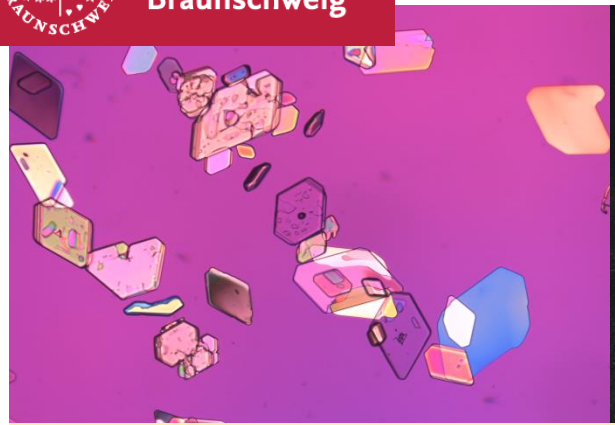
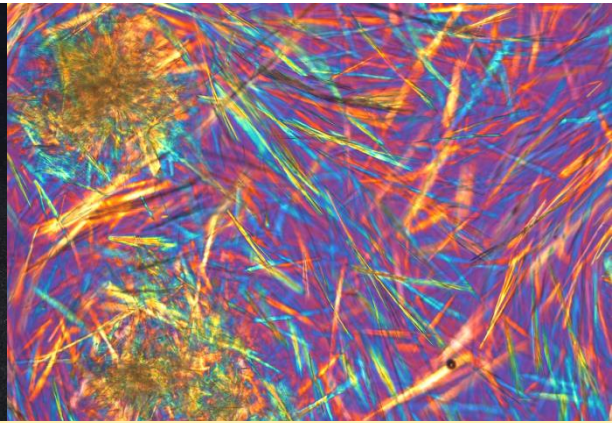
Technische Universität Braunschweig

pvz Zentrum für Pharmaverfahrenstechnik

Institut für Pharmazeutische Technologie und Biopharmazie
pharmazie in braunschweig





Phospholipid-based self-dispersing formulations

Heike Bunjes, Linda Grüne

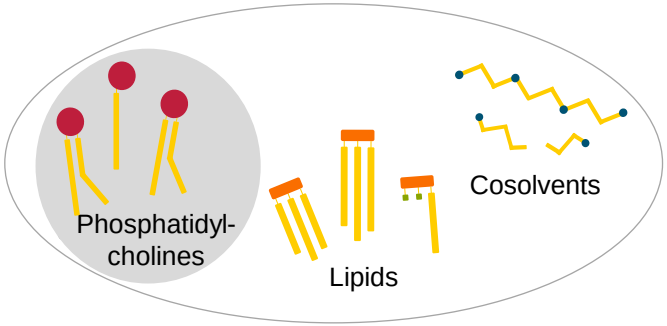
8th International Symposium on Phospholipids in Pharmaceutical Research, Heidelberg, September 10, 2024

Background: Lipid-based drug delivery systems

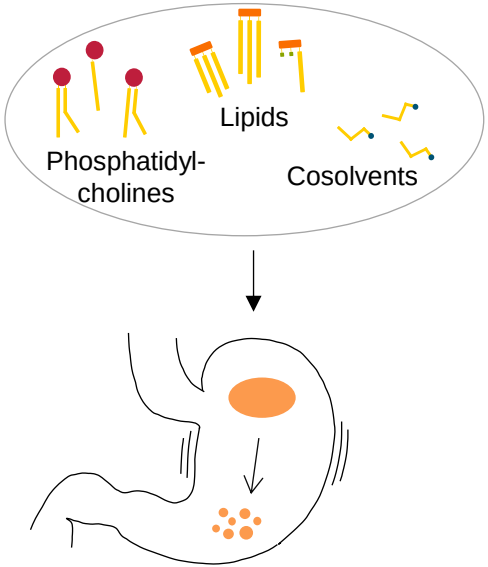
- Poor aqueous solubility of many modern drugs
- Lipid-based formulations → bioavailability ↑
- Self-dispersing drug delivery systems

  → 30 - 60 % synthetic surfactants and cosolvents
- Phospholipids as alternative?
- Diacyl phosphatidylcholines (PC)

