Influence of Filler Type in the Blend Uniformity of Micronized Drugs

Zahra N. Mahmoudi, Ngoc Do, Thomas P. Farrell and Ali R. Rajabi-Siahboomi

Colorcon Inc., Global Headquarters, 275 Ruth Road, Harleysville, PA 19438 USA; www.colorcon.com/about/contact

Purpose

Achieving blend homogeneity is an important criterion for formulating micronized drugs. The micronized drugs often have a tendency to segregate during blending due to their increased surface area and particle agglomeration. Blending of micronized low-dose drugs may be challenging and cause content uniformity issues and physical instability.[1, 2] The choice of filler in a formulation, for a low-dose micronized drug, may assist uniform dispersibility of the drug throughout the blend with no segregation during compression. The objective of this study was to investigate the influence of various fillers on blend uniformity of binary mixtures of fillers and a micronized model drug. The effect of four fillers (microcrystalline cellulose, Starch 1500® [partially pregelatinized maize starch], lactose monohydrate, and dibasic calcium phosphate) were evaluated. Two concentrations of 1% and 10% of the micronized drug were used in this study.

Methods

Composition and Preparation of the Blends

Table 1 shows the compositions of eight mixtures of a micronized model drug (sildenafil citrate), with four different fillers including: microcrystalline cellulose NF (MCC, Microcel 102, Blanver), partially pregelatinized maize starch (Starch 1500, Colorcon), lactose monohydrate (FF lactose, 316 FastFlo, Foremost Farms) and dibasic calcium phosphate (DCP, Emcompress, JRS Pharma).

Table 1. Blends Compositions

	1% Drug Load	10% Drug Load
Ingredients	**W/W (%)**	**W/W (%)**
Micronized sildenafil citrate	**1**	**10**
Filler*	**98.5**	**89.5**
Magnesium stearate	**0.5**	**0.5**
Total	**100**	**100**

Fillers: MCC, Starch 1500, FF lactose, and DCP

The volume mean particle diameter of the model drug was 35 μm. Each filler and the delumped micronized drug was weighed to make a 3 kg batch and placed in an 8-q V-blender (Patterson Kelly, USA) in layers and blended up to 12 minutes (min).

Blend Uniformity Testing

Samples for blend uniformity (BU) testing were taken from six predefined locations in the blender, ie, top, center and bottom, on the left and right side of the blender, using a powder sampling thief after 3-min intervals of blending, ie, 3, 6, 9 and 12 min. Powder sample size was 250 mg to 750 mg, equal to 1-3 times the tablet target weight. Samples were assayed individually, and the results were used to calculate the arithmetic mean and the relative standard deviation (RSD). Blends were considered uniform if the mean value was within the range of ±10% of the target potency, and the RSD value was less than 5% (based on FDA draft guidance).[3]

Compression and Physical Testing of Tablets

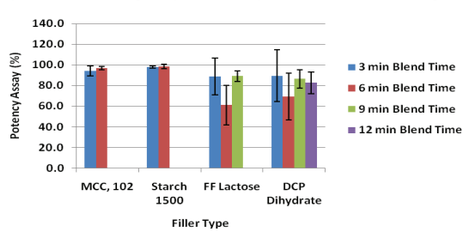
Each blend was lubricated with 0.5% magnesium stearate (MgSt, Hyqual, Mallinckrodt) for three minutes, and compressed into 250 mg tablets using four sets of 5/16" (7.94 mm) SRC tooling, except for the DCP blend for which four sets of 9/32" (7.2 mm) SRC tooling was used due to its higher density. Samples of tablets from the beginning, middle and end of a 70-min run were collected for weight variation evaluation and content uniformity (CU) testing. Tablets (n=10) were assayed individually, and the results were used to calculate the arithmetic mean and the RSD. Tablets were considered uniform if the mean value was within the range of ±15% of the target potency and the RSD was less than 6%.

Results

Blend Uniformity of 1% Blends

Blend uniformity of the binary mixtures of 1% micronized drug is shown in **Figure 1**. Rank order of BU of the 1% blends at 3-min blend time is as follows: Starch 1500 (1.2% RSD) >MCC (4.9% RSD), FF lactose (18% RSD) and, DCP (25% RSD).

