# Supplementary Materials: DoE-Based Design of a Simple but Efficient Preparation Method for a Non-Effervescent Gastro-Retentive Floating Tablet Containing Metformin HCl

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**Table S1.** The full factorial design for a screening step and dissolution profiles (mean ± SD, *n* = 12), and information on similarity factors, floating lag time and floating retention time of non-EFTs.

| Run order | X variable (Factor) | | Y variable (Response) | | | Sample mean ($f_2$) | FLT (s) | FRT (h) |
|---|---|---|---|---|---|---|---|---|
| | (A)Cetyl alcohol (mg) | (B)HPMC (%) | (R1)Mean diss. at 60min (%) | (R2)Mean diss. at 240min (%) | (R3)Mean diss. at 480min (%) | | | |
| F1 | 50 | 5 | 53.0±3.5 | 94.4±2.6 | 98.9±1.6 | 29.35 | - | Not |
| F2 | 50 | 5 | 51.1±3.2 | 92.5±3.0 | 98.7±1.0 | 30.56 | - | Not |
| F3 | 250 | 5 | 44.1±0.7 | 78.5±1.4 | 91.0±1.3 | 41.90 | < 3 | > 24 |
| F4 | 250 | 5 | 43.4±0.6 | 77.7±1.0 | 90.4±1.8 | 42.92 | < 3 | > 24 |
| F5 | 50 | 25 | 41.6±2.9 | 74.0±3.2 | 94.0±2.0 | 44.67 | < 3 | > 24 |
| F6 | 50 | 25 | 41.0±1.2 | 73.4±1.8 | 93.3±2.9 | 45.77 | < 3 | > 24 |
| F7 | 250 | 25 | 30.9±0.9 | 58.1±1.4 | 75.3±1.7 | 69.38 | < 3 | > 24 |
| F8 | 250 | 25 | 31.4±0.6 | 58.6±1.0 | 76.0±1.5 | 71.46 | < 3 | > 24 |
| F9 | 150 | 15 | 38.6±1.0 | 74.1±1.2 | 92.1±1.0 | 47.26 | < 3 | > 24 |
| F10 | 150 | 15 | 37.4±0.4 | 73.4±1.4 | 92.0±1.6 | 48.50 | < 3 | > 24 |

**Table S2.** The response surface methodology for optimization step and dissolution profiles (mean ±SD, n=12), and information on similarity factors, floating lag time and floating retention time of non-EFTs.

| Run order | X variable (Factor) | | Y variable (Response) | | | Sample mean ($f_2$) | FLT (s) | FRT (h) |
|---|---|---|---|---|---|---|---|---|
| | (A) Cetyl alcohol (mg) | (B) HPMC (%) | (R1) Mean diss. at 60min (%) | (R2) Mean diss. at 240min (%) | (R3) Mean diss. at 480min (%) | | | |
| M1 | 150 | 15 | 39.6±0.4 | 73.5±0.5 | 91.8±0.5 | 47.36 | < 3 | > 24 |
| M2 | 250 | 15 | 37.1±1.5 | 67.9±2.2 | 86.4±2.2 | 58.15 | < 3 | > 24 |
| M3 | 150 | 25 | 34.1±0.6 | 64.8±1.5 | 84.3±2.1 | 69.08 | < 3 | > 24 |
| M4 | 250 | 25 | 30.2±1.1 | 58.2±2.3 | 77.1±3.3 | 75.47 | < 3 | > 24 |
| M5 | 150 | 20 | 37.0±0.6 | 69.0±1.5 | 88.5±2.0 | 55.41 | < 3 | > 24 |
| M6 | 250 | 20 | 33.1±0.8 | 62.9±1.2 | 83.2±1.9 | 76.76 | < 3 | > 24 |
| M7 | 200 | 15 | 38.1±1.1 | 68.9±1.0 | 86.0±0.8 | 56.15 | < 3 | > 24 |
| M8 | 200 | 25 | 32.8±0.7 | 62.3±1.1 | 79.4±1.7 | 77.88 | < 3 | > 24 |
| M9 | 200 | 20 | 34.5±0.7 | 64.8±1.0 | 80.1±1.6 | 69.32 | < 3 | > 24 |
| M10 | 200 | 20 | 34.1±0.6 | 63.8±1.1 | 79.6±1.2 | 71.74 | < 3 | > 24 |

