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Do Phospholipids Boost or Attenuate Oral Drug Absorption? In Vitro- and In Vivo- Studies on Mono- and Diacyl Phospholipid-Based Solid Dispersions of Celecoxib

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3 Drug Product Development, Janssen Research and Development, Johnson & Johnson, Beerse, Belgium

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Background | Recent additions: Literature | Recent additions: Results and discussion | Conclusions | Future perspectives

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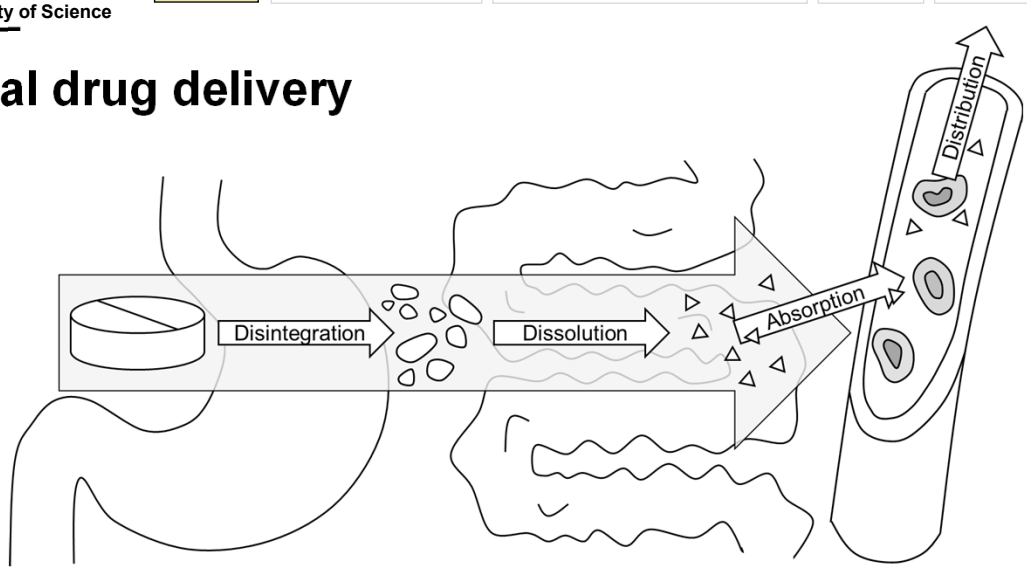
Oral drug delivery



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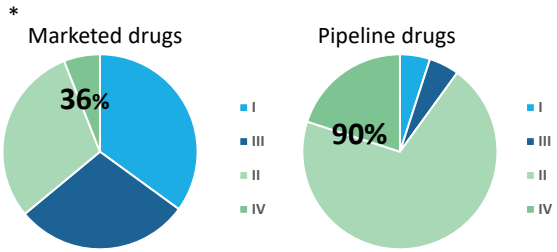
Biopharmaceutics Classification System

Permeability	Solubility
Class I High solubility High permeability	**Class II** Low solubility High permeability
Class III High solubility Low permeability	**Class IV** Low solubility Low permeability



*Lipp 2013, American Pharmaceutical Review https://www.americanpharmaceuticalreview.com/Featured-Articles/135982-The-Innovator-Pipeline-Bioavailability-Challenges-and-Advanced-Oral-Drug-Delivery-Opportunities/

