ADVANTAGES AND LIMITATIONS OF

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

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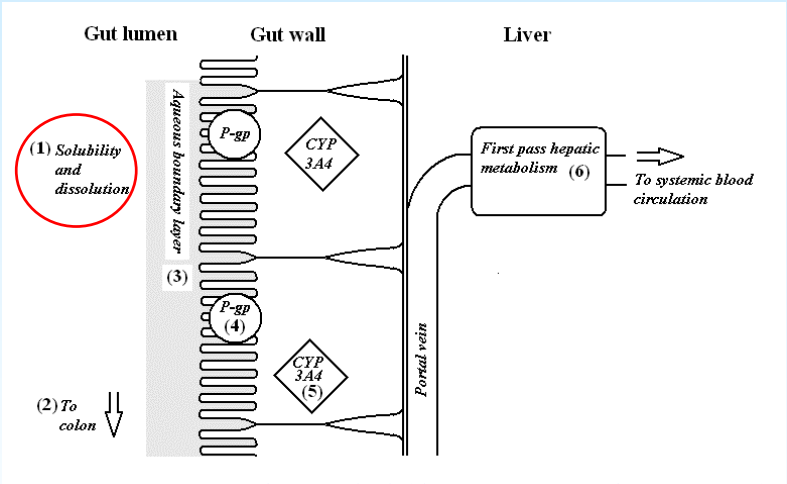
GPEN 2006

- 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

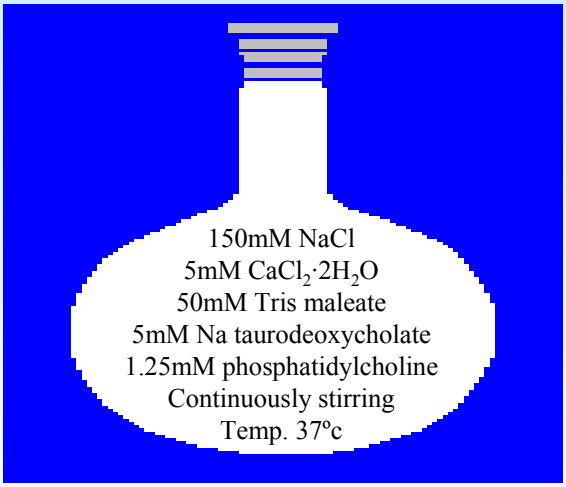


- In most cases, the solubilization in the intestinal milieu is the rate limiting step

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)



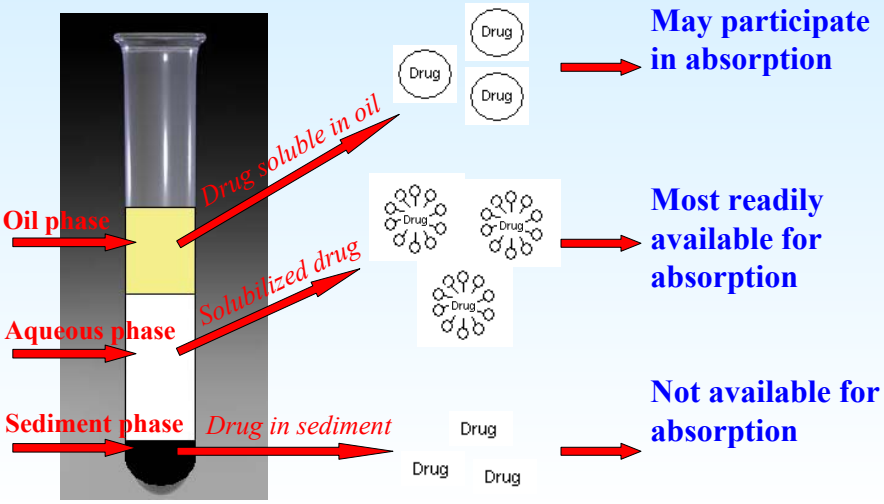
- System representative of fasted state intestinal environment, with maximum pseudo-physiological conditions

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:



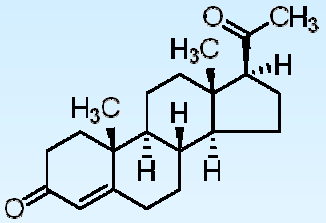
Purpose

- 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 D_3, dexamethasone and griseofulvin

4 model lipophilic drugs:

