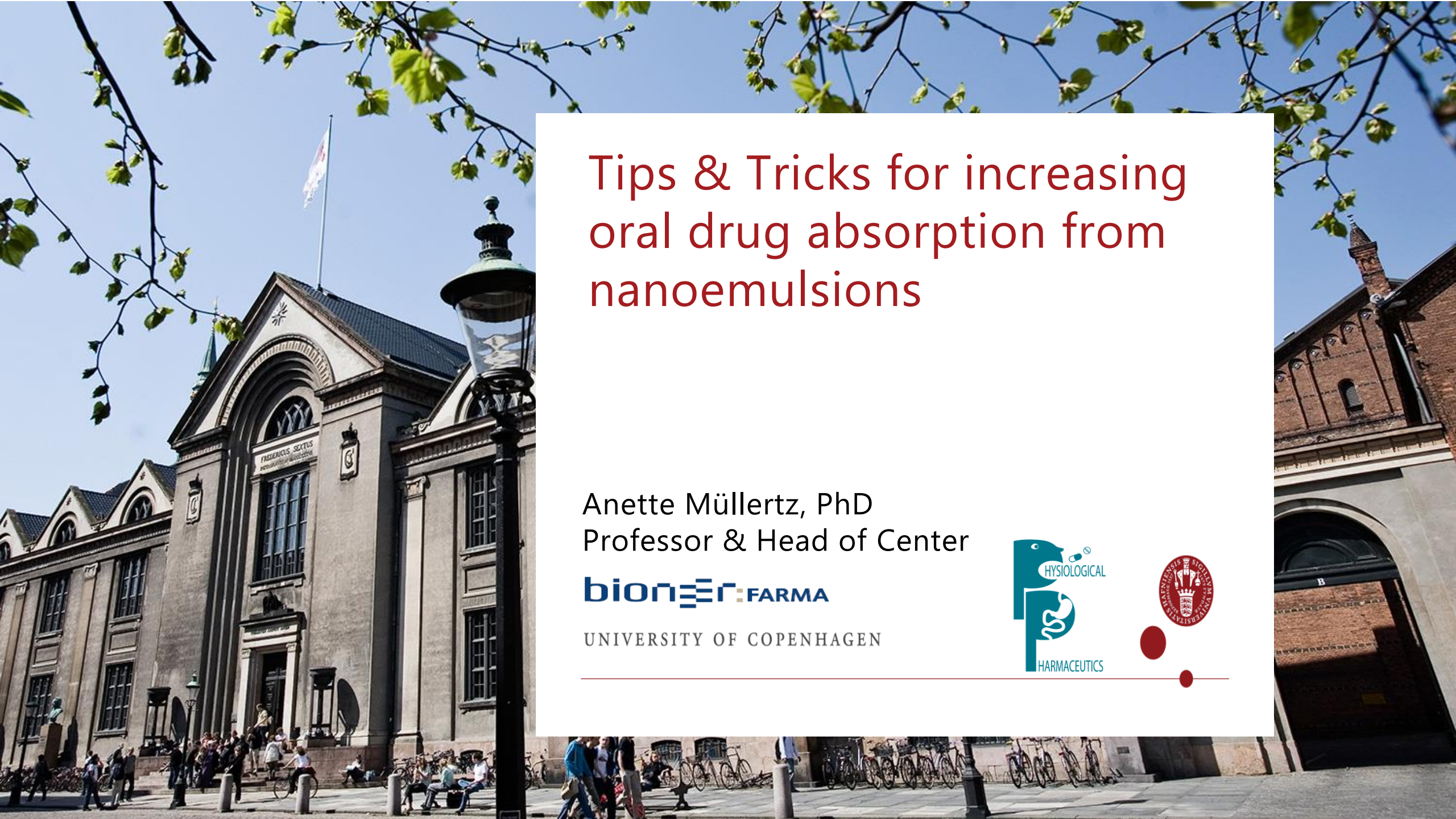


Tips & Tricks for increasing oral drug absorption from nanoemulsions

Anette Müllertz, PhD
Professor & Head of Center

bioneer:FARMA

UNIVERSITY OF COPENHAGEN

PHYSIOLOGICAL PHARMACEUTICS

Self-Nanoemulsifying Drug Delivery Systems (SNEDDS)

SNEDDS are **isotropic mixtures** of oil and surfactants forming **fine oil-in-water emulsions** when introduced into an aqueous phase under gentle agitation

