Lipid-based drug delivery systems

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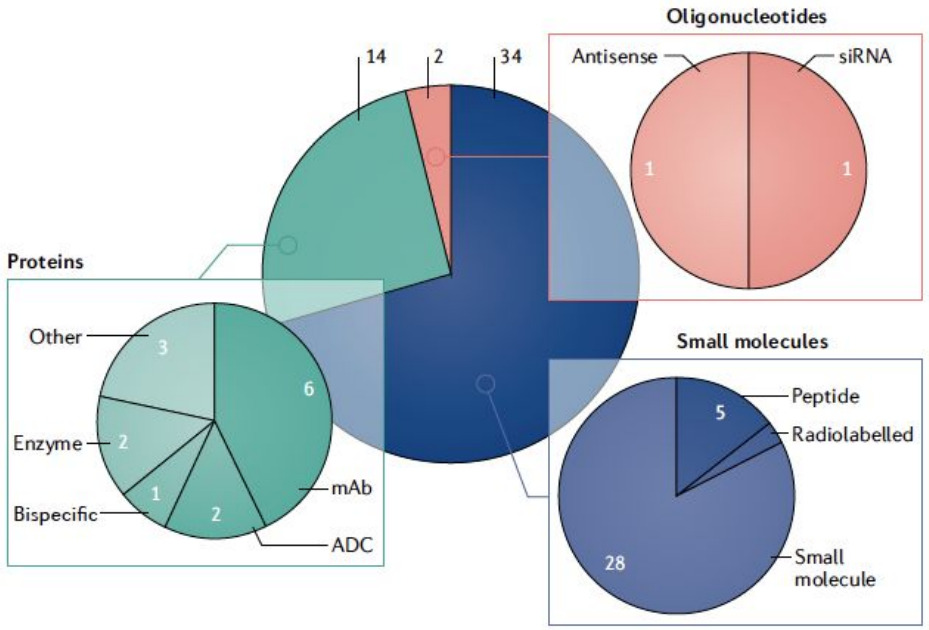
PHYSIOLOGICAL PHARMACEUTICS

Oral Drug Delivery



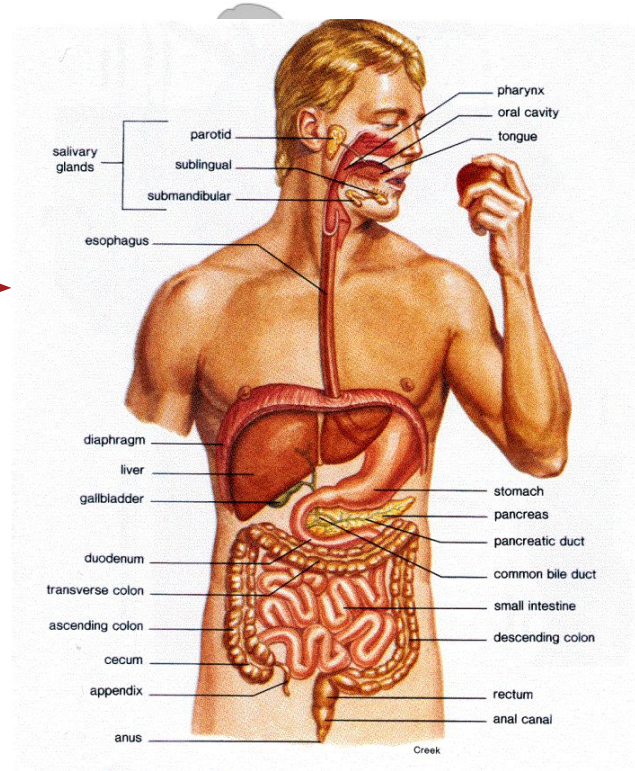
New drugs approved by the FDA in 2021

28 of 50 are small molecules

Oral Administration – preferred route

- Patient Compliance
  - No needles
- No healthcare personnel
- Drug stability
- Production Costs
  - No sterility

- Aqueous Solubility?
- Permeability?



Approx. 50% of all drugs are given orally

Poorly water-soluble drugs

$$\frac{dC}{dt} = \frac{AD(C_s - C)}{h}$$

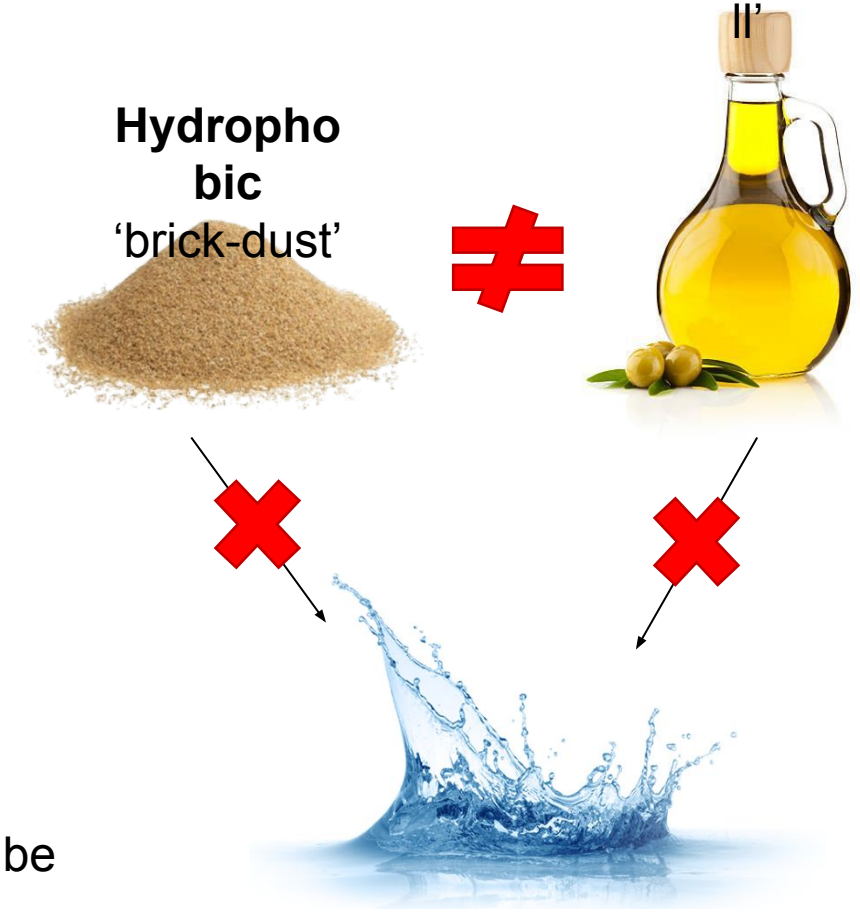
Noyes-Whitney equation describing the dissolution process [1]

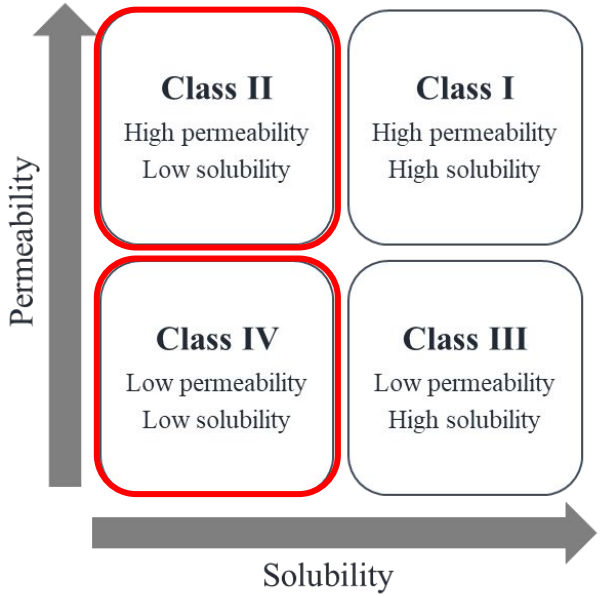
dC/dt **:** dissolution rate
D : diffusion coefficient of the drug
A **:** surface area of the drug particles
h **:** thickness of the diffusion layer
C_s **:** S_{eq} of the drug in the solution medium
C **:** concentration of the drug at a time *t*

Hydrophobic
'brick-dust'

≠

Lipophilic
'grease-ball'



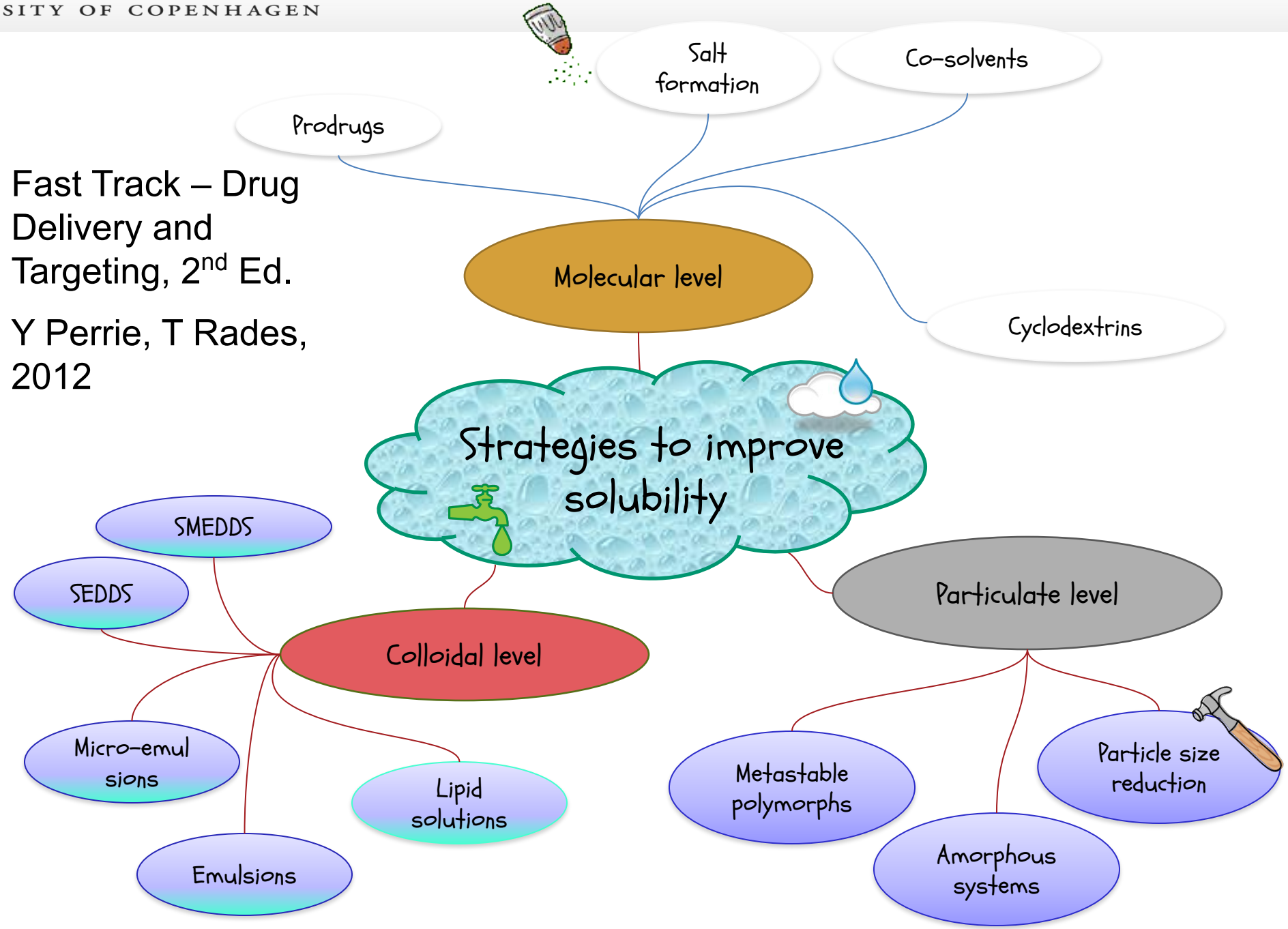


Biopharmaceutical classification system. Amidon *et al*. 1995

Drug have to be in solution to be absorbed

Fast Track – Drug Delivery and Targeting, 2nd Ed.

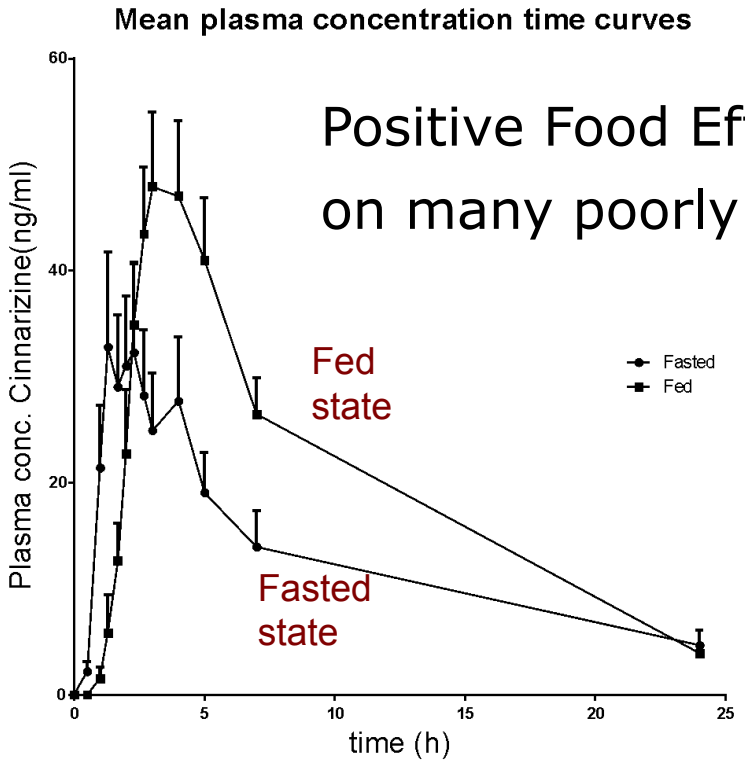
Y Perrie, T Rades, 2012



Lipid-based Drug Delivery Systems – "colloidal level"

Why lipids?

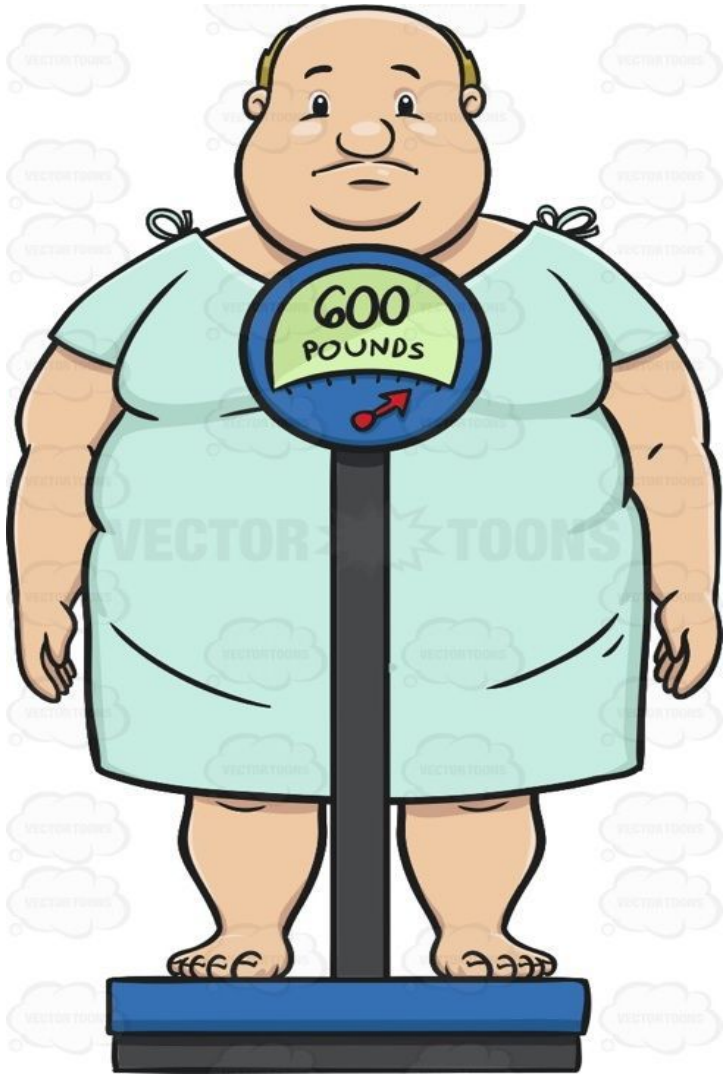
- Essential part of our diet
- Body well equipped for lipid digestion
- Uptake >95% absorbed



Positive Food Effect

on many poorly soluble drugs

Christiansen et al EJPS, 2016



Propranolol
Metoprolol
Labetalol
Propafenone
Hydralazine
Griseofulvin
Nitrofurantoin
Mebendazole
Flubendazole
Halofantrine
Phenytoin
Dicoumarol

Lipid-based Drug Delivery Systems (LbDDS)

Deliver drug in **solution** in LbDDS
Bypass dissolution in the gastro-intestinal tract
Increase Bioavailability
Important: Transfer between **colloidal phases**
Avoidance of precipitation