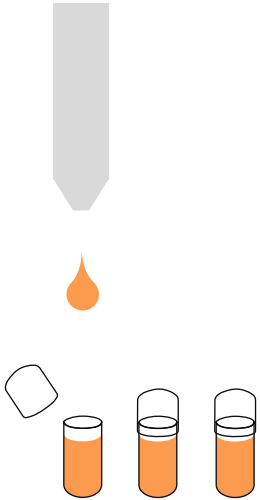
  ⟶ Monoacyl phosphatidylcholines



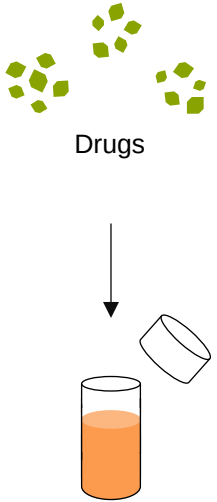
Specific approach: Development of lipid formulations



Self-dispersing
drug delivery systems



Liquid filling in
(hard) capsules



Loading with
lipophilic drugs

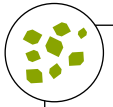
Aims

Miscibility

- Homogeneous, stable formulations
- High content of phospholipids
- Good dispersibility
- Clarification of underlying structures

Capsule filling

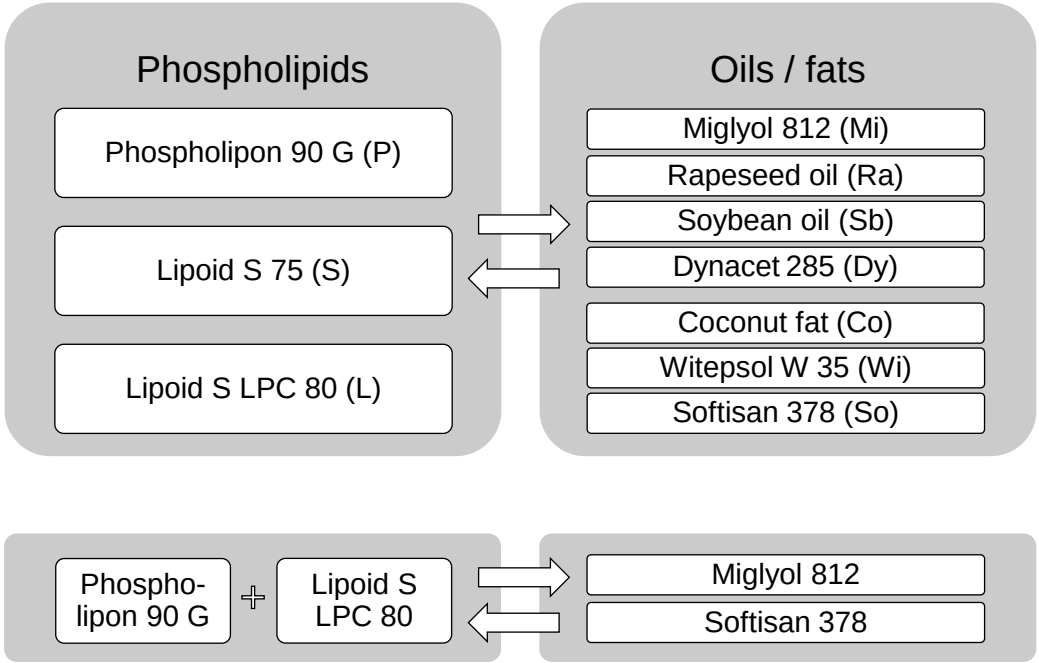
- Suitable filling behavior
- Compatibility with hard capsules



Drug loading

- High loading capacity for lipophilic drugs
- In bulk as well as dispersion
- Influence of composition on drug load
- Good dispersibility

