 1:1 (Eudragit® L 30 D-55) and poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1 (Eudragit® FS 30 D) aqueous coating dispersions were donated by Evonik Pharmapolymers (Piscataway, NJ). Hypromellose 2910 cp3 (Pharmacoat® 603 by Shin-Etsu) was provided by Biddle Sawyer (New York, NY), and triethyl citrate was obtained from Vertellus (Greensboro, NC).

Drug layering of Ceolus™ CP-305 spheres

An aqueous suspension containing 2% Pharmacoat® 603 and 10% theophylline was sprayed onto Ceolus™ CP-305 microcrystalline cellulose seed cores at a rate of 10g/min*kg in a Strea-1 fluid bed coater (Aeromatic Fielder, Switzerland) equipped with a Wurster column and a 1-mm fluid nozzle. The inlet temperature was set to 75°C (outlet temperature of 45–50°C) and the atomizing air pressure was 2.5 bars.

Enteric coating of active pellets

Drug-layered pellets were functionally coated with an aqueous dispersion of Eudragit® L 30 D-55 and Eudragit® FS 30 D (1:1 ratio) to achieve a polymer weight gain of 50%. The dispersion contained 12% polymer, triethyl citrate as plasticizer (TEC, 6.5% based on polymer weight), glyceryl monostearate (GMS, 5% based on polymer weight) as anti-tacking agent and Tween® 80 as surfactant (40% based on GMS). The coating dispersion was prepared as recommended by the polymer manufacturer[9]. Enteric coating was performed in the same fluid bed coater as described above, using 38°C as inlet temperature (27–30°C outlet temperature), 1.8 bars atomizing air pressure and a spray rate of 10 g/min*kg. The pellets were dried in a 40°C oven for 24 hours and then stored at room temperature and ambient humidity.

Preparation of tableting blends and direct compression of pellet-loaded tablets

Functionally coated pellets (50%, 425–600 µm size fraction), 5% Kiccolate™ ND-2HS and filler excipient(s) were mixed in a V-shell blender (Patterson-Kelley, Stroudsburg, PA) for 15 minutes at 25 rpm. Stearic acid was screened through a 30 mesh screen, added to the premixed composition at a 0.5% level and blended for another 3 minutes at 25 rpm. The type and level of lubricant, pellet content and compaction force were established in screening experiments. The formulations were directly compressed at 10 kN to yield concave tablets (400 mg, 10 mm diameter) using a single station manual Carver Press (Fred Carver, Menomonee, WI) connected to a digital force display (ISI Inc., Round Rock, TX) and equipped with 0.3937-inch diameter B tooling (04-04, #91459, Natoli Engineering, Saint Charles, MO).

Experimental design and blend optimization

A standard mixture design of experiments ({4, 2}simplex lattice) was generated using Design-Expert software version 8.0.4.1 (Stat-Ease, Inc., Minneapolis, MN). The influence of four microcrystalline cellulose grades as mixture components on the blend and tablet properties was

investigated at a significance level of $\alpha = 0.05$. The average particle sizes and bulk densities of the different Ceolus™ fillers are listed in Table 1.

Four response parameters were studied: The influence on the flow properties of the blend was expressed as the angle of repose of the filler blend. The segregation tendency of the tableting blend under forced motion was quantified as relative standard deviations of the pellet distribution after shaking. The influence of filler grades on tablet hardness was investigated. The ability of the different Ceolus™ fillers to function as cushioning agents and protect pellets from rupture of the functional coating during compression was quantified as the percent drug released from tablets after two hours dissolution at pH 1.2. The experimental design layout and the responses are listed in Table 2.

The optimum binary filler composition was determined by applying the optimization criteria shown in Table 3.

Angle of repose

Drained angle of repose testing according to USP 32 was performed by using a custom designed apparatus which consisted of a plastic funnel positioned 3.5 inches above a 3-inch diameter metal base. Filler blends were poured through the funnel and allowed to form a pile until a steady-state height was achieved. The cone height was measured and the angle of repose calculated. All measurements were performed in triplicate.

Forced blend segregation study

The blend segregation tendency was studied in a small-scale experiment simulating the mixture of horizontal and vertical motions which occur in feeders of automated tablet presses. Prior to the experiment, each blend was vigorously shaken in a plastic bag for 2 minutes to produce a homogeneous mixture. The material (60–65 g) was then poured into a polypropylene funnel (Nalgene® 150 mm, 30° angle, cylindrical orifice inner diameter 24 mm) which had been sealed at the bottom. The filled funnel was covered and placed in a sieve shaker (W. S. Tyler, Model RX-24, Salisbury, NC) for 20 minutes to force particle segregation.

