Mechanism of Bioavailability Enhancement of Solid Solutions/Solid Dispersions

M. Brandl[1], J. Kanzer[1,2], I. Tho[1,2], G. Fricker[2]

[1]Drug Transport & Delivery Group, Institute of Pharmacy, University of Tromsø,

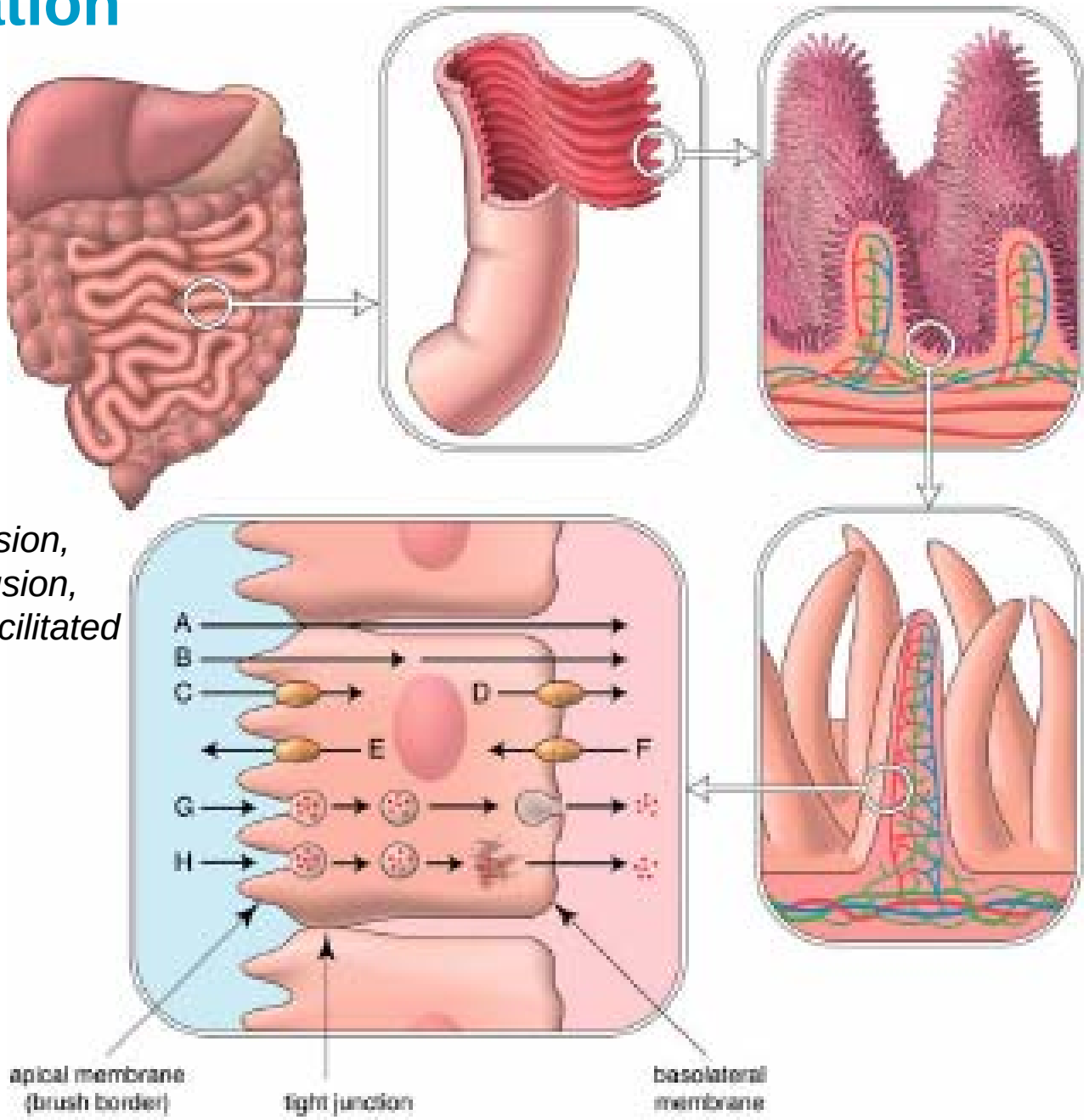
N-9014 Tromsø, Norway

[2]Institute of Pharmacy and Molecular Biotechnology, University of Heidelberg

69120 Heidelberg, Germany

Soliqs Symposium 2008

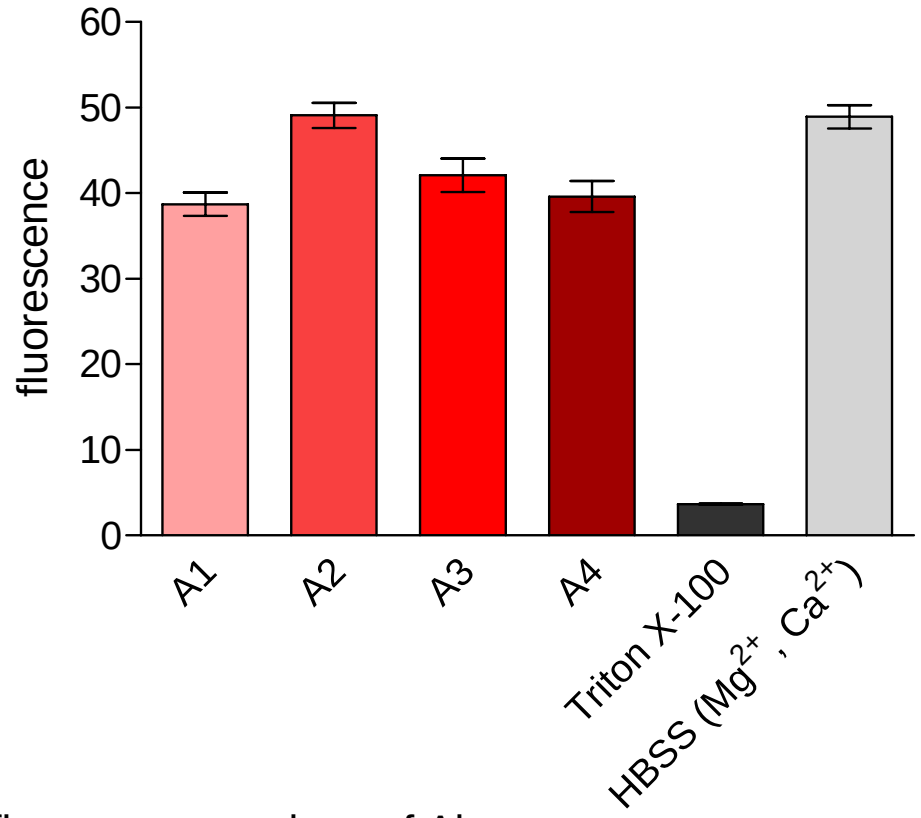
GI-Permeation pathways



A: paracellular passive diffusion,
B: transcellular passive diffusion,
C + F: membrane protein-facilitated (acive) transport
C: influx F: efflux,
G: transcytosis
H: endocytosis

(Våbenø, thesis Univ. Tromsø 2004)

