ADVANTAGES AND LIMITATIONS OF
AN IN-VITRO LIPOLYSIS MODEL
AS A PREDICTIVE TOOL
IN THE DEVELOPMENT
OF LIPID BASED ORAL FORMULATIONS
FOR LIPOPHILIC DRUGS

Arik Dahan
School of Pharmacy
The Hebrew University of Jerusalem

In recent years, the discovery of new active lipophilic molecules has been enormously increased.

However, major barriers facing the absorption of these lipophilic molecules following oral administration.
The barriers that a lipophilic molecule has to transverse along the intestinal absorption cascade

- In most cases, the solubilization in the intestinal milieu is the rate limiting step

Dahan and Hoffman, in *Enhancement in Drug Delivery*, CRC Press 2006

- Lipid based vehicle has been shown to enhance bioavailability of lipophilic drug.

- Currently, the design of appropriate lipidic vehicles remains primarily empirical.

- A dynamic in vitro model was proposed before that mimics the lipolysis process in the intestine (Porter and Charman 2001, Christensen et al 2004).
In vitro dynamic lipolysis model (stage 1)

- System representative of fasted state intestinal environment, with maximum pseudo-physiological conditions

In vitro dynamic lipolysis model (stage 2)

- Drug in formulation is dispersed in the system

- Experiment initiated with the insertion of pancreatic juice

- Throughout lipolysis, free FA are released and pH is decreased and titrated immediately utilizing pH-stat titration unit and maintained at 7.0

- At the end-point, pH remains steady without titration
In vitro dynamic lipolysis model (stage 3)

Following the completion of the lipolysis, aliquots are taken from the system and ultracentrifuged:

- **Oil phase**: Drug soluble in oil
- **Aqueous phase**: Sedimented drug
- **Sediment phase**: Drug in sediment

- **May participate in absorption**
- **Most readily available for absorption**
- **Not available for absorption**

**Purpose**

- To investigate the IVIVC of the lipolysis model
- To assess the model as a predictive tool for the influences of different vehicles on the in-vivo oral absorption of lipophilic drugs
- The advantages and limitations were investigated using 4 model drugs: progesterone, vitamin D₃, dexamethasone and griseofulvin
4 model lipophilic drugs:

- **Progesterone** – undergoes presystemic metabolism in the gut wall
- **Vitamin D₃** – undergoes lymphatic absorption
- **Dexamethasone** – comparatively high water solubility (100 µg/ml)
- **Griseofulvin** – practically insoluble in water

What is the effect of significant presystemic metabolism in the gut wall on the IVIVC of the lipolysis model?
**In vitro** dynamic lipolysis model

**Progesterone**

Conclusion:

Performance rank order: MCT > LCT > SCT

Dahan and Hoffman, *Pharm Res* 2006

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**In vivo** oral bioavailability

**Progesterone**

Conclusion:

Performance rank order: MCT > LCT > SCT

Dahan and Hoffman, *Pharm Res* 2006
Conclusion: Good IVIVC ($R^2 > 0.99$) 

Dahan and Hoffman, *Pharm Res* 2006

Vitamin D$_3$

- Highly lipophilic, Log $P = 9.1$
- Significant lymphatic absorption

What is the effect of significant lymphatic absorption on the IVIVC of the lipolysis model?
**In vitro dynamic lipolysis model**

**Vitamin D₃**

- Aqueous phase
- Sediment
- Lipid phase

Conclusion:
Performance rank order: MCT > LCT > SCT

Dahan and Hoffman, *Pharm Res* 2006

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**In vivo oral bioavailability**

**Vitamin D₃**

- LCT
- MCT
- SCT

Conclusion:
Performance rank order: LCT > MCT > SCT

No IVIVC

Dahan and Hoffman, *Pharm Res* 2006
Vitamin D₃ plasma and lymph profiles

Conclusion:
Lymphatic absorption stands for 75% of vitamin D₃ bioavailability

Pretreatment with cycloheximide eliminates the lymphatic transport, without affecting other absorption pathways

Cycloheximide
In vivo oral bioavailability of Vitamin D₃ in cycloheximide treated animals

Conclusion:
Performance rank order: MCT > LCT
Good IVIVC

Interim Conclusions

- The in-vitro lipolysis model managed to predict the performance of different lipidic vehicles in-vivo

- Presystemic metabolism in the gut wall did not influence this IVIVC

- Lymphatic absorption of the drug may interfere with this IVIVC, since LCT oil is necessary for chylomicron production

- The potential of a lipophilic drug to undergo lymphatic absorption has to be examined (see poster PS-04)
The correlation between in-vitro lipolysis, intestinal permeability and in vivo absorption

- Lipid based formulation has direct influence on the permeation of the drug through the gut wall

- To assess the IVIVC of the lipolysis model in light of the influence of different vehicles on the intestinal permeability

- 2 Model Drugs sharing the same Log $P$ (~2) but differ in their water solubility characteristics:
  - Dexamethasone - Relatively good water solubility
  - Griseofulvin - Practically insoluble in water

What is the effect of gut wall permeation abilities on the IVIVC of the lipolysis model?
**In vitro dynamic lipolysis model**

Dexamethasone

Conclusion:
Performance rank order: MCT = LCT = SCT

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**Ex vivo intestinal permeation model**

Dexamethasone

Conclusion:
Performance rank order: SCT > MCT ≥ LCT
**Conclusion:**

Performance rank order: MCT = LCT = SCT

IVIVC with lipolysis and not with permeation

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**Griseofulvin**

- Log $P = 2$
- Practically insoluble in water

What is the effect of gut wall permeation abilities on the IVIVC of the lipolysis model?
**In vitro** dynamic lipolysis model

*Griseofulvin*

- Aqueous phase
- Sediment phase
- Lipid phase

Conclusion:
Performance rank order: MCT>LCT>SCT>H2O

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**Ex vivo** intestinal permeation model

*Griseofulvin*

![Graph showing griseofulvin amount in the serosal side over time for different phases.]

Conclusion:
Performance rank order: SCT > MCT > LCT
In vivo oral bioavailability
Griseofulvin

Conclusion:
Performance rank order: MCT>LCT>SCT>H₂O

In vitro - in vivo correlation (IVIVC)
Griseofulvin

Conclusion:
Good IVIVC ($R^2$>0.98) with the lipolysis model
No correlation with the permeation studies
Conclusions (1)

- The *in-vitro* lipolysis model managed to predict the performance of different lipidic vehicles *in-vivo*

- Valuable information can be obtained from the *in-vitro* lipolysis model, leading to the intelligent selection of lipidic vehicles

Conclusions (2)

- For class 2 drugs, permeation studies may not predict actual *in-vivo* performance

- The influence of the vehicle on the permeability does not affect *in-vivo* bioavailability of class 2 drugs, hence does not damage the prediction of the lipolysis model

- SCT vehicle shown to be a potential intestinal permeability enhancer

- The differences between solubilization abilities of the various vehicles are less profound with the increase in the drug water solubility
Conclusions (3)

- Significant presystemic metabolism in the gut wall does not affect the ability of the model to predict *in-vivo* performance

- For drugs that undergo lymphatic absorption the model may not be able to predict *in-vivo* performance

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Thank you