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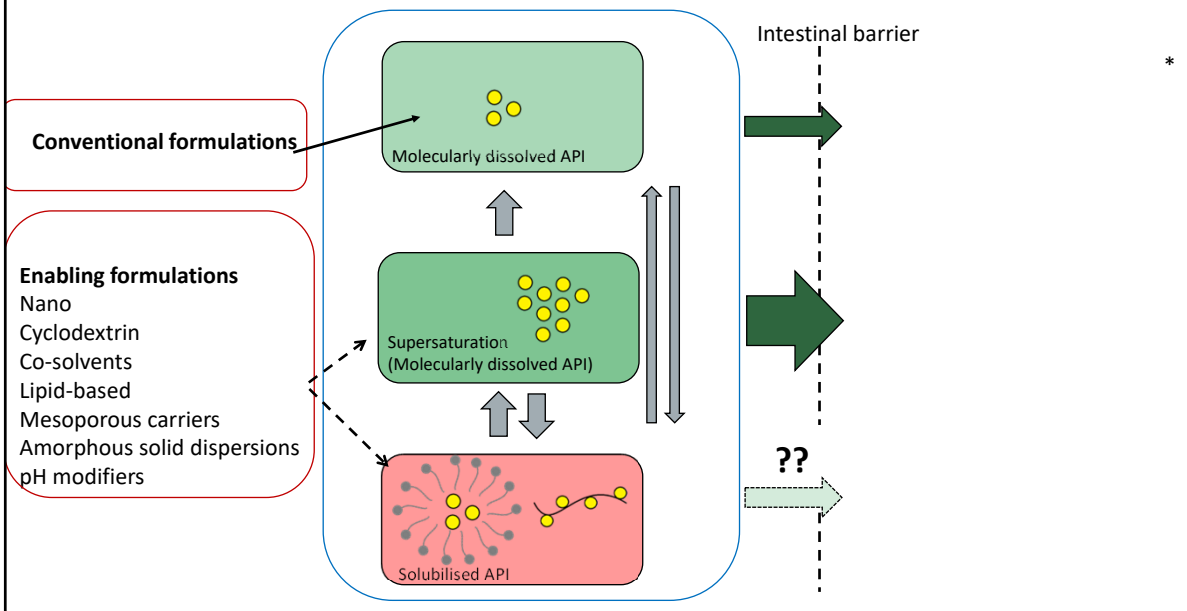
Influence of Dissolved States on Permeation



Buckley et al., Eur. J. Pharm. Sci. 50, 8-16 (modified)(2013)
*Brouwers et al., Journal of Pharmaceutical Sciences Volume 98, Issue 8, Pages 2549-2572 (2009)

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Influence of Dissolved States on Permeation

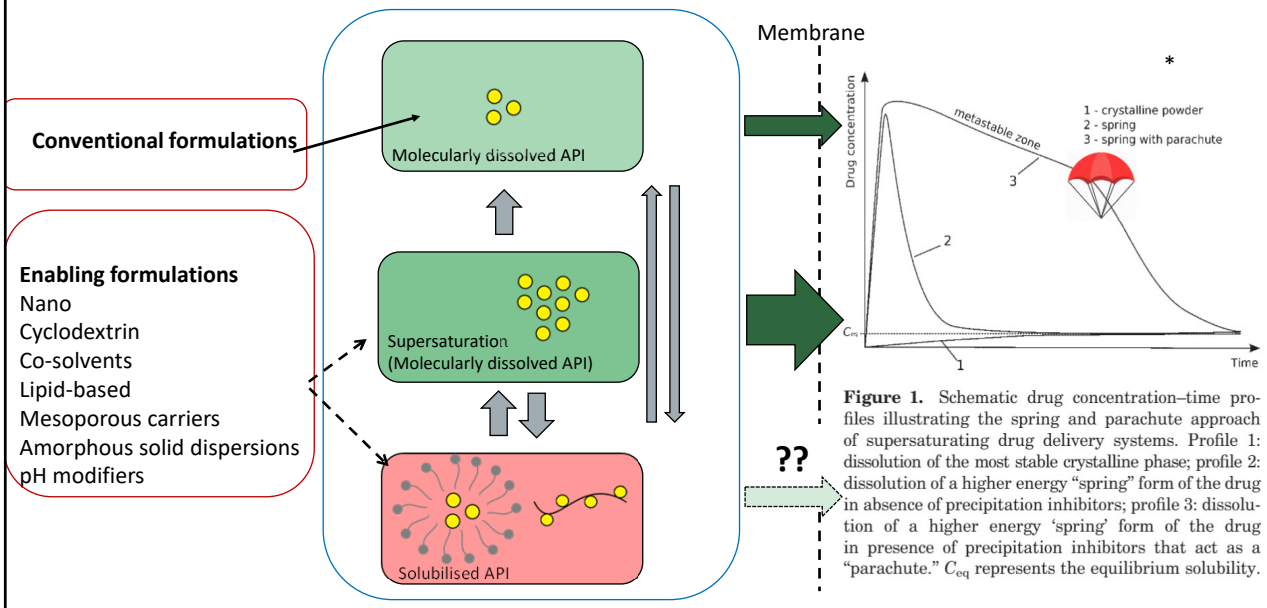

Figure 1. Schematic drug concentration–time profiles illustrating the spring and parachute approach of supersaturating drug delivery systems. Profile 1: dissolution of the most stable crystalline phase; profile 2: dissolution of a higher energy "spring" form of the drug in absence of precipitation inhibitors; profile 3: dissolution of a higher energy 'spring' form of the drug in presence of precipitation inhibitors that act as a "parachute." C_{eq} represents the equilibrium solubility.

