MARTIN-LUTHER-UNIVERSITÄT
HALLE-WITTENBERG

Formulations with phospholipids for the oral application

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Outline

- **Introduction: Challenges of oral administration**
- Phospholipids (PL):
  - Chemical structures and behavior in water
  - Biofate after oral ingestion
- How to design a PL-DDS for oral administration
- Examples
- Summary and outlook

Peroral administration

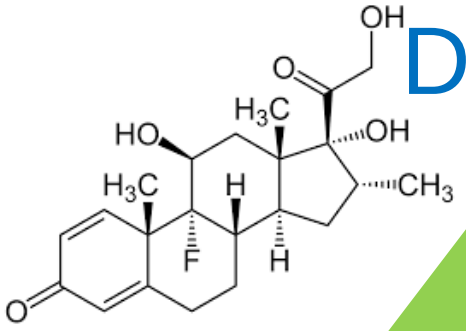
- Most commonly used
- Simple
- No pain
- Cost effective

Target:

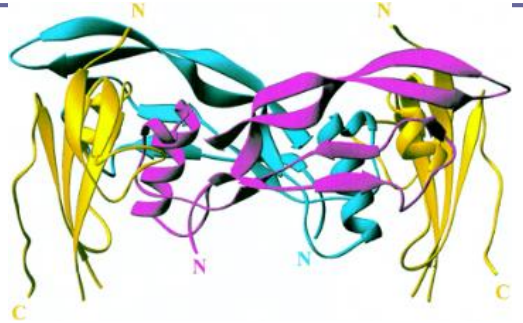
- 1 x daily
- Constant blood level
- Low variability

Oral Bioavailibility depends on

Food



Drug molecule



Oral Bioavailibility

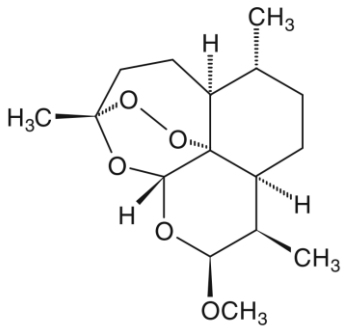
Patient

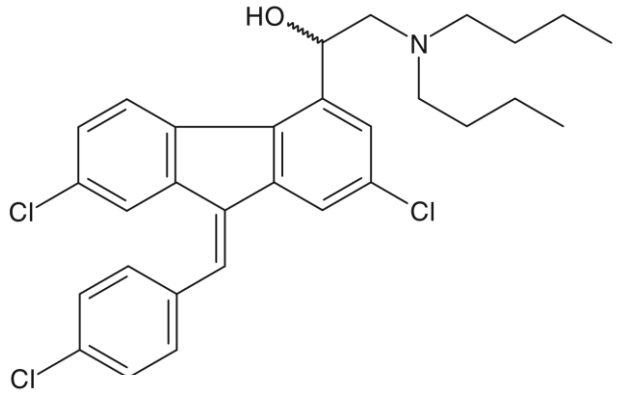
Formulation

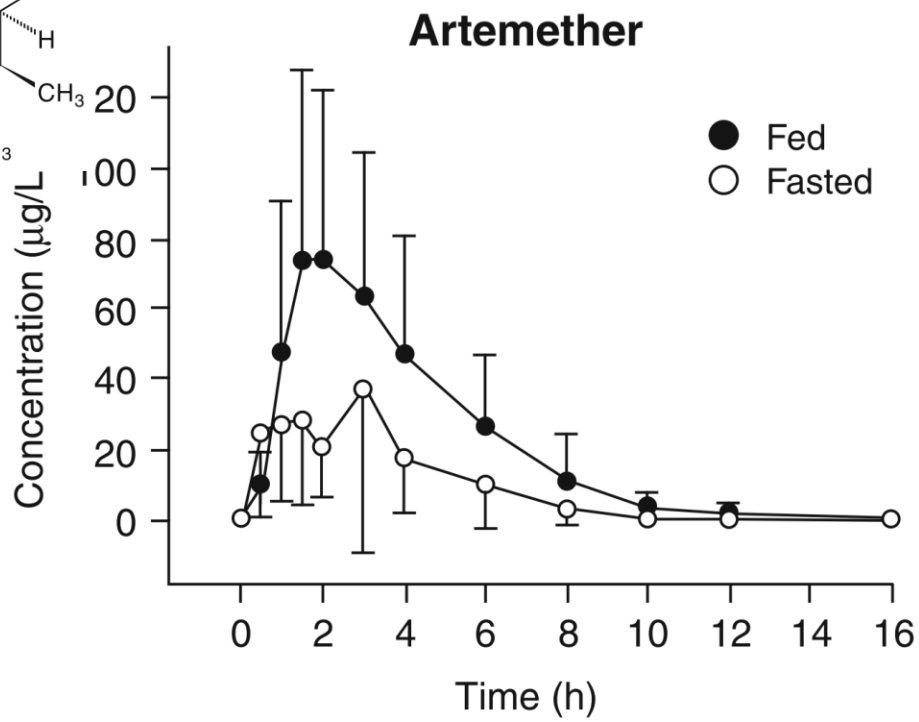
Common problems of oral administrations

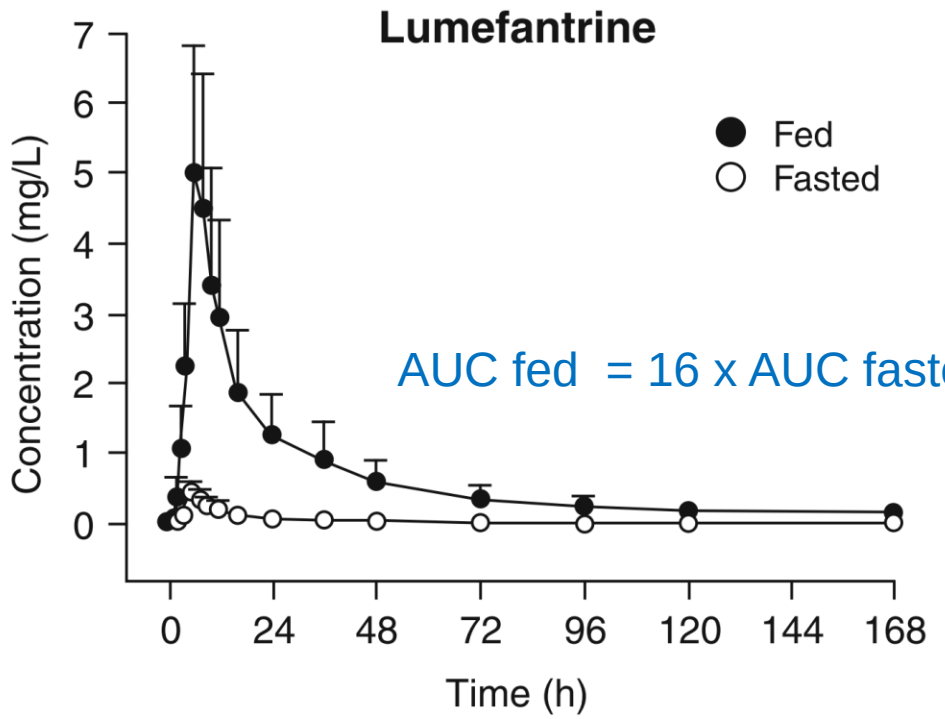
- **Low bioavailibility**
  - Poor permeability (e.g. BCS III drugs)
  - **Poor dissolution (e.g. BCS II drugs)**
  - Active processes (metabolism, excretion)
- **Food dependent variability**
- Short half-life

Example of food effect









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].

Clin Drug Invest 1999 Dec; 18 (6): 467-480

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."**

Biofate of DDS after oral administration

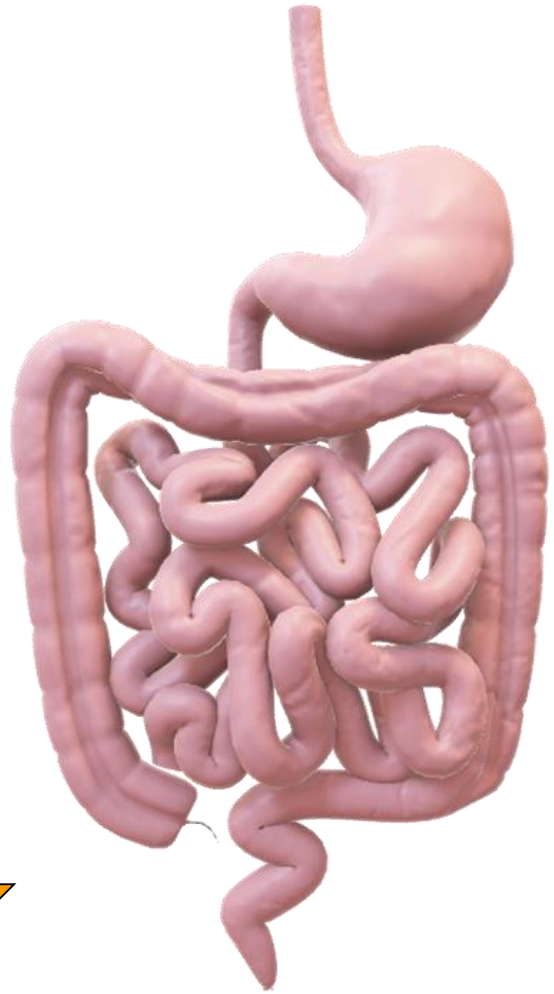
Mouth (short)

Esophagus (short)

Stomach (min – hours)

small intestine (3 h)

Colon (12-24 h)



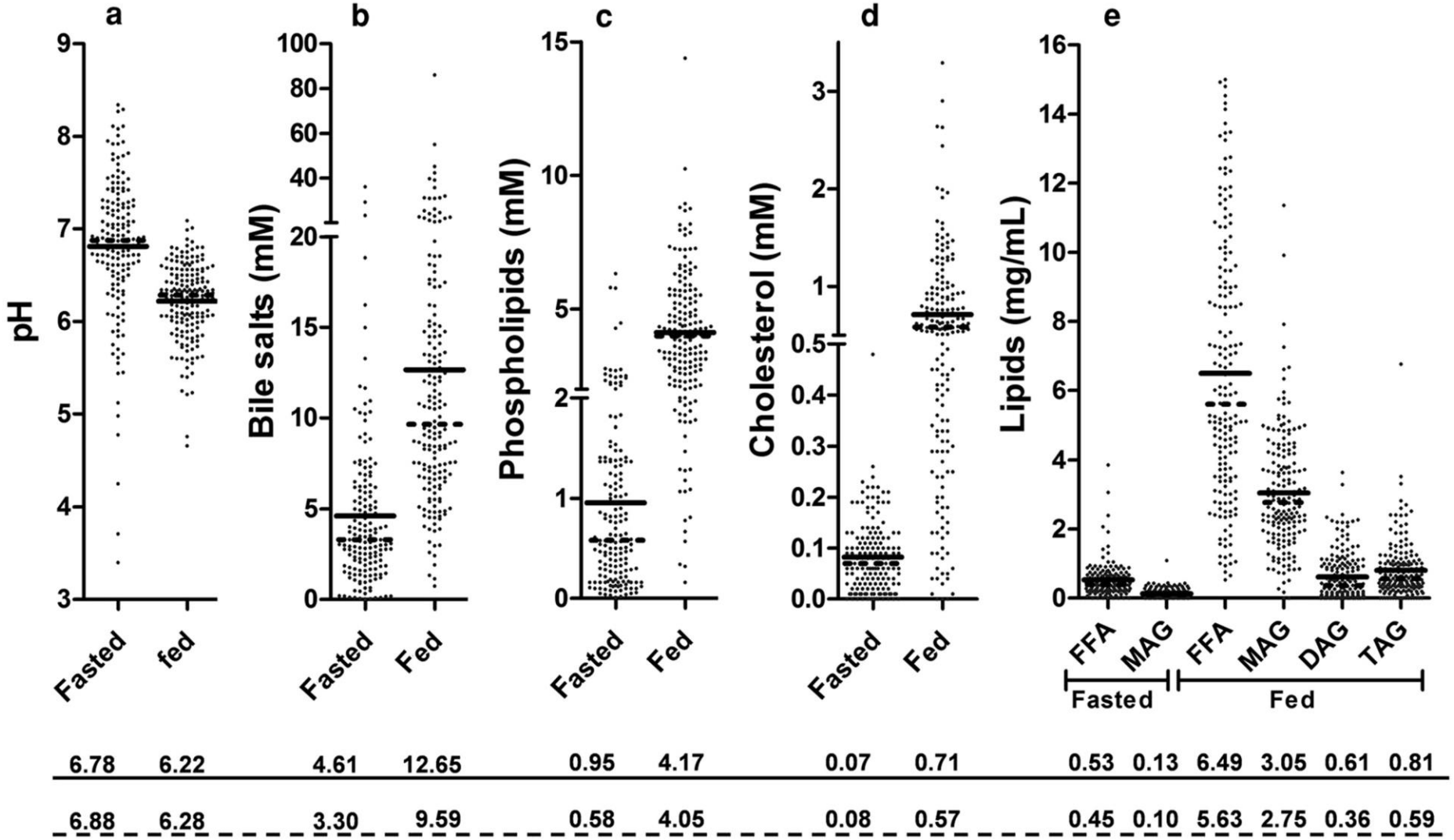
↑ ↑ **Bioavailability** ↑ ↑

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

Important processes

- Solubilisation
- Dilution
- Digestion

Composition of duodenal fluids



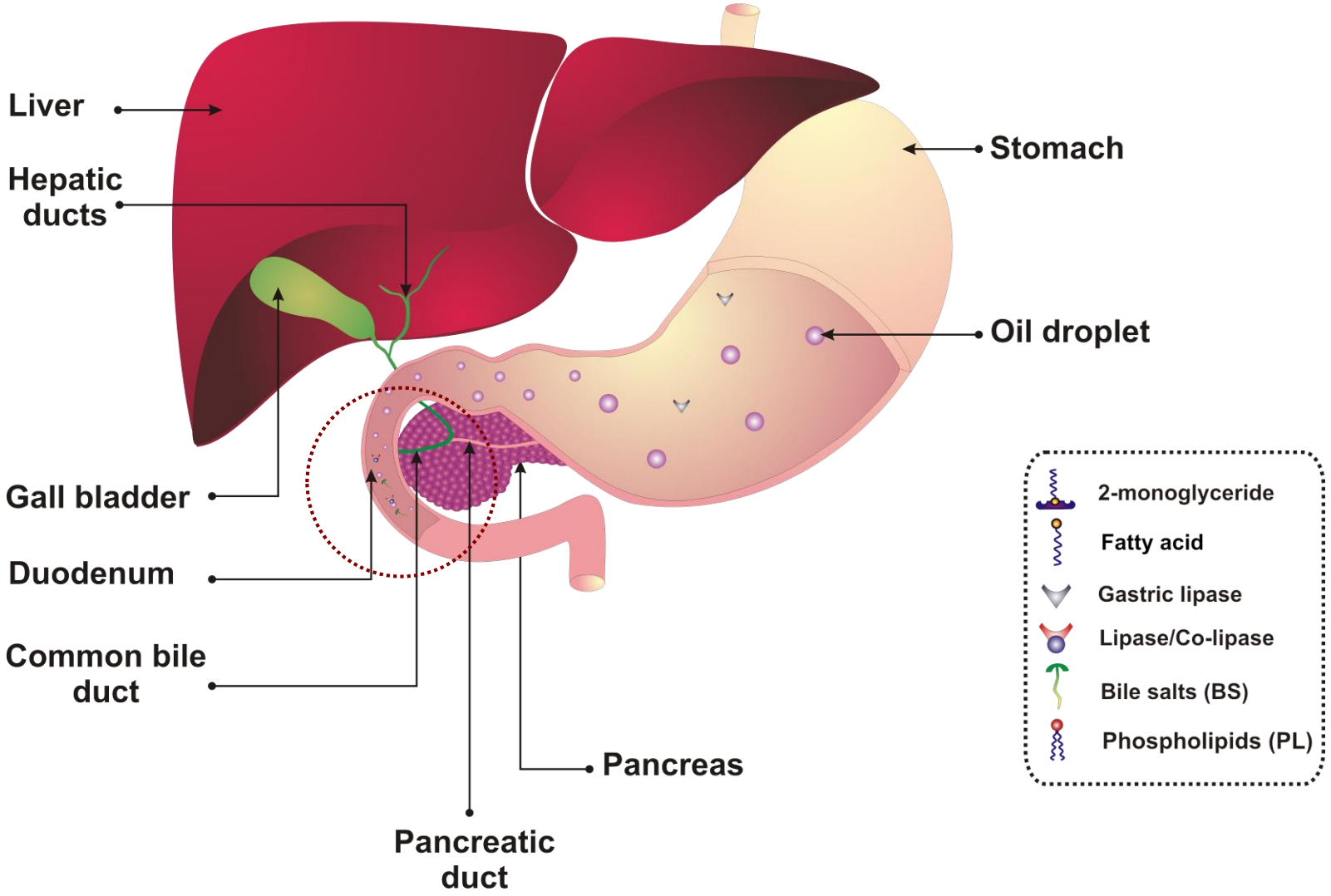
6.78	6.22	4.61	12.65	0.95	4.17	0.07	0.71	0.53	0.13	6.49	3.05	0.61	0.81
6.88	6.28	3.30	9.59	0.58	4.05	0.08	0.57	0.45	0.10	5.63	2.75	0.36	0.59