- **Progesterone** – undergoes presystemic metabolism in the gut wall
- **Vitamin D_3** – undergoes lymphatic absorption
- **Dexamethasone** – comparatively high water solubility (100 μg/ml)
- **Griseofulvin** – practically insoluble in water

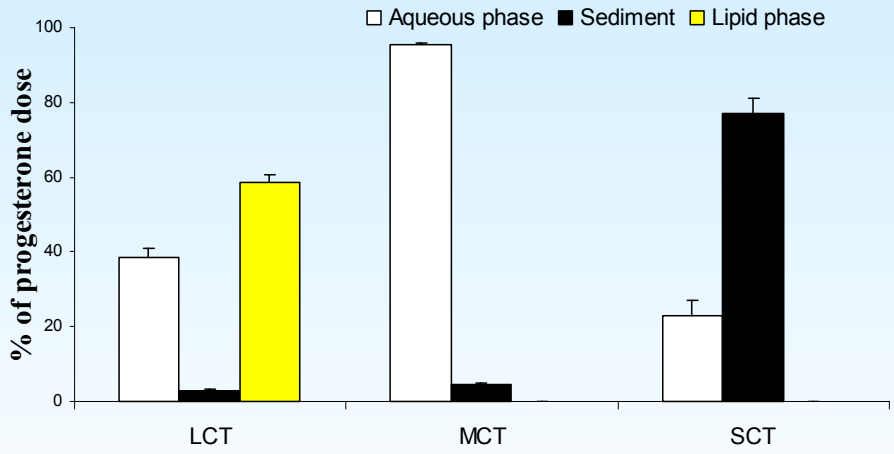
Progesterone



- Log $P = 4$
- Low oral bioavailability (less than 5%)
- 50% presystemic metabolism in the gut wall

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

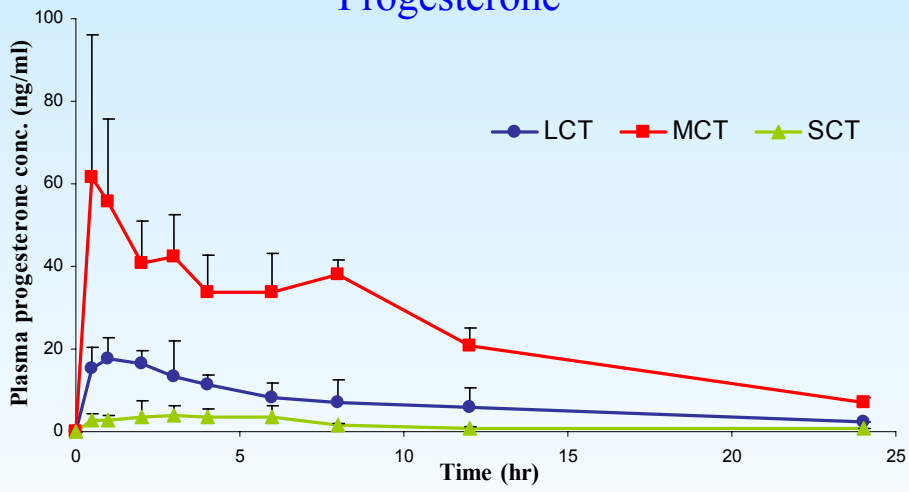


Conclusion:

Performance rank order: MCT > LCT > SCT

Dahan and Hoffman, *Pharm Res* 2006

In vivo oral bioavailability
Progesterone

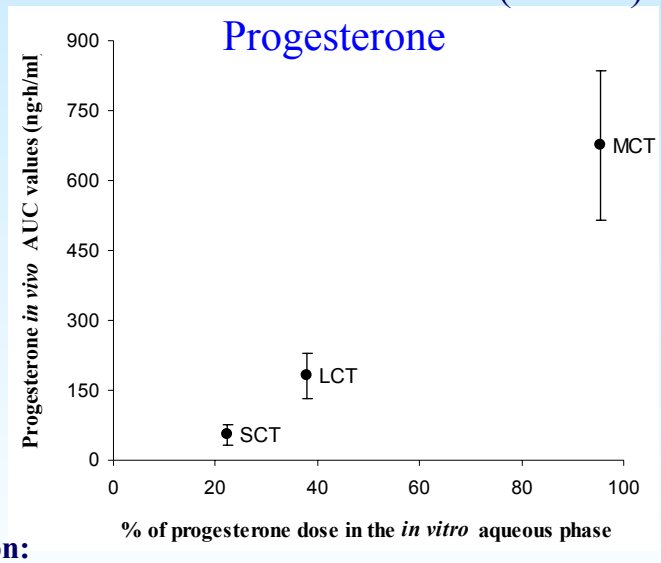


Conclusion:

