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RESEARCH ARTICLE

Use of highly compressible Ceolus™ microcrystalline cellulose for improved dosage form properties containing a hydrophilic solid dispersion

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Abstract

The development of amorphous solid dispersions containing poorly soluble drug substances has been well-documented; however, little attention has been given to the development of the finished dosage form. The objective of this study was to investigate the use of Ceolus™ microcrystalline cellulose, a highly compressible excipient, for the production of rapidly disintegrating tablets containing a hydrophilic solid dispersion of a poorly soluble drug, indomethacin. Solid dispersions of indomethacin and Kollidon® VA64 were prepared by hot melt extrusion and characterized for amorphous nature. Milled dispersion particles at 500 mg/g drug loading were shown to be amorphous by differential scanning calorimetry and provided rapid dissolution in sink conditions. Physical characterization of the milled extrudate showed that the particle size of the intermediate was comparable with Ceolus™ PH-102 and larger than the high compressibility grades of microcrystalline cellulose selected for the trial (Ceolus™ KG-802, Ceolus™ UF-711). Preliminary tableting trials showed that dissolution performance was significantly reduced for formulations at dispersion loadings in excess of 50%. Using a mixture design of experiments (DOE), the levels of PH-102, KG-802, UF-711, and PH-301 were optimized. Trials revealed a synergistic relationship between conventional grades (PH-102 and PH-301) and highly compressible grades (KG-802 and UF-711) leading to improved compression characteristics and more rapid dissolution rates. The formulation and resulting compressibility were also shown to have an impact on *in vitro* supersaturation indicating tablet formulation could impact oral bioavailability. Through the use of highly compressible microcrystalline cellulose grades such as Ceolus™ KG-802 and UF-711, it may be possible to maximize the bioavailability benefit of amorphous solid dispersions administered as tablet dosage forms.

Keywords: Melt extrusion, solid dispersion, compression, dissolution, supersaturation

Introduction

The use of amorphous solid dispersions to enhance the dissolution rate has been well-understood for nearly a half century and many new pharmaceutical products have been developed as such to improve oral bioavailability of the poorly soluble medication[1]. Several of the most prominent recent examples include Prograf®, Sporanox®, and Kaletra®; however, these products are not tablets or are designed to provide a prolonged dissolution rate. In many cases, it is necessary to provide a rapid dissolution rate in order to yield the most significant improvement in exposure. Dissolution rates for many poorly soluble compounds have been shown to correlate with exposure and this fundamental concept has become one of the pillars of the Biopharmaceutical Classification System (BCS)[2]. Amorphous formulations provide a very unique situation when examining the correlation of dissolution rate to exposure due to the underlying thermodynamics of the system. As a result of the higher free energy state, amorphous forms are

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capable of supersaturating the aqueous environment with the poorly soluble drug substance[3]. This supersaturation is transient and precipitation ultimately brings the system to thermodynamic equilibrium[4]. For effective drug delivery of these systems, the dissolution rate will determine both the degree and the extent of supersaturation. Situations of prolonged disintegration and delayed release increase the duration that solid dispersion particles are exposed in an aqueous environment and may contribute to recrystallization of the amorphous form in the solid state leading to decreased exposure[5]. This places increased importance on the development of an effective dosage form, which is able to provide rapid disintegration to facilitate dissolution of the solid dispersion. Although not commonly studied in the research literature, this issue has been cited as a potential limitation to the development of amorphous formulations and presents significant industrial limitations to the advancement of these dosage forms[6].

Conventional immediate release tablet formulations consist of several basic components, including: diluents, binders, disintegrants, glidants, and lubricants[7]. For many formulations, the application of standard materials is sufficient to provide the required release properties. When the drug substance is presented as a hydrophilic solid dispersion loading limitations may occur, which increase the size of the dosage form and potentially reduce patient compliance. Gelling tendencies of the material, which are readily observed when attempting to disperse such systems as a suspension also impact the tablet formulation and extend disintegration times. This may be compensated for by reducing the solid dispersion content and increasing the diluent and disintegrant levels. Compression force is also critical since it leads to a change of internal porosity, which plays a role in the observed disintegration behavior. The addition of binders improves compressibility[7,8] but may also further facilitate the gelling tendency of the dosage form. Exploiting the commonly cited advantage of fine particle microcrystalline cellulose to improve compressibility[9], these materials (Ceolus™ UF-711 and KG-802) were hypothesized to present potential advantages as an alternate material in solid dispersion drug product formulations, which may have a tendency to gel. Several new grades of microcrystalline cellulose, developed by Asahi Kasei, provide unique advantages for improved compressibility[10]. These fine particle grades exhibit excellent compressibility characteristics without the gelling tendency of many commonly used binder materials. It was hypothesized that incorporation of these materials as a type of binder additive could provide improved compressibility and disintegration characteristics that could improve overall dosage form performance.

The development of amorphous solid dispersions containing poorly soluble drug substances has been well-documented; however, little attention has been given to the development of the finished dosage form. The objective of this study was to investigate the use of Ceolus™ brand microcrystalline cellulose, a highly compressible excipient, for the production of rapidly disintegrating tablets containing a hydrophilic solid dispersion of a poorly soluble drug, indomethacin. Within the study design, prototype tablet formulations were evaluated for physical properties and drug delivery characteristics. A design of experiments approach was then utilized to investigate the impact of microcrystalline grades and respective levels on critical product attributes.

Materials and methods

Materials

Indomethacin, USP was purchased from Hawkins Chemical Company (Minneapolis, MN). Vinyl acetate–vinyl pyrrolidone copolymer (Copvidone, USP/NF, Kollidon® VA 64) was provided by BASF Corporation (Florham Park, NJ). Microcrystalline cellulose (Ceolus™ UF-711, Ceolus™ KG-802, Ceolus™ PH-102, Ceolus™ PH-301) was provided by Asahi Kasei America Inc. (New York, NY). Croscarmellose sodium, USP/NF (Ac-Di-Sol®) was provided by FMC Biopolymer (Philadelphia, PA). Colloidal silicon dioxide, USP/NF (Aerosil® 200) was provided by Evonik Corporation (Piscataway, NJ). Magnesium stearate was purchased from Spectrum Chemicals Corporation (Gardena, CA).

