Identification of Formulation Design Space for Quetiapine Fumarate Extended-release Tablets Across Strengths

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PURPOSE

Oral extended-release (ER) tablet drug products play a critical role in optimizing therapeutic outcomes by maintaining consistent drug levels, minimizing side effects, and enhancing patient compliance. Among FDA approved oral ER products, hydroxypropyl methylcellulose (HPMC) matrix-based formulations represent one of the most prevalent and well-established delivery platforms. To improve public access to these ER oral drug products, it is imperative to develop high-quality, cost-effective products across multiple strengths. However, at present, appropriate factors for scaling oral ER tablet formulations to support bioequivalence of additional strengths in leu of in vivo studies for generic ER products have yet to be identified. Filling this knowledge gap is critical to facilitate the development of generic oral ER tablet products across multiple strengths.

The present work aims to:

1. Identify key formulation variables affecting drug release mechanisms.
2. Determine formulation design spaces for HPMC matrix-based ER tablets across multiple strengths.

METHOD(S)

The marketed quetiapine fumarate (QF) ER matrix tablet, available in multiple strengths (e.g., EQ 200 mg Base and EQ 300 mg Base), Seroquel XR®, was chosen as the reference listed drug (RLD) product. Laboratory-made (LM) QF ER tablets produced at the same strengths as those of the RLD were prepared using wet granulation and tablet compression procedures. **Quality-by-Design (QbD) principles** were implemented to identify the impact of key formulation variables (e.g., HPMC amount (20%-40%, w/w) and ratio of different grades of HPMC (0.2-2)) and their potential interactions on in vitro QF release characteristics. Design of Experiment (DoE) studies (e.g., response surface model (RSM)) using JMP® by SAS were conducted separately for each strength. Critical quality attributes (e.g., content uniformity, dimension, and hardness) were systemically evaluated and compared to the respective RLD strength. In addition, in vitro dissolution tests of the QF tablet formulations were conducted at 37°C using USP apparatus I at 200 rpm (250 rpm after 24 h) with 20 mesh baskets in biphasic media (0.05 M citric acid and 0.09 N NaOH, pH 4.8 for first 5 h followed by the addition of 100 mL of 0.05 M dibasic sodium phosphate dodecahydrate and 0.46 N NaOH to achieve a final pH of 6.6) (mean±SD, *n*=3). Dissolution samples were withdrawn at pre-determined time points and analyzed using a validated high performance liquid chromatography (HPLC) method. For the comparison of dissolution profiles, the similarity factor (f_2) was calculated. The RLD products were studied as controls. Finally, statistical data analysis was conducted using JMP®.

RESULT(S)

➢ Response surface plots across strengths

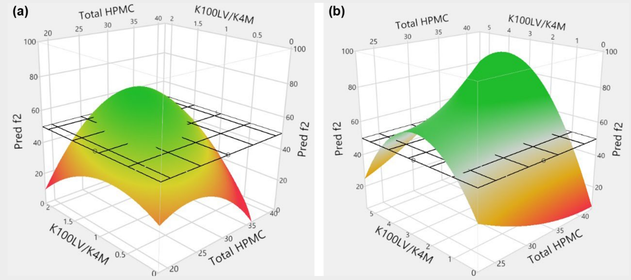
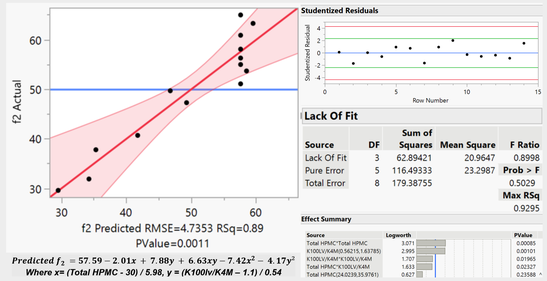


Figure 1. Response surface plots generated using JMP® to visualize the design space for (a) EQ 200 mg Base and (b) EQ 300 mg Base quetiapine fumarate extended-release tablet formulations. Formulation compositions with predicted similarity factor f_2 (Y axis) ≥ 50 (Green zone above the grid surface) compared to the reference listed drug Seroquel XR® products were defined as the safe formulation design space. Two grades of HPMC K100LV and K4M were studied.

