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Technical Information

Blending Efficacy of PROSOLV® SMCC with Caffeine by Near-Infrared Spectroscopy

Abstract

In drug production, manufacturing efficiency and the effectiveness of the final product (i.e., bioavailability, content uniformity, compression uniformity, ease of ejection, etc.) largely depends on the blending process. Not only do the chosen excipients used in the formulation matter, but any modification of these materials can contribute to major differences in the length of blending needed as well as the functionality of the blend, itself.

PROSOLV® SMCC (Co-processed Silicifed Microcrystalline Cellulose) was developed by JRS Pharma over 20 years ago. This monographed, Inactive Ingredient Database (IID) listed, highly functional excipient has been well regarded in formulation and processing. PROSOLV® SMCC improves compactability, exhibits superior flow, and enhances mixing characteristics, optimizing content uniformity thus enabling rapid formulation development. Direct compression processing remains the most economical process within pharmaceutical manufacturing due to a smaller processing equipment footprint with less steps and lower energy costs.

In this study, a series of blending experiments evaluated the uniformity of caffeine in blends with the co-processed excipient silicified microcrystalline cellulose (PROSOLV® SMCC) versus physical blends of microcrystalline cellulose and the glidant colloidal silicon dioxide (CSD). The blending process was monitored with Near-Infrared Spectroscopy (NIRS). The effects of mixing on particle size attenuation were investigated by measuring each of the resultant blends with a LASER light-scattering (LLS) device. The blends were tableted and the results (ejection force, hardness, and assay) compared.

For this un-optimized formulation with a challenging active, use of co-processed PROSOLV® SMCC yielded robust formulations with significant benefits over using MCC blended with CSD glidant. These benefits included faster blend uniformity and improved tablet content uniformity, as well as both increased tablet hardness and reduced ejection forces. PROSOLV® SMCC can be used to simplify formulation optimization and process scale-up, potentially avoiding costly reworks later on.

Aim of the Study

The goal of this study was to use NIRS to compare the blending efficacy of PROSOLV® SMCC with a physical blend of the same nominal components, using a challenging API in a non-optimized model.

The blending efficacy of PROSOLV® SMCC has been demonstrated visually, using pigments as a surrogate for the API in the formulation. NIRS was chosen for this study to allow measurement of blending efficacy with an API. There have been a large number of publications where NIRS has been used to determine the efficacy of mixing at any particular time point (ref. 1-5), though the focus has historically been on NIRS usability, relevant math treatments, or apparatus design.

Caffeine was used as the model API since it is needle-like and has a high static charge, thus presenting challenges to insuring content uniformity.

Two blenders were used, one with a more vigorous motion, and another similar to plant-scale blenders, in order to observe the effects of both changing the excipients and the type of blender.

Formulation

PROSOLV® SMCC 90 and EMCOCEL® 90 M were chosen for the blending study because these materials have similar particle sizes and are both direct compression (DC) excipient grades. The commercial lots of PROSOLV® SMCC 90 and EMCOCEL® 90 M (JRS Pharma) used had similar bulk densities (0.36 g/mL and 0.33 g/mL, respectively) to reduce density effects on blending. The CSD used for the EMCOCEL® -CSD blend was the same grade as is used in PROSOLV® SMCC.

Two formulations were made targeting the same final composition of API (caffeine, 10%) and the same nominal composition of excipients (see Table 1). There was no formulation optimization. Sodium starch glycolate (SSG, EXPLOTAB®) was incorporated into the blend first, then the CSD (Cab-O-Sil® M-5P), before the caffeine was finally added. Caffeine (USP) was obtained from Spectrum Chemical.

Sodium stearyl fumarate (SSF, PRUV®) was screened and added to each blend after NIRS measurements were complete, with an additional five minutes of blending time.

Component	PROSOLV® SMCC 90	MCC+CSD
Caffeine	10.0	10.0
PROSOLV® SMCC 90	88.65	-
EMCOCEL® 90	-	86.88
Cab-O-Sil® M-5P	-	1.77
EXPLOTAB®	0.90	0.90
PRUV®	0.45	0.45
Total (%w/w)	100.0	100.0

Tab. 1 Target compositions (%w/w).

