Drug Development and Industrial Pharmacy, 2009; 35(9): 1066–1071

informa
healthcare

ORIGINAL ARTICLE

Functional performance of silicified microcrystalline cellulose versus microcrystalline cellulose: a case study

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Abstract

Background: During the development of a tablet dosage form of an investigational compound, R411, several aspects were identified as critical quality attributes that required optimization. The use of nonsolvent processing prevented the moisture-induced physical changes in the drug product but presented manufacturing challenges related to sticking during compression and slowdown in dissolution after storage at stress conditions. *Aim*: The aim of this study was to evaluate silicified microcrystalline cellulose (SMCC), microcrystalline cellulose (MCC), and physical mixture of MCC–colloidal silicon dioxide (MCC/CSD at 98:2 ratio) as extragranular compression aids to address the processing and dissolution stability issues of this formulation. *Methods*: The compactibility and stickiness upon compression over extended period of time as well as the dissolution of R411 formulations incorporating the aforementioned compression aids were investigated. In addition, the water sorption/desorption properties of these compression aids were determined. *Results*: All formulations showed comparable compactibility irrespective of the compression aid used. Nevertheless, MCC alone or in a physical mixture with CSD showed sticking of the lower punches, whereas SMCC resulted in clean punch surface during extended compression runs. Furthermore, the three compression aids were compared for their effect on dissolution stability after storage at stress conditions. The formulations containing SMCC provided superior dissolution stability over the other compression aids evaluated in the study. *Conclusions*: Novel functionalities of SMCC are presented in terms of sticking prevention while having the most beneficial effect on dissolution stability in R411 formulation.

Key words: *Anti-adherent; colloidal silicon dioxide; compactibility; compression aid; microcrystalline cellulose; silicified microcrystalline cellulose*

Introduction

Formulation development efforts of the investigational compound, R411, presented several challenges with regard to the physico–chemical and biopharmaceutical properties of the drug. The moisture-mediated stability problems were addressed by the use of a melt granulation process. The use of poloxamer 188 as a meltable binder provided bioavailability advantages. Although biopharmaceutical problems were resolved satisfactorily using the melt granulation process, the manufacturability challenges associated with the sticky nature of the drug and the formulation during compression and the dissolution stability after exposure to accelerated stress conditions required further development. To that effect a systematic study was conducted evaluating several external compression aids that will not only improve the processing of the formulation but also minimize dissolution stability concerns. Several compression aids were evaluated in the first screen using dissolution as a response variable and from there three systems were selected for detailed evaluation. The three systems include silicified microcrystalline cellulose (SMCC) (ProSolv SMCC®), microcrystalline cellulose (MCC), and MCC/colloidal silicone dioxide (CSD) (98:2) physical mixture as extragranular compression aids. The effect of these compression aids on compaction and dissolution stability of the resultant tablets is presented in this article.

ProSolv SMCC® is silicified microcrystalline cellulose made by co-processing MCC with CSD at 98:2 ratio.

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(Received 11 Jun 2008; accepted 24 Jan 2009)

ISSN 0363-9045 print/ISSN 1520-5762 online © Informa UK, Ltd.
DOI: 10.1080/03639040902774131

The silicification process imparted superior functionality to SMCC over MCC, when used in direct compression manufacturing processes, in terms of (1) improved compactibility and tablet strength; (2) superior flow properties; and (3) resistance to lubricant sensitivity[1–4]. The last improvement can be attributed to silicon dioxide competitive inhibition of stearate at the sites of adhesion[4,5]. On the other hand, SMCC did not offer major improvements in compactibility over MCC when the granules were prepared by wet granulation process[6]. Although a number of publications in the literature demonstrated the advantages of SMCC over MCC or physical mixture of MCC and CSD, yet all the excipient functionalities are not fully understood. Comparison of the mechanical properties of compacts made of MCC, dry mixtures of MCC/CSD, and SMCC indicated that these functionality gains are not because of simple composite material model[7]. Tobyn and coworkers compared the physicochemical properties of MCC and MCC/CSD wet and dry mixtures with those of SMCC[8]. They concluded that the bulk chemical and polymorphic properties are practically the same with no observable changes being induced by the silicification process. Similar conclusions were reported, as well, by Buckton et al.[9]. Nevertheless, silicification is suggested to modify the microscopic surface characteristics of MCC as indicated by high magnification scanning electron microscopy (SEM)[7]. Except for a small amount that was detected in the internal region of the MCC particles, the majority were located on the surface leading to an anticipated fivefold increase in the specific surface area of Porsolv as compared to MCC[10].

