The Effect of Silicification on the Roller Compaction Performance of Microcrystalline Cellulose

Abstract

Roller compaction, or dry granulation, is a manufacturing method for pharmaceutical and nutraceutical tablets that continues to gain importance. In order to achieve the desired granule properties, it is vital to use efficient binder-filler systems, which enable easy compaction, reproducible grinding results, and high re-compactibility during the final tableting step.

In this study, microcrystalline cellulose (**VIVAPUR® 101**), as well as two grades of silicified microcrystalline cellulose (**PROSOLV® SMCC 50** and **PROSOLV® SMCC 50LD**) were tested in regards to their performance as roller compaction binders.

All three binders were found to be highly efficient in roller compaction. Differences in their powder characteristics translated into modification of the resulting granule properties. Proper selection of the initial microcrystalline cellulose (MCC) or silicified microcrystalline cellulose (SMCC) material can, therefore, be used to fine-tune the granules in terms of their flowability, particle size, and tabletability.

Introduction

Today, direct compression, or tableting of powder blends without prior granulation, is the health science industry's preferred manufacturing method. There are, however, formulations which do not lend themselves to direct compression and still require a granulation step in order to achieve the desired tablet flow in compression to yield satisfactory properties.

Wet processing, the traditional granulation technique, is a time and cost intensive procedure which stresses active pharmaceutical ingredients (APIs) by exposure to heat and moisture. Roller compaction is a powerful alternative to wet granulation. Granulation is achieved via compaction of a powder blend and subsequent grinding to the required particle size.

This method continues to become more popular because it needs no water and, thus, requires no drying step. Furthermore, it can easily be scaled up since the output of granulated material is only dependent on the roller speed settings. In order to achieve uniform granules, it is of utmost importance to use highly compactible binders of constant quality.

Study Design

Different MCC-based excipients were evaluated for their suitability for roller compaction. They were used in combination with a brittle fracturing material (dicalcium phosphate dihydrate, **EMCOMPRESS®**) in order to obtain the best compaction results [1].

The cellulosics used for this study were traditional MCC (**VIVAPUR® 101**) and two grades of silicified MCC (**PROSOLV® SMCC 50**, **PROSOLV® SMCC 50LD**). All three grades exhibit very similar particle size distributions as determined by laser diffraction. **PROSOLV® SMCC 50** was used as the reference material because the effect of silicification on **VIVAPUR® 101** and the effect of bulk density in comparison to **PROSOLV® SMCC 50LD** could be analyzed.

Dicalcium phosphate dihydrate (**EMCOMPRESS®**) was added as a filler with a purely brittle deformation mechanism.

In order to obtain the best individual compaction results, different compaction forces were tested during roller compaction. All resulting compacts were compressed into tablets and compared regarding their hardness.

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Materials and Methods

The powder blends used consisted of 75 % of the cellulosic compound (either MCC or SMCC) and 25 % dicalcium phosphate dihydrate. Materials were blended in a drum hoop mixer for 10 minutes. The ingredients are listed in Table 1.

Different roller compaction forces were adjusted and the compacts were milled using the Hosokawa sieve mill. The resulting powder was tested for particle sizes and flowability. Furthermore, placebo tablets containing 0.5 % of the lubricant, sodium stearyl fumarate (**PRUV®**), were compressed (400mg, round, biplane, 13mm diameter) and their hardness, as well as disintegration time, was analyzed.

All tests were performed in triplicate.

List of Ingredients	
Microcrystalline cellulose (MCC)	**VIVAPUR® 101**
Silicified microcrystalline cellulose (SMCC)	**PROSOLV® SMCC 50**
Silicified microcrystalline cellulose (SMCC)	**PROSOLV® SMCC 50LD**
Dicalcium phosphate dihydrate	**EMCOMPRESS®**
Sodium stearyl fumarate	**PRUV®**

Table 1

Equipment List	
Drum hoop mixer	Engelsmann AG RRM ELTE 650
Roller compactor	Hosokawa Bepex Pharmapaktor 200/50P
Sieve mill	Hosokawa A FC 200
Flowability tester	Copley Scientific BEP 2
Tap density	Engelsmann AG STAV 2003
Particle size distribution	Malvern Instruments Mastersizer 2000
Shear cell	Dr. Dietmar Schulze RST XS
Tablet press	IMA Kilian Pressima 13EU-D
Tablet hardness tester	Erweka TBH 425 TD
Disintegration tester	Pharmatest PTZ