CaCo-2 Cell viability upon exposure to melt extrudates

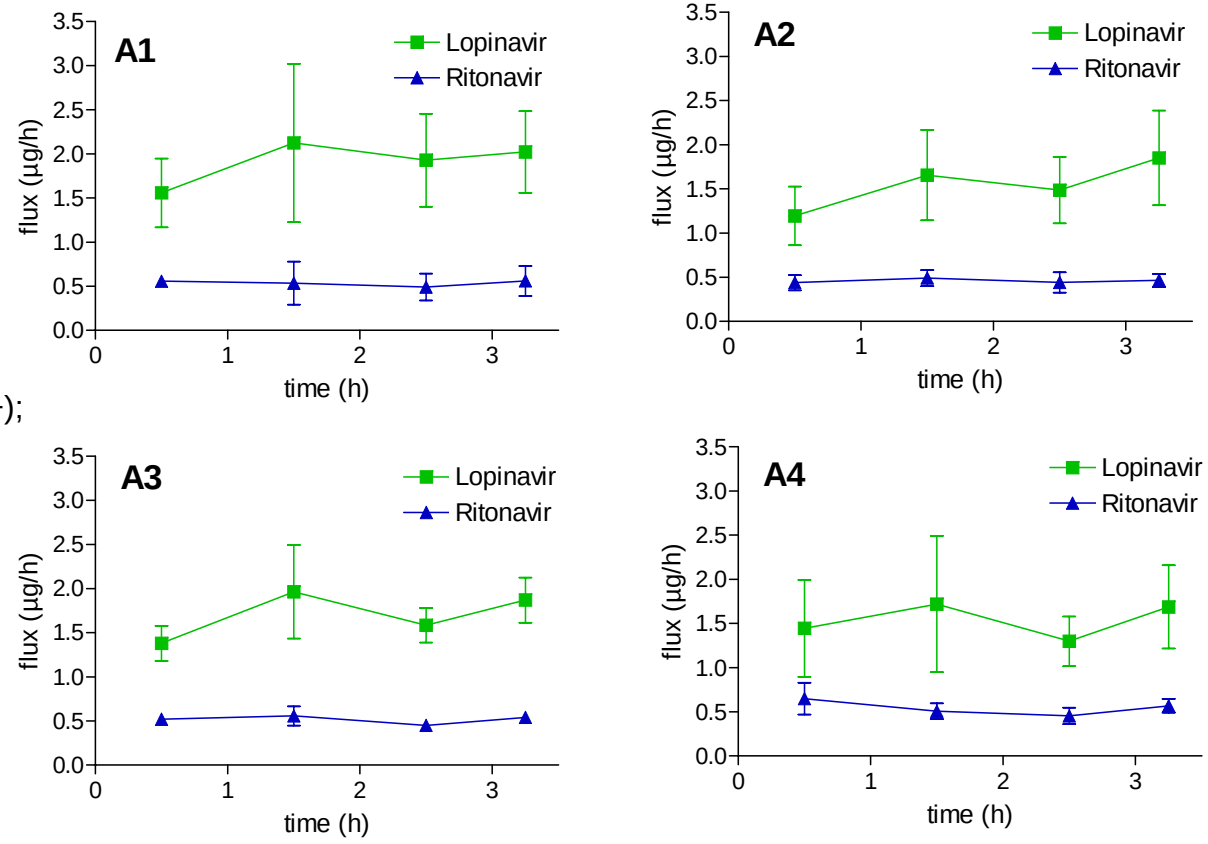


60 minutes-fluorescence values of Alamar BlueTM following 3.5 hours of incubation with formulations A1, A2, A3 and A4, respectively versus control HBSS-buffer (n=9, mean±SD)

J. Kanzer et al., Transact. CRS Ann. Meeting (2008)

Caco-2-Permeability

Flux from formulations A1 - A4 across Caco-2 cell monolayers



in HBSS (Mg2+, Ca2+);
means±SEM (n=9)

J. Kanzer et al., Transact. CRS Ann. Meeting (2008)

Structure of ”Phospholipid vesicle-based barrier”

