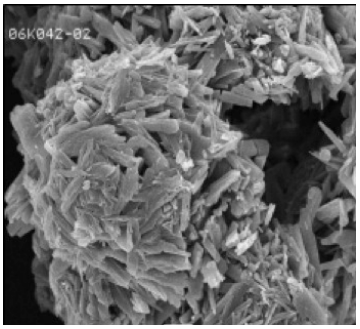
# Carrier-Mixing of Mannogem EZ with Micronized Low dose Furosemide: Uniformity of dosage unit study

Authors: Sunil Kumar N*, John K Tillotson, Praveen Saligram, Robert Duffy
**SPI Pharma Inc.**

## Introduction

To produce solid dosage forms such as tablets or capsules with acceptable content uniformity, it is critical to prepare a powder blend which not only contains uniformly mixed API, but also defies segregation in blend. Therefore, granulation is usually the first choice for preparation of homogeneous, segregation-resistant blends because of the strong API-excipient bonds formed by the agglomeration process. Although a homogeneous blend is usually attainable, the challenge of obtaining a segregation-resistant blend precludes the widespread use of the simpler direct-compression (DC) process, which would otherwise be desirable for manufacture of low-dose drugs. To empower the DC process for low-dose tablet manufacturing, ordered mixing is the central operation to ensure good content uniformity at production scale. Practically, a uniform API distribution should not only be achieved immediately following blending, but also maintained at the final tableting stage.[1]

Figure 1: SEM Mannogem EZ (1000x)




Carrier mixing occurs when an active is internalized into the structure of a larger carrier particle during mixing. When this happens, it is possible to generate an ordered mix having a low RSD for the active component. Due to the porous nature of Mannogem EZ (Figure 1) it is postulated that it can act as a carrier particle.

The aim of this experiment was to test this theory and to demonstrate the utility of Mannogem EZ as a carrier for micronized actives, a Central Composited Design of experiments was implemented studying the effect of API concentration and mix time on the relative standard deviation (RSD) of active in tablets compressed from a direct compression blend (Table 1).

## Materials

To manufacture ODT's with dosages of 80mg, 160mg, and 500mg of acetaminophen Mannogem EZ (SPI Pharma Inc), PVP K29/31 (ISP), Micronised Furosemide (IPCA Ltd), Lubripharm (SPI Pharma Inc)

## Methods

Micronized furosemide (d (0.5) = 12µm) was employed as a model API in the study. 500g blends containing API (concentration per design stipulation) was varied according to the percentages listed in table 1. Lubripharm concentrations were held at 2.5% for all experimental runs, with Mannogem EZ in quantity sufficient to complete the formulation. The Micronised furosemide and Mannogem EZ were mixed in an 8-quart V-blender for the time indicated in table 1. Subsequently, the Lubripharm was added to each run and blended in for 2 minutes. Resultant blends were tableted (1000mg) on a GP-8 rotary tablet press operated at 25rpm and outfitted with 0.625" FFBE type "D" punches to a hardness of 7kP. Tablets were analyzed for active drug content by HPLC.

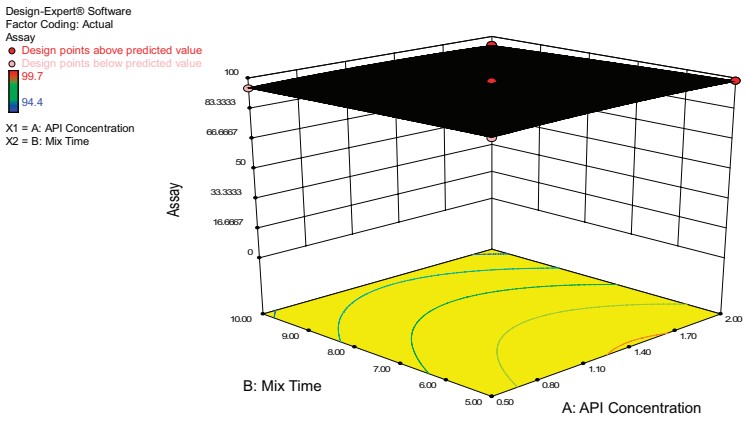
Table 1: Central Composited Design for Mixing Experimentation

| Run | API Concentration (%) | Mix Time (min) |
|---|---|---|
| 1 | 0.5 | 5 |
| 2 | 2 | 5 |
| 3 | 0.5 | 10 |
| 4 | 2 | 10 |
| 5 | 0.19 | 7.5 |
| 6 | 2.31 | 7.50 |
| 7 | 1.25 | 4 |
| 8 | 1.25 | 11 |
| 9 | 1.25 | 7.5 |
| 10 | 1.25 | 7.5 |
| 11 | 1.25 | 7.5 |
| 12 | 1.25 | 7.5 |
| 13 | 1.25 | 7.5 |

## Results

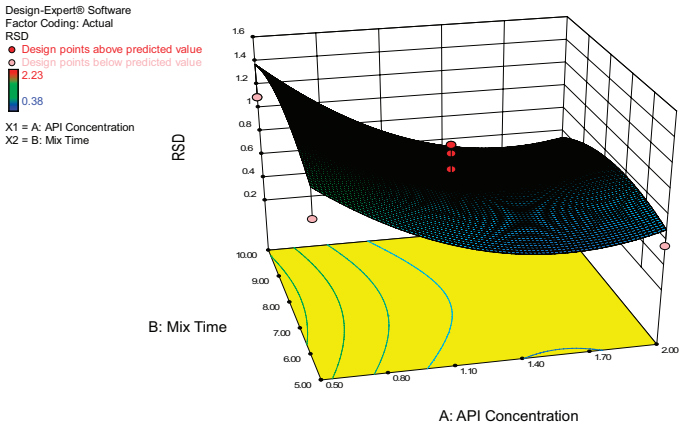
Mix time and API concentration had no significant impact on API concentration leading to consistent Assay throughout range of these variables.