Table 2

Roller Compactor Details

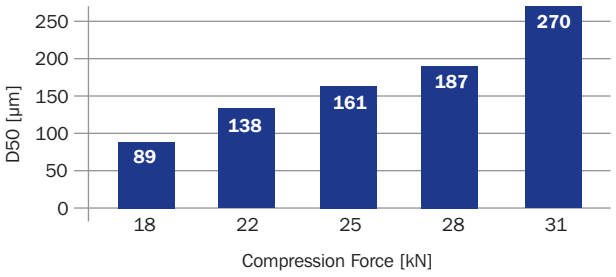
The roller compactor was equipped with interlocking serrated rolls and was used as follows:

Diameter of rolls	200 mm
Working width	50 mm
Roller speed	6 rpm
Preload force	9 kN
Screw speed	Variable
Compression forces (nominal values)	18 kN, 21 kN, 25 kN, 28 kN, 31 kN

Table 3

Results

Graph 1 shows the particle size (expressed as D50) of milled compacts made from **PROSOLV® SMCC 50**.



Graph 1: Particle size of **PROSOLV® SMCC 50** compacts as a function of compression force during roller compaction.

The average particle size became higher as compaction forces increased. Even the particles obtained at the lowest compression forces were in a range suggesting passable to good flow.

Flow properties

Flow characteristics	Speed of flow	Angle of repose [°]	Hausner ratio	Flowability acc. Jenike (FF1-2C)
Extremely bad	No flow	> 66	> 1.60	< 1
Very bad	Low	56 - 65	1.46 - 1.59	1 - 2
Bad		46 - 55	1.35 - 1.45	2 - 4
Sufficient		36 - 45	1.19 - 1.34	4 - 10
Good		31 - 35	1.12 - 1.18	> 10
Very good	High	25 - 30	1.00 - 1.11	

Table 4

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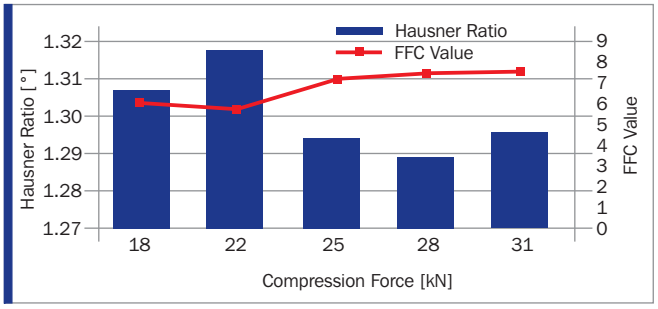
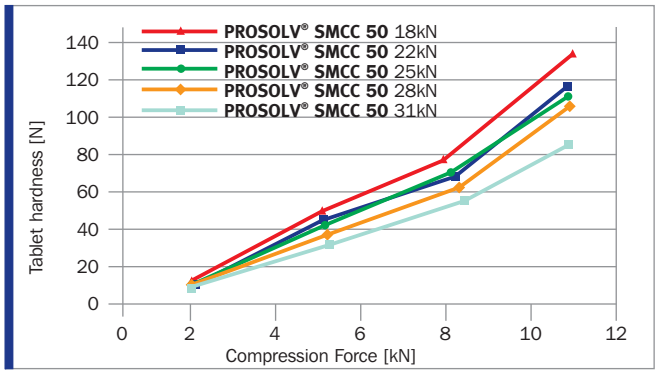
The flowability of the roller compacted substances was determined either with the Schulze shear cell (FF1-2C value) or using the Hausner ratio (Graph 2). To obtain flow index (FFC) values indicating good flow, a minimum of 25 kN compaction force during roller compaction was needed. At the same time, all samples exhibited good flowability according to the Hausner ratio.



Graph 2: Flowability of **PROSOLV® SMCC 50** compacts as a function of compression force during roller compaction.

Next, the tableting characteristics of these compacts were tested. Graph 3 displays the results of this testing.



Graph 3: Hardness of tablets made from different **PROSOLV® SMCC 50** compacts.

Hard tablets could be obtained even at the lowest compression forces, irrespective of the compaction force used during roller compaction. At higher tableting forces, it became evident that the final compactibility was affected by the primary compaction forces during roller compaction. Granules produced at a lower roller compaction force (18 kN) yielded harder tablets than those pre-compacted at 31 kN.