The material was then collected from the funnel in three fractions (top, middle, and bottom) and sifted through a 45-mesh sieve (355 μm) to separate the pellets from the powder excipients. The pellet weight content in each fraction was determined. All experiments were performed in triplicate. The relative standard deviation for the pellet distribution in each blend was calculated using the average weight percentages of pellets in the top, middle and bottom fraction.

Tablet hardness

The tablet breaking force was determined with a tablet hardness tester (Vankel VK 200, Varian, Palo Alto, CA) and reported as the mean of 3 or 6 determinations.

Dissolution testing and drug assay

The drug release properties of the pellets and the multiparticulate tablets were studied in a paddle apparatus (Varian, Palo Alto, CA) according to USP 31 chapter <724> method A for delayed-release articles. One 400 mg tablet or 200 mg pellets was placed in

Table 1. Properties of different Ceolus™ microcrystalline celluloses (MCC). (Product information obtained from Asahi Kasei America, Inc. homepage).

MCC grade Ceolus™	Average particle size [μm]	Bulk density (g/cm^3)
PH-102	90	0.30
PH-200	170	0.35
KG-802	50	0.21
UF-711	50	0.22

Table 3. Criteria for the optimization of the filler blend for the compression of 50% pellets.

Name	Goal	Lower limit	Upper limit	Importance
A: UF-711	is in range	0.0	45.0	3
B: PH-102	is in range	0.0	45.0	3
C: PH-200	is in range	0.0	45.0	3
D: KG-802	is in range	0.0	45.0	3
Blend angle of repose	minimize	37.3	46.2	3
RSD blend segregation	minimize	2.55	5.00	3
Tablet hardness	maximize	7.7	10.8	3
Release in acid at 2 hrs	minimize	6.99	10.00	3

Table 2. Experimental design layout and responses for tablet formulations containing 50% pellets and 5% superdisintegrant.

Run	Component A UF-711 [%]	Component B PH-102 [%]	Component C PH-200 [%]	Component D KG-802 [%]	Response 1 Blend angle of repose [°]	Response 2 RSD blend segregation [%]	Response 3 Tablet hardness [kP]	Response 4 Release in acid at 2 hrs [%]
1	0.0	22.5	0.0	22.5	44.0	4.84	9.2	9.00
2	22.5	22.5	0.0	0.0	43.7	3.84	7.9	7.82
3	22.5	0.0	0.0	22.5	45.7	7.42	8.9	9.17
4	0.0	0.0	0.0	45.0	45.5	6.17	10.8	7.41
5	0.0	0.0	45.0	0.0	37.3	17.35	8.5	13.15
6	22.5	0.0	22.5	0.0	39.7	2.55	8.8	8.23
7	45.0	0.0	0.0	0.0	46.2	6.37	9.4	8.54
8	0.0	0.0	22.5	22.5	43.2	6.36	8.0	6.99
9	0.0	45.0	0.0	0.0	39.4	7.53	9.3	8.09
10	0.0	22.5	22.5	0.0	40.8	17.45	7.7	8.80

750 mL simulated gastric fluid pH 1.2 (SGF without pepsin) at 37.0 ± 0.5°C at a paddle rotation speed of 100 rpm (n = 3). After two hours, the pH was adjusted to 6.8 by adding 250 mL 0.2M tribasic phosphate buffer. The theophylline content in withdrawn samples was analyzed by HPLC (Waters Inc., Milford, MA) using a C_{18}-reversed phase column (Capcell PAK 3 mm * 100 mm, Shiseido Co, Japan) and a UV detector (996-PDA, Waters Inc. Milford, MA) extracting at 271.5 nm. A mixture of 20 mM phosphate buffer pH 5 and acetonitrile (9:1) was used as the mobile phase at a flow rate of 0.5 mL/ min, and the theophylline peak areas (retention time of 3.5 min) were determined with Empower version 5.0 software (Waters Inc.).

Results and discussion

Establishment of constant parameters and design layout

Screening experiments were conducted to establish constant formulation and process parameters. Tablets with pellet loadings ranging from 25–75% and containing all four fillers at an equal mass ratio were prepared. The 50% pellet level yielded tablets with high pellet load in combination with low friability (<1%) and sufficient hardness.

