In vitro lipolysis model to predict food effect of poorly soluble drugs

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PURPOSE

The objective was to assess the ability of in vitro lipolysis to anticipate a positive food effect.

INTRODUCTION

- It is desirable to predict positive food effect of oral formulations due to food mediated dissolution enhancement of lipophilic drugs.
- Food can have a significant effect on drug absorption of orally administered drugs, compared to when taken fasted, particularly for drugs that have low water solubility.
- An in vitro lipolysis model has been developed to reflect the composition and environment of fed state gastrointestinal tract and to simulate the dynamic nature of the lipid digestion process within the intestine

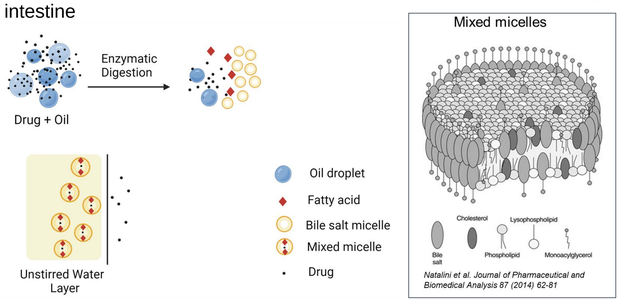


Figure: Lipolysis process

- An underlying basis for lipid lipolysis to be able to predict in vivo positive food effect is the hypothesis that partially hydrolyzed lipids contribute to the enhanced solubilization of poorly water-soluble drugs, resulting in greater drug dissolution and drug absorption.

EXPERIMENTAL METHOD

The initial composition of Fe-lipolysis and Fa-lipolysis media[1].

Composition	Fe-lipolysis media	Fa-lipolysis media
Porcine bile extract	20mM	3mM
L-α phosphatidylcholine	2mM	0.2mM
Porcine pancreatic lipase	800 USP unit/ml	-
Trizma maleate	2mM	2mM
Sodium chloride	150mM	150mM
Calcium chloride	0.4 or 1.2ml/min*	-

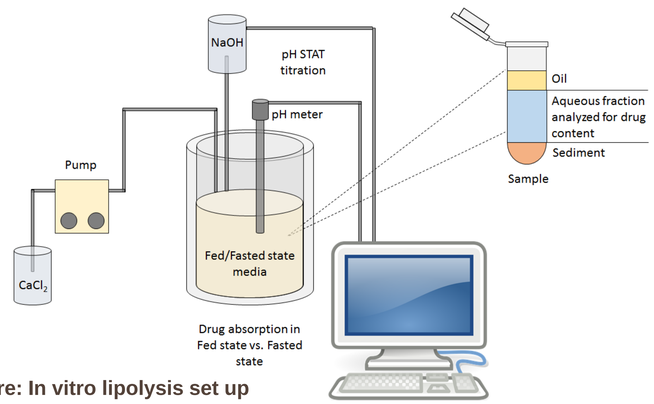


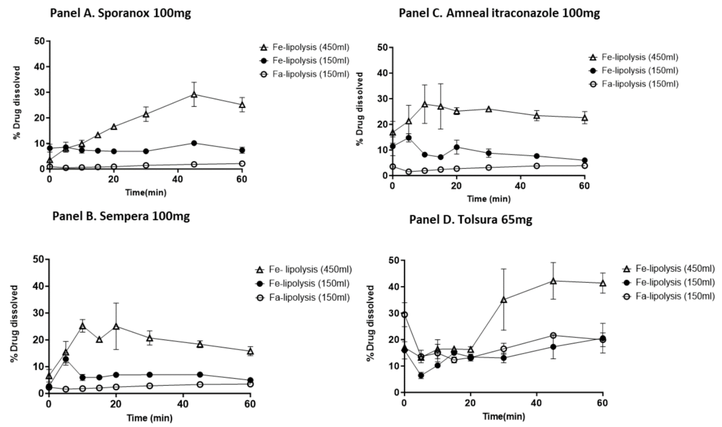
Figure: In vitro lipolysis set up

RESULTS & DISCUSSION

1. Scope of lipolysis studies and summary of findings. Rivaroxaban, itraconazole, and ritonavir products and APIs were subjected to Fe-lipolysis (each 150ml and 450ml volumes) and Fa-lipolysis (150ml volume only).