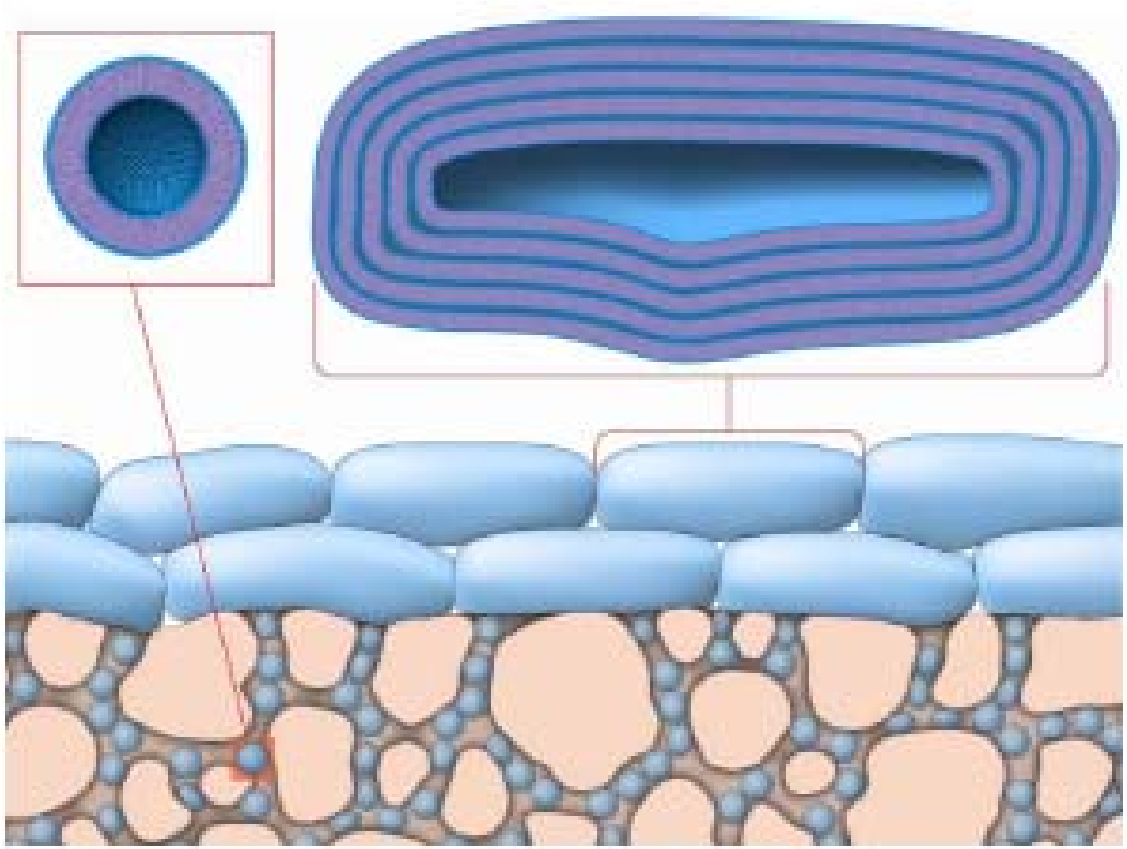
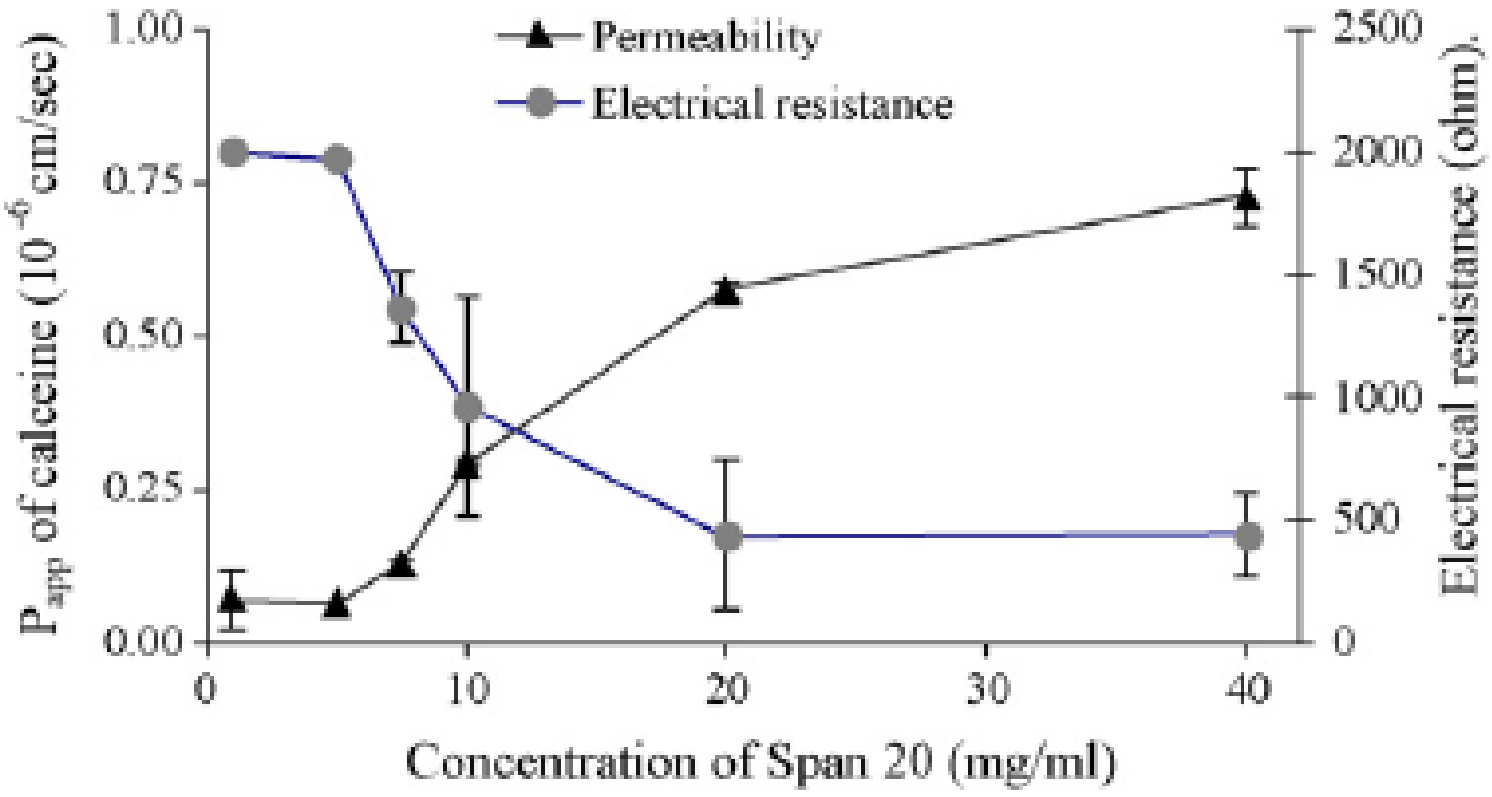


Figure 4.6: A schematic illustration of the structure of the phospholipid vesicle-based barrier based on the results from the characterization studies.