Performance rank order: MCT > LCT > SCT

Dahan and Hoffman, *Pharm Res* 2006

In vitro - in vivo correlation (IVIVC)

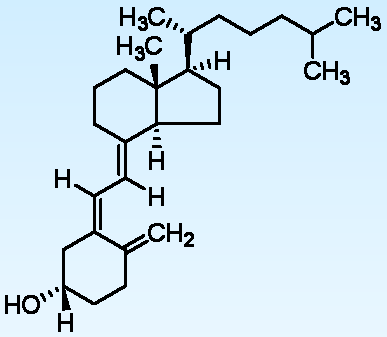


Conclusion:

Good IVIVC (R^2>0.99)

Dahan and Hoffman, *Pharm Res* 2006

Vitamin D_3

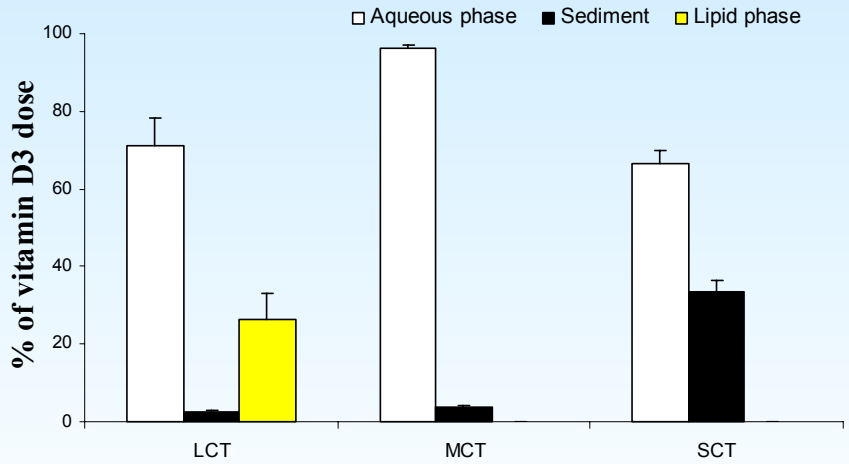


- Highly lipophilic, Log *P* = 9.1
- Significant lymphatic absorption

What is the effect of significant lymphatic absorption on the IVIVC of the lipolysis model?

In vitro dynamic lipolysis model

Vitamin D_3



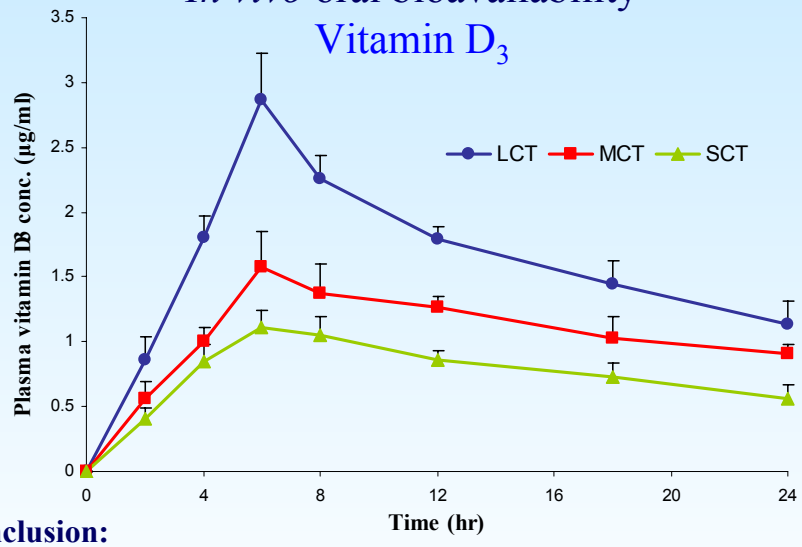
Conclusion:

Performance rank order: MCT > LCT > SCT

Dahan and Hoffman, *Pharm Res* 2006

In vivo oral bioavailability

Vitamin D_3



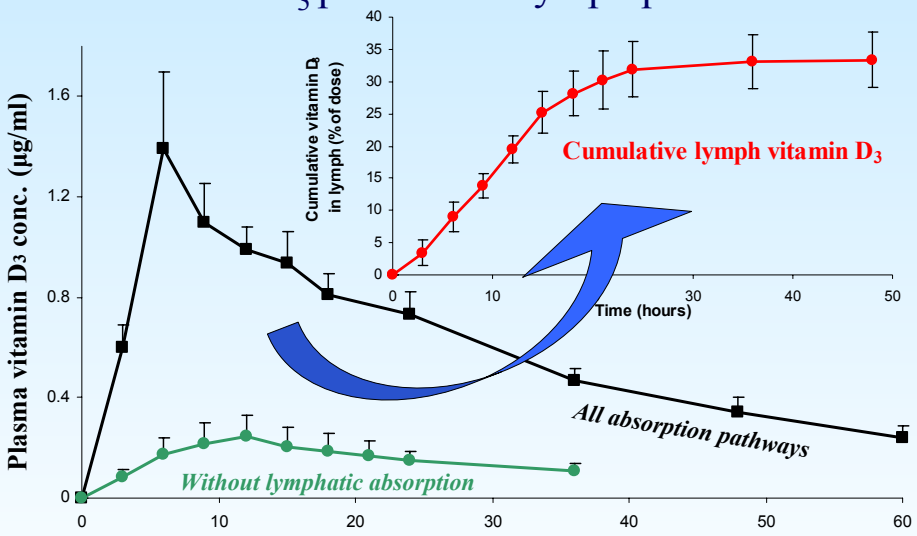
Conclusion:

Performance rank order: LCT > MCT > SCT

⇒ No IVIVC

Dahan and Hoffman, *Pharm Res* 2006

Vitamin D_3 plasma and lymph profiles

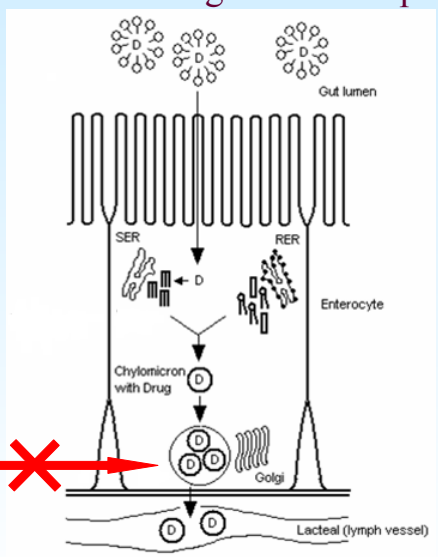


Conclusion:

Lymphatic absorption stands for 75% of vitamin D_3 bioavailability

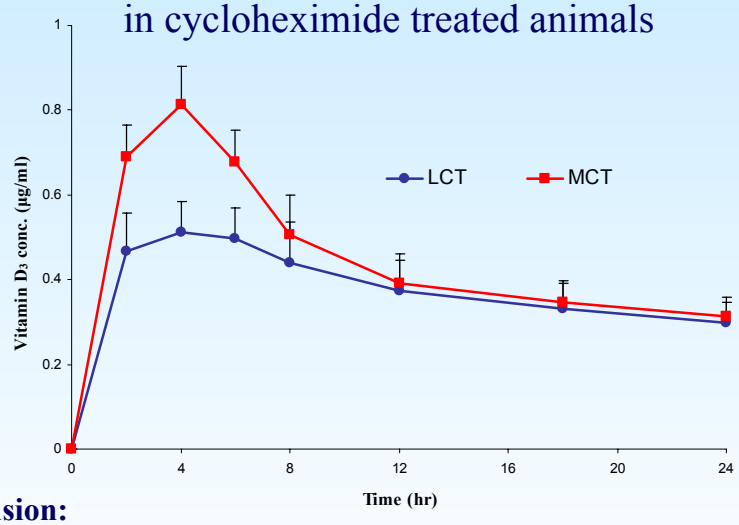
Dahan and Hoffman, *Eur J Pharm Sci* 2005

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



Dahan and Hoffman, *Eur J Pharm Sci* 2005

In vivo oral bioavailability of Vitamin D_3 in cycloheximide treated animals



Conclusion:

Performance rank order: MCT > LCT

⇨ Good IVIVC

Dahan and Hoffman, *Pharm Res* 2006

Interim Conclusions

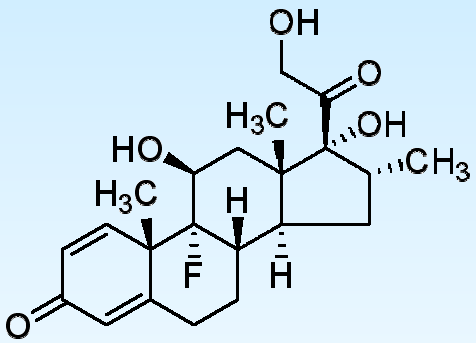
- The in-vitro lipolysis model managed to predict the performance of different lipidic vehicles in-vivo
- Presystemic metabolism in the gut wall did not influence this IVIVC
- Lymphatic absorption of the drug may interfere with this IVIVC, since LCT oil is necessary for chylomicron production
- The potential 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

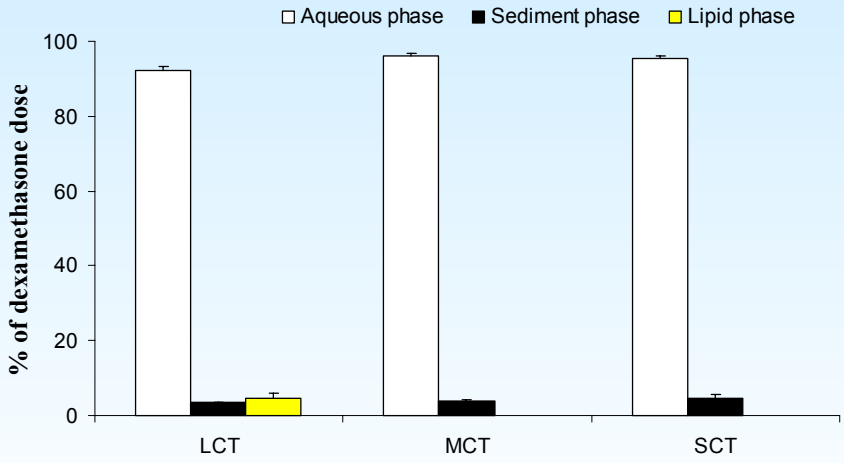
Dexamethasone



- Log *P* = 2
- Relatively good water solubility (100 µg/ml)

What is the effect of gut wall permeation abilities on the IVIVC of the lipolysis model?

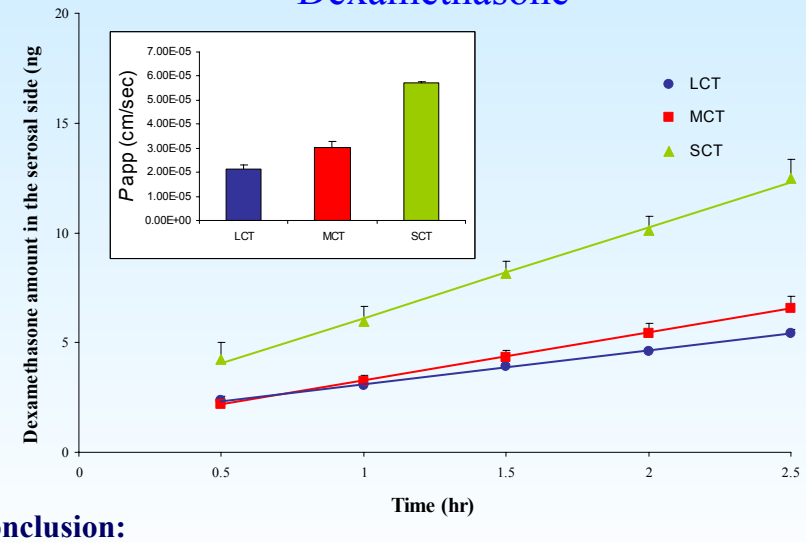
In vitro dynamic lipolysis model
Dexamethasone



Conclusion:

Performance rank order: MCT = LCT = SCT

Ex vivo intestinal permeation model
Dexamethasone

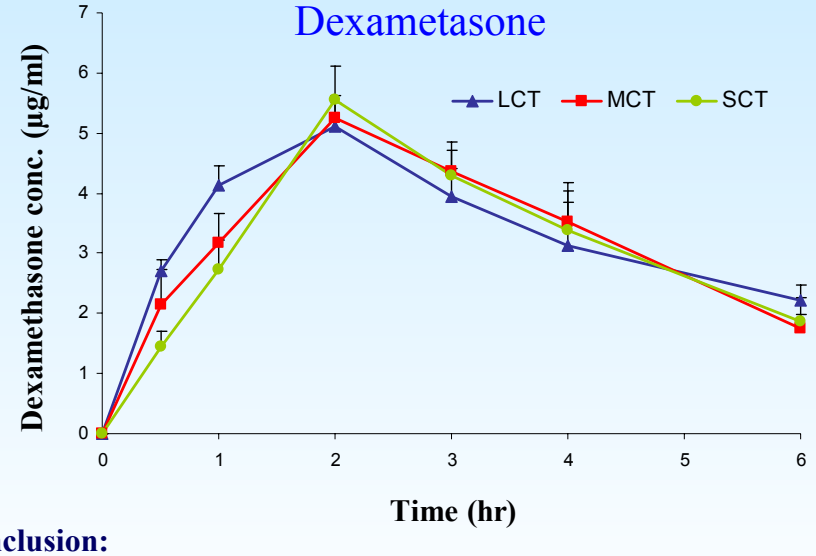


Conclusion:

Performance rank order: SCT > MCT ≥ LCT

In vivo oral bioavailability

Dexametasone

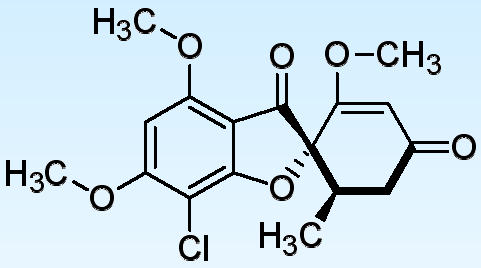


Conclusion:

Performance rank order: MCT = LCT = SCT

IVIVC with lipolysis and not with permeation

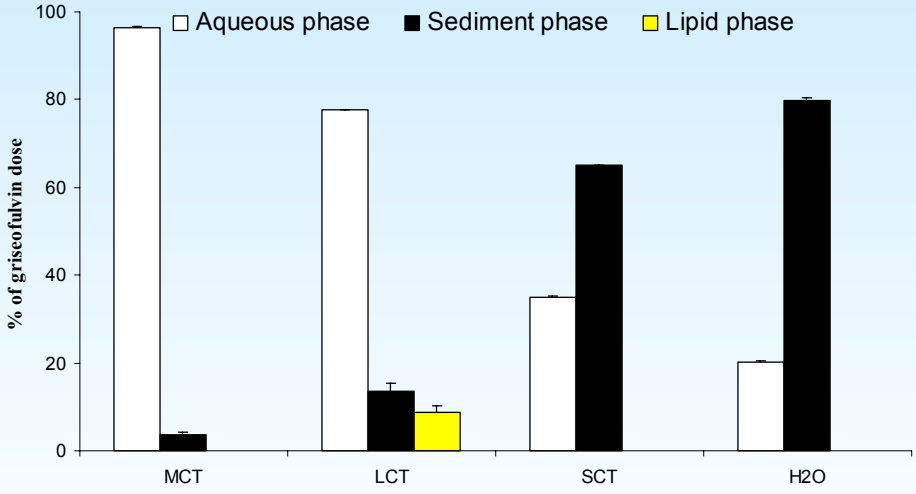
Griseofulvin



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

What is the effect of gut wall permeation abilities on the IVIVC of the lipolysis model?

