Particle-stabilized lipid-based formulations for 3D printing of solid lipid tablets by semi-solid extrusion

Malhar Manik Pathare, Jenny Johannesson, Mathias Johanson,
Christel A.S. Bergström, **Alexandra Teleki**

Science for Life Laboratory
Department of Pharmacy, Uppsala University, Sweden

CRS Annual Meeting Montreal 2022

email: alexandra.teleki@farmaci.uu.se
website: https://www.scilifelab.se/researchers/alexandra-teleki/ @AlexandraTeleki

UPPSALA UNIVERSITET

Personalized solid oral dosage forms for children

- Challenges with pediatric drug delivery
  - Lack of age appropriate formulations
  - Dose specificity
  - Oral administration preferred: easy to swallow and palatable

Tablet manipulation

- Inaccurate dosing
- Stability
- Solubility, bioavailability

Patient compliance and acceptability

Observed manipulations, medicinal product, type of drug manipulation, and administration via enteral feeding tube, by age group.

Age group	Medicinal product (API)	Dosage form	Type of manipulation[a]	Administration via enteral feeding tube
Neonates (0–28 days)	–	–	–	–
Infants and toddlers (1–23 months)	Allopurinol Teva (allopurinol)	tablet	split, crush, dispersion in liquid	Yes
	Emend (aprepitant)	capsule, hard	open, dispersion in liquid, proportion of drug dose	Yes
Children, pre-school (2–5 years)	Allopurinol Teva (allopurinol)	tablet	split, crush, dispersion in liquid	Yes
	Celebra (celecoxib)	capsule, hard	dispersion in liquid, proportion of drug dose	Yes
	Emend (aprepitant)	capsule, hard	open, dispersion in liquid	Yes
	Lanvis (tioguanine)	tablet	dispersion in liquid	Yes
	Spironolactone Accord (spironolactone)	film-coated tablet	proportion of drug dose	Yes
	Stesolid (diazepam)	tablet	crush, dispersion in liquid	Yes
Children, school (6–11 years)	Probecid (probenecid)	tablet	dispersion in liquid	Yes[b]

Johannesson et al., *Biomedicine & Pharmacotherapy* **146**, 112576 (2022).

UPPSALA UNIVERSITET

Manipulations and age-appropriateness

Jenny Johannesson

ATC-code		API		
Anatomical group	**Therapeutic subgroup**	**Class I**	**Class II**	**Class III**
A: Alimentary tract and metabolism	02	metoclopramide		omeprazole
	03		bisacodyl	sterculia gum, lactitol
	06			multienzymes
	09			
	12			calcium carbonate, calcium lactate gluconate, zinc sulfate
C: Cardiovascular system	03	metoprolol	spironolactone	
	07			
	09		enalapril, losartan	
H: Systemic hormonal preparations	01	prednisolone	desmopressin	
	02		fludrocortisone, hydrocortisone	betamethasone, dexamethasone
J: Anti-infective for systemic use	01		tetracycline, nitrofurantoin	
L: Antineoplastic and immune-modulating agents	01	cyclophosphamide, temozolomide, tioguanine azathioprine, methotrexate	imatinib, nilotinib	
	04			
M: Musculo-skeletal system	01		diclofenac, naproxen, allopurinol	
	04			
N: Nervous system	03	gabapentin	clonazepam	
	05		diazepam	
R: Respiratory system	01		phenylpropanolamine	
	03			montelukast
	06		meclozine	
V: Various	03	calcium folinate	deferasirox	
Total		**10**	**19**	**10**

Class I: lack of child-friendly dosage form and appropriate dose strength

Class II: lack of either child-friendly dosage form or appropriate dose strength

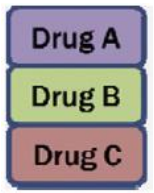
Class III: age-appropriate oral formulation available

29 of 39 APIs needed personalized dosage forms!

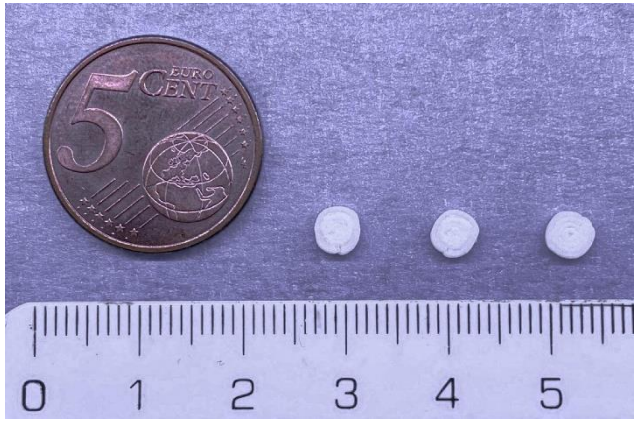
[1] Johannesson et al., *Biomedicine & Pharmacotherapy* **146**, 112576 (2022).

3D printing technologies

- *Frontier* in pharmaceutical manufacturing: 3D-printed personalized drug products[1]
  - FDA approved product in 2015
  - varying shape
  - varying composition



oral tailored-dose therapies in a hospital setting, acceptability[2]



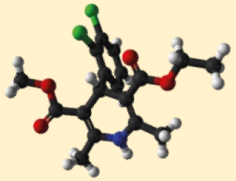
orodispersible printlets for pediatric use[3]

Fused deposition modeling (FDM)
- High temperature (140-200 °C)
- Slow printing speed

Semi-solid extrusion (SSE)
- Suitable for thermolabile APIs
- Faster printing speed

[1] Norman et al., *Adv. Drug Deliv. Rev.* **108**, 39 (2017). [2] Goyanes et al., *Int. J. Pharm.* **567**, 118497 (2019). [3] Eduardo et al., *Int. J. Pharm.* **605**, 120854 (2021).

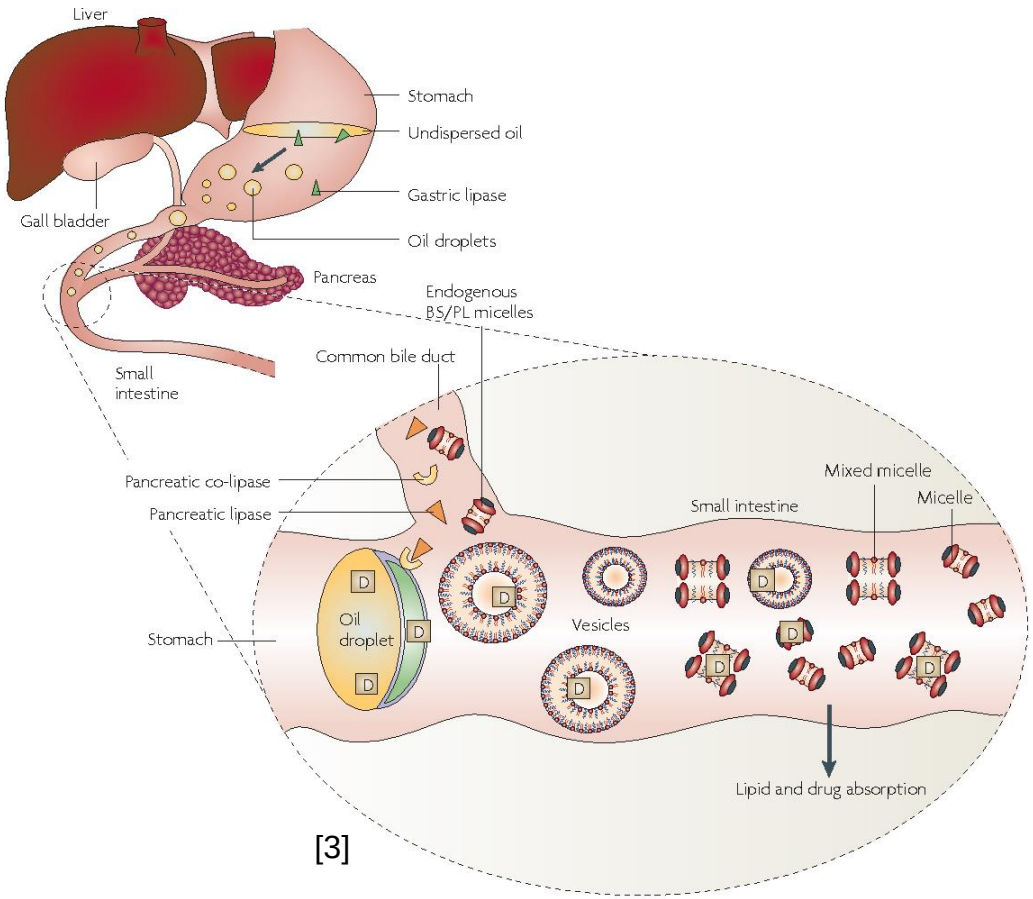
Poorly water-soluble drugs and lipid formulations