It was noted that lubrication had a strong impact on tablet hardness. For this reason, the influence of type and level of lubricant on the hardness-compression force profile was investigated in a second set of experiments. As shown in Figure 1 for 400 mg tablets comprising 50% pellets, blends without lubricant yielded the highest hardness values over the investigated force range (5–30 kN). Magnesium stearate and stearic acid in the blend decreased tablet hardness, due to coating of the MCC filler particles during blending which antagonizes bond formation during compaction, a behavior that is characteristic of plastically deforming tableting excipients[10]. Tablet hardness was further impacted by the level of agitation as could be demonstrated by shaking a magnesium stearate blend in a plastic bag which yielded tablets of low mechanical strength. Since the negative effects of magnesium stearate on friability and hardness of multiparticulate tablets have been reported previously[5], stearic acid was studied as an alternative lubricant at three levels (0.25%, 0.5%, 1%). Blends comprising 0.25% stearic acid yielded hard tablets, but the lubrication efficiency was insufficient. The intermediate level provided sufficient lubrication in combination with acceptable tablet hardness.

Based on these results, the following constant parameters were used for the experiments: 400 mg tablets containing 50% pellets, 5% superdisintegrant and 0.5% stearic acid were compressed at 10 kN. A {4, 2} simplex lattice mixture design was applied to investigate the effects of four Ceolus™ MCC qualities on blend and tablet properties. Binary blends corresponding to 22.5% of each component in the blend (midpoints of lattice edges) and pure blends corresponding to 45% of one filler in the blend (lattice vertices) were prepared and characterized regarding flowability, segregation tendency, tablet hardness and gastric resistance as summarized in Table 2.

Characterization of blends: flow properties and segregation tendency

The flow properties of powdered excipients are influenced by a multitude of factors including particle size,

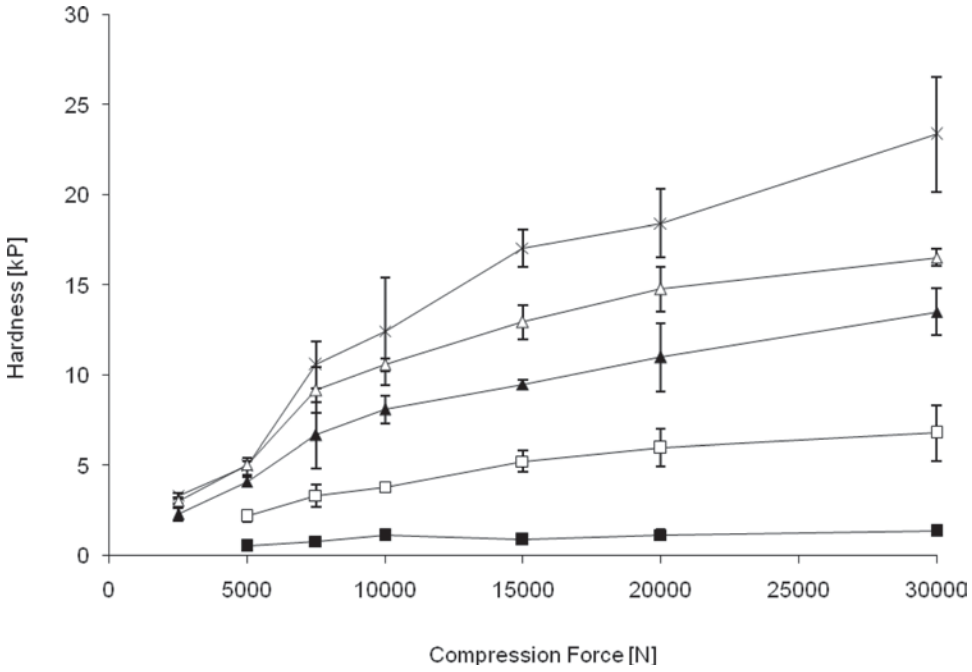

Figure 1. Influence of lubrication on the hardness-compression force profiles of tablets containing 50% pellets. (×) no lubricant; (△) 0.5% stearic acid, admixed in V-shell blender; (△) 1.0% stearic acid, admixed in V-shell blender; (□) 1.0% magnesium stearate, admixed in V-shell blender; (■) 1.0% magnesium stearate, admixed in plastic bag under vigorous shaking ($n = 3$).

shape, surface morphology and cohesive interactions. Acceptable blend flowability during tableting is pivotal for tablet mass uniformity and hence dosing accuracy. The results of filler blend flowability testing confirmed that highly compactable MCC grades (Ceolus™ UF-711 & KG-802) yielded larger angles of repose than blends containing MCC grades with more spherical particles and higher bulk densities (Ceolus™ PH-102 & PH-200, Table 2). The effect of the main factors (filler blend composition) on the angle of repose was highly significant ($p = 0.0049$), linear and free of interactions. This means that mixtures of different MCC qualities yielded intermediate flow angles in between the pure blends. As illustrated in Figure 2, the angle of repose of Ceolus™ UF-711 was reduced when blended with Ceolus™ PH-102 or PH-200.