Buckley et al., Eur. J. Pharm. Sci. 50, 8-16 (modified)(2013)
*Brouwers et al., Journal of Pharmaceutical Sciences Volume 98, Issue 8, Pages 2549-2572 (2009)

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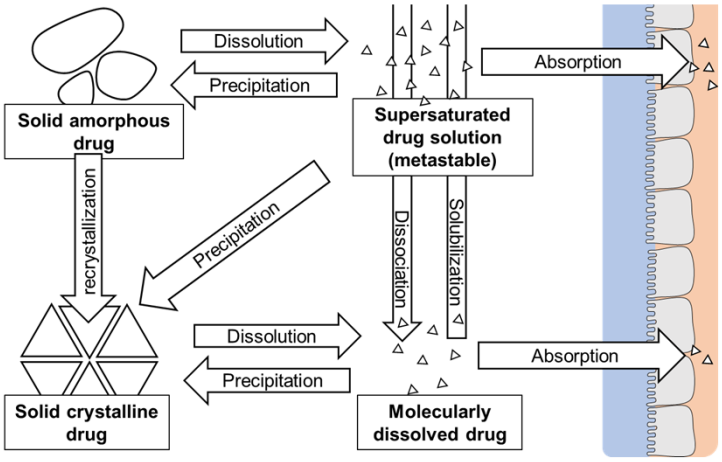
Micelles ? Liposomes?



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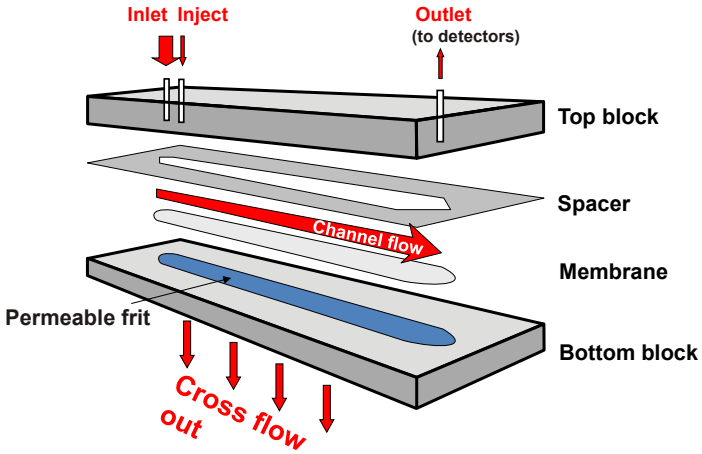
Flow Field-Flow

AF4 Channel Design



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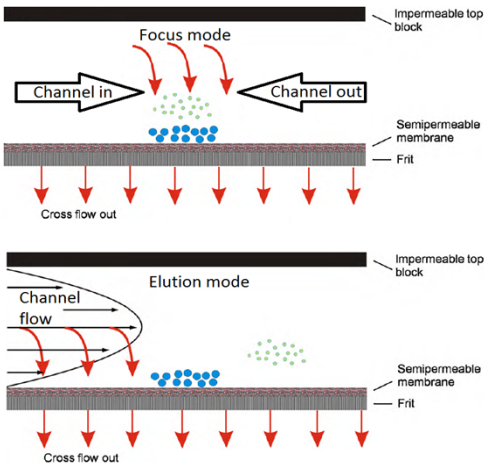
Asymmetrical flow field-flow fractionation AF4



(Adapted from Hupfeld, 2009)

