Direct Compression

Microcrystalline Cellulose Grade 12 versus Classic Grade 102

Masaki Hasegawa

The author compared the behavior of two grades of microcrystalline cellulose during the direct-compression process. Tablets and mixtures with high and low concentrations of a fine active ingredient were compared. Results showed that the coarse grade 12 offered clear advantages over the classic grade 102, particularly in terms of weight and content uniformity.

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Because direct compression is more economic and straightforward in terms of good manufacturing practice requirements than are wet granulation and dry compaction, the pharmaceutical industry is focusing increasingly on this process. Although coarse microcrystalline cellulose (MCC) grade 12 offers outstanding flow properties, the most commonly used grade for direct compression is the well-known fine grade 102. The reason for this preference is that many users expect segregation (and subsequent poor weight- and content-uniformity results) when combining fine active ingredients with coarse-grade excipients.

A comparison study was conducted to find out if this apparently logical assumption was correct. Following the Japanese Standard Formulation Research Association (www.iijnet.or.jp/SPJT) guidelines, fine-quality acetaminophen was chosen as the active ingredient (1). In addition, the two grades of MCC were compared in various mixtures with lactose because this binder–filler combination is used widely.

Materials

The materials used in the study are shown in Table I, which lists particle-size properties, density, and flowability (angle of repose) details. Magnesium stearate was provided by Taihei Chemical Co. Ltd. (Osaka, Japan).

Equipment

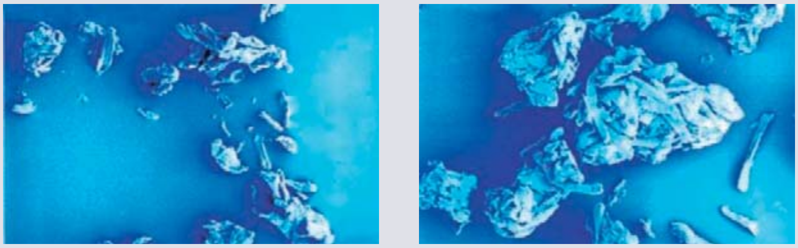
The equipment and suppliers used in the study are detailed in Table II.

Physical stability of MCC grade 12 during mixing

Method. Whereas MCC grade 102 consists mainly of single fibers, MCC grade 12 forms agglomerates during the manufacturing process (see "Grades of MCC" sidebar). Because these agglomerates might influence flow and tableting properties, pure MCC grade 12 was mixed in various mixer types for ≤120 min. The aim was to find out if the agglomerates would be destroyed by mixing. Particle-size distribution was determined with an LMS-30 laser micron sizer (Seishin Enterprise Co. Ltd.).

Results and discussion. The particle-size distribution of grade 12 MCC was influenced neither by the type of mixer nor by the mixing time (see Figure 1). Any differences were attributable to variation inherent in the measurement technique.

Grades of MCC



Grade 102 (magnification 130 ×)   Grade 12 (magnification 130 ×)

(see Figure 2). To show that tablets of acceptable hardness could be obtained from these mixtures, the test also was conducted at a compression force of 1.6 t. For this part of the study, the 45-punch press (production scale) with its larger turntable was chosen to increase mechanical stress. The author expected to see obvious differences in hardness when doing so. For the other parts of the study, a smaller, 12-punch press was used because the formulation performance mainly was influenced by the mixing process.

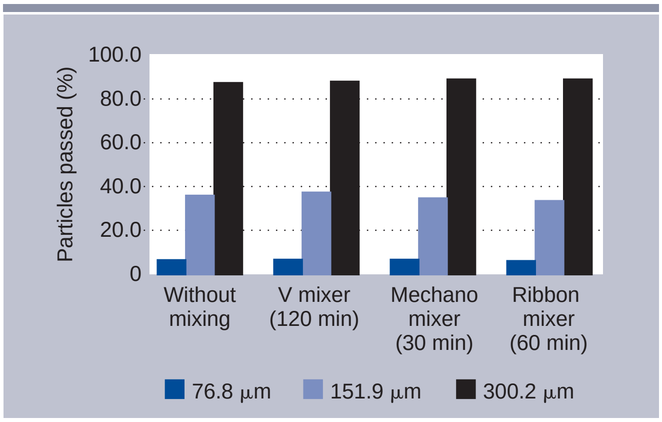


Figure 1: Particle-size distribution of MCC grade 12.