In this article, a systematic evaluation of the key excipients not only helped resolve the formulation concerns but also provided a greater insight into the role of excipients in developing successful drug product.

Materials and methods

R411 is a Roche investigational drug (Figure 1). ProSolv SMCC® 50 was obtained from JRS Pharma LB (Patterson, NY, USA). Microcrystalline cellulose (Avicel PH 101) was from FMC Corporation (Newark, DE, USA). Colloidal silicon dioxide (Aerosil 380) was from Degussa (Parsippany, NJ, USA). Lutrol micro F68 MP was from BASF Corporation (Florham Park, NJ, USA).

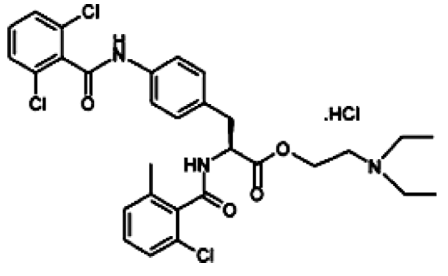

Figure 1. Chemical structure of the investigational drug R411.

Hot melt granulation

The manufacturing principle was based on hot melt granulation[11]. The detailed composition of the formulation is described elsewhere[12]. Briefly, all intragranular components were dry-mixed in a bottom-driven, jacketed high shear granulator model VG 25 (Glatt Air Techniques Inc., Ramsey, NJ, USA) for 2 minutes at room temperature with impeller and chopper speeds set at 200 ± 20 and 1000 ± 100 rpm, respectively. Using a circulating water bath set at 60°C ± 3°C, the product temperature was increased to 53°C ± 3°C with intermittent mixing of the powder. Once the target temperature was reached, heating was discontinued and the powder blend was mixed continuously until the desired granulation is achieved. The resultant granules were delumped and then cooled in a fluid bed dryer (GEA Process Engineering Inc., Columbia, MD, USA) at ambient conditions. The cooled granules were milled using a hammer mill (Fitzpatrick Company, Elmhurst, IL, USA) fitted with 062R screen (~1.4 mm). The granules were separated into three sublots for further downstream processing. For each sublot, the following extragranular excipients were evaluated at 5% level:

1. SMCC
2. MCC
3. MCC/CSD (98:2) physical mixture

All other processing aspects were maintained constant except for the inclusion of one of these three excipients in the extragranular phase.

Compaction studies

The various final blends were compressed on an instrumented Korsch PH 106 (Korsch America Inc., South Easton, MA, USA and IL, USA) rotary tablet press. Compression force analysis to construct the compaction profiles was performed using a Data Acquisition System installed on the Korsch PH 106 tablet press (Metropolitan Computing Corp., East Hanover, NJ, USA). At each compression force used, the crushing forces of five tablets were tested using a hardness tester (Key International, Inc., Englishtown, NJ, USA) and the average was used to construct the corresponding compactibility profile. Tableting was continued at the target compression force to evaluate the effect of compression run time on tablet properties of the different powder blends.

Hygroscopicity

Water sorption/desorption isotherms of SMCC, MCC, and MCC/CSD (98:2) were determined using a VTI SGA-100 systemic vapor sorption analyzer (VTI Corporation, Hialeah, FL, USA) equipped with an integrated microbalance system to measure the uptake or loss of water. All experiments were conducted at 25°C. The water sorption and desorption isotherms were then plotted as the percentage change in sample weight as a function of relative humidity (RH).

