VolkswagenStiftung

MARTIN-LUTHER-UNIVERSITÄT HALLE-WITTENBERG

MUHAS

UFZ

Workshop

Drug lifecycle control in Subsaharan Africa

From production to responsible safe disposal and elimination in wastewater treatment plants

(Med4Africa)

MARTIN-LUTHER-UNIVERSITÄT
HALLE-WITTENBERG

Formulation of antimalaria drugs: challenges and solutions

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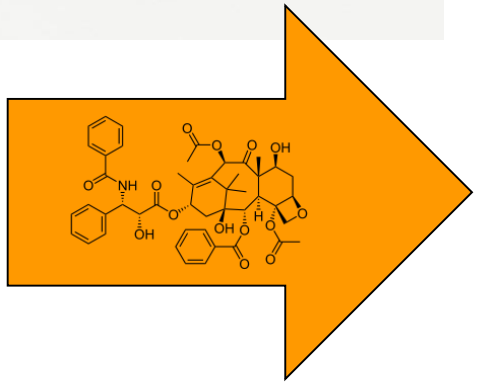
Drug therapy (aim)



Illness

How does the drug know where to go?

Health

Drugs

Wish list

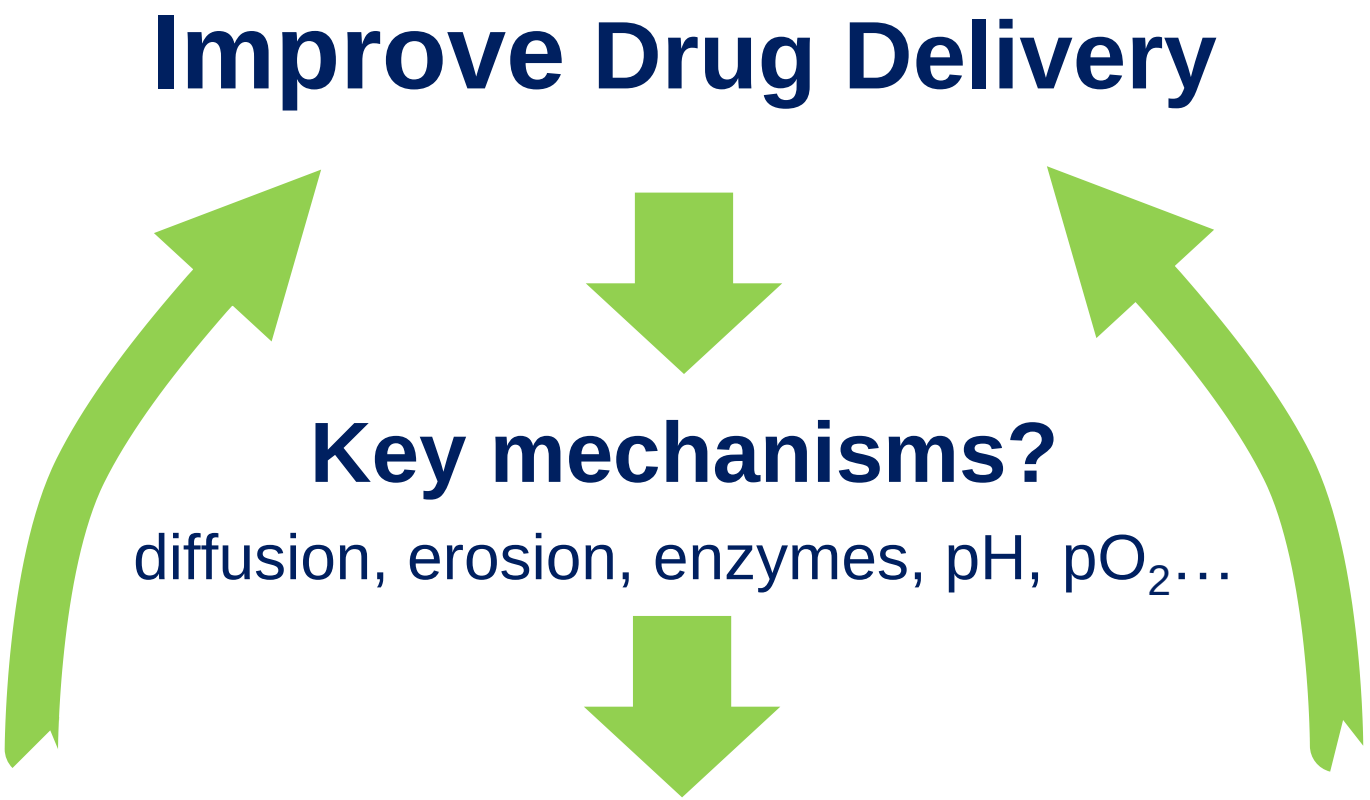
- Oral administration
- Highly specific and efficient
- No side effects
- Pharmakokinetics: low variability
- Low costs

Reality

- No or low oral uptake
- Short half lives
  - Metabolism
  - Excretion
- Parenteral administration required
- Low specificity
- High toxicity

How to solve these problems?

Our goal and rationale

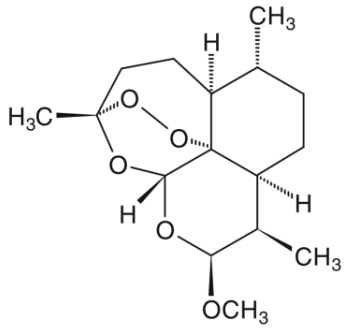


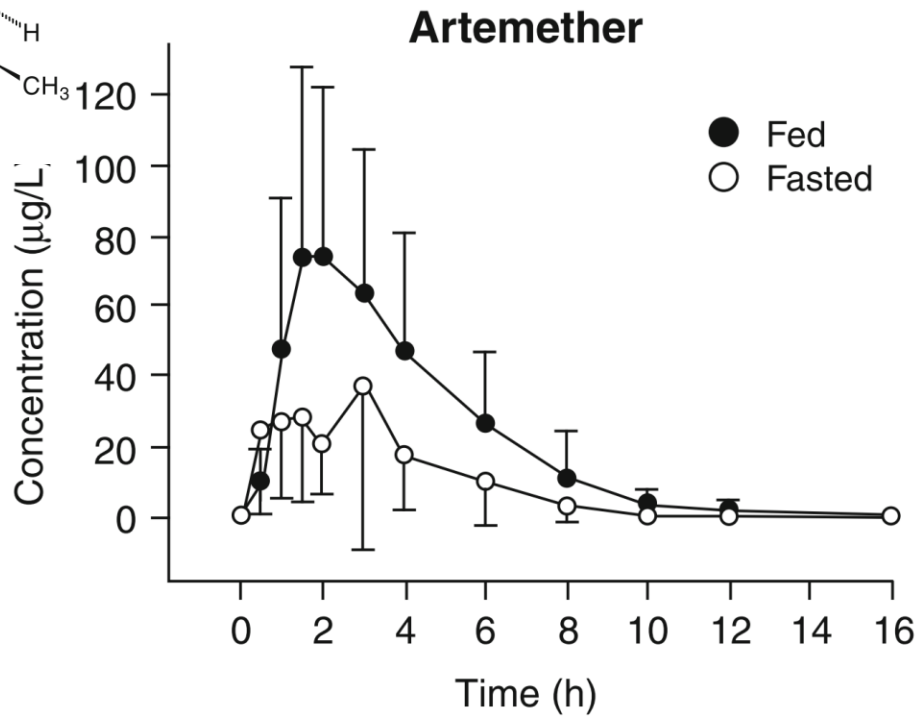
Common problems of antimalaria drug delivery

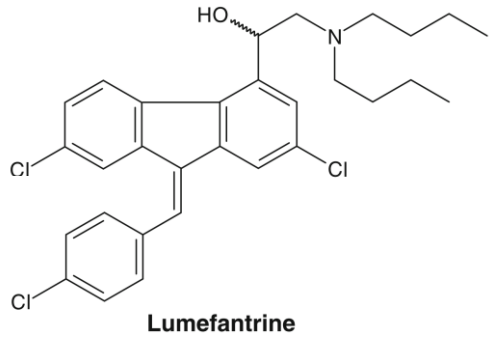
- Low drug stability ➔ problems with shelf life
- Poor and food dependent oral absorption ➔ high variability PK
- Short half lifes in vivo ➔ repeated administration
- Undesired tissue distribution ➔ low efficacy, more side effects

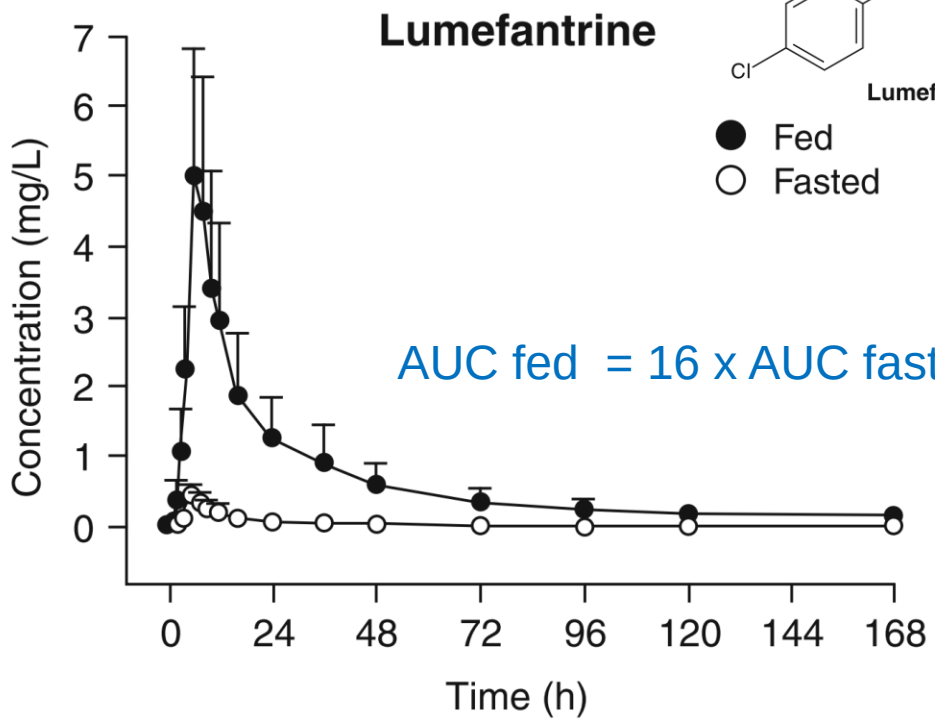
Example: Riamet

Lefèvre, G., Thomsen, M.S. Clinical Pharmacokinetics of Artemether and Lumefantrine (Riamet®). *Clin. Drug Investig.* **18**, 467–480 (1999).









AUC fed = 16 x AUC fasted!

Fig. 3. Effect of food on plasma concentrations of artemether and lumefantrine in 16 healthy Chinese participants following a single oral administration of co-artemether (80/480mg) [mean ± SD].