Triglycerides

+

Hydrophilic surfactants

+

Lipophilic surfactants

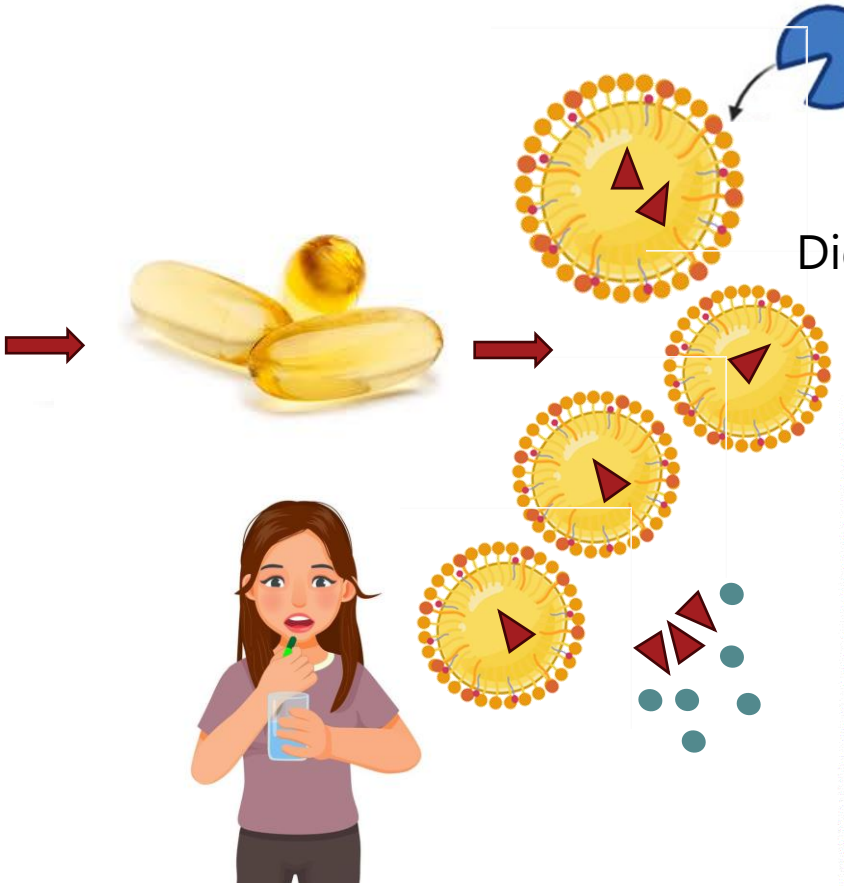
+

Co-solvent

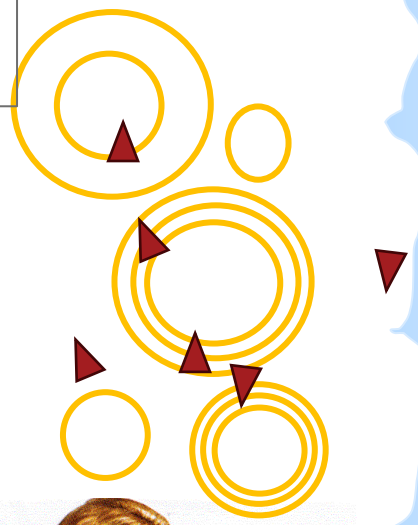
+

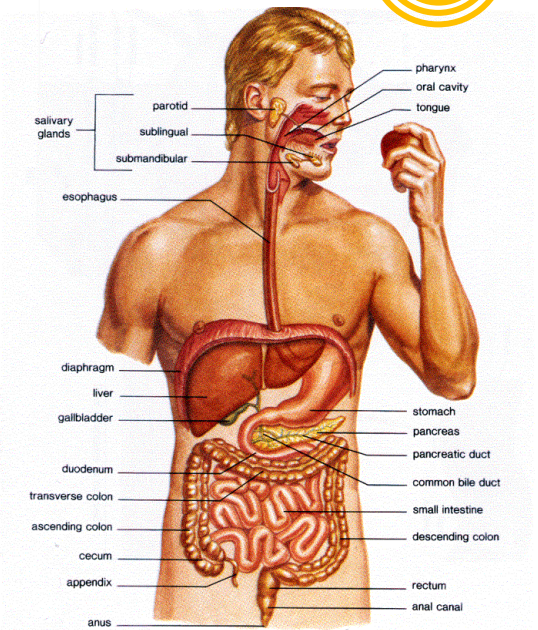
Drug

SNEDDS



Digestion

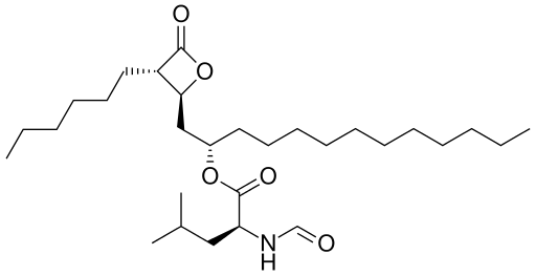




Simple, Sustainable, Scalable

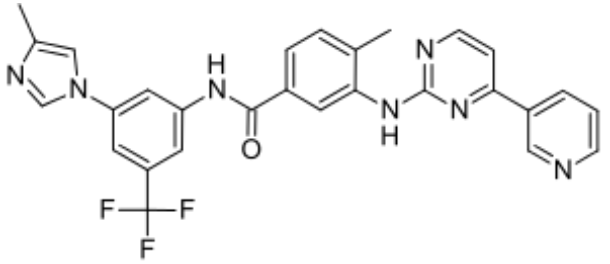
Aim and Research Questions:

- Does size matter?
- Does digestion matter?



Orlistat
- Tetrahydrolipstatin
- Lipophilic lipase inhibitor

- Can the drug load ("solubility") be increased?



Nilotinib

Chronic myelogenous leukemia

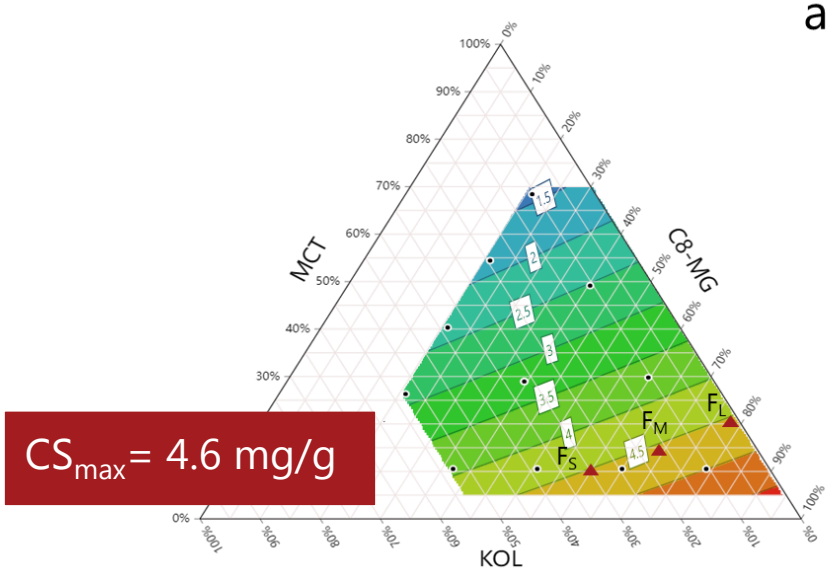
Bioavailability < 25%

Property	Nilotinib
S_{eq} (water) 25°C	0.024 µg/ml
Log P	5.0
Melting point	230-240°C
pKa	5.1-5.6 (pKa_1)

Design of Experiment for medium-chain lipid SNEDDS

Maximum degree of supersaturation (Cs_{max})