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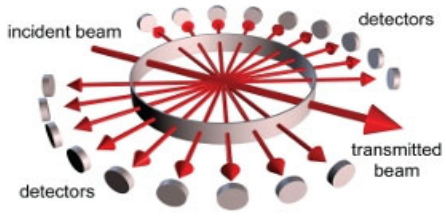
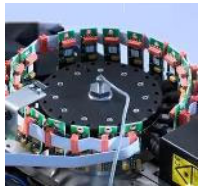
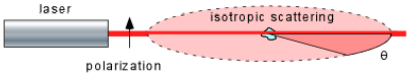
Multi-angle Laser Light Scattering (MALLS)

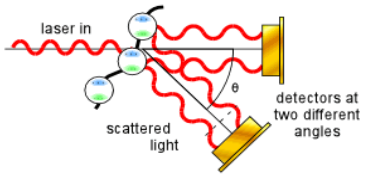


http://www.americanlaboratory.com/913-Technical-Articles/147482-The-Story-of-MALS/



http://www.azom.com/images/videos/VideoImage_1937.jpg





Particles > 15 nm
=> angular dependence of scattered light

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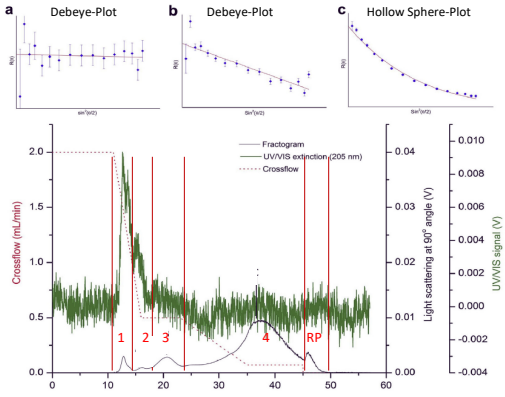
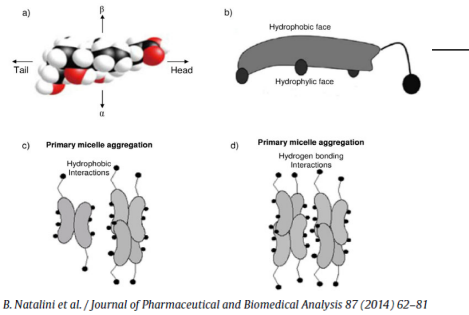
Nanoparticulate lipid assemblies

Fasted state aspirated human intestinal fluid

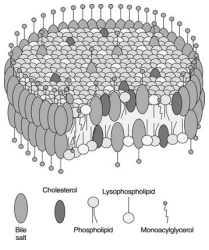
Sample/Peak No.	Time Interval (min)	AF4/MALLS D_{10} (nm)	D_{50} (nm)	D_{90} (nm)	D_z (nm	UV Absorption (205 nm)
FaHIF/1	12-14	n.a.	n.a.	n.a.	n.a.	+
FaHIF/2	15-17	n.a.	n.a.	n.a.	n.a.	+
FaHIF/3[a]	18-23	40.3	48.0	54.7	48.6	(+)
FaHIF/4[b]	30-45	114.5	237.1	337.1	287.0	–
FaHIF/R.P.[b]	45-47	377.9	406.7	455.5	413.8	–

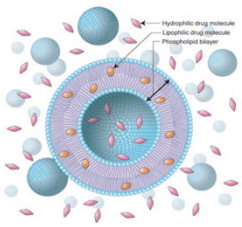
P.A. Elvang et al. / Journal of Pharmaceutical Sciences 105 (2016) 2832–2839





B. Natalini et al. / Journal of Pharmaceutical and Biomedical Analysis 87 (2014) 62–81





Picture from: https://www.cliffsnotes.com/study-guides/biology/biochemistry-ii/fatty-acid-oxidation/dietary-fat-absorption