Fachinformation (Zusammenfassung der Merkmale des Arzneimittels/SmPC)

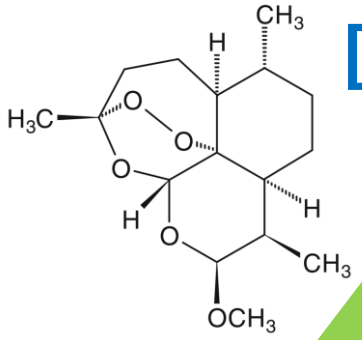
Novartis Pharma — **Riamet® 20 mg/120 mg Tabletten**

„Die Ergebnisse der Nahrungsinteraktionsstudien deuten darauf hin, dass die Resorption von Lumefantrin ohne gleichzeitige Nahrungsaufnahme sehr gering ist. Unter der Annahme einer 100%igen Aufnahme nach einer fettreichen Mahlzeit würden unter Nüchtern-Bedingungen < 10 % der Dosis aufgenommen. Die Patienten sollten daher aufgefordert werden, die Medikation zusammen mit einer Mahlzeit einzunehmen, sobald Nahrung toleriert wird.“

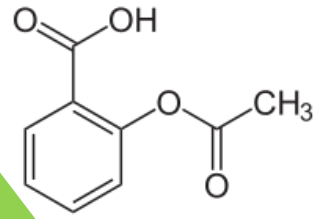
"The results of the food interaction studies suggest that the **absorption of lumefantrine is very low without concomitant food intake**. **Assuming a 100% intake after a high-fat meal, < 10% of the dose would be absorbed under fasting conditions.** Patients should therefore be encouraged to **take the medication with a meal as soon as food is tolerated."**

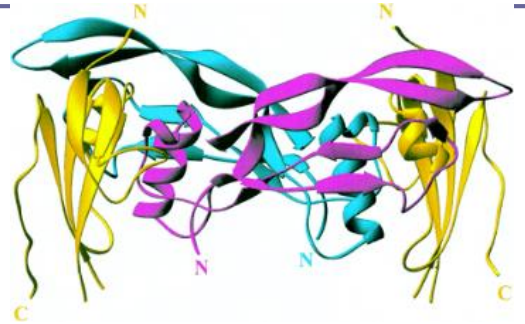
Oral Bioavailibility depends on

Food



Drug molecule





Patient

Oral Bioavailibility

Formulation

Biofate of DDS after oral administration

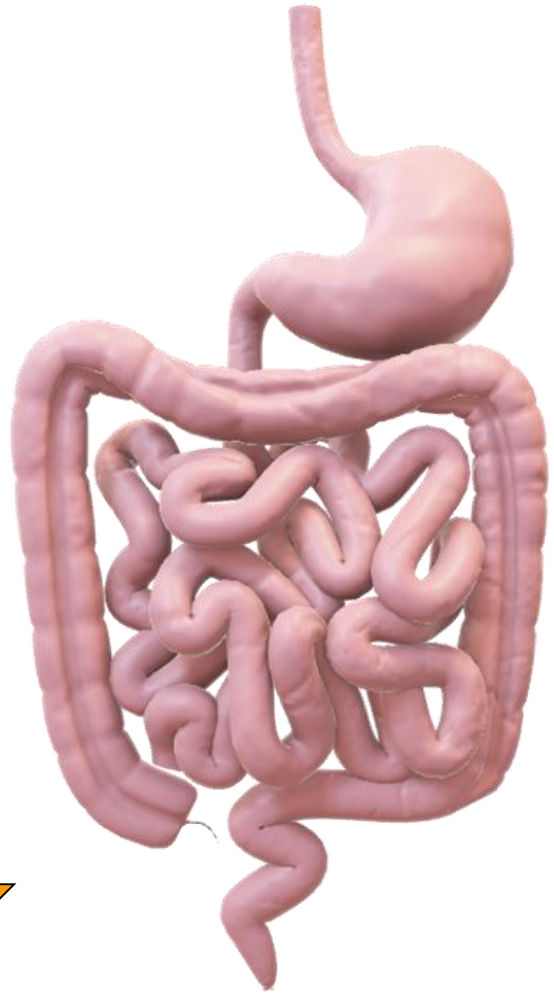
Mouth (short)

Esophagus (short)

Stomach (min – hours)

small intestine (3 h)

Colon (12-24 h)



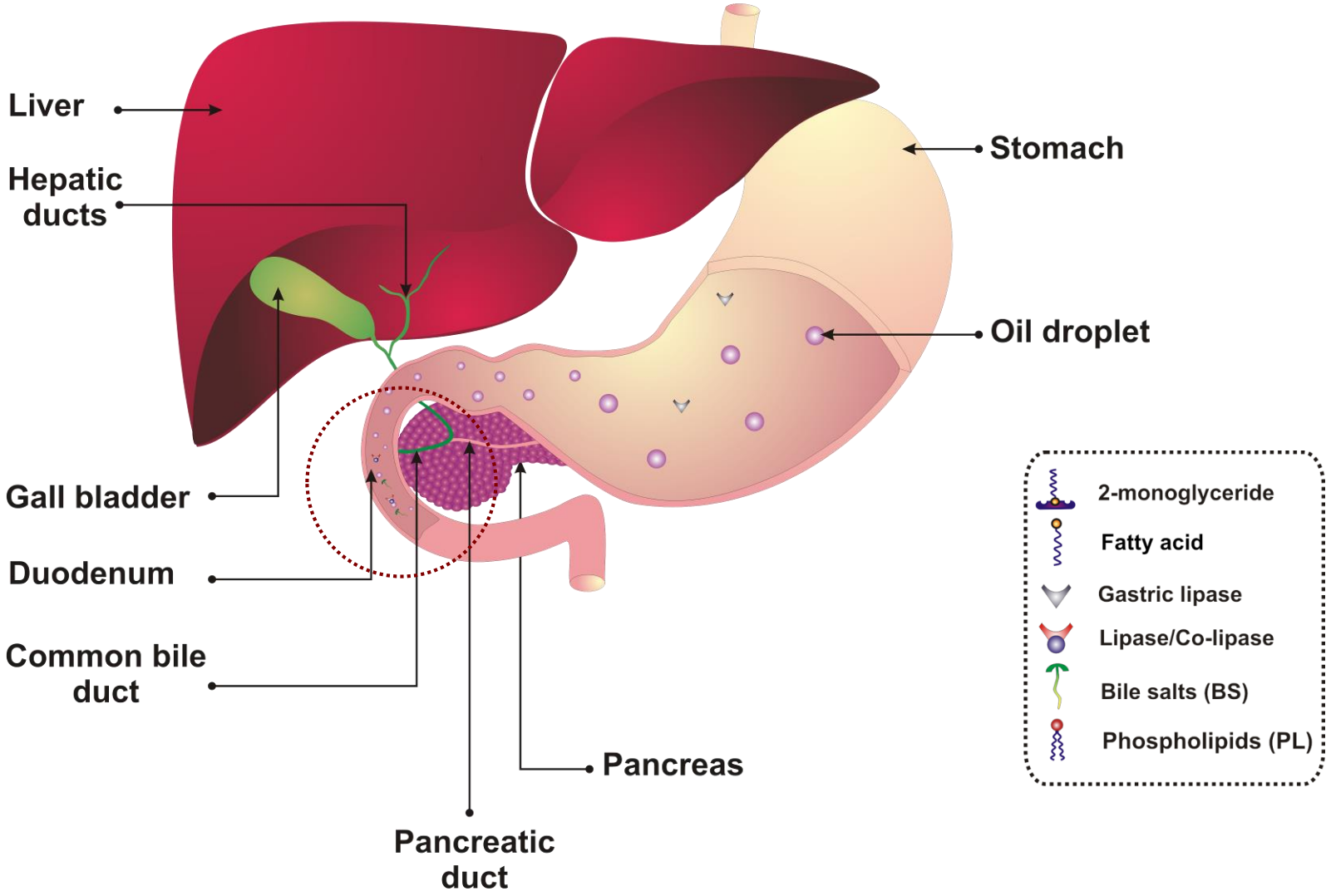
↑ ↑ **Bioavailability** ↑ ↑

- ↑ Amount of **solubilized drug**
- ↑ Drug **permeability**
- ↑ Resorption area
- ↑ Residence time

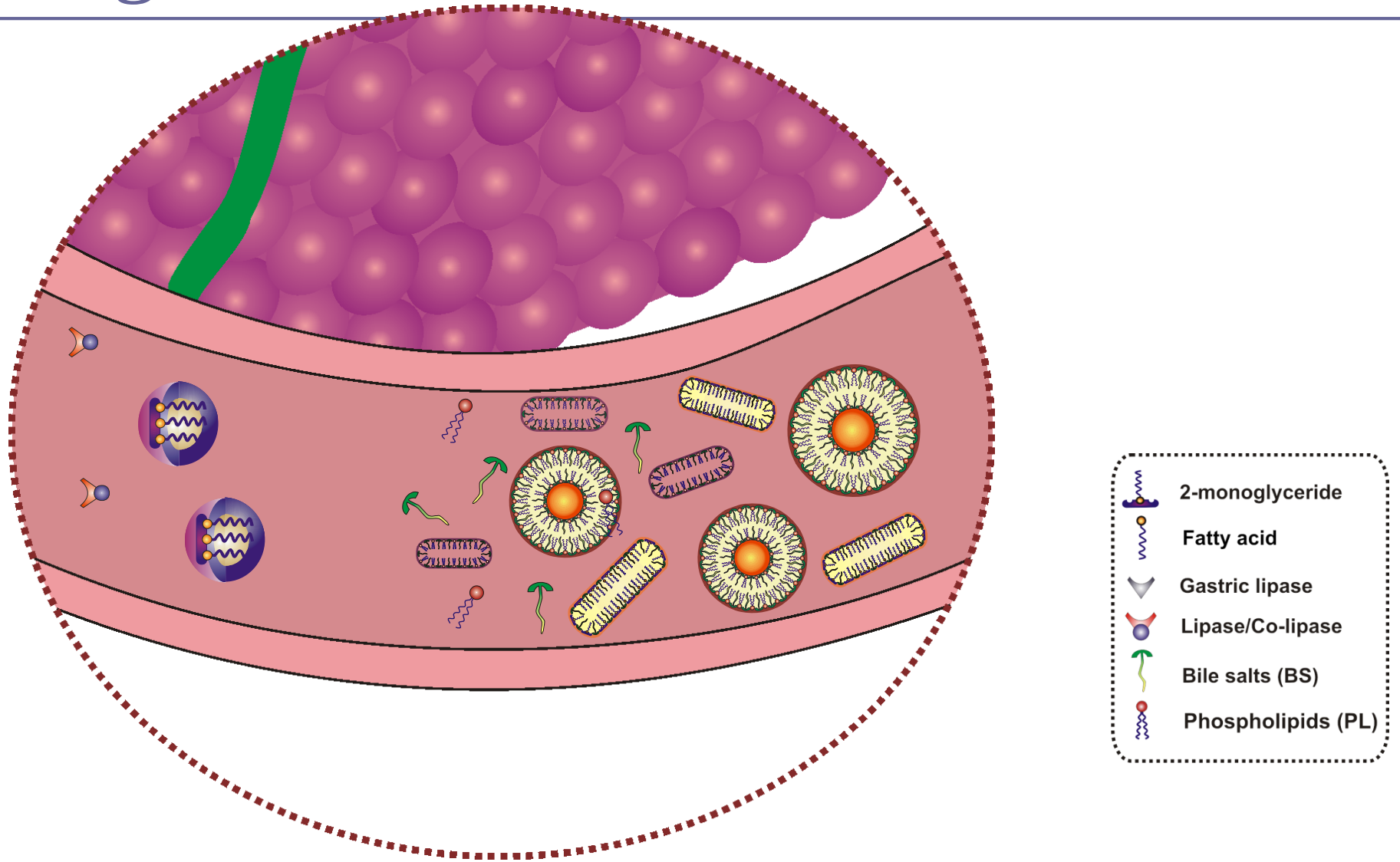
Important processes

- Solubilisation
- Dilution
- Digestion

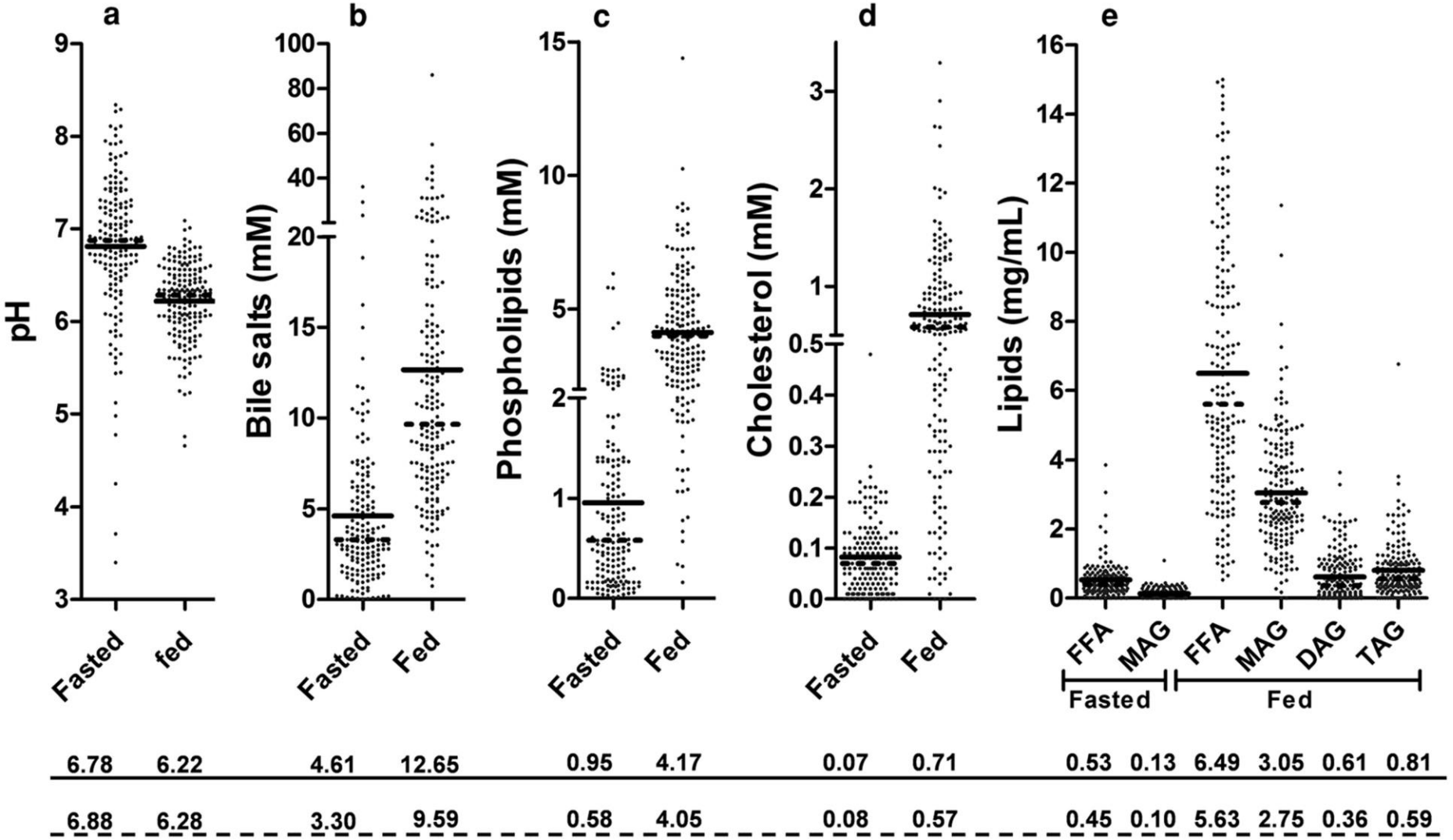
Digestion of lipids (triacylglycerides)