Figure 2: Response Surface graph for Assay



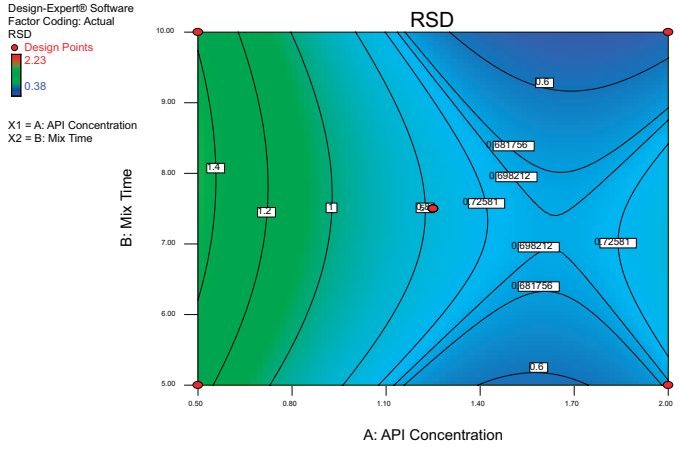

Mix time had minimal impact on RSD, while API concentration was inversely proportional to RSD.

Figure 3: Response Surface graph for RSD




As indicated in figure 4, RSD tends to drop as API concentration increases; indicating a significant effect of API concentration on content uniformity. In contrast, the furosemide-Mannogem EZ mix time did not significantly affect the RSD, indicating that for the furosemide concentration ranges studied adjusting Carrier mix times over the range of 4 to 11 minutes had little effect on the content uniformity of the manufactured furosemide tablets. The highest RSD (2.23%), with respect to furosemide content occurred at a furosemide concentration of 0.19% and a mix time of 7.5 minutes.

Figure 4: Contour Plot of furosemide RSD



As indicated in table 2, the calculated acceptance value for all runs was below the L1 acceptance value of 15 outlined in the USP2 on the Uniformity of Dosage Units, demonstrating that despite relatively low concentration of furosemide (0.19 – 2.31%) all manufactured tablets passed USP criteria for content uniformity without the employment of geometric blending.

Table 2: USP acceptance value for uniformity of dosage units

| Run | API Concentration (%) | Mix Time (min) | Acceptance value |
|---|---|---|---|
| 1 | 0.5 | 5 | 3.8 |
| 2 | 2 | 5 | 1.3 |
| 3 | 0.5 | 10 | 6.6 |
| 4 | 2 | 10 | 4.5 |
| 5 | 0.19 | 7.5 | 5.1 |
| 6 | 2.31 | 7.50 | 5.5 |
| 7 | 1.25 | 4 | 1.6 |
| 8 | 1.25 | 11 | 5.1 |
| 9 | 1.25 | 7.5 | 4.9 |
| 10 | 1.25 | 7.5 | 3.7 |
| 11 | 1.25 | 7.5 | 1.4 |
| 12 | 1.25 | 7.5 | 2.8 |
| 13 | 1.25 | 7.5 | 2.6 |

## Conclusion

Based on the current experimentation, tablets manufactured from blends of Mannogem EZ and micronized furosemide were highly uniform. Drug concentration was inversely proportional to furosemide content RSD over studied concentration range. Mix time had no significant effect on the content uniformity of manufactured tablets over the studied ranges. All combinations of mix time and furosemide concentration produced tablets which met the USP Uniformity of Dosage Units acceptance requirements. Due to the relatively large difference in particle size between Mannogem EZ (d(0.5) = 120µm) and the furosemide (d(0.5) = 12µm), the most likely cause of the relatively low RSD's for active content observed in the study is carrier mixing resultant from Mannogem EZ's porosity.

## References

1) Harnessing ordered mixing to enable direct-compression process for low-dose tablet manufacturing at production scale Chen Mao et al Powder technology 239 (2013) PP 290-299

2) United States Pharmacopeia 34. <905> Uniformity of dosage units Pharmacopeial Forum, 35 (3) (2011), p. 724

Your Partner for Formulating Success

www.spipharma.com

Americas
SPI Pharma, Inc.
Rockwood Office Park
503 Carr Rd., Suite 210
Wilmington, DE 19809

T 302 576 8600
800 789 9755 Ext. 8600
F 302 576 8567

Europe/Middle East/ Africa
SPI Pharma SAS
Chemin du Vallon du Maire
13240 Septemes-Les Vallons
France

T 33 4 9196 3600
F 33 4 9196 3633

Asia/Pacific
SPI Pharma, Inc – India Branch
21 B, Veerasandra Industrial Area
Hosur Road, Bangalore – 560100
Karnataka, India

T 91 80 3027 0005
F 91 80 3027 0050

Australia Distribution Company
Anzchem
1 Braidwood Street
Enfield NSW 2136
Australia

T 61 2 9475 2200
F 61 2 9475 2211