Miscibility study

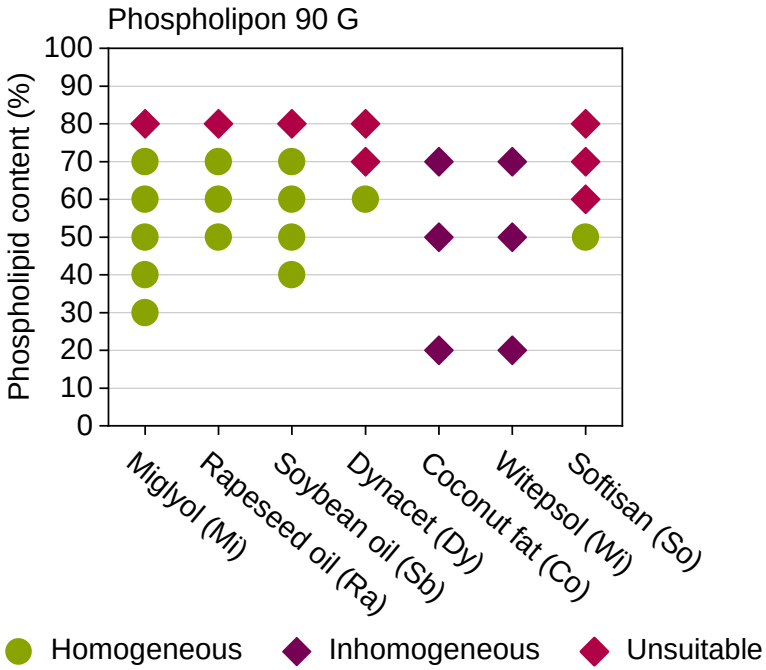


- Oils → liquid mixtures
- Fats → semisolid mixtures
- Combination PL90G + LPC80 → better dispersibility?
- Formulations with 5% ethanol
- Favorable processability with dual centrifugation

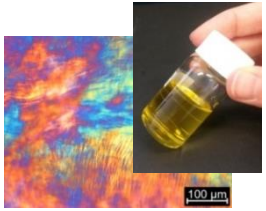
[1]

[1] Modified after Andreas Hettich GmbH

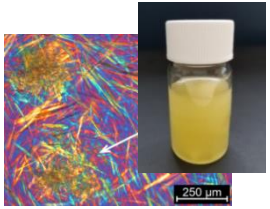
Miscibility: PL90G and S75



Mi30P70



Mi20P80



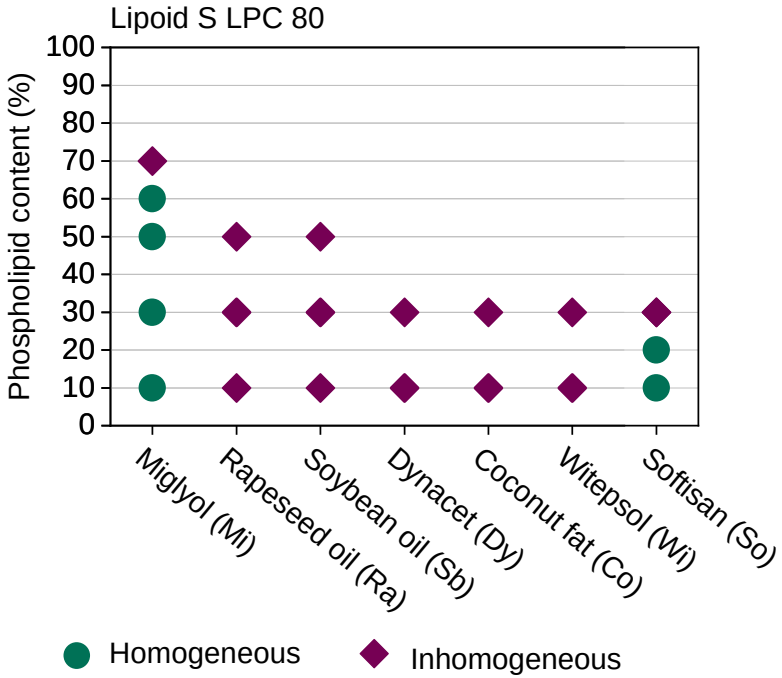
Co50P50

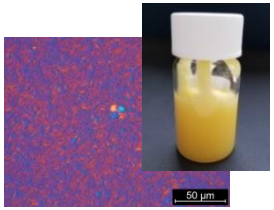
- Oils: max. 60 - 70% PL90G
- Softisan: max. 50% PL90G, inhomogeneous with other fats
- 10% less S75 in oils
- Reverse micelles or liquid-crystalline structures