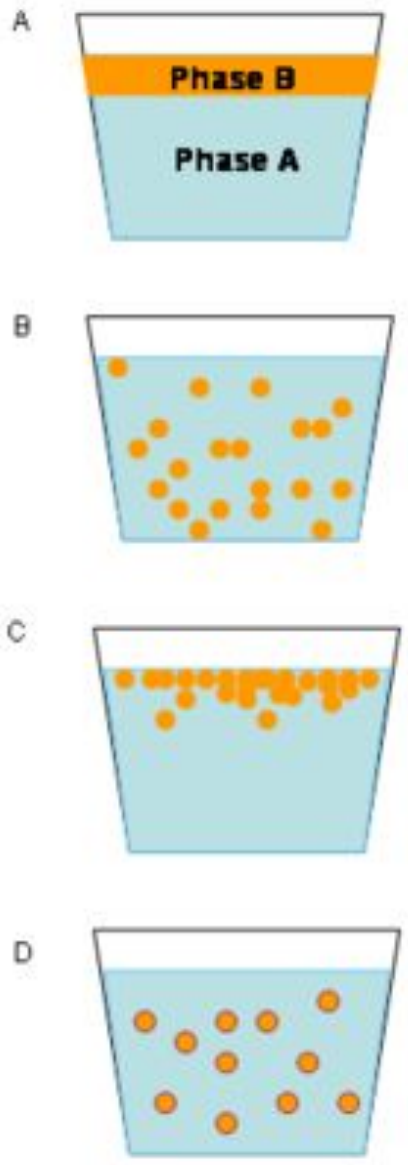
Liposomes

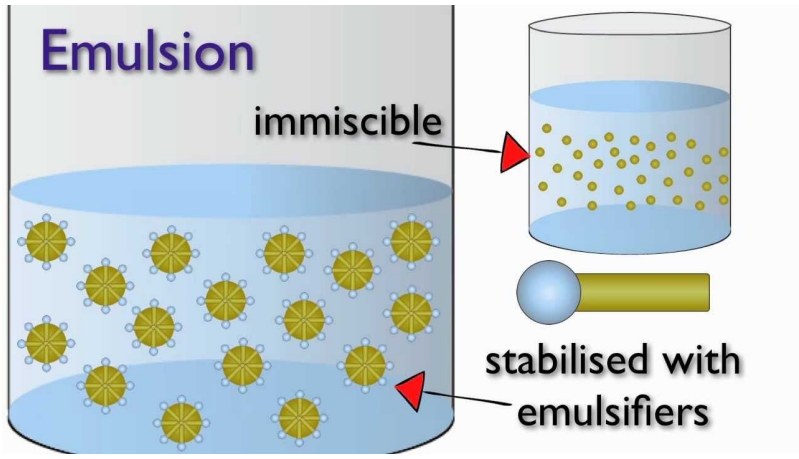
Oil solution

Emulsions

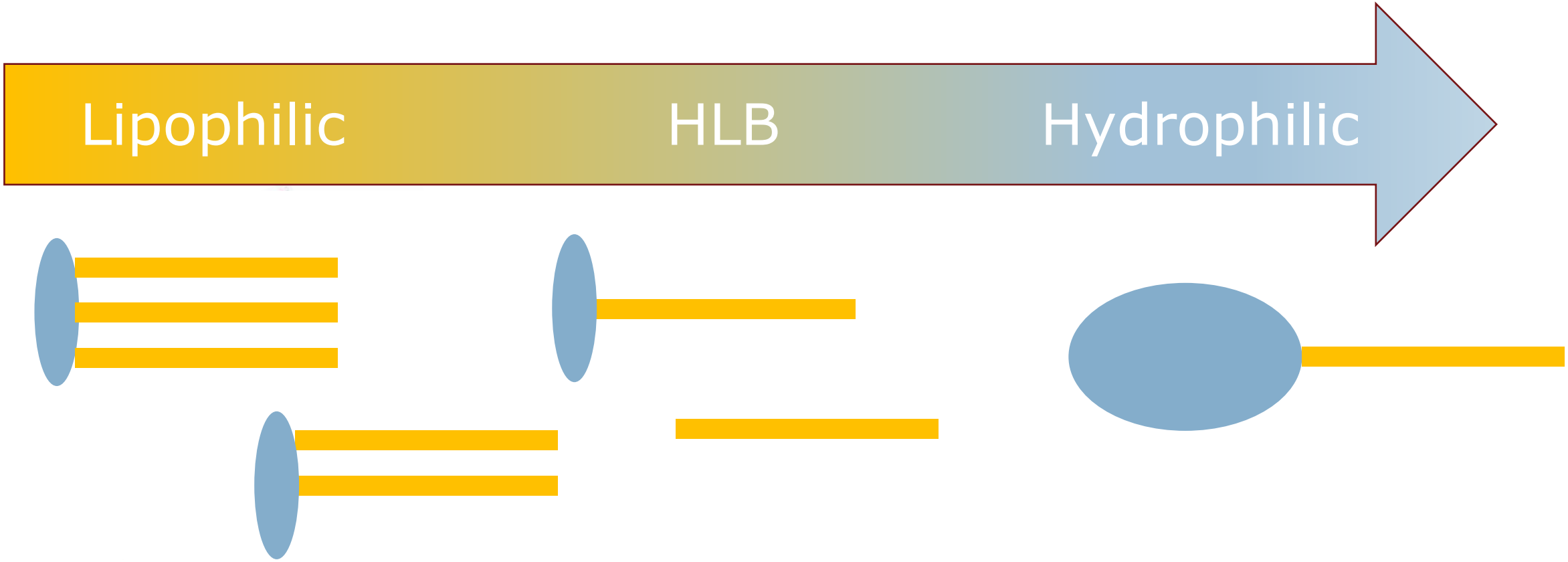
Self Emulsifying Drug Delivery Systems (**SEDDS**)
Self Nano-Emulsifying Drug Delivery Systems (**SNEDDS**)

Surfactant / cosolvent systems


A
Phase B
Phase A
B
C
D


Emulsion
immiscible
stabilised with
emulsifiers

Hydrophilic-lipophilic balance (HLB)



HLB ~ 1
Triacylglycerides
Diacylglycerides

2 > HLB < 6
Monoacylglycerides
Propylene glycol esters

6 >HLB <12
Polyoxylglycerides:
- Capryol 90, PGMC
- Labrafil M1944

HLB>12
Polysorbates (Tweens)
Kolliphor RH40, EL
Labrasol

Lipid-based Formulation Classification System (LFCS)

	Type I	Type II	Type IIIA	Type IIIB	Type IV
Typical composition	**Oil solution**	**SEDDS**	**SEDDS SNEDDS**	**SNEDDS**	**Micelles**
TG, DG, MG	**100**	**40-80**	**40-60**	**<20**	**-**
Surfactants (HLB<12)	**-**	**20-60**	**-**	**-**	**0-20**
Surfactants (HLB>12)	**-**	**-**	**20-40**	**20-50**	**30-80**
Hydrophilic cosolvents	**-**	**-**	**0-40**	**50-100**	**0-50**
Droplet size (nm)	coarse	250-2000	100-250	50-100	30-80

Dispersion in water

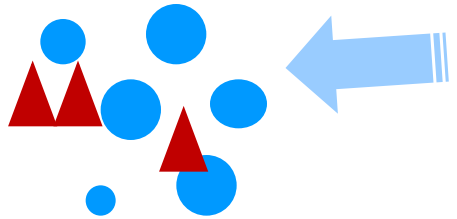
Pouton 2006, EJPS

SNEDDS - Homogenous Preconcentrate in Capsule

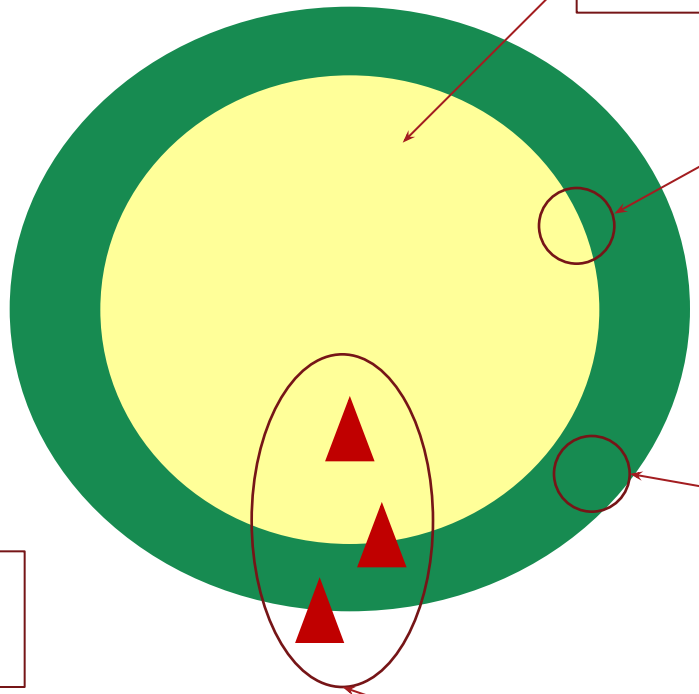
- Oil
- Hydrophilic Surfactants
- Co-surfactants (lipophilic)
- Co-solvent
- Drug

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

Dispersion (not to scale!)



Hydrophilic co-solvents
ethanol, PEG,
propylene glycol, transcutol®



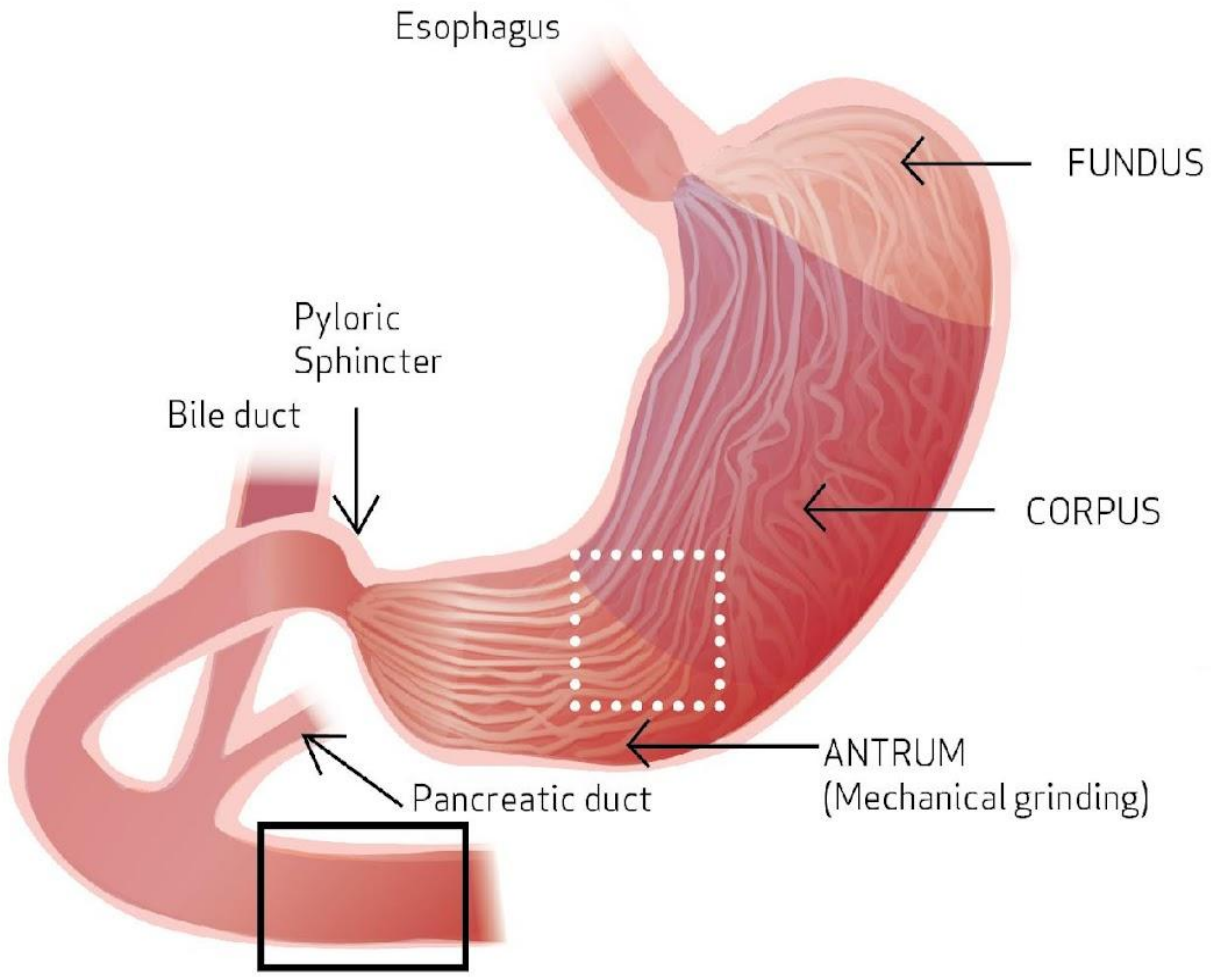
Lipid phase
triacylglycerides, diacylglycerides

Hydrophobic surfactants (HLB<12)
Span, Maisine, Labrafil®

Hydrophilic surfactants (HLB >12)
Gelucire®, Cremophor®, Tween, Labrasol®

Drug compound

The Stomach



Gastric secretions:
Pepsin
Gastric Lipase
HCl
Mucins

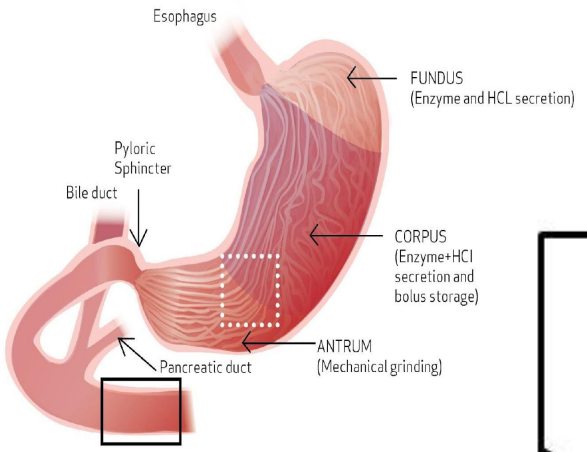
Gastric content
Fasted state:
pH: 1.6 - 3
Vol: 25-75 ml

Fed state:
pH: Food dependent
Vol: Food intake dependent

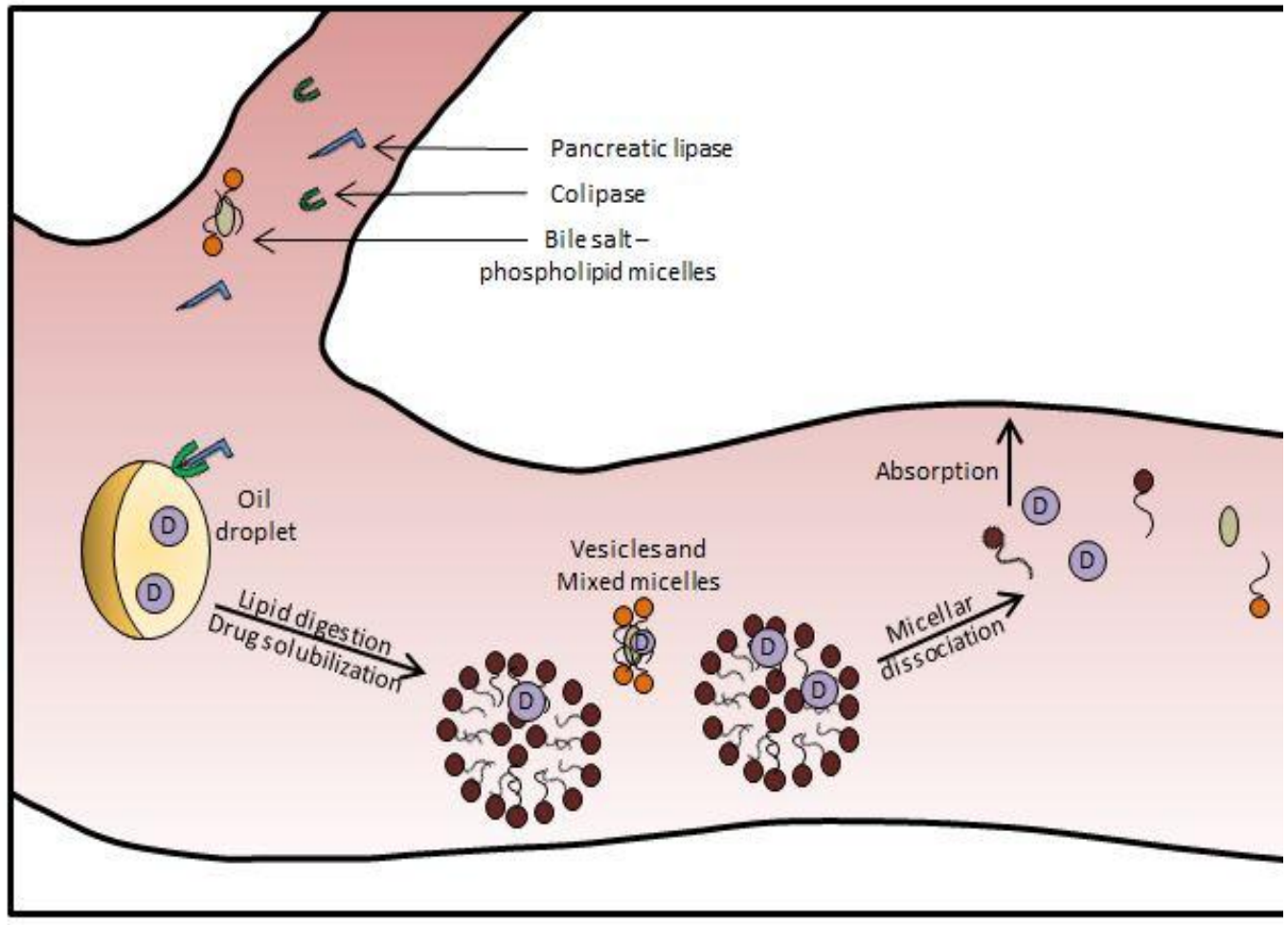
Leaky container – releasing digested food to the duodenum in a well controlled manner

Berthelsen et al, 2016

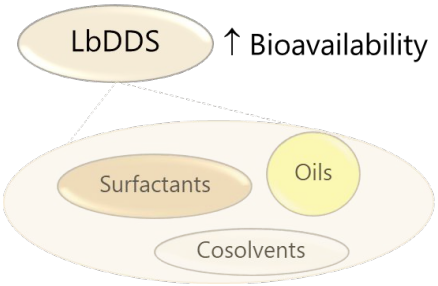
Digestion: Duodenum / Small Intestine

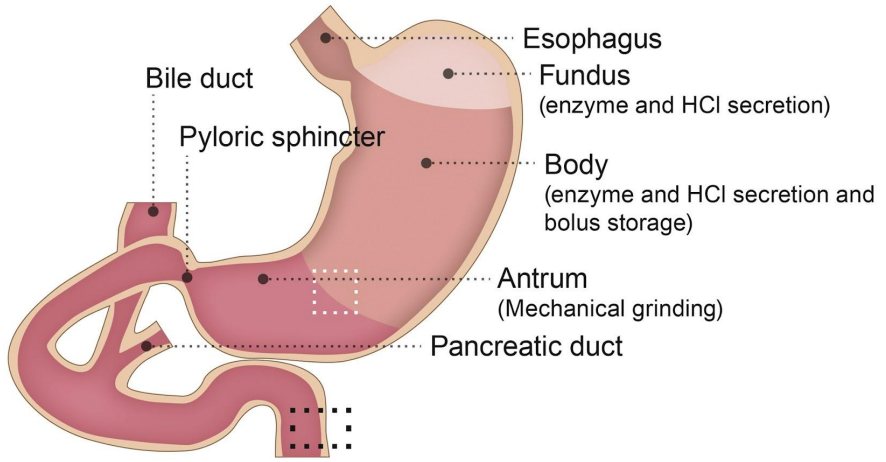


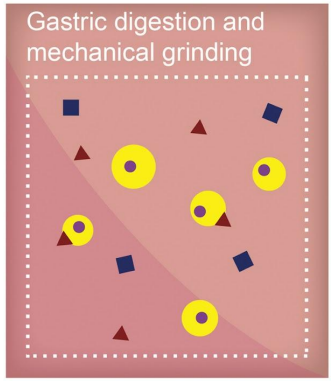
Bile & pancreatic duct

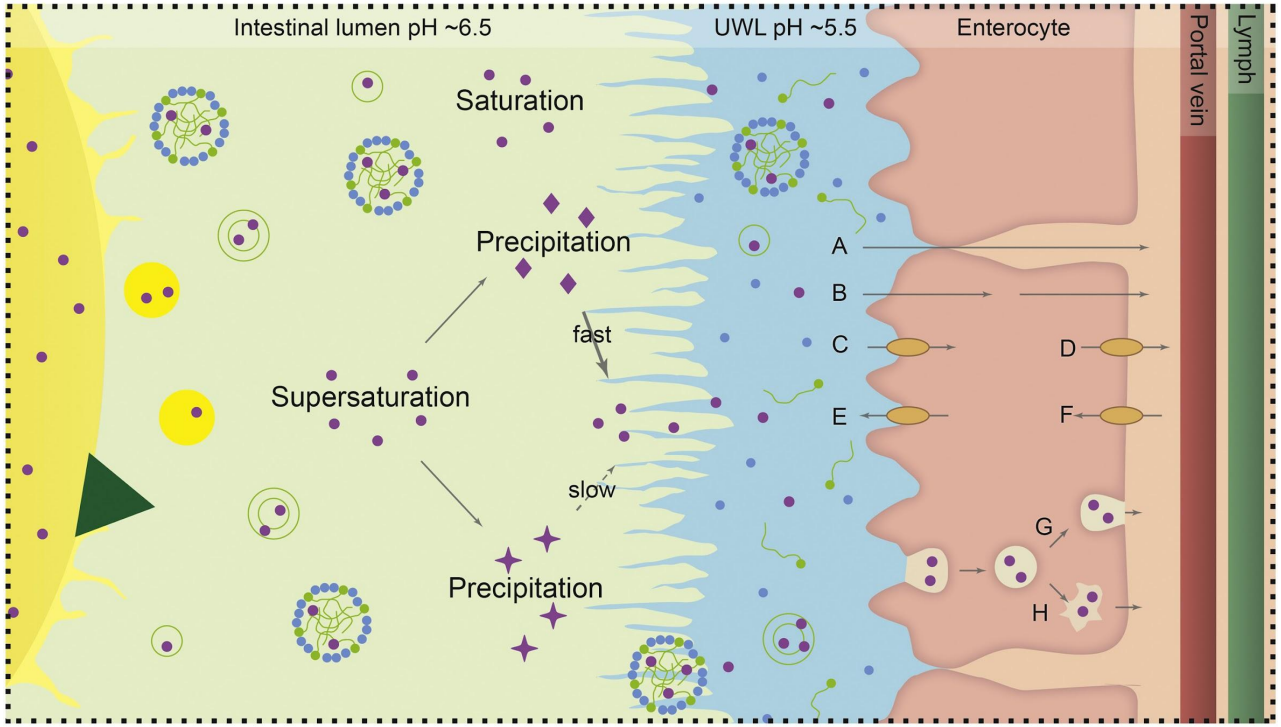


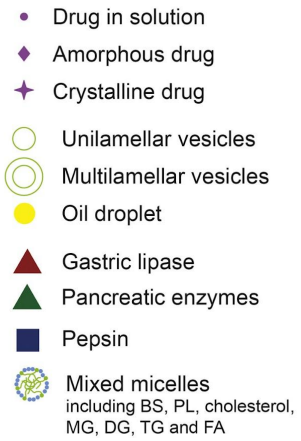
Absorption from Lipid Based Drug Delivery Systems