Lipid digestion



Composition of duodenal fluids



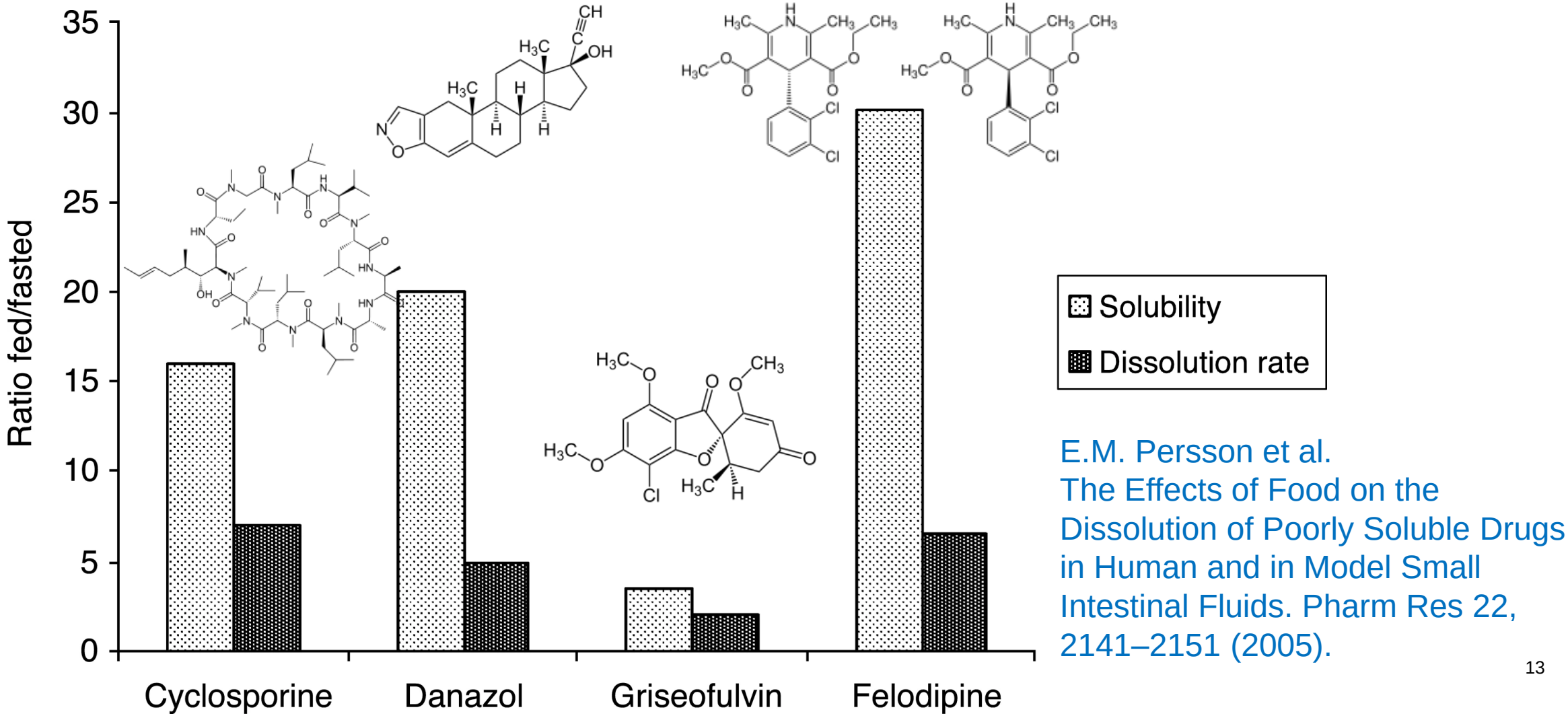
6.78	6.22	4.61	12.65	0.95	4.17	0.07	0.71	0.53	0.13	6.49	3.05	0.61	0.81
6.88	6.28	3.30	9.59	0.58	4.05	0.08	0.57	0.45	0.10	5.63	2.75	0.36	0.59

Characterization of Human Duodenal Fluids in Fasted and Fed State Conditions

Danny Riethorst, Raf Mols, Guus Duchateau, Jan Tack, Joachim Brouwers, Patrick Augustijns

JPharmSci
Volume 105 Issue 2 Pages 673-681

Food intake increases solubility and dissolution kinetics of poorly soluble drugs in intestional fluids



E.M. Persson et al.
The Effects of Food on the Dissolution of Poorly Soluble Drugs in Human and in Model Small Intestinal Fluids. Pharm Res 22, 2141–2151 (2005).

Consider variability of pH-values: stomach

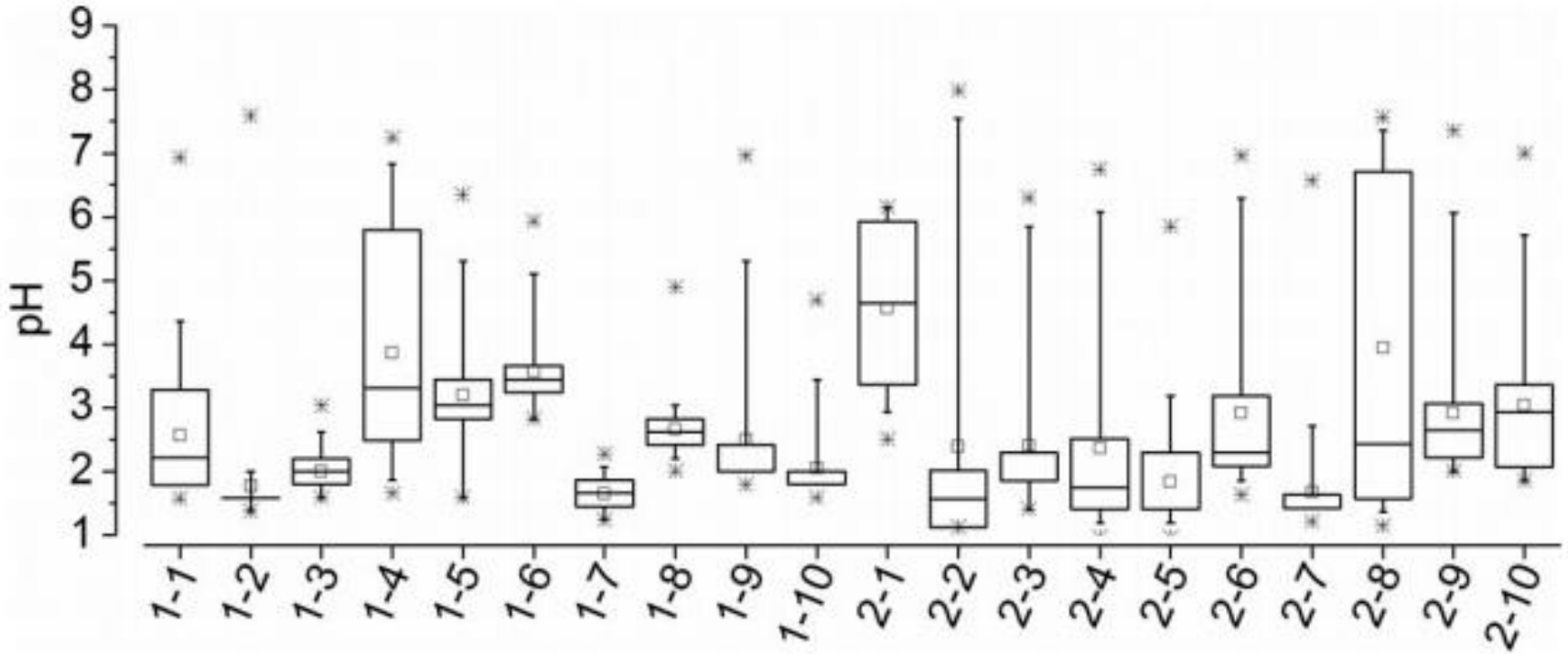
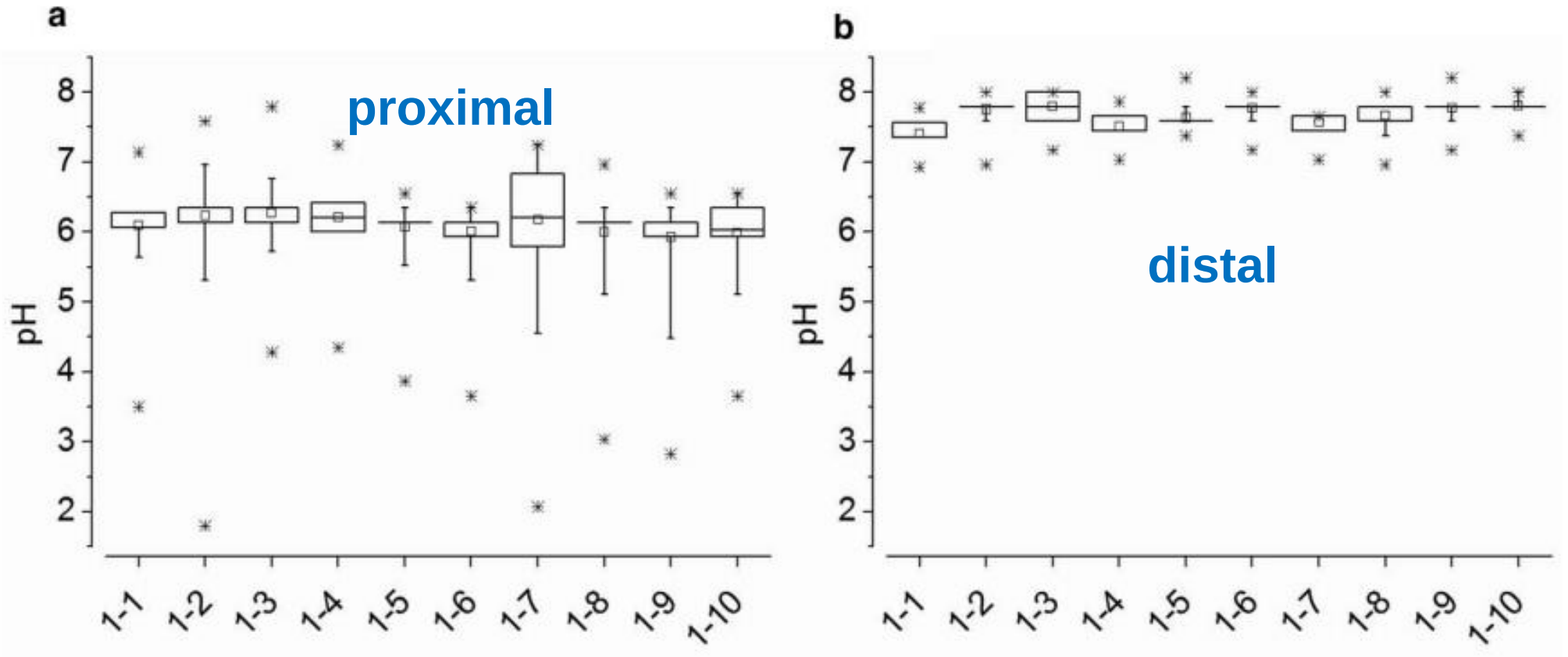


Figure 3. Box plots (box: 50%, whisker: 5%–95%, square: mean, asterisks max/min) of gastric pH values for both studies.