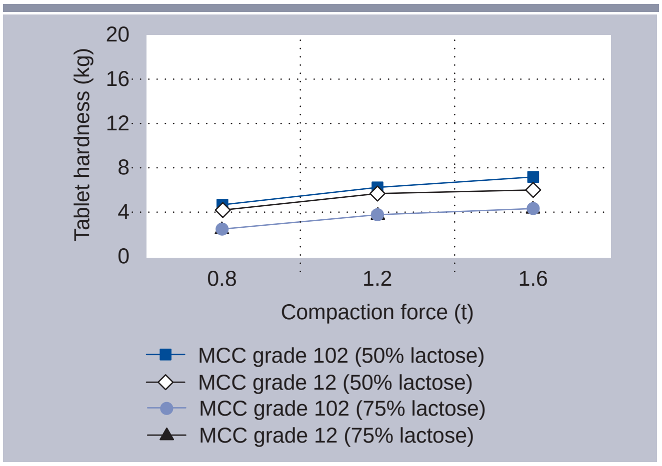


Figure 2: Tablet hardness results (50 and 75% lactose, 40 rpm).

Tableting of lactose–MCC mixtures

Method. This test was conducted because coarse grades of lactose often are used as a filler in combination with MCC, particularly when low concentrations of active ingredient are used. Lactose (100 mesh) and MCC in various ratios were mixed in a ribbon mixer for 10 min. After magnesium stearate (0.5%) was added and mixing was performed for 1 min, 180-mg tablets were compressed on a rotary press (Aquarius 3, 8-mm flat punches) at 20 and 40 rpm and various compaction forces (0.4, 0.8, 1.2 t). For formulations containing higher percentages of lactose (50 and 75%), tableting at a force of 0.4 t did not produce reasonable results — the tablets became weak and soft

Results and discussion. For both grades of microcrystalline cellulose, tablet hardness decreased as the percentage of lactose increased. Comparing the results of tablets made with 100% MCC, those made with grade 102 were 36–63% harder than tablets made with grade 12 (see Figure 3). It is probable that the finer MCC particles (grade 102) have larger surface areas with which to contact each other, resulting in higher hardness values. In addition, finer grades have a higher degree of crystallinity, which also could be a reason for these differences (2). Nevertheless, the grade 12 mixture with 75% lactose showed a tablet hardness of approximately 4 kg at a compaction force of 1.6 t. This value is considered to be the minimum value for a satisfactory tablet (3,4). The influence of MCC on tablet hardness decreases with increasing percentages of lactose. In formulations with more than 25% lactose, the differences in hardness became irrelevant (see Figures 2 and 3). Because free-flowing lactose strongly influences the flow of the tableting mixture

Table I: Materials and particle-size properties.

Product	Producer	Lot No.	Particle Size	Bulk Density	Angle of Repose
Microcrystalline cellulose (Vivapur 12)	J. Rettenmaier & Söhne (Rosenberg, Germany)	5601290724 5601291347	>400 µm: <1% >160 µm: 45% >50 µm: 89%	0.33 g/cm^3	36°
Microcrystalline cellulose (Vivapur 102)	J. Rettenmaier & Söhne	5610295441 5610201008	>250 µm: <1% >75 µm: 58% >32 µm: 82%	0.30 g/cm^3	42°
Lactose (100 mesh)	DMV International (Veghel, The Netherlands)	120222	<45 µm: 18.5% <150 µm: 51.5% <250 µm: 88%	0.75 g/cm^3	39°
Acetaminophen powder (fine)	Yoshitomi Fine Chemicals, Ltd. (Osaka, Japan)	YO25	<221 µm: 97.7% <140 µm: 88.9% <74 µm: 61.1%	0.26 g/cm^3	>60°