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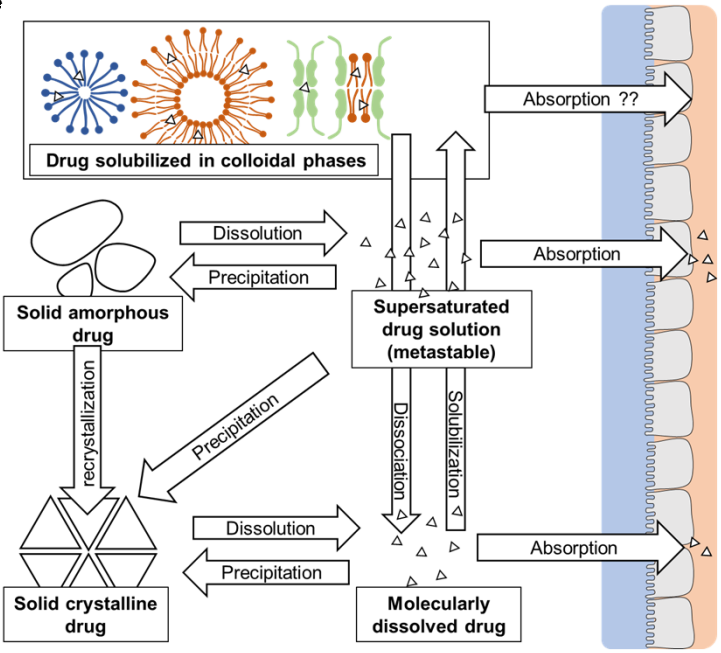

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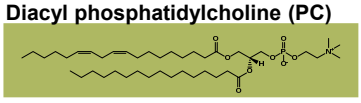
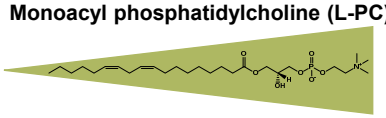
Enabling formulations – Phospholipid-based solid dispersions

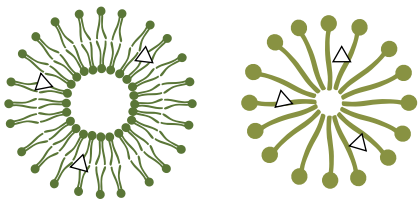
- The (amorphous) drug dispersed in an amorphous phospholipid matrix
- Solubilizing colloidal phases are formed in contact with aqueous media

Diacyl phosphatidylcholine (PC)



Monoacyl phosphatidylcholine (L-PC)





Vesicle **Micelle**

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Preparation of Amorphous Solid Phospholipid - Dispersions of Model Drug Celecoxib

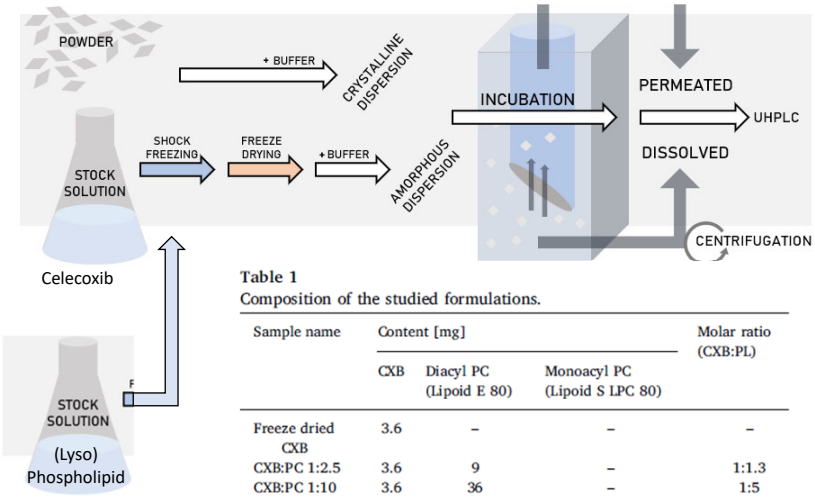

Table 1
Composition of the studied formulations.

Sample name	Content [mg]			Molar ratio (CXB:PL)
	CXB	Diacyl PC (Lipoid E 80)	Monoacyl PC (Lipoid S LPC 80)	
Freeze dried CXB	3.6	–	–	–
CXB:PC 1:2.5	3.6	9	–	1:1.3
CXB:PC 1:10	3.6	36	–	1:5
CXB:PC 1:50	3,6	180	–	1:25
CXB:L-PC 1:2.5	3.6	–	9	1:1.8
CXB:L-PC 1:10	3.6	–	36	1:7.5
CXB:L-PC 1:50	3.6	–	180	1:36

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Background | Recent additions: Literature | Results and discussion | Conclusions | Future perspectives