Drug Product/API name	Dose (mg)	*In vivo* observed food effect (per FDA label)	*In vitro* predicted food effect (*in vitro* lipolysis model)	Concordance yes/no
Rivaroxaban API	2.5	No Positive food effect (assumed)	No Positive food effect	Yes
Rivaroxaban API	10	No Positive food effect (assumed)	No Positive food effect	Yes
Rivaroxaban API	20	Positive food effect (assumed)	Positive food effect	Yes
Xarelto tablet	2.5	No Positive food effect	No Positive food effect	Yes
Xarelto tablet	10	No Positive food effect	No Positive food effect	Yes
Xarelto tablet	20	Positive food effect	Positive food effect	Yes
LP095 generic tablet	20	Positive food effect	Positive food effect	Yes
LP064 generic tablet	20	Positive food effect	Positive food effect	Yes
Sporanox capsule	100	Positive food effect	Positive food effect	Yes
Sempera capsule	100	Positive food effect	Positive food effect	Yes
Itraconazole capsule	100	Positive food effect	Positive food effect	Yes
Tolsura capsule	65	No positive food effect	No positive food effect	Yes
Ritonavir API	100	Unknown	Positive food effect	Unknown
Norvir tablet	100	No Positive food effect	Positive food effect	No
Norvir Powder	100	No Positive food effect	Positive food effect	No

2. Lipolysis dissolution profiles of itraconazole in Fe-lipolysis (450ml), Fe-lipolysis (150ml), and Fa-lipolysis (150ml).



3. Food effect results from lipolysis studies of various itraconazole products.

Drug Product	Fe-lipolysis media volume (ml)	$AUC_{0\text{-}15\ min}$ ratio (SEM)	$AUC_{0\text{-}30\ min}$ ratio (SEM)	$AUC_{0\text{-}60\ min}$ ratio (SEM)
Sporanox capsule 100mg	150	12.1 (2.1)	8.63 (1.34)	6.04 (0.54)
Sporanox capsule 100mg	450	13.6 (1.4)	15.4 (1.5)	14.9 (1.6)
Sempera capsule 100mg	150	4.31 (0.74)	3.39 (0.47)	2.55 (0.29)
Sempera capsule 100mg	450	9.58 (3.46)	9.28 (2.66)	7.06 (1.37)
Amneal itraconazole capsule 100mg	150	4.98 (0.72)	4.11 (0.73)	3.15 (0.52)
Amneal itraconazole capsule 100mg	450	12.0 (3.7)	10.9 (2.5)	8.43 (1.66)
Tolsura capsule 65mg	150	0.587 (0.049)	0.759 (0.073)	0.813 (0.134)
Tolsura capsule 65mg	450	0.934 (0.243)	1.24 (0.20)	1.68 (0.16)

4. Comparison of rank-order of in vitro and in vivo positive food effect for itraconazole and rivaroxaban products.

Drug Product	In vitro AUC0-30min (rank)	In vivo AUC ratio (rank)
Sporanox	15.4 (1)	2.63 (2)
Amneal	10.9 (2)	2.63 (2)
Sempera	9.28 (3)	2.63 (2)
Xarelto 20mg	4.84 (4)	1.39 (4)
Xarelto 10mg	2.27 (5)	1 (5.5)
Tolsura	1.24 (6)	0.78 (6)
Xarelto 2.5mg	1.02 (7)	1 (5.5)

CONCLUSIONS

- We have assessed the ability of in vitro lipolysis to predict the positive food effect of oral formulations of lipophilic drugs.
- Media Fe-lipolysis and Fa-lipolysis, mimicking fed and fasted intestinal conditions, were employed.
- We hypothesize that partially hydrolyzed lipids contribute to the enhanced solubilization of poorly water-soluble drugs, resulting in greater drug dissolution and drug absorption.
- This research aimed to predict the dose-dependent food effect of rivaroxaban, as well as the formulation-dependent positive food effect of itraconazole.
- In all cases of four tablet products and two unformulated API doses, lipolysis was sensitive to rivaroxaban's dose-dependent food effect, where 20mg showed a positive food effect, while 2.5mg and 10mg did not.
- Lipolysis findings were also favorable for amorphous solid dispersions of itraconazole. Sporanox, Sempera, and Amneal itraconazole capsules 100mg showed a positive food effect in lipolysis, in agreement with in vivo.
- Meanwhile, Tolsura capsule 65mg exhibited no positive food effect in lipolysis, in agreement with in vivo.
- Overall, results that in vitro lipolysis model holds promise for anticipating positive food effects of formulations containing poorly soluble APIs.

ACKNOWLEDGEMENTS

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