Characterization of Human Duodenal Fluids in Fasted and Fed State Conditions

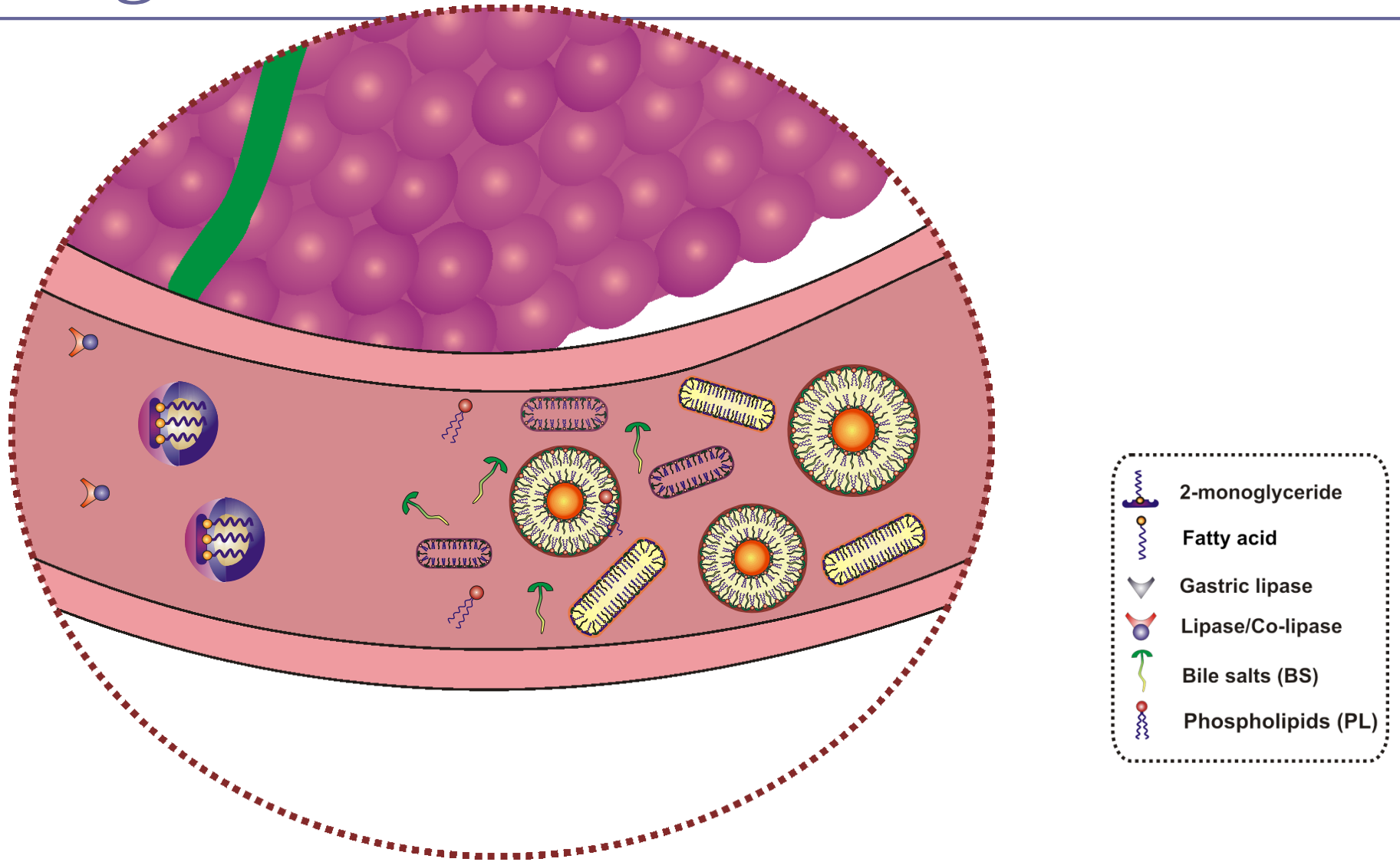
Danny Riethorst, Raf Mols, Guus Duchateau, Jan Tack, Joachim Brouwers, Patrick Augustijns

JPharmSci
Volume 105 Issue 2 Pages 673-681

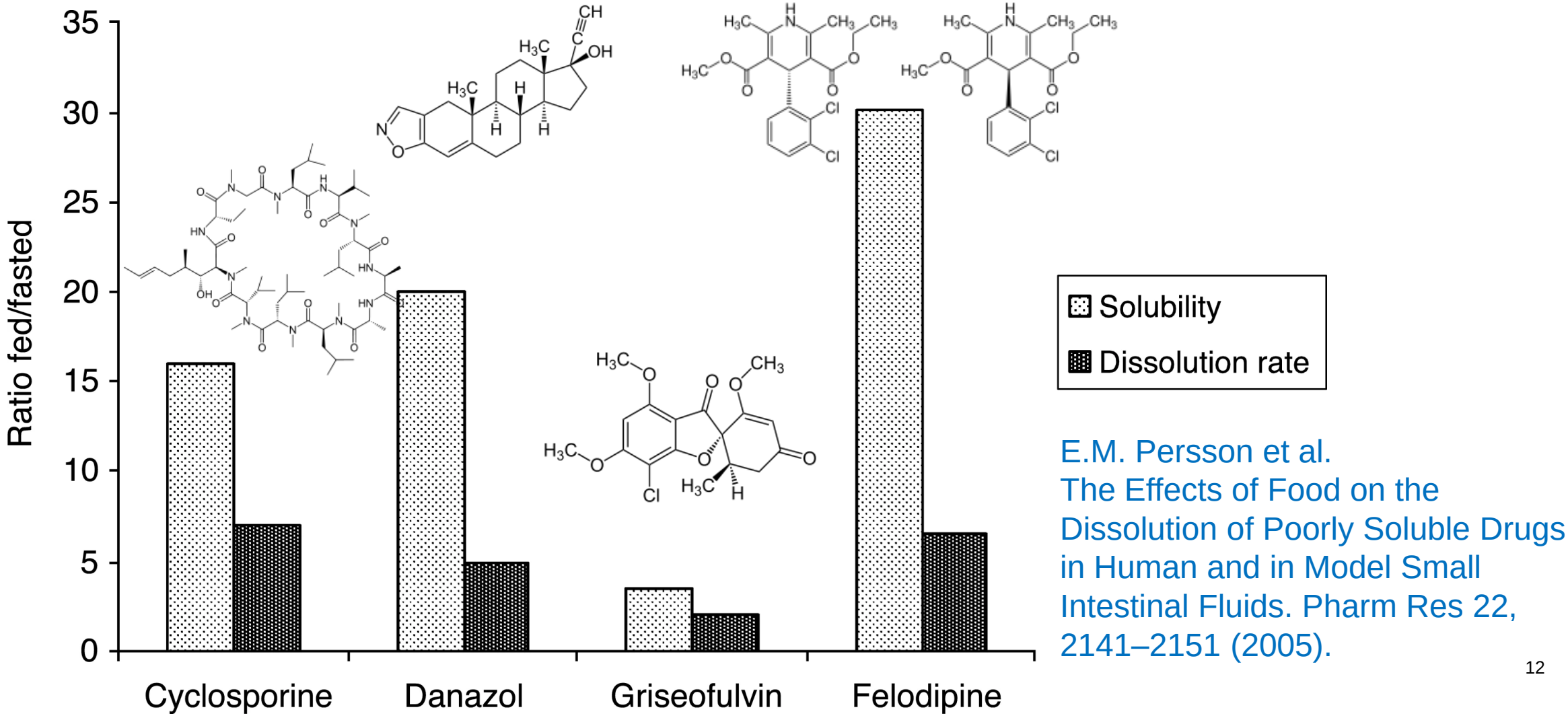
Digestion of lipids (triacylglycerides)



Lipid digestion



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).

Outline

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- **Phospholipids (PL):**
  - **Chemical structures and behavior in water**
  - **Biofate after oral ingestion**
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- Examples
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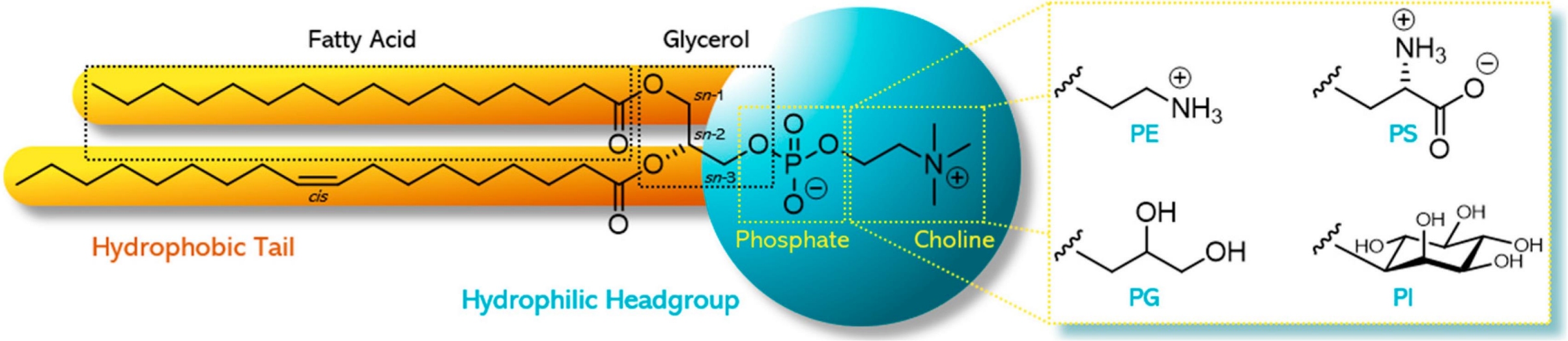
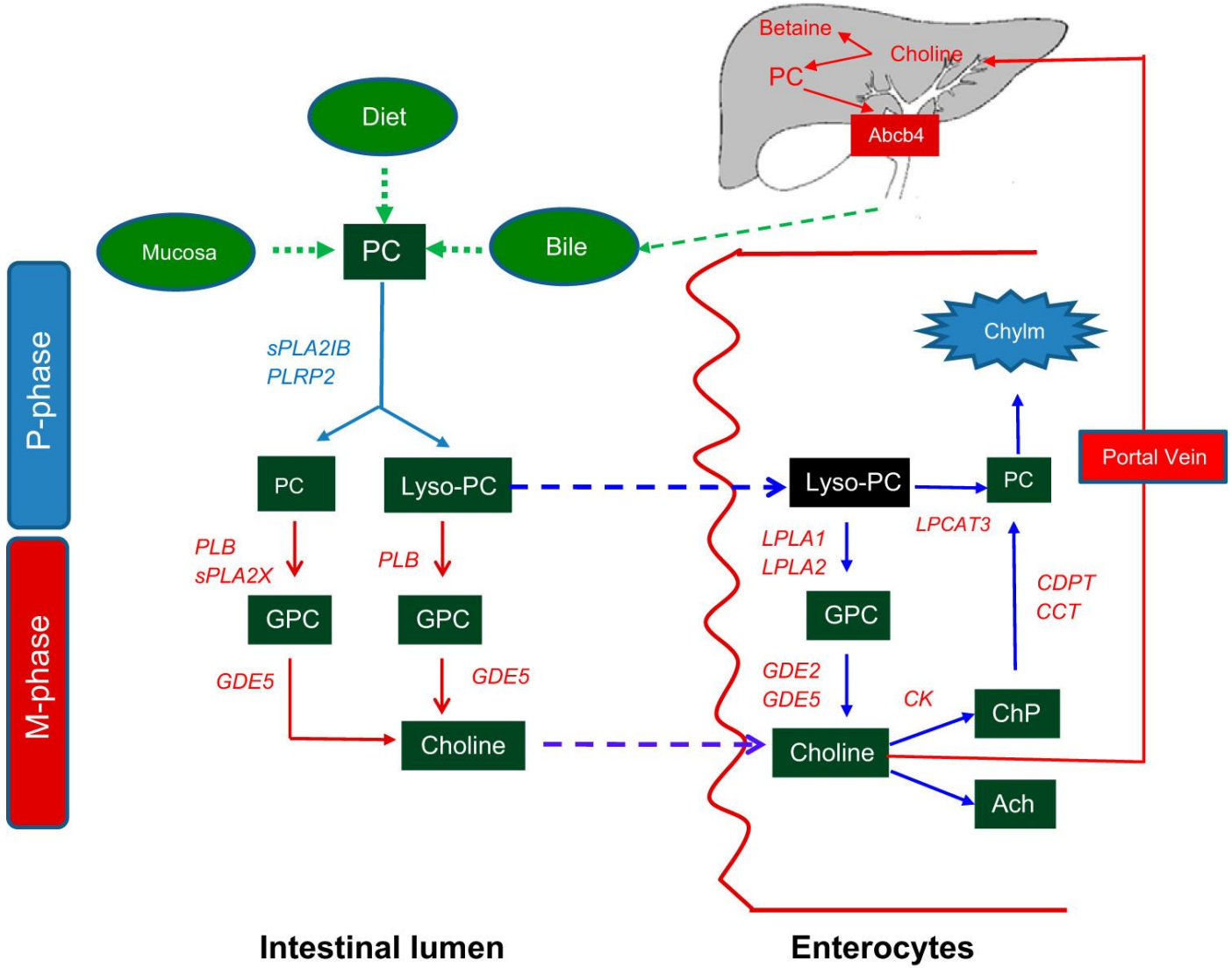
Structure of Phospholipids