Blend segregation into pellet-enriched and filler-enriched domains due to vibrational motions during tableting represents another pitfall which will result in the failure of unit dose uniformity. The extent of segregation is dependent on process and equipment parameters as well as on material properties. The obvious differences between pellets and powder excipients including particle size, shape, density, cohesive and adhesive forces promote diverging particle flow, convective transports and fluidization tendencies inside the hopper. The most common strategy to reduce segregation and improve the content uniformity of multiparticulate tablets is granulation of the tableting excipients to match the size of the pellets[5,11]. However, this procedure requires an additional processing step and may result in deteriorating compressibility and disintegration behavior of the filler[7].

To simulate the tableting process and force segregation, homogenized blends were subjected to vigorous shaking in a sieve shaker, and the pellet content in different locations of the blend (top, middle and bottom fraction) was determined (Figure 3). The relative standard deviation (RSD) for the pellet distribution between these three fractions was calculated and evaluated as response parameter (Table 2).

Figure 3 shows that pellets tended to cumulate in the top third of the blend when high-density MCC grades with low length-to-diameter ratios (Ceolus™ PH-200 & PH-102) were used as fillers. Vertical movements and the good flowability of these MCC qualities promoted the slippage of the smaller MCC particles into temporary voids created underneath the larger pellets, while the opposite motion (pellet slippage underneath dislocated powder excipients) was less likely to occur[12]. Percolation of fine particles through pellet interstices may have further contributed to this observation. As reported by Wagner and coworkers, blends prepared with coarse MCC grades exhibited a higher tendency for segregation during tableting on a high speed rotary press, than blends containing fibrous grades[13]. Some of the binary mixtures with low-density MCC fillers (Ceolus™ PH-200 & KG-802) yielded the highest pellet content in the middle fraction, which may be attributed to a combination of this effect with fluidization and hence enrichment of the light, highly porous MCC particles in the top fraction.

The RSD values listed in Table 2 demonstrate that formulations containing pure blends of Ceolus™ UF-711, KG-802 or mixtures thereof yielded intermediate blend homogeneity (RSD = 6–8%), while the blends containing pure Ceolus™ PH-200 or in mixture with PH-102 were highly inhomogeneous after shaking (RSD > 17%). These results suggest that fibrous, low-density grades were superior to prevent blend segregation, which was

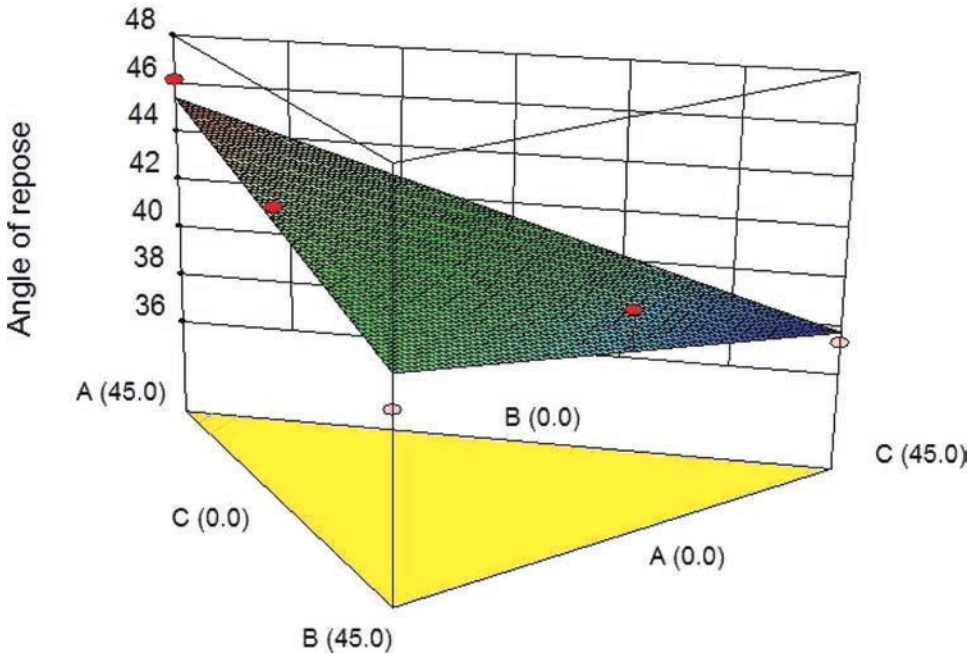

Figure 2. 3D response surface plot showing the angle of repose of the filler blend as a function of the mixture components. A: Ceolus™ UF-711; B: PH-102; C: PH-200 (D: KG-802 = 0.0).