G. Flaten, Thesis Univ. Tromsø (2007)

Tensides may induce leakiness of the permeation barrier

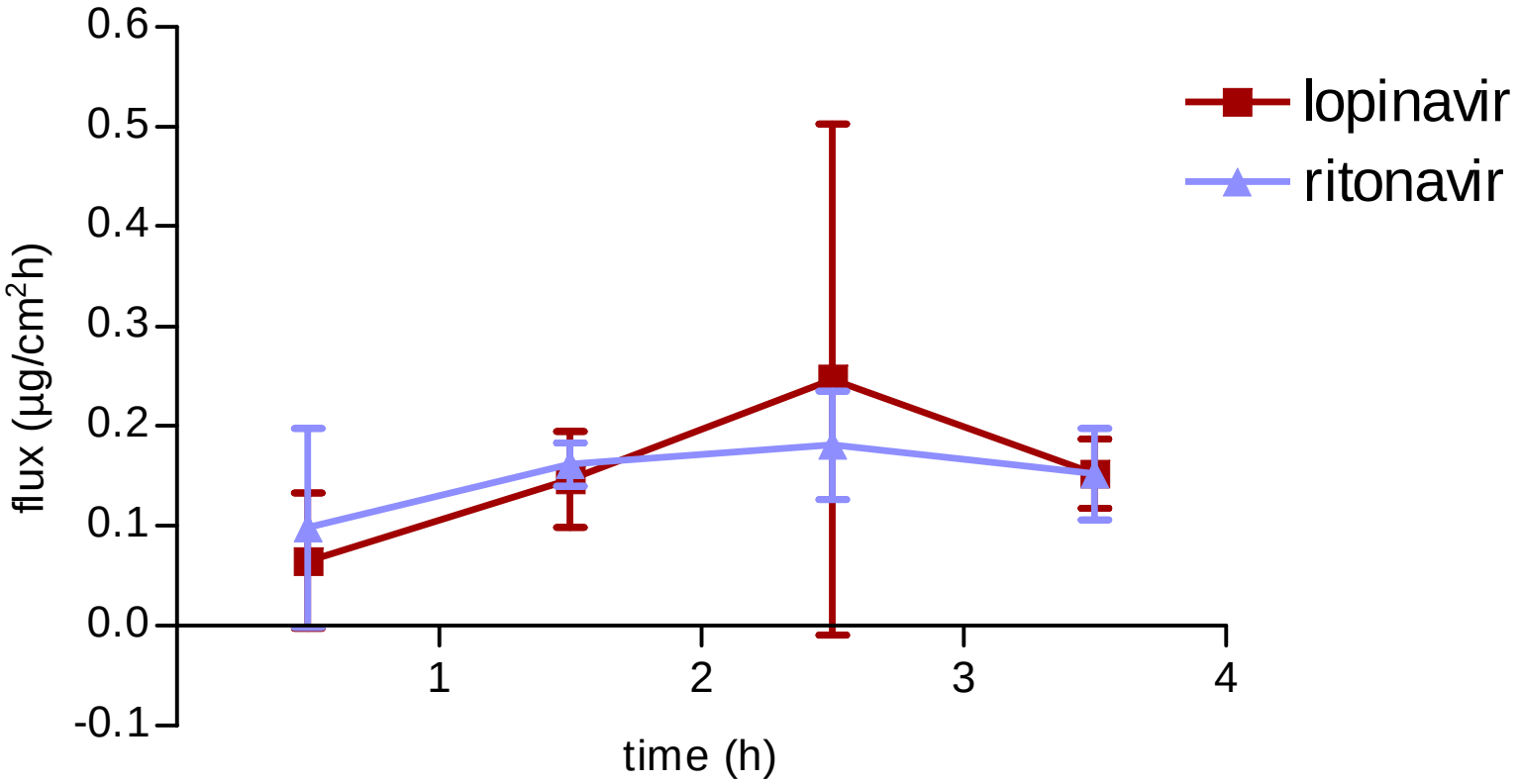
Electrical resistance and permeability (*P*app) values for calcein in the presence of Span 20



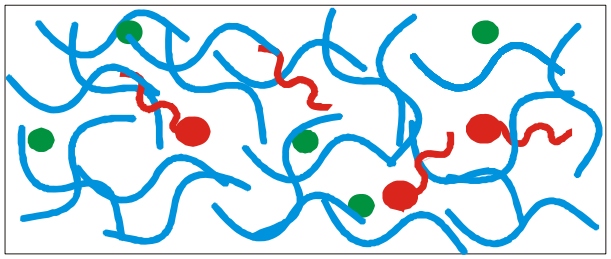
G. Flaten et al., Eur. J. Pharm. Sci. 34 (2-3), 173-180 (2008)

Liposome-barrier: Permeability

Flux from melt-extrudate formulation across phospholipid vesicle-based barrier



What kind of structures may we expect in aqueous melt extrudate-dispersions?