S. Drescher and P. van Hoogevest, *Pharmaceutics*, **12**, 1–36, 2020

Neutral: PC, PE
Negatively charged: PG, PS, PI

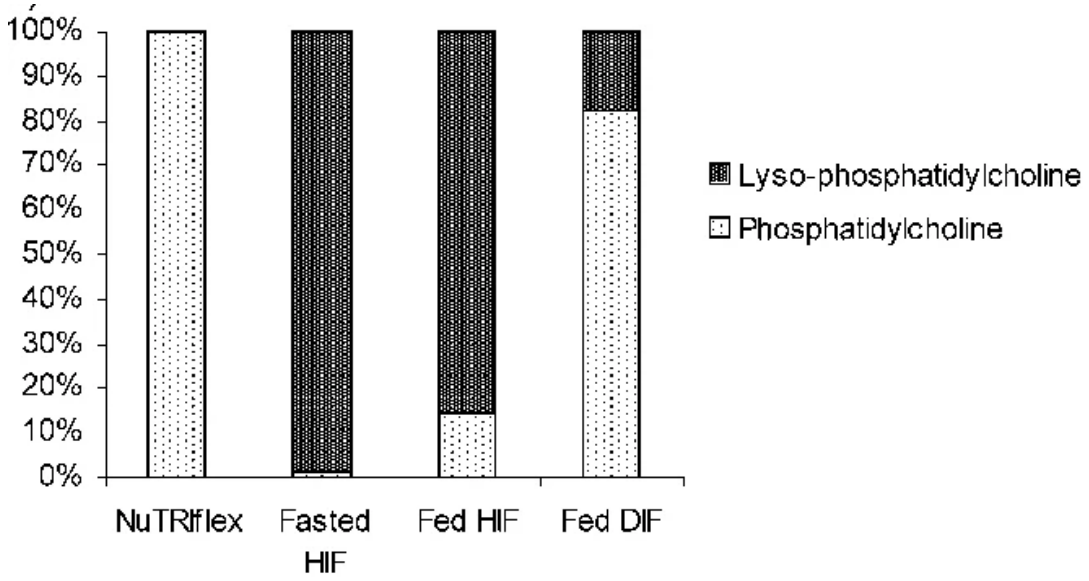
Sources and biofate of Phospholipids



Nilsson A, Duan RD.
Pancreatic and mucosal enzymes in choline phospholipid digestion.
Am J Physiol Gastrointest Liver Physiol. (2019) 316:G425–45.

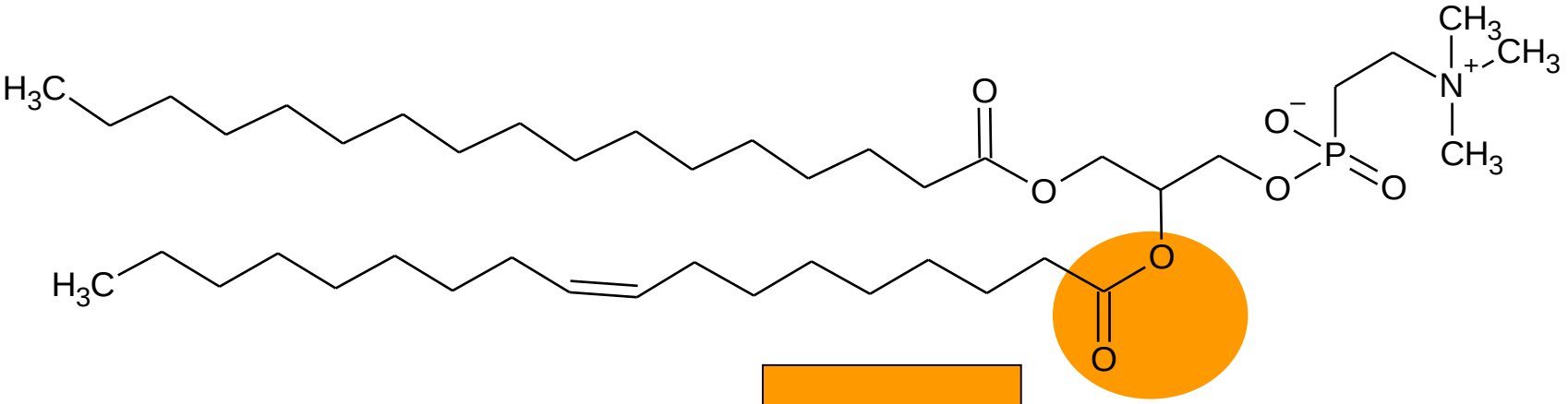
Biofate of Phospholipids (example PC)

- Enzymatic hydrolysis by sPLA2: formation of
  - Lyso-PC
  - Fatty acid
- Absorption > 90%
- Resynthesis of PC in enterocytes

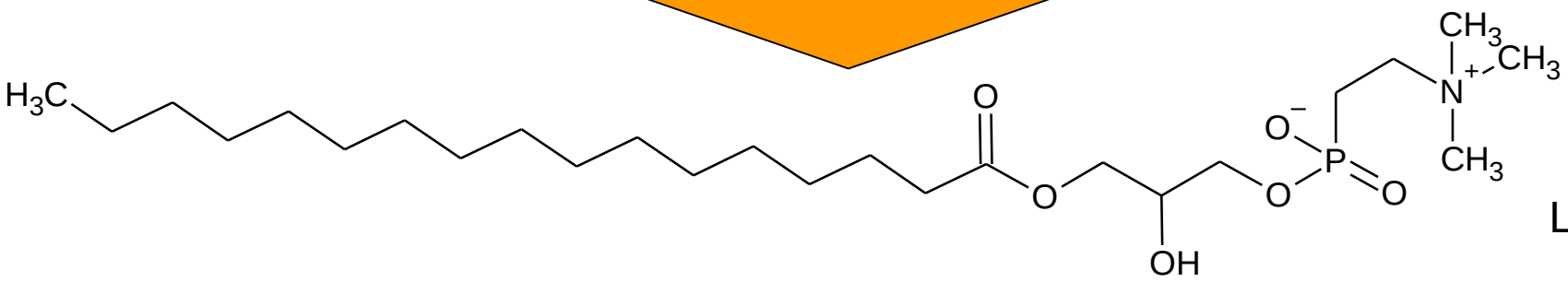


E.M. Persson et al.
The Effects of Food on the Dissolution of Poorly Soluble Drugs in Human and in Model Small Intestinal Fluids. Pharm Res 22, 2141–2151 (2005).

Intestinal digestion of PC by sPLA2IB



sPLA2



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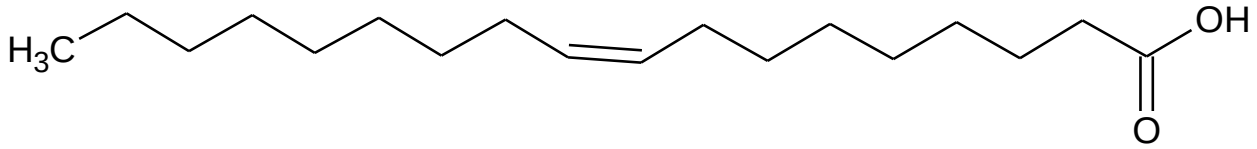
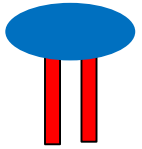