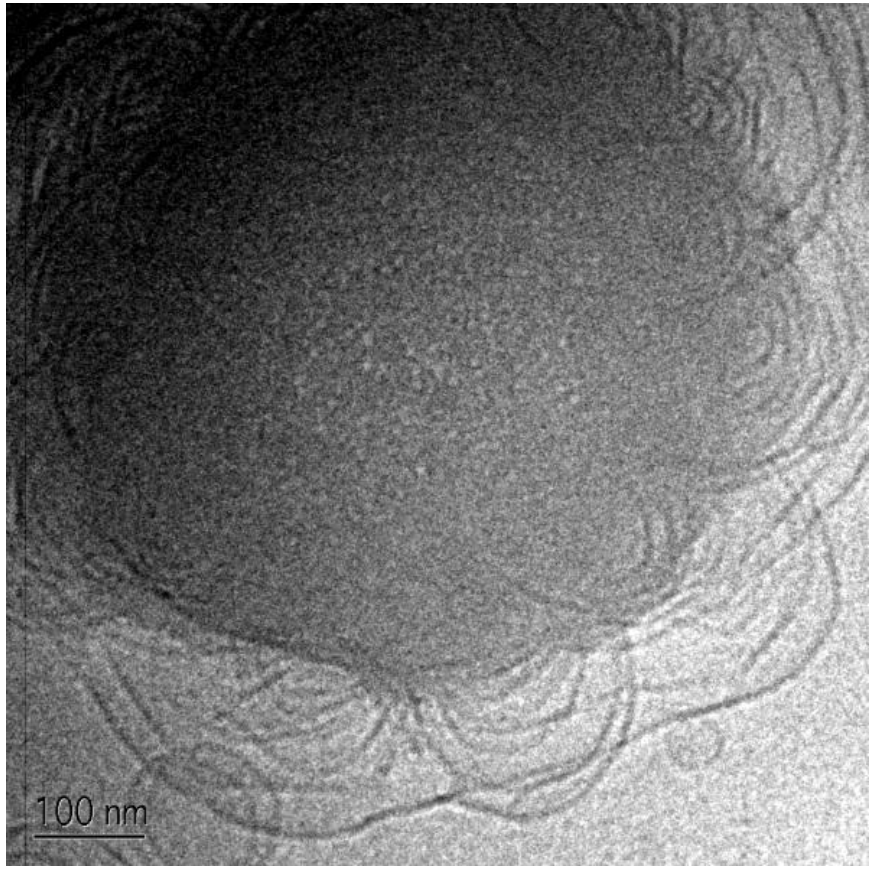


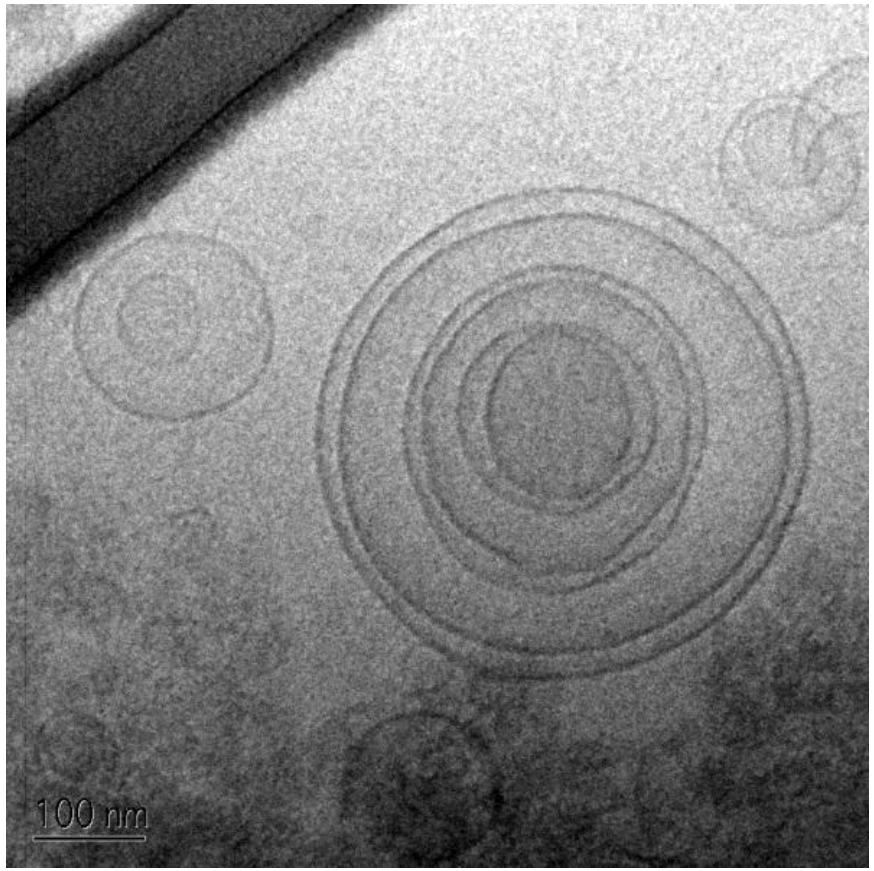


Berthelsen *et al.* ADDR 2019

Human intestinal fluids

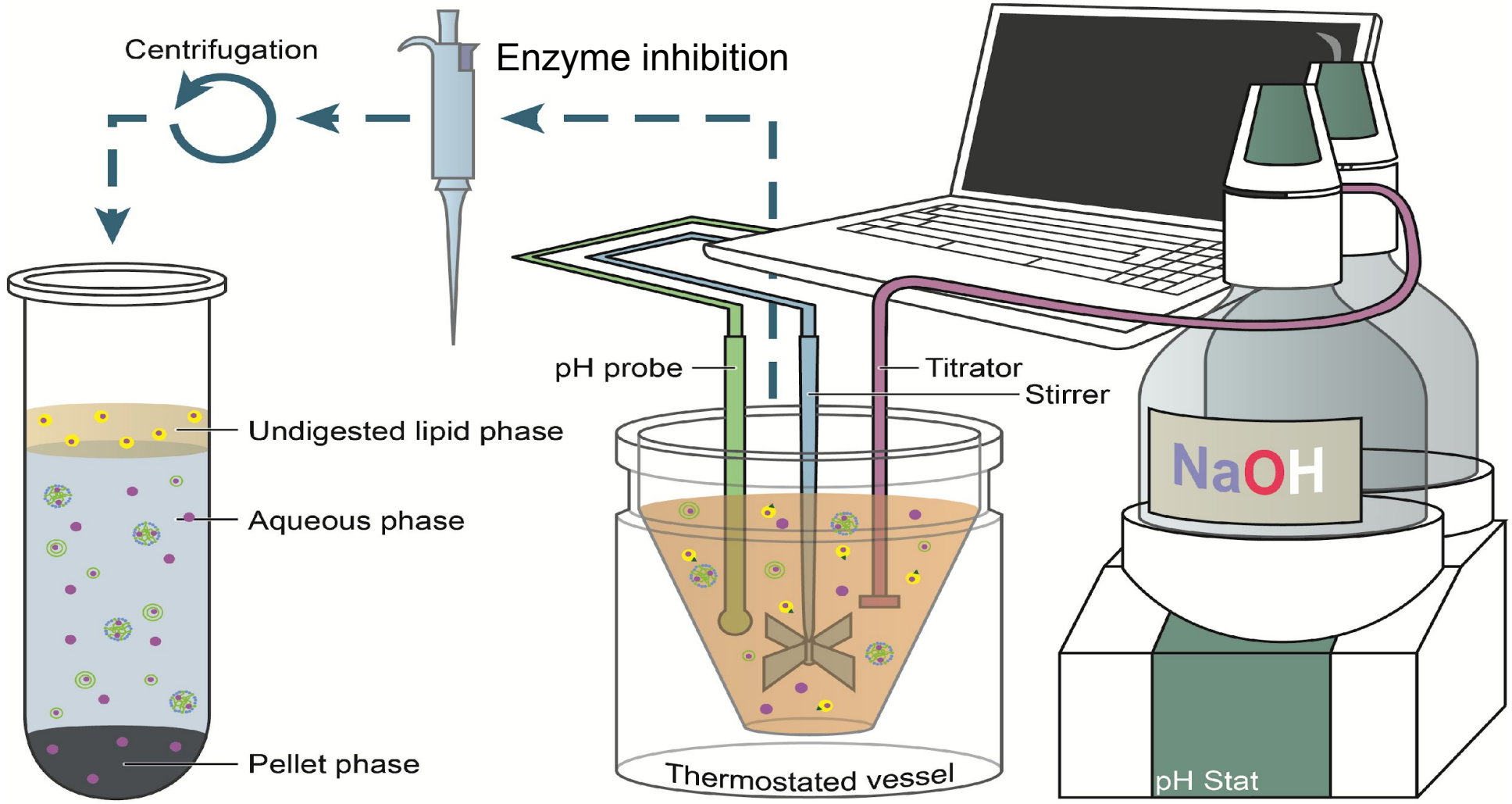
Fed state: 60 min after intake of an emulsion





Müllertz et at, JPP, 2013

In vitro lipolysis model



Drug
Oil droplet
Unilamellar vesicles
Multilamellar vesicles
Pancreatic enzymes
Mixed micelles
including BS, PL, cholesterol, MG, DG, TG and FA

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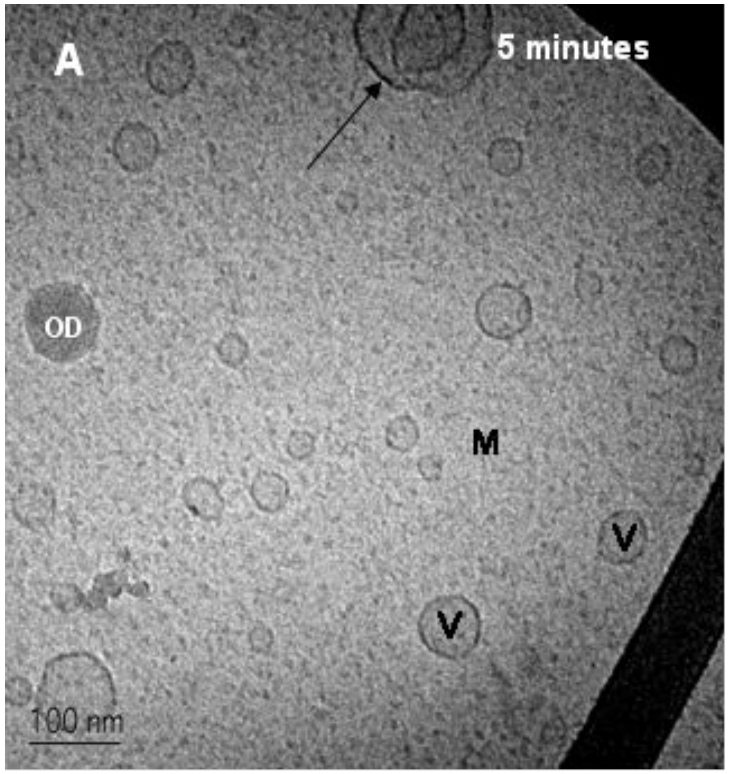
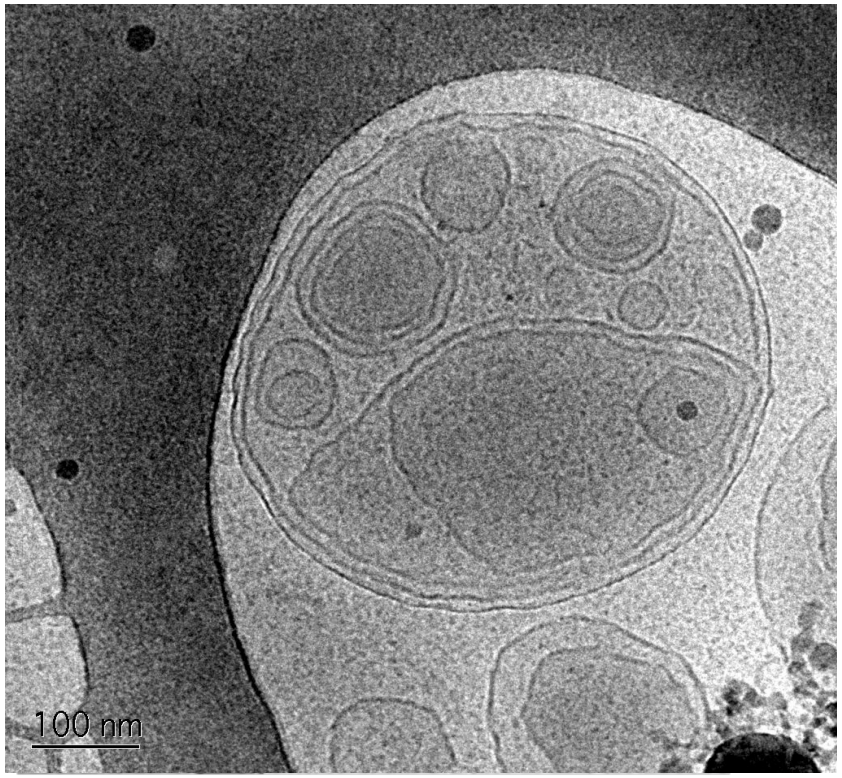
Cryo-TEM of Lipolysis media

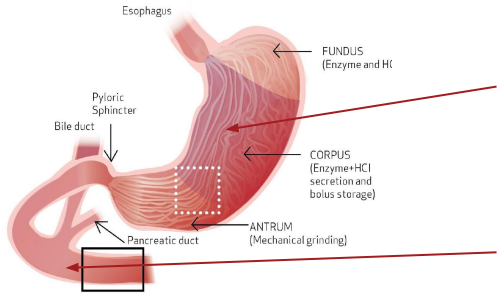
Fasted state
5 mM BS / 1.25 mM PL



Fed state
20 mM BS / 5 mM PL

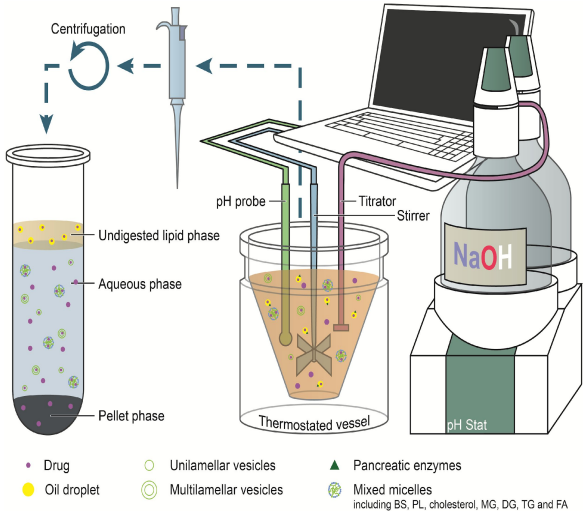


In vitro digestion (lipolysis) models
- simulating the gastro-intestinal tract



Including the stomach ?
Gastro-intestinal transfer ?

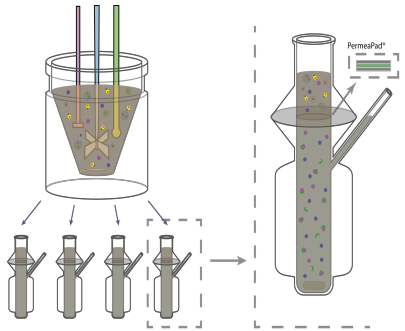
- Or only intestinal lipolysis ?



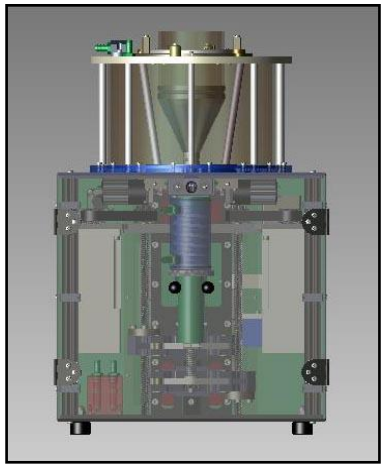
Simulating special populations: pediatrics, geriatrics – or inflammatory bowel disease

Simulating gastric hydrodynamics or emptying
(e.g. for entire dosage forms)?

Simulating preclinical species: Rats, dogs etc.



Including an absorptive step ?