⇨ Mixtures with high phospholipid content

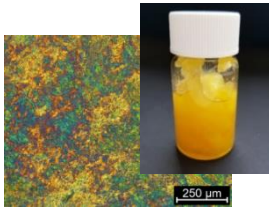
⇨ More PL90G than S75 possible

Miscibility: LPC80 and ternary mixtures

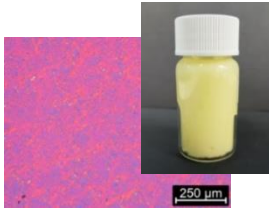




Mi50L50



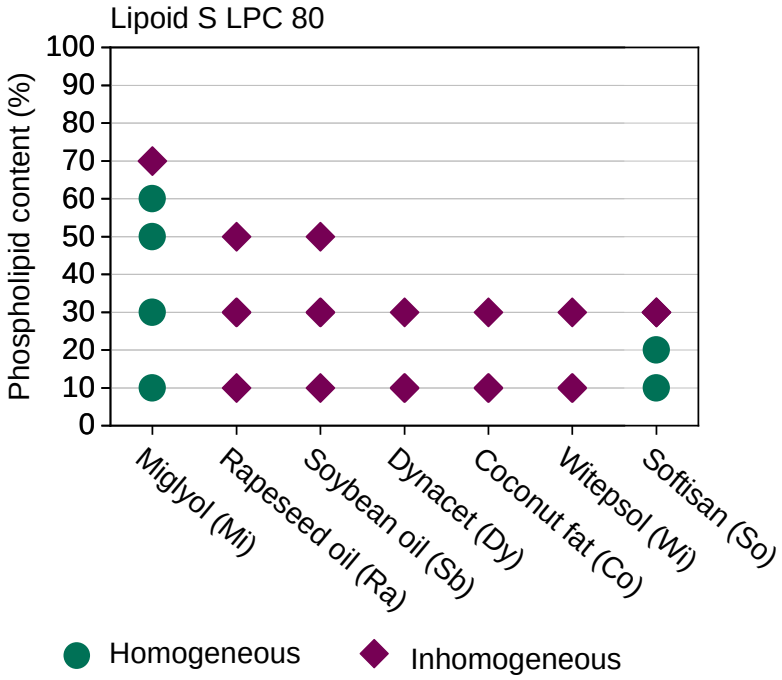
Sb50L50



So80L20

- LPC80 only miscible with Miglyol & Softisan
- Miglyol: max. 60% LPC80, lamellar (liquid) crystals
- Softisan: max. 20% LPC80, liquid-crystalline structures