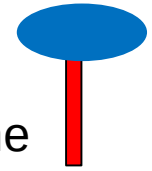
PC

phosphatidylcholine



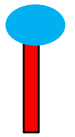
L-PC

Lysophosphatidylcholine

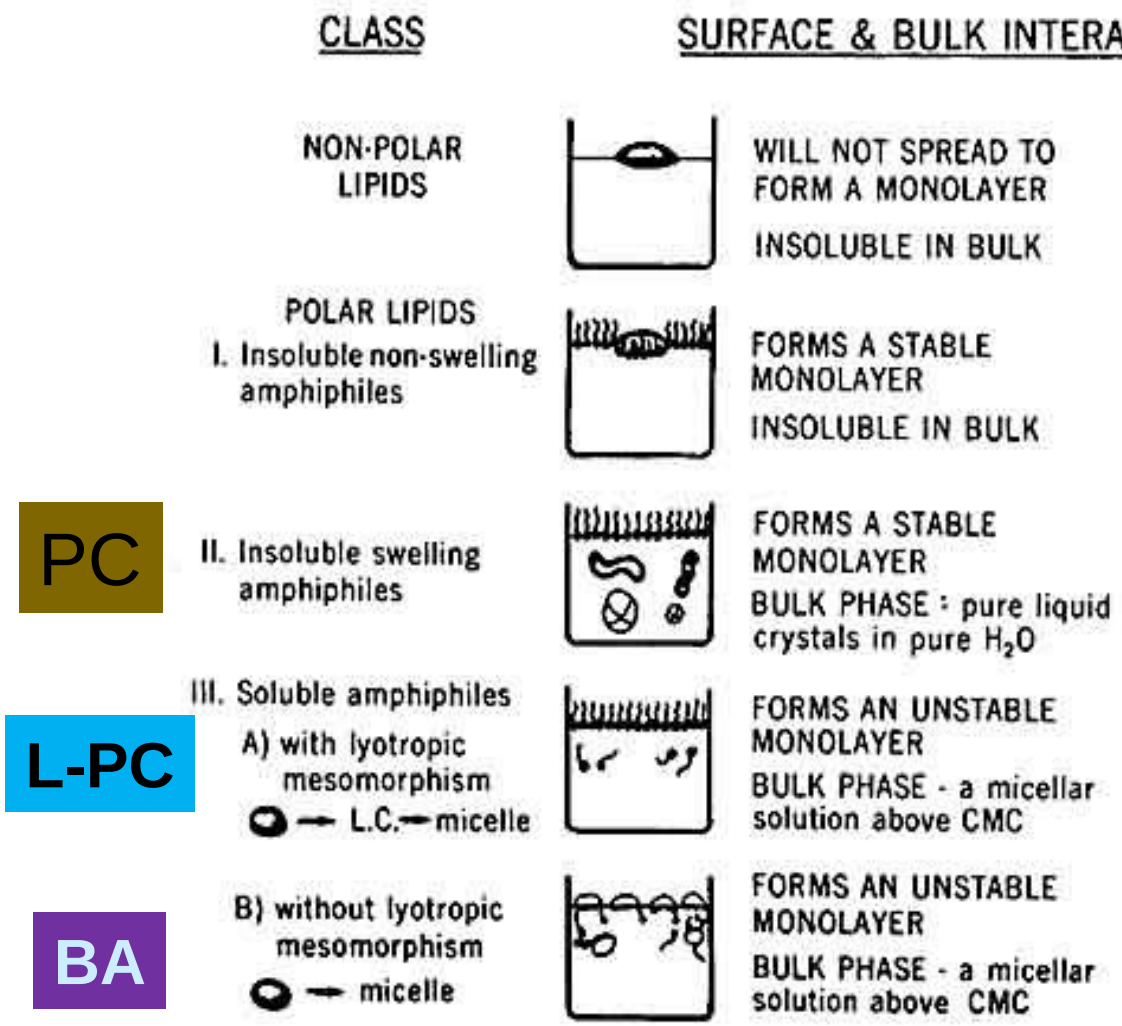


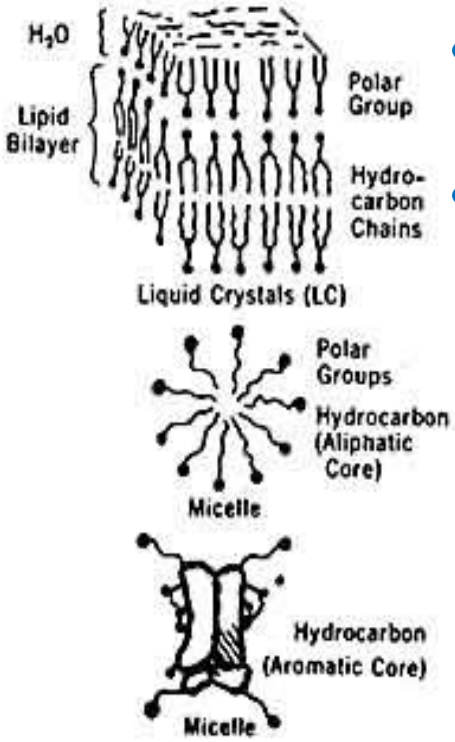
FA

Fatty acid

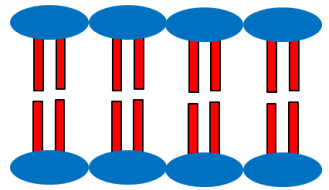


Lipid classification after Prof. Small



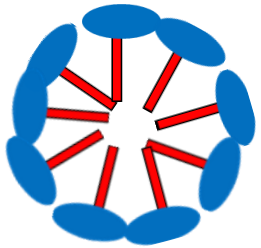


PC



Not dissolving,
Swelling,
Lamellar phase

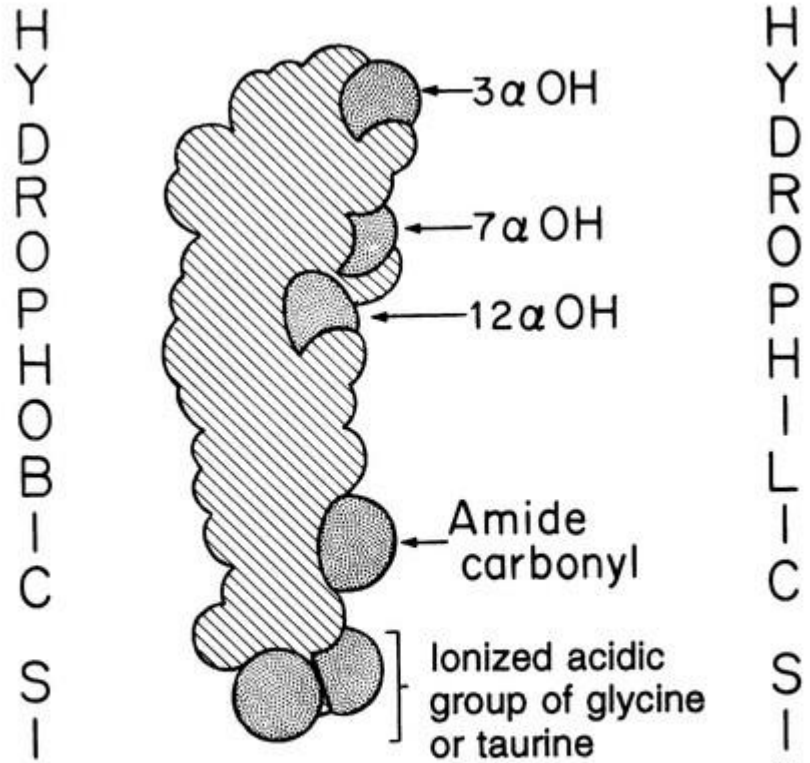
L-PC



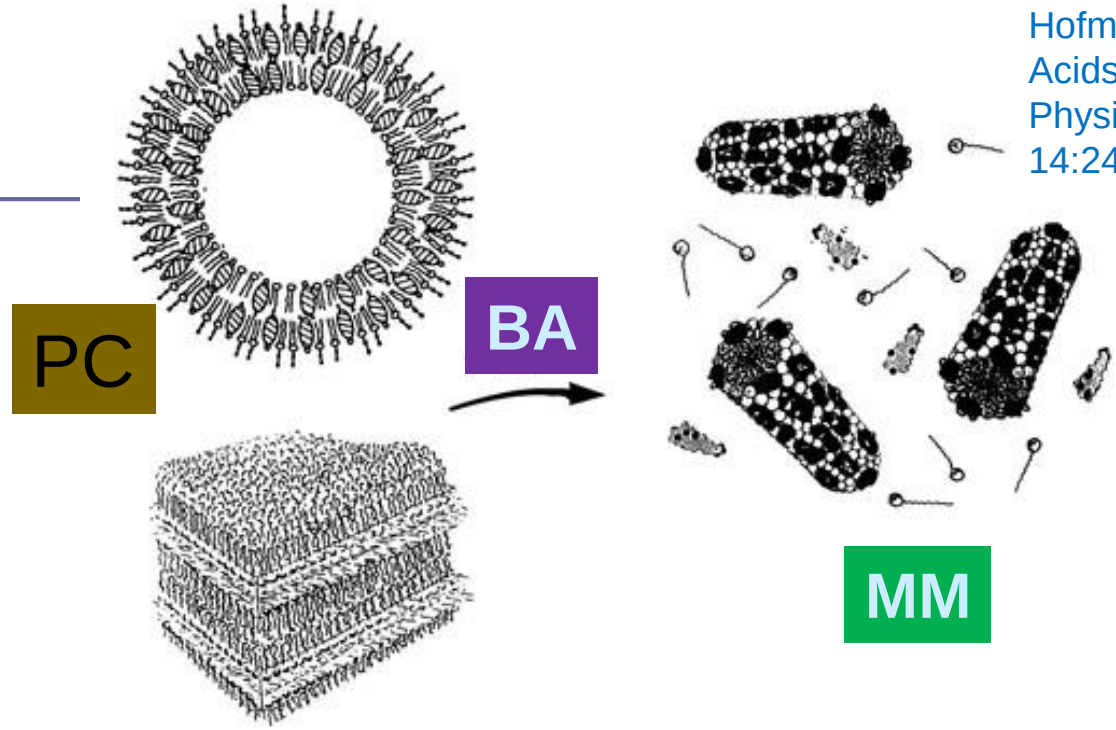
Dissolving
Micelle formation

Figure from Small. Handbook of lipids

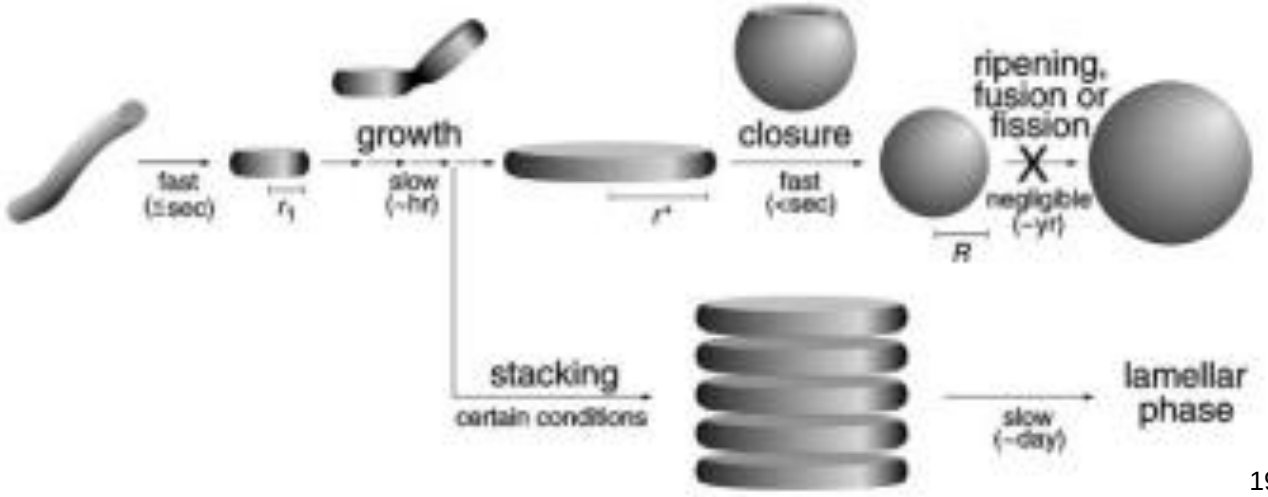
Bile acids, PC



BA
Bile Acids



Hofmann AF. Bile Acids: News Physiol Sci. 1999 14:24-29.



Leng J, Egelhaaf SU, Cates ME. Biophys J. 2003;85(3):1624-1646.

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How to design a PL-DDS for oral administration?

- Clear definition of goal
  - Increase of dissolution speed and solubility
  - Increase of permeability
  - Prolonged release
- Development of formulation strategy
- Selection of excipients and processes
- Relevant in vitro tests (dilution in relevant media, digestion assay)
- Preclinical in vivo studies
- Clinical studies

Consider variability of pH-values: stomach

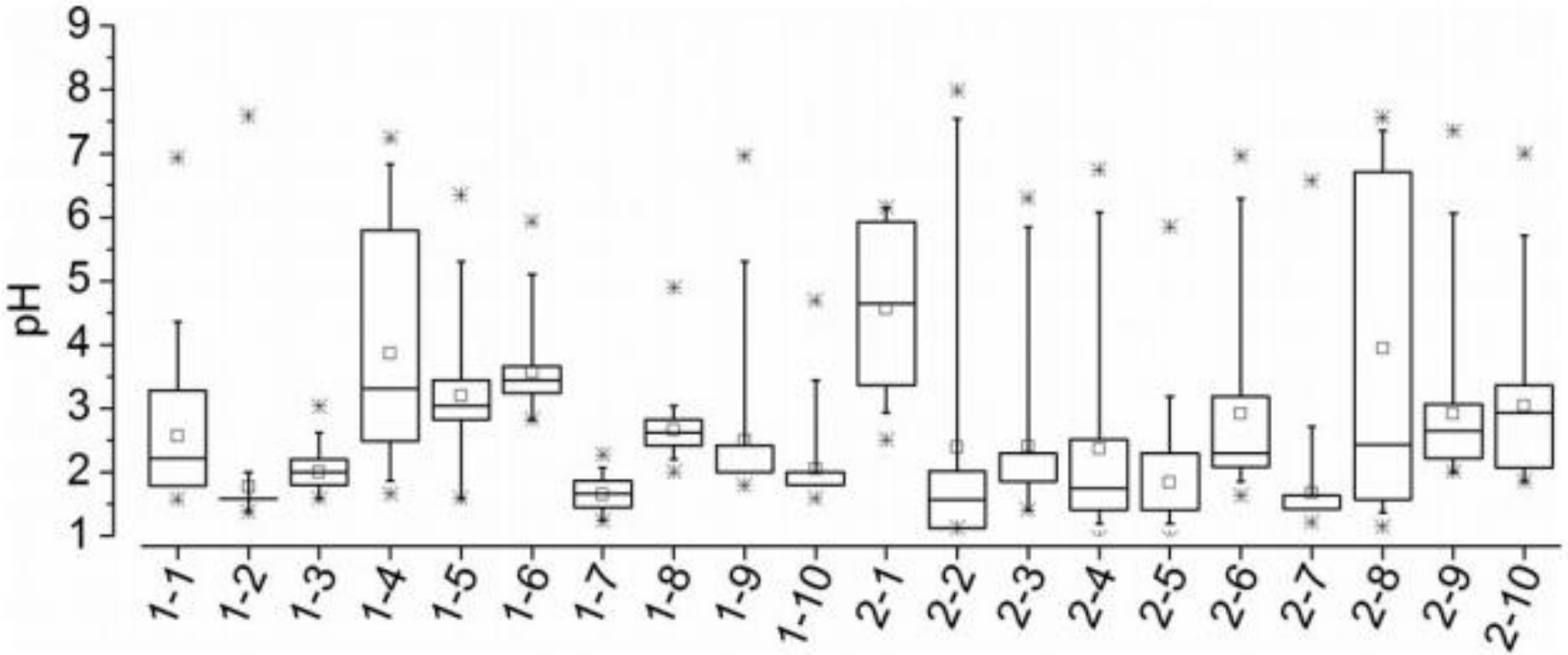
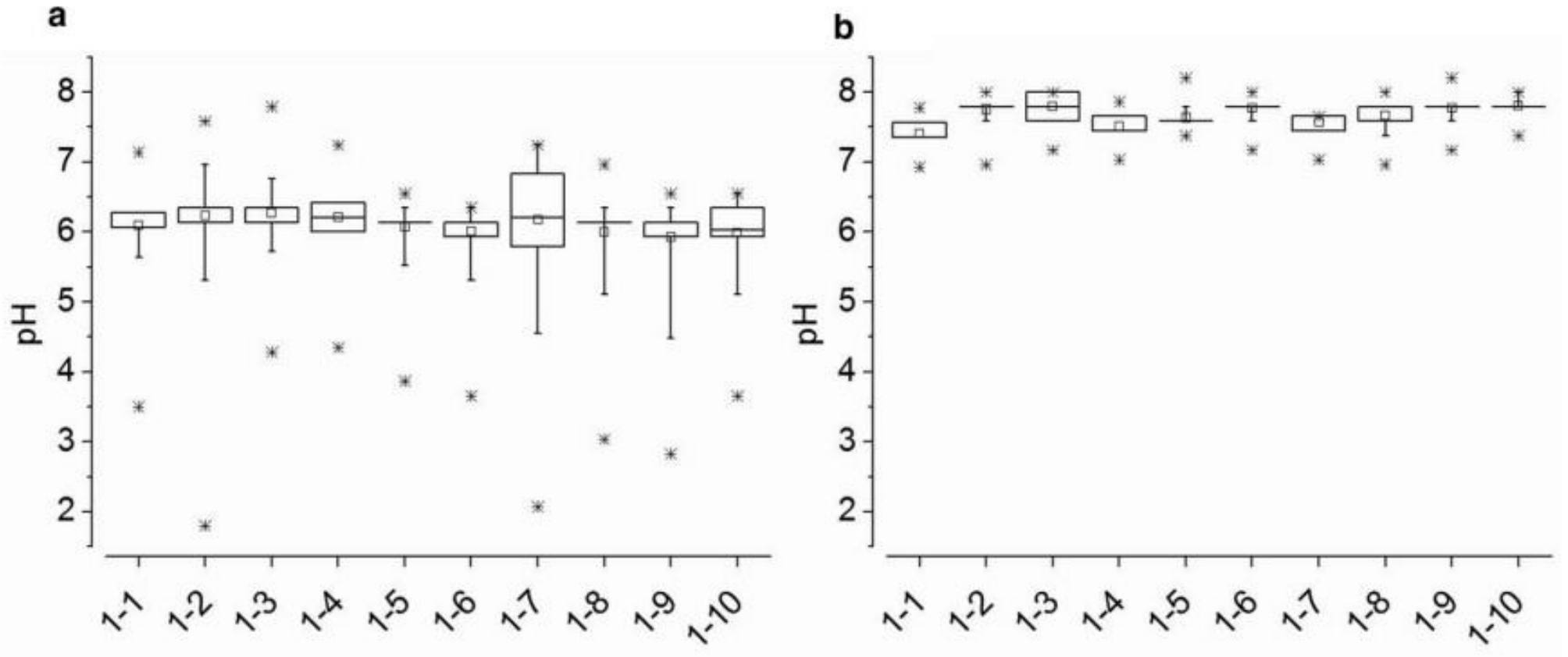


Figure 3. Box plots (box: 50%, whisker: 5%–95%, square: mean, asterisks max/min) of gastric pH values for both studies.

Gastric pH values
(fasted state)

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

Consider variability of pH-values: 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

Examples of physiological dissolution media

BA

PC

Fasted State Simulated Intestinal Fluid (FaSSIF)	Fed State Simulated Intestinal Fluid (FeSSIF)	Simulated Gastric Fluid (SGF)	Simulated Intestinal Fluid
Sodium taurocholate **3 mM** Phosphatidylcholine **0,75 mM** Sodium hydrogen-phosphate 28.66 mM Sodium chloride 106 mM Sodium hydroxide q.s. pH: 6.5	Sodium taurocholate **15 mM** Phosphatidylcholine **3,75 mM** Acetic acid 144 mM Sodium chloride 173 mM Sodium hydroxide q.s. pH: 5.0	NaCl 34.2 mM HCl 82.2 mM Pepsin (800-2500 u/mg) 3.2 g Water ad 1000ml pH: 1.2	Monobasic potassium phosphate 39 mM Sodium hydroxide 15.4 mM Pancreatin 10 g Water ad 1000 ml pH: 6.8

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Phospholipids as drug products

Fachinformation

SANOFI

Essentiale® Kapsel 300 mg

1. Bezeichnung des Arzneimittels

Essentiale® Kapsel 300 mg
Hartkapsel

2. Qualitative und quantitative Zusammensetzung

Wirkstoff:
1 Hartkapsel enthält:
300 mg entölte angereicherte Phospholipide aus Sojabohnen. Die Phospholipide sind quantifiziert auf 73–79 % Phosphatidylcholin, enthalten bis zu 7 % Phosphatidylethanolamin und weniger als 0,5 % Phosphatidylinositol.

Alter bzw. (Körpergewicht)	Einzeldosis	Tagesgesamtdosis
Jugendliche (ca. 43 kg) und Erwachsene	2 Hartkapseln (600 mg Phospholipide aus Sojabohnen)	3 mal täglich 2 Hartkapseln (1800 mg Phospholipide aus Sojabohnen)

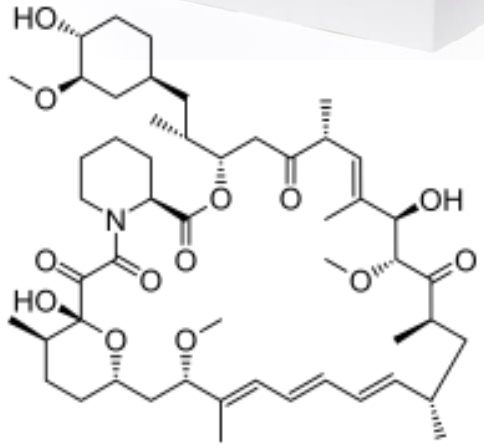
Zunahme der Beschwerden sowie bei Auftreten anderer unklarer Beschwerden sollte ein Arzt aufgesucht werden."

Kinder
Zur Anwendung von Essentiale Kapsel 300 mg bei Kindern liegen keine ausreichen-

Erkrankungen des Gastrointestinaltrakts
Häufigkeit nicht bekannt: gastrointestinale Beschwerden in Form von Magenbeschwerden, weichem Stuhl und/oder Diarrhoe.