Hot melt extrusion

Hot melt extrusion was conducted using a Haake Minilab conical co-rotating twin screw extruder. Formulations of indomethacin and Kollidon® VA64 were prepared using a mortar and pestle. Powder blends were manually fed into the extruder, maintained at a temperature of 150°C, screw speed of 150 rpm, and 2.0 mm single bore round opening die. After processing the extrudate was milled using an impact mill and passed through a 60 mesh US sieve to achieve a particle size of <250 μm. Extrudate powder was stored in double lined polyethylene bags until used in subsequent testing.

Differential scanning calorimetry

Differential scanning calorimetry was performed using a TA Instruments Model 2920 DSC (New Castle, DE) and analyzed using TA Universal Analysis 2000 Software. Samples were weighed to 15 ± 2 mg in aluminum crimped pans (Kit 0219-0041; Perkin-Elmer Instruments, Norwalk, CT). Testing was conducted at a ramp rate of 10°C/min from 5°C to 200°C.

Blending

Prior to blending, microcrystalline cellulose and croscarmellose sodium were screened using an 18-mesh sieve. Colloidal silicon dioxide was screened a 40-mesh screen. Pre-screened indomethacin extrudate, microcrystalline cellulose, croscarmellose sodium, and colloidal silicon dioxide were added to the V-shell blender and mixed for 10 min at 25 rpm. Magnesium stearate was screened using a 30-mesh sieve and charged into

the V-shell blender. The blend was lubricated by mixing the V-shell blender for 4 min at 25 rpm. The final blends were discharged and stored in polyethylene bags until use.

Bulk and tapped density testing

Bulk and tapped density testing were conducted based on the USP method. In brief, a known amount of powder was added to a 250-mL graduated cylinder. The resulting volume was measured. Following measurement, the cylinder was tapped for 1250 iterations and the volume was measured. Density values were then calculated based on the weight of material and measured volumes. All testing was performed in triplicate.

Particle size distribution by sieve analysis

Particle size distribution was performed by sieve analysis using a mechanical sieve shaker (W.S. Tyler, Model RX-24, Salisbury, NC). A known amount of powder was accurately dispensed and charged to a sieve nest consisting of a 40, 60, 80, 120, 170, and 325 US standard mesh series. Samples were shaken for 15 min and the resulting amount of powder retained on each screen was accurately weighed. Based on the mass distribution, cumulative particle size distribution plots were generated. Mean particle size was identified as the point at which 50% cumulative retention was achieved.

Angle of repose

Angle of repose testing was performed according to USP 32 using a custom designed apparatus. In brief, a funnel was placed 3.5 inches above a 3-inch diameter metal base. Powder blends were poured through the funnel and onto the base forming a cone. When the cone reached steady state, the height of the cone was measured and the corresponding angle was calculated. All measured are reported in triplicate.

Tablet compression

The formulations were directly compressed at the target compression force using a single station manual Carver Press (Fred Carver, Menomonee, WI) with a digital force display (ISI Inc., Round Rock, TX) and using standard concave 0.3937″ round tooling (04-04, #91459; Natoli Engineering, Saint Charles, MO). Tablet hardness was determined using a Vankel VK 200 hardness tester (Varian, Palo Alto, CA). Total tablet strength was 100 mg of indomethacin.

Sink dissolution testing

Sink dissolution testing was performed based on the USP XXIX Apparatus II dissolution test operated at 50 rpm using a VK 7010 dissolution apparatus (Varian, Inc., Palo A lot, CA) and VK 8000 autosampler (Varian, Inc.) by placing 1 × 100 mg tablet into each dissolution vessel. Testing was conducted using 900 mL of 50 mM pH 6.8 phosphate buffer to ensure ionization of indomethacin and sink conditions. Samples (5 mL) were withdrawn using the autosampler containing in-line 10 μm filters at 5, 10, 15, 30, 45, and 60 min.

Non-sink dissolution testing

Supersaturated dissolution testing was performed based on the USP XXIX Apparatus II dissolution test operated at 50 rpm using a VK 7010 dissolution apparatus (Varian, Inc., Palo Alto, CA) and VK 8000 autosampler (Varian, Inc.) by placing 1 × 100 mg tablet into each dissolution vessel. During testing each apparatus contained 900 mL of 0.1 N HCl media. Under these conditions, indomethacin was unionized and the system was considered non-sink. Samples (5 mL) were withdrawn without replacement at 5, 10, 15, 30, 45, and 60 min. The samples were immediately filtered using 0.2 μm PTFE membrane filters (Pall Corporation, East Hills, NY) and diluted with mobile phase at a 1:1 ratio.

High performance liquid chromatography

High performance liquid chromatography (HPLC) was conducted using a Waters (Waters Corporation, Milford, MA) HPLC system consisting of dual Waters 515 Syringe Pumps, a Waters 717 Autosampler and a Waters 996 Photo Diode Array extracting at a wavelength of 254 nm. Analysis was conducted using an isocratic method with a 250 mm × 4 mm column containing Pheonomenex Luna C18(2) 100Å and mobile phase of 1:1 sodium phosphate and acetonitrile. During testing, an injection volume of 20 μL was used and system suitability for linearity and reproducibility was assessed, $r^2 \geq 0.999$ and %RSD NMT 2.0%.

Statistical analysis

Minitab 14 was used as the statistical software package. ANOVA with Tukey pairwise testing was used to assess statistical differences between groups using an evaluation criteria of $P < 0.05$. Mixture design of experiment (DOE) features were used for the generation and analysis of the experimental protocol.

Results and discussion

Melt extrusion formulation verification

Melt extrusion of indomethacin was performed at 150°C and yielded a clear transparent glass having a green hue, which indicated solubilization of the drug substance in the polymer during the melt extrusion process. Motor torque was maintained to less than 100 N × cm during production and mass flow from the 2.0-mm die was consistent throughout production. These results were similar to results reported by Chokshi et al.[11], indicating that the melt extrusion method was appropriate for the production of indomethacin extrudate. The amorphous nature of the extrudate was confirmed using DSC, as shown in Figure 1. Crystalline indomethacin exhibited a melting endotherm at 163°C, whereas the physical mixture provided a substantial melting point depression. This indicated a high solubilization capacity of the molten

polymer for indomethacin. Examination of the DSC profile for melt extruded indomethacin showed the absence of a melting endotherm, indicating an amorphous form. Additionally, the melting point depression at 145°C for the physical mixture supported the use of processing temperatures at 150°C for the generation of an amorphous form.