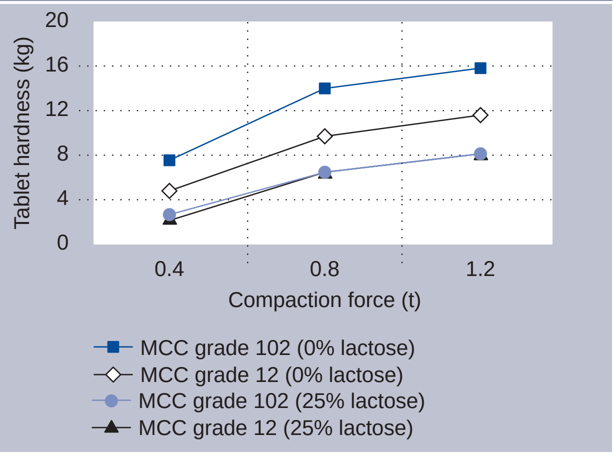


Figure 3: Tablet hardness results (0 and 25% lactose, 40 rpm).

when it is used in high concentrations, significant differences regarding tablet uniformity (weight, thickness, and hardness) were not observed. The results for tableting at 20 and 40 rpm were very similar; therefore, only the 40-rpm results are shown.

Mixing and tableting of MCC with high concentrations of fine acetaminophen

Method. Working with high concentrations of fine, powdered actives may cause problems during direct compression because of poor flow properties of the mixture. MCC was mixed with fine acetaminophen in various proportions (10, 25, and 50% acetaminophen) in a twin-shell mixer (V mixer) for 5, 15, and 30 min. The author then tested the mixture for content uniformity by taking samples from three different points in the mixer (right side: 5 cm below the surface, left side: 5 cm below the surface, and middle: 5 cm above the bottom) with a sampling thief (4). In addition, the angle of repose and the compressibility (see explanation in this section) of the mixtures were determined. The angle of repose was measured using the Multi tester 1000 (Seishin Enterprise Co. Ltd.). In this measuring process, the material falls through a funnel onto a plate (8 cm in diameter) until a cone is formed and the addition of more material does not lead to a further increase in the cone's height. The angle of repose is calculated using the plate's diameter and the height of the cone. During the compressibility determination, the bulk density is measured as follows: The material falls through a funnel into a cup (100 mL in volume), and the density is calculated from the volume and weight of the cup before and after filling. Because the author expected the shortest mixing time to be the worst case in terms of tablet-weight variation and content uniformity, tablets were made from the 5-min mixture. After 0.5% magnesium stearate was added and mixing for an additional 5 min was performed, the mixture was compressed into 180-mg tablets on a rotary press (Correct 12 8-mm flat punches, Kikusui Seisakusho Co. Ltd.) at 20 and 40 rpm and a compaction force of 1.0 t. When a poorly flowing mixture is tableted at high speed, weight uniformity results will be worse than those of a free-flowing mixture because die filling will not be particularly uniform. In addition, the content uniformity of the mixture is influenced not only by the mixing step but by the tableting step as well. While flowing through the filling system of the machine, the mixture is influenced in a certain way. This influence might change when another speed is used, resulting in a different content uniformity. Therefore the author conducted tests at two different speeds. The tablets then were tested for weight variation and content uniformity.

Results and discussion. The content uniformity (CV, relative standard deviation [RSD]) of the mixtures made with MCC grade 12 was better than that with grade 102 (see Figure 4), although the results were not absolutely uniform in this evaluation. In seven out of nine mixtures, the grade 12 results were better, and the average CV value was 1.9 compared with 3.9 for grade 102. The advantage of grade 12 was particularly noticeable at short mixing times (5 min) when the average CV value was 1.2 compared with 3.8 for grade 102. These results were confirmed by the tableting data. Regarding tablet content uniformity (RSD), grade 12 led to better results in all cases (see Figure 5). Whereas the difference at a concentration of 10% acetaminophen is not great (0.3% at both speeds), the influence was more significant at 25% acetaminophen. In this example, the difference was 2% at 40 rpm and 2.2% at 20 rpm. Because of its poor flow properties, the 50% acetaminophen mixture was not compressible with grade 102 but showed good results with grade 12. The weight uniformity of the tablets (see Figure 6) made with grade 12 also was better. The results were very similar to the

Table II: Equipment and manufacturers.