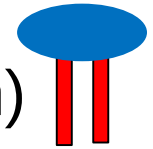
Erkankungen der Haut und des Unterhautzellgewebes

PLs as solubilizers: organic solutions



Rapamune 1mg/ml Oral Solution

- Polysorbate 80
- Phosal 50 PG:
  - ((3-sn-Phosphatidyl)choline (soy) (= lecithin)



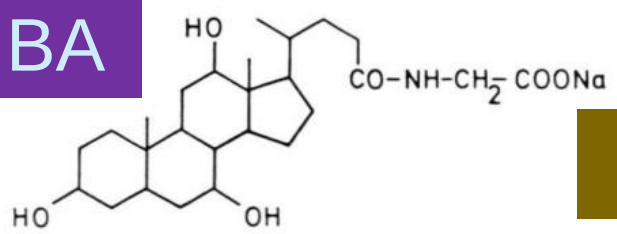
  - Propylene glycol
  - Glycerolmono/dialkanoate
  - Ethanol
  - Soy derived fatty acids
  - Palmitoylascorbic acid

Phosal = brand of Lipoid

1 mL contains: < 25 mg Ethanol, around **350 mg PG**, 20 mg soy oil

History of MM

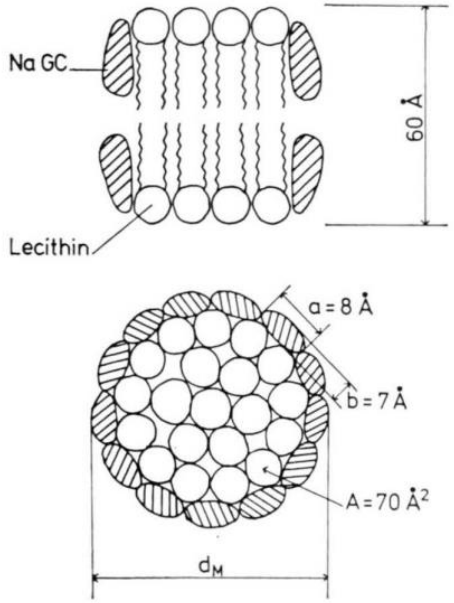
BA



Na Glycocholate

PL

Egg Lecithin

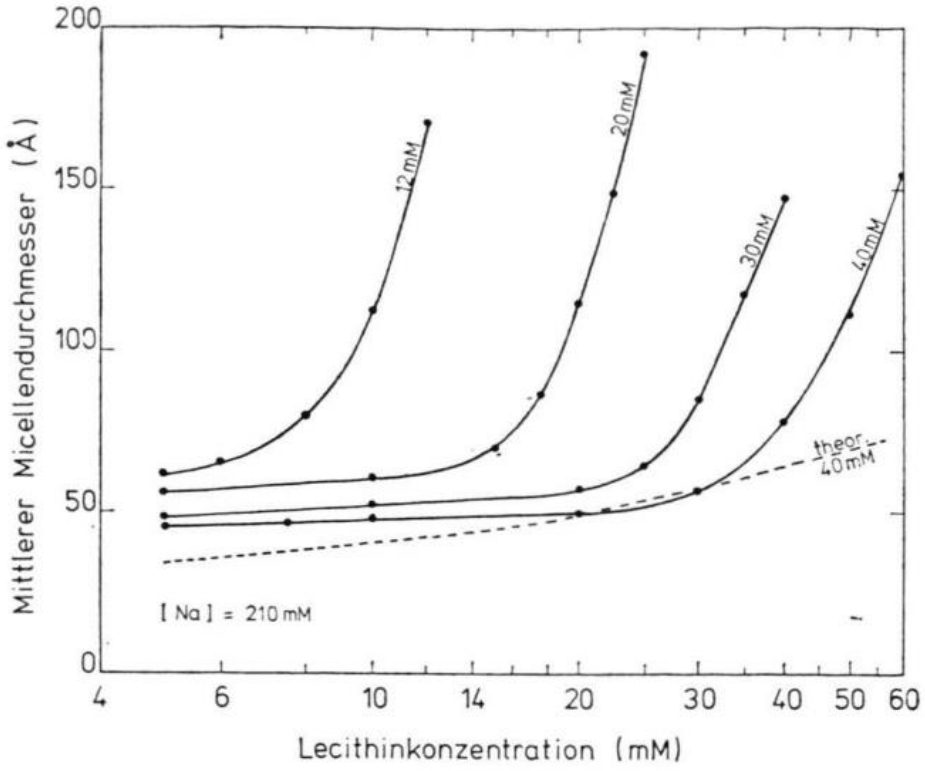


Untersuchungen über die Größe, Struktur und Dynamik von Gallensäure/Lecithin-Mischmicellen

Size, Structure, and Dynamics of Bile Salt/Lecithin Mixed Micelles

Ch. Gähwiller, C. von Planta, D. Schmidt und H. Steffen
Zentrale Forschungseinheiten F. Hoffman-La Roche A.G. Basel

(Z. Naturforsch. **32 c**, 748–755 [1977]; eingegangen am 8. Juni 1977)



Roche

Diazepam MM
Konakion MM

Phospholipids as solubilizers: MM for oral/ i.m. / i.v

Since 2018
Cheplapharm
Arzneimittel

Fachinformation

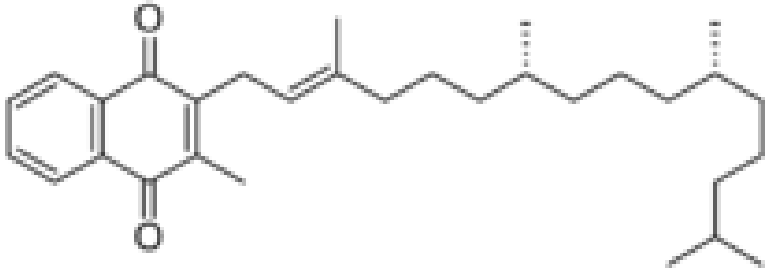
CHEPLA PHARM Arzneimittel

Konakion® MM 10 mg

1. BEZEICHNUNG DES ARZNEIMITTELS

Konakion® MM 10 mg

Dosierungsempfehlungen zur Vitamin-K_1-Therapie bei Patienten mit asymptomatisch hohem INR mit oder ohne leichte Blutungen



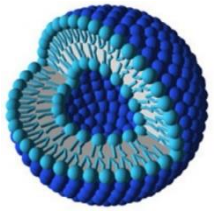
- Glycocholic acid
- (3-sn-Phosphatidyl)cholin (soy)
- NaOH, HCl, water for injection

Learning from nature!
MM as solvent
Long history (Diazepam MM)
Thermodynamic stable system
No organic solvents

Example antiinflammatory PLs

Dr. Miriam Klein

- PS and PG have anti-inflammatory properties

Liposomes  vs. 

Mixed micelles

- What is the best DDS?
  - Production
  - Stability
  - Activity

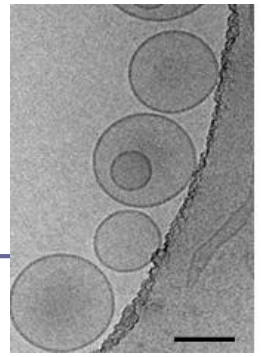
ELSEVIER

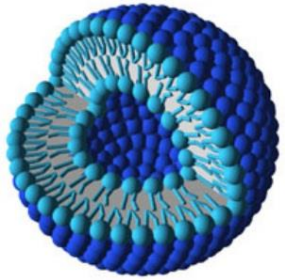
European Journal of Pharmaceutical Sciences
Volume 152, 1 September 2020, 105451

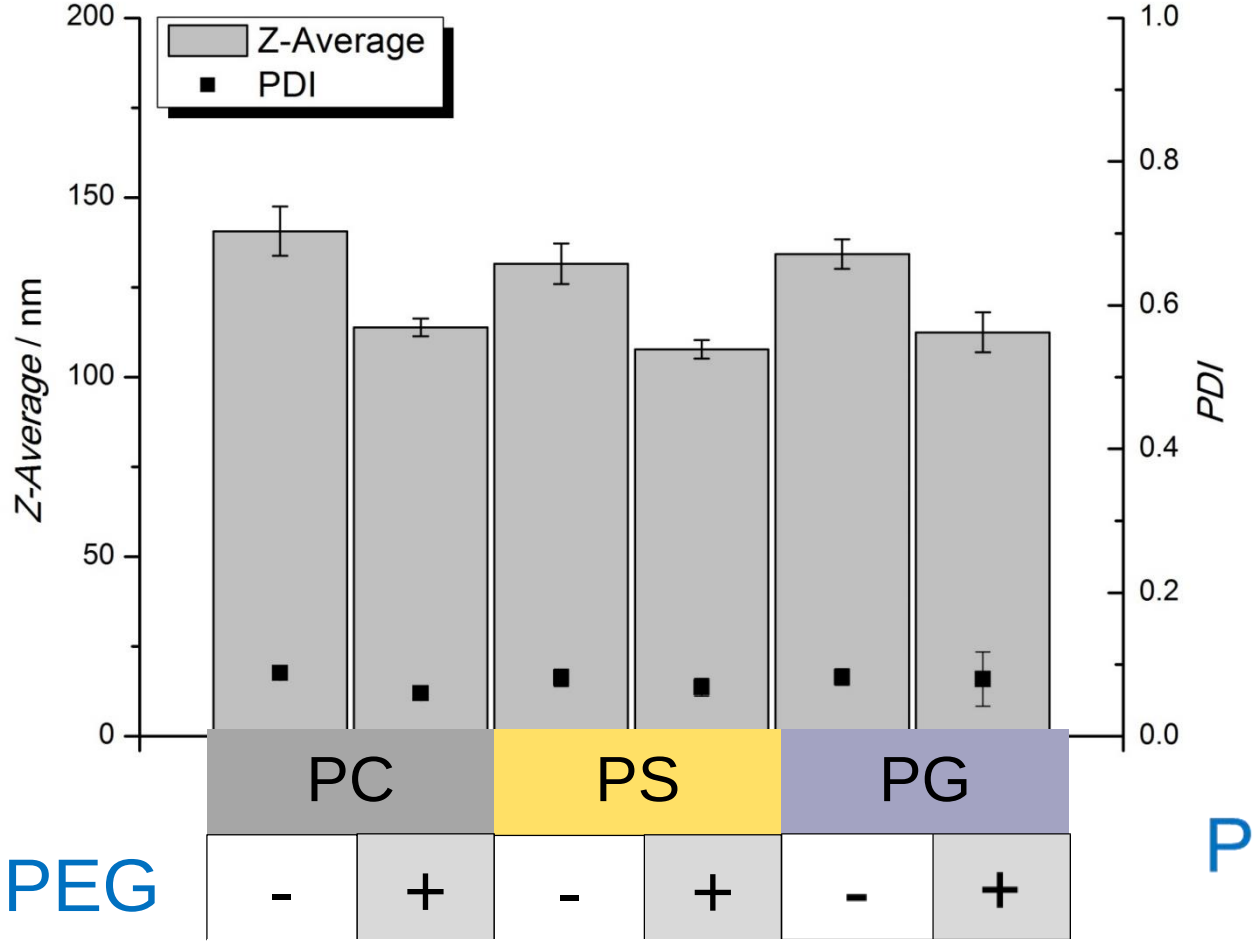
Phosphatidylserine (PS) and phosphatidylglycerol (PG) enriched mixed micelles (MM): A new nano-drug delivery system with anti-inflammatory potential?

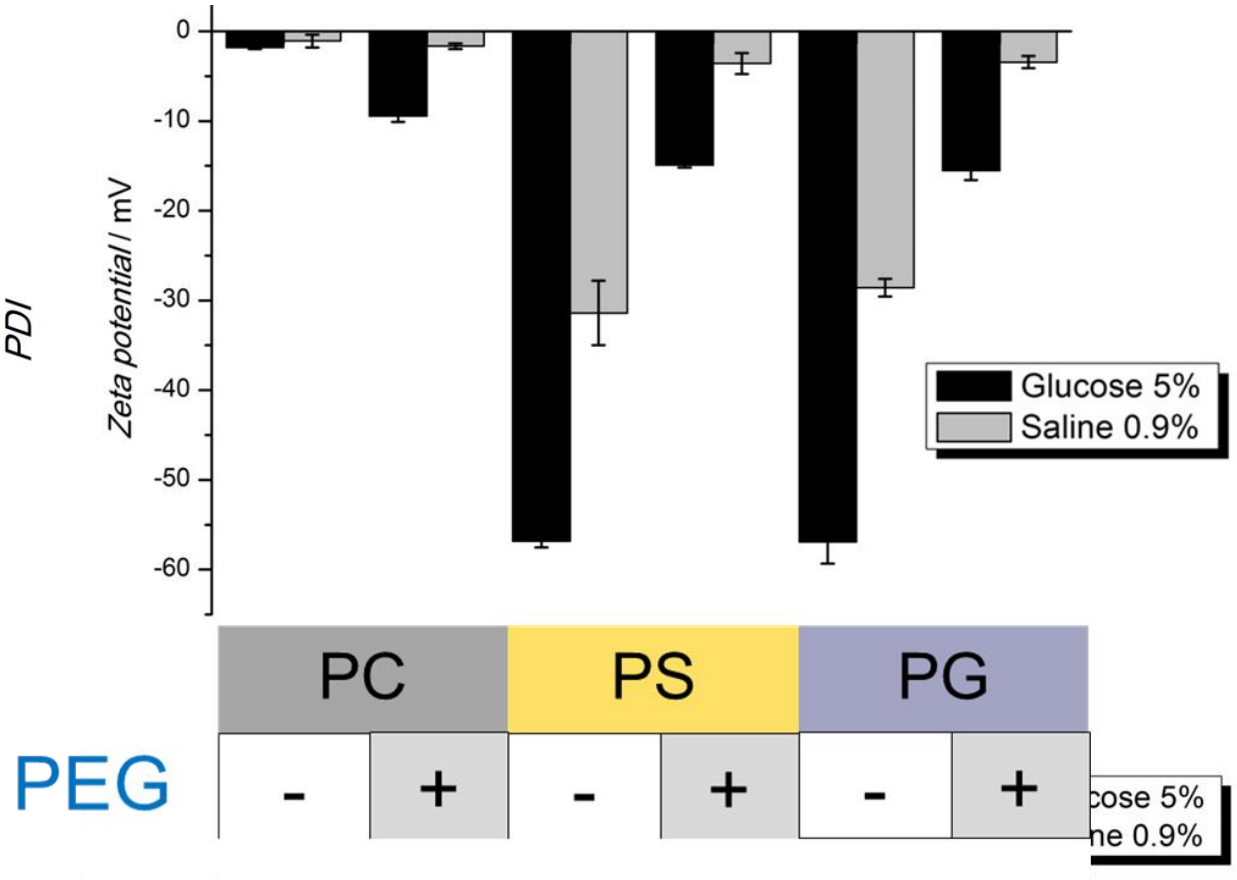
Miriam Elisabeth Klein [a], Max Rieckmann [b], Henrike Lucas [a], Annette Meister [c], Harald Loppnow [b], Karsten Mäder [a]