Gastric pH values
(fasted state)

Koziolek et al., JOURNAL OF PHARMACEUTICAL SCIENCES 104:2855–2863, 2015

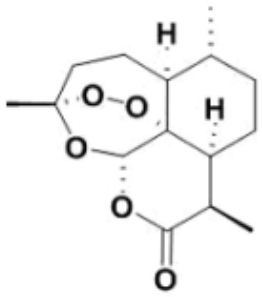
Consider variability of pH-values: small intestine



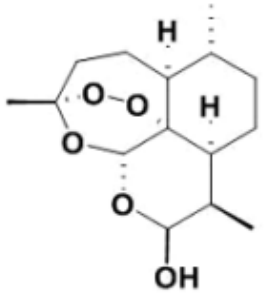
Comparison of pH ranges in proximal (a) and distal (b) small intestine (box: 50%, whisker: 5%–95%, square: mean, asterisks max/min) (*n* = 10).

Koziolek et al., JOURNAL OF PHARMACEUTICAL SCIENCES 104:2855–2863, 2015

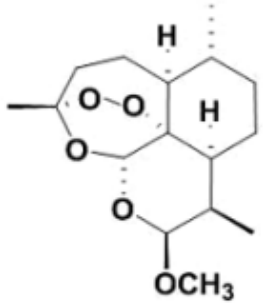
Artemisinins



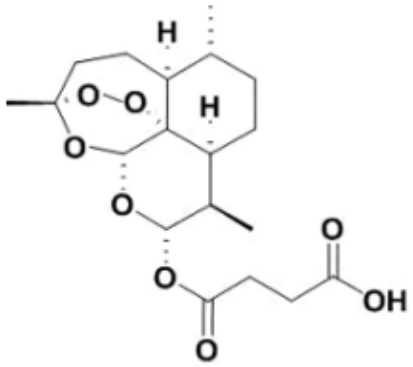
Artemisinin



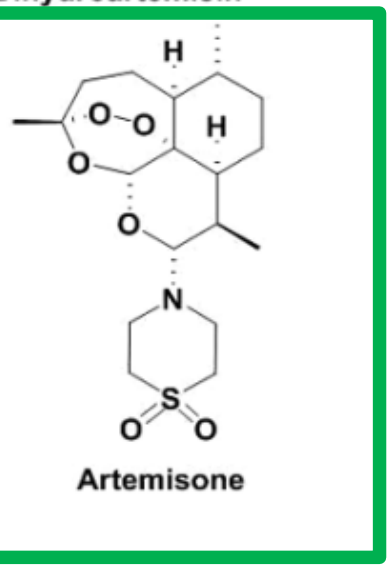
Dihydroartemisin



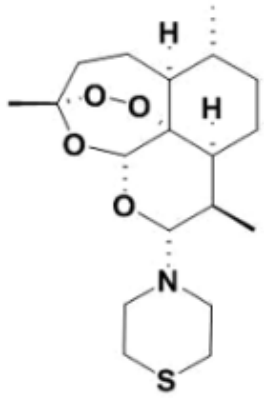
Artemether



Artesunate



Artemisone



Artemiside

- Bioactive against malaria, schistosomiasis, cancer, …
- Lipophilic molecules with peroxide structure
- Problems:
  - Solubility
  - Stability
  - Food dependent bioavailibility

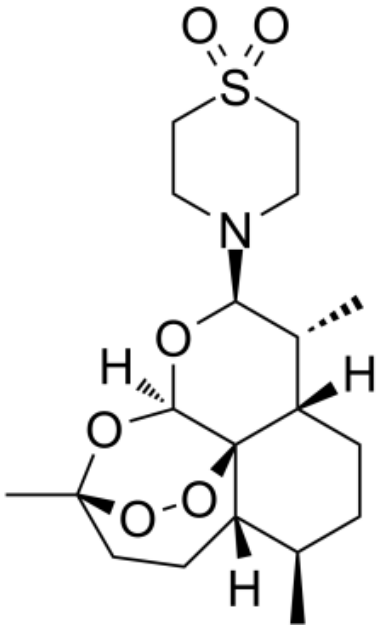
Artemisone formulations

Drawbacks of published formulations:

- Complex process (dispersions, protective gas)
- Poor storage stability
- Limited bioavailibility

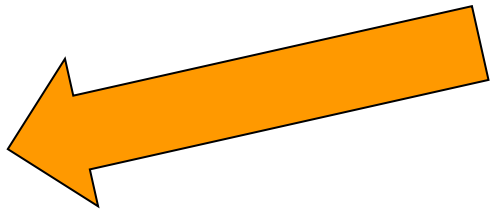
Our Goals:

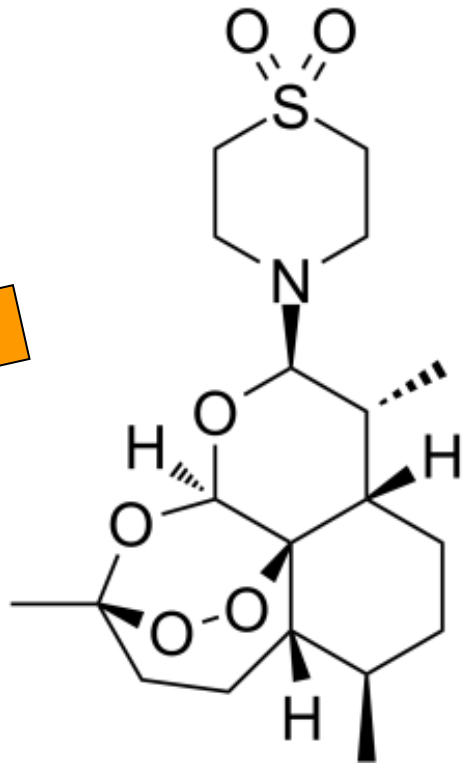
- Simple formulation process
- High chemical and physicochemical stability
- High bioavailibility



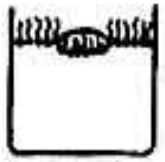
Formulation principles for poorly soluble drugs

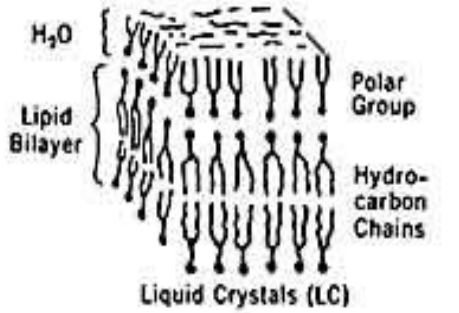
- Micro- and Nanomilling
- Salt formation
- Cyclodextrin complexes
- Amorphous systems
- Lipid DDS
- …..

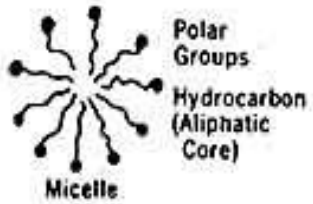


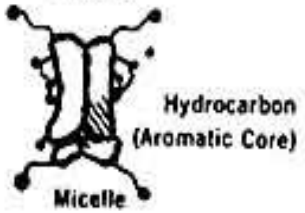


Lipid classification after Small

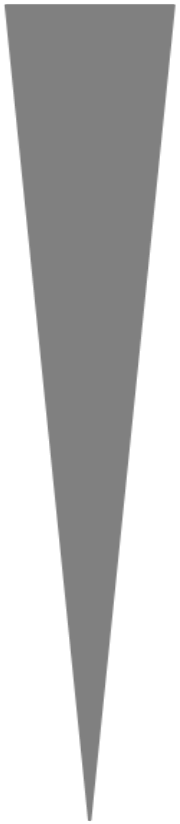
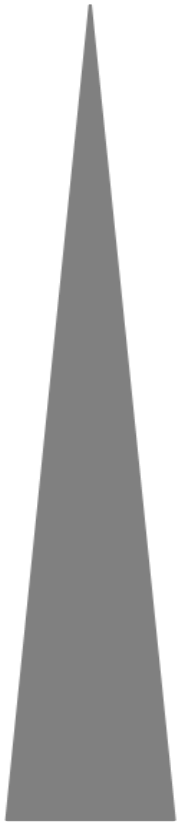
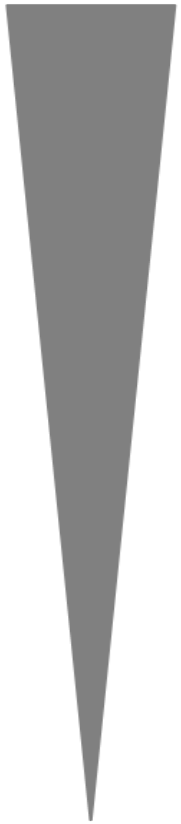
CLASS	SURFACE & BULK INTERACTIONS WITH WATER	
NON-POLAR LIPIDS		WILL NOT SPREAD TO FORM A MONOLAYER INSOLUBLE IN BULK
POLAR LIPIDS I. Insoluble non-swelling amphiphiles		FORMS A STABLE MONOLAYER INSOLUBLE IN BULK
II. Insoluble swelling amphiphiles		FORMS A STABLE MONOLAYER BULK PHASE : pure liquid crystals in pure H_2O
III. Soluble amphiphiles A) with lyotropic mesomorphism L.C. — micelle		FORMS AN UNSTABLE MONOLAYER BULK PHASE - a micellar solution above CMC
B) without lyotropic mesomorphism micelle		FORMS AN UNSTABLE MONOLAYER BULK PHASE - a micellar solution above CMC







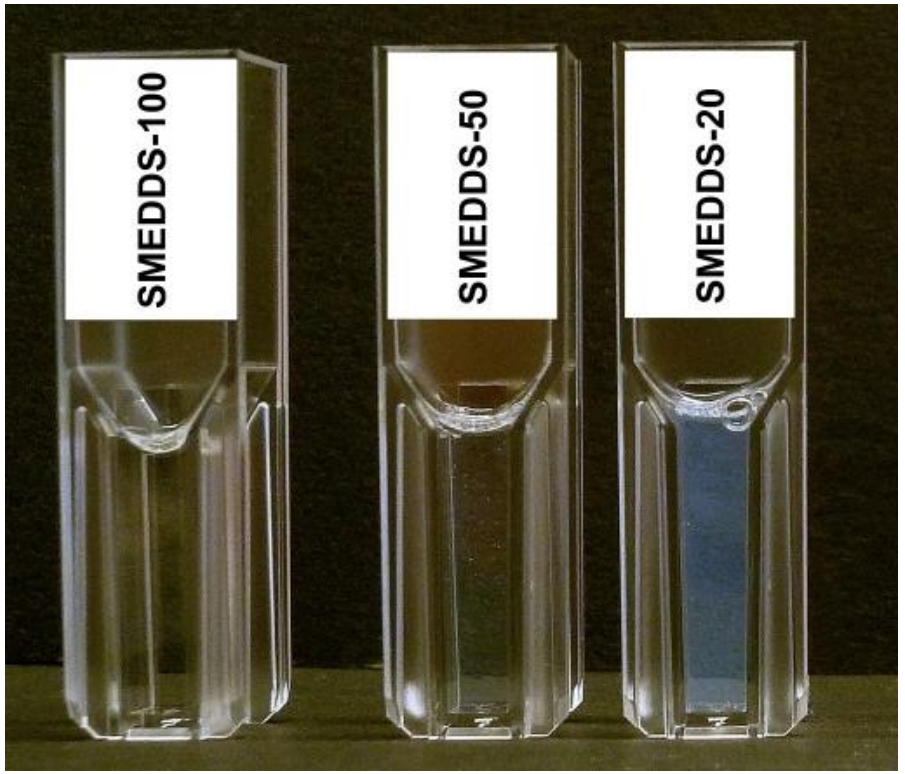
Lipid Formulation Classification System (Pouton)

Type	*Composition*	*Characteristics*	lipophilicity	Significance of dilution	Significance of digestion
I	100% oils (Mono-, Di- and Triglycerides)	Non-dispersing oils			
II	40 – 80% oils 20 – 60% surfactants (HLB < 12)	SEDDS without water soluble components			
III-A	40 – 80% oils 20 – 40% surfactants (HLB > 12) 0 – 40% co-solvents	SEDDS/SMEDDS with water soluble components			
III-B	< 20% oils 20 – 50% surfactants (HLB > 12) 20 – 50% co-solvents	SMEDDS with water soluble components & low oil content			
IV	0 – 20% surfactants (HLB < 12) 30 – 80% surfactants (HLB > 12) 0 – 50% co-solvents	Oil-free formulations based on surfactants & cosolvents			

