

# Supplementary Materials: Development of Extended-Release Mini-Tablets Containing Metoprolol Supported by Design of Experiments and Physiologically Based Biopharmaceutics Modeling

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**Table S1.** Parameters used in the coating of the MS mini-tablets.

| Parameter                                  | Preheat  | Application | Drying   |
|--|----------|-------------|----------|
| Inlet air temperature (°C)                 | 50       | 50 to 70    | 50       |
| Product temperature (°C)                   | 42 to 45 | 42 to 55    | 40 to 45 |
| Air flow (m <sup>3</sup> h <sup>-1</sup> ) | 10       | 10 to 18    | 10 to 12 |
| Time (min)                                 | 15       | -           | 15       |
| Coating nozzle diameter (mm)               | -        | 0.8         | -        |
| Peristaltic pump speed (rpm)               | -        | 3 to 4      | -        |
| Spray pressure (bar)                       | -        | 0.1 to 0.5  | -        |
| Microclimate pressure (bar)                | -        | 0.05 to 0.1 | -        |

**Table S2.** Composition (%) of coating films.

| Components  | E1   | E2   | E3   | E4   | E5   | E6   | E7   | E8   | E9   | E10  | E11  | E12  |
|---|------|------|------|------|------|------|------|------|------|------|------|------|
| Kollicoat® SR 30D   | 48.0 | 48.0 | 48.0 | 48.0 | 48.0 | 48.0 | 48.0 | 48.0 | 48.0 | 48.0 | 48.0 | 48.0 |
| Kollicoat® IR (50:50 w/w mixture of White II:Brilliant Blue) <sup>1</sup> | -    | 13.7 | 6.9  | 13.7 | 6.9  | -    | 6.9  | -    | 13.7 | 1.7  | 3.4  | 5.1  |
| Talc <sup>2</sup>   | 3.9  | 0.4  | 2.7  | 0.4  | 2.7  | 3.9  | 2.7  | 3.9  | 0.4  | 4.4  | 3.9  | 3.3  |
| Titanium dioxide <sup>3</sup>   | 1.1  | -    | -    | -    | -    | 1.1  | -    | 1.1  | -    | -    | -    | -    |
| Purified water  | 47.0 | 37.9 | 42.4 | 37.9 | 42.4 | 47.0 | 42.4 | 47.0 | 37.9 | 45.9 | 44.7 | 43.6 |

<sup>1</sup> Corrected amount according to the percentage of Kollicoat® IR in the compositions of Kollicoat® IR White II and Kollicoat® Brilliant Blue = 58.1% (manufacture's information). <sup>2</sup> Added to complete 5% pigments in the coating composition (Kollicoat® IR White II and Kollicoat® Brilliant Blue contain 33.6% pigments (manufacture's information)). <sup>3</sup> Used as an opacifying agent.

**Table S3.** Characterization results of the MS mini-tablets. The values of average weight, true density, hardness, and drug content are presented by the mean and standard deviation (SD) according to the number of determinations: twenty, five, ten, and three, respectively.

| Formulation | Average Weight (mg) ± SD | True Density (g cm <sup>-3</sup> ) ± SD | Hardness (N) ± SD | Drug Content * ± SD | Friability (%) |
|-------------|--------------------------|---|-------------------|---------------------|----------------|
| F1          | 16.7 ± 0.6               | 1.43 ± 0.00                             | 26.7 ± 4.4        | 40.2 ± 0.4          | 0.2            |
| F2          | 16.4 ± 0.7               | 1.34 ± 0.01                             | 36.4 ± 4.0        | 39.0 ± 0.3          | 0.5            |
| F3          | 15.0 ± 0.7               | 1.37 ± 0.01                             | 24.4 ± 4.3        | 40.3 ± 0.2          | 0.2            |

\* Results of drug content expressed in grams of MS per 100 g of mini-tablets.

**Table S4.** Analysis of variance (ANOVA) for the dissolution efficiency (DE%) parameter. Results with p value < 0.05 are considered significant. Percentage of explained variation ( $R^2_{\text{adjusted}}$ ) = 99.54.

| Effect                  | Sum of Squares | Degrees of Freedom | Average of Squares | F        | p        |
|-------------------------|----------------|--------------------|--------------------|----------|----------|
| (1) Formulation         | 39.26          | 2                  | 19.631             | 2.2631   | 0.306457 |
| (2) Weight coating gain | 130.46         | 2                  | 65.231             | 7.5199   | 0.117372 |
| (3) Kollicoat® IR       | 14793.02       | 2                  | 7396.508           | 852.6780 | 0.001171 |
| Error                   | 17.35          | 2                  | 8.674              |          |          |

**Table S5.** Models used to analyze the results of the percentages of drug dissolved (Q%) at the times adopted as responses (2, 4, 10 and 20 h) and respective parameters derived from the analysis of variance and multiple regression to verify the adequacy of adjustment. p-value < 0.05 indicate the significance of the model.

| Parameter         | Model  | p-value | R <sup>2</sup> | R <sup>2</sup> <sub>adjusted</sub> |
|-------------------|--------|---------|----------------|------------------------------------|
| Q% <sub>2h</sub>  | linear | 0.0060  | 0.9423         | 0.9231                             |
| Q% <sub>4h</sub>  | linear | <0.0001 | 0.9993         | 0.9991                             |
| Q% <sub>10h</sub> | linear | <0.0001 | 0.9999         | 0.9998                             |
| Q% <sub>20h</sub> | linear | <0.0001 | 0.9997         | 0.9997                             |

**Table S6.** Equations of the regression models used to optimize the MS dissolution profile from the mini-tablet mixtures.

| Response          | Coefficients of the equations |
|-------------------|-------------------------------|
| Q% <sub>2h</sub>  | 0.58667 * E11 + 0.65667 * E12 |
| Q% <sub>4h</sub>  | 0.89467 * E11 + 1.56467 * E12 |
| Q% <sub>10h</sub> | 3.04133 * E11 + 4.82133 * E12 |
| Q% <sub>20h</sub> | 5.23467 * E11 + 6.30467 * E12 |