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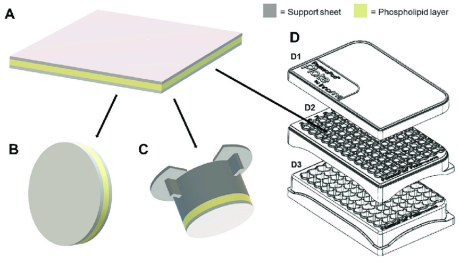
Dissolution/permeation testing of diacyl- and monoacyl-phospholipid-based solid dispersions of celecoxib



Permeation barrier:
Permeapad®
Dispersion medium:
PBS or FaSSIF
Acceptor medium:
1% SDS in 'FaSSIF blank buffer

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Jacobsen, A.-C., et al., 2019. A dynamic in vitro permeation study on solid mono- and diacyl-phospholipid dispersions of celecoxib. Eur. J. Pharm. Sci. 127, 199–207

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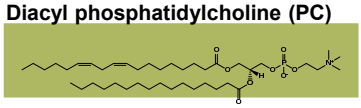
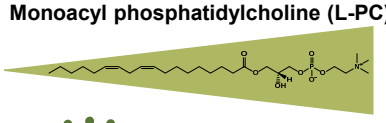
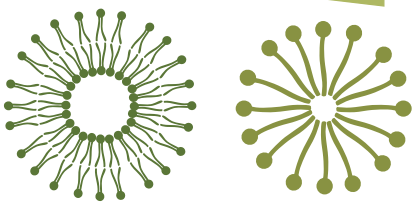
Dissolution testing of diacyl- and monoacyl- phospholipid-based solid dispersions of celecoxib

Diacyl phosphatidylcholine (PC)

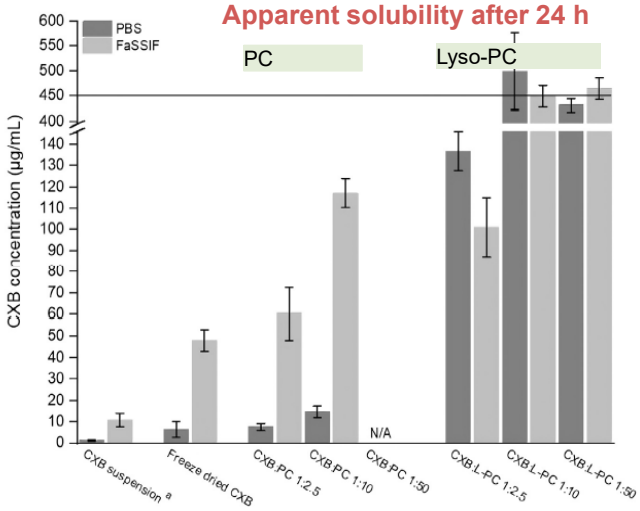


Monoacyl phosphatidylcholine (L-PC)





Apparent solubility after 24 h



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Jacobsen, A.-C., et al., 2019. A dynamic in vitro permeation study on solid mono- and diacyl-phospholipid dispersions of celecoxib. Eur. J. Phar Sci. 127, 199–207

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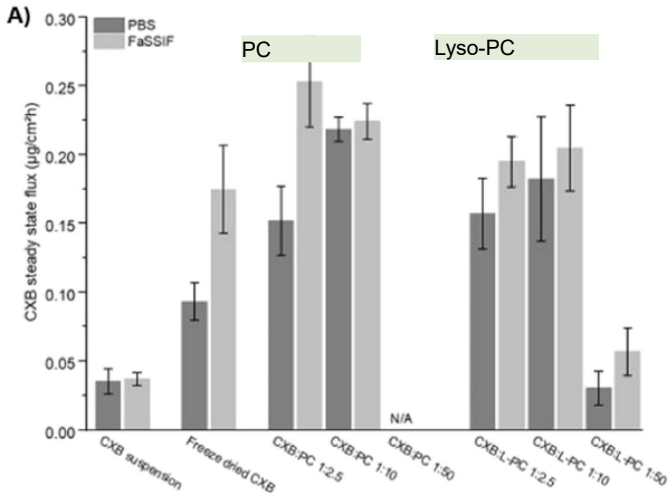
Dissolution/permeation testing

Permeation data from D/P experiment



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Jacobsen, A.-C., et al., 2019. A dynamic in vitro permeation study on solid mono- and diacyl-phospholipid dispersions of celecoxib. Eur. J. Pharm. Sci. 127, 199–207