Miscibility: LPC80 and ternary mixtures

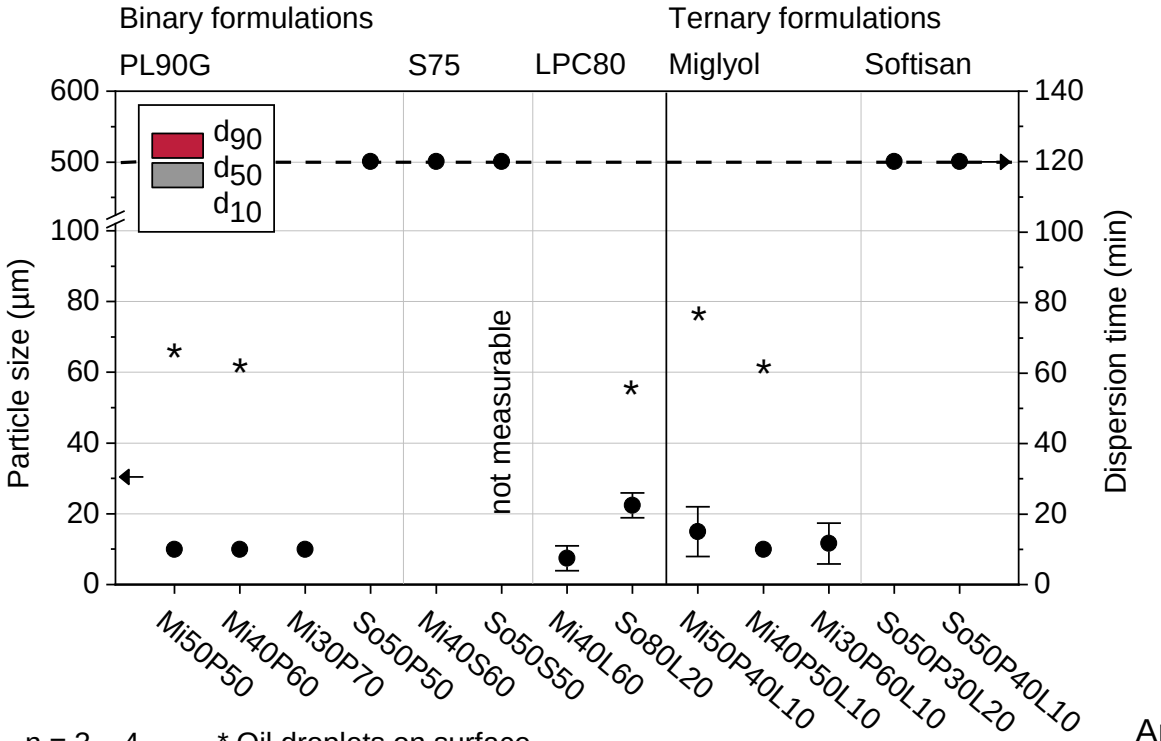


Mi30P60L10

So50P30L20

- LPC80 only miscible with Miglyol & Softisan
- Miglyol: max. 60% LPC80, lamellar (liquid) crystals
- Softisan: max. 20% LPC80, liquid-crystalline structures
- Ternary mixtures: max. 10 - 20% LPC80
  - ⇨ LPC80: different miscibility and structures
  - ⇨ Ternary mixtures with little LPC80

Dispersibility



n = 3 – 4

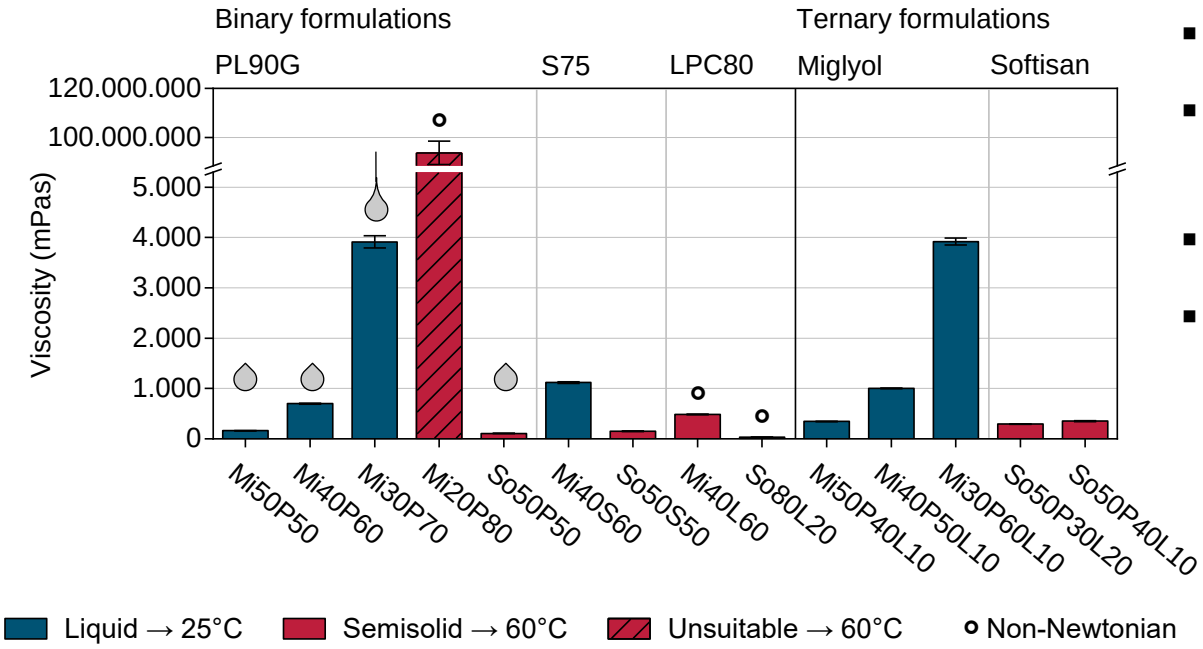
* Oil droplets on surface

- Short dispersion time:
  PL90G + Miglyol, LPC80
- Long dispersion time:
  PL90G + Softisan, S75
- Ternary mixtues:
  no improvement