**Table S3.** Comparison of dissolution profiles (mean ± SD, *n* = 12) for the external validation set, model prediction accuracy and bootstrap analysis.
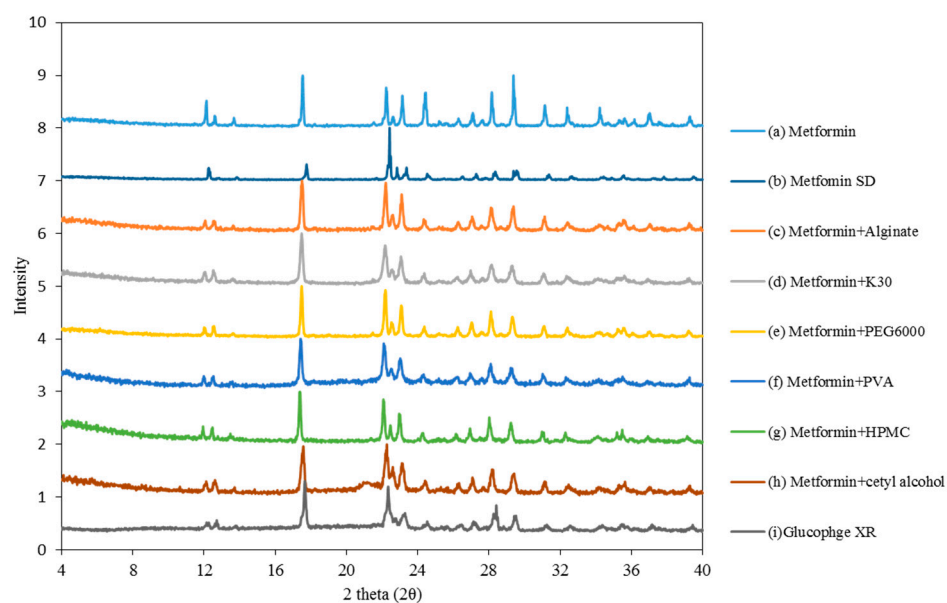
| Code | Cetyl alcohol (mg) | HPMC (%) | Cont. | 60 min (%) | 240 min (%) | 480 min (%) | Sample mean ($f_2$) | Bootstrap analysis (500) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | $f_2$ | $E(f_2)$ | PI | Bc$\alpha$ |
| | | | Gluco-phage XR | 29.4 ± 0.9 | 60.4 ± 1.2 | 81.6 ± 1.3 | - | - | - | - | - |
| E1 | 150 | 5 | True mean | 43.9 ± 0.7 | 82.3 ± 2.6 | 97.1 ± 1.4 | 37.68 | 37.69 | 37.67 | (36.88, 38.49) | (36.84, 38.44) |
| | | | Linear Pred. mean | 45.6 | 81.2 | 98.3 | 37.18 | | | | |
| | | | Quad. Pred. mean | 45.6 | 81.2 | 99.9 | 36.58 | | | | |
| E2 | 150 | 10 | True mean | 40.9 ± 0.6 | 77.1 ± 0.5 | 94.2 ± 0.3 | 42.98 | 42.98 | 42.95 | (42.29, 43.62) | (42.35, 43.67) |
| | | | Linear Pred. mean | 42.7 | 77.0 | 94.4 | 42.13 | | | | |
| | | | Quad. Pred. mean | 42.7 | 77.0 | 96.0 | 41.39 | | | | |
| E3 | 200 | 5 | True mean | 43.3 ± 0.4 | 79.4 ± 0.8 | 95.4 ± 0.5 | 40.09 | 40.06 | 40.04 | (39.47, 40.69) | (39.50, 40.74) |
| | | | Linear Pred. mean | 43.9 | 78.1 | 95.3 | 40.58 | | | | |
| | | | Quad. Pred. mean | 43.9 | 78.1 | 93.0 | 41.50 | | | | |
| E4 | 200 | 10 | True mean | 40.2 ± 0.2 | 73.4 ± 0.9 | 90.7 ± 1.3 | 47.68 | 47.73 | 47.64 | (46.79, 48.53) | (46.91, 48.75) |
| | | | Linear Pred. mean | 41.0 | 73.9 | 91.4 | 46.45 | | | | |
| | | | Quad. Pred. mean | 41.0 | 73.9 | 89.1 | 47.55 | | | | |
| E5 | 250 | 5 | True mean | 44.1 ± 0.6 | 77.1 ± 1.1 | 91.9 ± 0.8 | 42.40 | 42.45 | 42.43 | (41.69, 43.18) | (41.70, 43.19) |