C.W. Pouton (2000 & 2006)

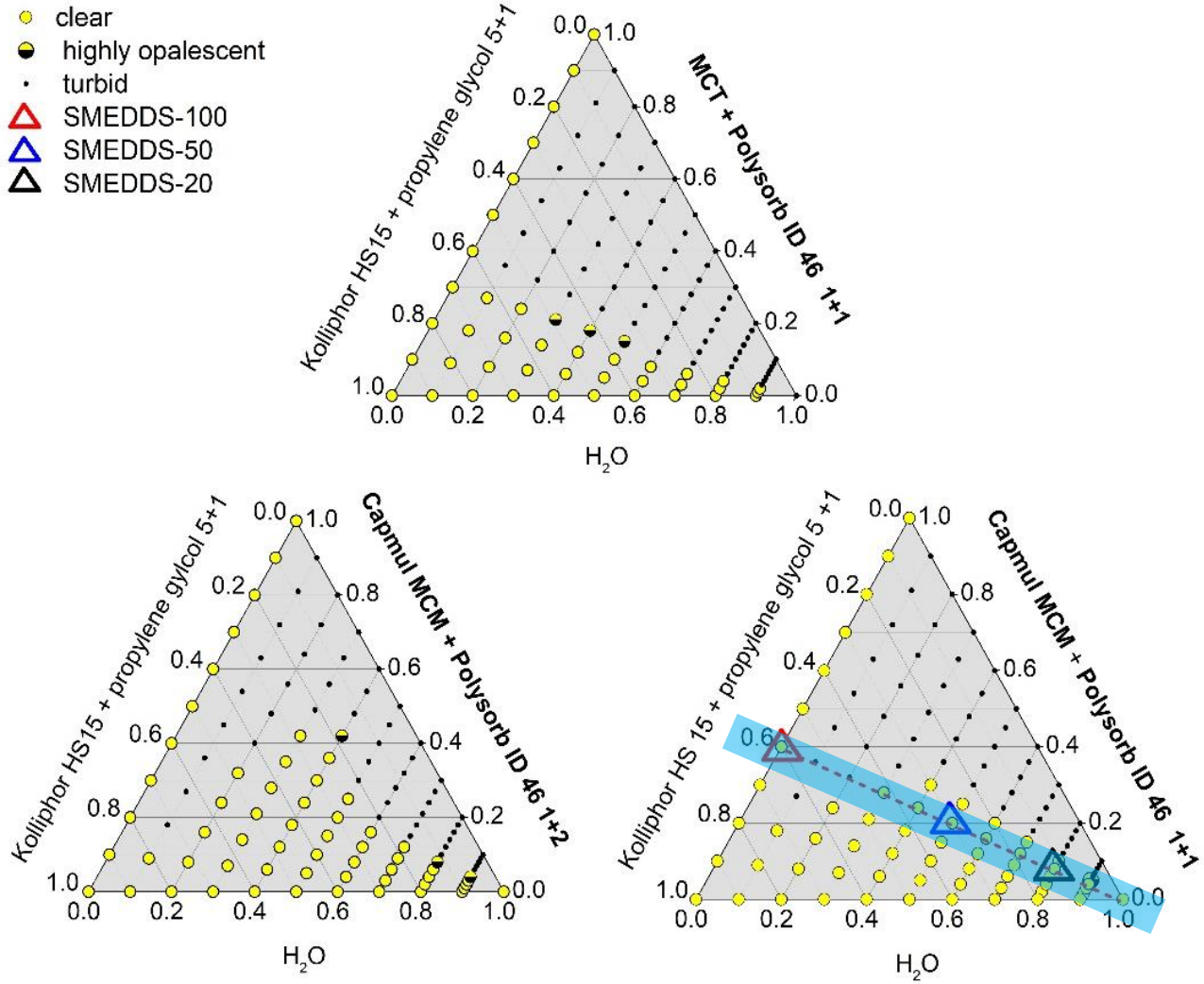
SMEDDS: composition and properties

Excipient	SMEDDS - 100	SMEDDS - 50	SMEDDS- 20
Kolliphor® HS15	50	25	10
Propylene glycol	10	5	2
Polysorb® ID 46	20	10	4
Capmul® MCM	20	10	4
PBS	0	50	80

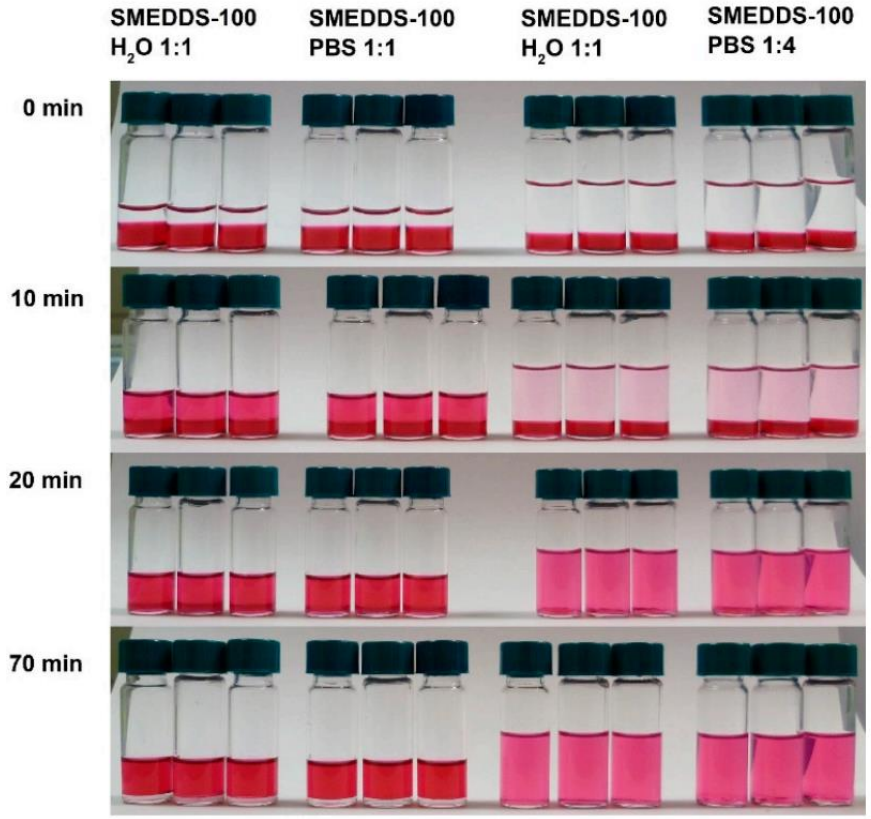


DLS size (Z-av.)	28 nm	86 nm
Viscosity	118 mPas	10 mPas

Artemisone SMEDDS: Phase behaviour

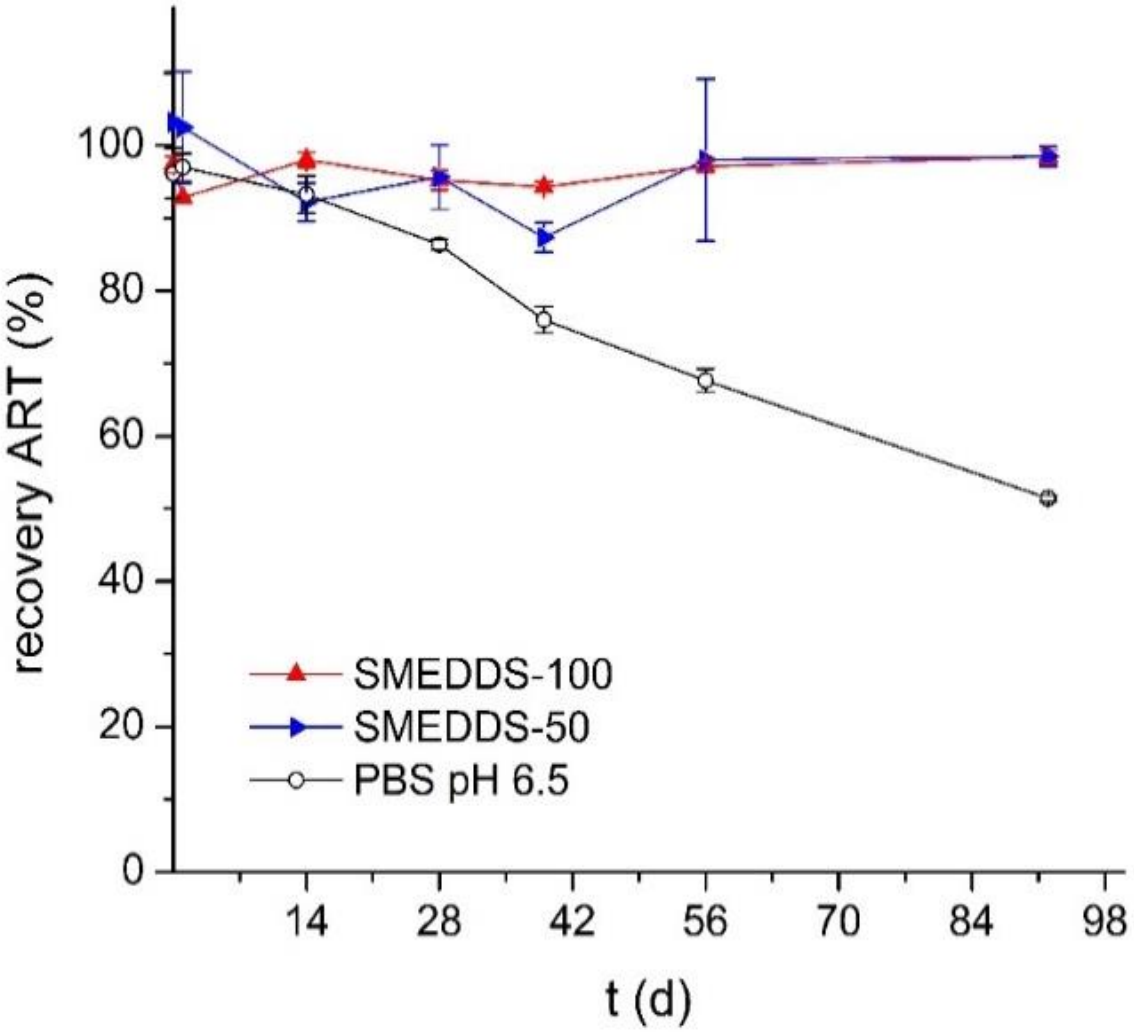


Dilution assay with Sudan red loaded SMEDDS

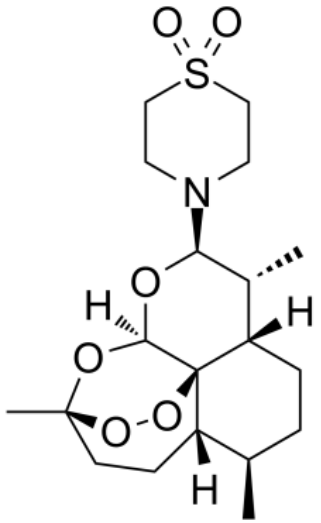


„Dilution axis“

Artemisone SMEDDS: stability at 30°C



High stability of solubilized drug at higher temperature



Biological activity

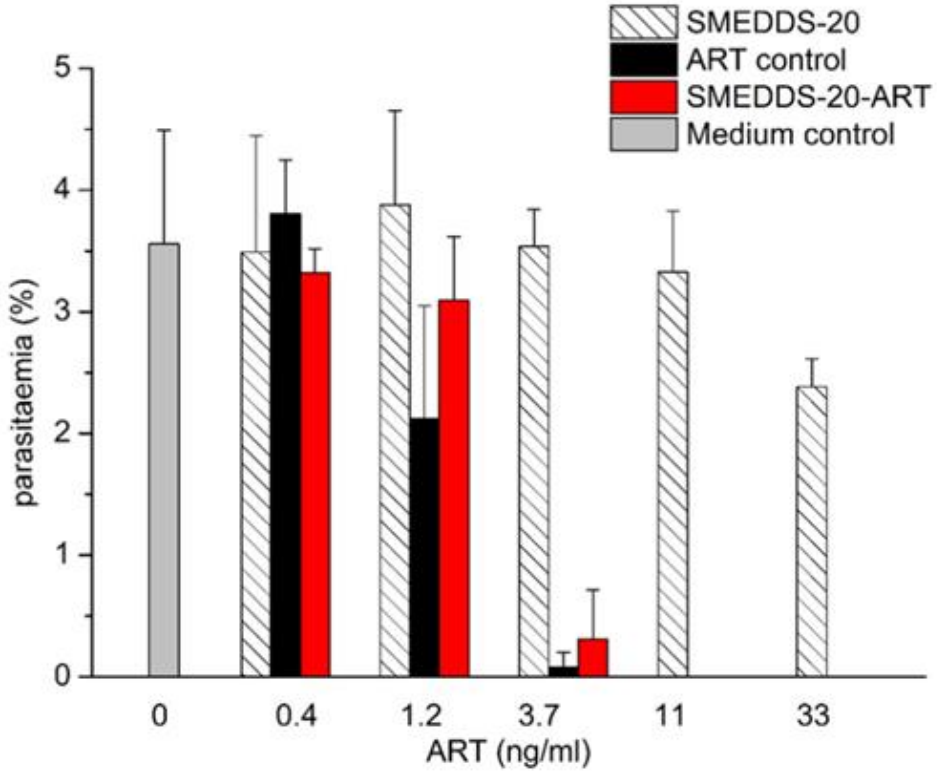
- Against malaria and schistosomiasis
- In vitro and in vivo (mice)
- Investigated parameters;
  - Dose
  - Dosing frequency
  - Application route
  - Application time (prophylaxis vs. treatment)