Excipients

PROSOLV® SMCC (silicified microcrystalline cellulose - SMCC), is a unique combination of MCC co-processed with colloidal silicon dioxide. A high functionality and multifunctional excipient, it facilitates less complex processing, has higher inherent functionality, and passes that functionality on to the drug formulation. It nominally contains 98 % MCC and 2.0 % CSD.

EMCOCEL® Microcrystalline Cellulose (MCC) is one of the most widely used binder excipients in tablet formulations. Derived from pharmaceutical grade wood pulp, it offers a wide range of chemical, technical, and economical benefits in formulation and processing.

PRUV® (Sodium Stearyl Fumarate) is a tablet lubricant that offers a high degree of API compatibility and robustness to over-lubrication.

EXPLOTAB® (Sodium Starch Glycolate) is a swelling-type superdisintegrant for tablets and other oral solid dosage forms.

Cab-O-Sil M-5P (Colloidal Silicon Dioxide) is used as a flow aid in the tableting process.

Procedure

Equipment

3D Powder Mixer	Glen Mills Turbula
Tumbler Blender	PK V-Blender
Sampling Thief	Sampling Systems 10 mL-25 mL Powder Thief
NIR Instrument	Metrohm Model 6500 RCA NIR
Particle Size Analyzer	Malvern Mastersizer 2000 with a Scirocco 2000 Powder Sampling Accessory
Tablet Press	Piccola Rotary Instrumented Tablet Press
Hardness Tester	Sotax Model HT10 Hardness Tester
Dissolution Apparatus	PharmaTest ADS-L 1220 Dissolution System

Blending

Each blend was prepared twice, once with a batch size of 330 g (for a 2L Glen Mills Turbula), and again with a batch size of 660 g (for a 4 qt PK V-blender), in both cases targeting between one third to half of the fill volume. The Turbula was run at 72 rpm, and the V-blender at 25 rpm. Five samples were taken at pre-chosen intervals, each transferred into a 25 mL sample vial, and NIR spectra were obtained. In consideration of sampling and its potential impact to the blend, the thieved samples were returned to the blender prior to the next mix point.

NIRS Measurements

In order to follow the variance in the homogeneity of the ingredients in the mixes, caffeine was selected as the "spectroscopic marker" for the analyses. A caffeine peak at 1670 nm was chosen as the analytical marker, as it is easily identified in the spectrum (Figure 1).

Five samples (taken from various locations/depths at each time point) by the "sample thief," were transferred to glass vials and scanned (reflection mode through the bottom of the vial) via NIRS. The diffuse reflection spectra were obtained in triplicate for each sample, with reproducible shaking and tapping between measurements.

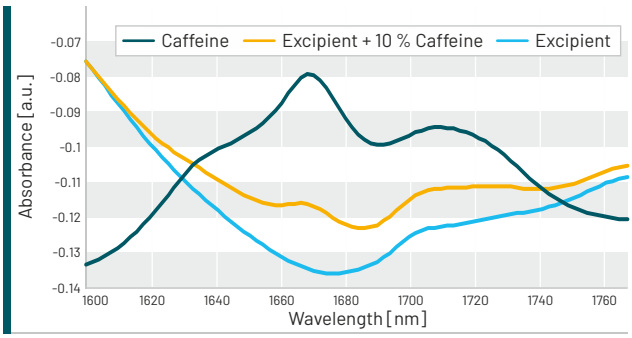

Fig. 1 NIR of blend study materials – caffeine peak at 1670 nm.

Tableting

After addition of the lubricant at the end of each blending experiment, each blend was compacted into tablets. Best practice is for samples to be no more than 3x a unit dosage. As the sampling thief could remove up to three grams of sample for NIR measurements, a final target weight of 1500 mg was chosen. A 0.875" (22.2 mm) round flat faced beveled edge tooling was used to accommodate the large tablet size. Each blend was compacted at five different compaction forces, on an instrumented tablet press.