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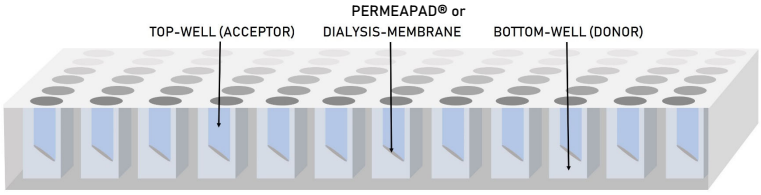
High-throughput dissolution/permeation testing

Starting point → 96-well format

Advantages:

- High number of samples in a single experiment
- Compatible with standard laboratory equipment (e.g. multichannel pipettes, liquid handling stations)



Jacobsen, A.-C., et al., 2019. High-Throughput Dissolution/Permeation Screening -A 96-Well Two-Compartment Microplate Approach. Pharmaceutics 11, 227

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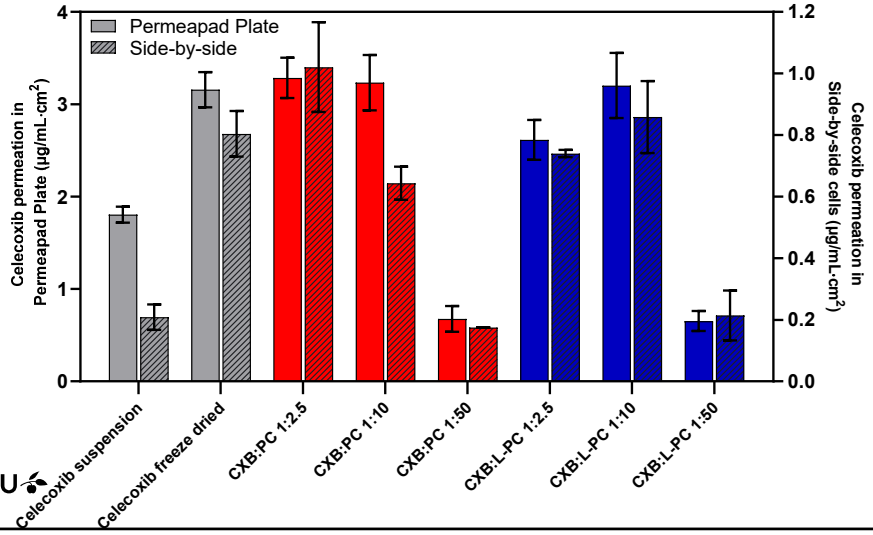
Dissolution/permeation testing in 96-well format

Cumulative amount permeated



Experimental parameters:
Permeation barrier: Permeapad®
Dispersion medium: FaSSIF
Acceptor medium: 1% SDS in 'FaSSIF blank buffer
Donor concentrations:
Side-by-side → 0.45 mg/mL
96-well plate → 5 mg/mL

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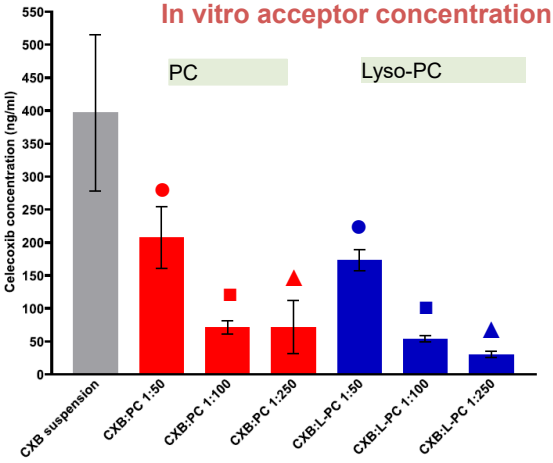
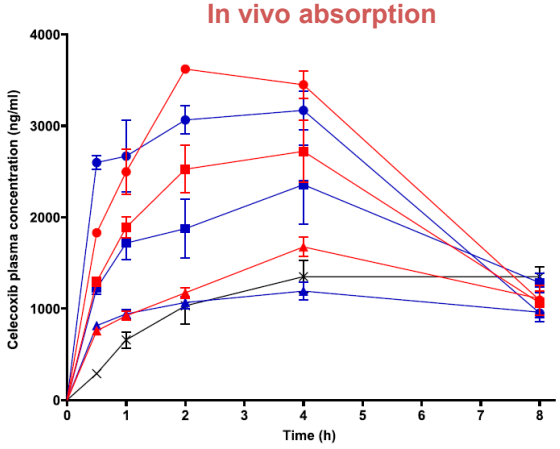
Diacyl and monoacyl phospholipid-based solid dispersions of celecoxib with high phospholipid content – In vitro and in vivo evaluation