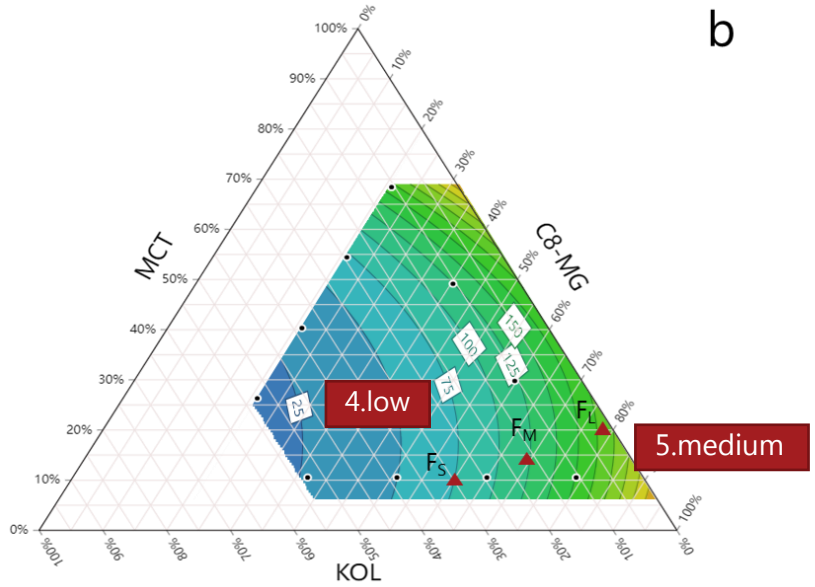
a

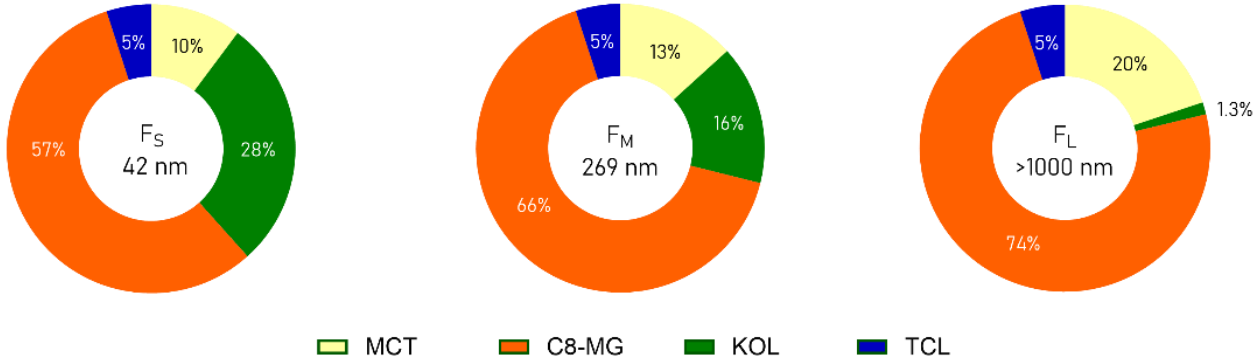


CS_{max}= 4.6 mg/g

Droplet size upon dispersion

b



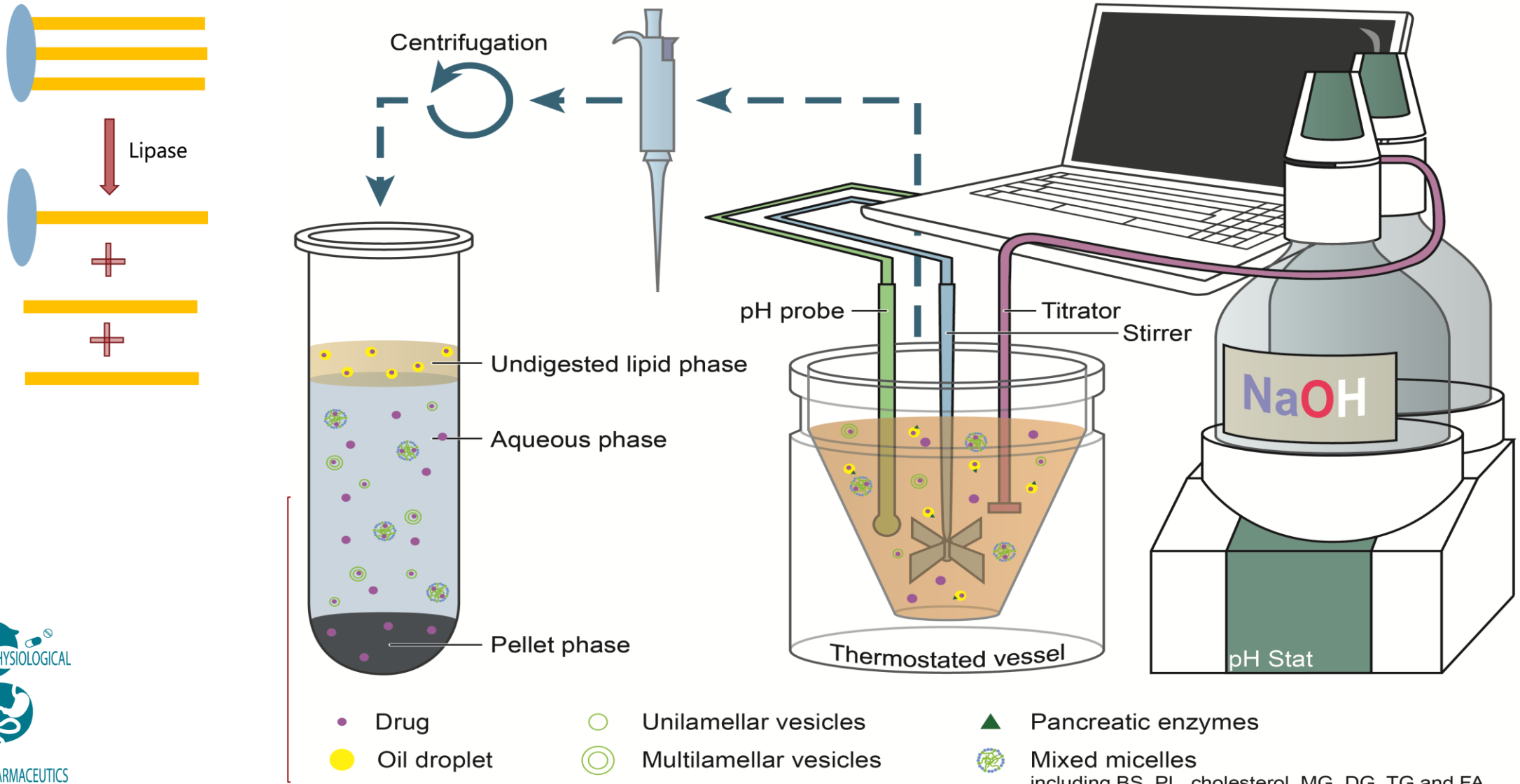


