TIM-1 as a Biorelevant Dynamic In Vitro Tool to Screen Lipid-Based Formulations

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PURPOSE

Lipid-based formulations (LBFs) offer a promising strategy to **enhance the oral bioavailability** of poorly water-soluble drugs, such as **BCS Class II, III and IV** compounds [1]. However, their **evaluation** remains **challenging** due to the dynamic and complex processes governing drug **dispersion, solubilization, absorption and lipid digestion.** Conventional static in vitro tests often fail to capture these dynamics and may not adequately discriminate between formulations [2].

OBJECTIVE

The aim of this study was to **evaluate the TNO gastrointestinal model (TIM-1) as a biorelevant dynamic in vitro tool** to screen and compare LBFs, using ticagrelor as a BCS IV model compound.

METHOD

- A **panel of ticagrelor LBFs** with **different specificities** was developed for evaluation (Table 1).
- Each formulation was evaluated in the **TIM-1** system under **fasted-state** conditions. Two grams of formulation, dosed at **90 mg/g** of ticagrelor, were introduced into the gastric compartment together with 200 mL of mineral water corresponding to a total dose of 180 mg, which matches the therapeutic dose.

RESULT

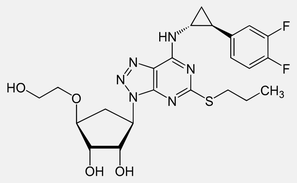


Figure 1 *– Ticagrelor molecule*

Table 1 *– Lipid-based formulations composition and specificities*

Name	Composition (%w/w)	Formulation Specificities
F5	100% Transcutol®HP	Ticagrelor solvent
F1	100% Labrasol®ALF	Solubilization + Absorption enhancement
F2	70% Labrasol®ALF 30% Labrafac™MC60	Solubilization + Absorption enhancement
F3	70% Tween®80 30% Maisine®CC	Solubilization + Lymphatic transport enhancement
F4	70% Labrasol®ALF 30% Maisine®CC	Solubilization + Absorption enchancement + Lymphatic transport enhancement
Pure API	-	Reference

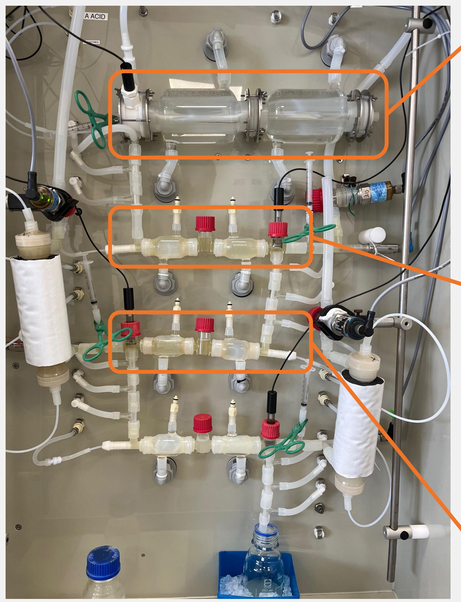
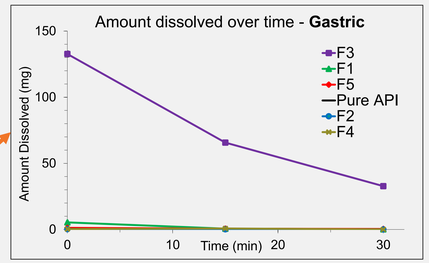
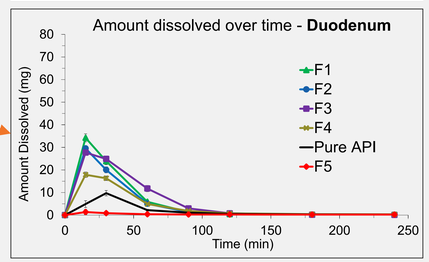
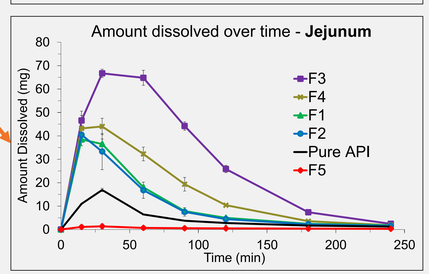


Figure 2 *– TIM-1 Apparatus*





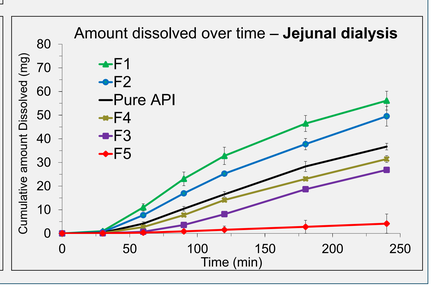


Gastric release was minimal for most LBFs due to rapid precipitation, except F3 (Tween®80).

In the **duodenum**, F1, F2 and F3 released ~30 mg, F4 ~18 mg while F5 and API alone were lowest.

In the **jejunum**, F3 and F4 accumulated more (67 and 44 mg) due to limited dialysis absorption, while F1 and F2 showed higher absorption. Ileal release was negligible.

Overall, **LBFs outperformed the API alone** across all compartments, with **good reproducibility**.



CONCLUSIONS

- ✓ This study demonstrates that **TIM-1** is a **powerful** and **highly biorelevant in vitro tool**, closely mimicking human gastrointestinal physiology by integrating **transit**, **motility**, **pH changes**, **bile salt** and **enzyme** secretions.
- ✓ The model enables **detailed evaluation of LBFs under dynamic conditions**, providing insights that go beyond standard in vitro tests.
- ✓ Our results indicate that **maximal intestinal solubilization does not necessarily increase bioaccessibility**. Highly **solubilizing surfactants** can even **reduce drug flux** across dialysis membranes, despite increasing total drug concentration, **by lowering the free diffusible fraction** [3].
- ✓ The present results will be **correlated with data from an in vivo study** to evaluate the predictive power of the model.

REFERENCE

[1] O. M. Feeney et al., « 50 years of oral lipid-based formulations: provenance, progress and future perspectives », Advanced drug delivery reviews, vol. 101, p. 167-194, 2016.

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