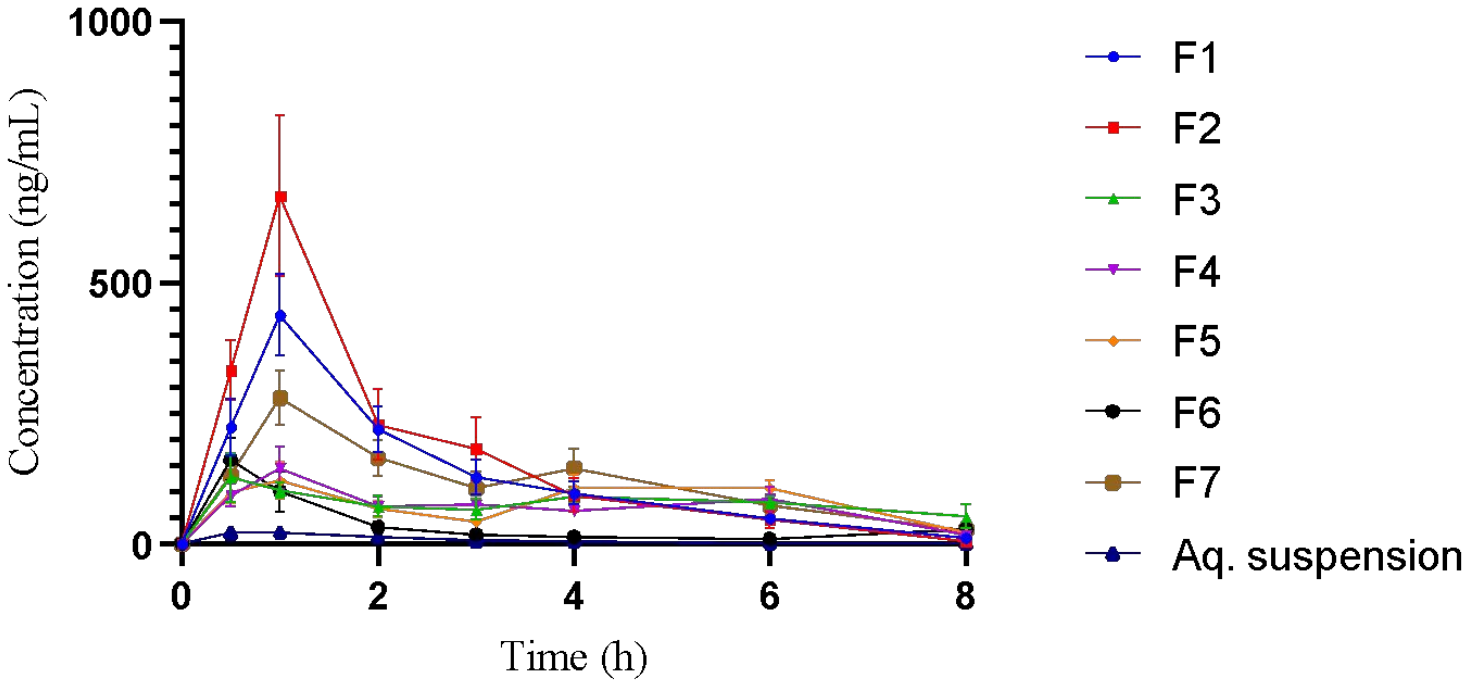


Dynamic Gastric Model

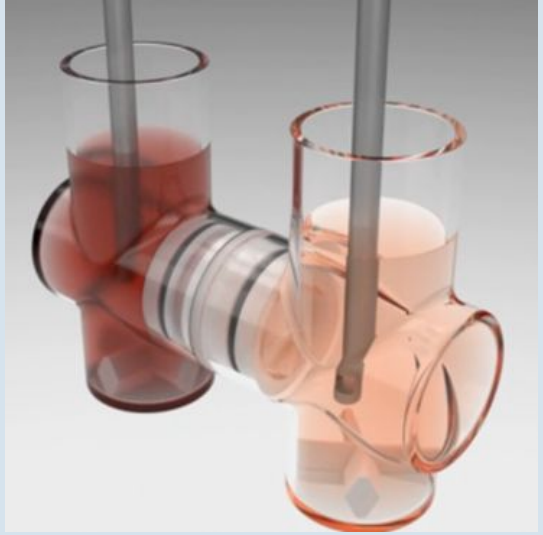
Case study - SNEDDS
In Vivo vs *In Vitro*

7 different SNEDDS – w. 80% drug load
– Oral gavage study in rats

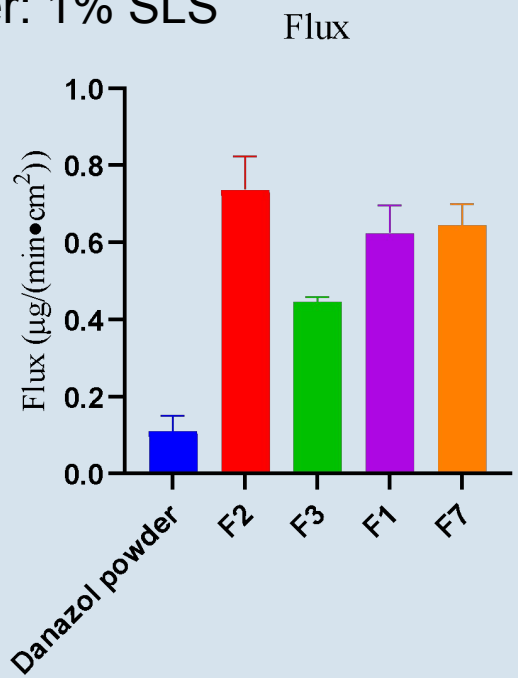
F2 > F1 > F7 > F3 = F4 = F5 = F6 > Aq. Susp.



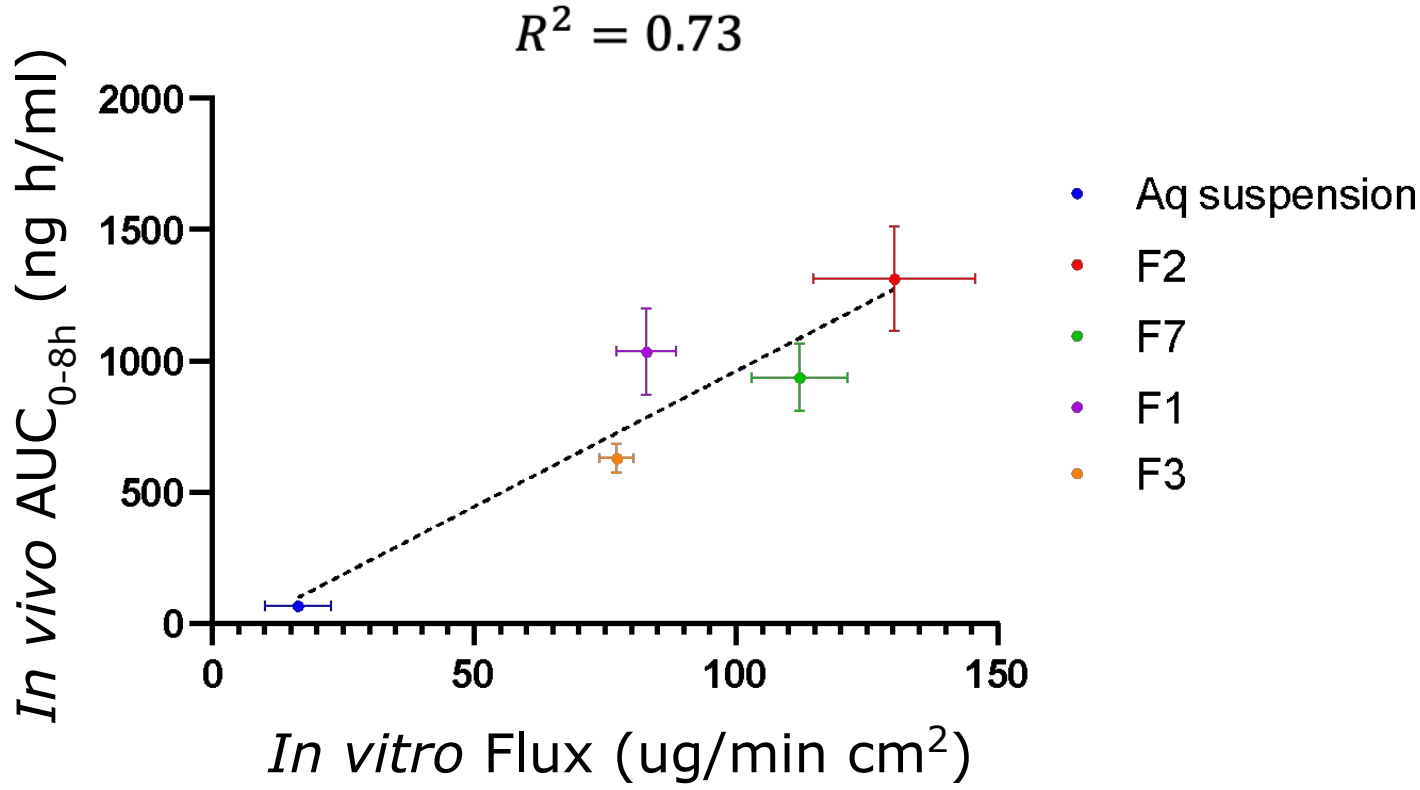
microFlux



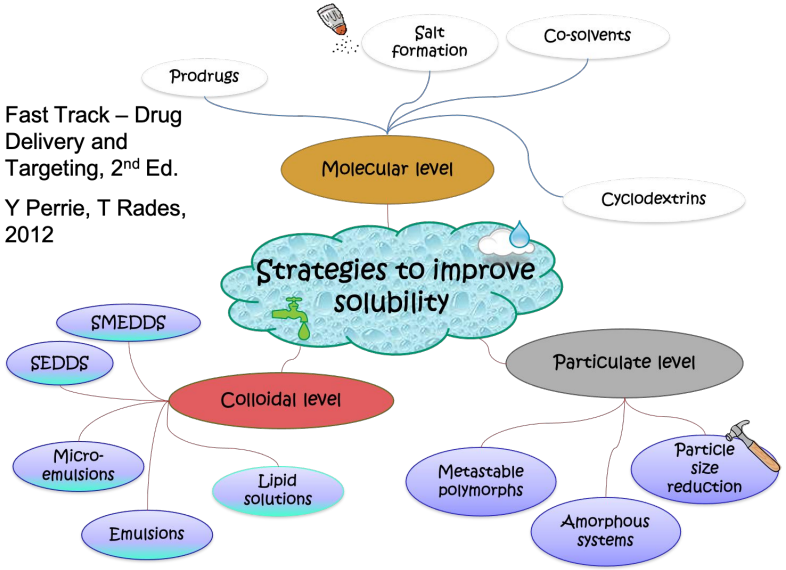
Donor: SNEDDS in FaSSIF
PAMPA membrane
Receiver: 1% SLS



Case study - SNEDDS
In Vivo vs *In Vitro*



Good *in vivo in vitro* correlation



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Y Perrie, T Rades, 2012

Enabling formulations – what to use..... ?

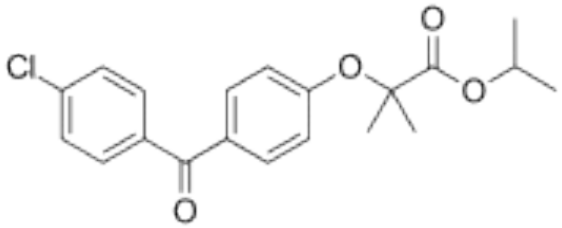
SNEDDS or amorphous solid dispersions (ASD)

Fenofibrate

Comparison of SNEDDS and amorphous solid dispersions

Determination of fenofibrate solubility:

- In SNEDDS by HPLC
- In polymers by DSC
  - and the Flory-Huggins model



Composition	%
Soybean oil	25.7
Maisine 35.1	27.5
Kolliphor RH40	35
EtOH	10

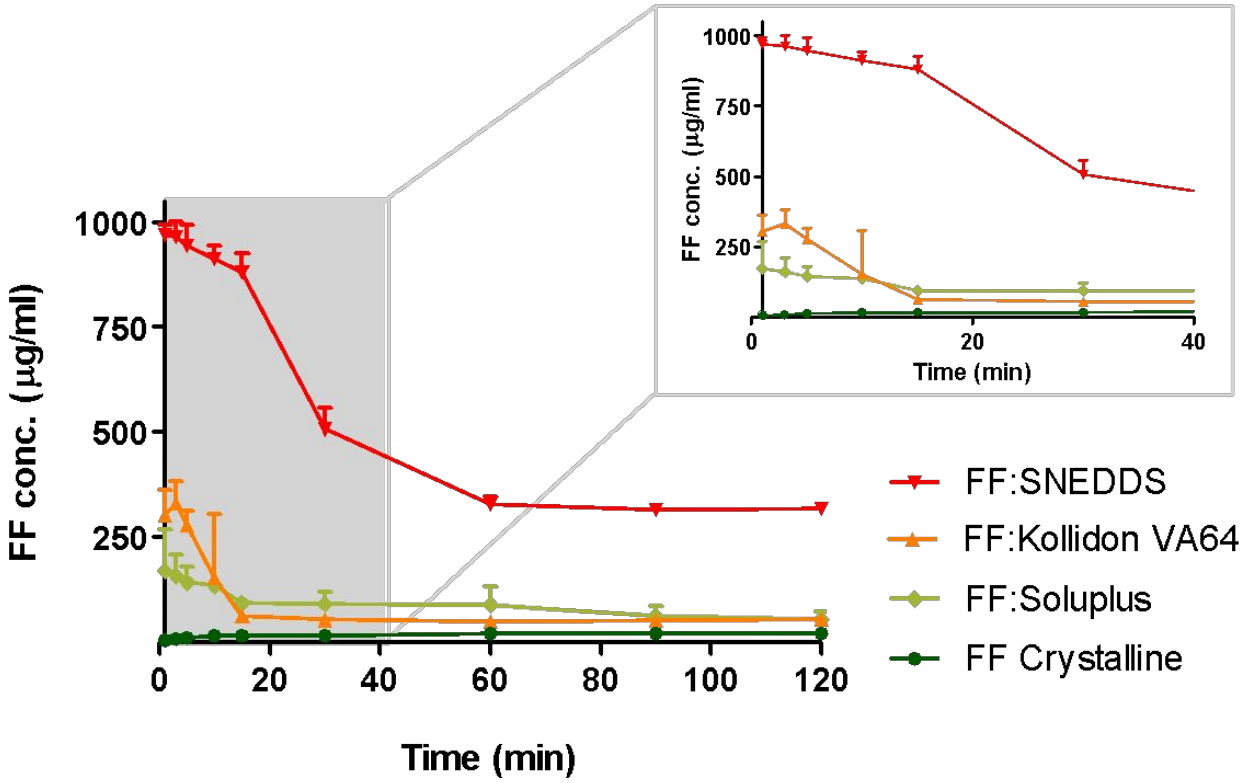
Fenofibrate selected
– due to rather similar solibility in excipients

Fenofibrate loaded to SNEDDS
at 85% of solubility

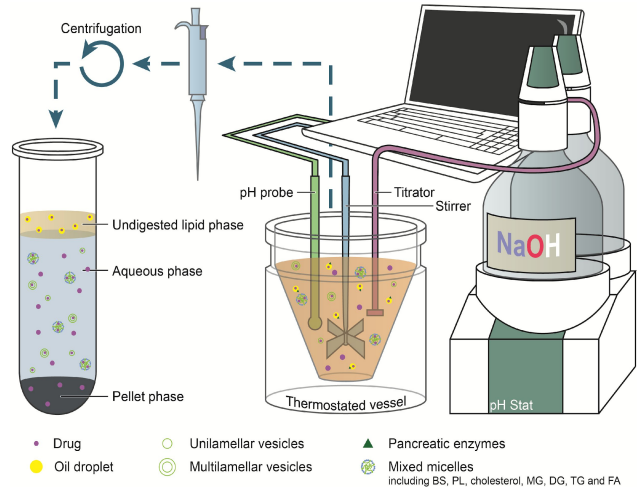
	Fenofibrate solubility (mg/g)
SNEDDS	62 ± 6
Kollidon VA64	42 (31.7-56.0)
Soluplus	43 (35.0-53.1)

Fenofibrate - *in vitro* lipolysis

Solubilisation of fenofibrate during lipolysis



Rat intestinal in vitro lipolysis



AUC - combination of dissolution rate and crystallization inhibition

	$AUC_{0\text{-}2h}$ (µg min ml^{-1})	Maximum conc. (µg ml^{-1})	Time to reach maximum conc. (min)
SNEDDS	5804 ± 282	969 ± 25	[a]
Kollidon VA64	876 ± 85	330 ± 52	[a]
Soluplus	1039 ± 240	158 ± 50	[a]
Crystalline FF	227 ± 0	22 ± 1	120

[a] Right after dosing the formulation in the vessel.

Fenofibrate - oral gavage PK *study*

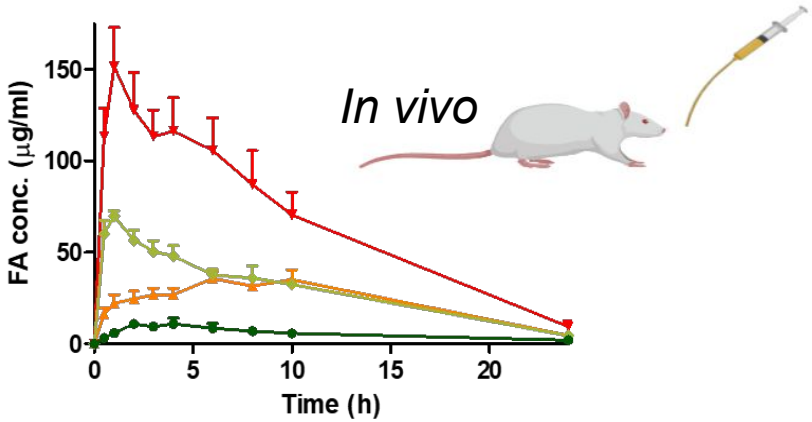
30 mg/kg dosed by oral gavage

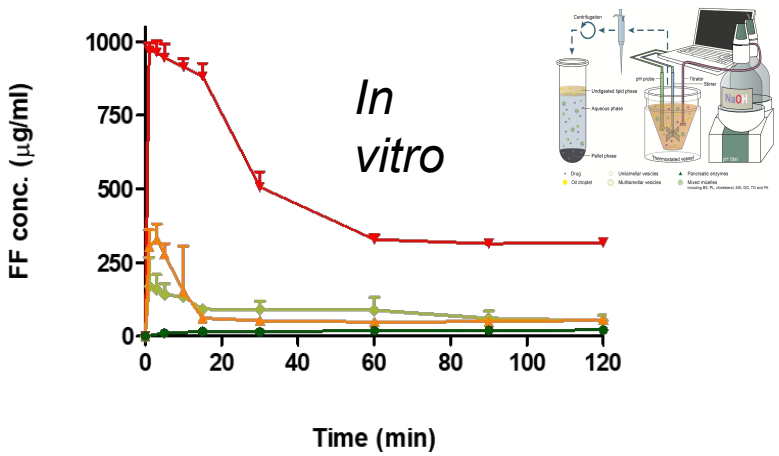
Formulations	T_{max} (h)	C_{max} (µg/ml)	$AUC_{0\text{-}24h}$ (µg h/ml)
SNEDDS	1.3 ± 0.3	151.6 ± 47.2	1570 ± 265
Kollidon VA64	5.8 ± 1.3	35.5 ± 8.8	560 ± 63
Soluplus	1.0 ± 0.2	69.7 ± 7.4	684 ± 52
Crystalline FF	2.8 ± 0.4	10.9 ± 7.7	134 ± 44

