Improving the Solubility of a BCS Class ll Drug Through Excipient Selection

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1. Introduction

BCS class II APIs are classified as low soluble and highly permeable, therefore the barrier to their absorption is dissolution based on the solubility of the API. Multiple strategies have been developed to improve the solubility of poorly soluble drugs, including co-crystallization with soluble carriers, nanosizing of APIs, and holt-melt co-extrusions with soluble carriers. These are all process based solutions requiring additional unit operations to be conducted prior to final formulization. However, it is also possible to improve API solubility through selection of formulation excipients. The current study employs two separate binary mixture experiments to statistically evaluate the effect of Mannogem® EZ, a spray—dried mannitol, and spray—dried lactose (SDL), both independently and in conjunction with microcrystalline cellulose (MCC) (100µm average particle size), on the release of ibuprofen from directly compressible tablets.

2. Methods

2.1 Tablet Manufacture

200mg tablets containing 20mg of ibuprofen (model BCS class II API) and 2.0% Lubripharm® SSF were manufactured with the other 88.0% of the formulation excipients varied as indicated in tables 1 and 2 according to two-separate D-optimal binary mixture experimental designs.

For tablet manufacture all ingredients were passed through a #20-mesh screen, and subsequently all formulation ingredients for each respective run were small volume blended for 5 minutes with a mortar and pestle. Subsequently the batches were tableted on a GP-8 rotary tablet press outfitted with 0.374" FFBE “D” punches at 25 rpm with no pre-compression to a target tablet hardness of 7kP.

Table 1: Mannogem EZ and MCC Binary Mixture Design

Run	Mannogem EZ	MCC (100µm)
1	66.0%	22.0%
2	22.0%	66.0%
3	44.0%	44.0%
4	0.0%	88.0%
5	88.0%	0.0%
6	88.0%	0.0%
7	44.0%	44.0%
8	0.0%	88.0%
9	88.0%	0.0%
10	0.0%	88.0%
11	0.0%	88.0%
12	88.0%	0.0%
13	44.0%	44.0%

Table 2: SDL and MCC Binary Mixture

Run	SDL	MCC (100µm)
1	44.0%	44.0%
2	0.0%	88.0%
3	0.0%	88.0%
4	88.0%	0.0%
5	88.0%	0.0%
6	44.0%	44.0%
7	0.0%	88.0%
8	44.0%	44.0%
9	88.0%	0.0%
10	22.0%	66.0%
11	88.0%	0.0%
12	0.0%	88.0%
13	66.0%	22.0%

2.2 Tablet Dissolution

Tablets were dissolved in 900mL of USP pH 7.2 phosphate buffer employing apparatus 2 at 50 rpm and a media temperature of 37.5°C. 5mL of sample was withdrawn with media replacement at the following times: 5, 15, 30, and 60 minutes. The samples were subsequently filtered and ibuprofen content was calculated by UV-Vis spectrometry at 221nm. The percent ibuprofen release was calculated by comparison with a standard.

2.3 Experimental Design

Two separate D-optimal, binary mixture experiments were employed, one for Mannogem EZ with MCC and one for SDL with MCC. The treatments for both experiments were the percent participation of the respective soluble filler (e.g. Mannogem EZ or SDL) and the percent participation of the insoluble filler (MCC). The responses for both experiments were the percent ibuprofen release at 5, 15, 30, and 60 minutes. Statistical modeling of the treatment to response relationship was conducted employing Design Expert 7 software.

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3. Results

3.1 Ibuprofen Release

Figures 1 and 2 present the dissolution data obtained for pure blends of each ingredient and the 50:50 binary blends of MCC with both Mannogem EZ and SDL.

The results displayed in figure 1 and figure 2 indicated that Mannogem EZ releases the ibuprofen faster than either SDL or MCC. Additionally, the 50:50 combination of Mannogem EZ and MCC release the ibuprofen more rapidly than a 50:50 combination of SDL and MCC, indicating an increased synergism for the Mannogem EZ and MCC formulation as compared to the SDL and MCC formulation, with regard to ibuprofen dissolution.

Figure 1: Pure Blend Dissolutions

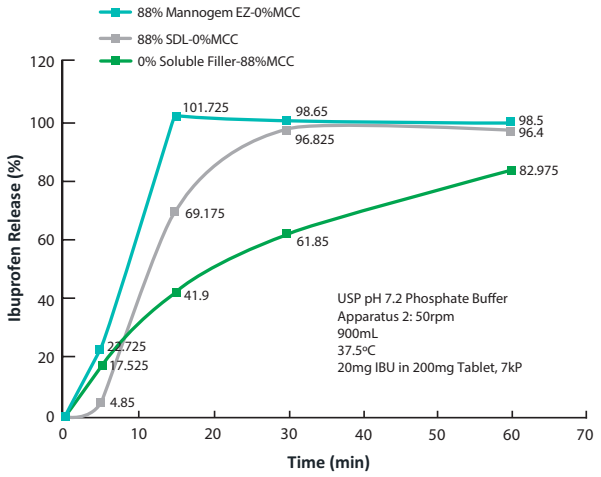
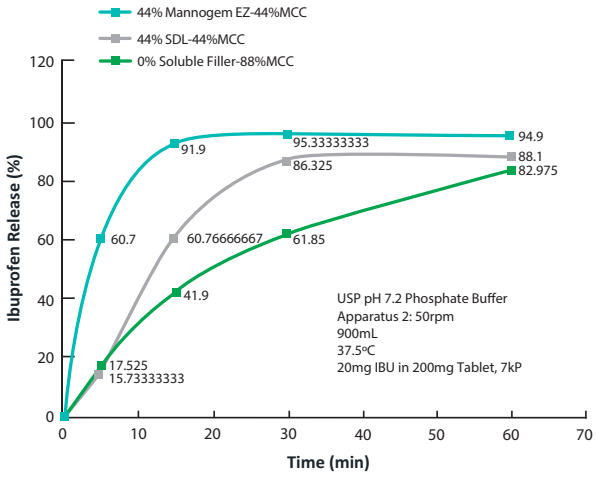