poorly water soluble drug

- Lipid-based formulations (LBF)[1]
- LBFs filled in gelatin capsules
- Advantages of solid dosage form[2]
  - physicochemical stability
  - reduced production costs

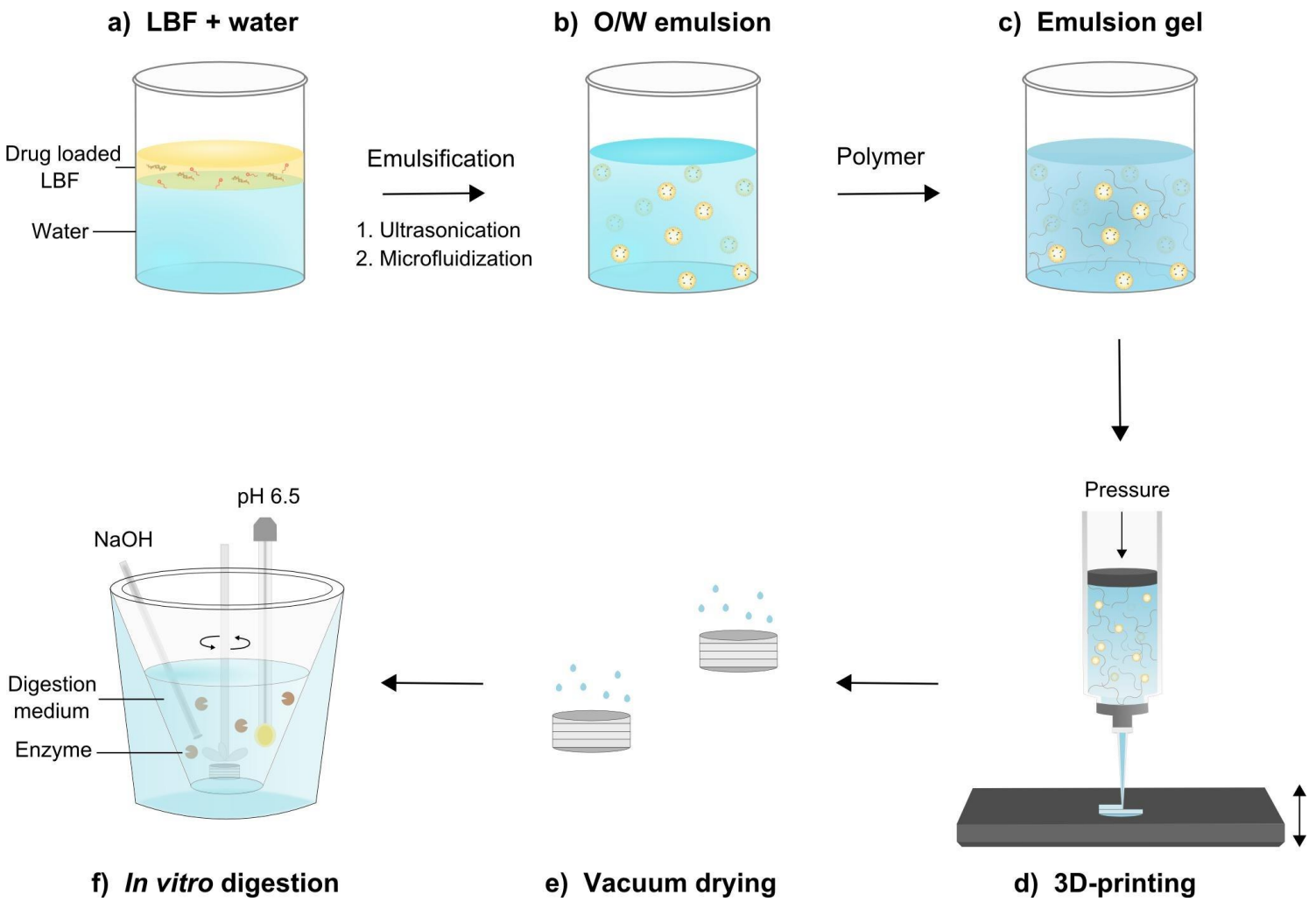
Aim: design lipid based formulations (LBFs) carrying poorly water soluble drugs suitable for 3D printing into minitablets



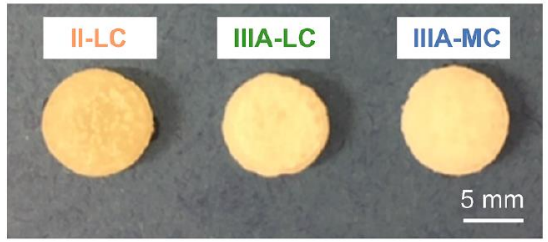
[3]

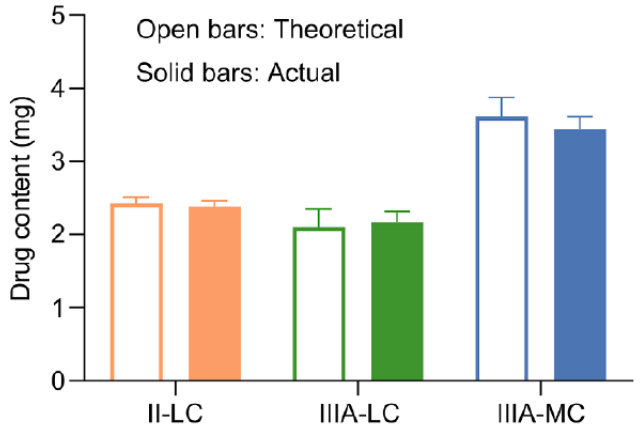
[1] Feeney et al., *Adv. Drug Deliv. Rev.* **101**, 167 (2016). [2] Joyce et al., *Adv. Drug Deliv. Rev.* **142**, 102 (2019). [3] Porter and Pouton, *Nat. Rev. Drug Discov.* **6**, 231 (2007).