Size: **42 nm** **270 nm** **>1000 nm**

Peng et al., in prep

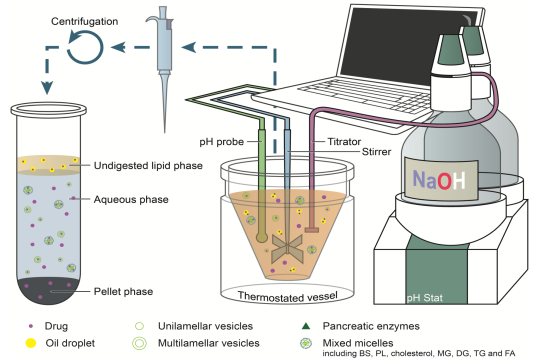
In vitro lipolysis model

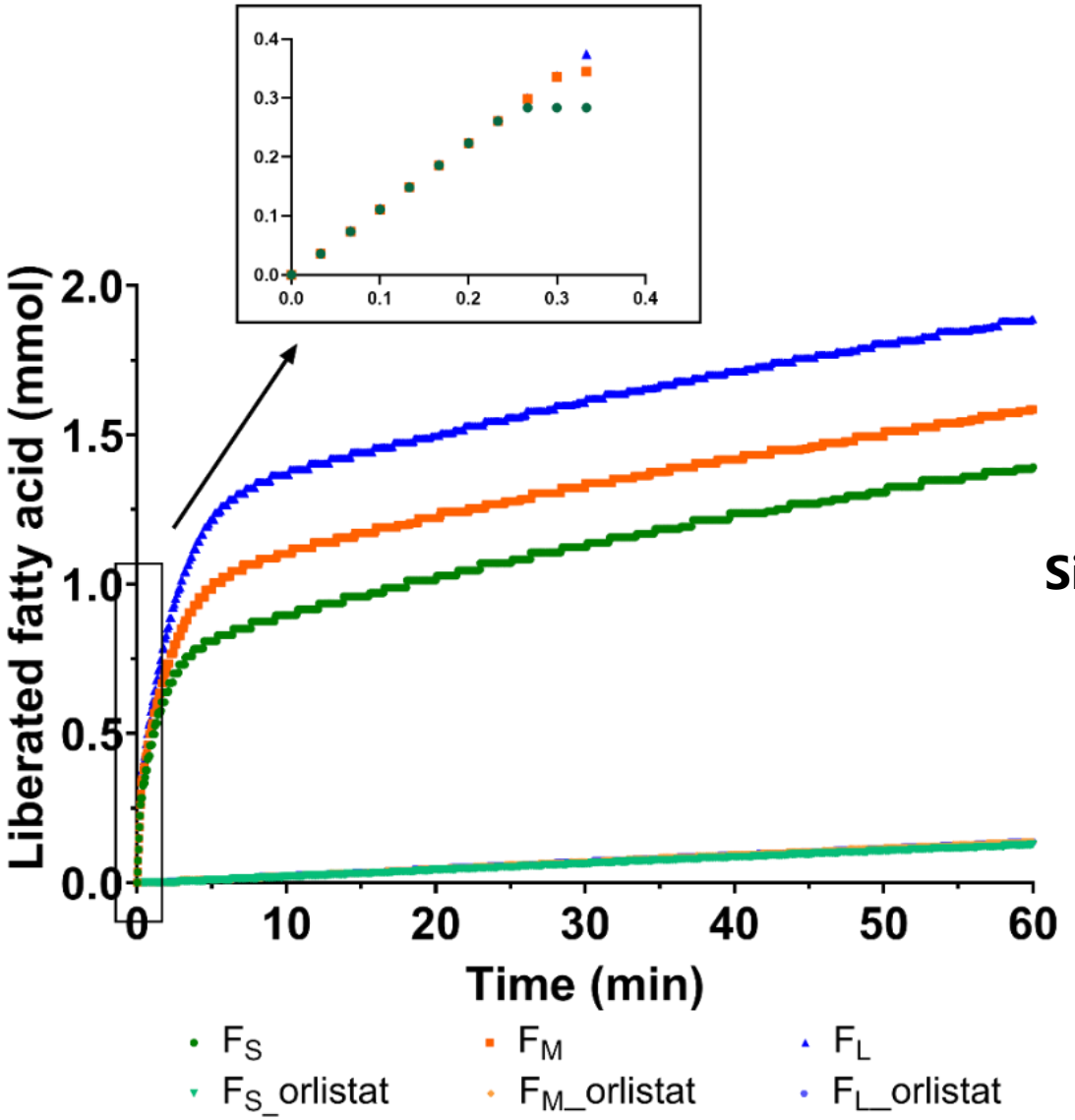
Release of fatty acids
- lead to pH reduction