Machine	Type/Size	Manufacturer
V mixer (twin-shell mixer)	VM 5	Fuji Powdal Co. Ltd. (Osaka, Japan)
Ribbon mixer	AR-400 LK5	ERWEKA International AG (Baettwill, Switzerland)
Mechano mixer	Mechanomil	Okada Seiko Co. Ltd. (Okayama, Japan)
Rotary press	Aquarius 3 (45 stations)	Kikusui Seisakusho Co. Ltd. (Kyoto, Japan)
Rotary press	Clean Press Correct 12 HUK (12 stations)	Kikusui Seisakusho Co. Ltd.
Punches	8 mm, biplane	Kikusui Seisakusho Co. Ltd.
Sampling thief	9 × 12 × 15 mm	Shionogi Qualicaps (Osaka, Japan)
Particle-size determination	Laser micron sizer LMS-30	Seishin Enterprise Co. Ltd. (Osaka, Japan)
Hardness tester	TM 3-3	Kikusui Seisakusho Co. Ltd.
Hardness tester	Auto checker	Okada Seiko Co. Ltd.
Weight tester		Chyo Balance Co. Ltd. (Kyoto, Japan)
Thickness tester		Ono Sokki Co. Ltd. (Yokohama, Japan)
UV spectrometer	UV 160	Shimadzu Seisakusho Co. Ltd. (Kyoto, Japan)

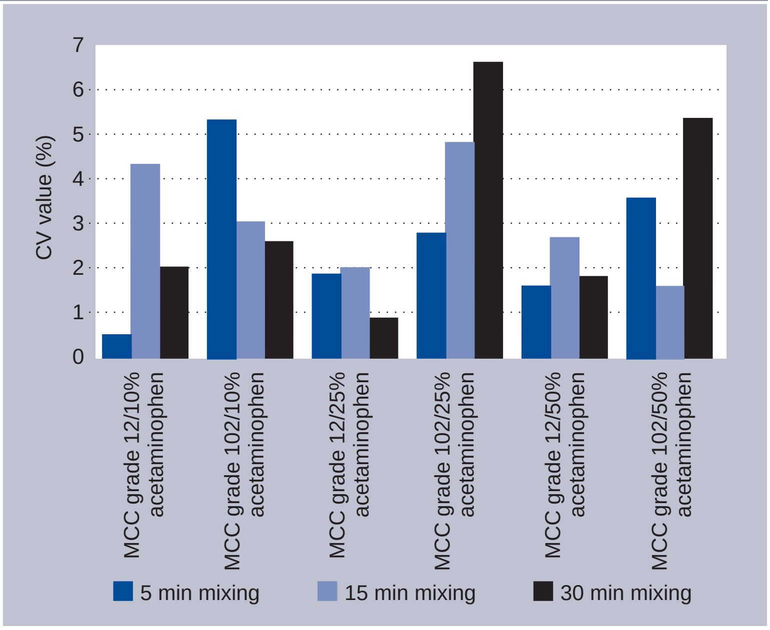


Figure 4: Content uniformity of the various mixtures.

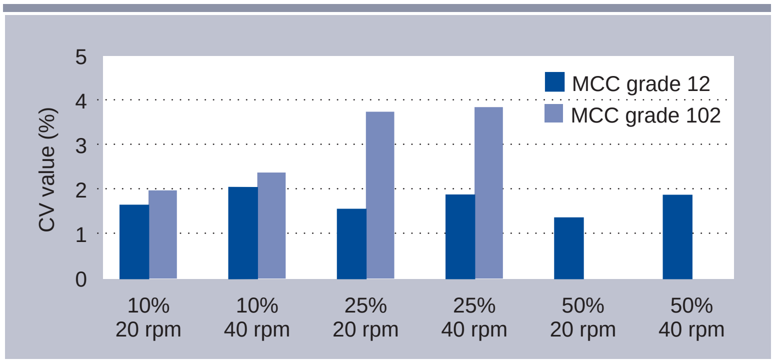


Figure 5: Tablet content uniformity.