3D printing of solid lipid tablets from emulsion gels



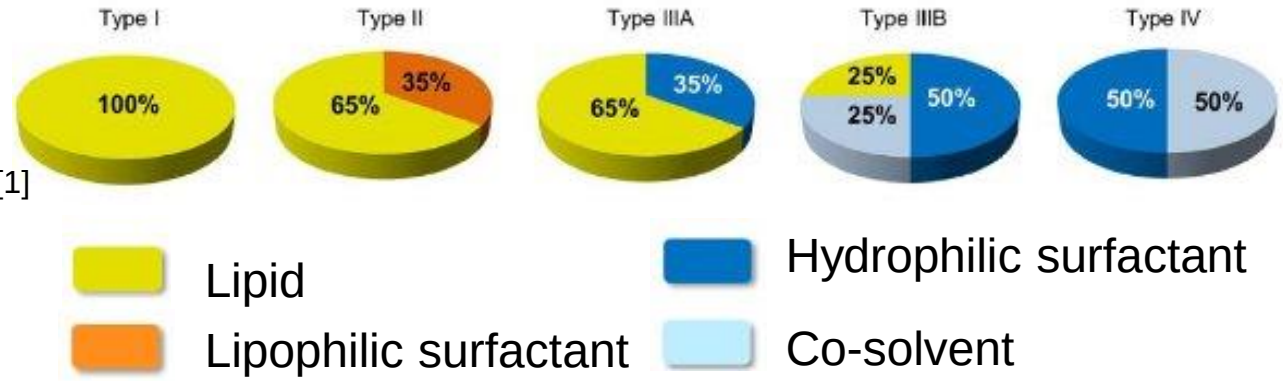
Conventional O/W emulsions with **type II and III** LBFs were successfully 3D printed (SSE) into solid lipid tablets





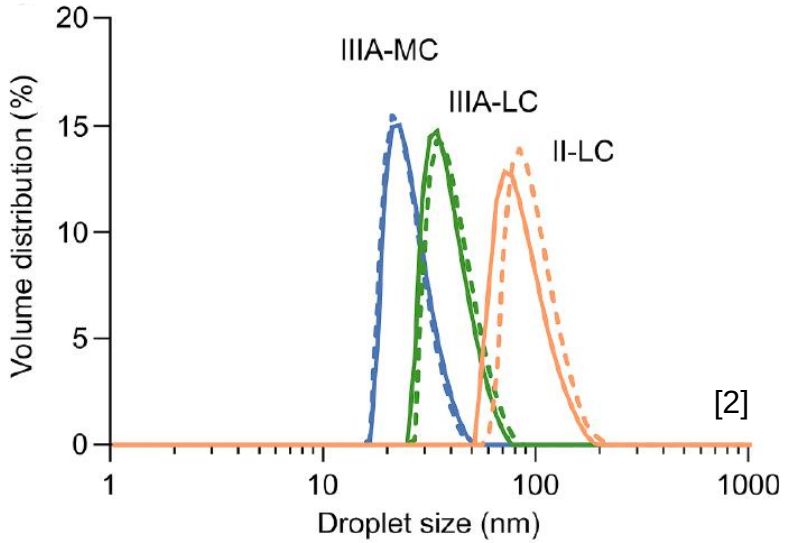
Johannesson et al., *Int. J. Pharm.* **597**, 120304 (2021).

LBF type I formulations



[1]

Lipid
Lipophilic surfactant
Hydrophilic surfactant
Co-solvent

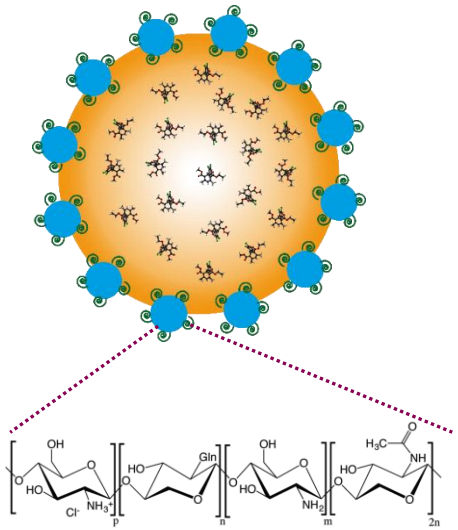


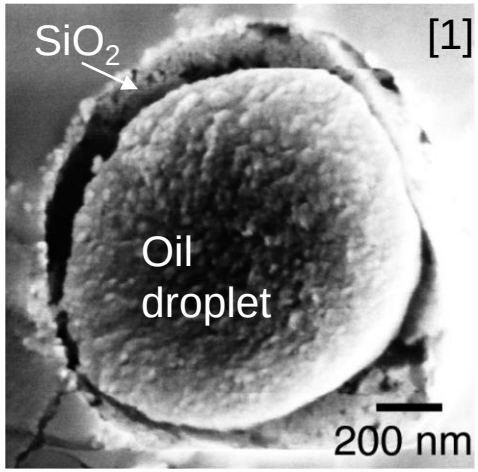
[2]

[1] https://www.americanpharmaceuticalreview.com/Featured-Articles/154717-The-LFCS-Consortium-Supporting-Rational-Design-and-Testing-of-Lipid-Based-Formulations/

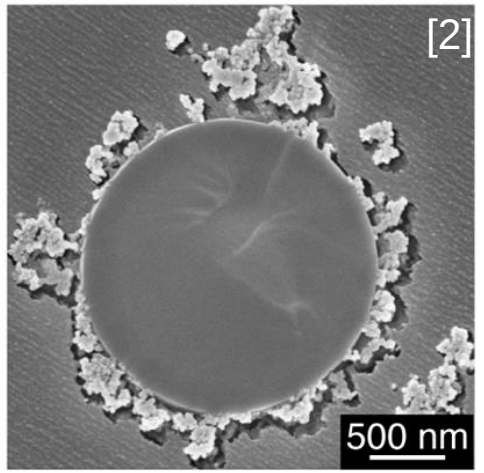
[2] Johannesson et al., *Int. J. Pharm.* **597**, 120304 (2021).

Particle-stabilized emulsions for 3D printing

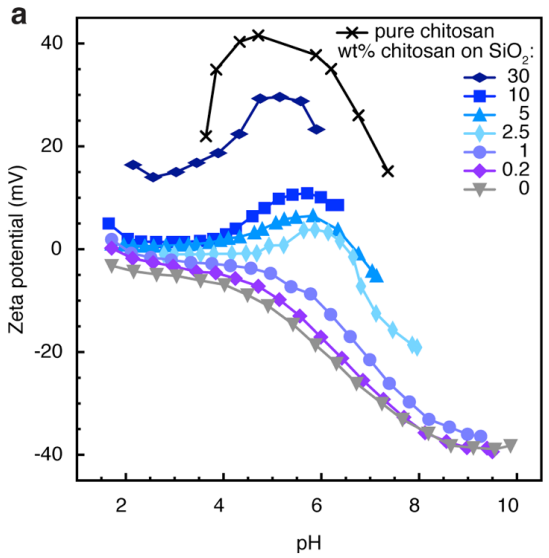


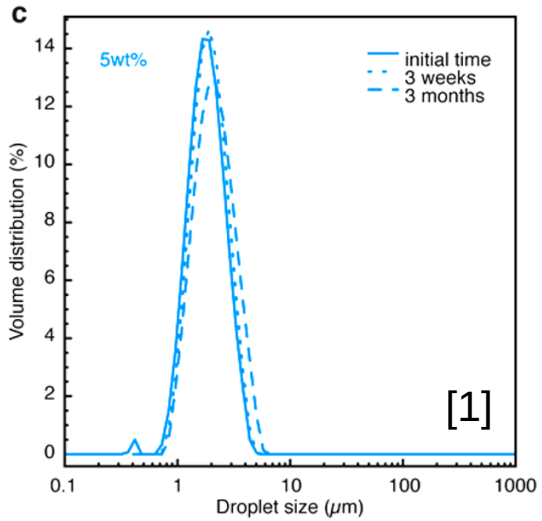


Pickering stabilization



Gel-like emulsion by particle agglomerates





- Emulsions with μm-sized oil droplets stable > 3 months
- Pickering emulsions can be 3D printed[3]

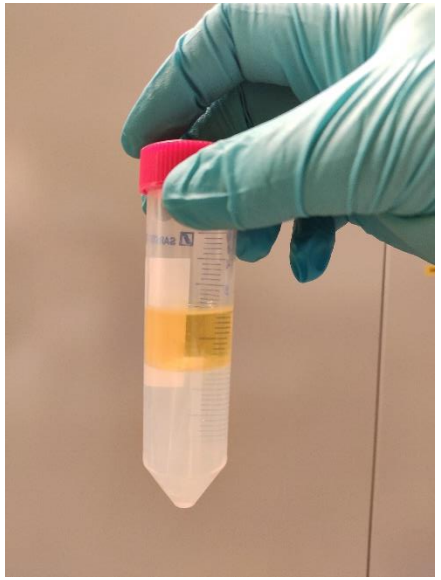
[1] Alison et al., *Langmuir* **32**, 13446 (2016). [2] Alison et al., *Langmuir* **34**, 6147 (2018). [3] Sommer et al., *Soft Matter* **13**, 1794 (2017).