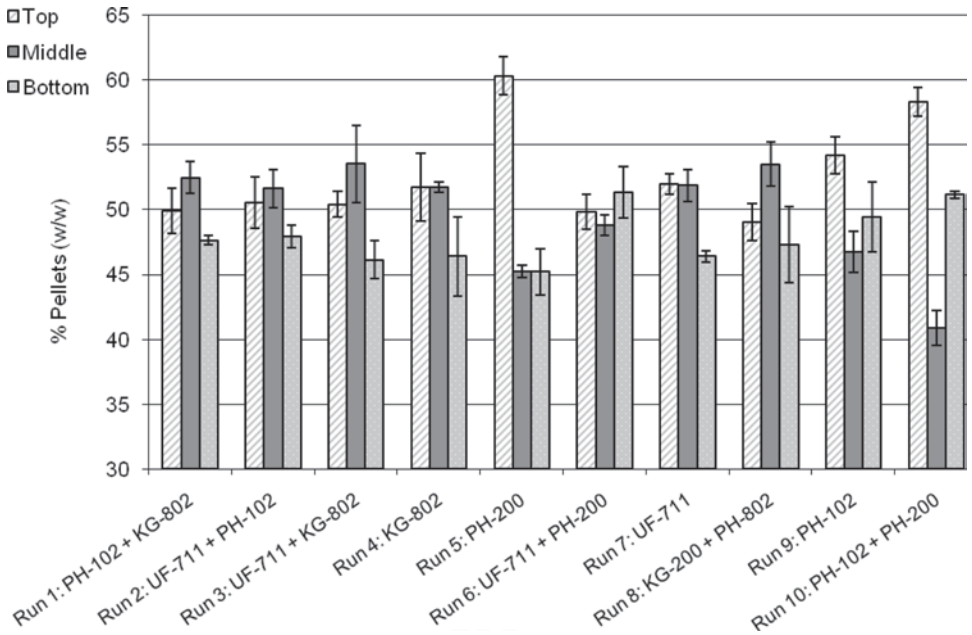

Figure 3. Pellet weight distribution in the top, middle and bottom fraction of the tableting blends after forced segregation. (Error bars show the standard deviation of 3 replicates.)

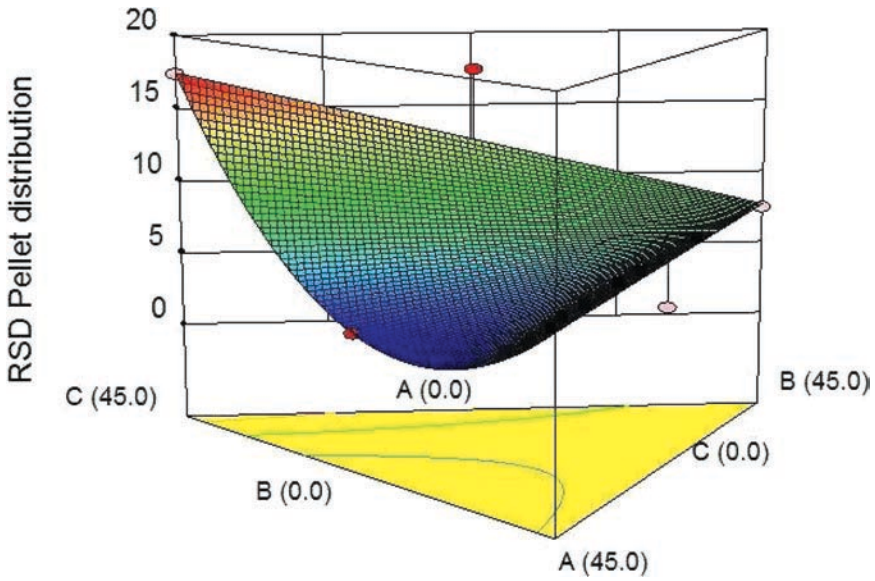

Figure 4. 3D response surface plot showing the relative standard deviation of the pellet distribution in the tableting blend after forced segregation as a function of the mixture components. (A) Ceolus™ UF-711; (B) PH-102; (C) PH-200 (D: KG-802 = 0.0).

presumably due to their ability to stabilize the pellets in their blend position during shaking. The binary blend of Ceolus™ UF-711 with PH-200 yielded the most uniform pellet distribution (RSD = 2.55%). The response surface plot in Figure 4 illustrates a marginally insignificant interaction between these two MCC qualities ($p = 0.0784$) with reduced blend segregation when Ceolus™ UF-711 was mixed with a small percentage of PH-200.