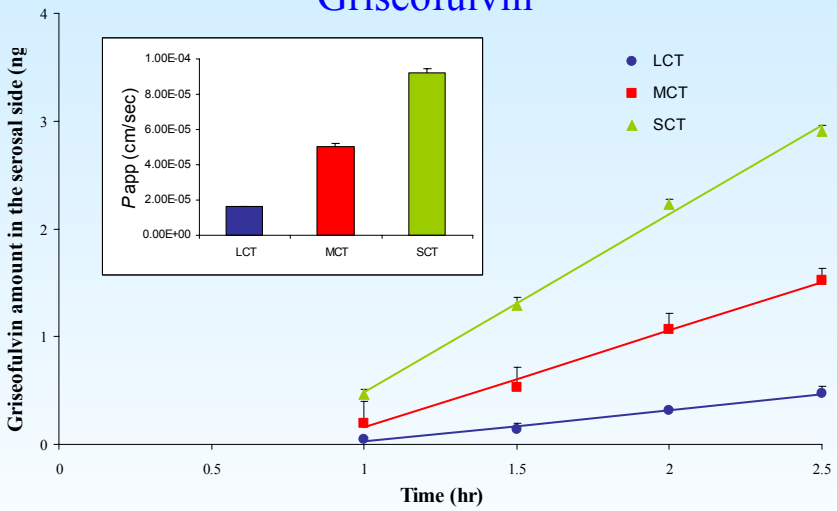
In vitro dynamic lipolysis model
Griseofulvin



Conclusion:

Performance rank order: MCT>LCT>SCT>H_2O

Ex vivo intestinal permeation model
Griseofulvin

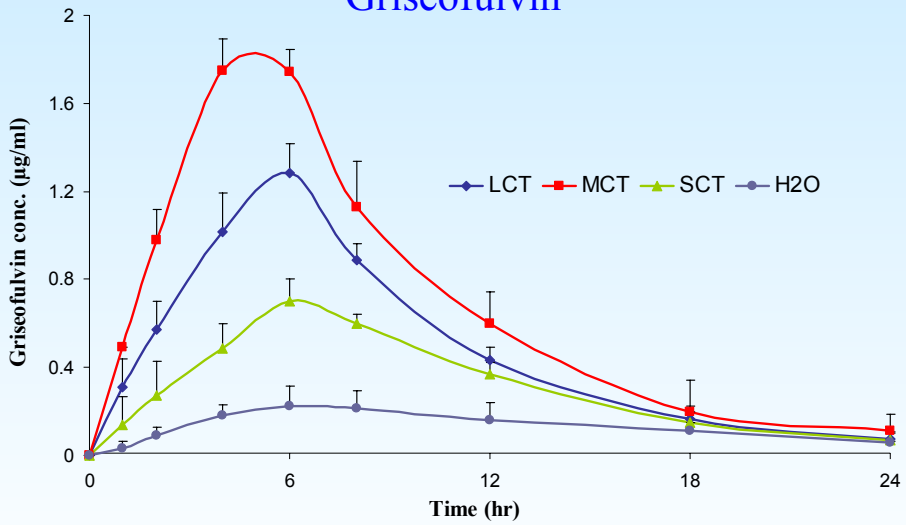


Conclusion:

Performance rank order: SCT > MCT > LCT

In vivo oral bioavailability

Griseofulvin

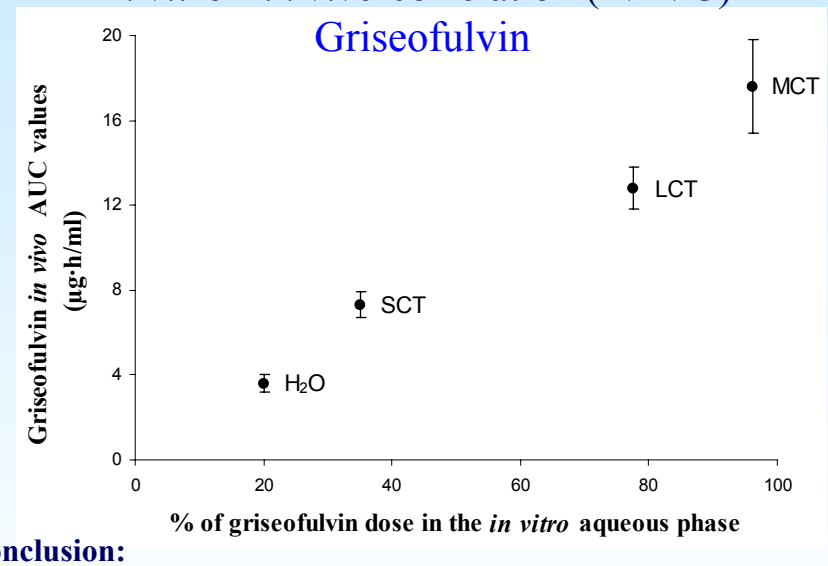


Conclusion:

Performance rank order: MCT>LCT>SCT>H_2O

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

Acknowledgments

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The Hebrew University of Jerusalem

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Thank you