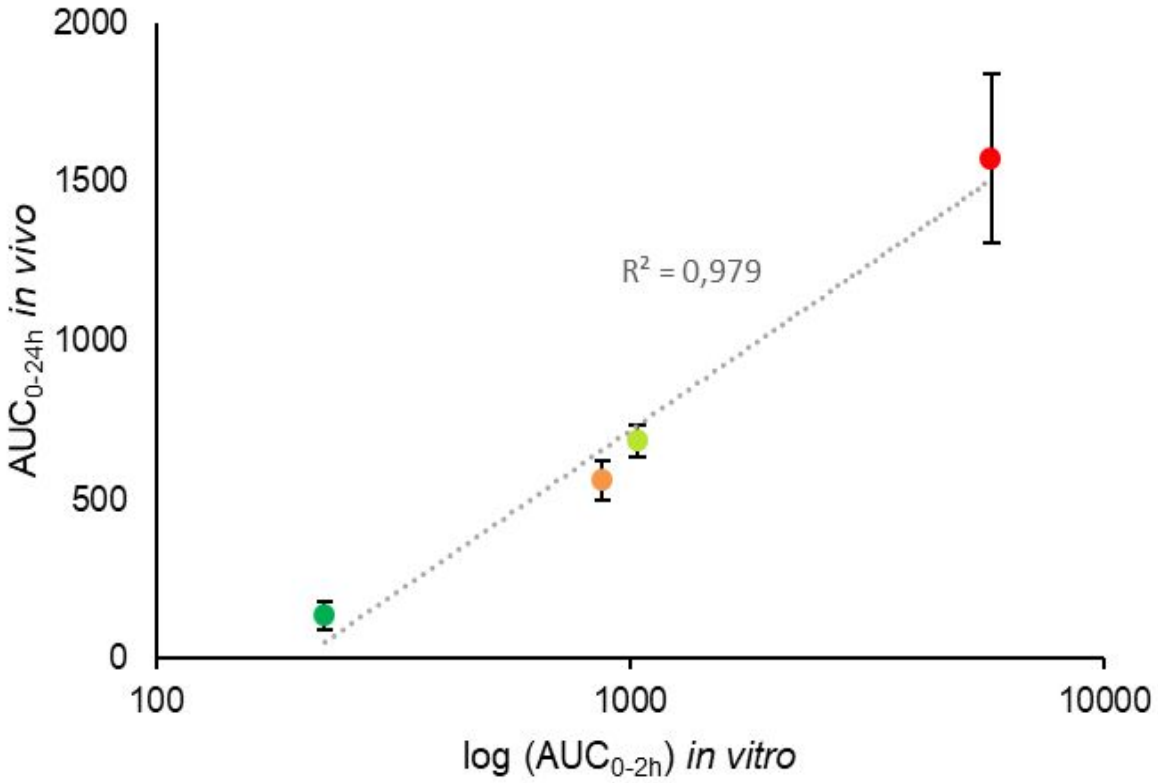
$AUC_{0\text{-}24h}$: SNEDDS>Soluplus>Kollidon VA64 >Crystalline FF

T_{max} varied from 1.0 to 5.8 h

IVIV correlation





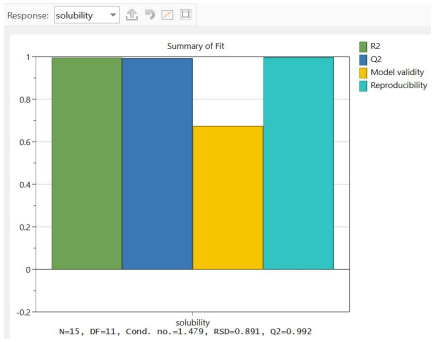


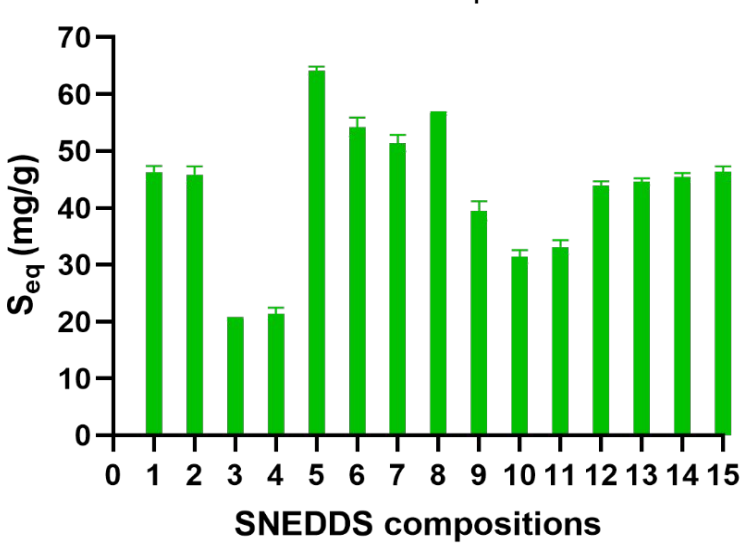
Good correlation between rat *in vivo* AUC and and *in vitro* lipolysis

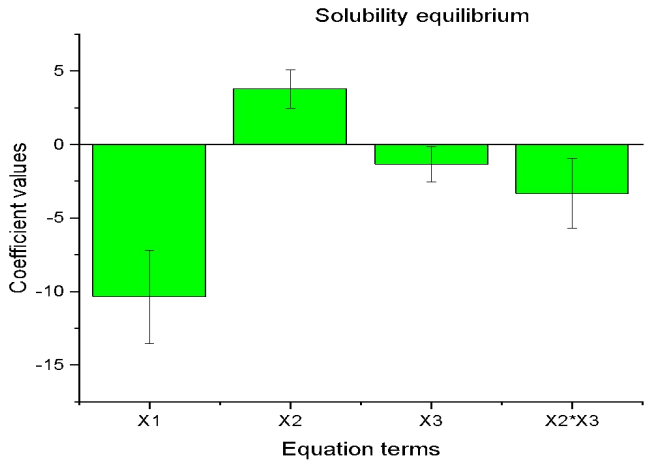
Development Strategy – SNEDDS

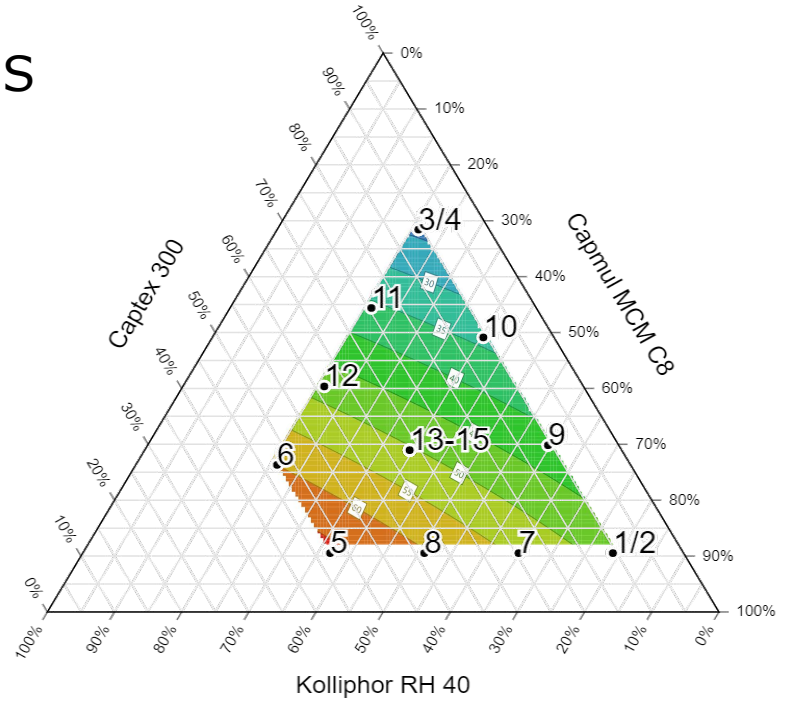
S_{eq} – carvedilol in SNEDDS (medium chain lipids & Kolliphor RH40)

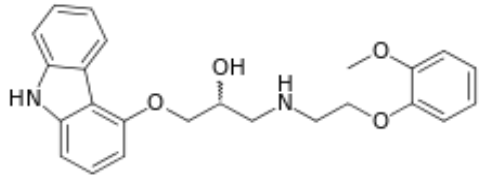
SNEDDS compositions by DoE				
	MC-TG	Kolliphor RH40	MC MG/DG	Transcutol
1	0,1	0,1	0,75	0,05
2	0,1	0,1	0,75	0,05
3	0,65	0,1	0,2	0,05
4	0,65	0,1	0,2	0,05
5	0,1	0,5	0,35	0,05
6	0,25	0,5	0,2	0,05
7	0,1	0,23	0,62	0,05
8	0,1	0,37	0,48	0,05
9	0,28	0,1	0,57	0,05
10	0,47	0,1	0,38	0,05
11	0,52	0,23	0,2	0,05
12	0,38	0,37	0,2	0,05
13	0,275	0,3	0,375	0,05
14	0,275	0,3	0,375	0,05
15	0,275	0,3	0,375	0,05











Equilibrium solubility:

- Kolliphor RH40 increases
- MCT decreases

Cases - Development of SNEDDS - and predictive in vitro models

Traditionally:

API in solution at 70-80% of SNEDDS solubility

BUT:

Solubility of API in SNEDDS is often LOW!

SO:

What about **supersaturation** .... etc…..?

super-SNEDDS preparation

prepare SNEDDS by mixing lipid, surfactant, cosolvent

add drug **above** s_{eq}(150%)

suspension

supersaturated solution

heating cycle

3 h at 60° C

cooling cycle

overnight at 37°C

super-SN EDDS

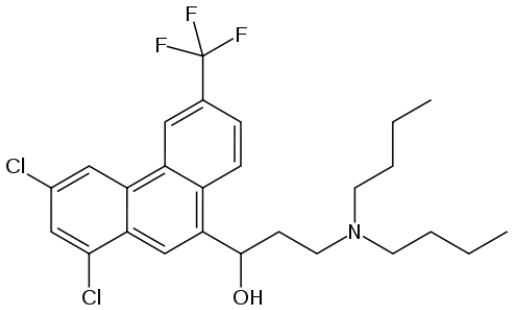
in vitro characterisation
physical stability

Physical & chemical stability in focus
To be considered upon dosing

Halofantrine Super-SNEDDS

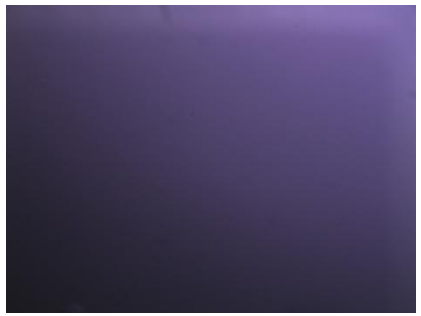
Excipient	MC
Captex 300	18.3
Capmul MCM	36.7
Cremophor RH40	35
Ethanol	10

- Antimalarial drug: $pK_a \approx 9$, logP ≈ 8.5, BCS II
  - MC-SNEDDS: 28.2 mg HAL (75%); 1x, 2x
  - MC-super-SNEDDS: 56.4 mg HAL (150%); 1x

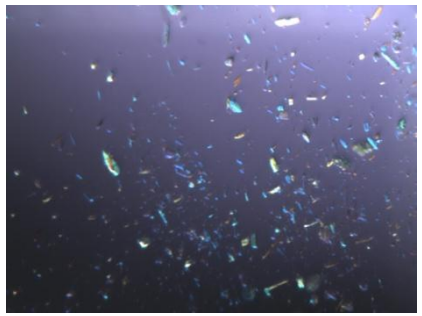


- Polarised light microscopy (PLM):
  - no drug crystals in MC-Super-SNEDDS detected
  - Stability > 8 months (25°C) in glass vials

S-SNEDDS (200%) day 0



S-SNEDDS (200%) after 8 months



Spiked SNEDDS

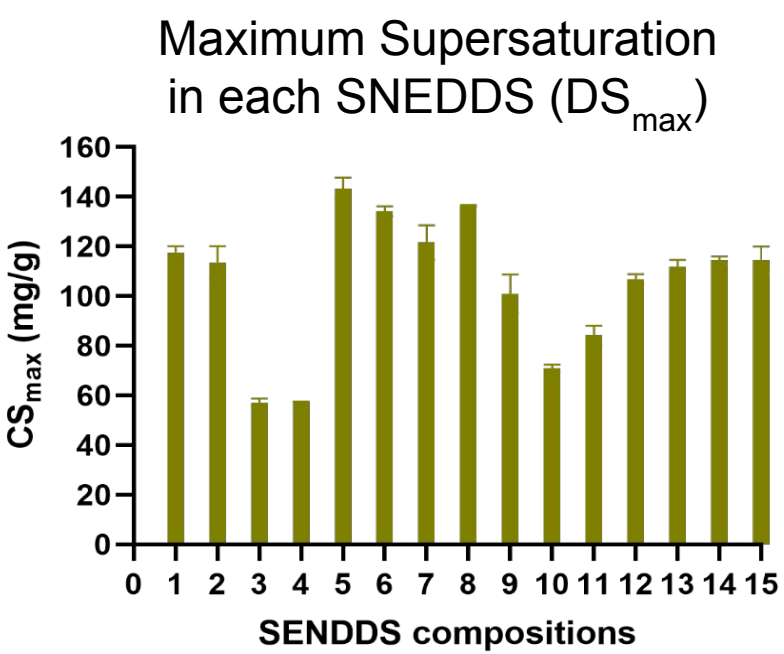
Chemical stability:

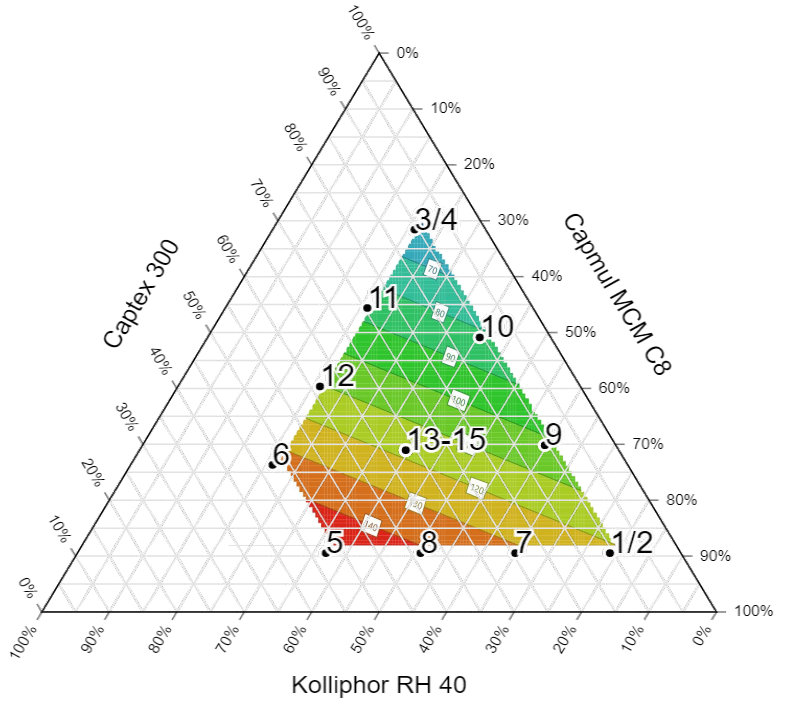
97% of declared HAL content after 5 months storage at 25°C of MC-super-SNEDDS

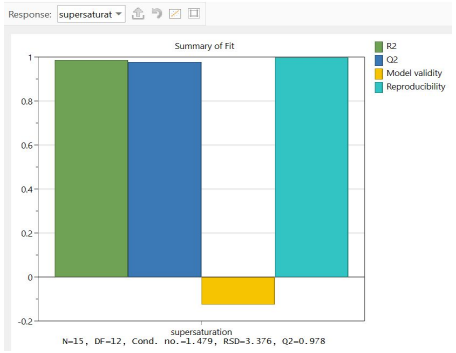
Thomas et al 2012

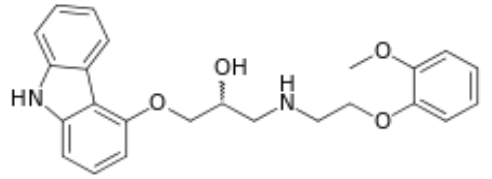
SNEDDS Excipient impact on absolute supersaturation - carvedilol

SNEDDS compositions by DoE				
	MC-TG	Kolliphor RH40	MC MG/DG	Transcutol
1	0,1	0,1	0,75	0,05
2	0,1	0,1	0,75	0,05
3	0,65	0,1	0,2	0,05
4	0,65	0,1	0,2	0,05
5	0,1	0,5	0,35	0,05
6	0,25	0,5	0,2	0,05
7	0,1	0,23	0,62	0,05
8	0,1	0,37	0,48	0,05
9	0,28	0,1	0,57	0,05
10	0,47	0,1	0,38	0,05
11	0,52	0,23	0,2	0,05
12	0,38	0,37	0,2	0,05
13	0,275	0,3	0,375	0,05
14	0,275	0,3	0,375	0,05
15	0,275	0,3	0,375	0,05





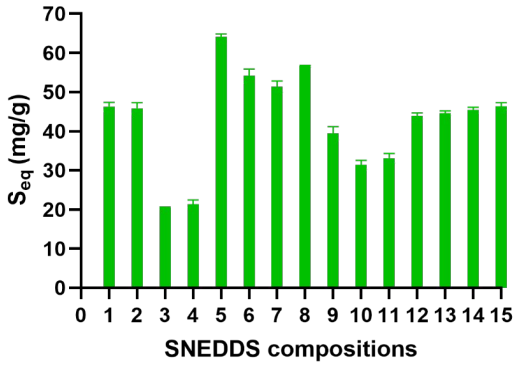




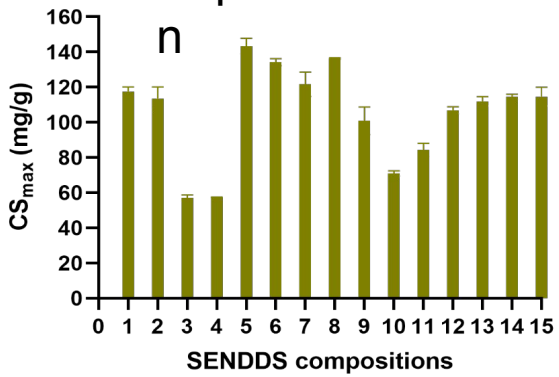
Maximum Supersaturation
- RH40 & MC MG/DG increases
- MC-TG decreases

SNEDDS Excipient impact on absolute supersaturation – carvedilol
Comparing solubility and supersaturation