Characterization of tablets: hardness and delayed-release dissolution properties

Compression of blends at 10 kN yielded tablets with hardness values ranging between 7.7 and 10.8 kP (Table 2). Tablets of maximum hardness (≥10 kP) were obtained when highly compactable Ceolus™ KG-802 was used in the blend, but the influence of different mixture components on tablet hardness was not statistically significant ($p = 0.2795$ for linear mixture model). The response surface plot illustrates the lack of effect of different MCC fillers on tablet hardness (Figure 5). It is likely that the high pellet load extenuated differences in compactibility between the different MCC qualities. At 50% pellet loading, the formation of a coherent MCC matrix was disturbed, and tablet failure was triggered by crack initiation at pellet locations independently of the mechanical strength of the MCC matrix.

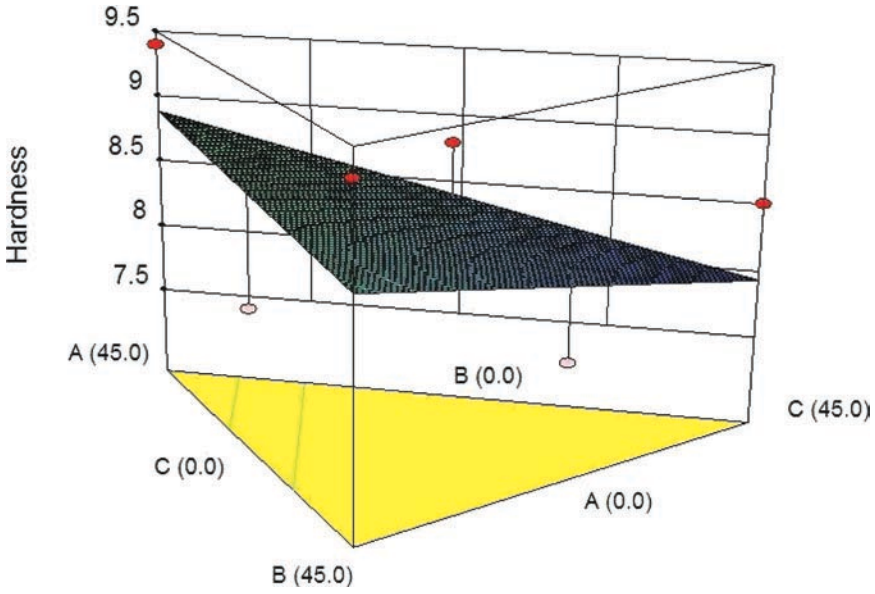

Figure 5. 3D response surface plot showing the hardness of tablets compressed at 10kN as a function of the mixture components. (A) Ceolus™ UF-711; (B) PH-102; (C) PH-200 (D: KG-802 = 0.0).

Addressing the release properties, it is well known that pellets may lose their modified-release characteristics during compression due to particle deformation, fragmentation and damage of the functional coating. It has been reported that pellets located at the tablet surface are more prone to damage than pellets in the interior of the tablet as they came directly in contact with the steel punches during compression[14,15]. Film damage was also demonstrated to be more pronounced at high pellet loadings due to an increase in pellet-pellet contacts[16–18]. Numerous strategies have been explored to minimize film damage during tableting including using harder pellets[19] or lower compaction forces[20], increasing the thickness or the flexibility of the functional film[19,21,22], preparing films with self-healing properties[23], and adding plastically deforming excipients that cushion the pellets against compression forces[6,20,24–27].