J. Golenser
Hebrew University

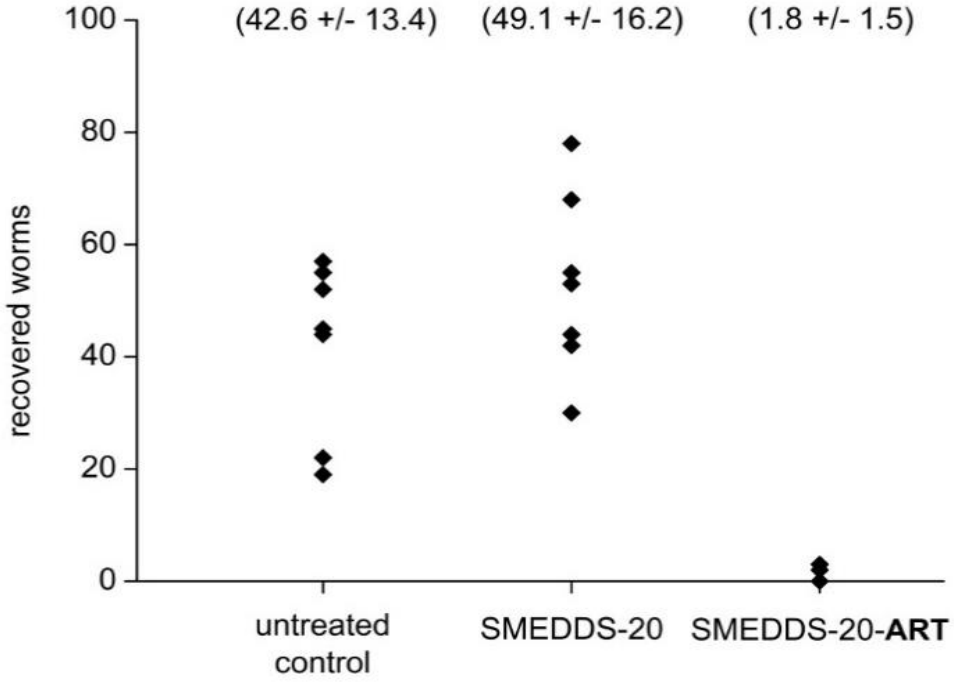
J. Zech, et al.: *Pharmaceutics, 12(6),* 509*;* (2020).

Oral Administration of Artemisone for the Treatment of Schistosomiasis: Formulation Challenges and In Vivo Efficacy

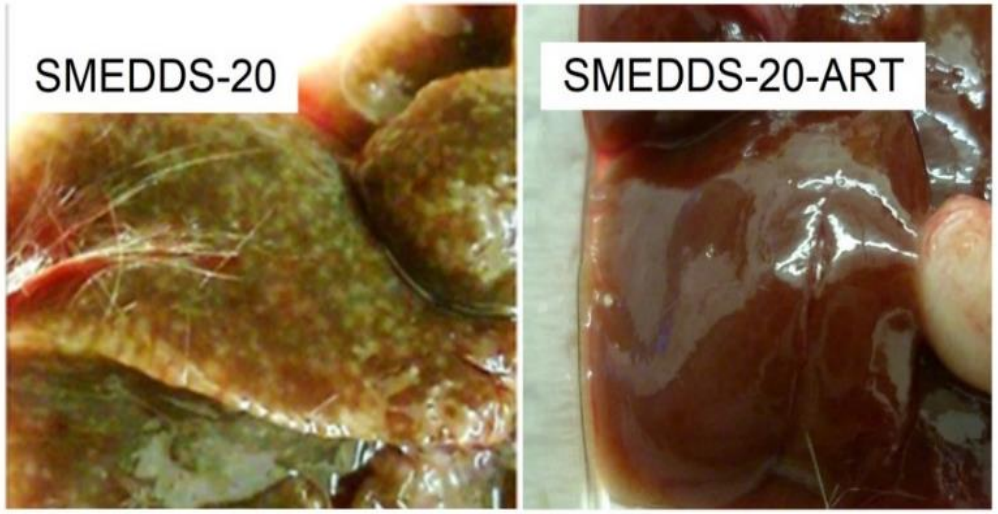
Johanna Zech [1], Daniel Gold [2], Nadeen Salaymeh [3], Netanel Cohen Sasson [4], Ithai Rabinowitch [4], Jacob Golenser [3,*,†] and Karsten Mäder [1,*,†]



In vitro activity against *Plasmodium falciparum*



In vivo: *Schistosoma mansoni* infected mice



Antimalarial activity

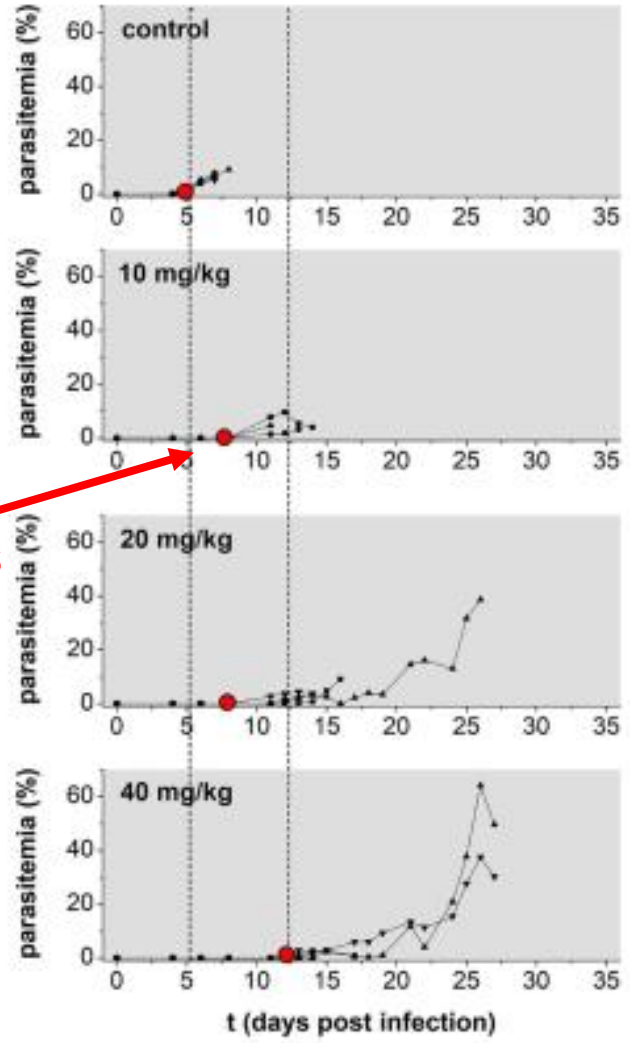
J. Zech, et al.: *Antimicrobial Agents and Chemotherapy, 65(4):e02106-20 (2021).*

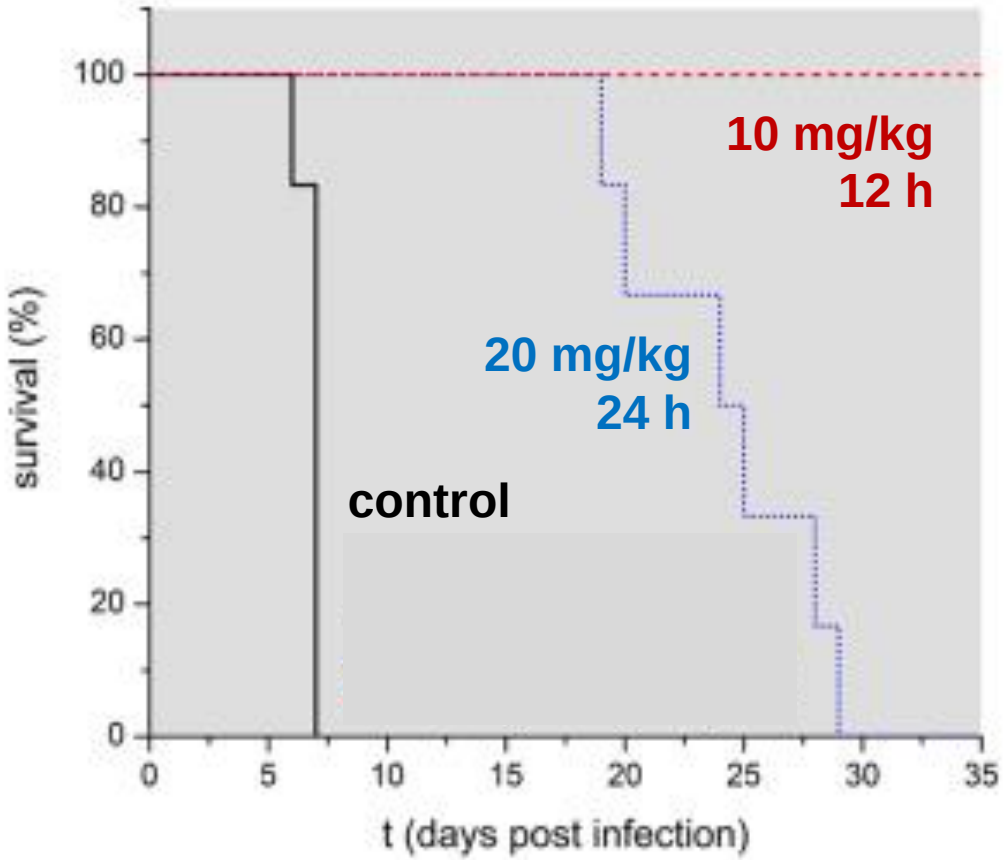
Efficient Treatment of Experimental Cerebral Malaria by an Artemisone-SMEDDS System: Impact of Application Route and Dosing Frequency

Johanna Zech,[a] Nadeen Salaymeh,[b] Nicholas H. Hunt,[c] Karsten Mäder,[a] Jacob Golenser[b]