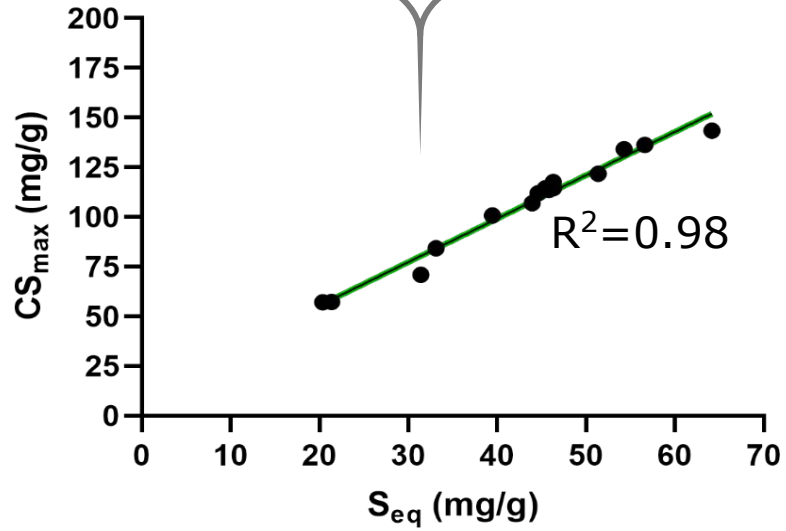
Solubility

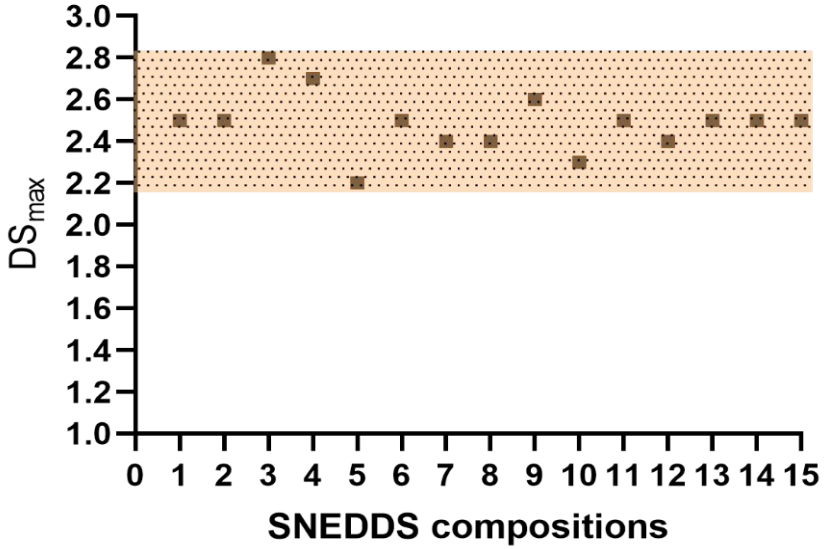


Supersaturation



S_{eq} and DS_{max} are correlating





RSD%= 5.5%

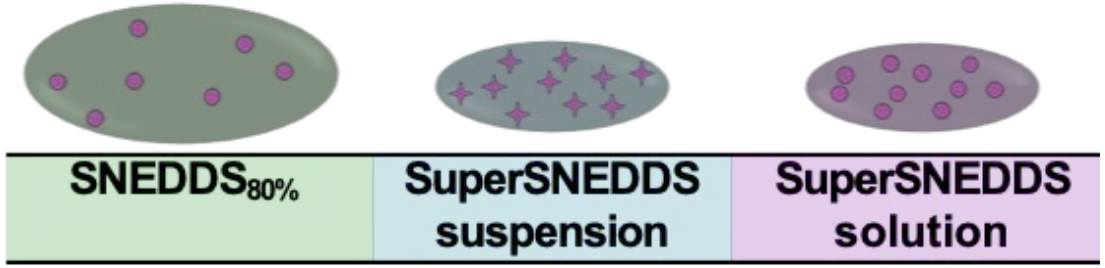
The "preferred" preclinical species – the rat

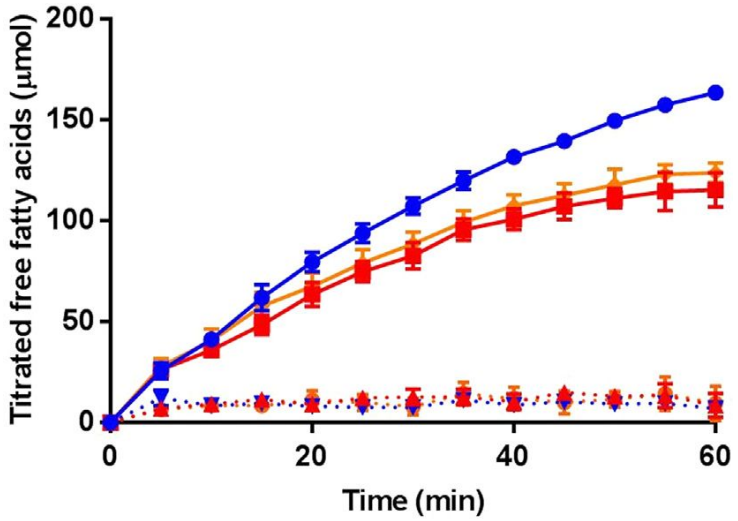
Excipient	%
Soybean oil	27.5
Maisine 35-1	27.5
Kolliphor RH40	35
Ethanol	10

Aims / research questions:

1. Does the SUPERSATURATION principle work?
2. How important is DIGESTION for absorption from SNEDDS?

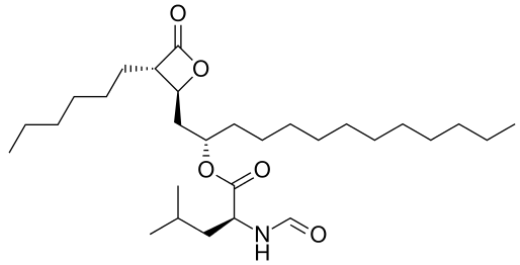
Model drug: Fenofibrate





Tool: **Orlistat** (tetrahydrolipstatin)

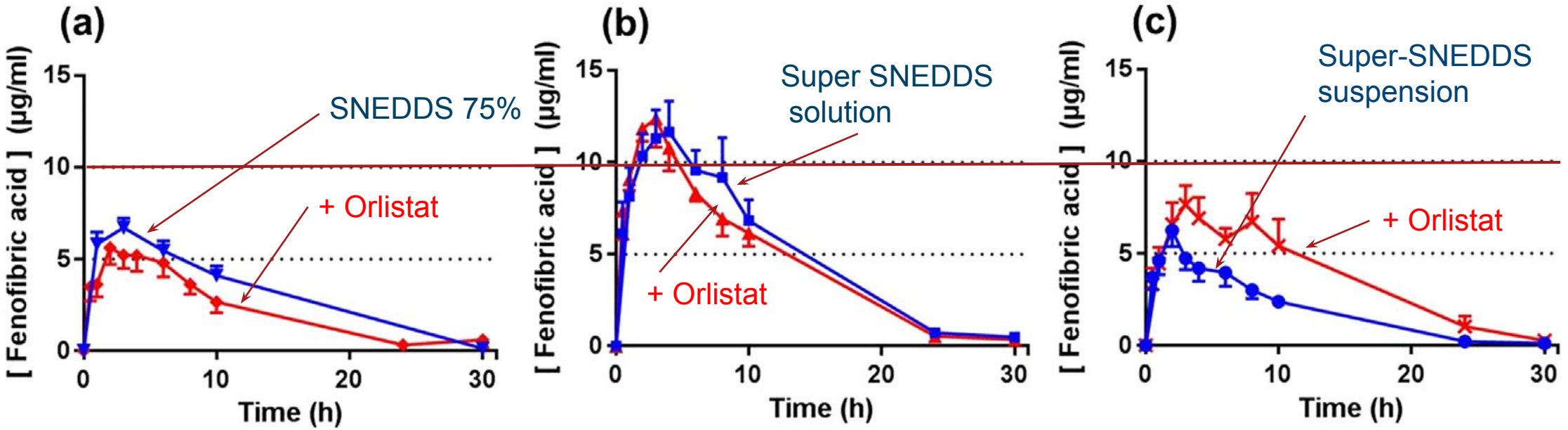
- Lipase inhibitor – lipid soluble
- Can be incorporated into SNEDDS (up to 10%)



Michaelsen et al. AAPS J 2019

Case study: Fenofibrate (Rats, 8 mg/kg)

SNEDDS approaches with & without Orlistat – in vivo PK data



Compared to SNEDDS 75%:

- Super-SNEDDS solution → AUC ↑
- Super-SNEDDS suspension → AUC →

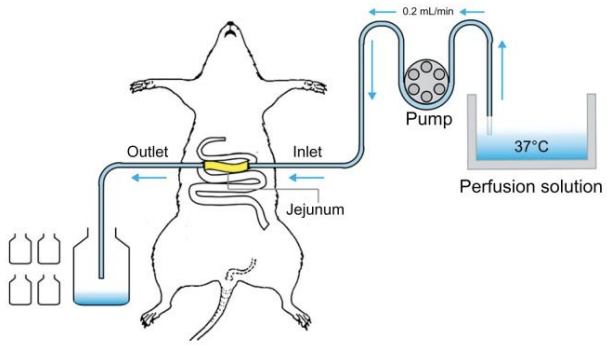
Lipolysis needed for drug absorption?

Orlistat:

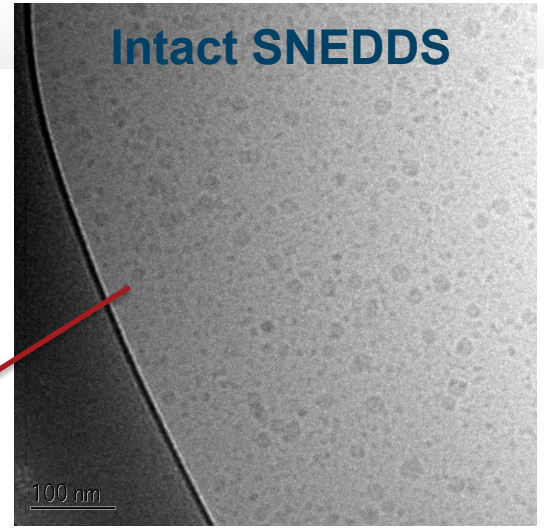
- SNEDDS 75% & Super-SNEDDs solution → AUC →
- Super-SNEDDS suspension → AUC ↑

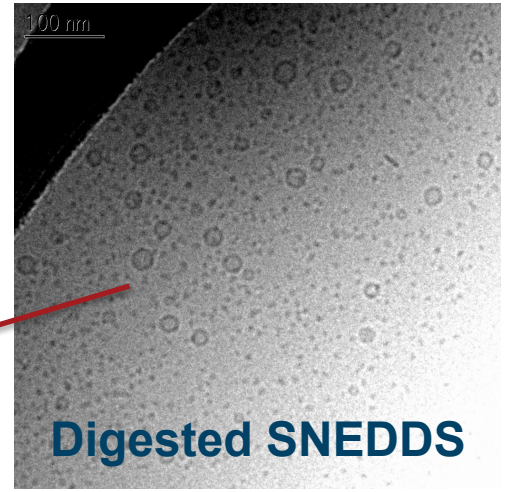
Michaelsen et al. EJPB 2019

Intestinal perfusion in rats

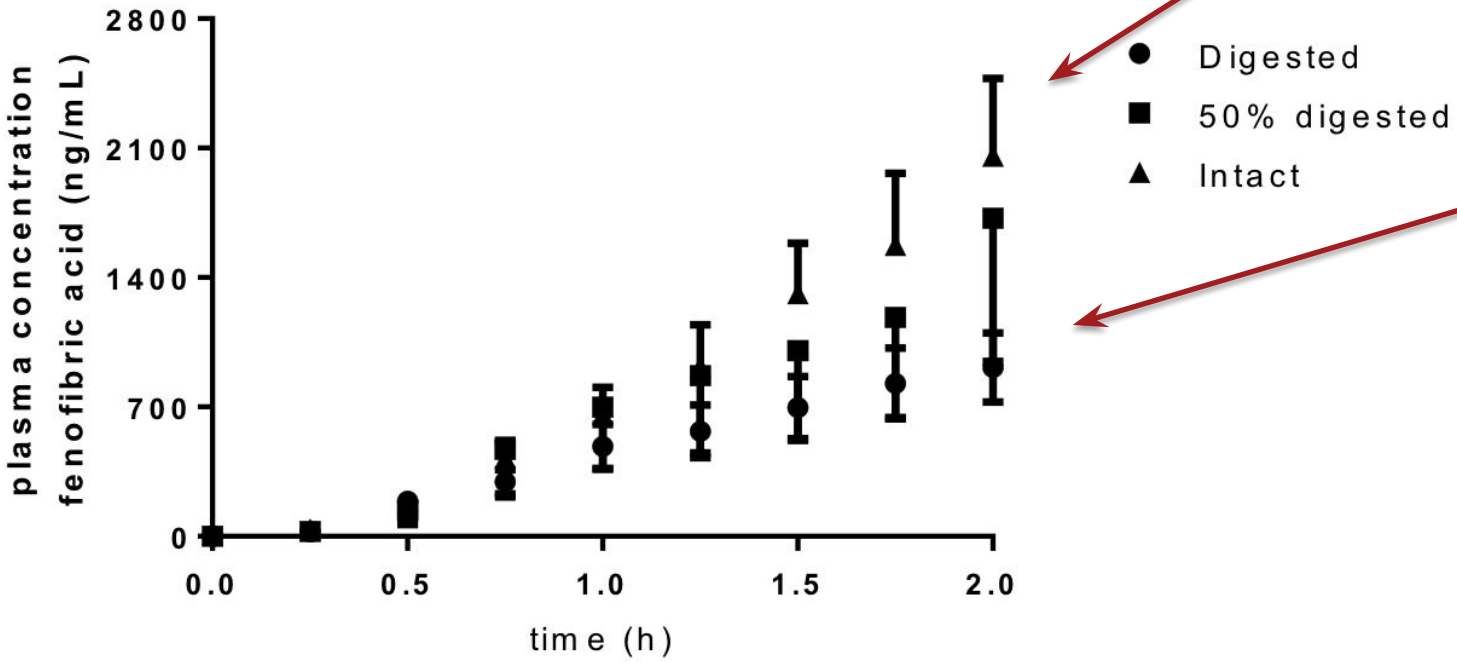


Digested SNEDDS:
Sesame oil replaced by fatty acids : monoglyceride (2:1) with the same fatty acid composition





Model drug:
Fenofibrate / Fenofibric acid



Excipient	SNEDDS
Sesame oil	20.6
Oleic acid	15.4
Cremophor RH40	45
Brij 97	9
Ethanol	10

Supersaturation and lipid drug delivery

	Halofantrin	Simvastatin	Cinnarizine	Danazol	Fenofibrate	R3040	Carvedilol	Loratidine
Phys chem	Weak base LogP 8 pKa 6.9	Neutral LogP 4.6	Weak base LogP 5.8 pKa_1 2.7 pKa_2 7.5	Neutral LogP 4.5	Neutral LogP 4.6	Neutral LogP	Weak base LogP 8 pKa 6.9	Weak base LogP 3.9 pKa 5.3
Supersaturation in oil (preconcentrate)	Yes (10 month)	Yes (10 month)	Short-term	Yes (days)	Short-term	Yes	?	?
Supersaturation during lipolysis	No	Yes (possibly)	No	Yes	?	No	?	?
Precipitate during lipolysis	amorphous	amorphous	amorphous	crystalline	crystalline	amorphous	amorphous	amorphous
Super-SNEDDS Increase BA compared to SNEDDS	Yes	Yes	No	?	Yes	=	?	?
Chasing Principle works ?	No	?	Yes	Yes	?	No	?	?

Supersaturation and lipid drug delivery

	Halofantrin	Simvastatin	Cinnarizine	Danazol	Fenofibrate	R3040	Carvedilol	Loratidine
Phys chem	Weak base LogP 8 pKa 6.9	Neutral LogP 4.6	Weak base LogP 5.8 pKa_1 2.7 pKa_2 7.5	Neutral LogP 4.5	Neutral LogP 4.6	Neutral LogP	Weak base LogP 8 pKa 6.9	Weak base LogP 3.9 pKa 5.3
Supersaturation in oil (preconcentrate)	Yes (10 month)	Yes (10 month)	Short-term	Yes (days)	Short-term	Yes	?	?
Supersaturation during lipolysis	No	Yes (possibly)	No	Yes	?	No	?	?
Precipitate during lipolysis	amorphous	amorphous	amorphous	crystalline	crystalline	amorphous	amorphous	amorphous
Super-SNEDDS Increase BA compared to SNEDDS	Yes	Yes	No	?	Yes	=	?	?
Chasing Principle works ?	No	?	Yes	Yes	?	No	?	?

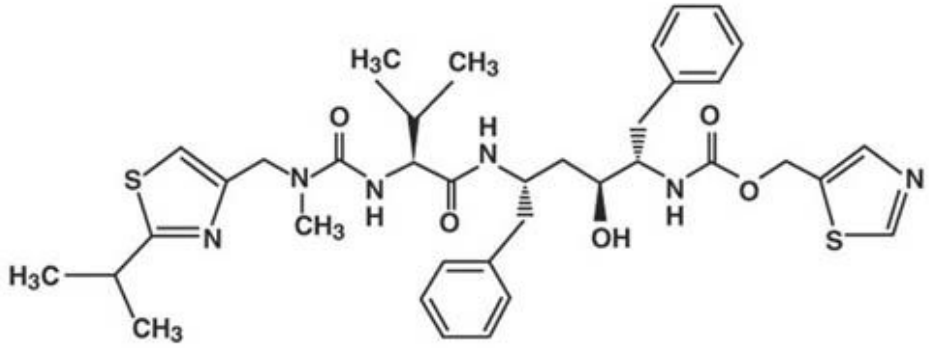
Other ways of increasing the dose in SNEDDS.... ?