Dissolution testing

A Distek dissolution system (Model 2100A; North Brunswick, NJ, USA) with a USP apparatus 2 was used for the dissolution studies of freshly prepared tablets as well as tablets stored in open condition at 40°C/75% RH. The dissolution medium was 900 mL of purified water at 37°C and the paddle rotating speed was 75 rpm. Sample analysis was carried out by an automated online UV system (Hewlett Packard Model 8452A, Palo Alto, CA, USA).

Results and discussion

Compression properties

Figure 2 shows the compaction profile of the formulations that contain SMCC, MCC, or MCC/CSD (98:2) physical mixture. All three formulations appear to be comparable from a compactibility perspective, with no additional advantage resulting from using the more compactable SMCC at the level employed in the formulation. Apparently, using SMCC at 5% level extragranularly is too low to show any compactibility gain compared to MCC.

The compression trial runs of all three formulations were evaluated at compression force of 14 ± 2 kN. Based on visual observation, all three formulations at small batch sizes (short running time) showed comparable performance with no tendency to sticking. However, this was not the case at prolonged tableting runs. The formulations containing SMCC were far superior to MCC or MCC/CSD physical mixture during the extended compression. The SMCC formulation did not show any sticking up to 3.5 hours of compression (Figure 3A). On the other hand, severe sticking to the punches as well as

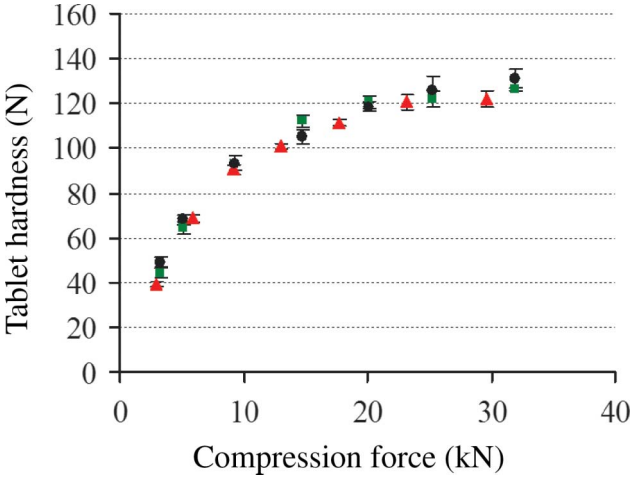

Figure 2. Compactibility profiles of various formulations of R411 with 5% extragranular SMCC (▲), MCC (■), or MCC/CSD physical mixture (●).

(a)

(b)

Figure 3. Punches after compression of various R411 formulations. (A) After 3 hours compression run of formulation containing SMCC and (B) after 2 hours compression run of formulation containing MCC/CSD physical mixture.

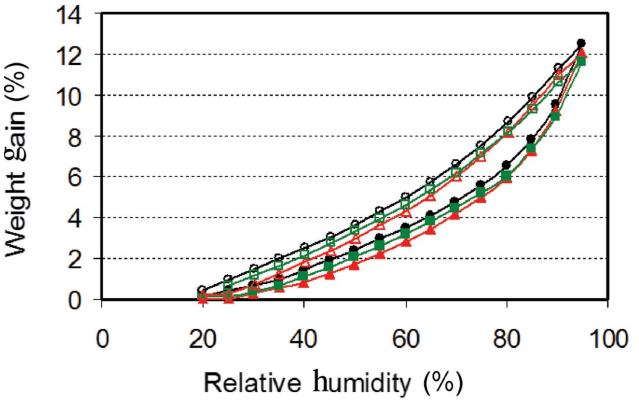

Figure 4. Moisture adsorption (closed) and desorption (open) isotherms of (a) SMCC (▲), (b) MCC (■), and (c) MCC/CSD physical mixture (●).

the die wall was observed with MCC or MCC/CSD physical mixture in less than 2 hours of compression (Figure 3B).