Figure 2: 50:50 Binary Blends Compared to MCC Pure Blend



3.2 DOE Analysis

3.2.1 5-minute response

Table 3 presents the coefficients for the release of ibuprofen at 5 minutes from both study systems in terms of the L-pseudo components, which is a system of coding variables typically employed in mixture-experiment regression equations.

The data in table 3 indicates that Mannogem EZ provides for a significantly faster release, due to both its main effect, 22.67, versus 5.08 for SDL, and its interacting effects with MCC which were both synergistic for ibuprofen release at 5 minutes. SDL exhibits an antagonistic effect, with regard to the 5-minute ibuprofen release at 5 minutes, when SDL is in higher proportion than MCC in the formula. This trend is reversed at the 5-minute time point for Mannogem EZ which exhibits a synergist effect when its concentration is higher than the MCC concentration.

Table 3: Equation Coefficients Relating Ibuprofen Release to Excipient Mix (5-minutes, L-pseudo components)

Model Term	Mannogem EZ	SDL
Soluble Filler	22.67	5.08
MCC	17.47	17.75
Filler*MCC	160.78	24.54
Filler*MCC* (Filler – MCC)	102.93	-96.87

3.2.2 15-minute response

Table 4 presents the coefficients for the release of ibuprofen at 15 minutes from both study systems in terms of the L-pseudo components.

The data in table 4 indicates that Mannogem EZ in association with MCC provides for a significantly faster release of Ibuprofen at 15-minutes than does SDL in association with MCC, due to both main effects, 101.74 for Mannogem EZ compared to 71.09 for SDL. Additionally, Mannogem EZ has a positive synergism of 81.77, while SDL exhibits no synergism at 15 minutes with MCC. The antagonistic response for Mannogem EZ can be eliminated by holding the Mannogem EZ concentration equivalent to the MCC, since the Mannogem EZ and MCC will be equivalent, the expression (Filler – MCC) will be zero.

Table 4: Equation Coefficients Relating Ibuprofen Release to Excipient Mix (15-minutes, L-pseudo components)

Model Term	Mannogem EZ	SDL
Filler	101.74	71.09
MCC	41.95	45.71
Filler*MCC	81.77	–
Filler*MCC* (Filler – MCC)	-71.44	–

3.2.3 30-minute response

Table 5 presents the coefficients for the release of ibuprofen at 30 minutes from both study systems in terms of the L-pseudo components.

The data in table 5 indicates that Mannogem EZ in association with MCC provides for a significantly faster release of ibuprofen at 30 minutes, for the 50:50 blend of Mannogem EZ with MCC, due mostly to Mannogem EZ's significant two-way interaction with MCC (62.14). At 30 minutes the Mannogem EZ and SDL main effects are roughly equivalent; however, Mannogem EZ exhibits a synergistic interaction with MCC at 30 minutes that SDL does not. The antagonistic interaction of Mannogem EZ with MCC is eliminated by holding the concentration of Mannogem EZ equivalent to that of MCC, as this will eliminate the -86.40 coefficient from the equation, since the Mannogem EZ and the MCC will be equivalent; therefore, the expression (Filler – MCC) will be zero.

Table 5: Equation Coefficients Relating Ibuprofen Release to Excipient Mix (30-minutes, L-pseudo components)

Model Term	Mannogem EZ	SDL
Filler	98.71	97.87
MCC	61.91	64.60
Filler*MCC	92.14	–
Filler*MCC* (Filler – MCC)	-86.40	–

3.2.4 60-minutes response

Table 6 presents the coefficients for the release of ibuprofen at 30 minutes from both study systems in terms of the L-pseudo components.

The data in table 6 indicates that Mannogem EZ and SDL provide for a similar release of ibuprofen at 60 minutes. The main effects of Mannogem EZ and SDL are roughly equivalent at 60 minutes; however, Mannogem EZ exhibits a slight synergism with MCC of 15.95, while SDL exhibits no synergism with MCC at 60 minutes. The antagonistic effect of Mannogem EZ is once again eliminated by holding the Mannogem EZ concentration equivalent to the MCC concentration, which eliminates the -47.80 coefficient from the equation, since both the Mannogem EZ and the MCC are equivalent the expression (Filler – MCC) will be zero.

Table 6: Equation Coefficients Relating Ibuprofen Release to Excipient Mix (60-minutes, L-pseudo components)

Model Term	Mannogem EZ	SDL
Filler	98.47	96.7
MCC	82.95	83.84
Filler*MCC	15.95	–
Filler*MCC* (Filler – MCC)	-47.80	–

4. Conclusion

The combination of Mannogem EZ with MCC provided for faster release of the model BCS class-II drug, ibuprofen, from directly compressible tablets than the combination of SDL with MCC. The greatest increase in overall release was most observable during the early phase dissolution of the ibuprofen at 5 and 15 minutes.

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