In vitro acceptor concentration



In vivo absorption



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Jacobsen, A.-C., et al., 2020. Do phospholipids boost or attenuate drug absorption? In vitro and in vivo evaluation of mono- and diacyl-phospholipid-based solid dispersions of celecoxib. J. Pharm. Sci., Article in press

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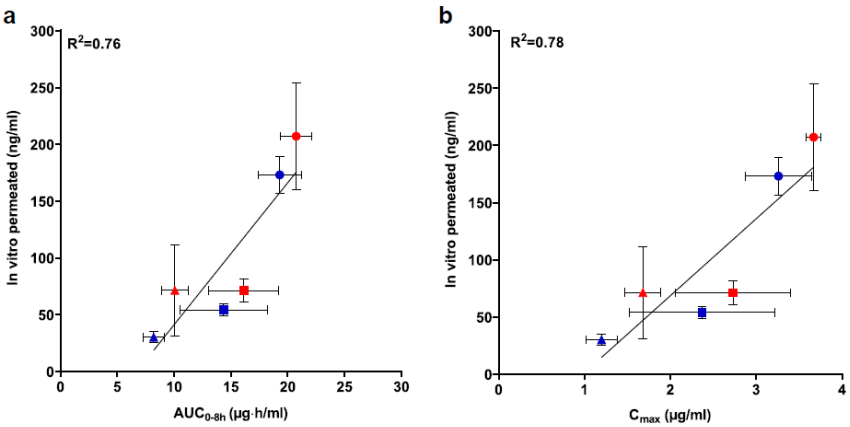
Dissolution/permeation testing of diacyl and monoacyl phospholipid-based solid dispersions of celecoxib with high phospholipid content in 96-well format

In vitro in vivo correlation



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Jacobsen, A.-C., et al., 2020. Do phospholipids boost or attenuate drug absorption? In vitro and in vivo evaluation of mono- and diacyl-phospholipid-based solid dispersions of celecoxib. J. Pharm. Sci., Article in press

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Conclusions

- Phospholipid-based Celecoxib formulations appear promising for enhancing oral bioavailability
- For Celecoxib PL-based ASDs, in vitro and in vivo performance depend on phospholipid/drug-ratio
- Dissolution/permeation testing
  - gave better mechanistic insights than mere dissolution testing
  - helped to screen for best performing formulation
- Even high throughput dissolution/permeation screening was feasible

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Future perspectives

- Investigation of
  - more drugs in PL-based ASDs is needed
  - to see if the observed Celecoxib case is representative for other BCS II drugs

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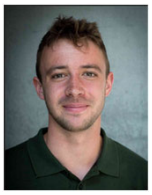
Drug Transport & Delivery-Team





A. Bauer-Brandl P.C. Stein Felix Paulus Florentin Holzem onas B Eriksen M.S. Bohsen T. Christiansen

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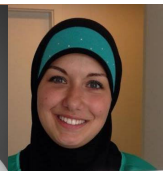
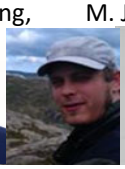
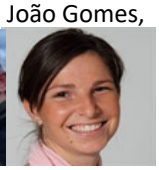


AC Jacobsen S.Y.K. Fong, M. João Gomes, D. Sironi, P. Elvang, H. Bibi

M. di Cagno, A. Hinna, S. Fischer, K. Frank (Schäfer), S. Buckley

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Collaborators & Sponsors

J. Rosenberg, AbbVie Ludwigshafen, DE

P. Skupin-Mrugalska, M. Czajkowski, Univ. Poznan, PL

J. Milsmann, R. Messerschmid, Boehringer Ing., DE

P. Augustijns, Univ. Leuven, BE

R. Holm, Janssen, BE (now SDU, Odens

A

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Questions?
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