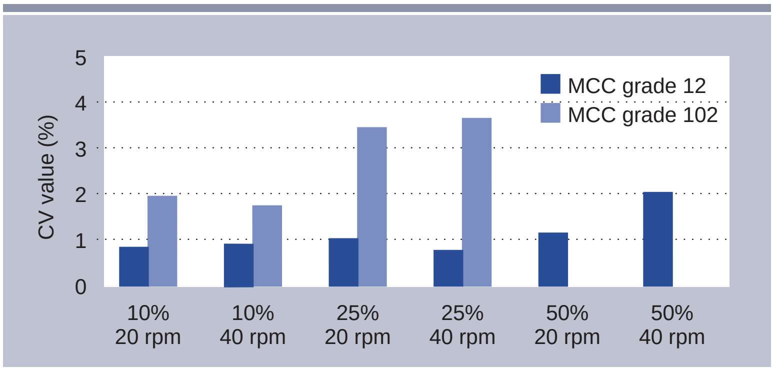


Figure 6: Tablet weight variation.

content uniformity results: Differences between the two MCC grades increased as the percentage of acetaminophen increased. To what extent the uniformity–nonuniformity in terms of content derives from the uniformity–nonuniformity in terms of weight is difficult to express numerically because content uniformity is dependent on many influences beside tablet weight (e.g., mixture uniformity and mixture stability during tableting).

Taking into consideration that the content uniformity results of the mixtures were better for grade 12 (see Figures 4 and 9–11), the uniformity–nonuniformity in weight is not the only reason for the uniformity–nonuniformity of content, even if the weight uniformity does influence the results in a strong way.

In general, the tableting results are more important than the mixing results because the tablet is the final product, and the content uniformity of the tablets can be determined more precisely in terms of sampling than can the content uniformity of the mixtures.

Both angle of repose and compressibility are used as measurements for the determination and description of powder flow properties (low values indicate good flow in both instances). In the example of the 50% acetaminophen tablet, the angle of repose of the grade 12 mixture was almost the same as that of the grade 102 mixture (see Figure 7). It could be expected that these mixtures would behave similarly, but the grade 102 mixture was not workable because of poor flow properties; therefore, the correlation was not satisfactory in this case. In addition to the angle of repose, the compressibility — as an effective index of compressibility (6) and flowability (7) — was determined. It is calculated using the following equation:

$$\text{compressibility}(\%) = \left(\frac{\text{bulk density (tapped)} - \text{bulk density (loose)}}{\text{bulk density (tapped)}}\right) \times 100$$

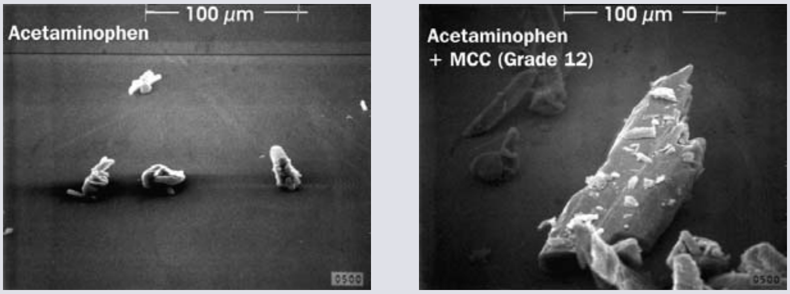
The compressibility values (see Figure 8) indicate clear differences between the mixtures; therefore, they correlate better with the tableting results obtained than with the corresponding angle of repose values.