UPPSALA UNIVERSITET

Manufacturing of particle-stabilized LBF I

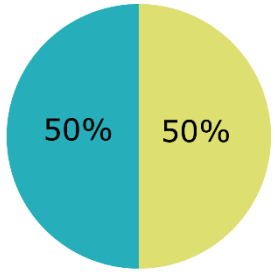
Malhar Pathare

Oil water (3:7)



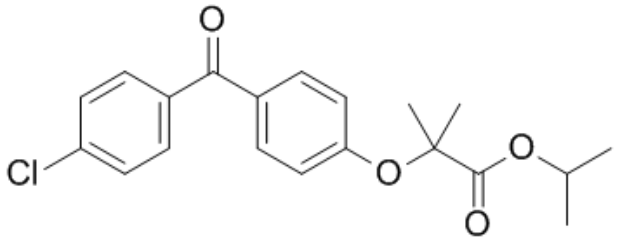
Oil phase

LBF I

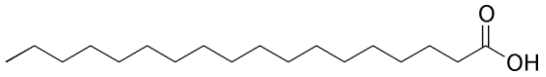


Soybean Oil

Maisine CC



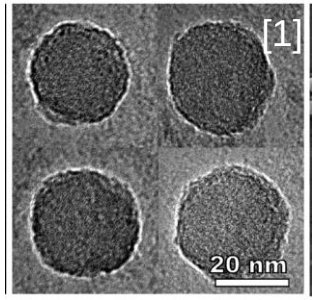
Fenofibrate (BCS Class II)



Stearic Acid

Water phase

- SiO_2 nanoparticle suspension (Ludox TM50)



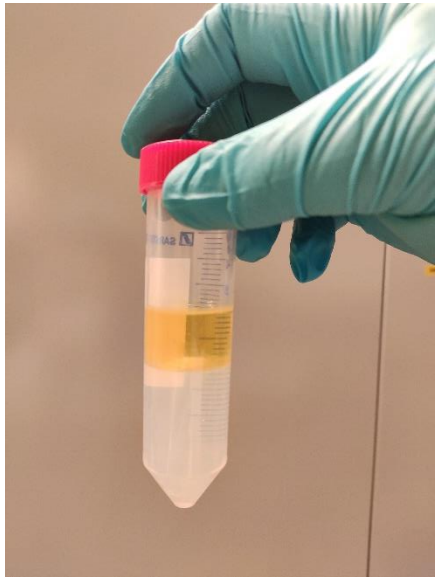
[1] Bollhorst et al., *Chem. Mater.* **25**,3464 (2013).

UPPSALA UNIVERSITET

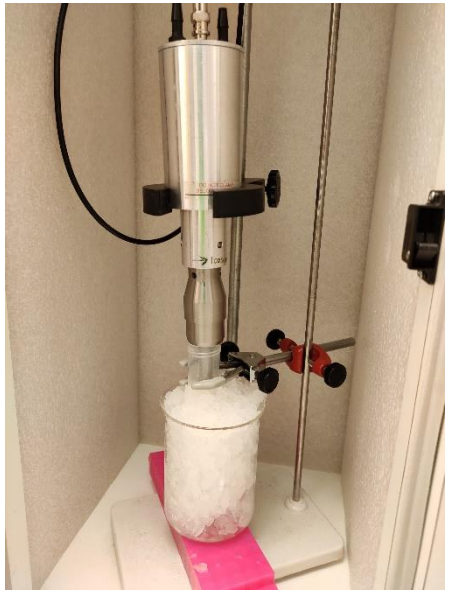
Manufacturing of particle-stabilized LBF I

Malhar Pathare

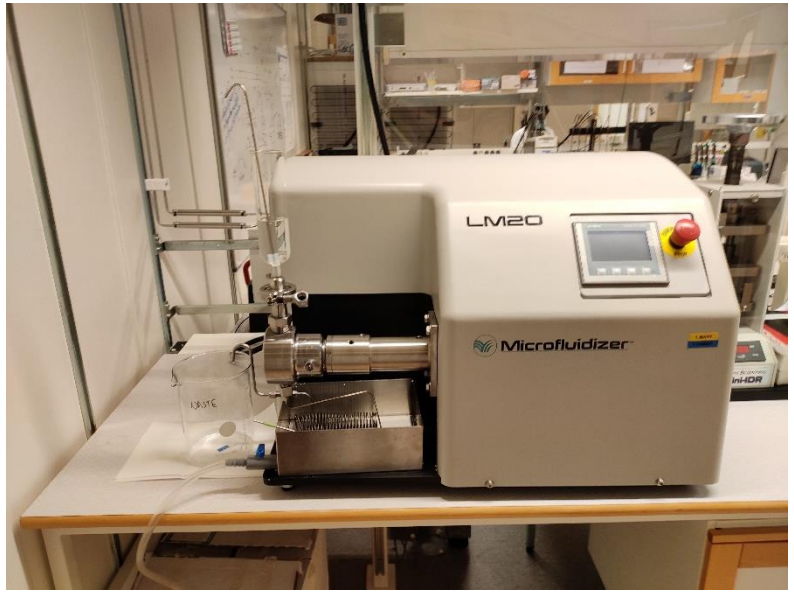
Oil water (3:7)