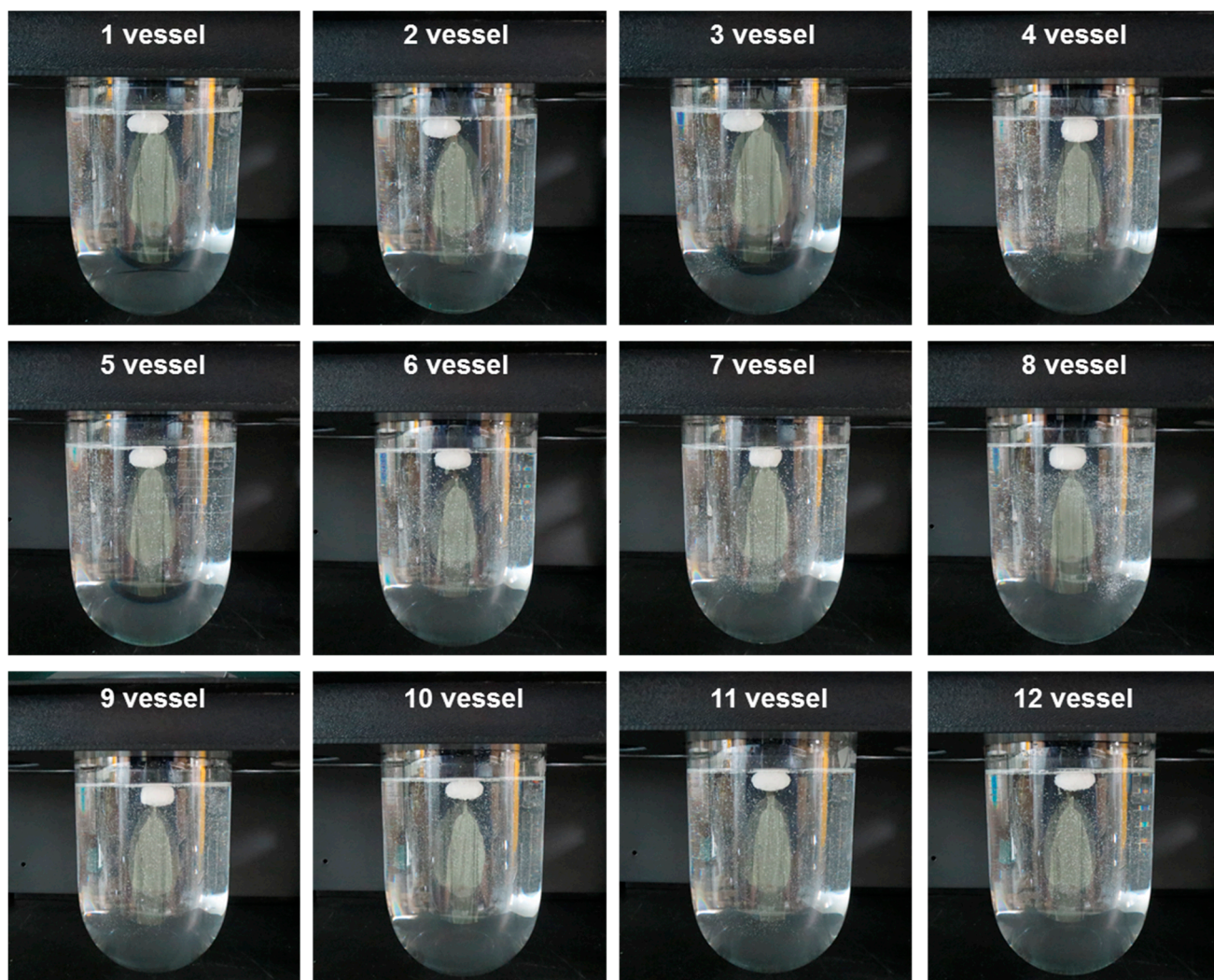| Code | Cetyl alcohol (mg) | HPMC (%) | Mean dissolution profile | 60min (%) | 240min (%) | 480min (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Linear Pred. mean | 42.2 | 75.1 | 92.4 | 44.46 | | | | |
| | | | Quad. Pred. mean | 42.2 | 75.1 | 93.9 | 43.74 | | | | |
| E6 | 250 | 10 | True mean | 39.6 ± 0.9 | 72.0 ± 1.1 | 87.9 ± 2.0 | 50.70 | 50.81 | 50.64 | (49.41, 51.73) | (49.43, 51.79) |
| | | | Linear Pred. mean | 39.3 | 70.9 | 88.5 | 51.60 | | | | |
| | | | Quad. Pred. mean | 39.3 | 70.9 | 90.0 | 50.68 | | | | |
| Linear model | | RMSEP | 1.34 | 1.18 | 0.66 | | | | | | |
| Quadratic model | | RMSEP | 1.34 | 1.18 | 2.17 | | | | | | |