SuperSNEDDS, polymers and amorphous solid dispersions (ASD)

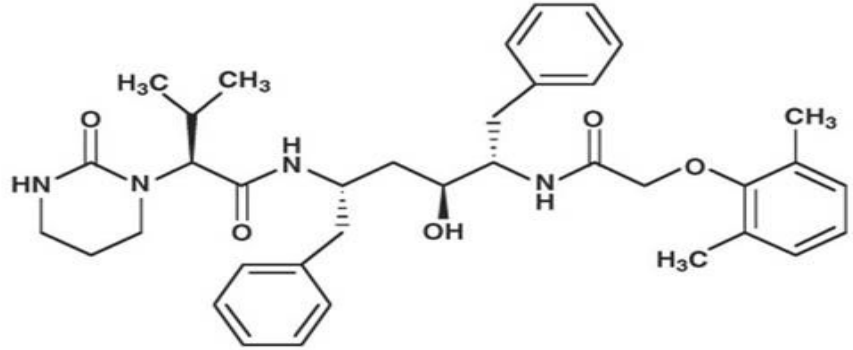
Model drugs

Physiochemical properties:

	Ritonavir	Lopinavir
Formula	$C_{37}H_{48}N_6O_5S_2$	$C_{37}H_{48}N_4O_5$
MW(g/mol)	720.95	628.8
Log P	3.9	5.9
Aqueous solubility at 25℃ (μg/mL)	3	7
T_m℃	122.3	96
T_g℃	50	70
pKa	2.8	-
ΔH (Kcal/mol)	4.3	-3.8

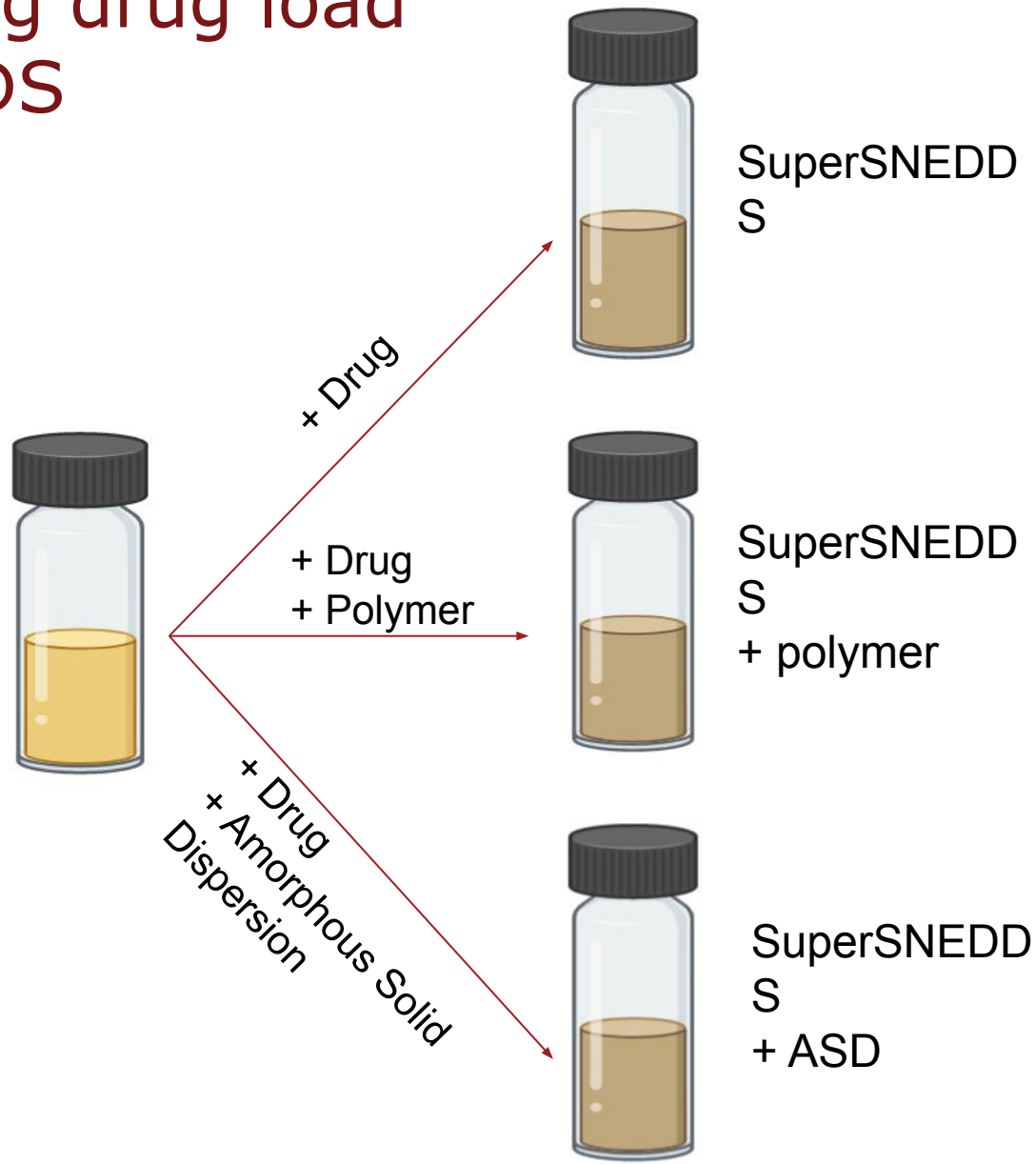


ritonavir



lopinavir

Increasing drug load in SNEDDS



Polymers:

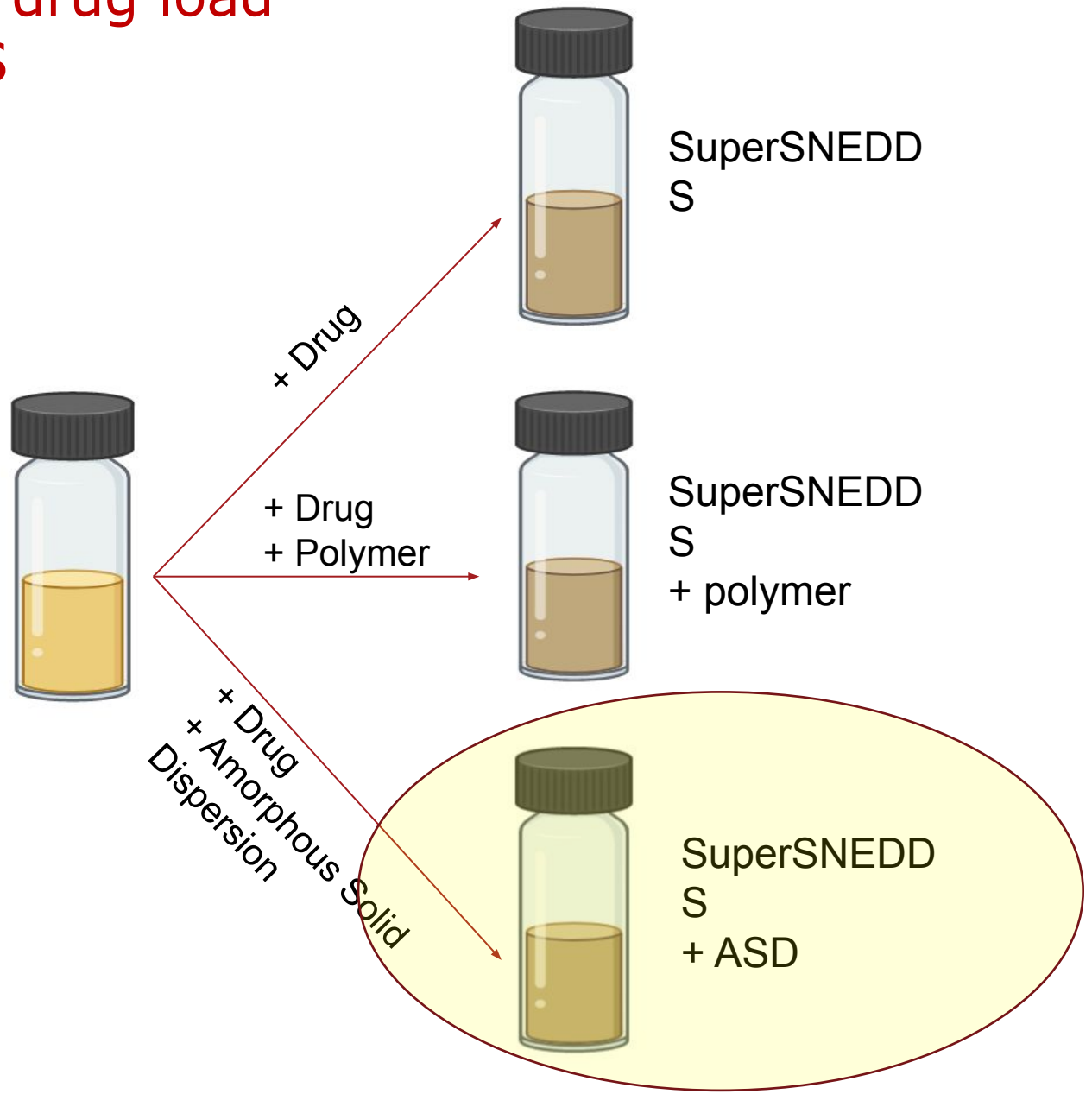
Precipitation inhibitor s

- in SNEDDS and dispersion

Effect on solubility in SNEDDS?

- Degree of supersaturation
- Stability
- In vitro lipolysis
- In vivo pharmaco-kinetics

Increasing drug load in SNEDDS



Polymers:

Precipitation inhibitor s

- in SNEDDS and dispersion

Effect on solubility in SNEDDS?

- Degree of supersaturation
- Stability
- In vitro lipolysis
- In vivo pharmaco-kinetics

Ritonavir - amorphous solid dispersion (ASD)

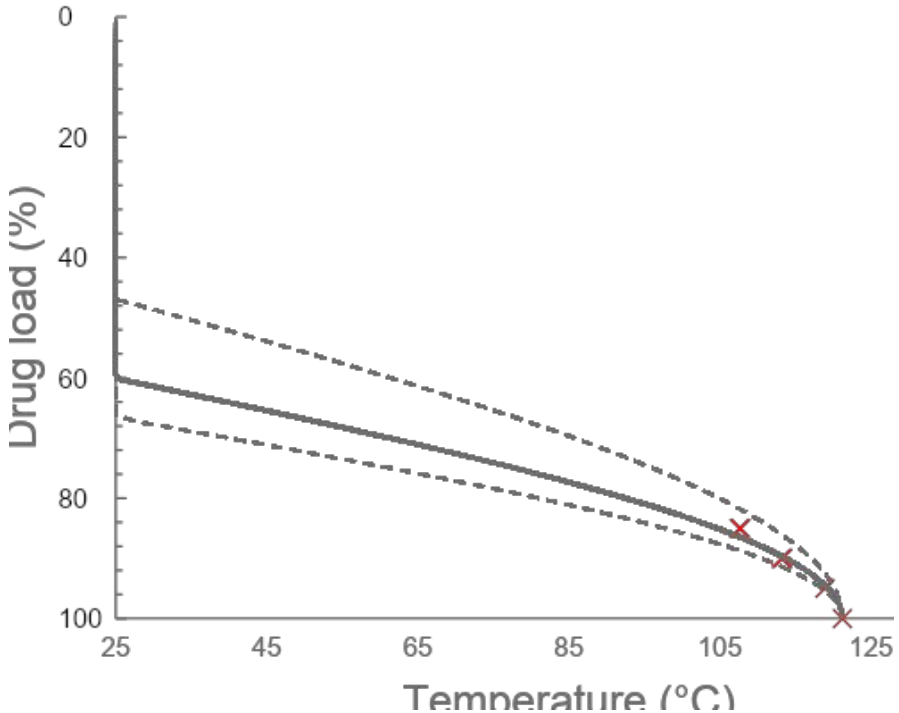
Ritonavir solubility in PVPVA64

Determined by DSC

- and the Flory-Huggins model

Solubility in polymer

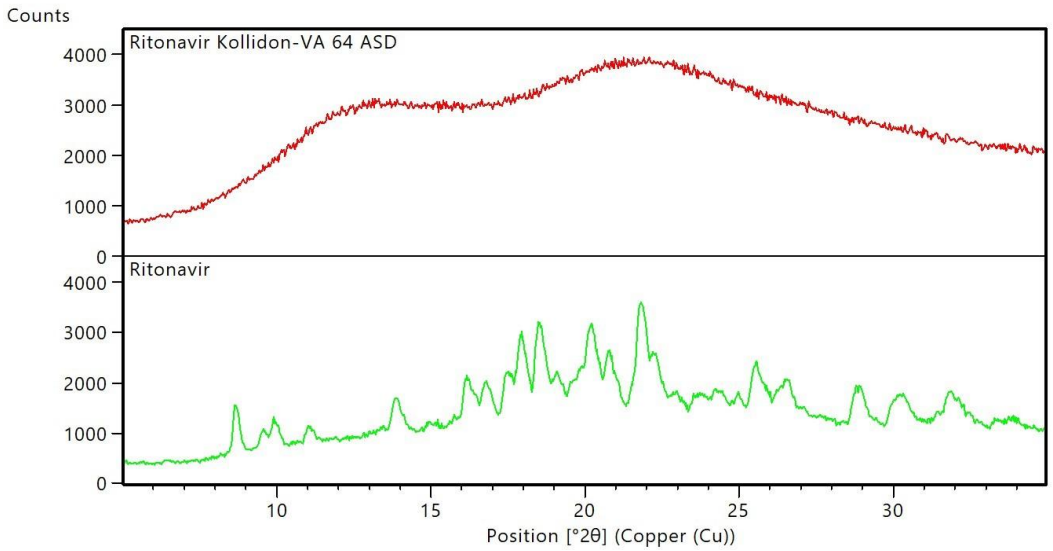
= 0.60 w/w



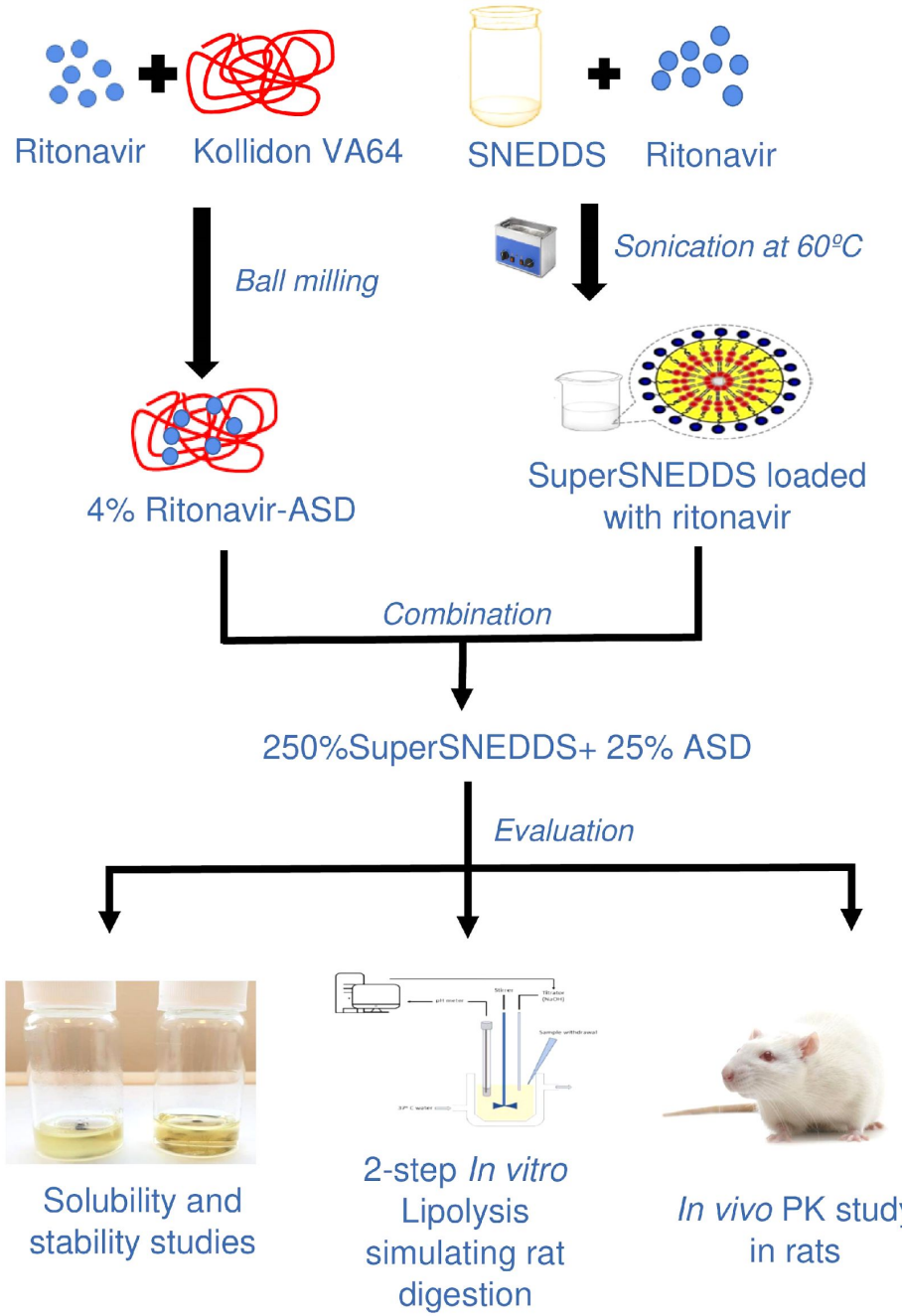
ASD with ritonavir – at 50% of solubility in PVPVA64 - was produced by ball-milling

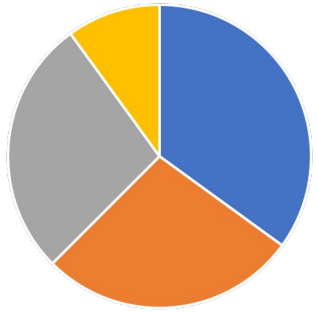
- and added to SNEDDS

Combining SNEDDS and ASD:
Ritonavir, Kollidon VA64 and SNEDDS



	%Saturation*	Concentration	Stability
Ritonavir 250%	250%	22.6±1,7 mg/g	48 hours
Ritonavir 250% +25%ASD[a]	275%	25.0±0,2 mg/g	1 month

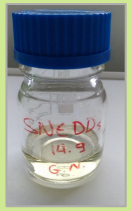




Combining SNEDDS and ASD

Crystalline drug in SNEDDs

(Concentration below Seq)



Stirring at 25°C

(1hr)

Conventional SNEDDS 90% Seq

Ball milling

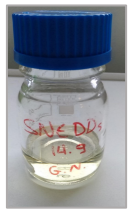
Crystalline drug +Polymer

30Hz, 4°C
90min-5min-90min

ASD

Crystalline drug in SNEDDs

(Concentration above Seq)



Sonication at 60 °C
(1hr)
Heating at 60 °C
(3hr)

Stirring at 37 °C

(overnight)

Supersaturated SNEDDS 250% S_{eq}

Addition of **polymer**

Adding drug
Stirring at 37 °C

(overnight)

Supersaturated SNEDDS w polymer & drug 275% Seq

Addition of **ASD**

Stirring at 37 °C

(overnight)

Supersaturated SNEDDS w ASD 275% Seq

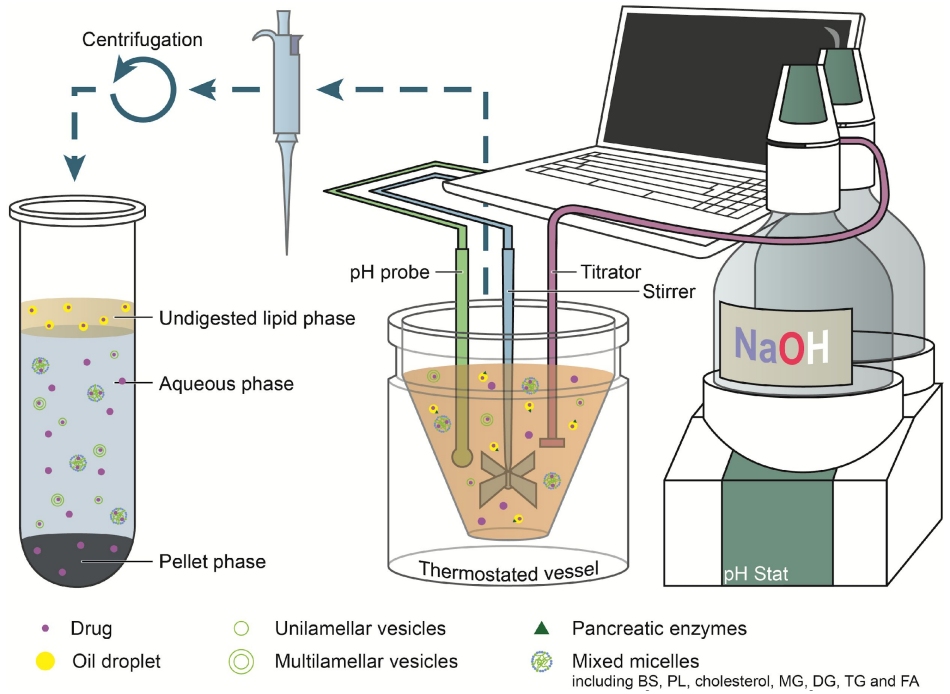
Gastro-intestinal *in vitro* lipolysis (rat model)

Two-compartment in vitro lipolysis

Composition of simulated gastric and intestinal media

Components	Gastric Medium composition	Intestinal Medium Composition
Bile salts (mM)	1.3	24.1
Phospholipids (mM)	0.8	3.7
Sodium Chloride (mM)	111.7	119.6
Hepes (mM)	-	17
HCl (mM)	4	-
Calcium Chloride (mM)	-	1.4
pH	2.4	7.5
Enzyme activity (U/mL)	450 U/mL (pepsin) 50 U/mL (Rhiz. Lipase)	179 USP/mL (pancreatin)

