

# Systemic Design and Evaluation of Ticagrelor-Loaded Nanostructured Lipid Carriers for Enhancing Bioavailability and Antiplatelet Activity

Gi-Ho Son <sup>1,2,†</sup>, Young-Guk Na <sup>1,†</sup>, Hyun Wook Huh <sup>1</sup>, Miao Wang <sup>1</sup>, Min-Ki Kim <sup>1</sup>, Min-Gu Han <sup>1</sup>, Jin-Ju Byeon <sup>1</sup>, Hong-Ki Lee <sup>1,\*</sup> and Cheong-Weon Cho <sup>1,\*</sup>

<sup>1</sup> College of Pharmacy and Institute of Drug Research and Development, Chungnam National University, 99, Daehak-ro, Yuseong-gu, Daejeon 34134, Korea; kyk2576@naver.com (G.-H.S.); youngguk@cnu.ac.kr (Y.-G.N.); wmclare@163.com (M.W.); hhw3573@nate.com (H.-W.H.); zkkang@naver.com (M.-K.K.); linuxfalcon@naver.com (M.-G.H.); jinju.byeon.cnu@gmail.com (J.-J.B.);

<sup>2</sup> Present affiliation: Korea United Pharmaceutical Co. Ltd., 25-23, Nojangongdan-gil, Jeondong-myeon, Sejong 30011, Korea

\* Correspondence: chocw@cnu.ac.kr (C.-W.C.); dvmlhk@gmail.com (H.-K.L.); Tel.: +82-42-821-5934 (C.-W.C.); +82-42-821-7301 (H.-K.L.)

† These authors contributed equally to this work.

Received: 15 April 2019; Accepted: 6 May 2019; Published: 8 May 2019

## 1. Supplementary tables

**Table 1.** Coefficient equations of responses according to the level of factors.

| Responses      | Coefficient equations                                                                                                                                                                                                                                                                                     |
|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Y <sub>1</sub> | 109.24 + 13.70X <sub>1</sub> + 26.00X <sub>2</sub> − 4.05X <sub>3</sub>                                                                                                                                                                                                                                   |
| Y <sub>2</sub> | 0.3164 − 0.0046X <sub>1</sub> − 0.0045X <sub>2</sub> + 0.0064X <sub>3</sub> + 0.0107X <sub>1</sub> X <sub>2</sub> − 0.0220X <sub>1</sub> X <sub>3</sub> − 0.0287X <sub>2</sub> X <sub>3</sub> + 0.0148X <sub>1</sub> <sup>2</sup> + 0.0185X <sub>2</sub> <sup>2</sup> − 0.0282X <sub>3</sub> <sup>2</sup> |
| Y <sub>3</sub> | 84.79 + 3.95X <sub>1</sub> − 5.23X <sub>2</sub> − 3.53X <sub>3</sub>                                                                                                                                                                                                                                      |

**Table 2.** Analysis of variance for model of particle size (Y<sub>1</sub>).

| Source         | df | Mean Square | F-value | p-value  |
|----------------|----|-------------|---------|----------|
| Model          | 3  | 2346.91     | 25.98   | < 0.0001 |
| X <sub>1</sub> | 1  | 1501.52     | 16.62   | 0.0013   |
| X <sub>2</sub> | 1  | 5408.00     | 59.836  | < 0.0001 |
| X <sub>3</sub> | 1  | 131.22      | 1.45    | 0.2496   |
| Residual       | 13 | 90.34       |         |          |
| Lack of fit    | 9  | 79.07       | 0.6833  | 0.7090   |
| Pure error     | 4  | 115.70      |         |          |
| Total          | 16 |             |         |          |

**Note:** df (degree of freedom); a large F-value implies a large impact on the modeling profile; a p-value of less than 0.05 means that it affects modeling profile.

**Table 3.** Analysis of variance for model of polydispersity index ( $Y_2$ ).

| Source                        | df | Mean Square | F-value | p-value |
|-------------------------------|----|-------------|---------|---------|
| Model                         | 9  | 0.0013      | 5.39    | 0.0185  |
| X <sub>1</sub>                | 1  | 0.0002      | 0.7038  | 0.4292  |
| X <sub>2</sub>                | 1  | 0.0002      | 0.6663  | 0.4412  |
| X <sub>3</sub>                | 1  | 0.0003      | 1.34    | 0.2855  |
| X <sub>1</sub> X <sub>2</sub> | 1  | 0.0005      | 1.90    | 0.2104  |
| X <sub>1</sub> X <sub>3</sub> | 1  | 0.0019      | 7.96    | 0.0257  |
| X <sub>2</sub> X <sub>3</sub> | 1  | 0.0033      | 13.60   | 0.0078  |
| X <sub>1</sub> <sup>2</sup>   | 1  | 0.0009      | 3.79    | 0.0925  |
| X <sub>2</sub> <sup>2</sup>   | 1  | 0.0014      | 5.96    | 0.0447  |
| X <sub>3</sub> <sup>2</sup>   | 1  | 0.0033      | 13.77   | 0.0075  |
| Residual                      | 7  | 0.0002      |         |         |
| Lack of fit                   | 3  | 0.0003      | 1.12    | 0.4403  |
| Pure error                    | 4  | 0.0002      |         |         |
| Total                         | 16 |             |         |         |

**Note:** df (degree of freedom); a large F-value implies a large impact on the modeling profile; a p-value of less than 0.05 means that it affects modeling profile.

**Table 4.** Analysis of variance for model of encapsulation efficiency ( $Y_3$ ).

| Source         | df | Mean Square | F-value | p-value  |
|----------------|----|-------------|---------|----------|
| Model          | 3  | 147.67      | 23.27   | < 0.0001 |
| X <sub>1</sub> | 1  | 124.58      | 19.63   | 0.0007   |
| X <sub>2</sub> | 1  | 218.82      | 34.48   | < 0.0001 |
| X <sub>3</sub> | 1  | 99.62       | 15.70   | 0.0016   |
| Residual       | 13 | 6.35        |         |          |
| Lack of fit    | 9  | 5.25        | 0.5954  | 0.7622   |
| Pure error     | 4  | 8.82        |         |          |
| Total          | 16 |             |         |          |

**Note:** df (Degree of freedom), a large F-value implies a large impact on the modeling profile; a p-value of less than 0.05 means that it affects modeling profile