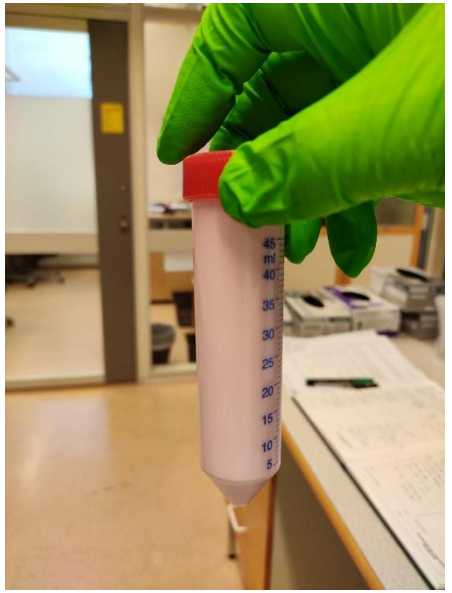
Pre-emulsification

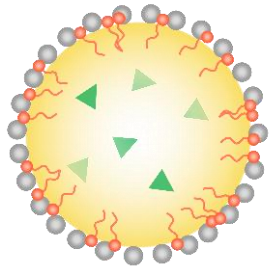


Microfluidization



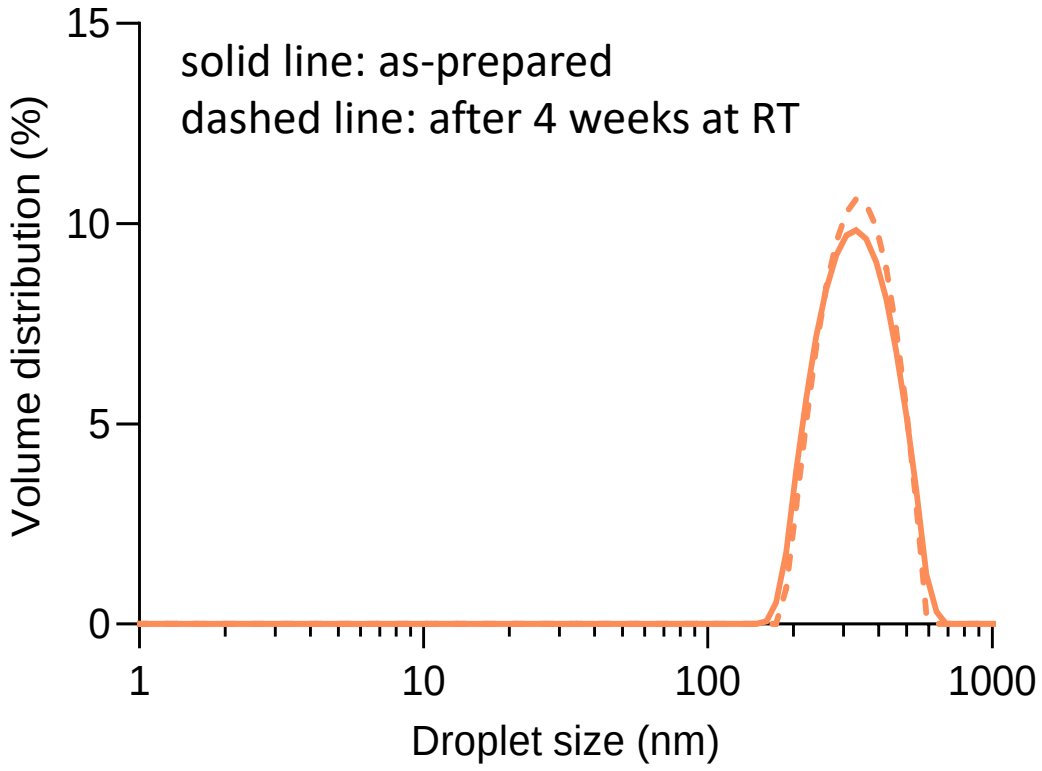
Emulsion

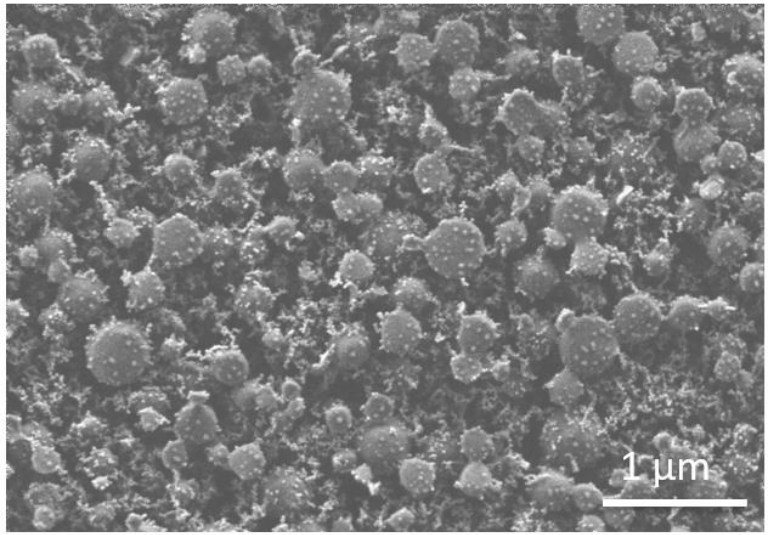


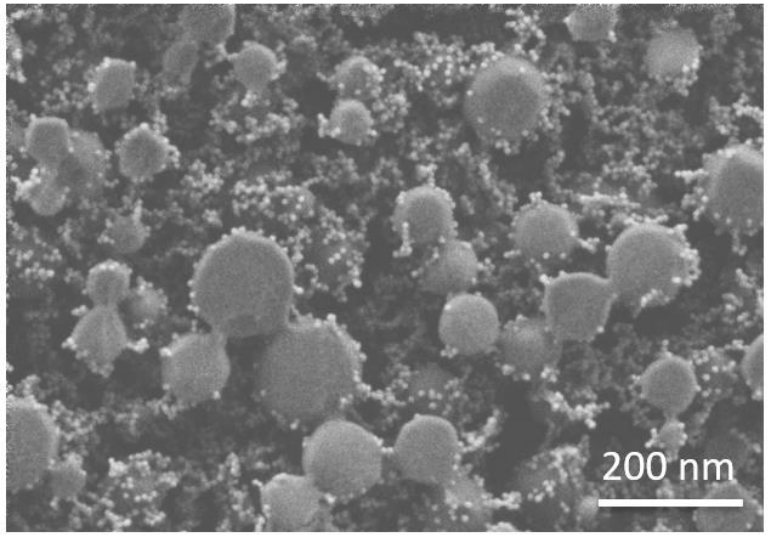


UPPSALA UNIVERSITET

Particle-stabilized LBF I formulations