Following extrusion, indomethacin extrudate was milled and screened to yield a final powder suitable for use in downstream blending and compression operations. Physical characterization of the milled extrudate relative to the proposed formulation excipients was conducted. As shown in Figure 2 and Table 1, indomethacin-milled extrudate provided a particle size similar to that

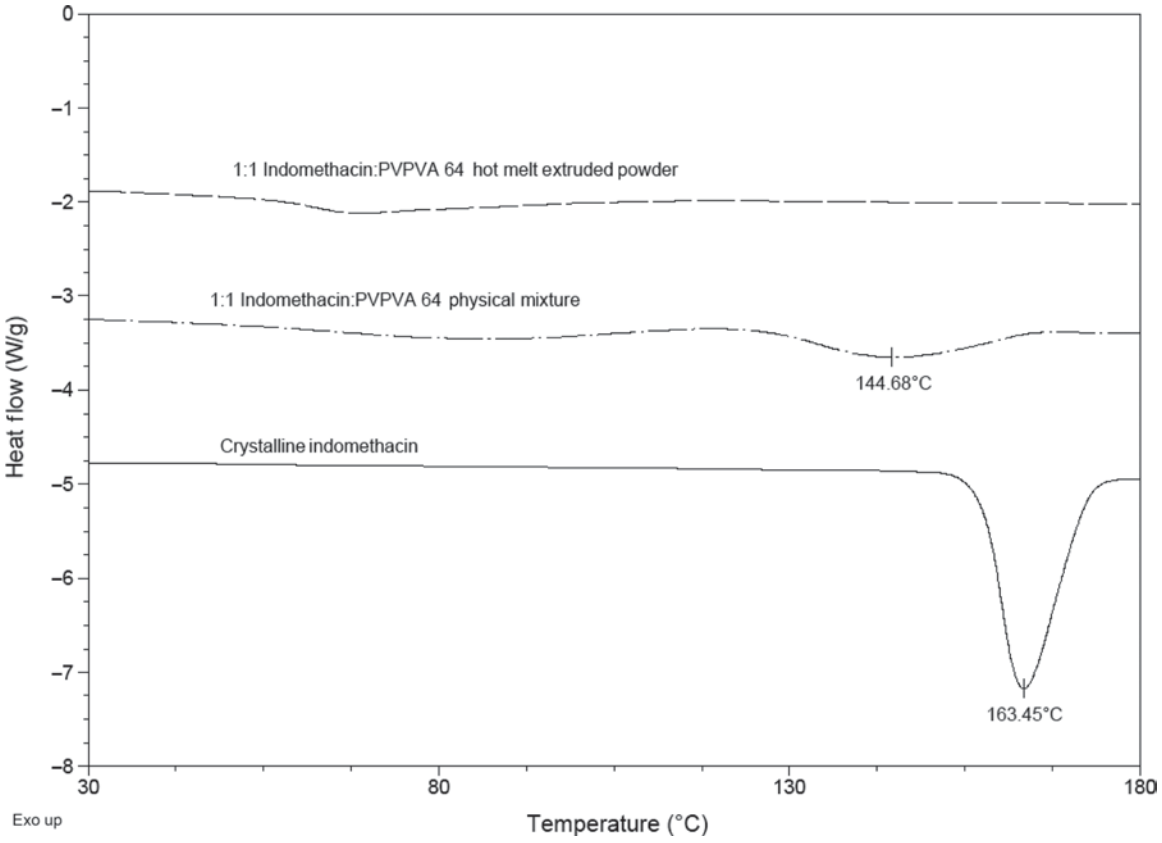

Figure 1. DSC profiles of crystalline indomethacin, physical mixture of indomethacin and Kollidon® VA 64, 500 mg/g and melt extruded indomethacin and Kollidon® VA 64, 500 mg/g.

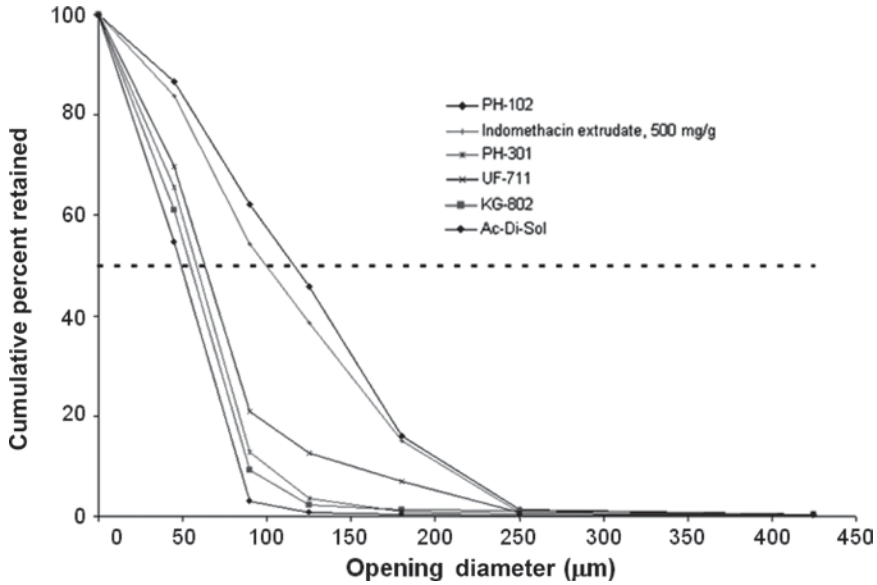

Figure 2. Particle size distribution of milled extrudate determined by sieve analysis.

of microcrystalline cellulose PH-102. This particle size was larger than that of the highly compressible grades of microcrystalline cellulose and also the superdisintegrant, croscarmellose sodium. Flowability properties of the milled extrudate also revealed acceptable characteristics for continued development. These data supported the use of melt extrusion and milling for the production of the amorphous indomethacin solid dispersion intermediate.

Prototype tablet formulation screening

Drug loading and superdisintegrant levels were also examined in order to establish an appropriate formulation range for use in the DOE phase of the study. Generally, increasing the level of extrudate within the formulation increases the potential for particle–particle contact between the solid dispersion particles. For hydrophilic dispersion particles which have a tendency to gel, the extent of particle–particle contact can lead to substantial gel formation which inhibits disintegration and dissolution. The level of superdisintegrant can also strongly influence formulation performance, with increasing levels generally correlated with improved tablet disintegration. The performance impact of superdisintegrant level was investigated within this study using a standard formulation consisting of solid dispersion (75%), microcrystalline cellulose (PH-102, level varied based on superdisintegrant level), colloidal silicon dioxide (1%), and magnesium stearate (1.0%). Dissolution studies of these tablets prepared at high compression forces illustrated the importance of superdisintegrant to provide robust dissolution performance. Tablets containing 5% and 10% exhibited limited impact to dissolution performance at high compression forces, whereas lower levels failed to provide robustness. Similar dissolution robustness has also been extensively shown for other tablet formulations. Based on these results, 10% superdisintegrant was selected to carry forward within the design of experiments (Figure 3).