Dosis finding
1 x daily oral

Red dot =
Occurance parasites

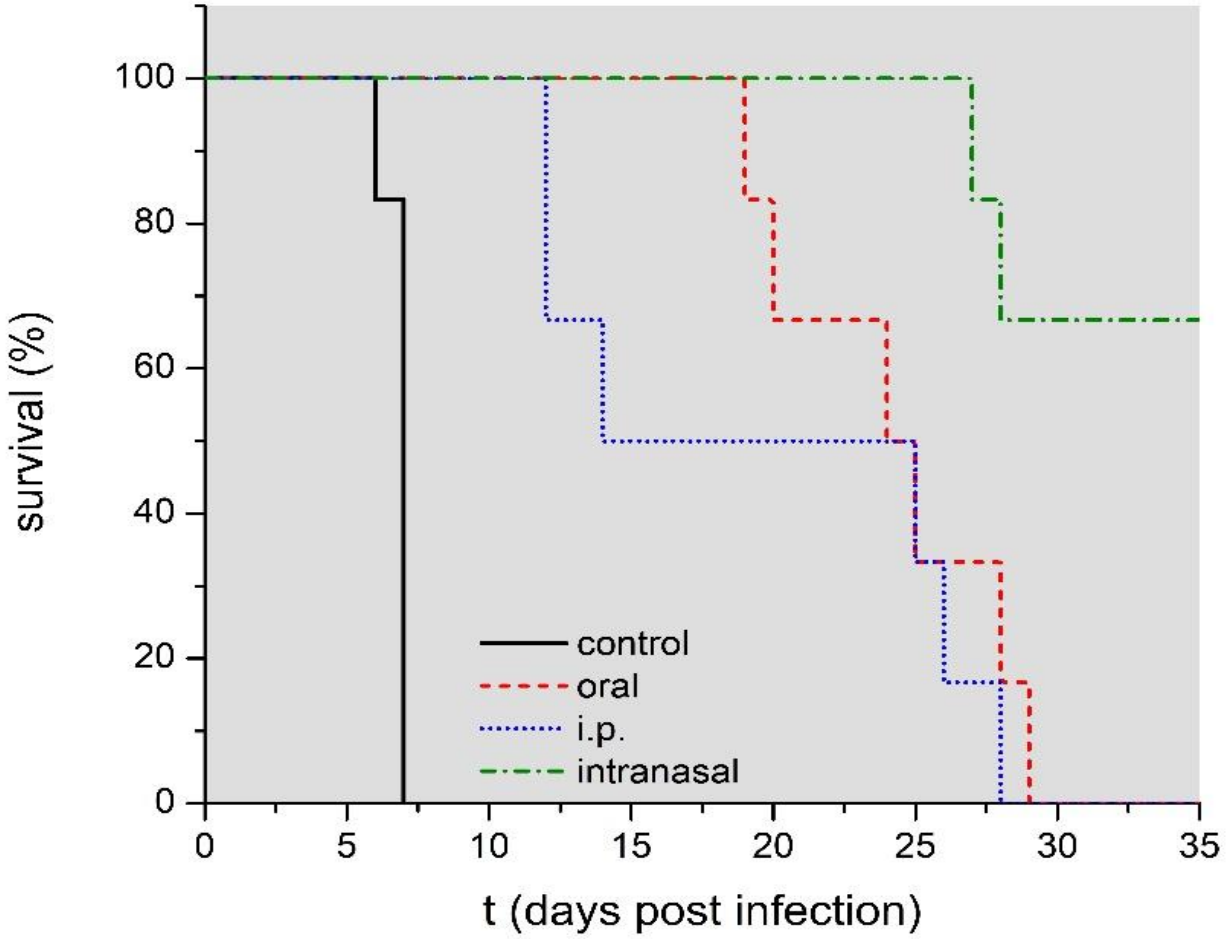




100 % parasite free survivel

Impact of administration route

J. Zech, et al.: ***Antimicrobial Agents and Chemotherapy, 65(4):e02106-20 (2021).***



Efficacy:

nasal > oral > i.p.

20 mg ART/ kg bw, treatment on

days 3-5 post infection, every 24 h

Dermal administration

- spray: simple administration
- avoids GIT tract
- also for unconscious patients
- SMEDDS promising for transdermal delivery
- Our study: Artemisone vs. Artesunate

International Journal for Parasitology: Drugs and Drug Resistance 16 (2021) 148–154

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Transdermal delivery of artemisinins for treatment of pre-clinical cerebral malaria

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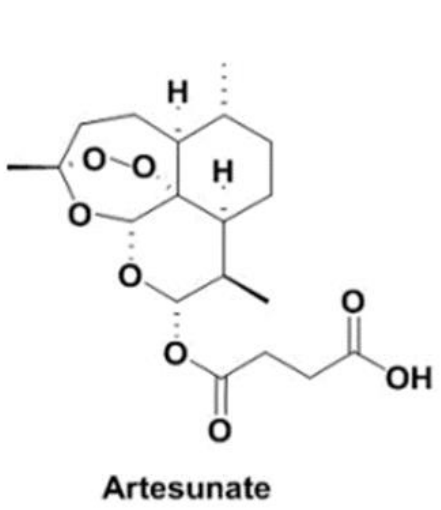
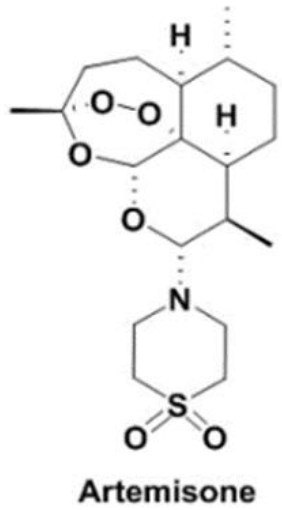




J. Zech, et al.: *Int. J. Parasitology – Drugs and Drug Resistance*, **16,** 148-154 (2021).

J. Zech, et al.: *Int. J. Parasitology – Drugs and Drug Resistance*, **16,** 148-154 (2021).

Efficacy Artemisone

- 40 mg/kg body weight
- 150 µl with an ART concentration of 1 mg/ml was sprayed twice daily, days 2-5 post infection.

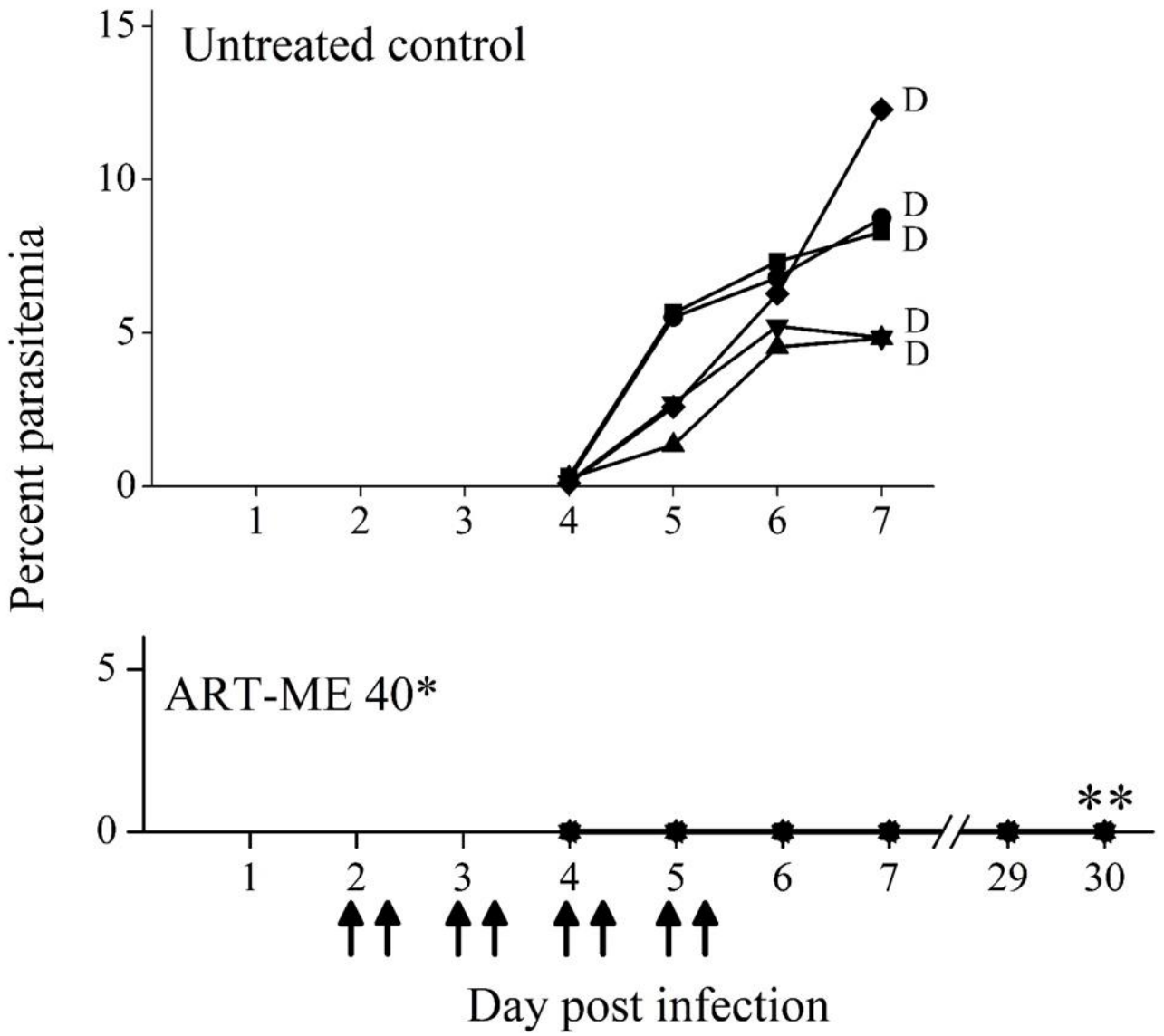
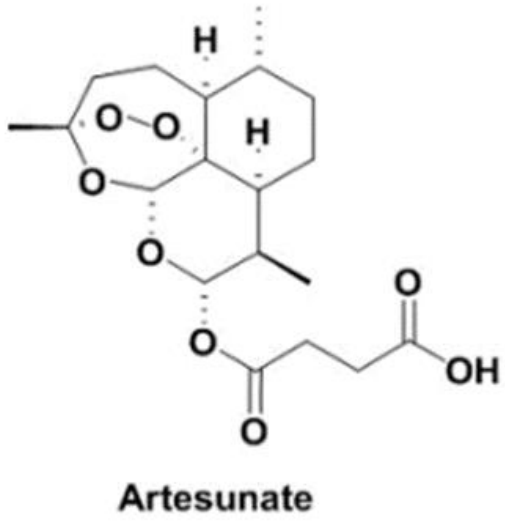
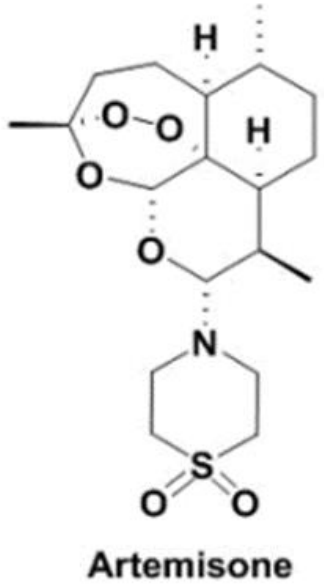
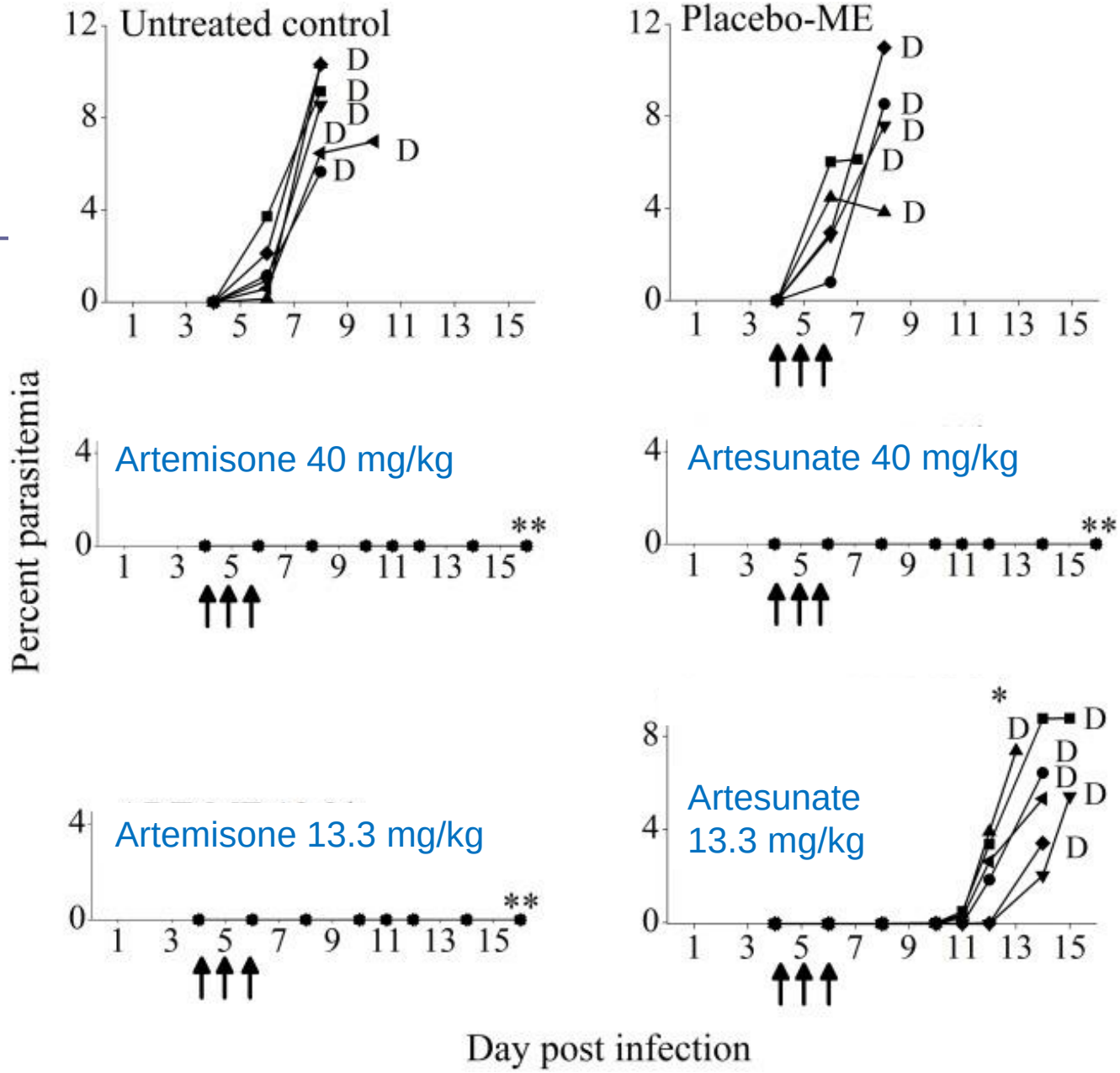


Figure legend:
↑ Spraying, the interval between treatments per day was 8 h; D = death; Each line represents one mouse, n = 6 for ME-ART, n = 5 for untreated control;
** Blood smears were negative throughout the experimental period of 30 days.

