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Tabletability of Roll Compacted Binary Mixtures of Dicalciumphosphate with Silicified and Non-Silicified MCC

Introduction

Roll compaction/dry granulation (RCDG) is nowadays not only applied for water or heat sensitive active pharmaceutical ingredients, but has become a standard technique in pharmaceutical manufacturing[1]. Compared to wet granulation, though, dry granules can comprise a high amount of fines and the hardness of tablets based on roller compacted granules is often reduced [2]. Aim of the present study was, to investigate the effect of raw material choice and process setting on the quality of the granules and resulting tablets.

Material and Methods

Experimental Plan for RCDG Studies

Experiments followed a 2^3 fullfactorial design (Table 1) for each of the two mixtures. Data was evaluated with Minitab statistical software and Python (3.12.0).

Exp.	Spec. Compact. Force [kN/cm]	Roll Speed [min^{-1}]	Screw Speed [min-1]
1	4.92	8	14
2	11.48	8	14
3	4.92	16	14
4	11.48	16	14
5	4.92	8	67
6	11.48	8	67
7	4.92	16	67
8	11.48	16	67

Tab. 1 Factors and levels for roll compaction / dry granulation studies of MCC:DCP (3:1) and SMCC:DCP (3:1)

Materials

Three materials were used for RCDG studies: microcrystalline cellulose (MCC, VIVAPUR® 101, JRS PHARMA, and silicified microcrystalline cellulose (SMCC, PROSOLV® SMCC 50, JRS PHARMA) as predominantely plastic deforming materials, and dicalcium phosphate (DCP, EMCOMPRESS® Anhydrous Powder, JRS PHARMA, as a brittle material. For the two test series, MCC:DCP (Exp.1-8a) and SMCC:DCP (Exp.1-8b) were mixed in a ratio of (3:1) in a V- mixer (JRS) for 20 min at 11 rpm.

Compaction and Tabletting

RCDG was performed with a compactor (Walzenpresse WP 50 N/75, Alexanderwerk), equipped with press rolls (Cavex CHUA 99, Flender) and a feeding screw (H4V41, Heynau Gears Production Service). The hopper agitator was constantly kept at level 5. The slugs were separated from the uncompacted fine grain before being granulated over an 800 µm sieve by a rotating mill. The compaction took place with a variable gap using a 7.5 cm long, axially profiled roller.

Tabletting of flat face tablets (13 mm diameter) was performed with an instrumented tablet press (Pressima, IMA KILIAN). Sodium stearyl fumarate (PRUV®, JRS PHARMA) was added as lubricant (1 %) to the granules (resulting from Exp.1-8a and Exp.1-8b) and mixed for 3 minutes in a cube mixer (AR 403, ERWEKA) at 24 rpm. Granules were tableted with different compaction forces in the range between 2 and 10 kN. For comparison, materials were also directly compressed as physical mixtures (MCC:DCP=PMa, SMCC:DCP=PMb), applying the same compaction forces.

Analysis

Laser Diffraction of Particles

Raw materials and granules were analyzed over 60 seconds with a laser diffractometer (LS230 Coulter). A background measurement was carried out prior each measurement. The volumetric particle size distribution was determined according to Fraunhofer.

Breaking Strength of Tablets

The breaking strength of all tablets was determined to the Ph. Eur., Method 2.9.8. 'Resistance to crushing of tablets'.

Results and Discussion

With all tabletting experiments, the theory of loss in tabletability due to initial RCDG[2] was proven. Thus, the breaking strength of the tablets based on RCDG material was almost without exception reduced compared to those of the directly compressed physical mixture (PM).

Experiments 3 and 4 (Table 1), conducted under mild compaction conditions (high roll speed and low speed of the feeding screws), resulted in tablets featuring high breaking strengths, comparable to those of the corresponding physical mixtures (PM). In Table 2 the tabletting behaviour is expressed as the slope [N/kN] of the breaking force / tabletting force function.
Analysis of the particle size, too, revealed that the particle size distributions of the granules matched those of the PM (Table 2).

		d10 [µm]	d50 [µm]	d90 [µm]	Coarse Fraction >d90 of PM [%]	Slope [N/kN]
MCC	PMa	12	45	128		23.7
	Exp. 1a	21	123	604	49	16.3
	Exp. 2a	21	165	684	56	16
	Exp. 3a	14	49	135	12	23.8
	Exp. 4a	14	53	147	15	22.6
	Exp. 5a	34	328	746	71	12.7
	Exp.6a	41	402	845	76	9.1
	Exp. 7a	22	146	662	53	16.8
	Exp.8a	23	149	673	54	15.9
SMCC	PMb	14	56	143		26.8
	Exp. 1b	15	63	228	19	23.5
	Exp. 2b	23	151	685	51	20.1
	Exp. 3b	14	52	129	7	26.5
	Exp. 4b	14	51	127	6	26.3
	Exp. 5b	33	345	761	67	11.6
	Exp.6b	252	652	970	94	10
	Exp. 7b	24	173	680	54	16
	Exp.8b	28	264	705	61	16.8

Tab. 2 Results of experimental series a and b. The coarse fraction represents the percentage of particles larger than the D90 of the corresponding physical mixture.