Hygroscopicity

Water sorption for the three compression aids evaluated in this study was analyzed from 20% to 95% RH, then in reverse for water desorption (Figure 4). All three compression aids exhibited similar sorption/desorption isotherms as reported elsewhere[13], suggesting that the water activity remains similar for MCC after silicification.

Dissolution stability

As mentioned previously, the dissolution of this product was decreasing after exposure to stress conditions. Therefore, it is of utmost importance to minimize the extent of the decrease in the dissolution rate as a function of storage in order to ensure a reproducible product performance. The dissolution profiles of all three formulations at time zero as well as after 10 days exposure to 40°C/75% RH are shown in Figure 5. All three formulations show a decrease in the dissolution rate after exposure to these stress conditions, irrespective of the compression aid used. However, the decrease in the dissolution rate is not the same with all of the three compression aids. To further illustrate this, the absolute difference in the percentage released between initial and exposed samples was plotted as a function of time (insert in Figure 5). Incorporation of SMCC in the formulation appears to offer more dissolution stability than the MCC alone or in a physical mixture with CSD. These experiments were repeated three times at different scales to confirm the favorable effect of SMCC. In agreement with the initial findings, the dissolution-stabilizing effect of SMCC was consistent after 14 days of exposure to elevated temperature and humidity in open condition (Figure 6).

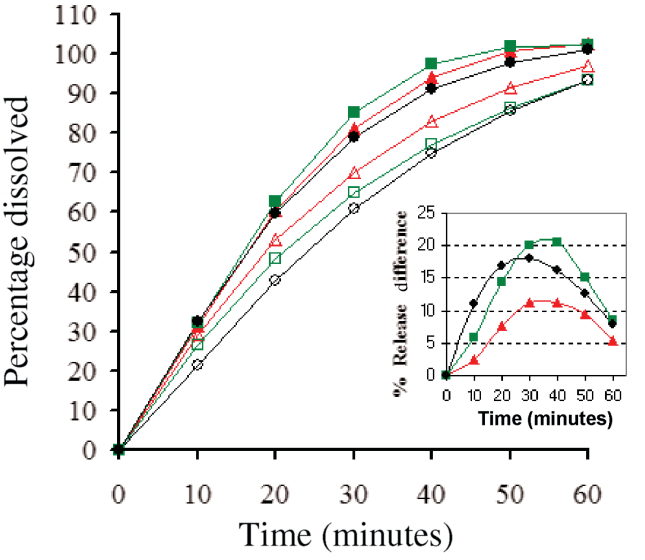

Figure 5. Dissolution profiles of various formulations of R411 initially and after 10 days exposure to 40°C/75% RH. (a) SMCC initial (▲) and exposed (△); (b) MCC initial (■) and exposed (□); (c) MCC/CSD physical mixture initial (●) and exposed (○). Insert: The difference in the percentage of released drug from various R411 formulations, tested at time 0 and after 10 days exposure to 40°C/75% RH. All experiments were done in triplicates. SDs were less than 5% and are not shown for clarity purposes.