Tablet Characteristics

Tablet Weight	1500 mg
Tablet Shape	0.8750" (22.2 mm) round flat faced beveled edge
Tablet Height	3.5 – 5.5 mm

Particle Size Measurements

Since the act of blending imparts shear and other forces upon the components of a blend, and particle size affects both blending and compression, it was deemed important to monitor any changes in particle sizes of the components. The effect of blending on the particle size(s) of the excipients and API was observed by measuring the blend by LASER diffraction particle size analysis, using a powder sample attachment.

Caffeine Assays

Ten tablets from each blend, compressed at ~12 kN, were assayed for caffeine content with a PharmaTest ADS-L 1220 dissolution system, which includes a UV-Vis spectrometer. Tablets were dissolved in 500 mL of 25 °C water with the stirrer set to 50 rpm. A solution of 150 mg of caffeine dissolved in 500 mL of water was used as a reference. Absorbance was measured at 275 nm, using quartz cuvettes with 0.1 cm path length.

Results and Discussion

Impact of Mixing on Blend Uniformity

The variation in caffeine absorbance was less for the PROSOLV® SMCC blends after the initial few minutes of mixing (Figure 2), indicating a more consistent caffeine content with this excipient when compared with EMCOCEL® -CSD. Additionally, at longer times (1-2 hours) the variation in caffeine absorbance began increasing for the EMCOCEL® -CSD blends, which may be an indication of "demixing." [Demixing is the term given to selective breaking of ingredients, causing a change in size and lessening homogeneity.] The EMCOCEL® -CSD V-blender blend became more consistent after approximately three hours of mixing. Regardless of the differences in processing between the two blender types, PROSOLV® SMCC promoted better blend uniformity than the physically blended excipients.

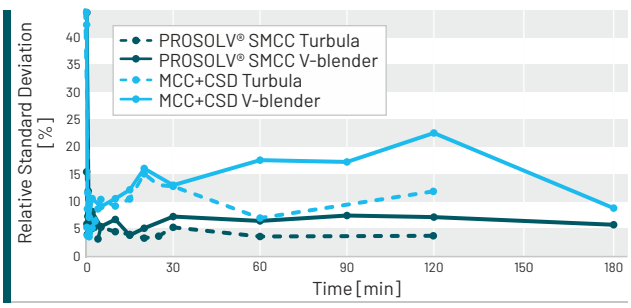

Fig. 2 Variance in peak height with blending.

Particle Size Measurements

Since the excipients were selected to have similar particle sizes, the effect of blending on particle size was also examined. Particle size was analyzed by LASER diffraction on all the final blends (after lubricant addition), as well as the individual excipients (Figure 3). The type of blender had little impact on particle size, possibly due to the increased time of blending for the lower impact V-blender blends (3 h vs. 2 h for the Turbula blends). Both the PROSOLV® SMCC and EMCOCEL® -CSD blends had similar, small reductions in particle size after blending.

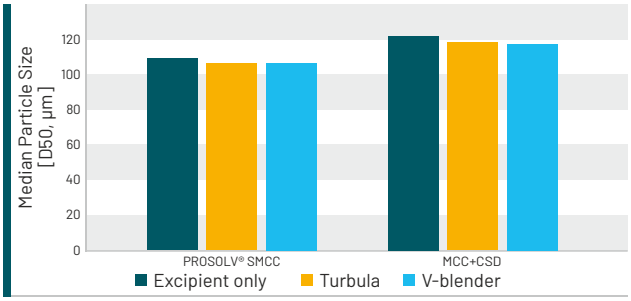

Fig. 3 Median particle size comparison via LLS.

Tableting Results

The tablet hardness values show that the Turbula and V-blender (Figure 4) caffeine blends produced similar trends, with the PROSOLV® SMCC blends giving much higher tablet hardness than the EMCOCEL® -CSD blends.