Drug molecule

tenside

polymer

Dispersion in aqueous medium

Micro- / Nanoparticles

(Super-)saturated Solution

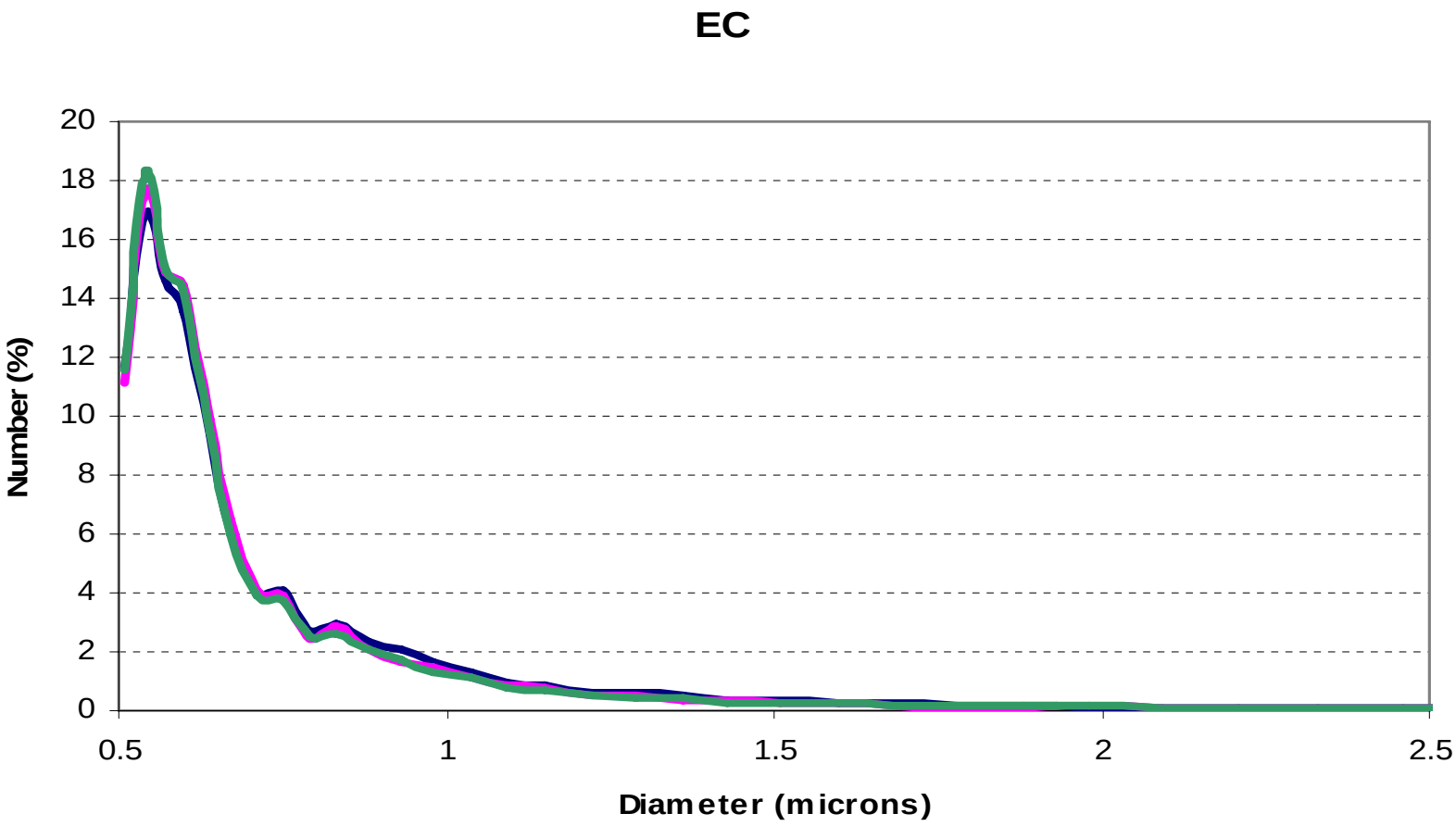
Micelles

Drug / Polymer-Complex

Particle size analysis by PCS

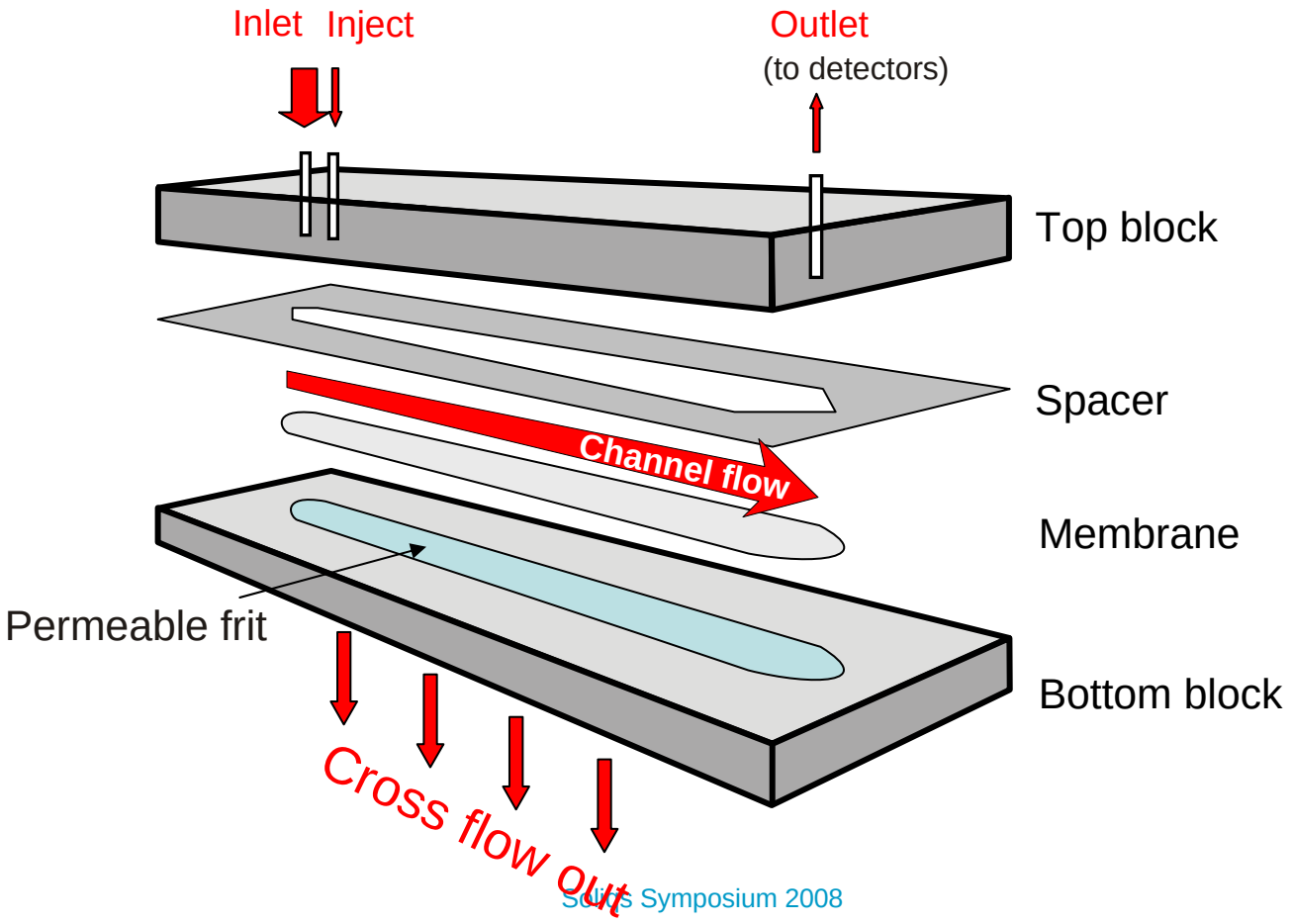