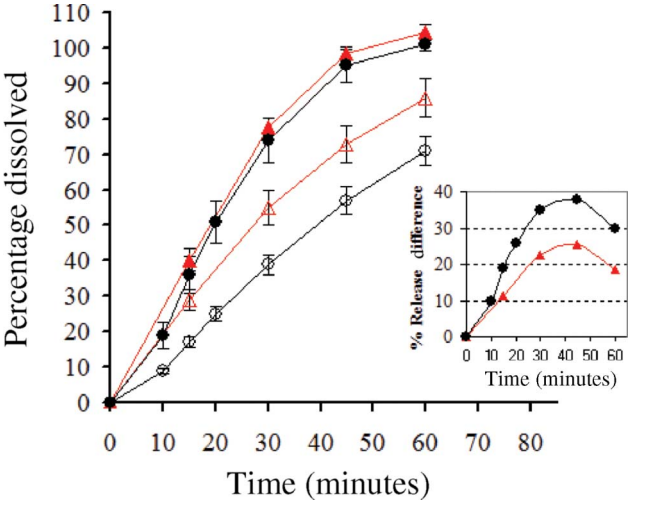

Figure 6. Dissolution profiles of verifying batches of R411 initially and after 14 days exposure to 40°C/75% RH. (a) SMCC initial (▲) and exposed (△); (b) MCC/CSD physical mixture initial (●) and exposed (○). Insert: The difference in the percentage of released drug from various R411 formulations, tested at time 0 and after 14 days exposure to 40°C/75% RH.

Insight on this unexpected outcome of SMCC can be obtained from the fundamental understanding of the mechanisms responsible for the observed decrease in the dissolution rate after exposure to stress conditions. First, the active ingredient, R411, has been found to

undergo gelation when stored under high RH conditions. Although the thermodynamic water activity is the same for all the variants, the superior performance observed with SMCC is suggested to be due to the large surface area thus making it a more effective scavenger for competitive water uptake compared to MCC or physical mixture. SMCC has a surface area of 5.9 m^2/g while that of MCC and MCC/CSD blend are 1.2 and 3.4 m^2/g, respectively. Furthermore, surface morphology analysis by SEM imaging shows increased roughness of SMCC particles in comparison to MCC[14]. The increased surface roughness is believed to assist in capturing the fine particles in the granules which, in turn, minimizes drug–drug interactions and thus, reduces the drug gelling tendency.

Second, Steele and coworkers investigated the adsorption of an amine drug onto different grades of MCC and SMCC[15]. Interestingly, they found that the silicification process of MCC reduced the adsorption of the model drug onto MCC by 12%–21%. This was attributed to the replacement of cellulosic area by the nonadsorbing silicon dioxide or the preferential adsorption of silicon dioxide onto the active sites in the surface of MCC. Consequently, the drug release from formulation containing MCC during dissolution studies may be lower than that from formulation utilizing SMCC. Since R411 is an amine drug (Figure 1), it is expected to adsorb more onto MCC as compared to SMCC, thus resulting in slower dissolution. Likewise, the performance of MCC/CSD physical mixture is not as effective as the co-processed excipients because of incomplete surface coverage of MCC. Overall, the improved dissolution stability with SMCC over other compression aids is attributed to high surface area, uniform mixing and surface morphology characteristics of this SMCC, in addition to the potentially lower interaction of R411 with SMCC than MCC or the physical mixture of MCC and CSD.

Conclusions

This work evaluated the compactibility, anti-adherent property, and dissolution stability of a formulation that incorporates 5% of either MCC, SMCC, or the physical mixture of MCC and CSD at a similar ratio to that found in SMCC.

A comparable compactibility was found for all three formulations. However, the anti-adherent properties of all three excipients differed widely. This was evident upon prolonged compression runs of formulation incorporating either of these excipients. The current findings indicate a superior anti-adherent ability of SMCC than its unsilicified counterpart. The use of physical mixture of MCC and CSD at a ratio similar to that of SMCC did not result in any improvement from an anti-adherent perspective over the formulation that incorporated MCC alone. From a dissolution stability point of view, the formulation with SMCC was more stable as indicated by the smaller drop in the dissolution rate after storage at 40°C/75% RH.

In summary, SMCC is shown to prevent sticking during compression while having the most beneficial effect on the dissolution stability after exposure to high humidity and temperature conditions. These novel functionalities of SMCC support its preferred use over MCC or a mixture of MCC and CSD in R411 formulation as well pharmaceutical formulations presenting similar problems.

Acknowledgments

The authors gratefully acknowledge Dr. Shangdong Zhan for the dissolution support and Mr. Maurice Munroe for hygroscopicity studies at Roche and Mr. J. Zeleznik at JRS Pharma for the technical data.

Declaration of interest: The authors report no conflicts of interest.

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