Comparison between PROSOLV® SMCC 50, PROSOLV® SMCC 50LD and VIVAPUR® 101

Based on the findings for **PROSOLV® SMCC 50**, corresponding tests were performed with **PROSOLV® SMCC 50LD** and **VIVAPUR® 101**. Table 5 displays the fundamental powder properties of the three excipients. A roller compaction force of 25 kN was selected for the comparison study.

	VIVAPUR® 101	PROSOLV® SMCC 50	PROSOLV® SMCC 50LD
D10 [µm]	20	25	20
D50 [µm]	65	75	55
D90 [µm]	140	150	115
Angle of repose [°]	45	38	35
Bulk density [g/mL]	0.32	0.35	0.29

Table 5: Powder properties

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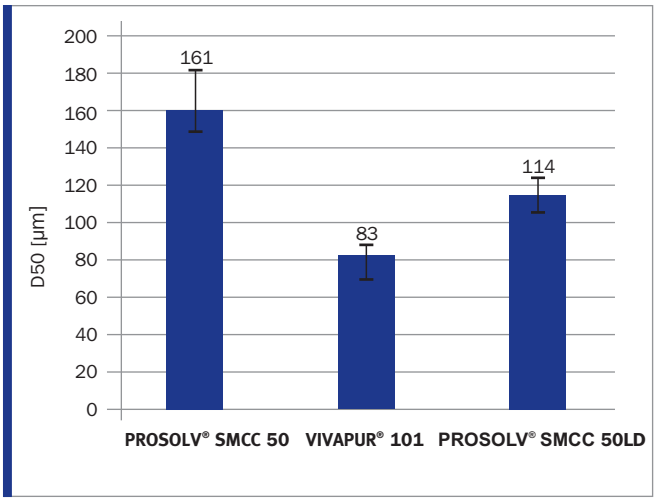
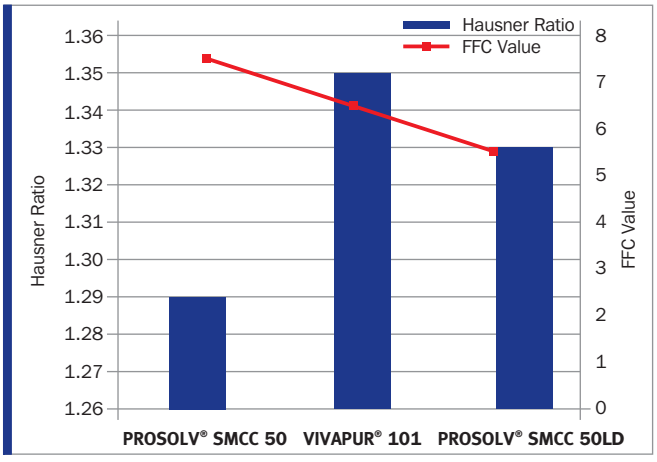
Graph 4 shows that the highest average particle sizes for the milled compacts was obtained if **PROSOLV® SMCC 50** was used.



Graph 4: Dependence of the mean particle size of milled compacts on the raw material

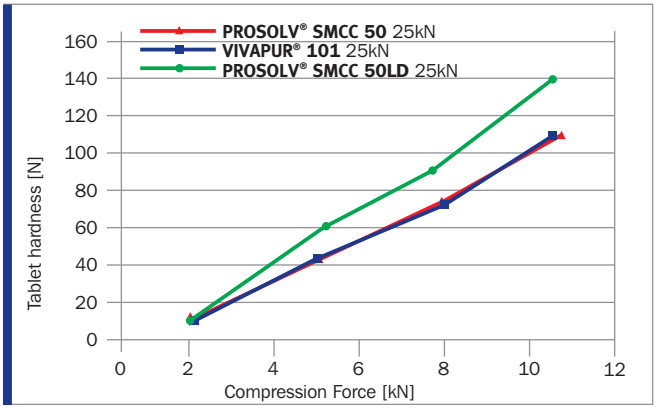
PROSOLV® SMCC 50 also exhibited better flow than both **VIVAPUR® 101** and **PROSOLV® SMCC 50LD** compacts (Graph 5).



Graph 5: Flowability of compacts made from either **VIVAPUR® 101**, **PROSOLV® SMCC 50**, or **PROSOLV® SMCC 50LD**

In terms of tableting performance, the compacts made from **VIVAPUR® 101** and **PROSOLV® SMCC 50** showed nearly identical tablet hardness values over the entire range of compression forces.

By comparison, the compacts based on **PROSOLV® SMCC 50LD** exhibited on average a 30 % higher hardness yield (Graph 6).