Experiments 5 and 6, by contrast, performed with more intense compaction (high level setting of the screw speed) resulted in tablets with lower breaking strength and bigger coarse sieve fractions

Our findings confirmed the general rule that those slugs with a higher tendency to break down into primary particles exhibit a higher tabletabilty[2]. Furthermore, we identified an inverse correlation between the breaking strength and the coarse sieve fraction (Figure 1).

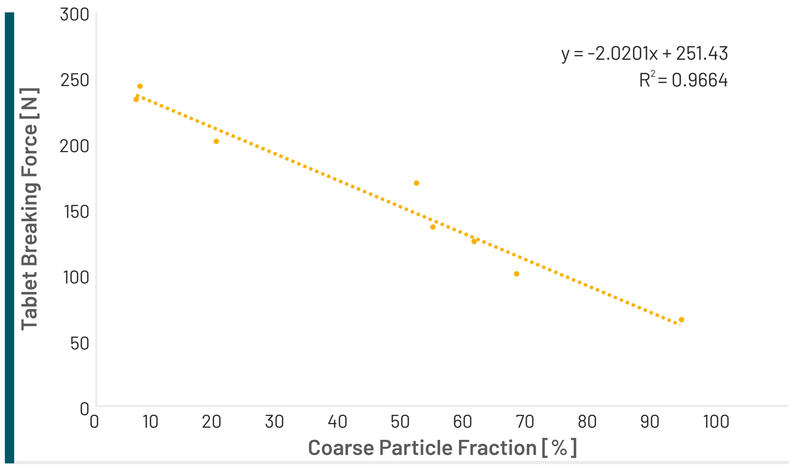

Fig. 1 Correlation between the coarse sieve fraction and the breaking strength of the SMCC:DCP (3:1) tablets (tablet weight 500 mg, compaction force 10 kN)

The contour diagrams of the breaking strengths of the tablets (Figure 2 and 3, for a roll speed of 8 min^{-1}) exhibit that the interaction of the two variable factors compaction pressure and screw speed is more pronounced in the SMCC test series. This indicates that formulations with MCC might be more robust in terms of process settings.

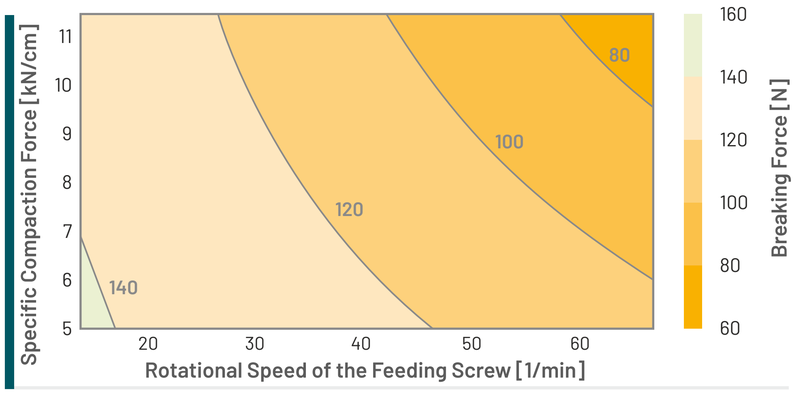

Fig. 2 Contourplot of the breaking force [N] of tablets (relating to a tableting compaction force of 10 kN). RCDG material of MCC:DCP was produced at a constant roll speed (8 min^{-1}), varying specific compaction forces and screw speeds

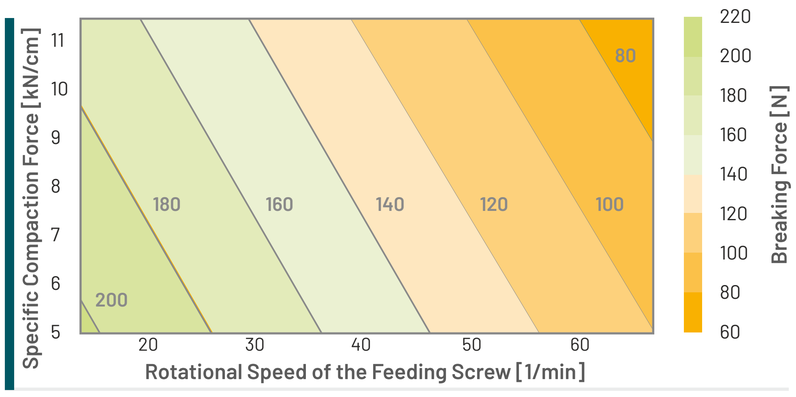

Fig. 3 Contourplot of the breaking force [N] of tablets (relating to a tableting compaction force of 10 kN). RCDG material of SMCC:DCP was produced at a constant roll speed (8 min^{-1}), varying specific compaction forces and screw speeds

Conclusion

Tabletability of granules produced with low level of screw speed and high level of roll speed was higher than the tabletability of those produced with faster screw speed and slower roll speed. The level of the specific compaction force was, however, of minor importance in the investigated setup. The general tabletability of SMCC is significantly increased compared to MCC, however, the latter is more robust in terms of process settings, especially at lower compaction forces.

References

1. Kleinebudde, P., Improving Process Understanding in Roll Compaction. J. Pharm. Sci., 111, 552-558 (2022)
2. Sun, C.C., Kleinebudde, P., Mini Review: Mechanisms to the loss of tabletability by dry granulation. Eur. J. Pharm. Biopharm., 106, 9-14 (2016)

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