Table 1. Physical properties of extrudate and tablet excipients.

Material	Mean diameter (μm)	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index	Angle of repose (θ)
Milled extrudate	100	0.694 ± 0.030	0.860 ± 0.009	0.192 ± 0.040	33.5 ± 2.2
KG-802	55	0.273 ± 0.014	0.412 ± 0.003	0.338 ± 0.031	35.6 ± 1.1
PH-102	116	0.372 ± 0.015	0.457 ± 0.006	0.188 ± 0.022	31.8 ± 1.1
UF-711	63	0.282 ± 0.014	0.407 ± 0.015	0.308 ± 0.012	34.9 ± 1.7
PH-301	58	0.427 ± 0.019	0.563 ± 0.037	0.241 ± 0.016	34.2 ± 1.2
Ac-Di-Sol	49	0.485 ± 0.041	0.657 ± 0.014	0.260 ± 0.078	36.9 ± 1.0

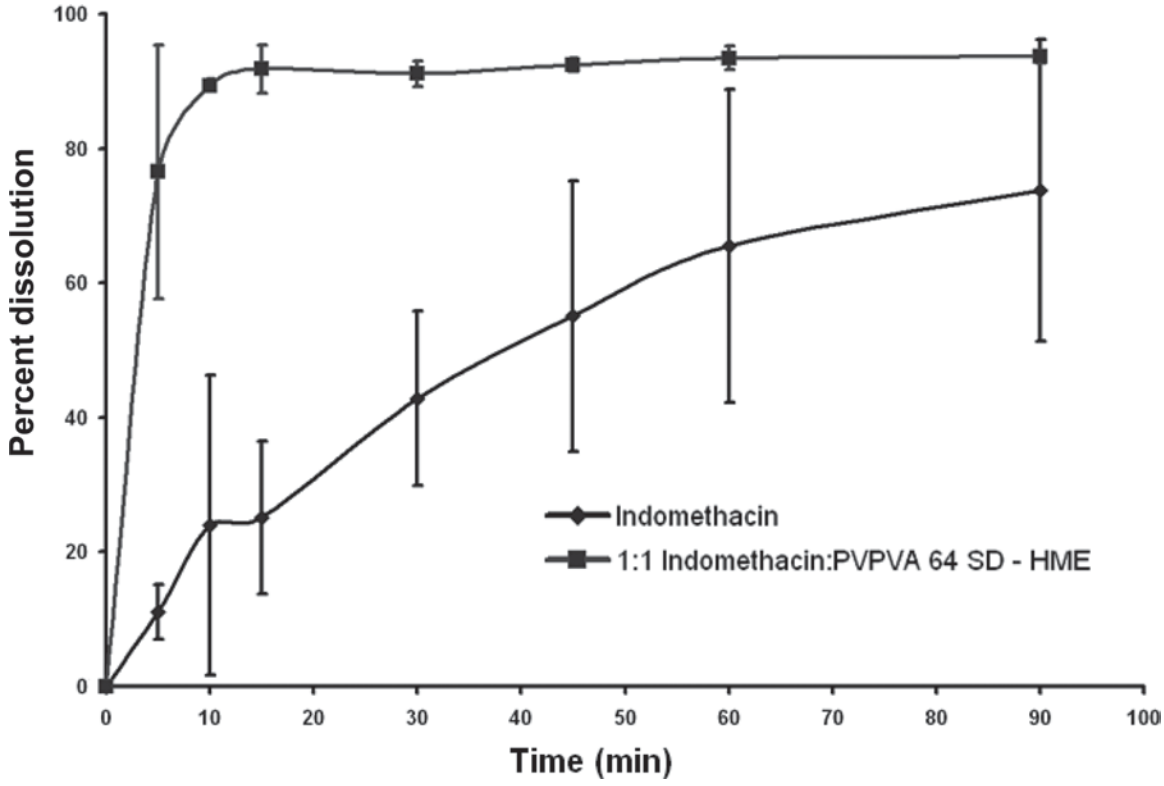

Figure 3. Dissolution behavior of crystalline indomethacin and indomethacin extrudate. Each vessel ($n = 3$) contained 900 mL of 50 mM pH 6.8 phosphate buffer using USP Apparatus II at 50 rpm. Error bars indicate ±standard deviation.

The impact of solid dispersion loading on dissolution rate was also examined to establish target levels for the design of experiments. Three different loading levels were examined (25%, 50%, and 75%) for sink dissolution behavior using tablets having a hardness of 13–17 kP. As shown in Figure 4, increasing the loading beyond 50% resulted in a reduction in dissolution rate for the solid dispersion suggested that the maximum loading for the study would be 50%. At loadings beyond 50% gelling of the tablets was observed, which resulted in incomplete disintegration and hindered dissolution. Interestingly, the release profile of the 25% formulation showed a muted release after initial burst. This behavior was attributed to the additional excipients present in the formulation, which provided a barrier for dissolution under the conditions used within this study as a result of the insoluble nature of the excipients. Although this decrease was observed at low dispersion loadings, the effect that it would have on bioavailability remains unclear. From the results of this work, the final solid dispersion loading for evaluation was selected at 50%. Further investigation of the non-sink performance for these formulations was not assessed.

Design of experiments evaluation

Data gathered during the prototype development sequence revealed that the maximum viable solid dispersion loading was ~50% and superdisintegrant levels were appropriately fixed at 10%. Selection of these levels at fixed values would minimize the potential impact on the formulations due to subtle batch to batch variation allowing for an unbiased evaluation of interactions between the levels and types of microcrystalline cellulose used in the study. The DOE selected for use in the trial is presented in Table 2. Within the scope of the study, density, flowability, and dissolution rate were evaluated to identify the optimum formulations.