	HBSS (Mg^{2+}, Ca^{2+}) (n=3)	10 mM $NaNO_3$ (n=6)
Mean diam (nm)	386,7	235,3
Stdev (nm)	3,0	5,5
Stdev (%)	0,8	1,3
PI	0,094	0,083
Stdev (PI)	0,035	0,010

Light blockage particle counting



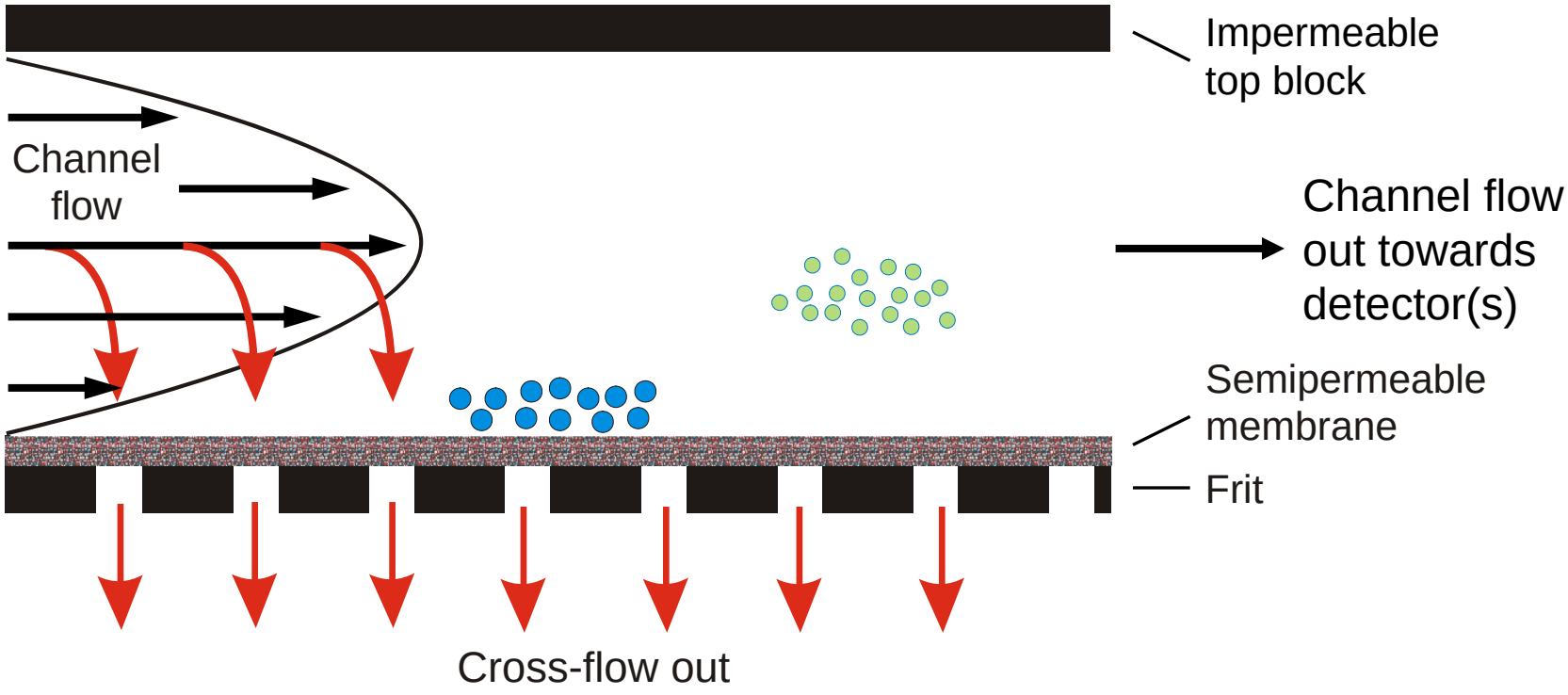
Fractionation of aq. Meltrex dispersions