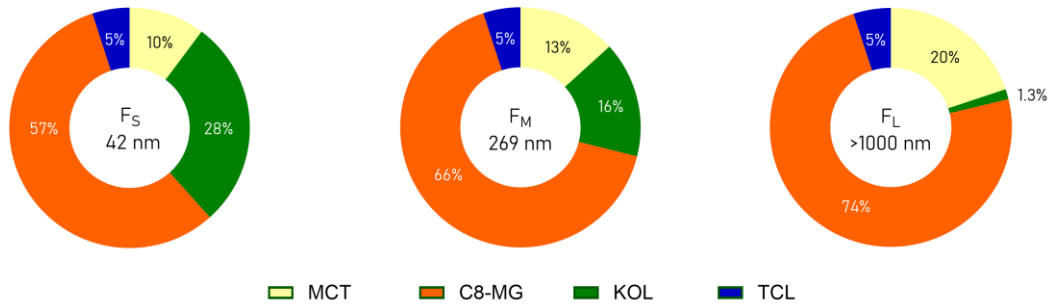


PHYSIOLOGICAL PHARMACEUTICS

Digestion profiles of SNEDDS





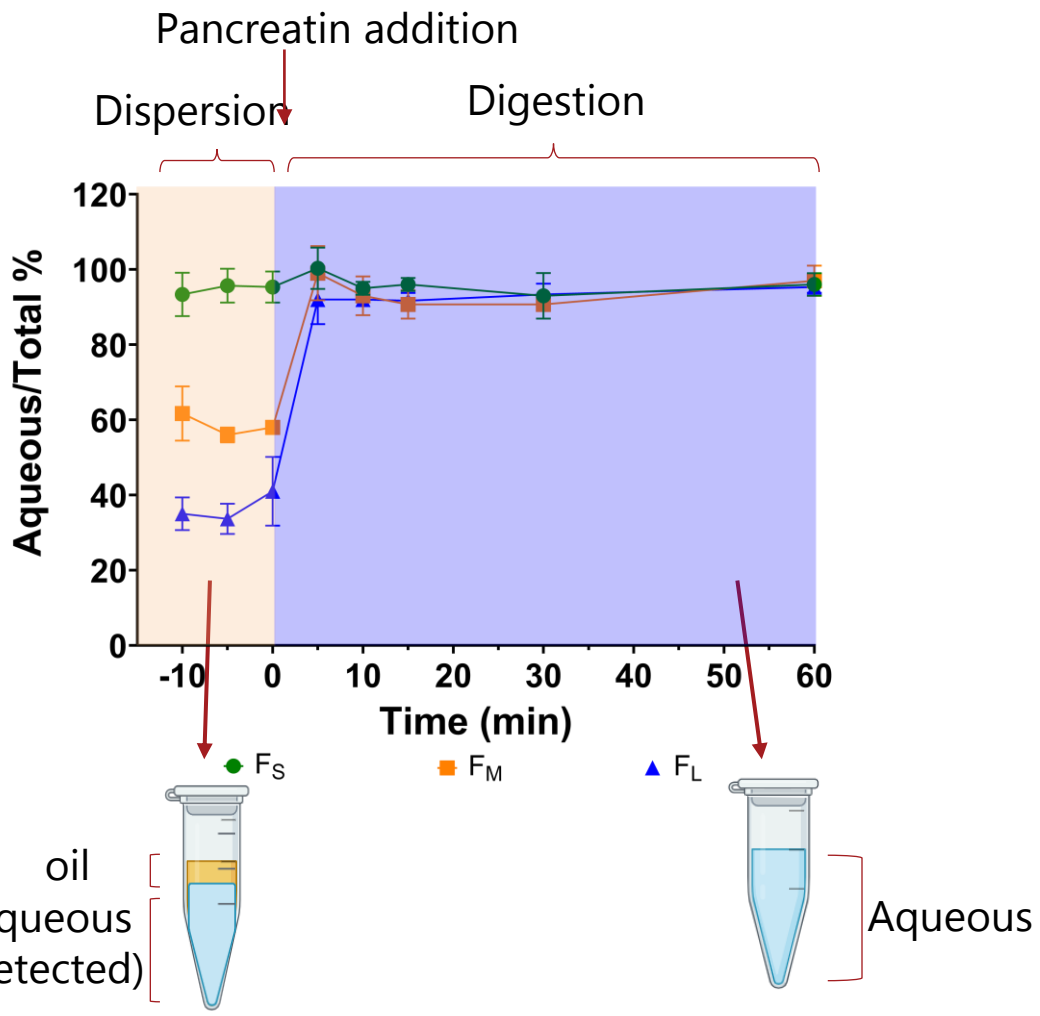


Size: **42 nm** **270 nm** **>1000 nm**

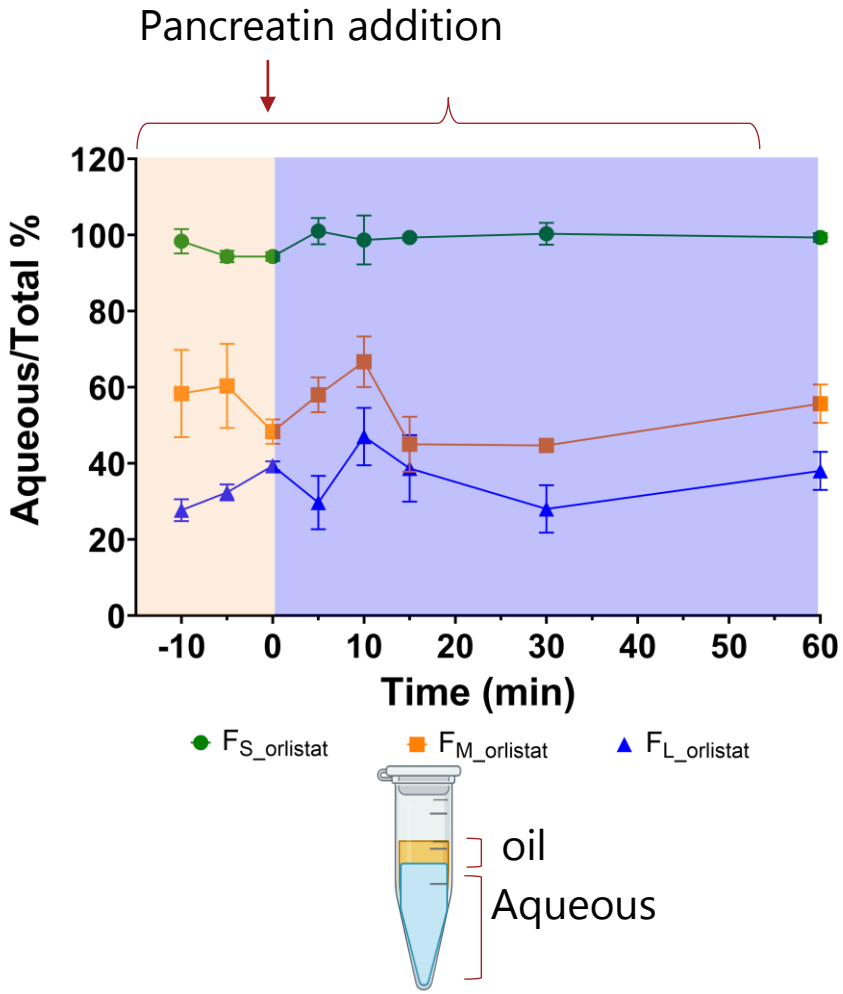
With Orlistat

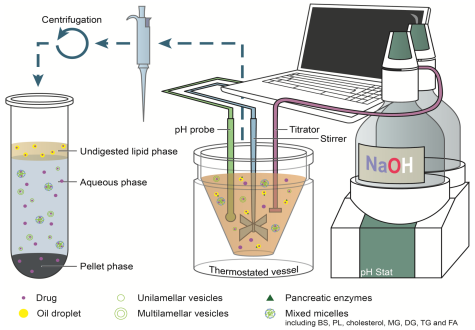
Drug distribution during *in vitro* lipolysis