Flowability metrics of powder formulations were evaluated using a combination of density measurements with angle of repose trials. The data, presented in Figure 5, showed that all formulations exhibited borderline flowability with a general trend of decreasing flowability with increases in low-density and highly compressible microcrystalline level. Although this trend was observed, there were no statistically significant factors that impacted performance. In general, these values were also greater than those reported for the major product constituents, milled extrudate and

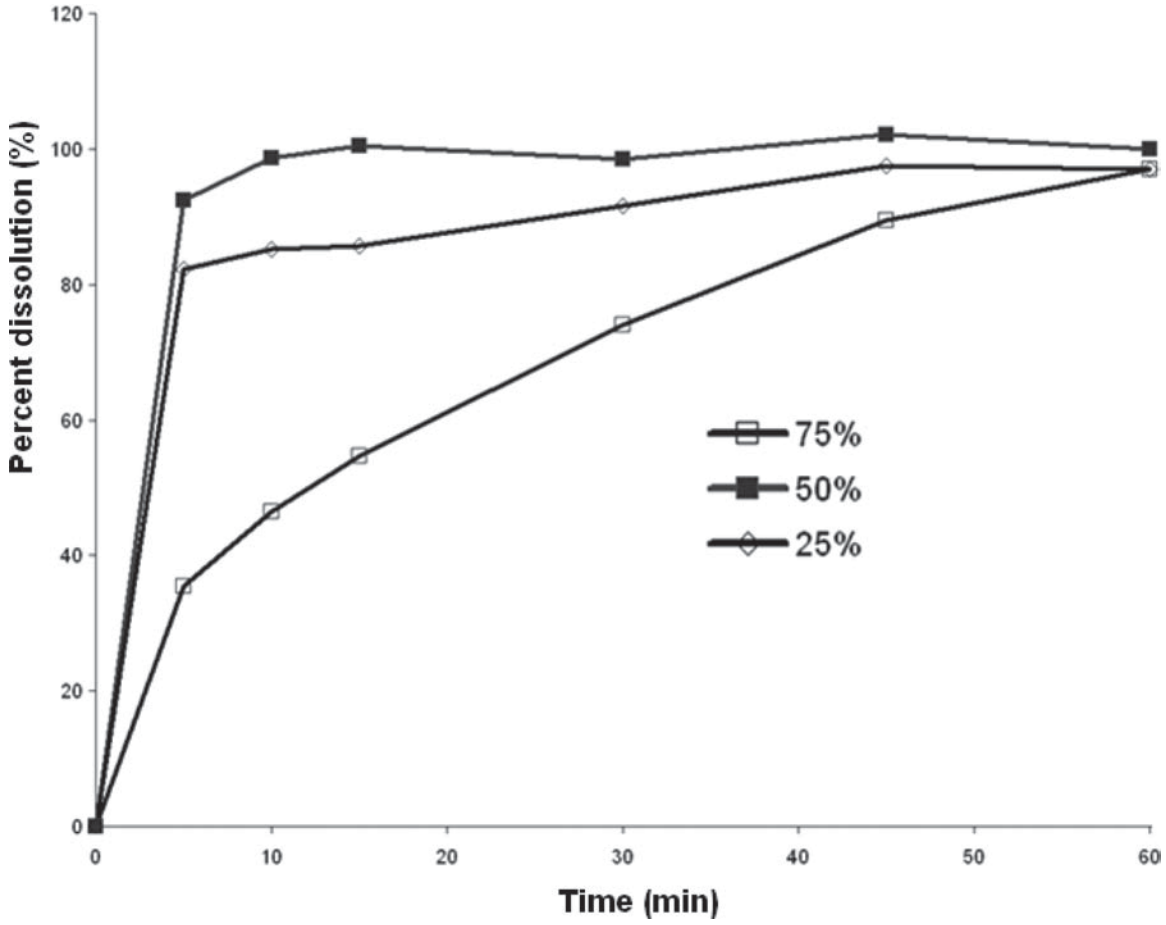

Figure 4. Sink dissolution profile for tablets containing varying levels of solid dispersion. Each vessel ($n = 1$) contained 900 mL of 50 mM pH 6.8 phosphate buffer using USP Apparatus II at 50 rpm.

Table 2. Design of experiments for tablet formulation development.

#	Extrudate	PH-102	UF-711	KG-802	PH-301	Ac-Di-Sol	Magnesium stearate
1	50.000	9.750	0.000	14.625	14.625	10.000	1.000
2	50.000	9.750	0.000	0.000	29.250	10.000	1.000
3	50.000	9.750	14.625	0.000	14.625	10.000	1.000
4	50.000	9.750	4.875	19.500	4.875	10.000	1.000
5	50.000	9.750	14.625	14.625	0.000	10.000	1.000
6	50.000	9.750	9.750	9.750	9.750	10.000	1.000
7	50.000	9.750	0.000	29.250	0.000	10.000	1.000
8	50.000	9.750	19.500	4.875	4.875	10.000	1.000
9	50.000	9.750	29.250	0.000	0.000	10.000	1.000
10	50.000	9.750	4.875	4.875	19.500	10.000	1.000
11	50.000	39.000	0.000	0.000	0.000	10.000	1.000
12	50.000	0.000	39.000	0.000	0.000	10.000	1.000
13	50.000	0.000	0.000	39.000	0.000	10.000	1.000

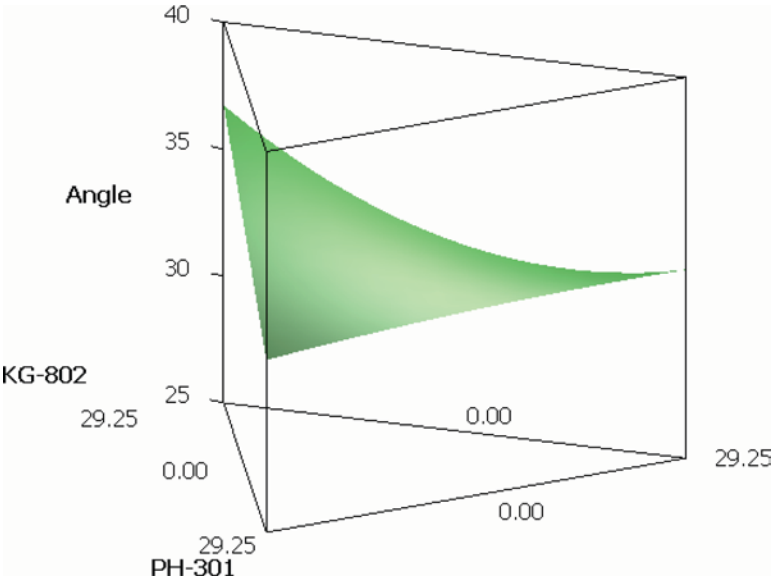

Figure 5. Surface response plot of flowability as a function of excipient level.