Liposome particle size / zeta potential

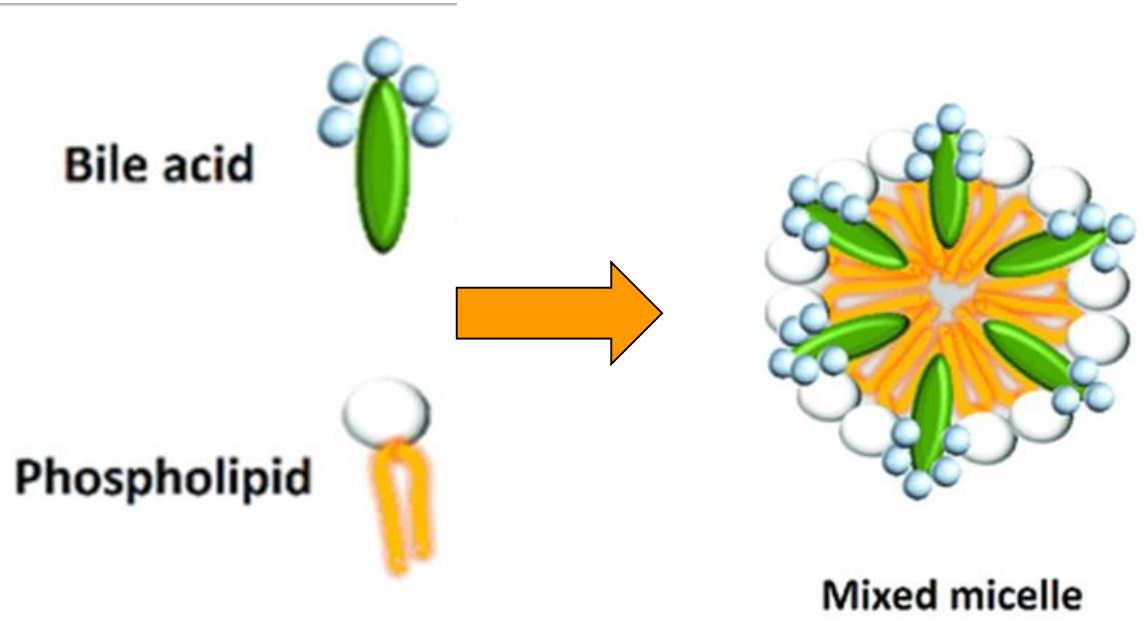




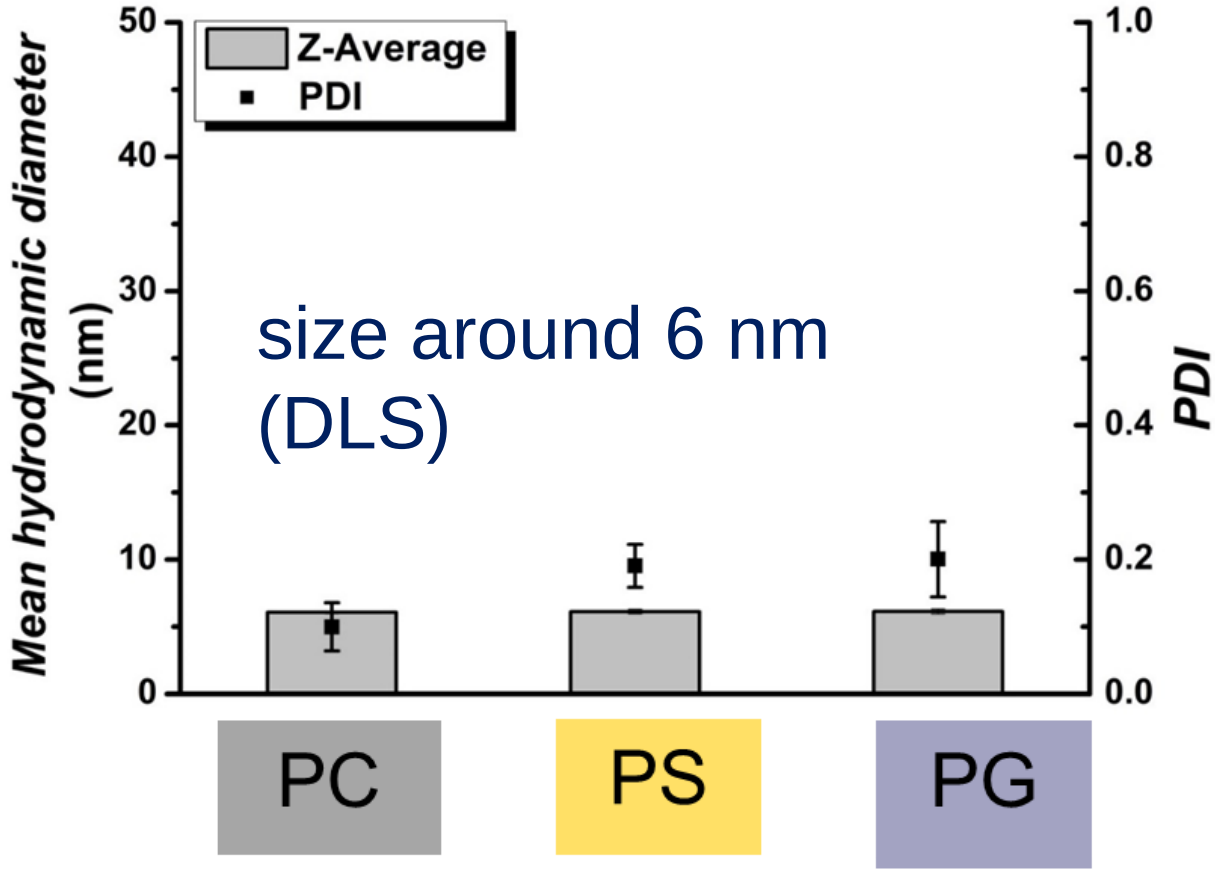




Mixed Micelles



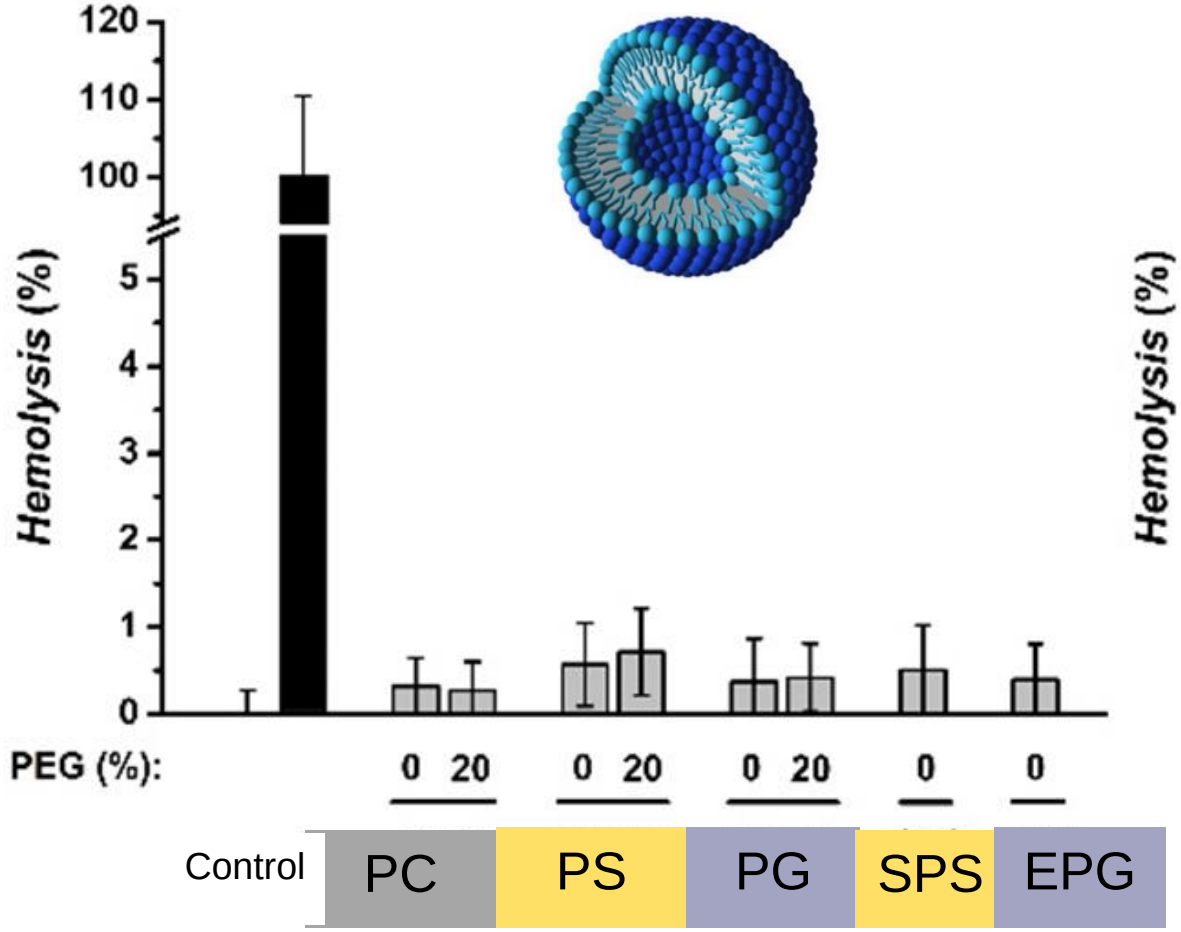
- Phospholipid – Na- Cholate 1:1 (w/w)
- Phospholipid:
  - Main component: PC
  - 0 – 30 % PS
  - 0 – 30 % PG



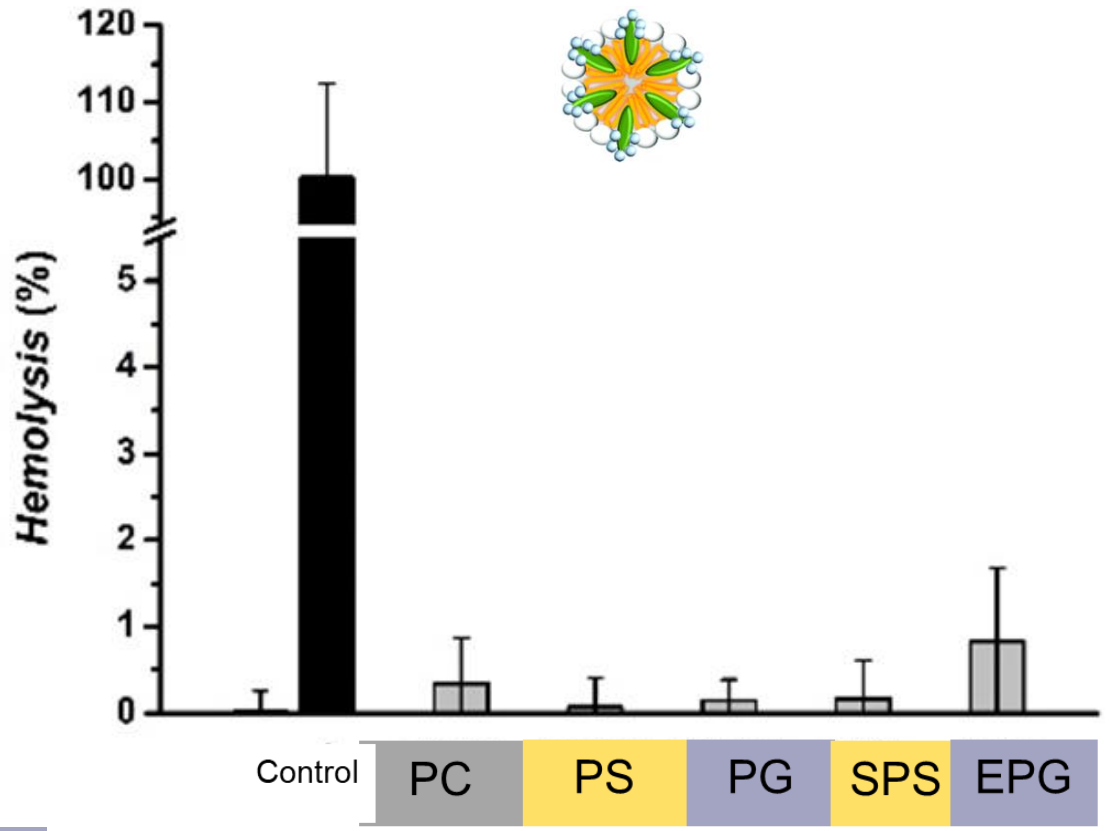
https://www.researchgate.net/figure/A-schematic-representation-of-mixed-micelle-and-bilosome-structures-Bilosomes-possess_fig3_328822017 [accessed 17 Sep, 2019]

No Hemolytic activity and cell toxicity of both

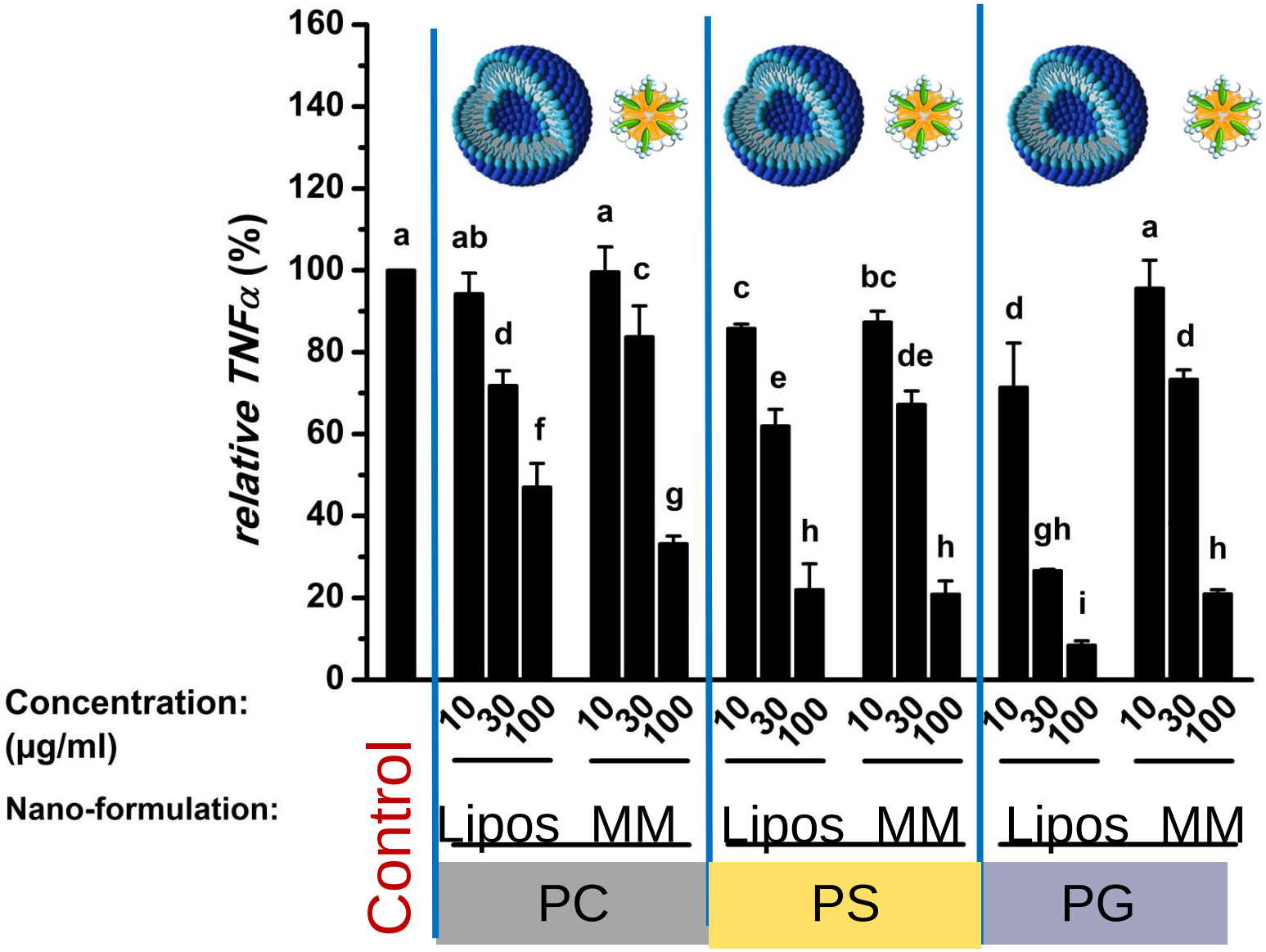
Liposomes



Mixed micelles



Bioactivity: liposomes vs. mixed micelles



similar anti-inflammatory activities of liposomes and MM

Advantages MM oral administration

- ✓ Easier to make
- ✓ Thermodynamic stable
- ✓ Easier to transform into a solid dosage form

