*Supplementary Materials*

# Development of a Scalable Process of Film Coated bi-Layer Tablet Containing Sustained-Release Metoprolol Succinate and Immediate-Release Amlodipine Besylate

**Nguyen Thi Linh Tuyen [1,*], Le Quan Nghiem [2], Nguyen Duc Tuan [2] and Phuoc Huu Le [3]**

[1] Faculty of Pharmacy, Can Tho University of Medicine and Pharmacy, 179 Nguyen Van Cu,
Can Tho City 94000, Vietnam

[2] Faculty of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh City,
41 Dinh Tien Hoang Street, District 1, Ho Chi Minh City 760000, Vietnam; lequannghiem55@gmail.com
(L.Q.N.); ductuan@ump.edu.vn (N.D.T.)

[3] Department of Physics and Biophysics, Faculty of Basic Sciences,
Can Tho University of Medicine and Pharmacy, 179 Nguyen Van Cu, Can Tho City 94000, Vietnam;
lhuuphuoc@ctump.edu.vn

\* Correspondence: ntltuyen@ctump.edu.vn; Tel.: +84-91-807-1943

## 1. System Suitability

**Table S1.** Mean values of chromatographic parameters and their relative standard deviation values calculated from 6 consecutive injections. $t_R$ is retention time, S is peak area, $A_s$ is asymmetric factor, $R_s$ is the resolution, N is theoretical plate numbers.

| | Active ingredient | | $t_R$ (min.) | S (µAU x sec.) | $A_s$ | $R_s$ | N |
|---|---|---|---|---|---|---|---|
| Standard mixture | Metoprolol succinate | Mean | 3.533 | 3300978 | 0.8 | - | 16461 |
| | | RSD | 0.12% | 0.49% | 1.27% | - | 1.79% |
| | Amlodipine besylate | Mean | 5.758 | 543754 | 1.2 | 6.0 | 24232 |
| | | RSD | 0.59% | 0.67% | 1.49% | 1.63% | 1.89% |
| Sample | Metoprolol succinate | Mean | 3.597 | 3017171 | 0.9 | - | 16412 |
| | | RSD | 0.13% | 0.10% | 1.08% | - | 1.81% |
| | Amlodipine besylate | Mean | 5.845 | 714285 | 1.2 | 5.7 | 23805 |
| | | RSD | 0.20% | 0.21% | 0.87% | 0.76% | 1.76% |

## 2. The Validation of the HPLC Method

**Table S2.** Validation parameters of the analytical HPLC procedure.

| Validation characteristics | Metoprolol succinate | Amlodipine besylate |
|---|---|---|
| Linearity range (µg/ml) | 40–140 | 4–14 |
| Regression coefficient ($R^2$) | $R^2 = 0.9987$ | $R^2 = 0.9984$ |
| Repeatability (*n* = 6) | RSD = 1.23% | RSD = 1.21% |
| Inter-day precision (*n*=18) | RSD = 1.45% | RSD = 1.27% |
| Accuracy (*n* = 9, *p < 0.05*) | | |
| Recovery (%) | 98.52%–101.14% | 98.16%–99.82% |
| RSD | 1.14% | 0.63% |

Validation results showed that the HPLC method was suitable, selective, high precision (RSD < 2%), and accuracy. Indeed, the recoveries were in the range of 98.0–102.0% of the expected values. Thus, the present procedure was applied for simultaneous determination of metoprolol succinate and amlodipine besylate.

### 3. Optimize Formulation of Film Coated Bi-Layer Tablet Containing Sustained-Release Metoprolol Succinate and Immediate-Release Amlodipine Besylate

**Table S3.** Variables in the experimental design for optimizing the drug formulation.

| Independent Variables | Level 1 | Level 2 | Level 3 | Level 4 |
|---|---|---|---|---|
| X1: polymer mixture (%) | 35 | 40 | 45 | - |
| X2: ratio of diluent | S:D (2:1) | S:D (1:1) | S:A (2:1) | S:A (1:1) |
| X3: hardness (kp) | 8–10 | 10–12 | - | - |
| **Dependent variables** | Maximum | | | |
| Y1: cumulative percentage of metoprolol succinate release at 1 hour | 0%–25% | | | |
| Y2: cumulative percentage of metoprolol succinate release at 4 hour | 20%–40% | | | |
| Y3: cumulative percentage of metoprolol succinate release at 8 hour | 40%–60% | | | |
| Y4: cumulative percentage of metoprolol succinate release at 20 hour | ≥ 80% | | | |

(with S – Starch 1500, D – Ditab, A – Avicel).

18 formulation were designed according to D-optimal model using Design Expert software (version 6.0.6, Stat-Ease Inc., Minneapolis, USA). These formulations were summarized in Table 4.