PH-102 grade material. This indicated that one may anticipate a slight decrease in flowability based on the level of low-density material present; however, the magnitude of such changes within the ranges of the formulation studied would not significantly impact material performance. In extreme cases where the low-density microcrystalline cellulose would make up the majority of the formulation, these issues would become more exaggerated.

Compression behavior of each formulation was evaluated over a series of compression forces, with tablet hardness plotted as the relevant product response. Compression profiles revealed an improvement in material compressibility for mixtures of PH-102, UF-711, and KG-802, as shown in Figure 6. Previously published manufacturer information on the use of UF-711 and KG-802 showed improved compressibility of a formulation due to the small particle size and greater porosity of the material. Similar applications to minimize deformation of coated pellets using highly compressible microcrystalline cellulose have also been shown[12,13]. In this work, combinations of the low-density and conventional grades showed synergistic behavior, with a statistically significant trend observed. Further examination of this behavior suggested that the small particle size microcrystalline cellulose functioned as a binder and cushioning agent, filling in voids between the PH-102 and solid dispersion particles, which represented the major fraction of the blend. Similar performance was also reported for compression of pressure sensitive materials such as pellets, where microcrystalline cellulose was used as a cushioning agent[14]. When exceeding a certain level of highly compressible material within the formulation, a slight reduction in tablet hardness as a function of compression force was observed. This behavior is shown on the surface response plot generated from the statistical analysis of compression performance in Figure 7. The reason for this decrease in tablet hardness at elevated excipient levels was unable to be conclusively determined within the scope of this study; however, the observed results

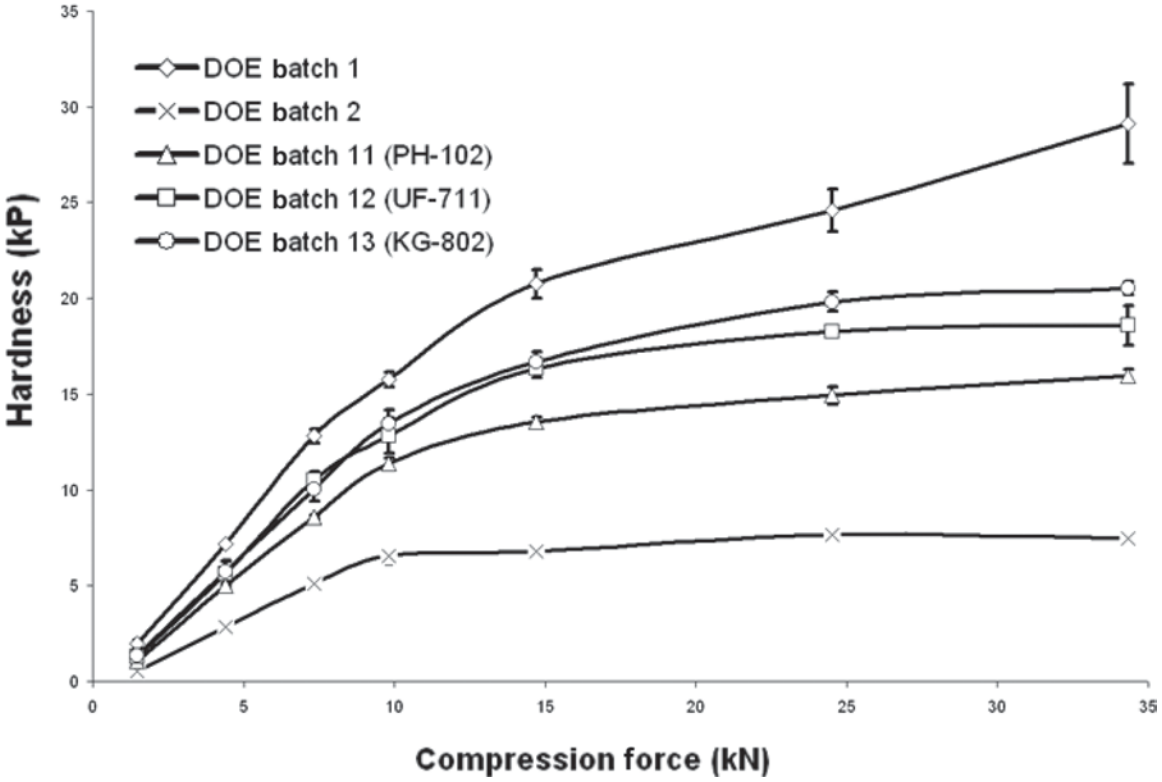

Figure 6. Compression profile of selected formulations containing different grades of microcrystalline cellulose. Hardness values measured as a set of $n = 6$ tablets. Error bars represent ±standard deviation.

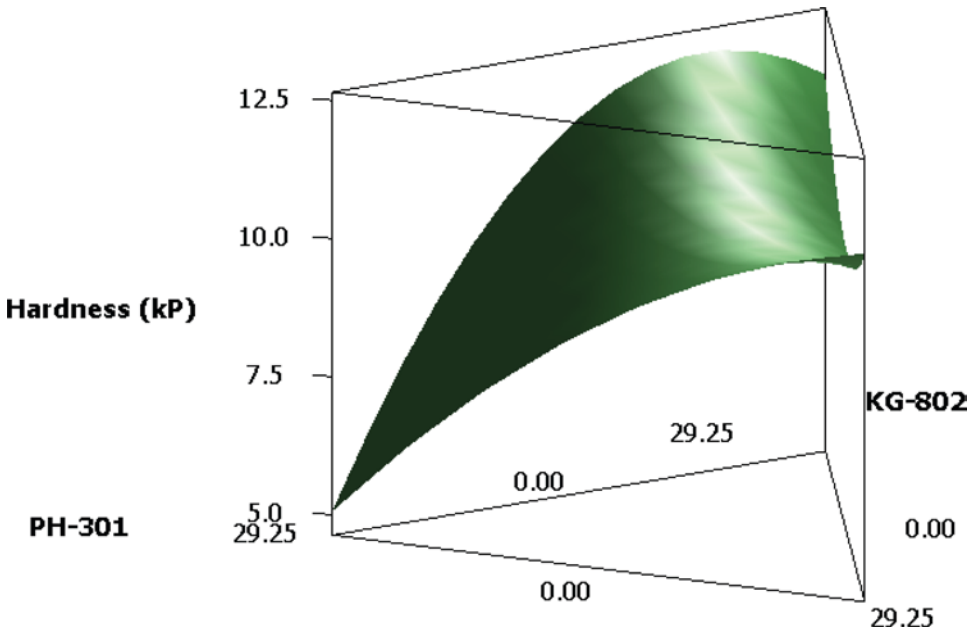

Figure 7. Surface response plot showing the correlation of tablet hardness to highly compressible excipient loadings.

were inconsistent to current theories where increasing surface area increases bonding efficiency and may point to an optimum loading of highly compressible material, which maximizes the number of particle–particle contacts based on percolation theory.