➢ Predictive model development



$$Predicted\ f_2 = 57.59 - 2.01x + 7.88y + 6.63xy - 7.42x^2 - 4.17y^2$$

Where x= (Total HPMC - 30) / 5.98, y = (K100lv/K4M – 1.1) / 0.54

Figure 2. Actual f_2 vs. predicted f_2 plot. RMSE and R^2 value of 0.89 indicate an excellent model, while the P-value confirmed the significance of formulation variables. Studentized residual plots is used to detect outlier. Lack of fit panel indicates the model has good fit and no evidence of bias. Model terms and corresponding p-values are also shown in the effect summary table, with the quadratic effect of total HPMC being the most statistically significant effect (blue line: α=0.01 cutoff). The mathematic expression of the model is provided below.

➢ Representative dissolution profiles with dissimilar composition

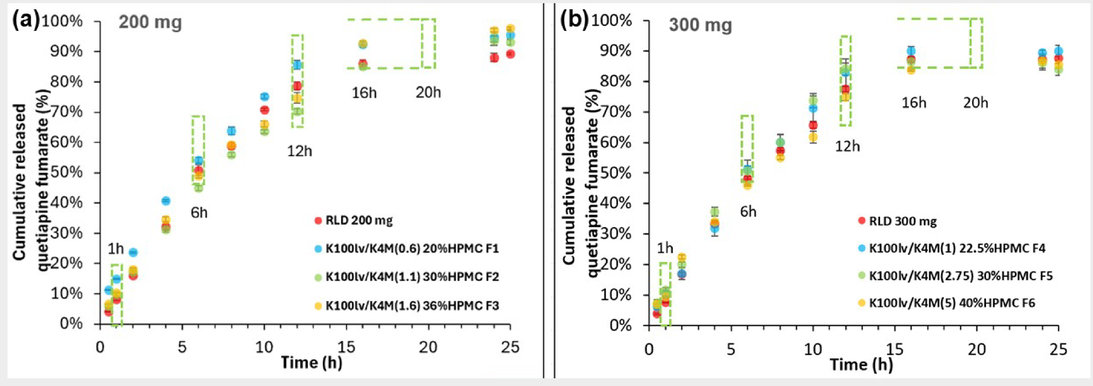
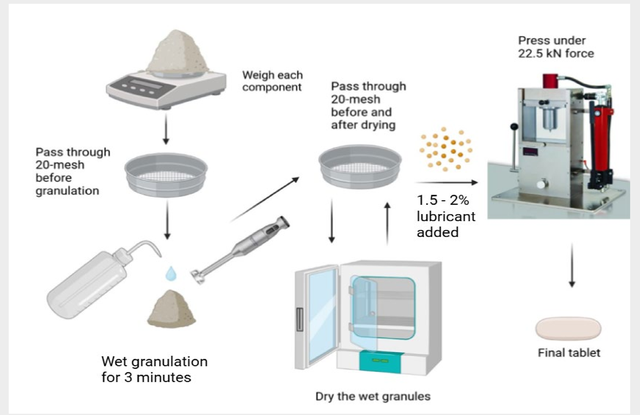


Figure 3. The in vitro dissolution profiles of LM QF ER tablet formulations with 200 mg and 300 mg strengths obtained using USP apparatus 1 (*n*=3, mean±SD). (a) EQ 200 mg Base strength: formulations F1 (K100LV/K4M ratio=0.6, 20% total HPMC), F2 (K100LV/K4M ratio=1.1, 30% total HPMC), and F3 (K100LV/K4M=1.6, 36% total HPMC) with f_2 factors of 59.71, 64.97, and 53.70, respectively, compared to Seroquel XR® EQ 200 mg Base strength. (b) EQ 300 mg Base strength: formulations F4 (K100LV/K4M=1, 22.5% total HPMC), F5 (K100LV/K4M=2.75, 30% total HPMC) and F6 (K100LV/K4M=5, 40% total HPMC) with f_2 factors of 71.79, 67.06, and 73.22, respectively, compared to Seroquel XR® EQ 300 mg Base strength. USP dissolution specifications (Test 1) for QF release are indicated by dashed green boxes.

➢ Schematic of LM QF tablet preparation



CONCLUSION(S)

This research provides insights into the impact of key formulation variables on the in vitro QF release characteristics from HPMC matrix-based oral ER tablet formulations.

Safe formulation design spaces were identified for LM QF ER tablet formulations across strengths to ensure dissolution similarity factor (f_2) values compared to the respective RLD products are above 50. Moreover, we have demonstrated that compositionally disproportional QF HPMC matrix-based ER tablets can have similar in vitro dissolution profiles.

Future studies will be focused on extending a similar QbD approach to additional strengths and identifying appropriate scaling factors for the development of additional strengths of oral ER tablet formulations that will demonstrate consistent bioavailability across strengths.

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