No orlistat



2% orlistat



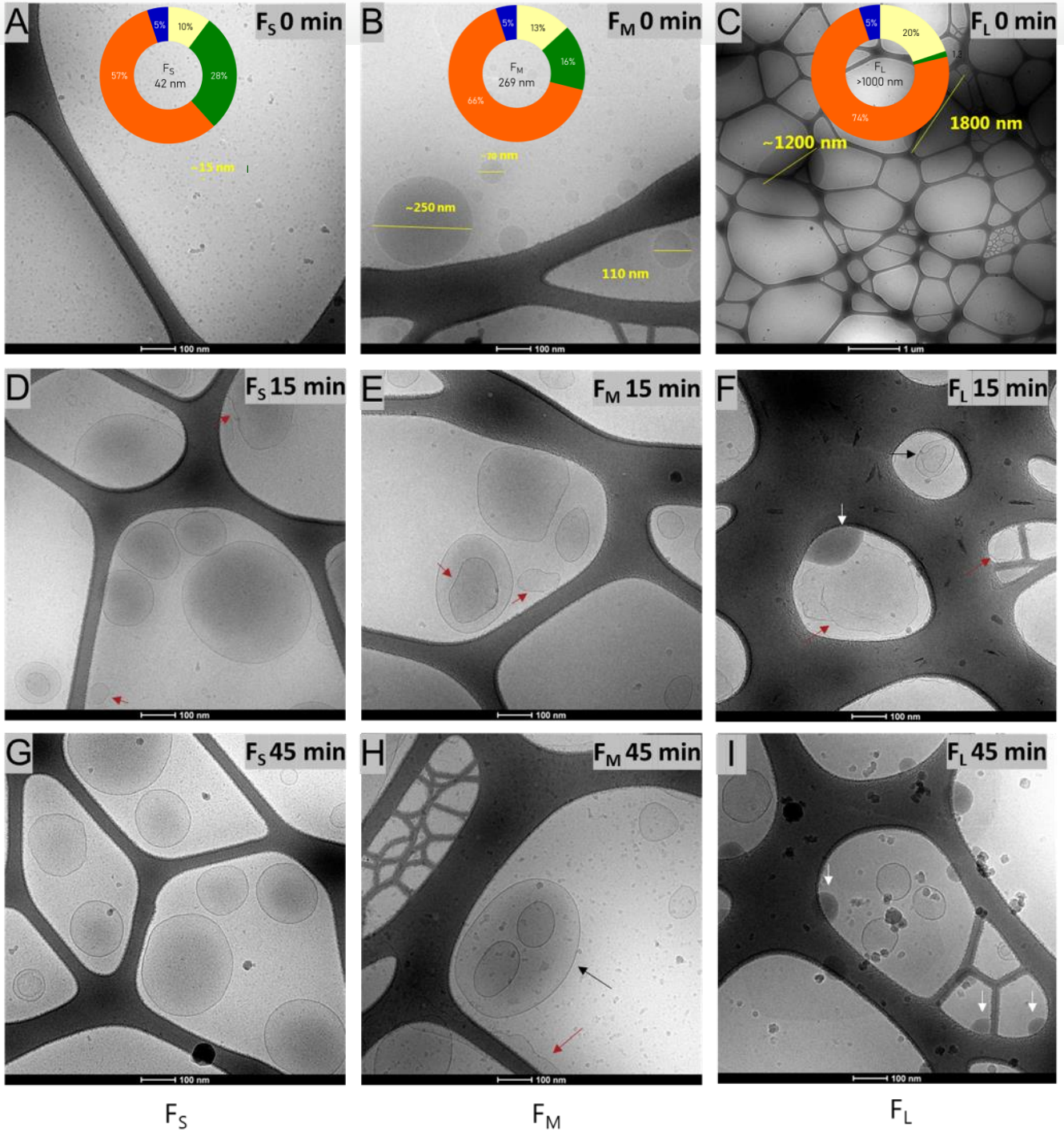


At T=0: lipid droplets

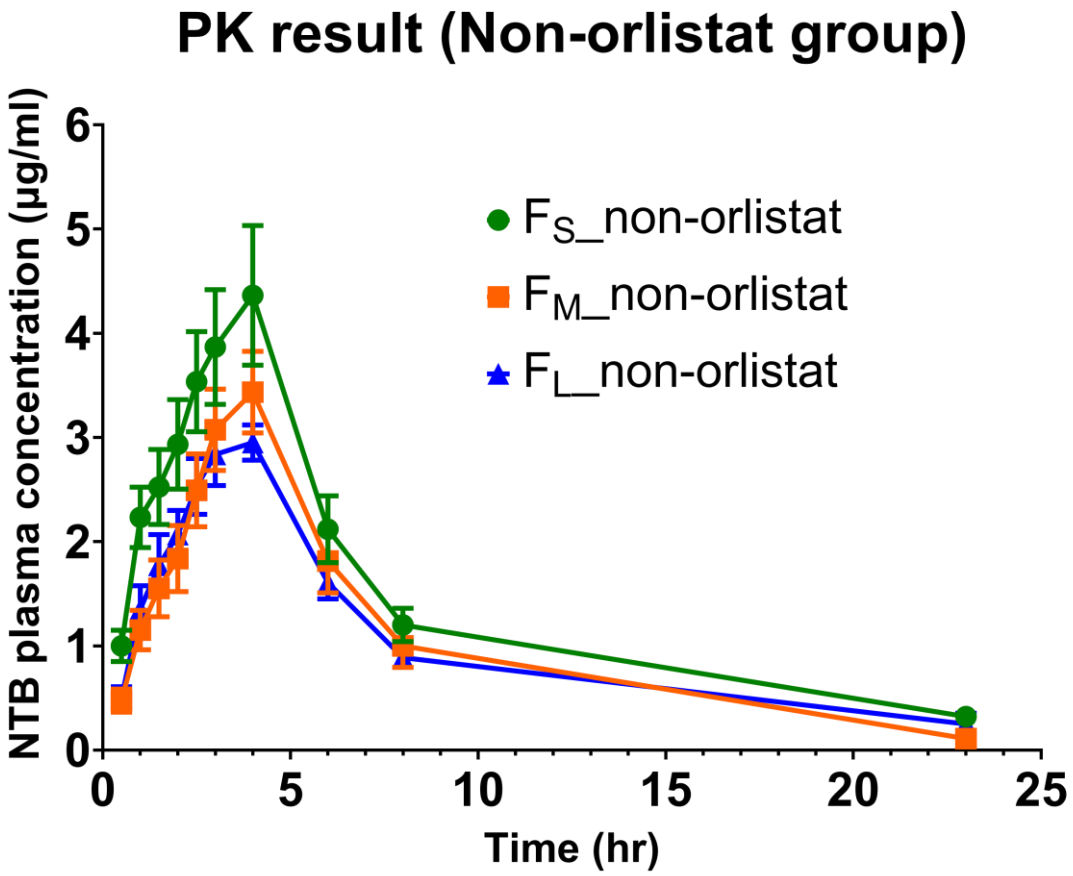
At T= 15 & 45 min:

Fs and Fm
- form spherical unilamellar vesicles

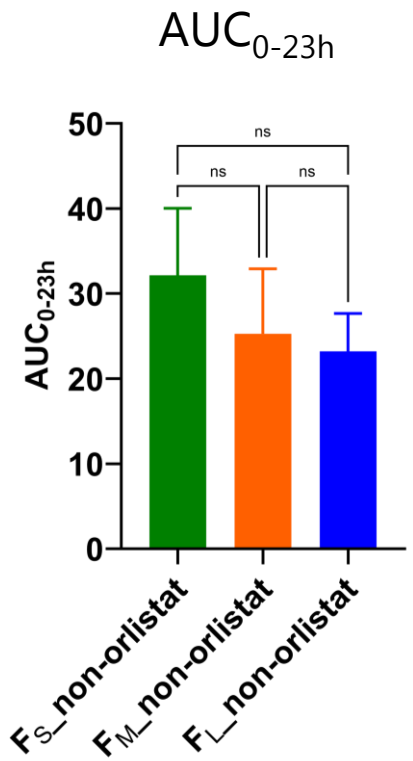
FL
- forms deformed unilamellar vesicles