Concepts for solid dosage forms of liposomes

- Problems:
  - Sticky and hygroscopic properties of many PLs
  - Liposomes do (in most cases) not form spontaneously.
- Possible solutions:
  - Encapsulation / embedding in solid materials (amphiphilic starches, maltodextrin)
  - Adsorption in porous carriers (phosphates, carbonates, silicates)

Adsorption porous $CaCO_3$

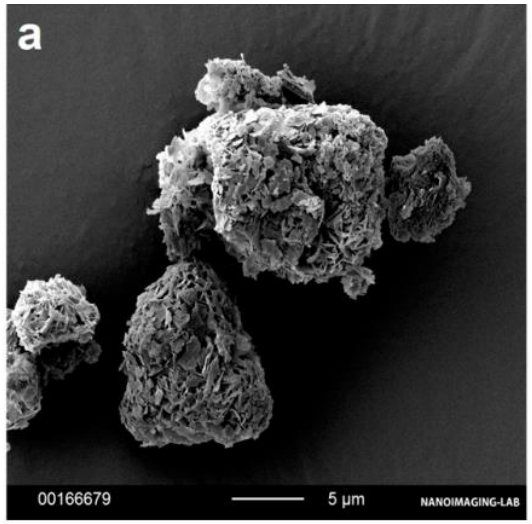
pharmaceutics

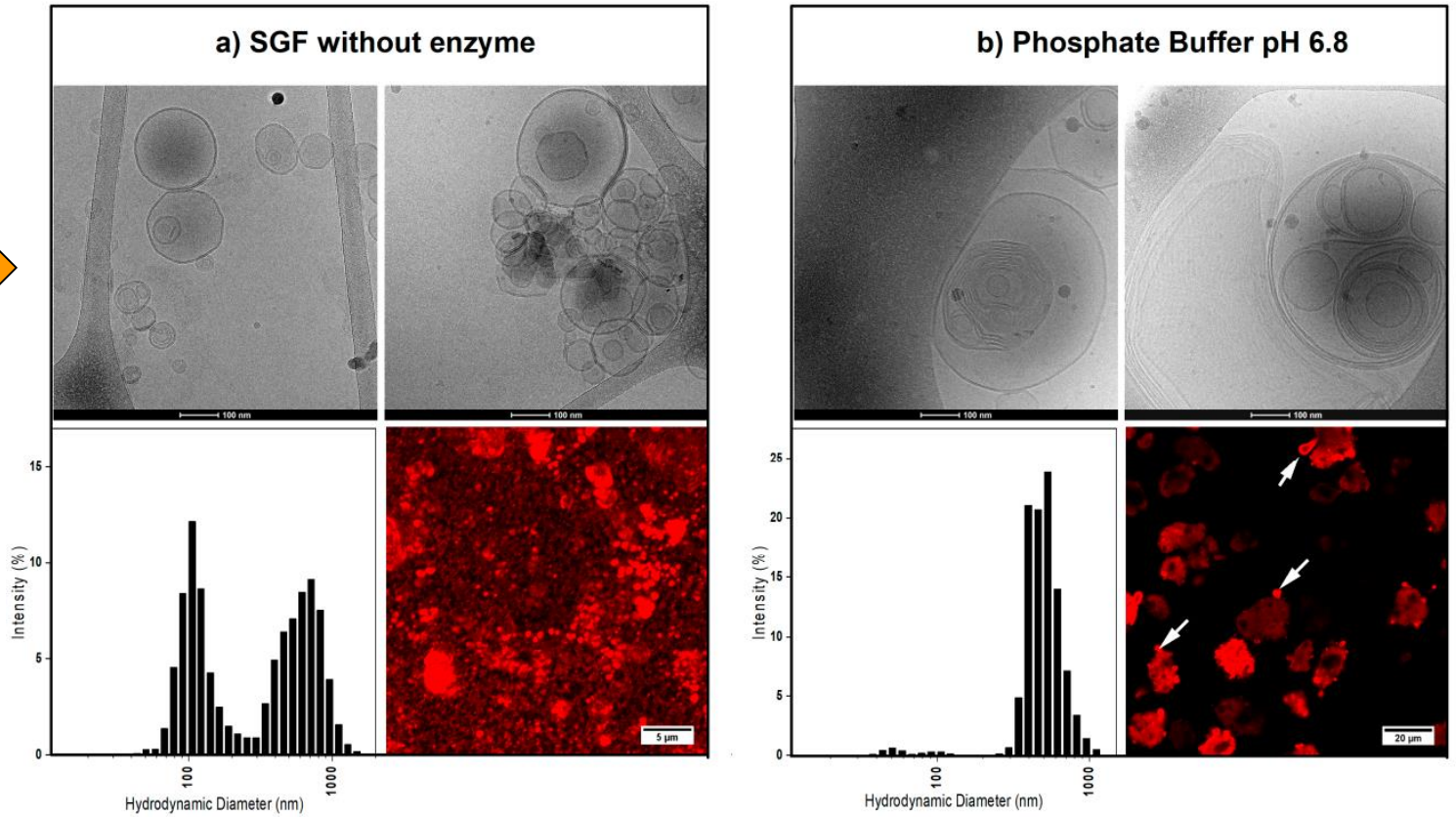
MDPI

Article

Spontaneous In Situ Formation of Liposomes from Inert Porous Microparticles for Oral Drug Delivery

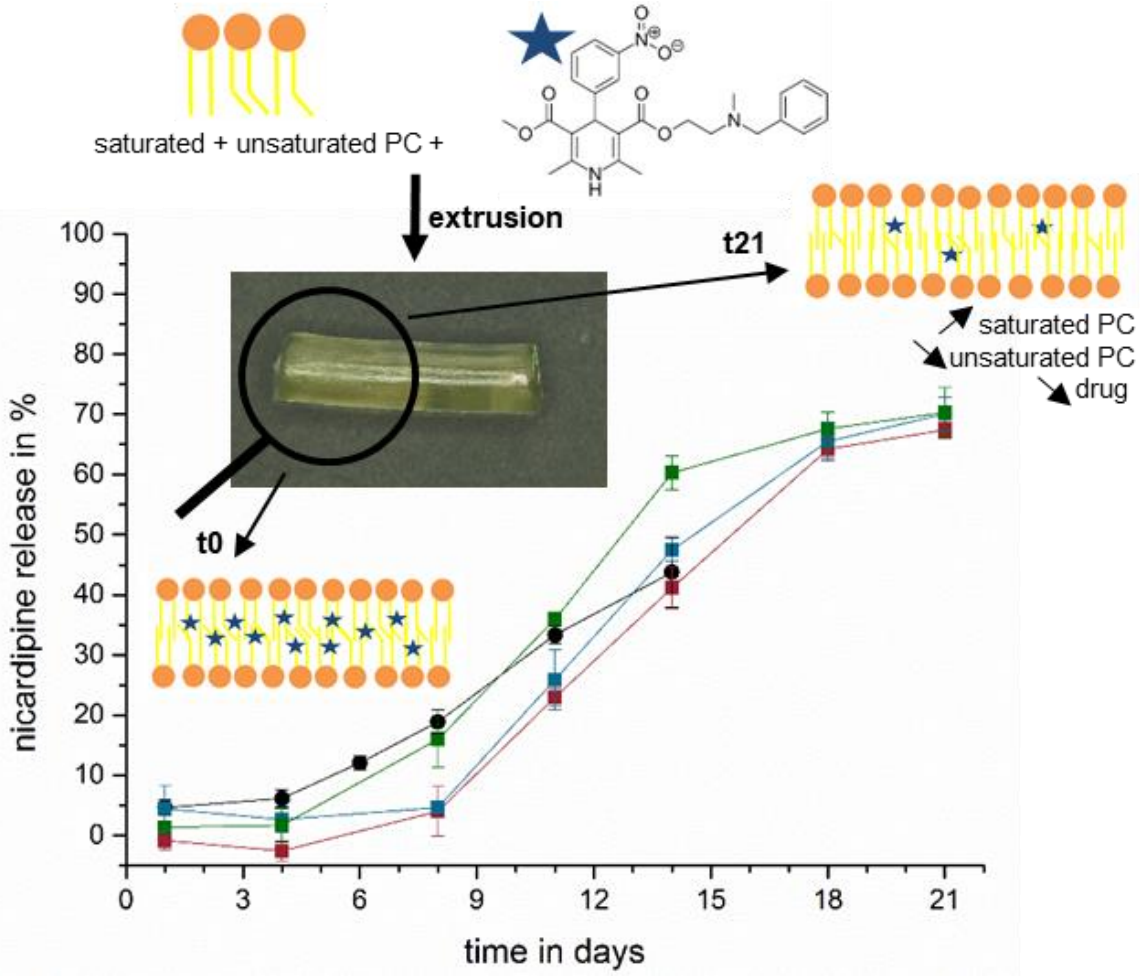
Maryam Farzan [1], Gabriela Québatte [1], Katrin Strittmatter [1], Florentine Marianne Hilty [2], Joachim Schoelkopf [2], Jörg Huwyler [1] and Maxim Puchkov [1,*]



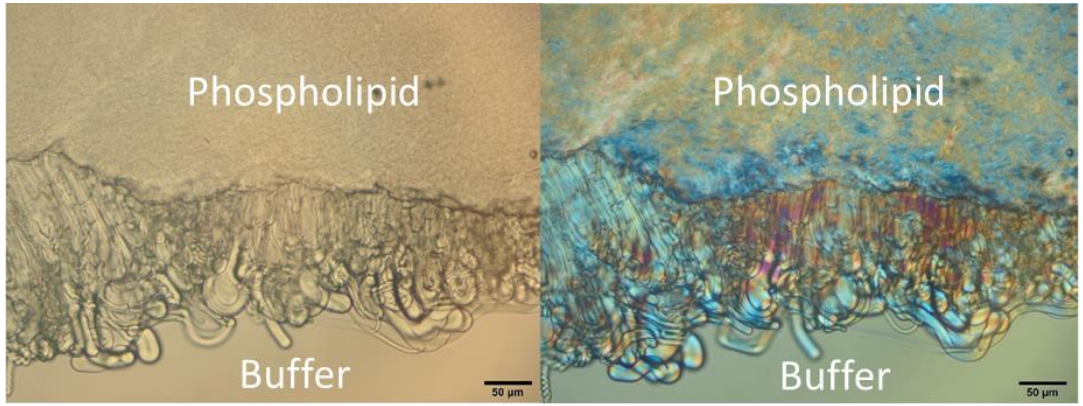


Example: Phospholipid extrudates

C. Zlomke, J. Albrecht, K. Mäder:
Pharmaceutics **2020**, *12*, 817.



- Goal here: local brain delivery, but oral applications possible
- Easy to extrudate at temp. < 100°C
- Ratio saturated / unsat. PC determines extrusion temp. and mechanical properties



Polarized light

Vesicle formation a the Interface

Example: Phospholipid extrudates oral

AAPS PharmSciTech (2019) 20: 159
DOI: 10.1208/s12249-019-1366-3

Check for updates

Research Article

Theme: Lipid-Based Drug Delivery Strategies for Oral Drug Delivery
Guest Editor: Sanyog Jain

Evaluation of Hydrogenated Soybean Phosphatidylcholine Matrices Prepared by Hot Melt Extrusion for Oral Controlled Delivery of Water-Soluble Drugs

Marina Kolbina,[1] Adrian Schulte,[2] Peter van Hoogevest,[3] Martin Körber,[4,5] and Roland Bodmeier[1]

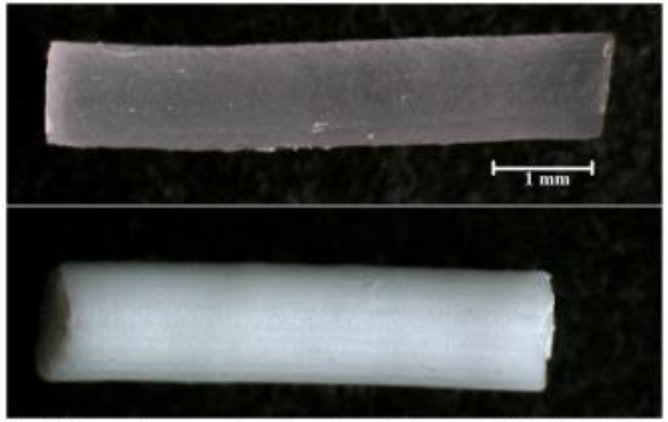
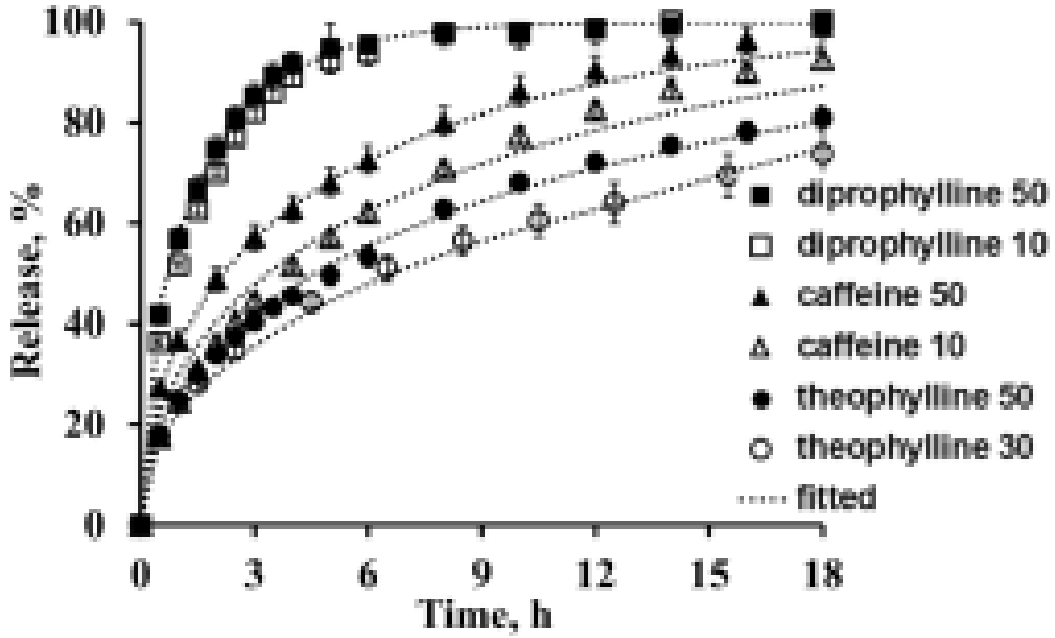