Chapter <724> of USP 31 limits the drug release from delayed-release dosage forms to maximum 10% after 2 hours at pH 1.2, while more than 80% of the drug has to be released within 45 minutes at pH 6.8. Prior to tableting, the enteric-coated pellets fulfilled these requirements with 0.9% theophylline released after 2 hours in acid and more than 99% theophylline released 45 minutes after pH increase to 6.8 (Figure 6). After compression, the drug release from tablets at pH 6.8 was even faster within the initial 30 minutes after pH change as the tablets disintegrated rapidly within 1 minute and the released pellets showed a lower tendency to stick or form cones in the bottom of the dissolution vessel. With regard to gastric resistance, the drug release after 2 hours in acid increased slightly after tableting to 6.99–13.15% depending on the filler composition (Table 2, Figure 6). While the linear mixture model was marginally insignificant ($p = 0.0597$), the quadratic term of factor C (Ceolus™ PH-200) was highly significant ($p = 0.0094$). This non-linear dependency of the gastric resistance from the amount of Ceolus™ PH-200 in the tableting blend is visualized in Figure 7. In the absence of Ceolus™ PH-200, the release is independent of the filler composition comprising the three other MCC qualities (release within 7.41–9.17%). When low amounts of Ceolus™ PH-200 were used in combination with other MCC grades, the drug release slightly decreased, demonstrating a positive effect on pellet protection during compressing. At high Ceolus™ PH-200 levels, however, the opposite effect was observed with the pure blend failing the 10% release limit (13.15% released). This behavior may be correlated with the previously described high tendency of the Ceolus™ PH-200 formulations for blend segregation. During the die filling process, blend segregation within the die cavity may promote pellet accumulation at the bottom and the top of the tablet, increasing the number of pellets that are exposed to the punches. Similarly, Wagner and co-workers observed increased pellet concentrations at the tablet surfaces when coarse MCC grades were used for tableting of pellets. This inhomogeneous pellet distribution correlated with more pronounced pellet damage, while smaller and more fibrous fillers stabilized the pellets at their location in the mixture during tableting[13,15].

The drug release results also demonstrated that Ceolus™ UF-711, KG-802, PH-102 or their mixtures were suitable fillers to preserve the enteric properties of pellets when tablets with 50% pellets were prepared. For these three grades, the protective effect did not correlate with bulk density or particle size. This particle size independence for MCC fillers within a certain size range is supported by the findings of Yao and coworkers[28]. They showed that while the protective effect of most studied

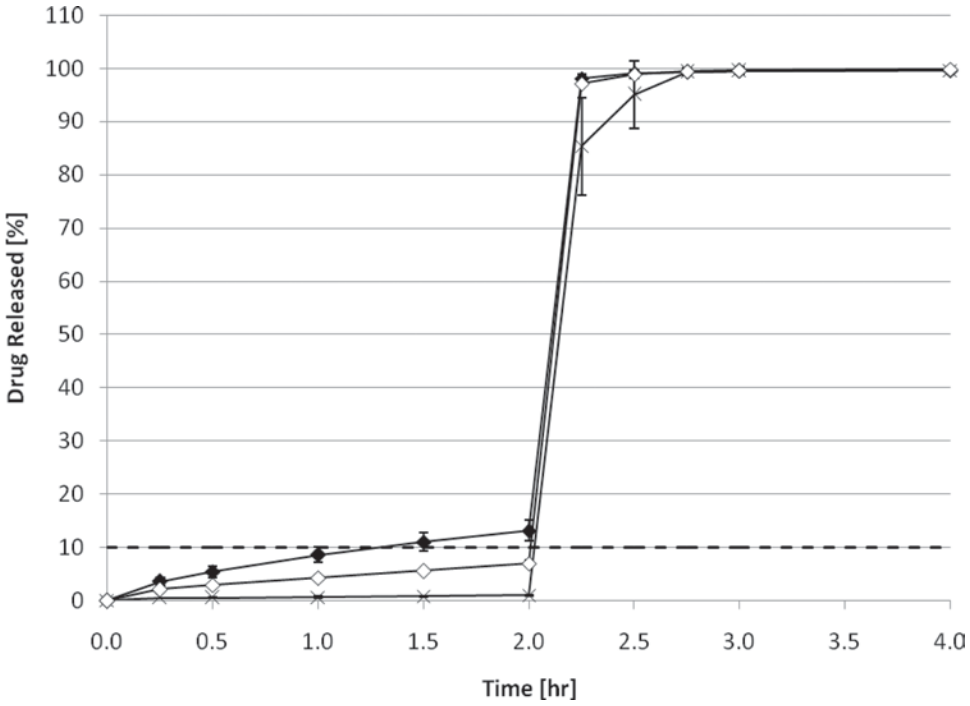

Figure 6. Dissolution properties of enteric-coated pellets: (×) before tableting; (◇) after tableting of 50% pellets with Ceolus™ PH-200 and Ceolus™ KG-802, (◆) after tableting of 50% pellets with Ceolus™ PH-200. Dissolution: USP paddle apparatus, 100 rpm, 37 ± 0.5°C, $n = 3$, 2 hours in 750 ml simulated gastric fluid pH 1.2 (without pepsin), after 2 hours pH change to pH 6.8 by addition of 250 ml 0.2 M tribasic phosphate buffer. (Error bars show the standard deviation of 3 replicates.)