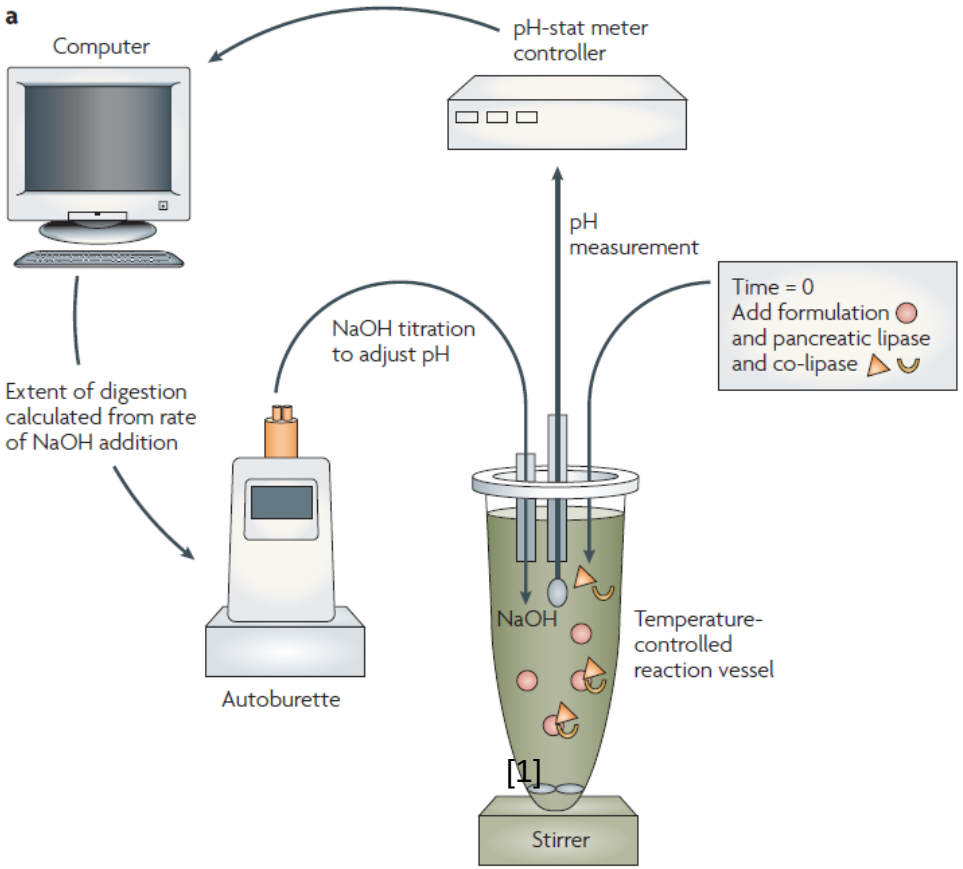


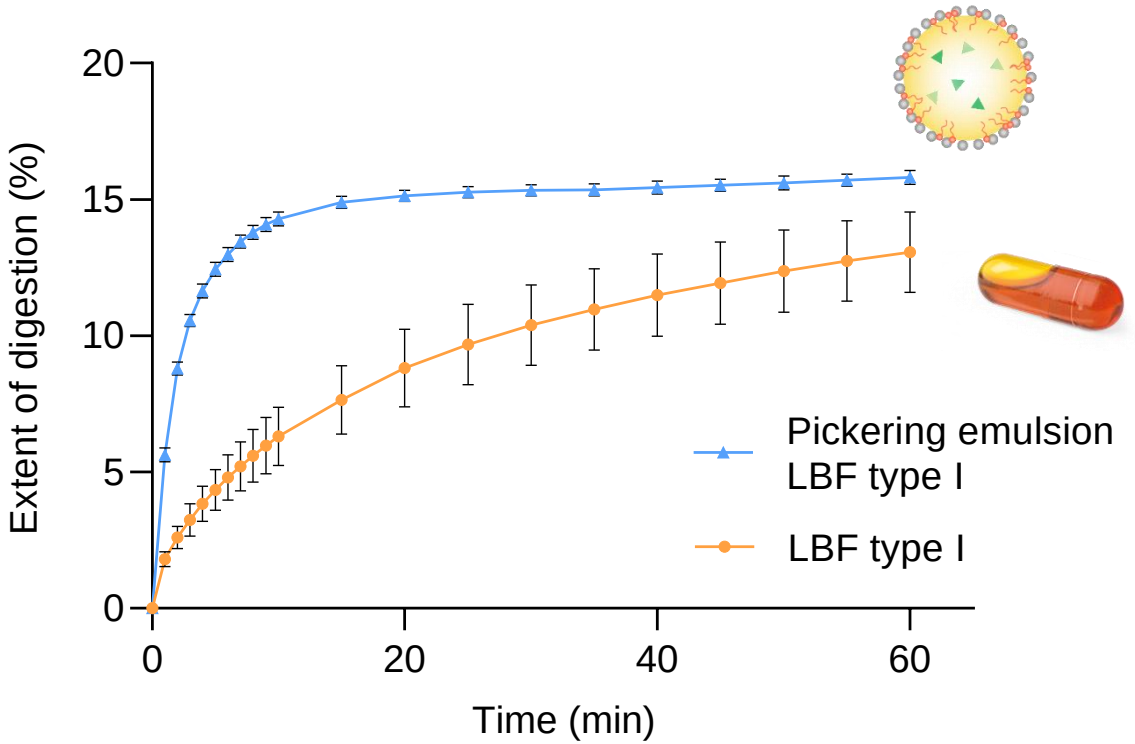
cryo-SEM images

- Stable LBF I emulsions with SiO_2 and stearic acid

UPPSALA UNIVERSITET

In vitro LBF digestion in the small intestine





[1] Porter and Pouton, *Nat. Rev. Drug Discov.* **6**, 231 (2007).

