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Novel Biphasic Lipolysis Testing of Nilotinib Lipid Based Suspensions to Predict *In Vivo* Performance.

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PURPOSE

- Due to the low aqueous solubility of many new chemical entities, lipid based formulations (LBF) have generated significant interest as a way to increase oral bioavailability.
- However, suitable *in vitro* lipolysis testing remains challenging, with many methods producing results which are quite distinct from *in vivo* performance [1].

OBJECTIVE(S)

- The objective of this study was to develop a new and quick two stage *in vitro* lipolysis protocol to incorporate the absorption of drug in the small intestine, using a decanol layer.
- Nilotinib, a weakly basic drug, was selected as an appropriate model 'brick-dust' drug. Results were compared to a standard *in vitro* lipolysis experiment (pH-stat method) and the results from an *in vivo* rat study [2].

METHOD(S)

- Four lipid suspensions were tested containing crystalline nilotinib. The biphasic lipolysis was carried out using the inForm (Pion Inc.) instrument with the experimental setup shown in Figure 1.
- At the end of the experiment in the intestinal sector, the pH was back to pH 9 to determine the release of non-ionized free fatty acids.
- Drug was quantified *in situ* in real time by fibre optic UV dip probes.
- A higher stirring rate (300rpm) was applied during the gastric sector and during the dispersion period with the pancreatic enzymes (compared to a stirring rate of 100rpm during the intestinal sector). This was done to ensure the formulations were well dispersed prior to the addition of the decanol layer and prevent 'non-physiological' mixing of the LBFs with the decanol layer.

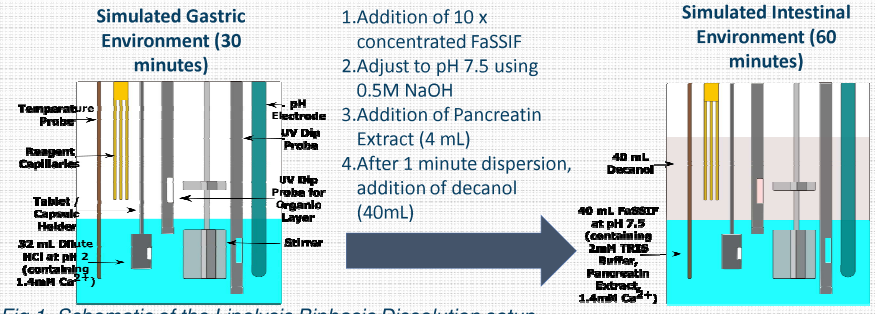

Fig 1. Schematic of the Lipolysis Biphasic Dissolution setup.

RESULT(S)

- Data from the standard *in vitro* method (pH-stat method) indicated a greater release from the Capmul MCM formulation than the Peceol formulation. This was in contrast to the results from the clinical study and biphasic lipolysis experiment (Table 1).
- The standard *in vitro* method showed a significant difference in the release of the Captex and Olive Oil formulations, unlike the *in vivo* and biphasic lipolysis results (Table 1).
- In addition, the low concentration of drug in solution after 60 minutes (<1% of the dose for all formulations) raises concerns about the pH-stat method.

Table 1. Overview of the in vivo and in vitro results for the Nilotinib formulation tested. Each data point represents the mean ± SD.

Formulation	Sprague Dawley rat $AUC_{0\text{-}inf.h}$ [ng*h/mL] (n=5) [2]	Standard Lipolysis Method: Percentage Released in Aqueous Phase after 60 minutes Digestion (n=3) [2]	Biphasic Lipolysis Method: Percentage Released in Decanol Layer after 60 minutes Digestion (n=3)
Peceol	13,103 ± 2557	0.51 ± 0.06	36.21 ± 1.49
Capmul MCM	11,210 ± 5476	0.99 ± 0.06	29.53 ± 1.01
Captex 1000	5,168 ± 2197	0.82 ± 0.09	20.09 ± 2.62
Olive Oil	3,548 ± 2711	0.22 ± 0.03	24.18 ± 1.13

CONCLUSION(S)

Results from the pH-stat method did not provide any reasonable insight into the respective *in vivo* performance.

Compared to the pH-stat method, this novel biphasic lipolysis method offered:

- an improved prediction of *in vivo* performance of nilotinib LBFs
- avoided the requirement for centrifugation and HPLC analysis
- facilitated a more rapid *in vitro* screening process of novel LBFs.

Further assessment of this method will be carried out using different types of LBFs with clinical data from other species.

REFERENCE

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