Mixing and tableting of MCC with low concentrations of fine acetaminophen

Method. MCC was mixed with fine acetaminophen in various proportions (0.1, 1.0, and 5.0% acetaminophen) in a twin-shell mixer for 5, 10, 15, and 30 min. The mixtures then were tested for content uniformity as described in the previous section. Because of the reasons mentioned in that section, tablets were made from the 5-min mixture. After 0.5% magnesium stearate was added and mixing was performed for an additional 5 min, the mixtures were compressed to 180-mg tablets on a rotary press (Correct 12 8-mm flat punches) at 20 and 40 rpm and a compaction force of 1.0 t. The tablets were tested for weight variation and content uniformity.

Results and discussion. As expected, the RSD of the mixtures decreased as the active-ingredient content increased. The values generally were much higher than those obtained from experiments involving high concentrations of acetaminophen (see the previous section). Mixtures of grade 12 showed better and more

Structure of acetaminophen



Before mixing **After mixing**

consistent CV values than those of grade 102 (see Figures 9–11). Regarding tablet content uniformity, grade 12 showed better results than grade 102 (see Figure 12). CV values for grade 12 were 2.0–5.1% and 2.9–8.2% for grade 102. The grade 12 results can be regarded as very good considering that, at such low active concentrations, a premix usually is done (it was not done to keep the results of the previous section and this section comparable).

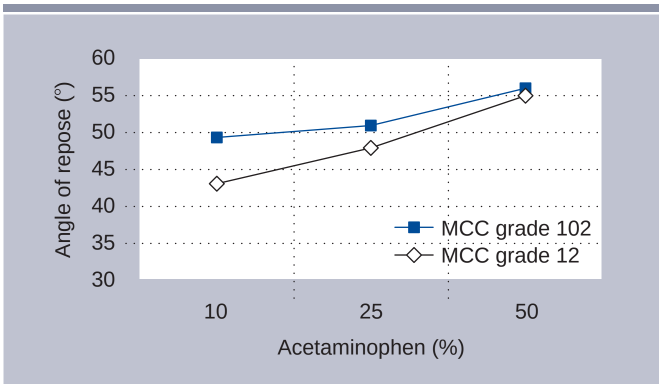


Figure 7: Angle of repose of the various mixtures.

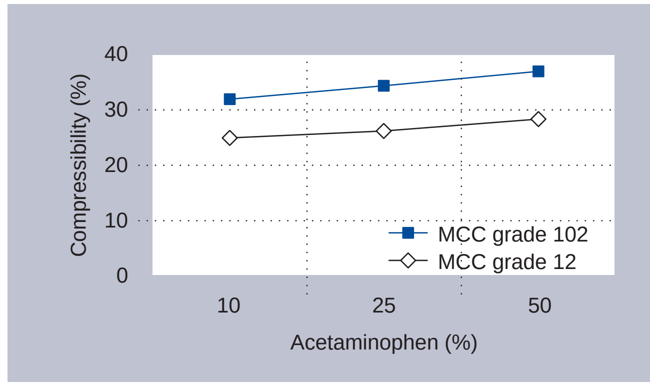


Figure 8: Compressibility of the various mixtures.

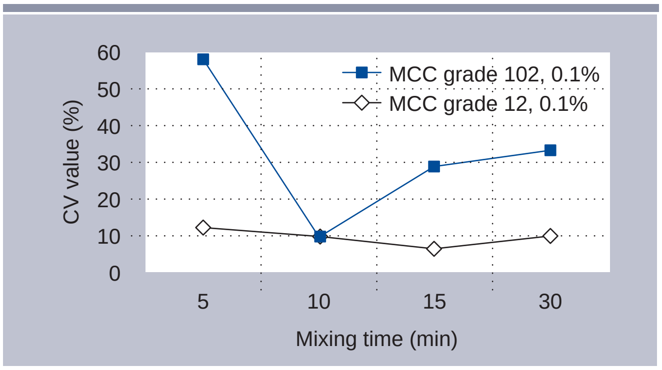


Figure 9: Content uniformity of the mixture: 0.1% acetaminophen.