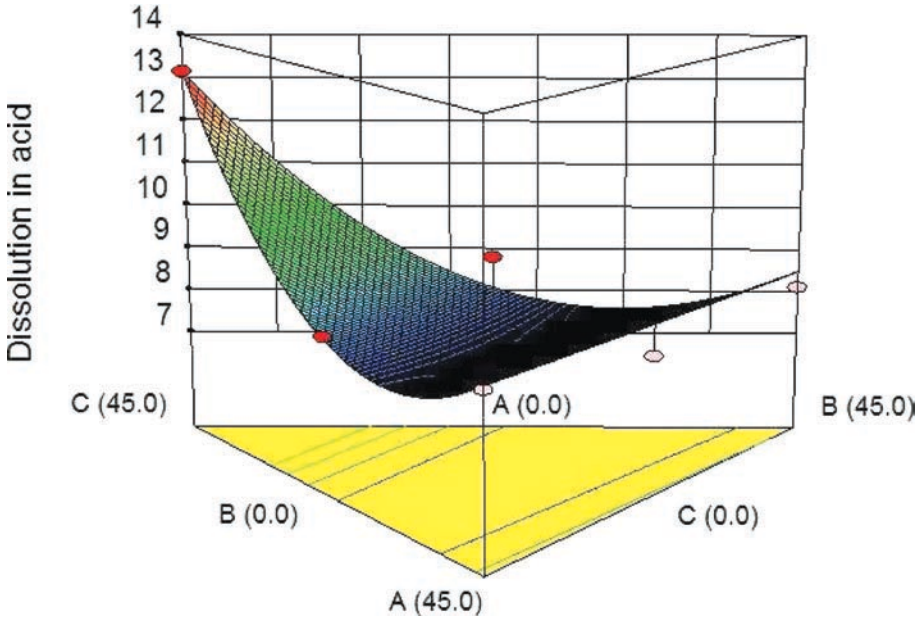

Figure 7. 3D response surface plot showing the percent of drug released from tablets after 2 hours dissolution at pH 1.2 as a function of the mixture components. (A) Ceolus™ UF-711; (B) PH-102; (C) PH-200 (D: KG-802 = 0.0).

fillers decreased with increasing particle size, two different particle sizes of MCC yielded similar cushioning properties.

Optimization of the filler composition

The optimum filler composition producing the most desirable overall performance was determined using the statistical software. All four responses were considered equally important, and the following optimization criteria were applied (Table 3): minimization of the angle of repose, minimization of the RSD of pellet distribution after forced segregation with a maximum value of 5%, maximization of tablet hardness and minimization of the drug release in acid with a maximum release of 10% after two hours. The three proposed filler compositions showing the most desirable overall performance

Table 4. Optimized filler compositions and predicted properties of tablet formulations containing 50% enteric-coated pellets.

Solutions: Number	UF-711 [%]	PH-102 [%]	PH-200 [%]	KG-802 [%]	Blend angle of repose [°]	RSD blend segregation [%]	Tablet hardness [kP]	Release in acid at 2 hrs [%]	Desirability
1	25.2	0.0	16.5	3.3	42.7	2.55	8.6	7.70	0.548
2	26.1	2.7	16.3	0.0	42.4	2.55	8.5	7.74	0.542
3	27.6	0.0	17.4	0.0	42.5	1.72	8.5	7.79	0.535

and their predicted properties are listed in Table 4. All proposed blends contain Ceolus™ UF-711 as the main filler in combination with smaller amounts of Ceolus™ PH-200 as second mixture component. As shown in the previous experiments, this combination was particularly desirable in terms of minimum blend segregation tendency.

Conclusions

The successful preparation of multiparticulate tablets containing 50% enteric-coated pellets was demonstrated using Ceolus™ microcrystalline celluloses as fillers for direct compression. Blend flow was passable and significantly influenced by the composition of the filler blend. Bulky, highly compressible celluloses reduced the segregation tendency between pellets and powder excipients. With respect to tablet hardness, a careful selection of type and level of lubricant was pivotal, while the filler composition showed no significant effect under the investigated conditions. Drug release from multiparticulate tablets remained below 10% after two hours at acidic pH due to the good cushioning properties of the studied microcrystalline celluloses during compression. However, inhomogeneous pellet distributions within the tablet due to blend segregation during die filling needs to be avoided. Optimization studies showed that the novel excipient Ceolus™ UF-711 was most beneficial for pellet compression and should be used in combination with smaller amounts of Ceolus™ PH-200 to achieve the best overall product performance.

Declaration of interest

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