The ability to achieve similar hardness values under lower compression forces for the combination formulations also led to a general increase of internal porosity when compared with the conventional formulations. Such behavior was theorized to have a favorable impact on dissolution behavior by limiting particle–particle contact of the solid dispersion and providing channels for rapid uptake of aqueous media to facilitate disintegration. In order to test this theory, tablet formulations were evaluated for dissolution performance under sink conditions. Representative dissolution profiles, shown in

Figure 8, exhibited a trend in line with the porosity and compression force relationship, where tablets manufactured at lower force with higher porosity provided a more rapid dissolution profile. Under extreme conditions, such as batch 13, where compressibility of formulation required the use of excessive force the dissolution rate was substantially delayed. As a result of extensive consolidation and greater interdispersion contact, extensive gelling occurred during dissolution. This resulted in the formation of a coherent gel layer rather than the rapid disintegration observed for the other formulations. For such formulations, a decrease of oral bioavailability would be expected.

Non-sink dissolution performance

Non-sink dissolution is a also a critical product metric used in the assessment of amorphous formulations. The ability to supersaturate the local aqueous environment is a unique property of amorphous dispersion formulations and other thermodynamically metastable systems. The impact of formulation and processing conditions on the dosage forms was investigated to see if the improved compressibility provided any substantial benefits. Similar to the results of the sink dissolution testing, compression characteristics impacted release profiles. In extreme cases of poor compressibility, tablets prepared without highly compressible grades of microcrystalline cellulose yielded muted release. As shown in Figure 9, formulation 13 which was prepared without UF-711 or KG-802 did not provide measurable supersaturation due to the poor disintegration characteristics of the formulation. Other formulations using varying mixtures of microcrystalline cellulose were capable of supersaturation. This behavior indicated that in extreme cases, formulation development of the dosage form could impact exposure of the dosage form. Further examination showed minor differences in the supersaturation behavior of the highly compressible formulations. In general, greater internal porosity led to a greater extent of supersaturation although the magnitude of the difference was not substantial. Additionally, the use of small particle and highly compressible microcrystalline cellulose may have contributed to a buffeting effect for the solid dispersion particles. This would minimize the consolidation of the milled particles into larger gelled aggregates and provide a further benefit for dissolution.

Conclusions

Disintegration and dissolution rates of dosage forms are critical product attributes which directly regulate performance of the product. Results from this study clearly demonstrated that the compressibility behavior of formulations containing solid dispersions played a direct role on the release characteristics of the product. This influence was seen both in the rate of dissolution and the extent of supersaturation, indicating that the exposure of the amorphous formulation was a function of both

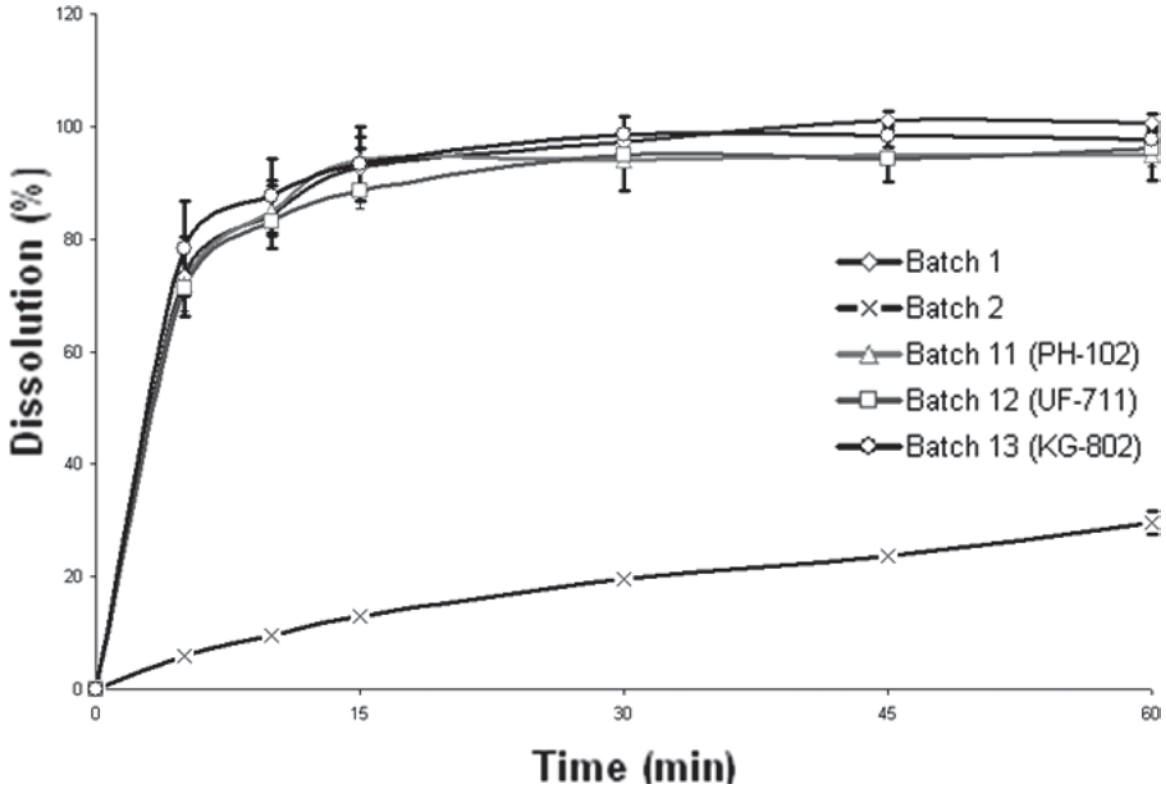

Figure 8. Representative sink dissolution profiles. Each vessel ($n=3$) contained 900 mL of 50 mM pH 6.8 phosphate buffer using USP Apparatus II at 50 rpm.