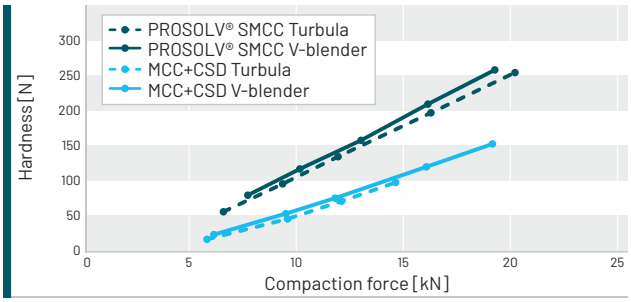

Fig. 4 Tableting hardness comparison

The ejection forces (effort to eject tablets from the press) again show similar trends for the Turbula and V-blender caffeine blends (Figure 5). While ejection forces were acceptable for the EMCOCEL®-CSD blends, ejection forces for the PROSOLV® SMCC blends were significantly improved.

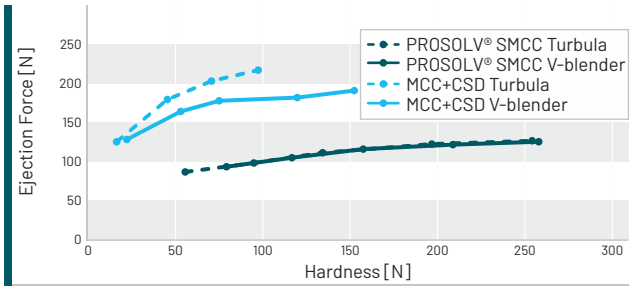

Fig. 5 Tableting ejection force comparison.

Content Uniformity

Tablets compacted at ~12 kN were used for the caffeine assays (in Figure 6).

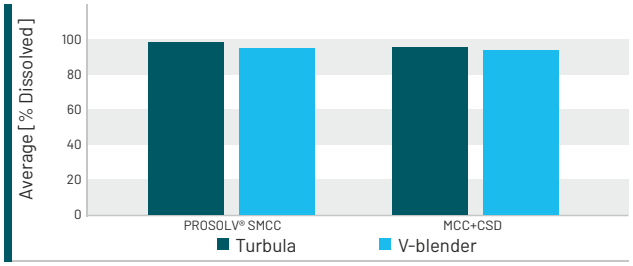

Fig. 6 Tablet caffeine assay results, with weight correction.

Based on USP <905>, Uniformity of Dosage Units, the acceptance values demonstrated that the assayed content was closest to target and most uniform for tablets produced from the PROSOLV® SMCC Turbula blend (Figure 7). PROSOLV® SMCC blends gave lower acceptance values than the EMCOCEL®-CSD blends regardless of blender type. All blends produced tablets with acceptance values within the standard limit of 15% maximum. As materials were blended for 2-3 hours, it would be unusual for any of the blends to have unacceptable content uniformity.

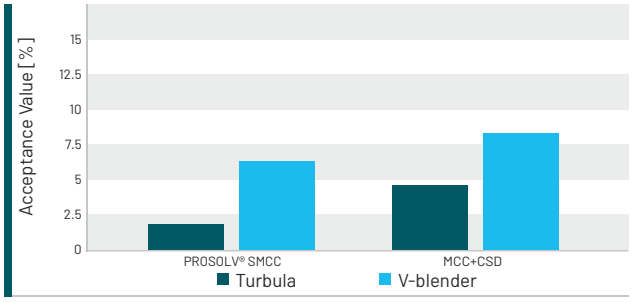

Fig. 7 Tablet caffeine assay acceptance values.

Conclusion

PROSOLV® SMCC produced blends with better uniformity (as measured by NIRS) than the EMCOCEL® -CSD blends. Use of PROSOLV® SMCC promoted faster blend uniformity with a challenging active, allowing shorter processing times. Blends with PROSOLV® SMCC demonstrated increased tablet hardness and reduced ejection forces as compared to those with EMCOCEL® -CSD. Caffeine assay results, particularly the acceptance value, pointed to the PROSOLV® SMCC Turbula blend as producing the best overall blend, improving both content uniformity and content accuracy of the resulting tablets.

For this un-optimized formulation with a challenging API, use of the co-processed PROSOLV® SMCC excipient yielded robust formulations with significant benefits over using MCC blended with CSD glidant. These benefits included faster blend uniformity and improved tablet content uniformity, as well as both increased tablet hardness and reduced ejection forces. PROSOLV® SMCC can be used to simplify formulation optimization and process scale-up.

Reference

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