PI: The percentile confidence interval; Bc$\alpha$: The bias corrected and accelerated confidence interval, RMSEP: The root mean squared error of prediction.

**Table S4.** Comparison of the dissolution profiles for the optimized formulations predicted using the RSM with the experimentally obtained dissolution profiles.

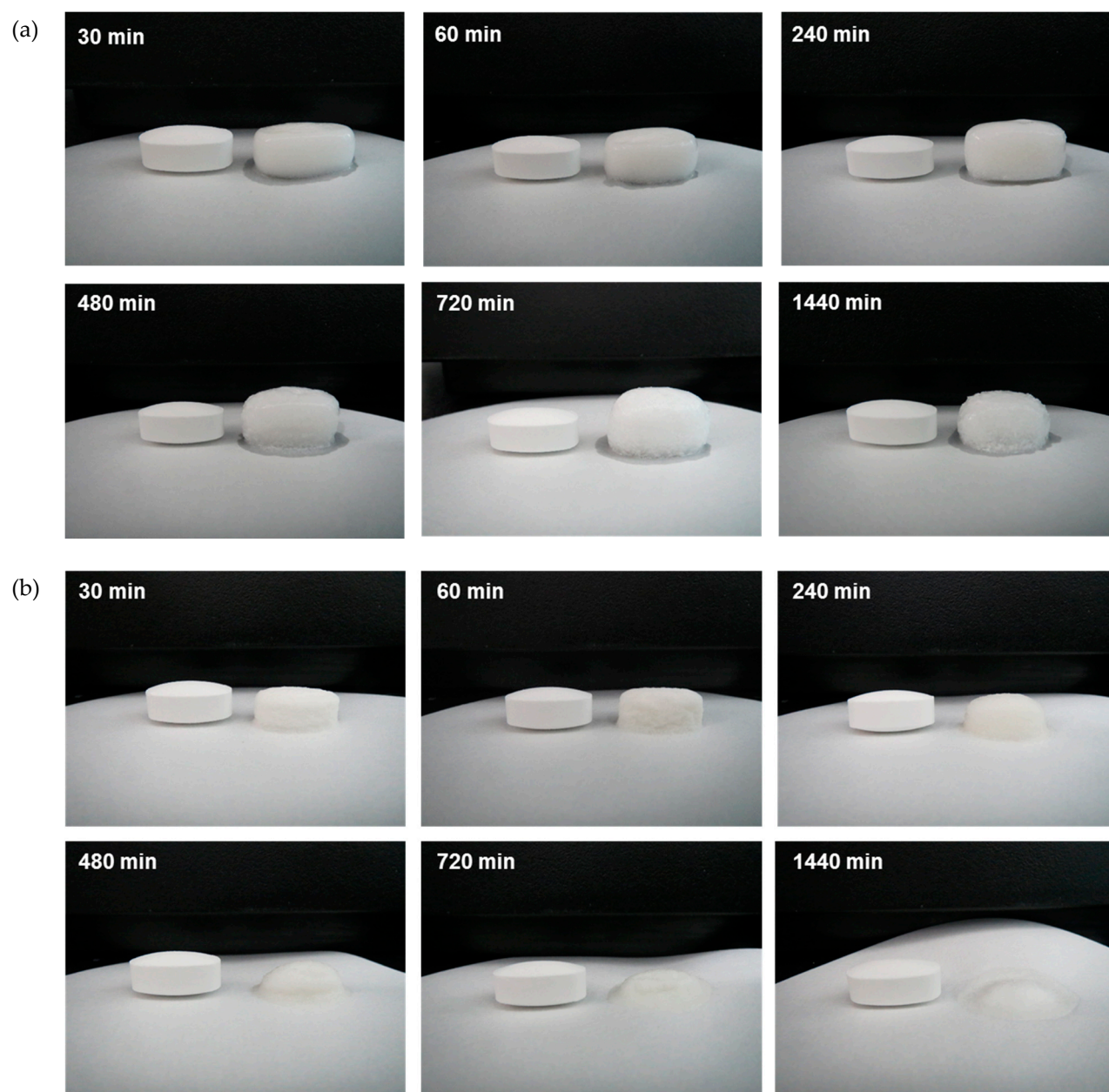| Code | Cetyl alcohol (mg) | HPMC (%) | Mean dissolution profile | 60min (%) | 240min (%) | 480min (%) | Sample mean ($f_2$) |
|---|---|---|---|---|---|---|---|
| P1 | | 16 | Predicted | 39.14 | 71.99 | 89.74 | 50.04 |
| | | | Experimentally obtained | 39.1 ± 0.7 | 72.2 ± 0.9 | 89.7 ± 1.5 | 49.85 |
| P2 | | 17 | Predicted | 38.55 | 71.16 | 88.96 | 51.68 |
| | 150 | | Experimentally obtained | 38.1 ± 0.3 | 70.7 ± 0.3 | 89.0 ± 0.9 | 52.41 |
| P3 | | 18 | Predicted | 37.96 | 70.33 | 88.18 | 53.44 |
| | | | Experimentally obtained | 37.2 ± 0.4 | 70.3 ± 0.4 | 88.5 ± 0.4 | 53.80 |
| P4 | | 19 | Predicted | 37.37 | 69.49 | 87.40 | 55.36 |
| | | | Experimentally obtained | 37.3±0.5 | 69.6±0.9 | 88.4±1.1 | 54.63 |

**Figure S1.** PXRD patterns for crystalline metformin HCl, co-spray dried solid dispersions, and Glucophage XR.



**Figure S2.** Images of non-EFTs in the vessels after the 24-h dissolution test (*n* = 12).

**Figure S3.** Images of non-EFTs during (**a**) swelling and (**b**) erosion tests over time. Non-EFTs were taken out from the vessels at predetermined times during the dissolution test.