  ⇨ Miglyol + PL90G (+ LPC80) advantageous properties

Artificial gastric juice, 37°C, 100 UpM

Filling behavior



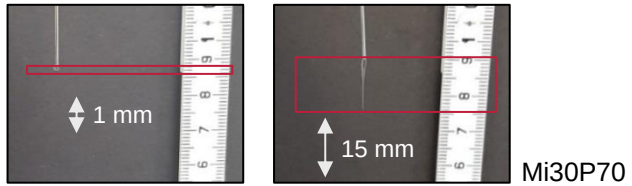
n = 3

Viscosity at 100 Pa

- Homogeneous: low viscosity
- Unsuitable:
  viscosity > 25.000 mPas [1]
- More PC → viscosity ↑
- LPC80: non-Newtonian

  ⇨ Most formulations „pumpable“

  ⇨ Clean drip-off up to 60% PL90G

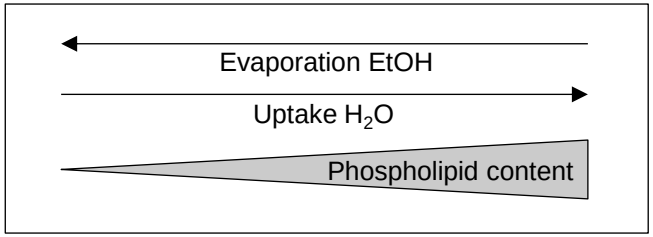


Mi50P50 Mi30P70

(500 µl/min, 0.57 mm cannula)

[1] G. Rowley, Filling of liquids and semi-solids into hard two-piece capsules, in: F. Podczeck, B.E. Jones (Hrsg.), Pharmaceutical Capsules, 2. Aufl., Pharmaceutical Press, London, 2004, S. 169–194.

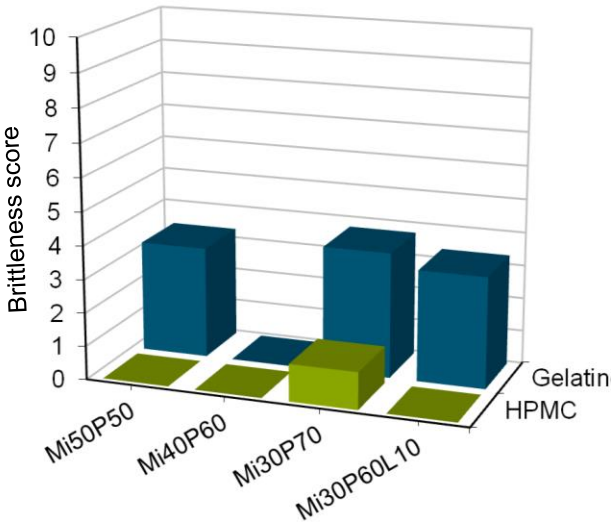
Compatibility with hard capsules



- More PC:
  hygroscopicity ↑, ethanol evaporation ↓

HPMC = Hydroxypropylmethylcellulose

Compatibility with hard capsules



- More PC:
  hygroscopicity ↑, ethanol evaporation ↓
- Gelatin capsule: Certain brittleness
- Exception: Mi40P60 → Optimum
- HPMC capsule: very low brittleness