**Table S4.** The independent variables of 18 formulations (M1-M18).

| Formula | X1 | X2 | X3 | | X1 | X2 | X3 |
|---|---|---|---|---|---|---|---|
| M1 | 35% | S:D (2:1) | 10–12 kp | M10 | 40% | S:A (1:1) | 10–12 kp |
| M2 | 35% | S:D (2:1) | 8–10 kp | M11 | 40% | S:A (1:1) | 8–10 kp |
| M3 | 35% | S:A (1:1) | 10–12 kp | M12 | 40% | S:D (1:1) | 10–12 kp |
| M4 | 35% | S:D (1:1) | 10–12 kp | M13 | 45% | S:A (2:1) | 10–12 kp |
| M5 | 35% | S:A (2:1) | 8–10 kp | M14 | 45% | S:D (2:1) | 10–12 kp |
| M6 | 35% | S:A (1:1) | 8–10 kp | M15 | 45% | S:A (2:1) | 8–10 kp |
| M7 | 40% | S:A (2:1) | 10–12 kp | M16 | 45% | S:A (1:1) | 10–12 kp |
| M8 | 40% | S:A (2:1) | 8–10 kp | M17 | 45% | S:D (1:1) | 8–10 kp |
| M9 | 40% | S:D (2:1) | 8–10 kp | M18 | 45% | S:D (1:1) | 10–12 kp |

Where $X_1$: % polymer mixture, $X_2$: ratio of diluent (S - Starch 1500, D - Ditab, A - Avicel), $X_3$: hardness.

**Table S5.** The metoprolol succinate release percentage of 18 formulations (M1–M18).

| Formula | Cumulative Metoprolol Succinate Release Percentage (%) | | | | Formula | Cumulative Metoprolol Succinate Release Percentage (%) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 h | 4 h | 8 h | 20 h | | 1 h | 4 h | 8 h | 20 h |
| **M1** | 18.96 | 44.36 | 64.04 | 85.08 | M10 | 22.10 | 50.20 | 70.70 | 93.09 |
| M2 | 17.03 | 45.23 | 64.71 | 87.77 | M11 | 17.51 | 42.59 | 61.6 | 93.18 |
| M3 | 20.33 | 48.17 | 73.19 | 94.96 | M12 | 19.22 | 48.88 | 71.22 | 92.31 |
| M4 | 17.21 | 42.24 | 63.66 | 86.18 | M13 | 14.69 | 37.08 | 54.2 | 69.87 |
| M5 | 17.96 | 43.86 | 65.70 | 85.56 | M14 | 13.65 | 35.61 | 52.27 | 83.93 |
| M6 | 16.33 | 37.81 | 56.44 | 80.35 | M15 | 16.38 | 44.27 | 63.04 | 75.02 |
| M7 | 15.84 | 39.54 | 57.96 | 89.26 | M16 | 18.13 | 45.03 | 63.72 | 73.95 |
| M8 | 21.29 | 51.34 | 73.68 | 93.27 | M17 | 21.22 | 47.05 | 63.37 | 91.97 |
| M9 | 15.89 | 39.66 | 59.67 | 85.52 | M18 | 20.76 | 43.69 | 65.86 | 89.78 |

The data in **Table S5** were used as the inputs for BCPharSoft OPT to optimize the formulation. The results of the accuracy of model statistics from BCPharSoft OPT outputs were presented in **Table S6**. The results show that the prediction ability of the models has good reliability. Therefore, these models could be used for multivariate optimization.

**Table S6.** Model statistical outputs obtained from BCPharSoft.

| R² | 1 h | 4 h | 8 h | 20 h |
|---|---|---|---|---|
| Training | 0.90 | 0.97 | 0.86 | 0.98 |
| Test | 0.96 | 0.91 | 0.85 | 0.96 |

**Table S7.** Optimal formula predicted by BCPharSoft OPT software.

| | X1 | X2 | X3 |
|---|---|---|---|
| Predicted parameters | 45% | S:D (2:1) | 10-12 kp |

**Table S8.** The metoprolol succinate release percentage of the optimal formulation versus the predicted formulation ($n$ = 3).

| | Cumulative Metoprolol Succinate Release Percentage (%) | | | |
|---|---|---|---|---|
| | 1 h | 4 h | 8 h | 20 h |
| Predicted | 13.75 | 35.53 | 52.05 | 84.03 |
| Observed | 13.90 ± 0.73 | 35.22 ± 1.94 | 52.36 ± 0.85 | 85.26 ± 1.40 |
| P-values | 0.751 | 0.808 | 0.591 | 0.268 |

**Table S9.** Dissolution test of film coated bi-layer tablet of three batches.

| Active Ingredient | Batch | Cumulative Percentage Drug Release (%) | | | | |
|---|---|---|---|---|---|---|
| | | 30 min | 1 h | 4 h | 8 h | 20 h |
| Metoprolol Succinate | 1 | - | 12.78 | 35.28 | 50.43 | 87.39 |
| | 2 | - | 14.33 | 36.32 | 53.86 | 88.31 |
| | 3 | - | 14.36 | 34.31 | 52.07 | 85.76 |
| | TB | - | 13.82 | 35.30 | 52.12 | 87.15 |
| | RSD% | | 0.91 | 1.01 | 1.72 | 1.29 |
| Amlodipine besylate | 1 | 96.74 | - | - | - | - |
| | 2 | 97.79 | - | - | - | - |
| | 3 | 103.43 | - | - | - | - |
| | TB | 99.32 | - | - | - | - |
| | RSD% | 2.97 | | | | |