Figure 1. Blend Homogeneity of the Binary Mixtures of 1% Model Drug



The average potency assay of 97.9% and the low RSD of 1.2% for Starch 1500 met the specification for BU at 3-min blending time with no significant change at 6-min blend time. This indicated that excipient type may have an influence on blending time for a micronized drug at a low dose of 1%. It has been reported that irregular surfaces of Starch 1500 particles are suitable for micronized drug adsorption, rendering content uniformity of a formulation with low dose drug.[4, 5]

Blend Uniformity of 10% Blends

The highest uniformity of the 10% blends at 3-min blend time (**Table 2**) was obtained for Starch 1500 followed by MCC (3.7% and 4.8% RSD, respectively) and the lowest for DCP (5.4% RSD). The average potency assay of 95.1% for the FF Lactose blend wasn't significantly different from 95.8% obtained at 6-min blend time, however, the RSD value improved at 6-min blend time. At this time, all blends except the DCP were uniform. The average potency assay results of the DCP blend at 3, 6, 9 and 12 min fluctuated, but they were generally within the specification range. The variable and high RSD values indicated a non-uniform blend.

Table 2. Comparison of BU of the 10% Blends at Different Blend Times

Filler/Binder	3 minutes		6 minutes		9 minutes		12 minutes	
	AVG Assay (%)	RSD (%)	AVG Assay (%)	RSD (%)	AVG Assay (%)	RSD (%)	AVG Assay (%)	RSD (%)
MCC, 102	91.5	4.8	94.9	4.0	-	-	-	-
Starch 1500	95.2	3.7	99.4	1.9	-	-	-	-
FF Lactose	95.1	5.6	95.8	3.6	-	-	-	-
DCP	95.2	5.4	87.5	7.1	93.7	3.8	93.0	7.2

Tablet Content Uniformity and Weight Variations

Figures 2 and **3** show the average tablet weights as a function of compression time. Tablet weight variations for both concentrations were low, which indicated a consistent tablet weight throughout the compression run.

Figure 2. Weight Variation of Tablets Comprising 1% Model Drug (n=10)

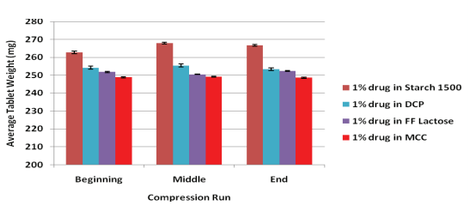
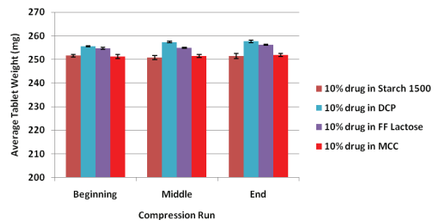


Figure 3. Weight Variation of Tablets Comprising 10% Model Drug (n=10)



The effect of different fillers on content uniformity of the tablets of 1% and 10% model drug is shown in **Figures 4** and **5**. Tabletting started with uniform blends, although the DCP blends had the poorest blend uniformity. Tablets of 1% of the micronized drug with MCC and Starch 1500 had acceptable CU throughout the tabletting run with no segregation. However, FF Lactose and, particularly, DCP tablets had poor CU due to the poor blend uniformity and possible blend segregation. Tablets of 10% micronized drug with all tested excipients had acceptable CU throughout the tabletting run with no segregation.

Figure 4. Content Uniformity of Tablets Comprising 1% Model Drug

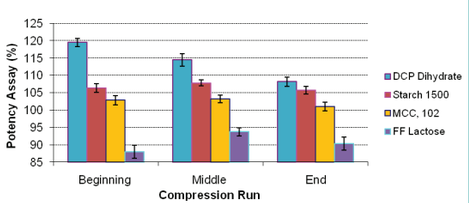
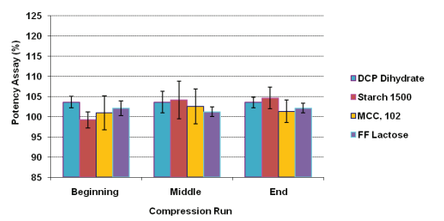


Figure 5. Content Uniformity of Tablets Comprising 10% Model Drug



Conclusions

The choice of filler for a low-dose micronized drug may assist dispersibility and uniformity of the drug throughout the blend. Although micronized drugs have a tendency to agglomerate, in this study it was shown that filler type assisted blend homogeneity. Fillers with irregular surface characteristics (such as Starch 1500) may provide favorable adsorption for micronized particles and behave as a carrier, rendering content uniformity. Previous tablet formulation studies have indicated that Starch 1500 and MCC mixtures provided excellent blend uniformity, with good compaction and disintegration properties.[6]

References

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