Graph 6: Hardness of tablets made from compacts from either **VIVAPUR® 101**, **PROSOLV® SMCC 50**, or **PROSOLV® SMCC 50LD**

Discussion

Formulations that contain both plastically deforming and brittle fracturing materials are known to yield hard compacts due to the synergistic combination of these different deformation mechanisms [1]. Furthermore, it has been demonstrated that the particle size of the starting material used for roller compaction has a significant influence on the hardness of the resulting tablets [2]. Consequently, a formulation containing primarily plastically deforming microcrystalline celluloses and brittle fracturing dicalcium phosphate dihydrate was studied. In order to avoid interfering influences due to different particle sizes, the chosen microcrystalline celluloses exhibited the same particle sizes. Thus, the influence of the silicification of microcrystalline cellulose, as well as the influence of different bulk densities, could be investigated.

In our study, **PROSOLV® SMCC 50** was tested in comparison to traditional MCC (**VIVAPUR® 101**).

PROSOLV® SMCC is a microcrystalline cellulose, which has been treated with colloidal silicon dioxide during the manufacturing process in order to increase the surface area.

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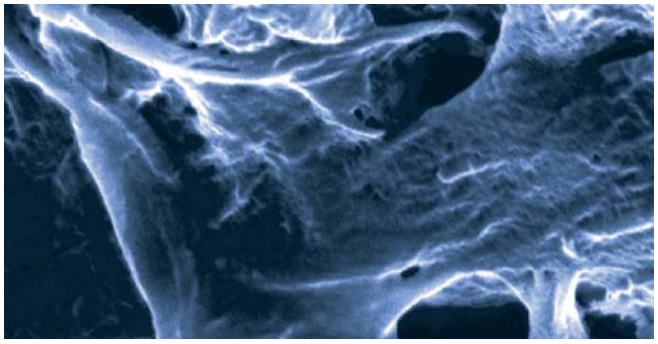
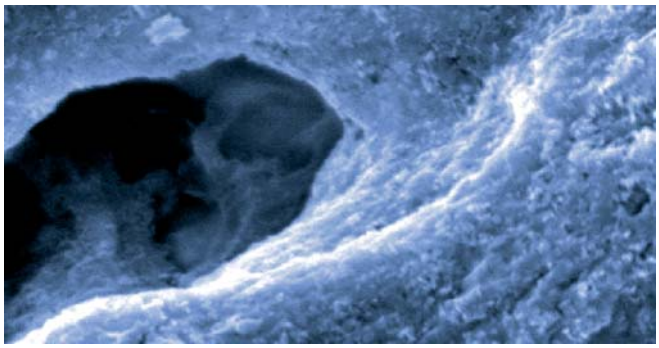
Thus, more area for binding interactions between the individual particles is available. Larger binding surfaces result in harder compacts. This has been proven for roller compacted SMCC before [3] and was verified in this study.



Picture 1: Surface structure of traditional MCC



Picture 2: Surface structure of silicified MCC (**PROSOLV® SMCC**)

When the hardness of tablets made from similarly treated roller compacted **VIVAPUR® 101** and roller compacted **PROSOLV® SMCC 50** were compared, the tablets made from SMCC exhibited the higher tablet hardness. This indicated that the higher surface area of **PROSOLV® SMCC 50** had a beneficial effect on the hardness. Furthermore, the compacts made from **PROSOLV® SMCC 50** exhibited larger particle sizes and better flowability, which is related to the unique structure of the silicified surfaces.

When **PROSOLV® SMCC** grades of different bulk densities were compared, the lower bulk density grade (**PROSOLV® SMCC 50LD**) resulted in a particle size smaller than the grade with the normal bulk density (**PROSOLV® SMCC 50**). Due to their smaller particle size, the flow of the **PROSOLV® SMCC 50LD** granules was reduced compared to the flow of the particles made from **PROSOLV® SMCC 50**. While the flowability of the milled compacts was better for **PROSOLV® SMCC 50**, the hardness of tablets made with **PROSOLV® SMCC 50LD** was higher than for **PROSOLV® SMCC 50**.

Conclusion

The silicification of MCC has been shown to significantly influence the hardness and the flowability of compacts, as well as the hardness of tablets made from these materials. If the overall target in tablet production is the highest possible tablet hardness the use of **PROSOLV® SMCC 50LD** in combination with **EMCOMPRESS®** is recommended. If both, the particle flow, and the tablet hardness, must be optimized **PROSOLV® SMCC 50** is the best choice.

Acknowledgement:
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