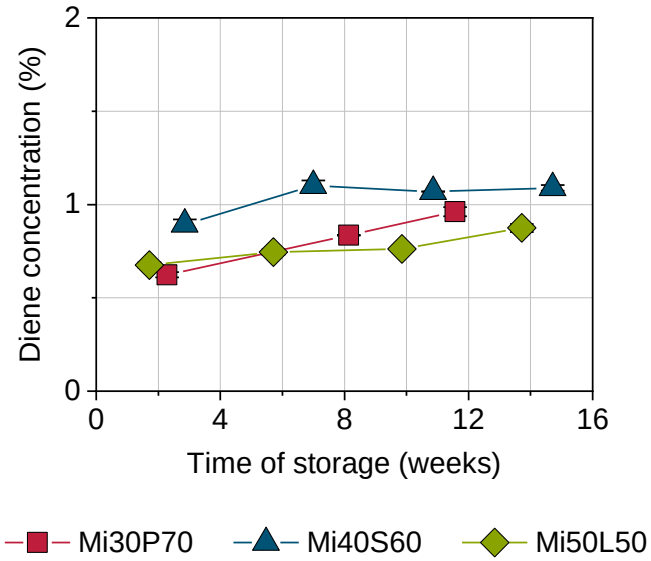
  ⇨ HPMC preferable material

0 = no splintered capsule
10 = all capsules splintered
n = 8 – 12

25°C, closed containers, tablet hardness tester

HPMC = Hydroxypropylmethylcellulose

Oxidative stability

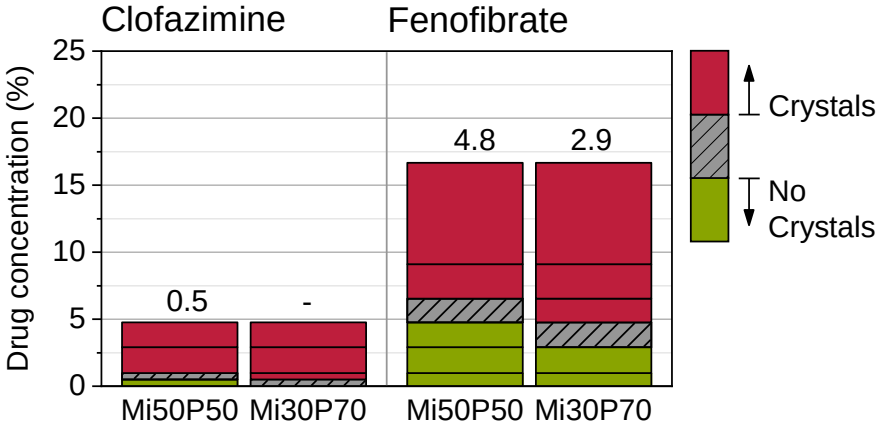


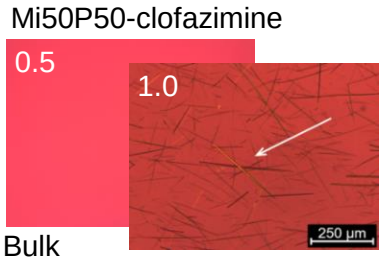
n = 2

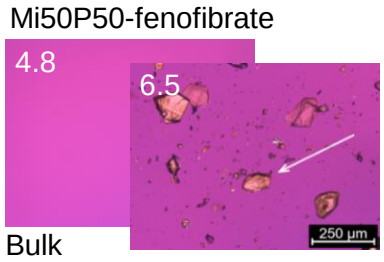
- Storage after flushing with nitrogen
- 0.8 - 1.1 % dienes after ca. 12 weeks (related to phospholipid content)
- No distinct dfferences between the different phospholipids