Fig. 2. Macroscopic pictures of extrudates: (upper) drug-free HSPC and (lower) 50% theophylline-loaded extrudate



Overcoming poor permeability with PLs

International Journal of Nanomedicine

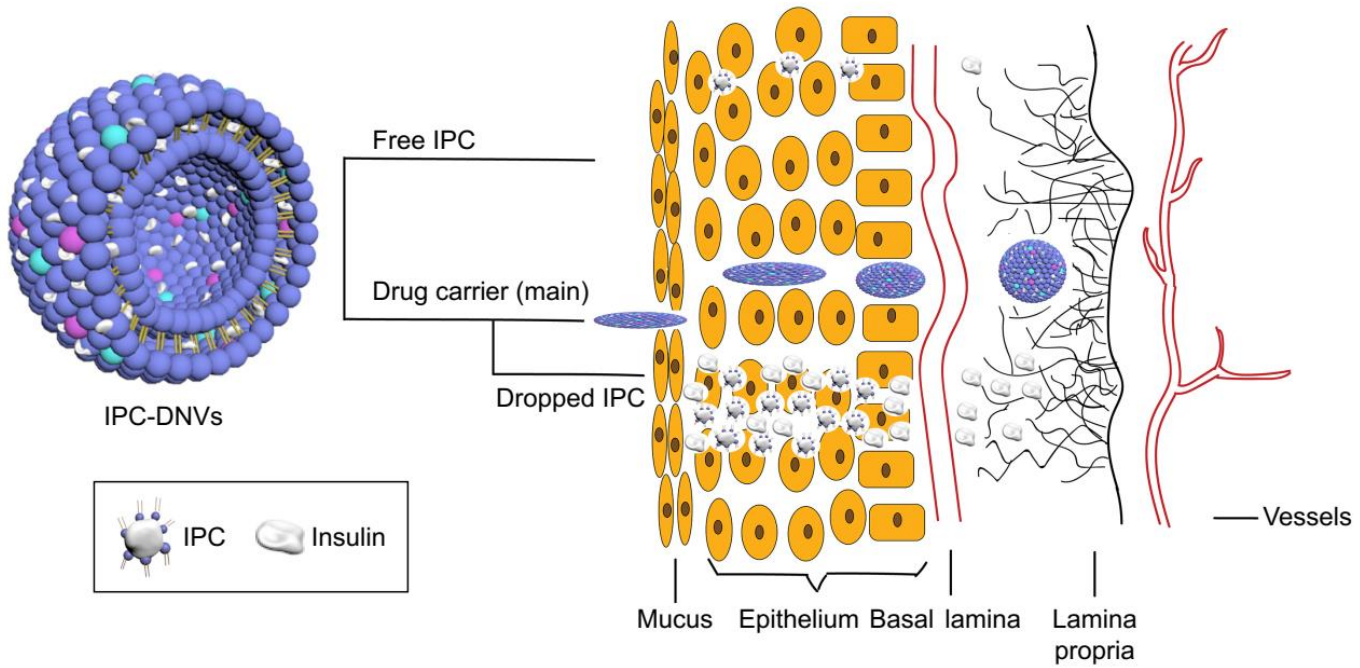
Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Mechanisms of deformable nanovesicles based on insulin-phospholipid complex for enhancing buccal delivery of insulin

You Xu[1,2]
Xing Zhang[1,2]
Yun Zhang[1,2]
Jun Ye[1,2]
Hong-Liang Wang[1,2]
Xuejun Xia[1,2]
Yuling Liu[1,2]



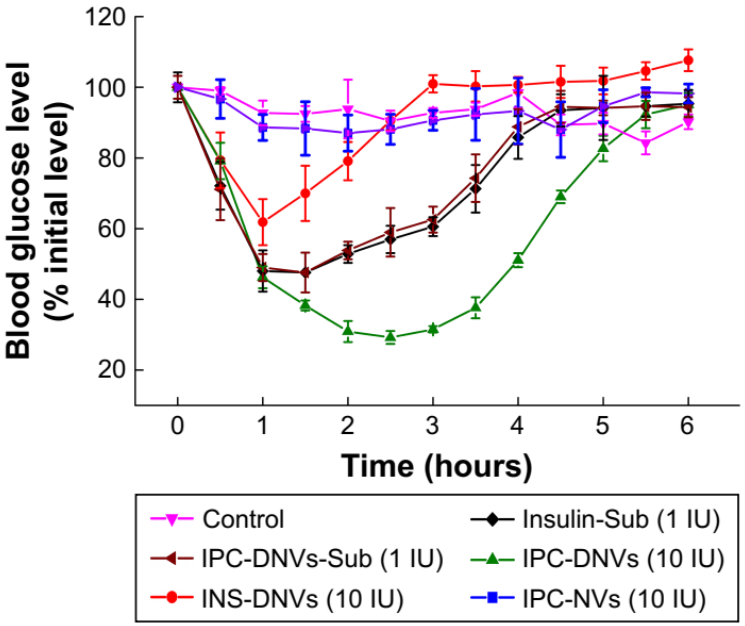


Figure 9 Mechanisms of IPC-DNV transport in mucosal permeation.
Abbreviations: DNVs, deformable nanovesicles; IPC, insulin-phospholipid complex.

Overcoming Efflux pumps by PLs?

European Journal of Pharmaceutical Sciences 108 (2017) 13–22

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

The application of P-gp inhibiting phospholipids as novel oral bioavailability enhancers — An *in vitro* and *in vivo* comparison

Manuel Weinheimer [a,*], Gert Fricker [b], Jürgen Burhenne [c], Patricia Mylius [a], Rolf Schubert [a]

[a] *Department of Pharmaceutical Technology and Biopharmacy, Albert Ludwig University Freiburg, Hermann-Herder-Str. 9, D-79104 Freiburg, Germany*
[b] *Institute of Pharmacy and Molecular Biotechnology, University of Heidelberg, Im Neuheimer Feld 329, D-69120 Heidelberg, Germany*
[c] *Department of Clinical Pharmacology and Pharmacoepidemiology, Heidelberg University Hospital, Im Neuenheimer Feld 410, D-69120, Heidelberg, Germany*

Increased lymphatic uptake by PLs?

Journal of Controlled Release 341 (2022) 676–701

Contents lists available at ScienceDirect

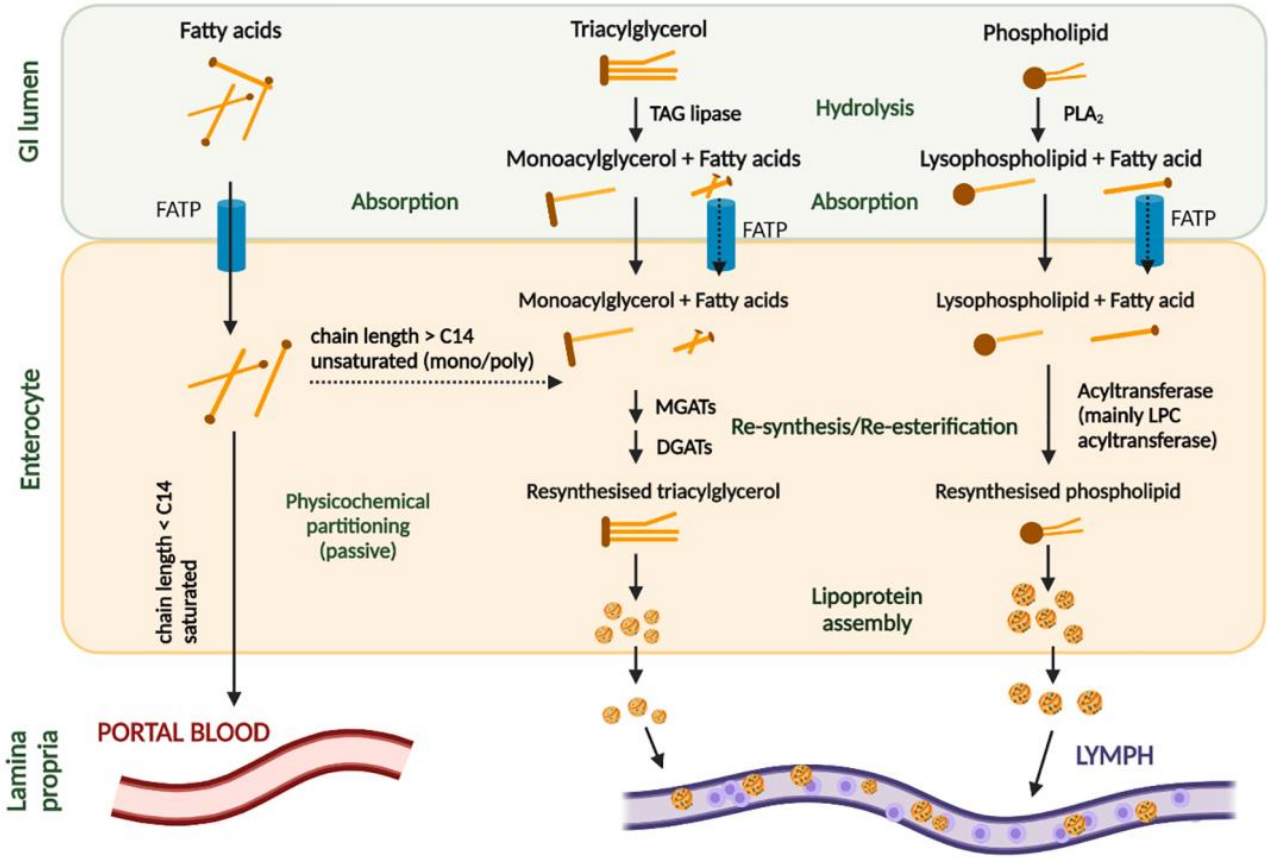
Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review article

Smart design approaches for orally administered lipophilic prodrugs to promote lymphatic transport

Aurelia S. Elz [a], Natalie L. Trevaskis [b], Christopher J.H. Porter [b], Joanne M. Bowen [c], Clive A. Prestidge [a,*]



Outline

- Introduction: Challenges of oral administration
- Phospholipids (PL):
  - Chemical structures and behavior in water
  - Biofate after oral ingestion
- How to design a PL-DDS for oral administration
- Examples
- **Summary and outlook**

PLs can contribute to solve these problems of oral administration:

- Poor permeability (e.g. BCS III drugs)
  - Enhance permeability drug **specific**
- Poor dissolution (e.g. BCS II drugs)
  - Increase dissolution kinetics
  - Increase solubility
- Food dependent variability
  - Develop formulations which are less food dependent
- Short half live
  - Develop formulation for oral controlled release – (requires absorption in colon)

Examples of projects

Phospholipid
Forschungszentrum / Research Center
Heidelberg

- Liposomes as oral delivery systems for poorly soluble compounds: behavior during digestion and absorption processes
- Phospholipids as excipients in Amorphous Solid Dispersions – an attempt to establish hot-melt-extrusion for oral formulations of poorly soluble drugs
- Bioactive liposomes for the treatment of Non-Alcoholic SteatoHepatitis (NASH)
- Co-amorphous drug-lecithin systems – bridging the gap between amorphous solid disperions and lipid based drug delivery
- Enabling oral delivery of peptides by designing phospholipid complexes for self-emulsifying drug delivery systems
- Oral mixed micelle formulations – a novel phospholipid-based platform for safe and effective pediatric drug delivery

https://www.phospholipid-research-center.com/funding/funded-projects/

Benefits and problems of phospholipids

Benefits

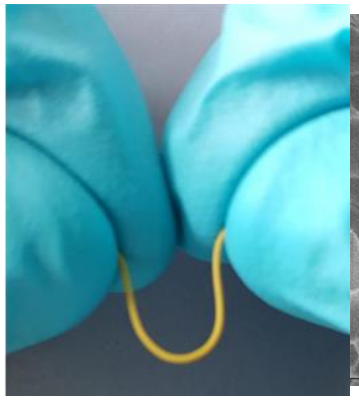
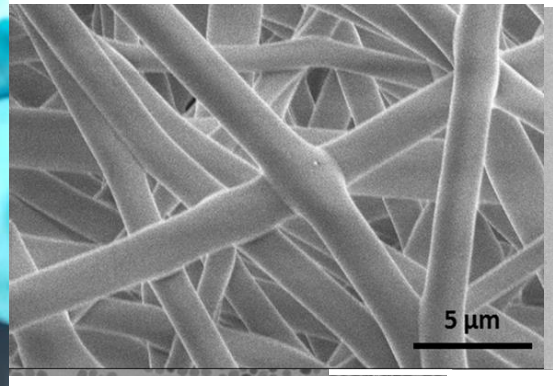
- Natural source
- Structure very common in nature, including the human body
- Biodegradable
- Excellent safety profile
- Decades of research, very good knowledge and database

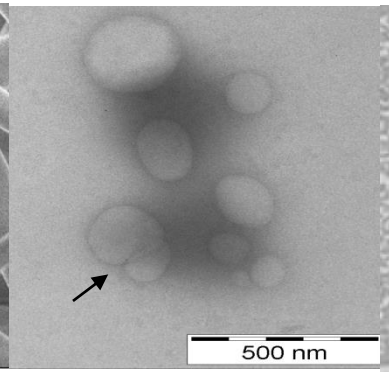
Problems

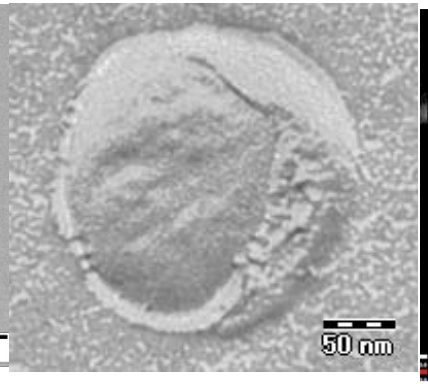
- Supplier dependent quality
- Often hygroscopic, sticky material
- Chemical degradation by oxidation and hydrolysis
- Precipitation by Ca^{2+} or Mg^{2+}

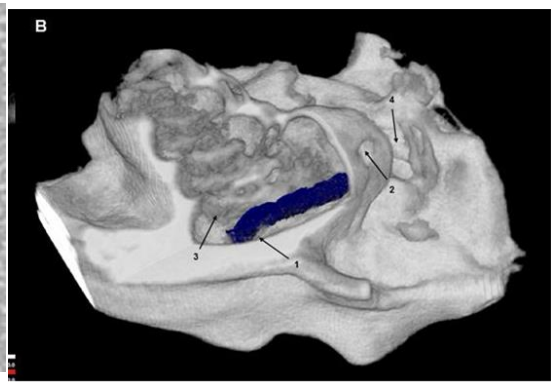
The future…

- ↑ Importance of PLs
  - Oral
  - Parenteral
  - Pulmonal
- ↑ ↑ Mixed Micelles
- ↑ ↑ ↑ Monoacyl-PLs







Thank you!

karsten.maeder@pharmazie.uni-halle.de