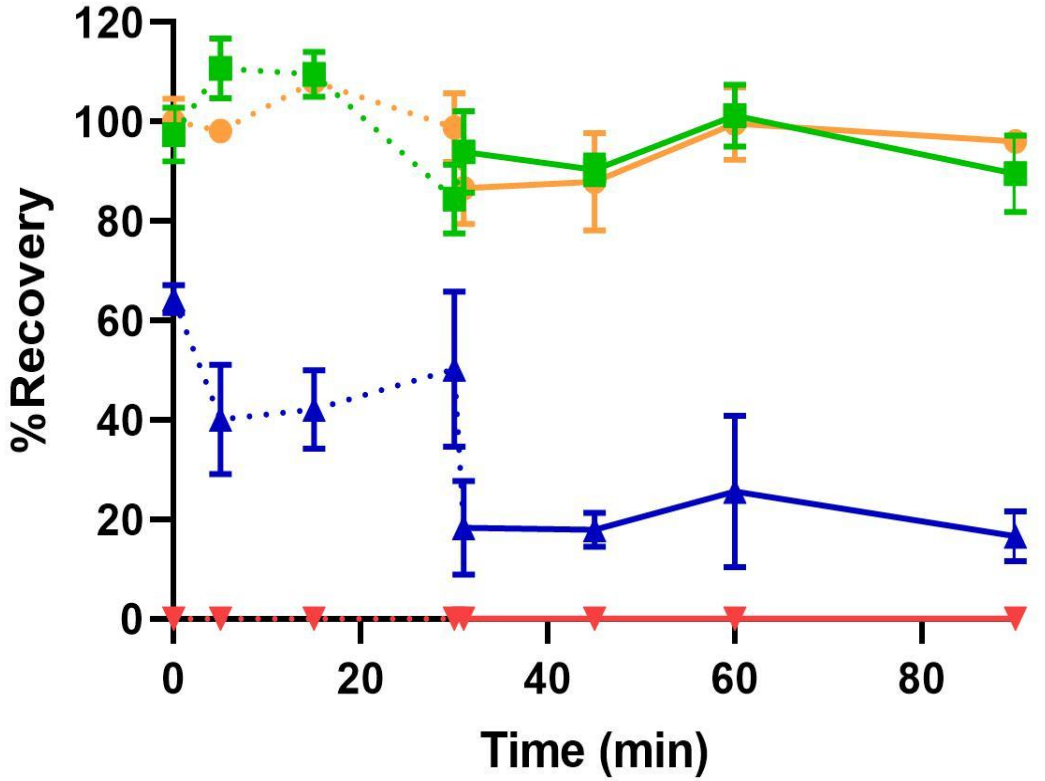
Enzyme inhibition



Two-compartment *in vitro* lipolysis (rat model)

In vitro lipolysis of ritonavir formulations

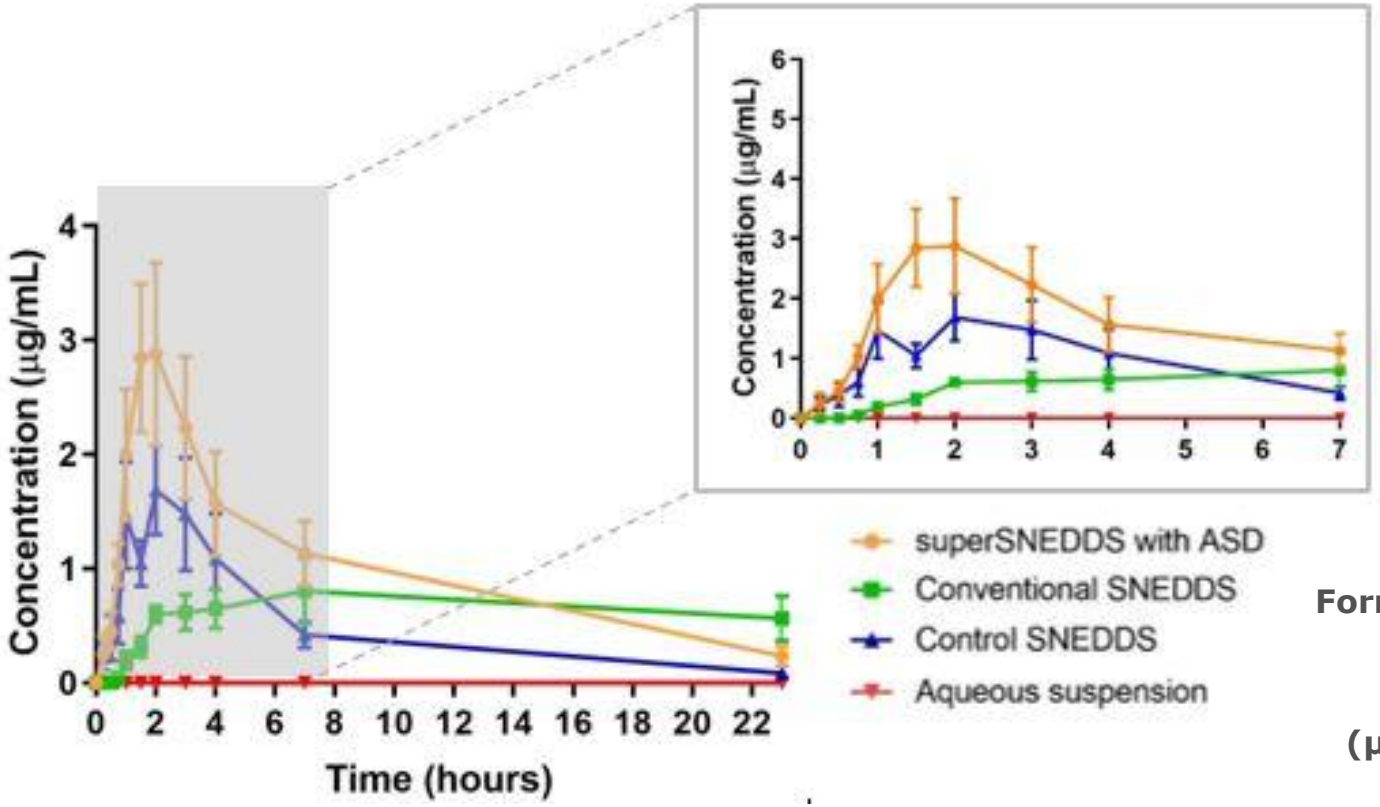
Sample	Composition of formulations					Ritonavir in formulation (mg)	Ritonavir dosed (mg)	Lipid dosed (mg)
	Cryst. Ritonavir (mg)	ASD (mg)	Kollidon VA 64 (mg)	SNEDDS (mg)	H2O (mg)			
Super SNEDDS with ASD	23.3	55.3	-	976.7	-	25.7	25.7	976.7
Conventional SNEDDS	8.4	-	-	991.6	-	8.4	25.7	3024.4
Super SNEDDS w P &C	25.7	-	53.0	976.7	-	25.7	25.7	976.7
Aqueous Suspension	25.7	-	-	-	974.3	25.7	25.7	-

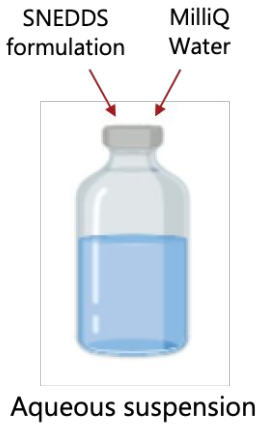


%Recovery – time profile of ritonavir in SNEDDS after *in vitro* lipolysis.

%Recovery = Danazol conc in aqueous phase *100/ danazol conc in total Sample

Pharmacokinetic study in rats





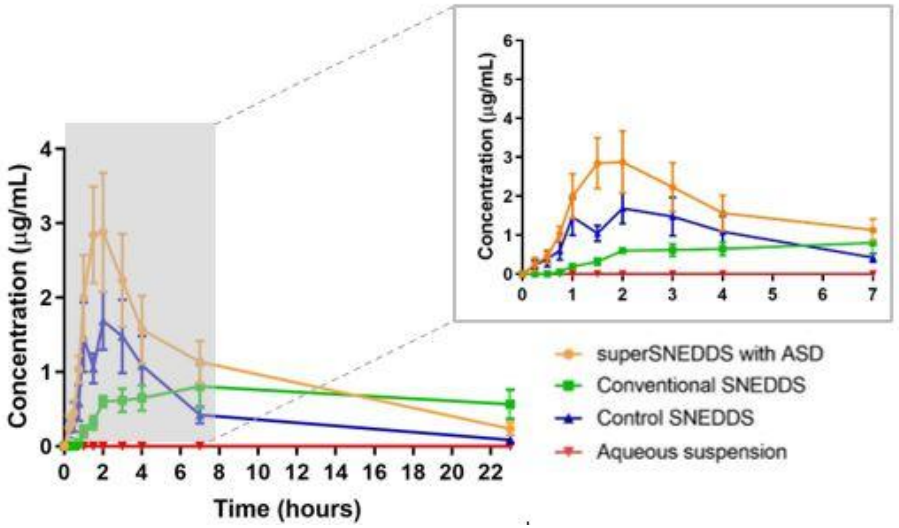
Ritonavir dose: 11 mg/rat

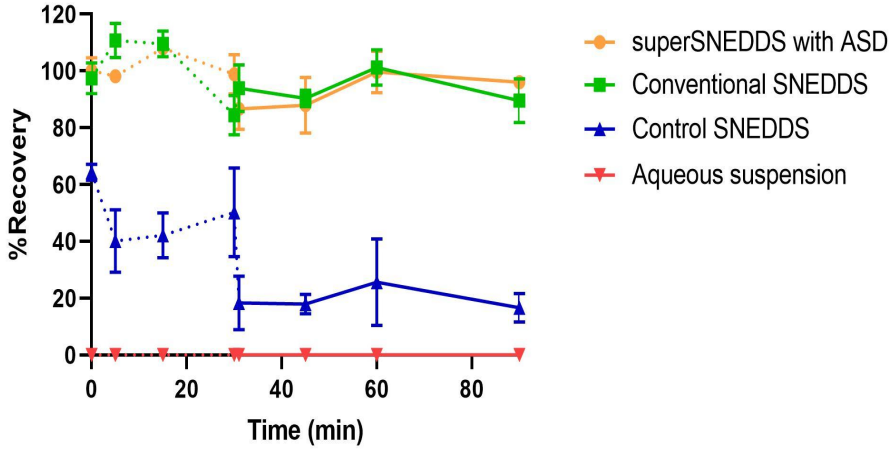
SNEDDS dose:
SuperSNEDDS - 418 mg/rat
Conv. SNEDDS - 1294

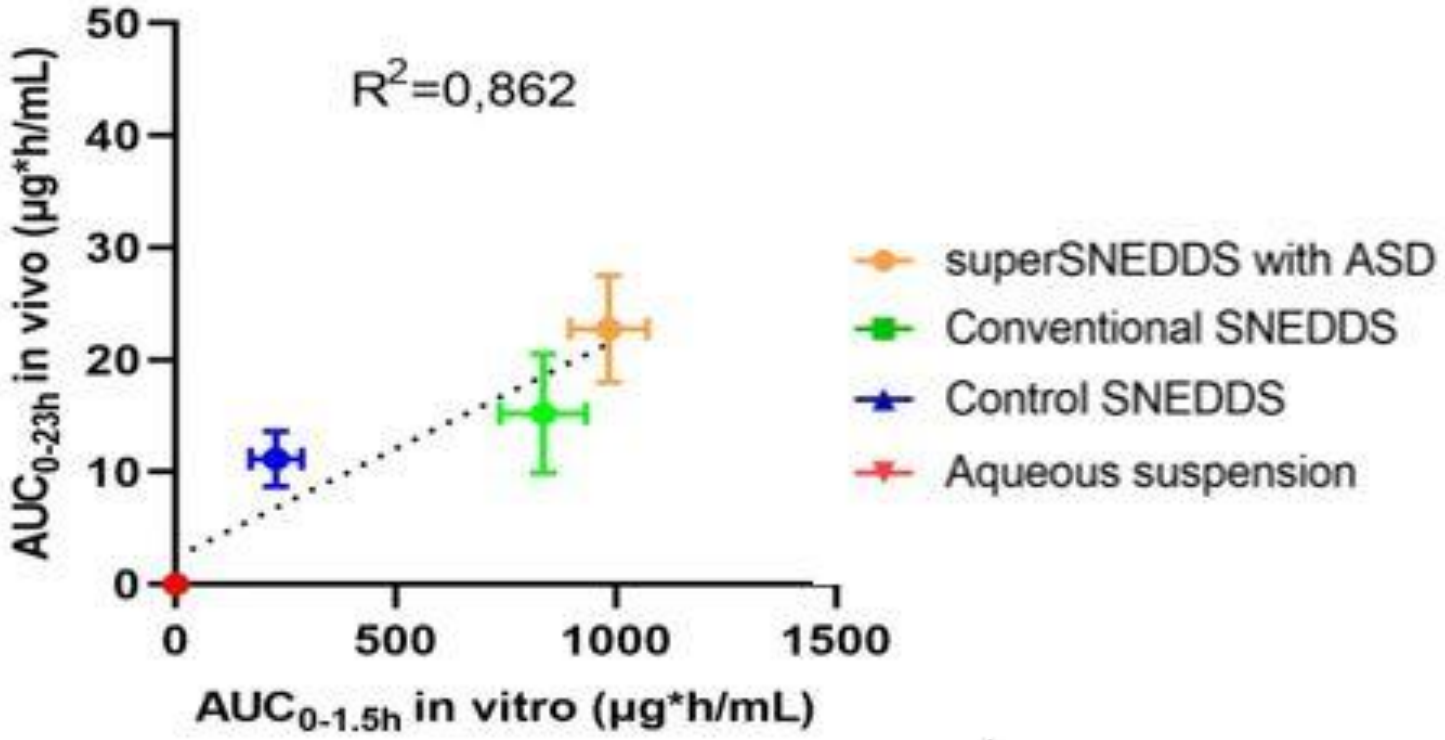
Formulation	Super SNEDDS w ASD	Conven-tional SNEDDS	Super SNEDDS w P D	Aqueous suspension
C_{max} (µg/mL)	3.2 ± 0.6	1.0 ± 0.2	1.9 ± 0.3	0.0 ± 0.0
T_{max} (h)	1.7 ± 0.2	4.5 ± 1.3	1.5 ± 0.2	0.0 ± 0.0
AUC_{0-7h} (µg.h.mL-1)	**11.8 ± 5.7[e]**	**3.9 ± 1.7[f]**	**7.2 ± 4.0**	**0.0 ± 0.0**
AUC_{0-23h} (µg.h.mL-1)	22.8 ± 5.8	14.8 ± 5.7	11.0 ± 2.9	0.0 ± 0.0

Data presented as mean ± SEM (n=4-6)

In vivo – in vitro correlation

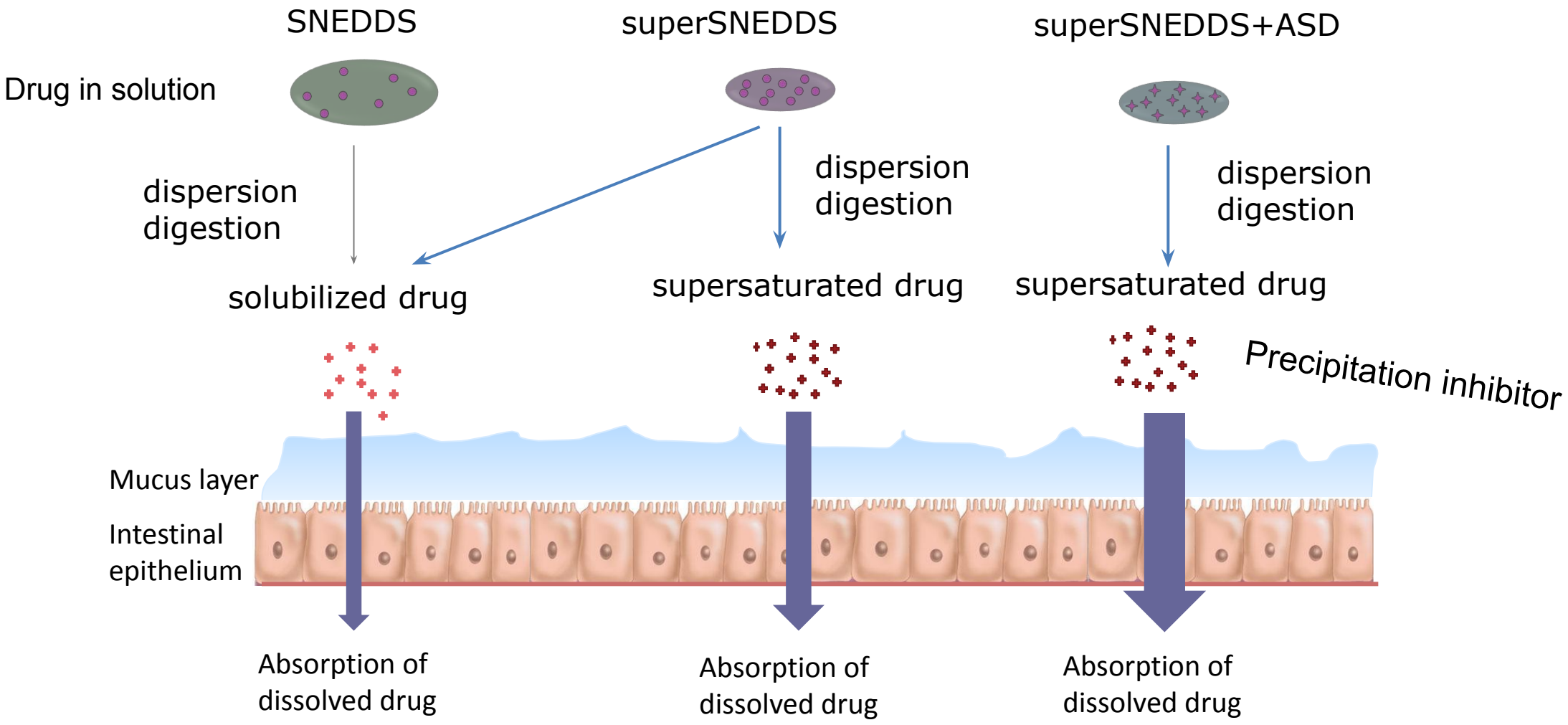






Correlation between in vitro and in vivo rat model obtained – for AUC

Drug absorption from SNEDDS



Conclusion I - superSNEDDS

Drug are dosed in **solution – below S_{eq}**
in Lipid-based Drug Delivery Systems (LbDDS)

Solubility in SNEDDS is often low – leading to high excipient dose

Supersaturated SNEDDS – and suspensions also work – for some drugs!

- This makes the use of lipids more versatile!

When developing SNEDDS, consider API properties:

- Propensity to supersaturate in lipids
- Propensity to supersaturate during *in vitro* digestion
- Crystalline / amorphous precipitation *in vitro* digestion
- Etc

Conclusion II – SuperSNEDDS with Polymer or ASD

Polymer in SNEDDS:

- The polymer (PVP VA64) dissolve in SNEDDS
  - and acts as a precipitation inhibitor in the SNEDDS

ASD in SEDDS:

- ASD can dissolve in SEDDS - and stabilise supersaturation

***In vitro / in vivo*:**

- Creating **supersaturation** – often **promote absorption**
- But what is the **mechanism?**
  - Where is the drug ?
    - in the oil droplets ?
    - In the aqueous phase ?
- PVP VA64 also work as precipitation inhibitor in the aqueous phase after dispersion

The Physiological Pharmaceutics Research Group

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Thank you for your attention

Questions?

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