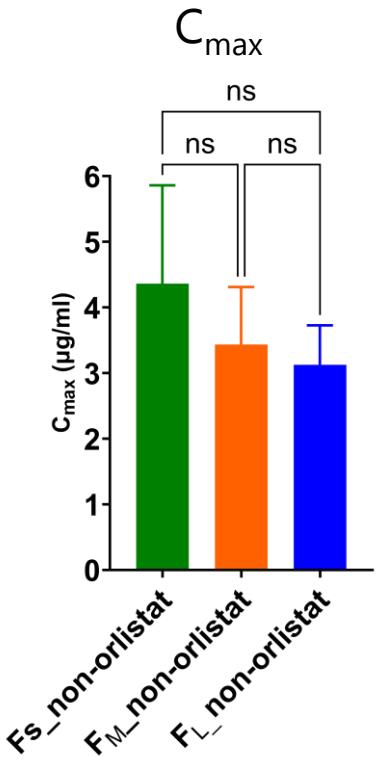


Does Size Matter? Nilotinib – SNEDDS



N=5-6

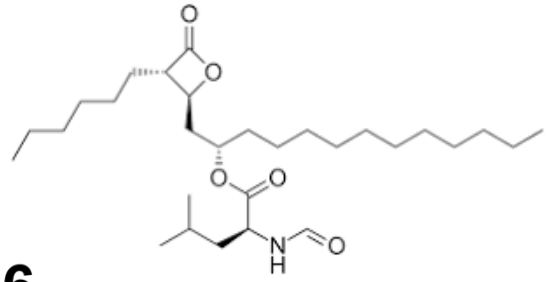




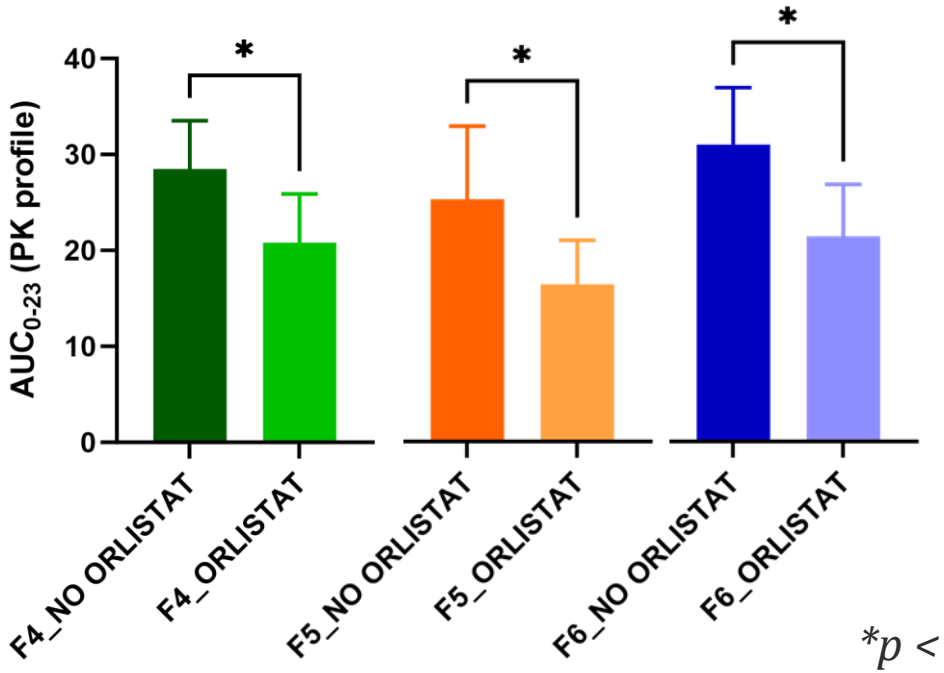
Rank order: $F_S > F_M > F_L$
No Significance

Peng et al., in prep

Does Digestion Matter? **(+2% orlistat)**



Orlistat
Lipophilic
lipase inhibitor



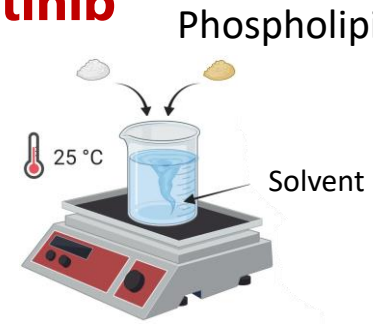
$*p < 0.05$

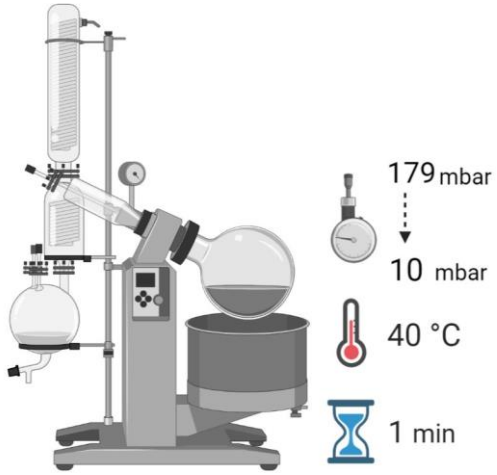
All SNEDDS sign > Cryst. Susp.
Orlistat addition to MC-SNEDDS
- significantly reduce drug absorption

Peng et al., in prep

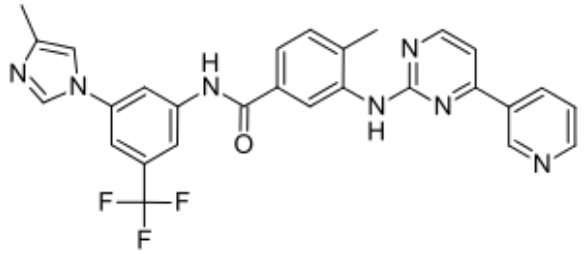
What about increasing the dose ?

Nilotinib

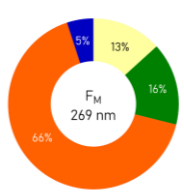




Rotary Solvent Evaporator (SE)



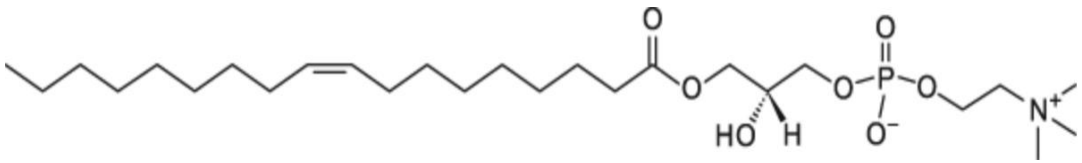
Formation of **Co-amorphous Drug-Phospholipid Complexes**



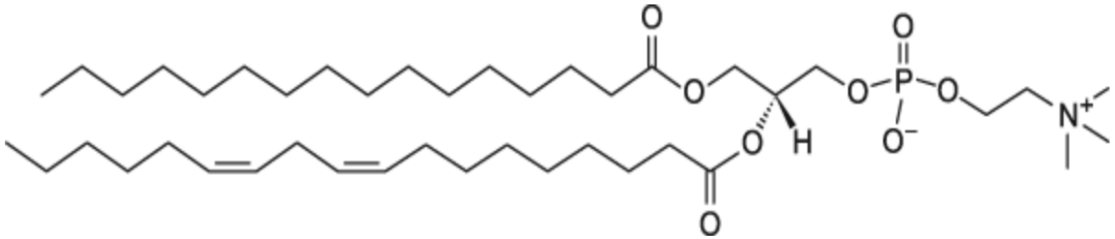
Addition to SNEDDS

- 4 x increased drug load
- No change in size

Monoacyl phosphatidylcholine (MAPC)