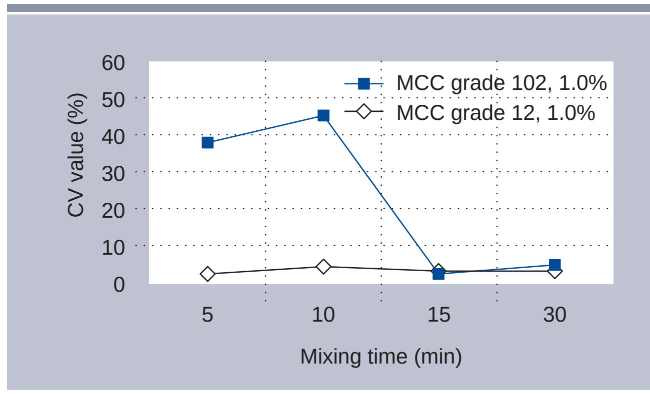


Figure 10: Content uniformity of the mixture: 1.0% acetaminophen.

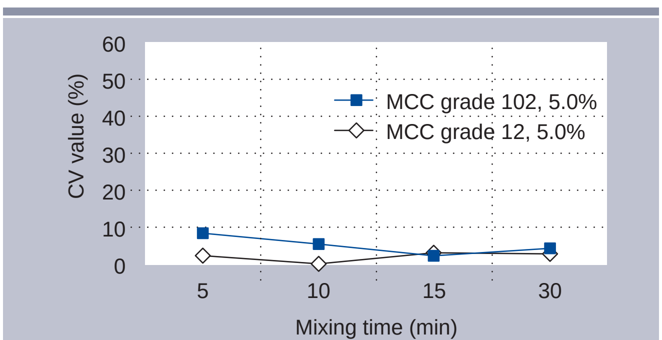


Figure 11: Content uniformity of the mixture: 5.0% acetaminophen.

Conclusions

Tablets made of MCC grade 102 showed slight advantages regarding hardness. This influence became smaller with increasing active concentrations, therefore the practical relevance can be regarded as low when summarizing the advantages of grade 12 in this study. Working with coarse material generally offers some practical advantages such as less dust development during production. MCC grade 12 showed a higher load capacity for fine actives because of improved flow properties. It led to better results regarding the content uniformity of both mixtures and tablets even when working with low concentrations of fine actives and short mixing times. Segregation, seen when fine active ingredients are combined with coarse excipients, was not observed, although it may have been expected from a physical standpoint. It has been found that acetaminophen of the quality used in this study consists of small agglomerates (see "Structure of acetaminophen" sidebar, left picture). During mixing, these agglomerates are destroyed and the distributed single particles stick to the surface of the MCC (see "Structure of acetaminophen" sidebar, right picture).

It seems that an interparticulate force between the two components is formed that is stronger than the tendency to segregate (resulting from the differences in particle size). It also must be considered that MCC is a material of crystalline structure with irregular surfaces, which makes it easy for small particles to cut teeth in.

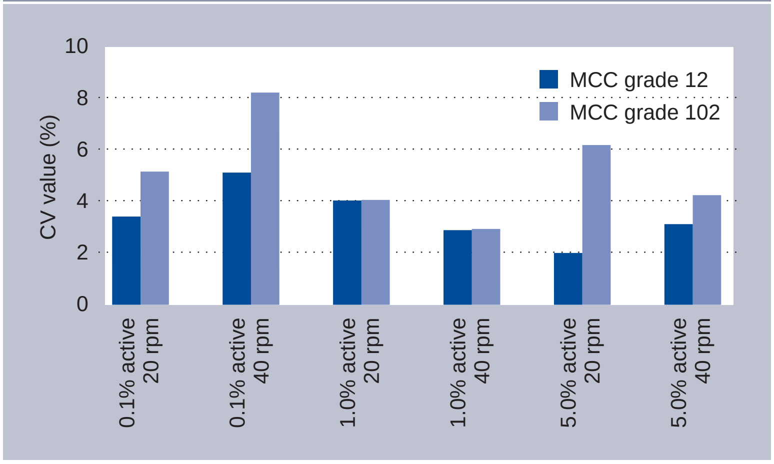


Figure 12: Content uniformity of the tablets.

Acknowledgments

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