

The Role of In Vitro Model Complexity in Lipid-Based Formulations Screening: A case study with Ticagrelor

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INTRODUCTION

Lipid-based formulations (LBFs) are a key strategy to **enhance oral absorption** of poorly soluble and permeable compounds (**BCS II-IV**), but their development requires **predictive in vitro models** reflecting gastro-intestinal physiology^[1]. **Ticagrelor**, a BCS IV antiplatelet drug, has **low solubility and permeability**, making it suitable to evaluate LBFs performance.

This study investigated how increasing in vitro model complexity influences the ranking of ticagrelor LBFs across a panel of biorelevant tools commonly used in academic and industrial pharmaceutical research.

MATERIALS & METHODS

Table 1. LBFs composition.

LBFs	Composition	Functionalities
F1	100% Labrasol® ALF	Permeation enhancer and solubilizer
F2	70% Labrasol® ALF 30% Labrafac™ MC60	Permeation enhancers and solubilizers
F3	70% Tween® 80 30% Maisine® CC	Solubilizer Lymphatic transport enhancer
F4	70% Labrasol® ALF 30% Maisine® CC	Permeation enhancer and solubilizer Lymphatic transport enhancer
F5	100% Transcutol® HP	Solvent
-	Pure API	Reference

USP II (Hanson) & IV (Sotax) biorelevant dissolution: Biorelevant dissolution was performed using a size 000 capsule filled with 1g of LBFs containing ticagrelor (90 mg/g). The formulation was exposed to 250mL FaSSGF, followed by the addition of 250mL FaSSIF after 30 min. Dissolution was carried out using USP II (50 rpm) or USP IV (16 mL/min), and drug release was quantified by HPLC.

Intestinal and gastro-intestinal lipolysis: Intestinal and gastro-intestinal (GI) lipolysis studies were performed using a pH-stat (Metrohm) system at 37°C. Ticagrelor-loaded LBFs (90 mg/g) were dispersed in lipolysis media and digestion was initiated by pancreatin (intestinal) or sequential gastric lipase/pancreatin addition (gastro-intestinal). The pH was maintained at 6.5, samples were collected over time, drug release was quantified by HPLC following centrifugation and filtration.

TIM-1 (InnoGI): TIM-1 studies were performed under mimicked fasted-state conditions. Two grams of LBF containing ticagrelor (90 mg/g) were administered with 200 mL water, and samples were collected from all gastro-intestinal compartments over 4h to evaluate drug release and transit by HPLC.

Materials: ticagrelor was obtained from Chanyoo Pharmaceutical Co., Ltd. (Nantong, Jiangsu, China). Tween® 80 was purchased from Sigma-Aldrich (Merck KGaA, Darmstadt, Germany). Labrasol® ALF, Transcutol® HP, Labrafac™ MC60 and Maisine® CC were kindly provided by Gattefossé (Saint-Priest, France).

RESULTS

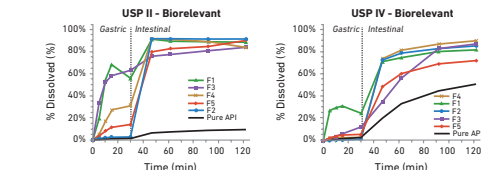
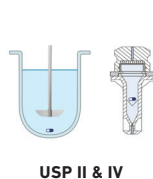


Figure 1. Two stages biorelevant dissolution profiles of ticagrelor LBFs in USP II and USP IV. Values are expressed as mean $\pm$ SD (n=4) for USP II. Values are expressed as mean $\pm$ SD (n=7) for USP IV.

Focusing on the **intestinal phase**, all formulations (F1, F2, F3, F4, F5) showed **good performance**. The discriminatory power is **low**.

• **Key mechanism:** Micellization

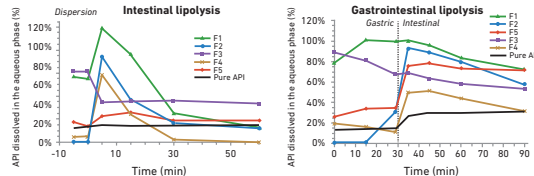


Figure 2. Lipolysis profiles of ticagrelor LBFs in intestinal and gastro-intestinal protocols. Values are expressed as mean $\pm$ SD (n=3).

Focusing on the **intestinal phase**, F1, F2 and F3 showed **good performance**. The methods showed **high discriminatory power**.

• **Key mechanisms:** Micellization + digestion

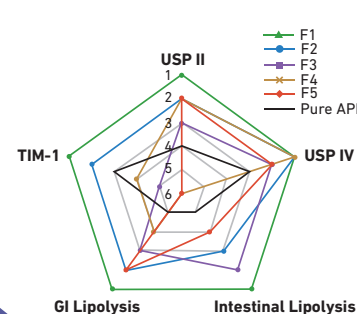


Figure 4. AUC-based formulation ranking across in vitro biorelevant models. Numbers (1–6) indicate formulation ranking, from best (1) to lowest performing (6).

- The ranking is **model-dependent**
Lines are crossing over
- Dissolution tests are **less discriminative**
LBFs sharing the same position
- Consistent and **robust performance** can be observed (F1/F2/API)

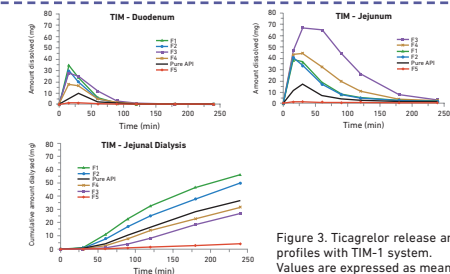


Figure 3. Ticagrelor release and absorption profiles with TIM-1 system. Values are expressed as mean $\pm$ SD (n=2).

Focusing on the **intestinal absorption**, F1 and F2 showed **good performance**. The method showed **high discriminatory power**.

• **Key mechanisms:** Micellization + digestion + secretions + transit + motility + absorption (synthetic membrane)

CONCLUSION

- LBFs performance was **strongly influenced** by the **complexity of the biopharmaceutical mechanisms** captured by the in vitro model.
- Differences in LBFs ranking across models highlight the importance of a **multi-model approach**.
- TIM-1 provided the **most physiologically relevant and robust assessment** by integrating dynamic gastric and intestinal processes together with a simulated absorption compartment, making it the most comprehensive in vitro tool evaluated^[2].

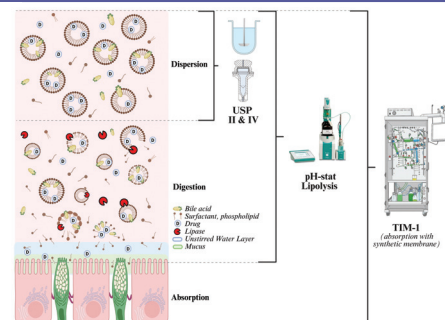


Figure 5. Comparison of Papp of ticagrelor and LBFs in monoculture and co-culture.

REFERENCES

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