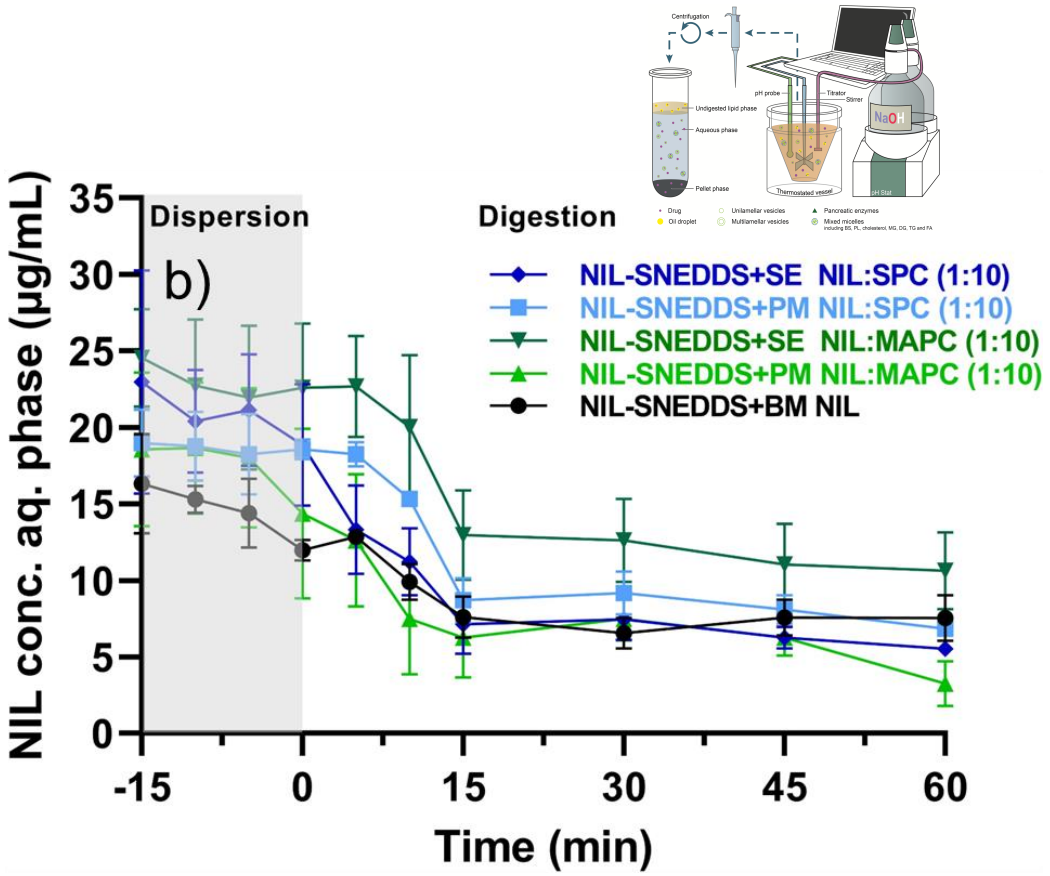


Soybean phosphatidylcholine (SPC)



Khoramy et al, in prep

In vitro lipolysis and oral pharmaco-kinetics of drug-PL complexes in SNEDDS



Significant increase in drug absorption by PL-complexes in SNEDDS
IVIVC should be improved

Conclusion

For nilotinib in medium-chain SNEDDS !

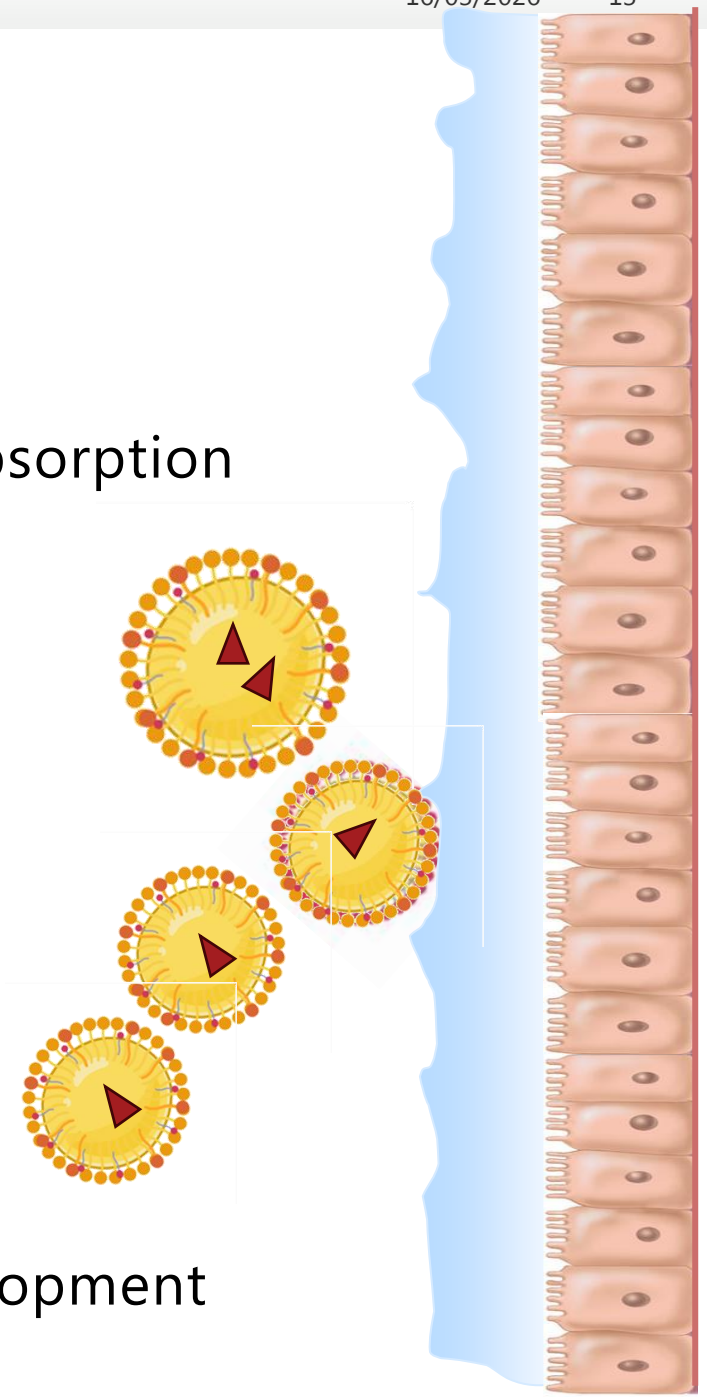
Reducing SNEDDS droplet size - non-significantly increase absorption

Inhibiting lipid digestion - decrease absorption

Co-amorphous nilotinib-phospholipid complexes

- Increase drug load (”solubility”)
- Increase drug absorption

Still looking for the optimal predictive tool for SNEDDS development



The Physiological Pharmaceutics Research Group

COLOTAN

RESPIRI NTM

RESPIRI TB

Phospholipid Forschungszentrum / Research Center Heidelberg

Innovation Fund Denmark RESEARCH, TECHNOLOGY & GROWTH

Brødrene Hartmanns Fond

Thank you for your attention

Questions?

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In vitro lipolysis