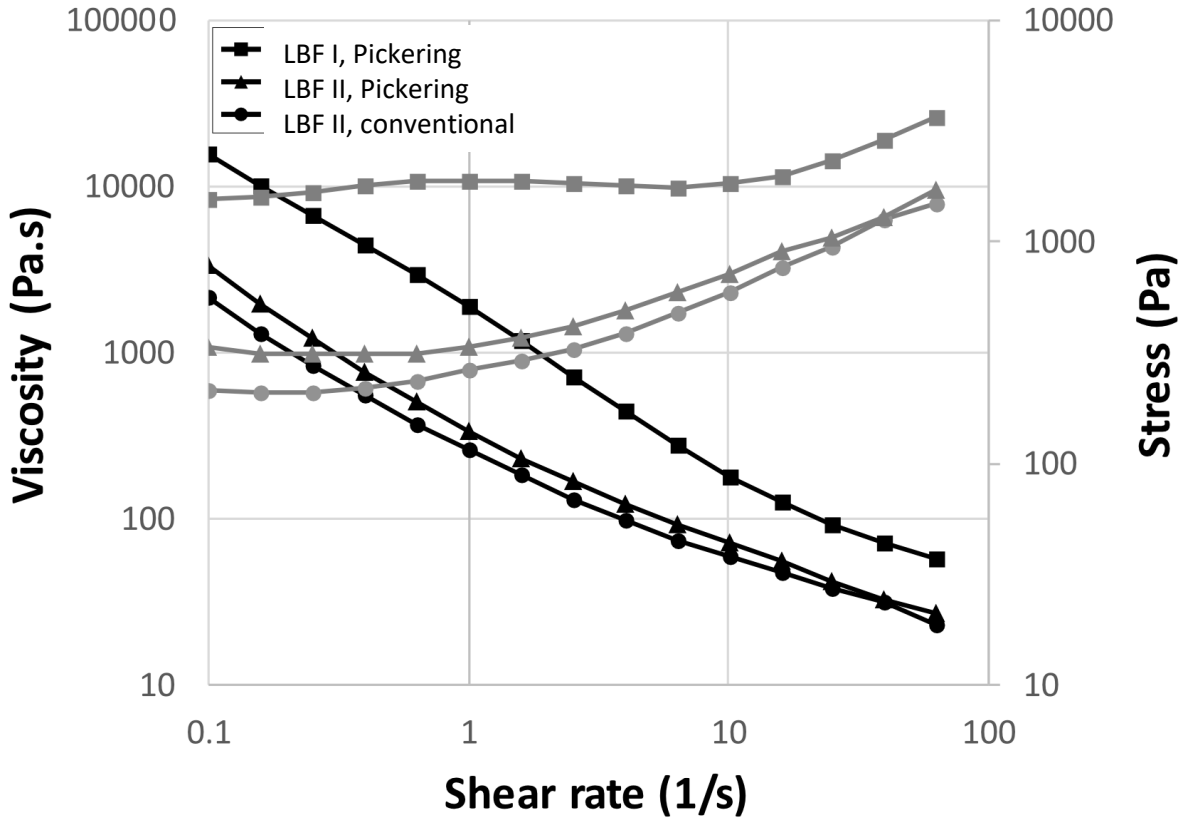
UPPSALA UNIVERSITET

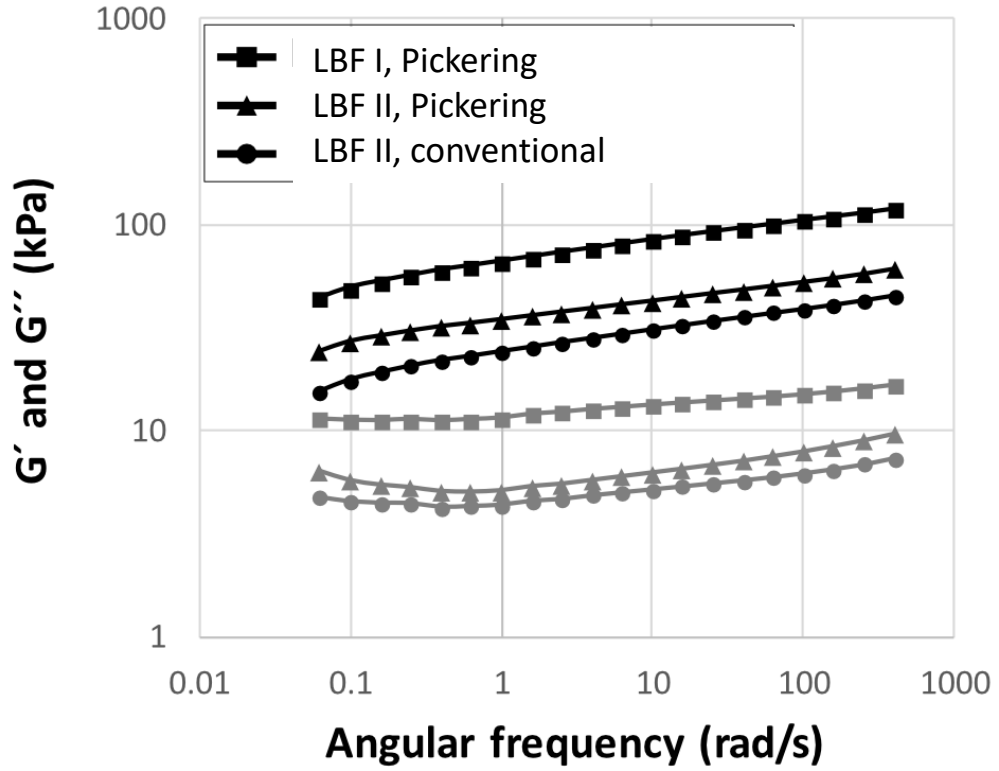
Preparation of emulsion gel

Product	Ingredient	Role of ingredient
Methocel™ A4M, Sigma-Aldrich	Methyl Cellulose	Viscosity enhancer
Methocel™E4M Premium, Colorcon	Hydroxypropyl methyl cellulose (HPMC)	Viscosity enhancer
Ac-Di-Sol® SD-711, DUPONT	Croscarmellose sodium	Disintegrant

UPPSALA UNIVERSITET

Rheological characterization of emulsion gel



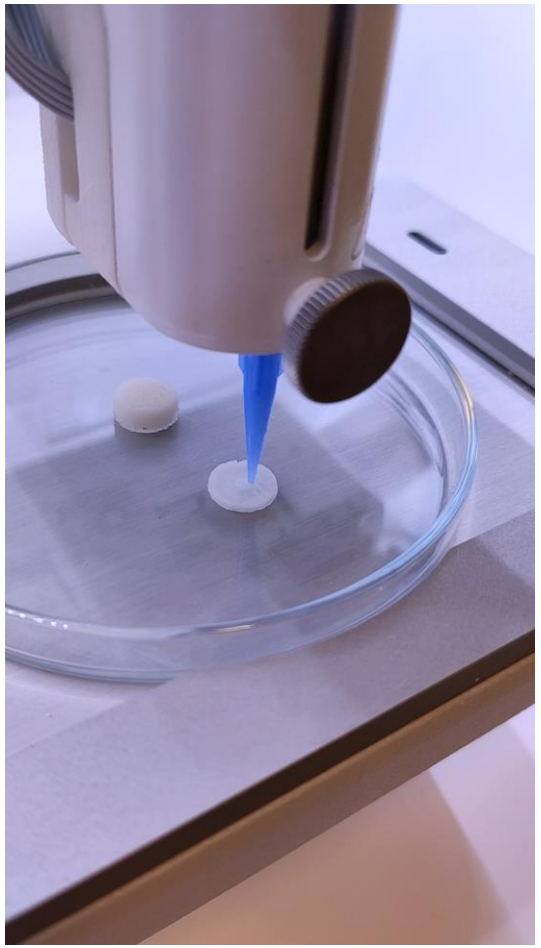


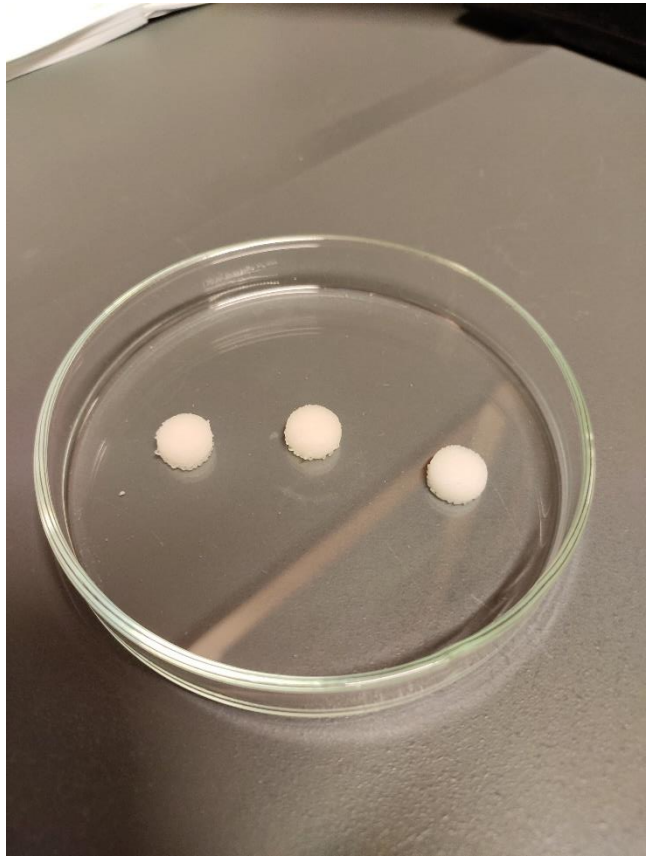
Emulsion gels	Apparent yield stress (Pa)
LBF I, Pickering	1682 ± 12
LBF II, Pickering	353 ± 5
LBF II, conventional emulsion	188 ± 9

- Shear-thinning behaviour
- Predominantly solid-like behaviour (G´>G´´) over the full frequency range
- G´>G´´ also at low frequencies indicate long term stability of gels

UPPSALA UNIVERSITET

3D printing of solid lipid tablets by SSE

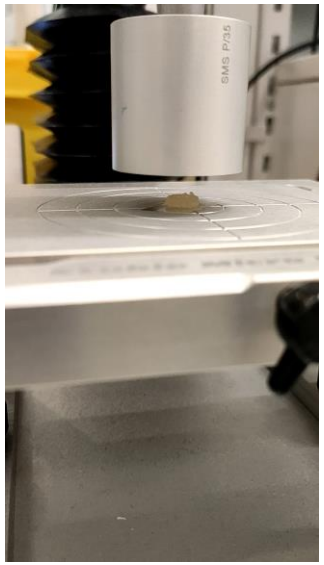




- 3D printed tablets about 150 mg (dry), ø8.7 mm, 2.9 mm thickness
- Disintegration time < 15 min in water (basket-rack assembly with discs)