  ⇨ Acceptable oxidative stability

Drug loading – clofazimine & fenofibrate

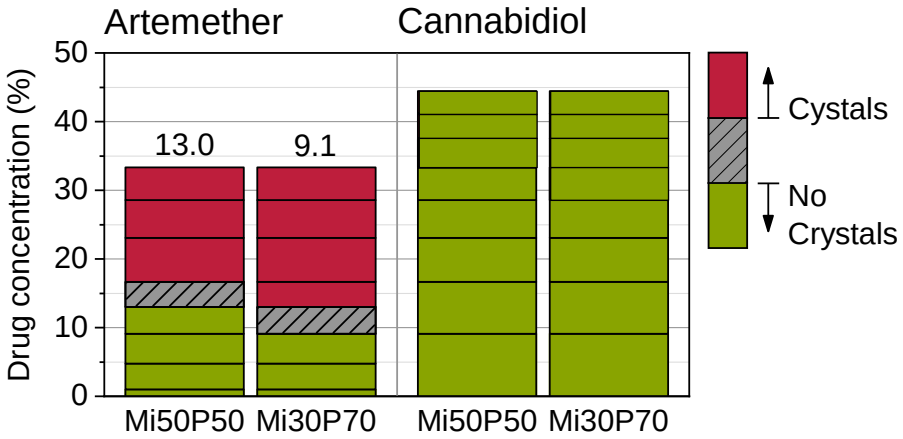


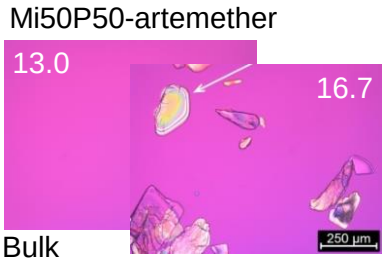


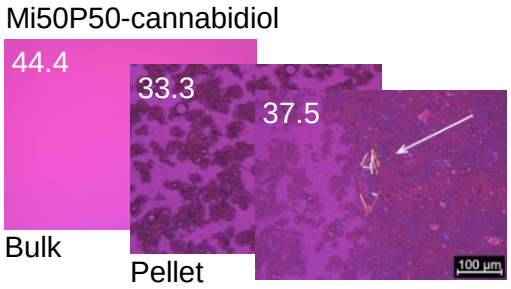


- Drugs with different physicochemical properties
- Loading screening with dual centrifugation at 23°C
- Clofazimine (T_M: ~211°C): very low drug load, needle-shaped crystals
- Fenofibrate (T_M: 81°C): medium drug load

Drug loading – artemether & cannabidiol



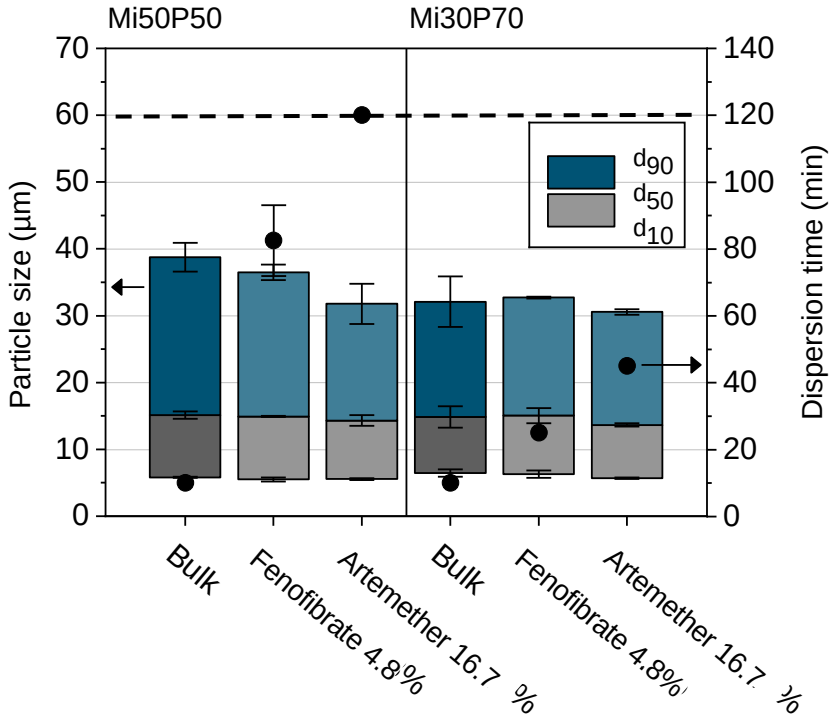




- Artemether (T_M: ~87°C): high drug load, platelet-shaped crystals
- Cannabidiol (T_M: 67°C): Crystals only after dispersion, very high drug load
  - ⇨ Higher solubility in Mi50P50 than in Mi30P70
  - ⇨ Lower solubility when T_M > 150°C [1]
  - ⇨ Artemether and cannabidiol: Unusually high solubility

[1] L.C. Alskär, C.J.H. Porter, C.A.S. Bergström, Tools for early prediction of drug loading in lipid-based formulations, Mol. Pharmaceutics 13 (2016) 251–261.

Dispersibility of drug-loaded formulations



- Similar particle sizes
- Drugs prolong dispersion time
  - ⇨ Higher dispersion time with
    - lower phospholipid content
    - Higher drug load
  - ⇨ High oil content → higher loading capacity
  - ⇨ High PC content → better dispersibility

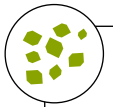
Summary

Miscibility

- Homogenous mixtures, high phospholipid content
- Miglyol + PL90G (+ LPC80) best properties
- Reverse micelles or (liquid-)crystalline structures

Capsule filling

- Homogenous formulations “pumpable“
- Clean drip-off up to 60% PL90G
- Higher compatibility with HPMC capsules
- Sufficient stability against oxidation



Drug loading

- High loading with low-melting drugs
- High phospholipid content decreases solubility
- Drug load increases dispersing time

Thank you!

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Hettich

Prof. Dr. Ulrich Massing