Artemisone vs. Artesunate







J. Zech, et al.: *Int. J. Parasitology – Drugs and Drug Resistance*, **16,** 148-154 (2021).

Summary

- Need to decrease food dependency
- Pharmaceutical Technology is important to improve the efficacy and stability of antimalarial drugs
- SMEDDS are an option for the formulation of lipophilic antimalarial molecules
- Dosing frequency is very important
- Developed SMEDDS formulations are
  - Simple to produce (mixing)
  - Thermodynamic stable
  - Increase the stability and efficacy
  - Versatile for different administration routes

Related publications

- J. Zech, D. Gold, N. Salaymeh, I. Rabinowitch, N.C. Sasson, J. Golenser, K. Mäder: Oral administration of artemisone against schistosomiasis: formulation challenges and *in vivo* efficacy. *Pharmaceutics, 12(6),* 509*;* (2020).
- J. Zech, R. Dzikowski, K. Simantov, J. Golenser, K. Mäder: Transdermal delivery of artemisinins for treatment of pre-clinical cerebral malaria. *International Journal for Parasitology – Drugs and Drug Resistance*, **16**, 148-154 (2021).
- J. Zech, N. Salaymeh, N.H. Hunt, K. Mäder, J. Golenser: Efficient treatment of experimental cerebral malaria by an artemisone-SMEDDS system: impact of application route and dosing frequency. *Antimicrobial Agents and Chemotherapy***, 65**(4):e02106-20 (2021).

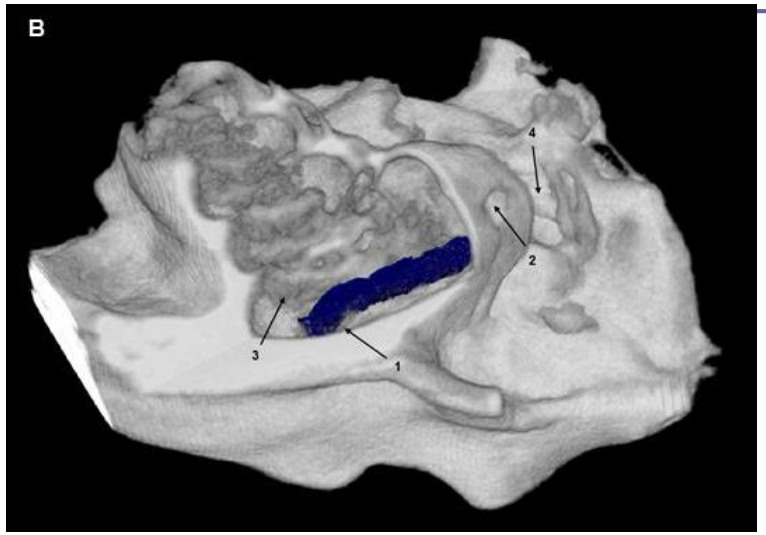
Outlook

- Use only „green excipients“
  - Nature derived
  - Fully biodegradble
- „green“ processes – no organic solvent
- Keep efficacy

Thanks

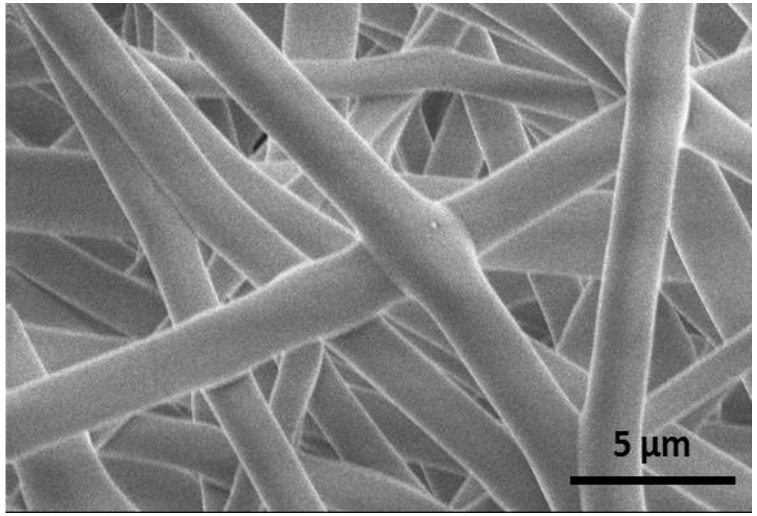
- Johanna Zech
- Jakob Golenser
- all other cooperation partners
- all present and former members of my research group
- Deutsche Forschungsgemeinschaft (MA 1648/12-2)

Mäder group research examples



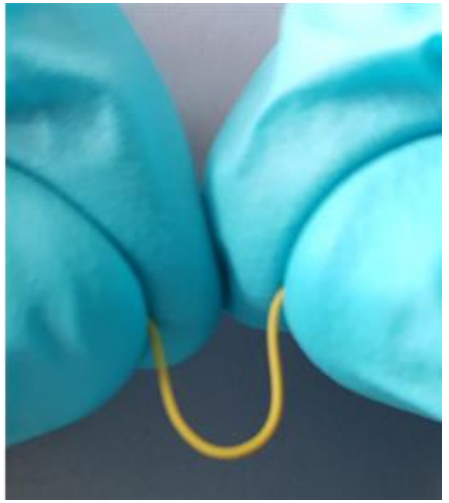
Biodegradable cochlear implants

Lehner et al. *Int. J. Pharm. X,* 2019



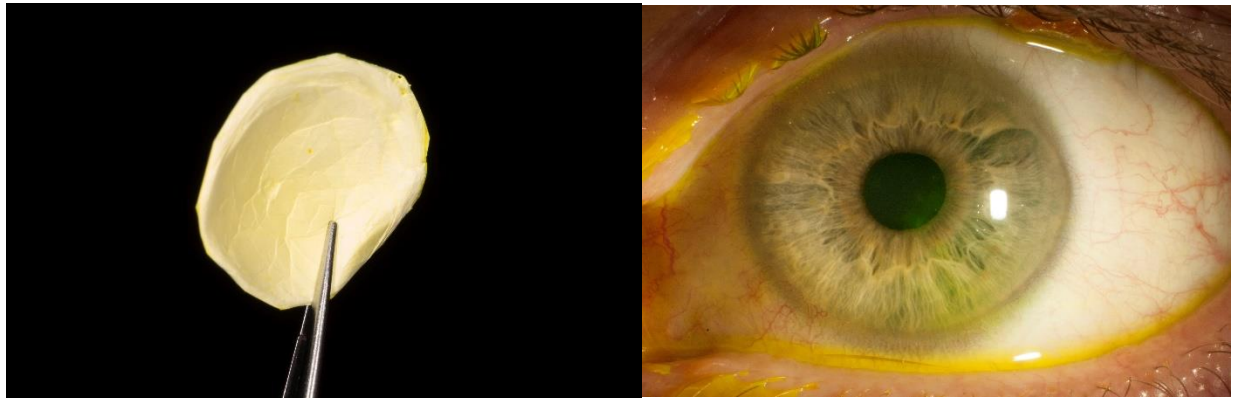
Neuroprotective DDS for brain

Zech et al. EJPB, 151, 116–126 (2020)



DDS against Periodontitis

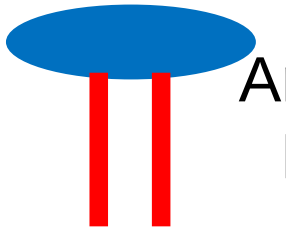
Kirchberg et al. *Int. J. Pharm.* 2019



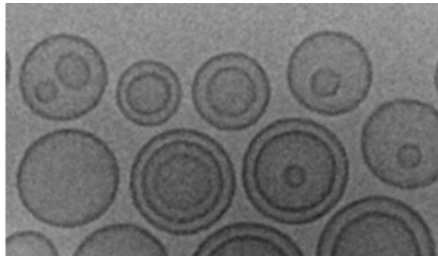
Ocular DDS

Göttel et al, EJPB146, 125-132 (2020)

Göttel et al. Front. Bioeng. Biotechnol., 8:600384, (2020).



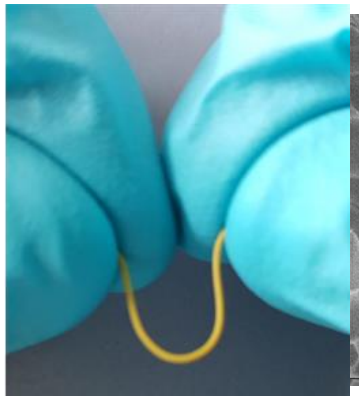
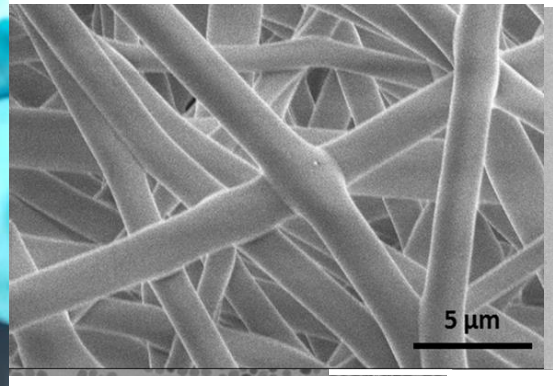
Antiinflammatory Phospholipids

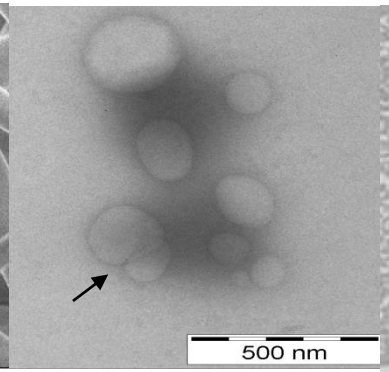


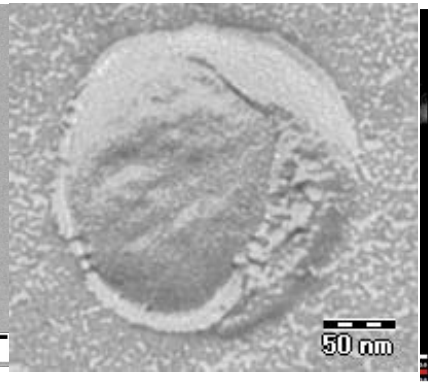
Klein et al. *Nanomedicine: Nanotech., Biol. Med.* 23, 102096, (2020)

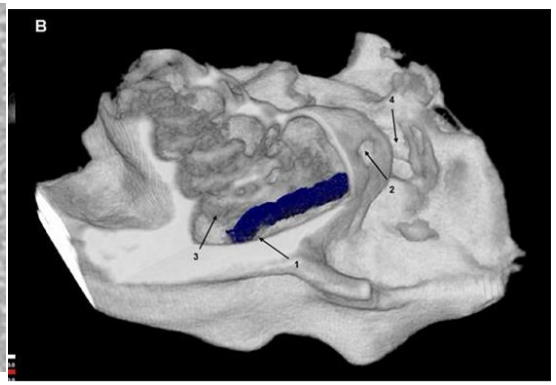
Klein et al. *Eur. J. Pharm. Sci*., 152, 105451 (2020).

Klein et al. Pharmaceutics, 13, 282, (2021).







Thank you!

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