UPPSALA UNIVERSITET

Texture analysis

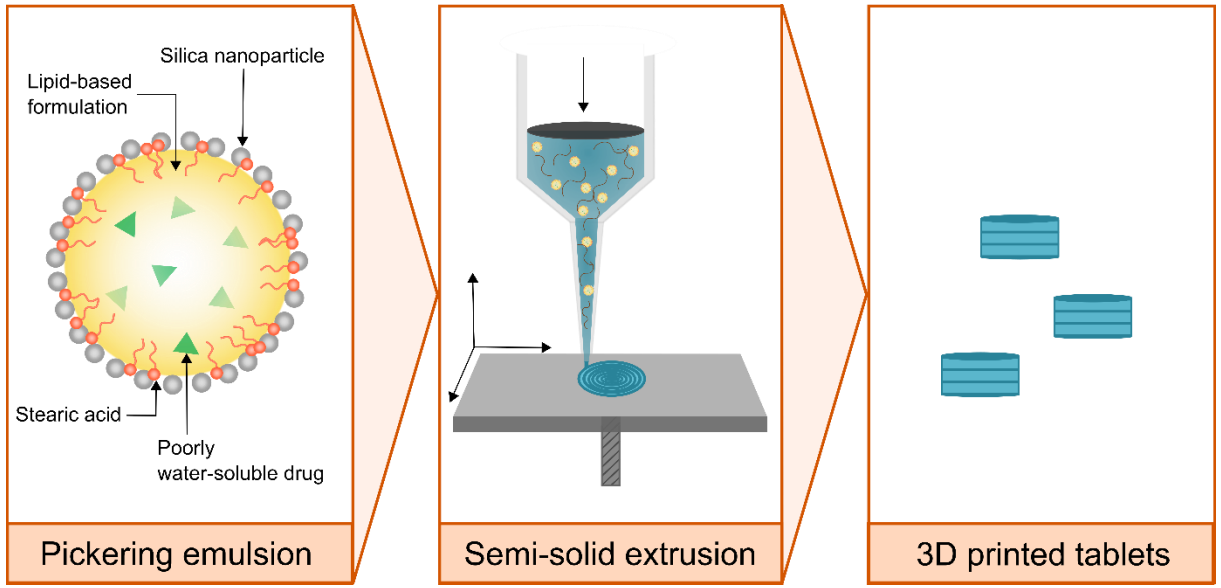


Sample	Hardness (g)	Adhesiveness (g s)	Springiness
LBF I, Pickering	2788.1 ± 379.1	-0.13 ± 0.026	2.5 ± 0.4
LBF II, Pickering	1715.0 ± 251.8	-0.032 ± 0.030	2.1 ± 0.3
LBF II, conventional O/W emulsion	1998.7 ± 156.5	-0.13 ± 0.028	2.0 ± 0.1
Multivitamin Monkids chewable tablets	348.5 ± 13.9	0.035 ± 0.006	5.0 ± 0.2
Haribo Goldbears gummybears	348.0 ± 20.4	0.024 ± 0.020	11.2 ± 0.1
Läkerol licorice pastilles	5025.7 ± 233.6	-0.54 ± 0.071	4.0 ± 0.1

UPPSALA UNIVERSITET

Conclusions

- Lipid-based formulations were successfully 3D printed from emulsions into minitablets
- Kinetically unstable LBF I formulations were stabilized by SiO_2 nanoparticles in printable Pickering emulsions
- Offers a way to develop personalized dosage forms intended for delivering poorly water-soluble lipophilic drugs



Acknowledgements

Uppsala University

- Teleki lab team members
  - **Malhar Manik Pathare**
  - Dr. Ann-Christin Jacobsen
  - Dr. Hannah Pohlit
  - Shno Asad
  - Shaquib Rahman Ansari
  - Yuming Zhang
  - Yael Suarez
  - Paarkavi Udayakumar
- **Prof. Christel Bergström**
  - **Jenny Johannesson**

SLU: Swedish University of Agricultural Sciences

- **Mathias Johanson**

Funding

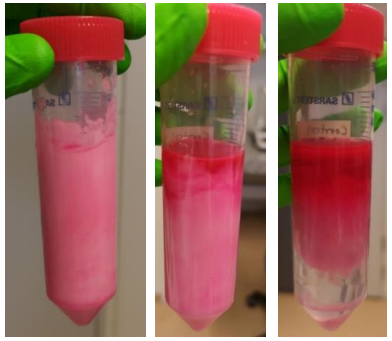
UPPSALA
UNIVERSITET

UPPSALA UNIVERSITET

LBF classification system

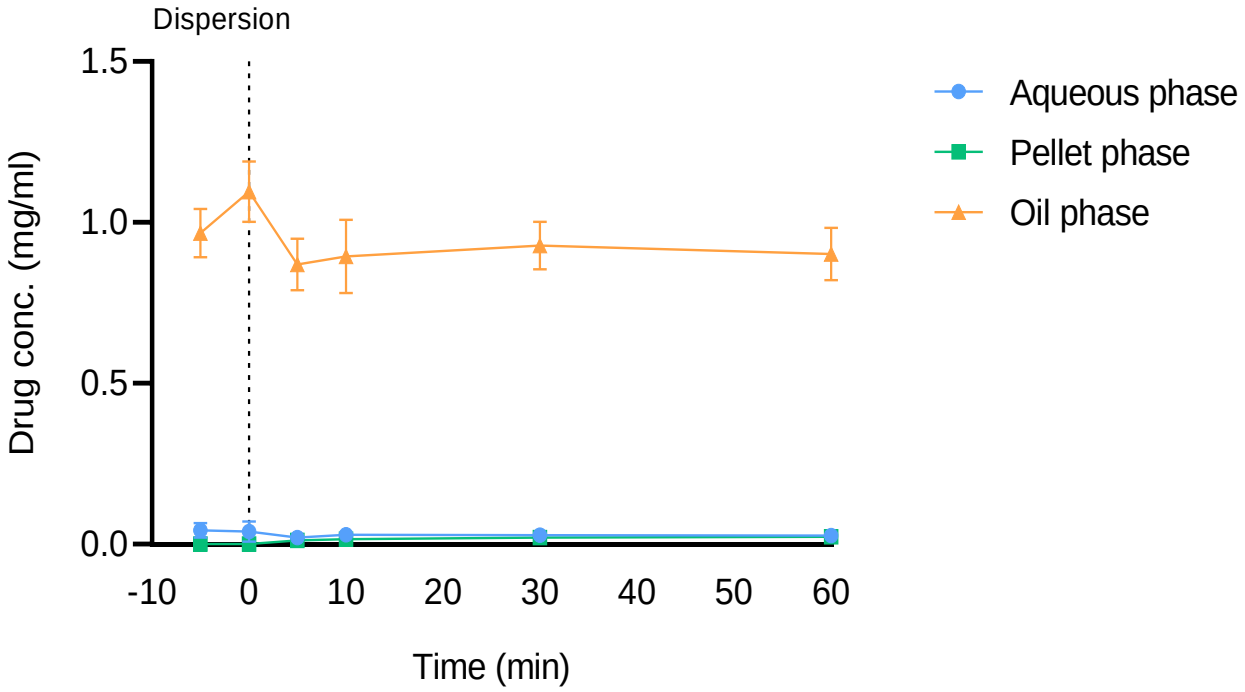
increasing hydrophilicity

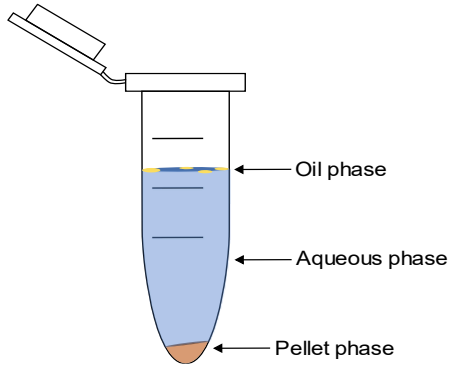
EXCIPIENTS (%, w/w)	TYPE I OIL	TYPE II SEDDS	TYPE IIIA SEDDS	TYPE IIIB SMEDDS	TYPE IV OIL-FREE
Oils: tri, di & mono glycerides	100	40-80	40-80	<20	-
Water insoluble surfactants	-	20-60	-	-	0-20
Water soluble surfactants	-	-	20-40	20-50	30-80
Hydrophilic co-solvents	-	-	0-40	20-50	0-50
Dispersion	Limited or no dispersion	Dispersing	Rapidly dispersing	Transparent dispersion	Micellar solution



Pouton, *Eur. J. Pharm. Sci* **9**, 278 (2006).

Drug distribution – LBF I





UPPSALA UNIVERSITET

Formulation dispersion in lipolysis buffer