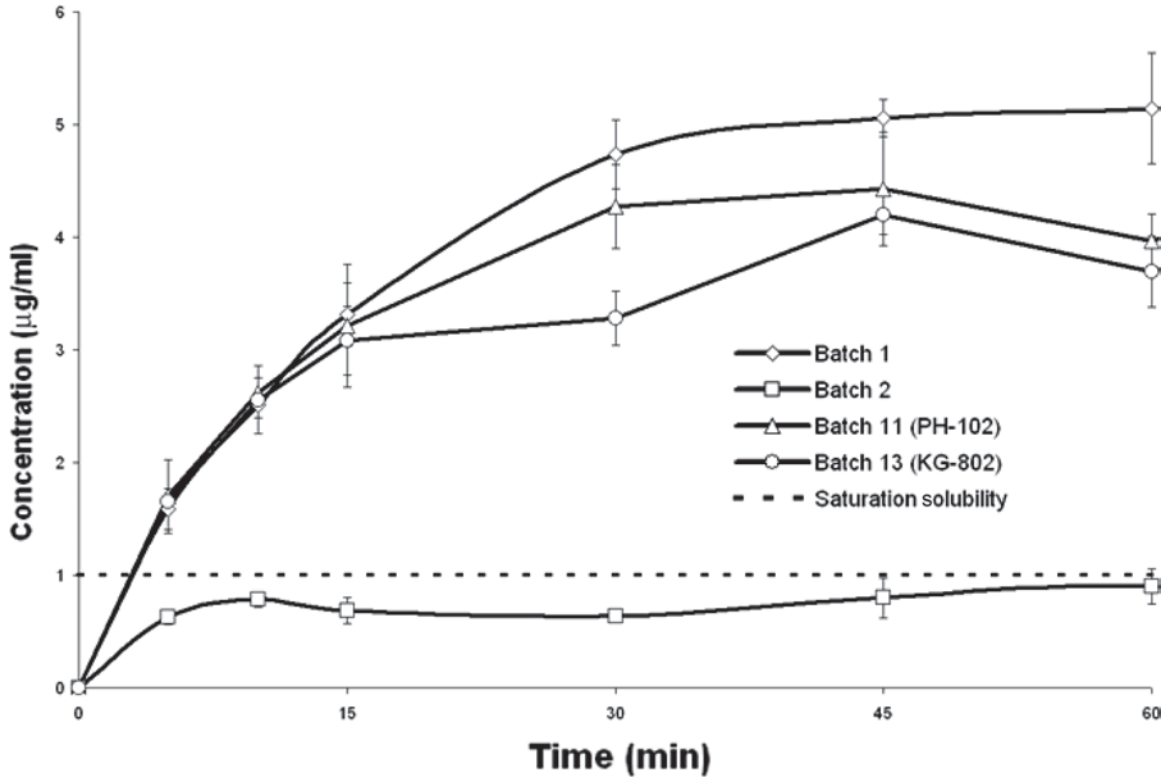

Figure 9. Non-sink dissolution profile of selected formulations each vessel ($n = 3$) contained 900 mL of 0.1 N HCl media using USP Apparatus II at 50 rpm.

solid dispersion properties and dosage form attributes. Utilization of Ceolus™ grades of highly compressible microcrystalline cellulose provided unique advantages leading to greater compressibility and higher internal porosity, which was able to facilitate drug release. The mechanism for this behavior from microcrystalline cellulose mixtures was attributed to the synergistic particle size of the highly compressible material. Based on the results of this study, the incorporation of highly compressible microcrystalline cellulose grades at additive levels in the formulation was an effective strategy for improving the compression and resulting release characteristics of the dosage form.

Declaration of interest

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References

1. Leuner C, Dressman J. (2000). Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm, 50:47–60.
2. Amidon GL, Lennernäs H, Shah VP, Crison JR. (1995). A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res, 12:413–420.
3. Janssens S, Van den Mooter G. (2009). Review: physical chemistry of solid dispersions. J Pharm Pharmacol, 61:1571–1586.
4. Brouwers J, Brewster ME, Augustijns P. (2009). Supersaturating drug delivery systems: the answer to solubility-limited oral bioavailability? J Pharm Sci, 98:2549–2572.
5. Alonzo DE, Zhang GG, Zhou D, Gao Y, Taylor LS. (2010). Understanding the behavior of amorphous pharmaceutical systems during dissolution. Pharm Res, 27:608–618.
6. Serajuddin ATM. (1999). Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. J Pharm Sci, 88:1058–1066.
7. Augsburger LL, Zellhofer MJ. (2006). Tablet formulation, in Encyclopedia of Pharmaceutical Technology, Swarbrick J, Editor. Informa Healthcare, New York, pp. 3641–3652.
8. Augsburger, Larry L. Brzeczko, Albert W. Shah, Umang Hahm, Huijeong Ashley Augsburger LL. (2006). Super disintegrants: characterization and function, in Encyclopedia of Pharmaceutical Technology, Swarbrick J, Editor. Informa Healthcare, New York, pp. 3553–3567.
9. van der Watt JG. (1987). The effect of the particle size of microcrystalline cellulose on tablet properties in mixtures with magnesium stearate. Int J Pharm, 36:51–54.
10. Ceolus. [cited 2010 November 1, 2009]. Available from: http://www.ceolus.com/eng/product/ceolus/
11. Chokshi, Rina J. Shah, Navnit H. Sandhu, Harpreet K. Malick, Ahmad W. Zia, Hossein Chokshi RJ. (2008). Stabilization of low glass transition temperature indomethacin formulations: impact of polymer-type and its concentration. J Pharm Sci, 88:2286–2298.
12. Schilling, Sandra U. DiNunzio, James C. Kaneko, Nobuya McGinity, James W. Schilling SU. (2011). Evaluation of CeolusTM microcrystalline cellulose grades for the direct compression of enteric-coated pellets. Drug Dev Ind Pharm, Submitted.
13. Zeeshan F, Peh KK, Tan YTF. (2009). Exploring the potential of a highly compressible microcrystalline cellulose as novel tabletting excipient in the compaction of extended-release coated pellets containing an extremely water-soluble model drug. AAPS PharmSciTech, 10:850–857.
14. Torrado JJ, Augsburger LL. (1994). Effect of different excipient on the tableting of coated particles. Int J Pharm, 106:149–155.