by asymmetrical Flow-Field-Flow-Fractionation:
AF4 Channel Design



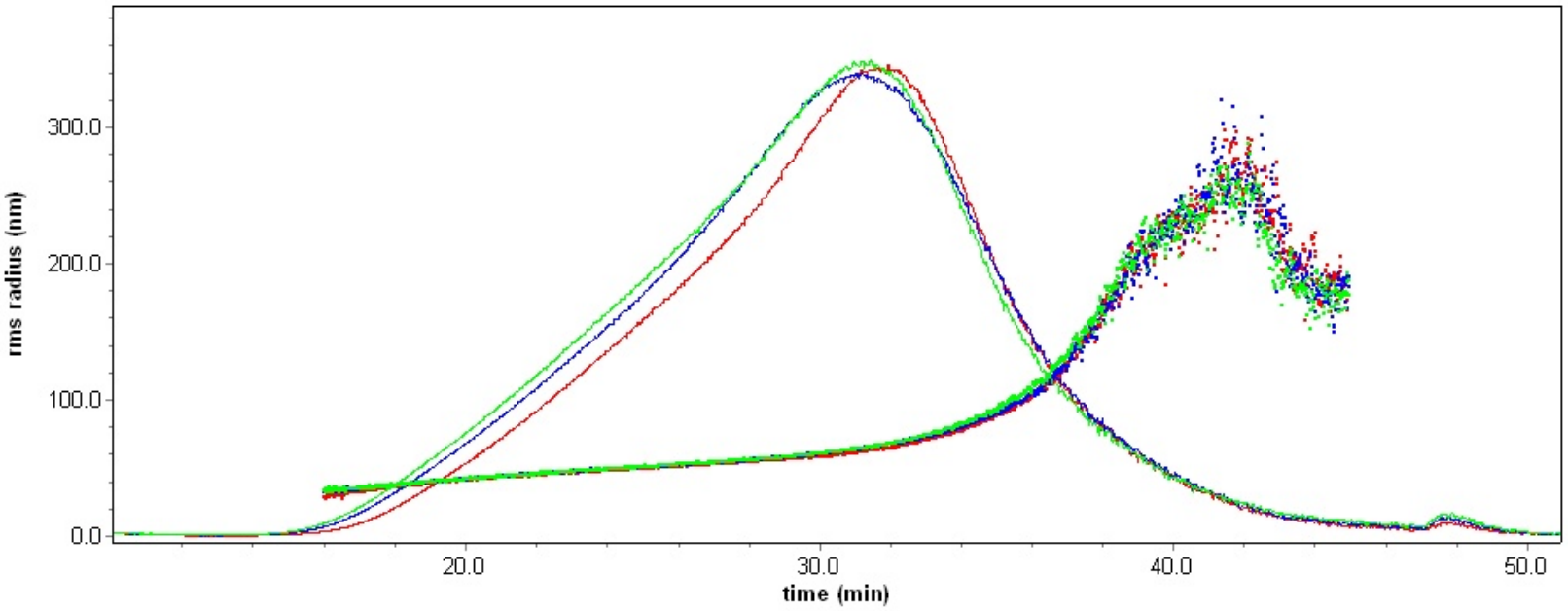
AF4

Fractionation Principle



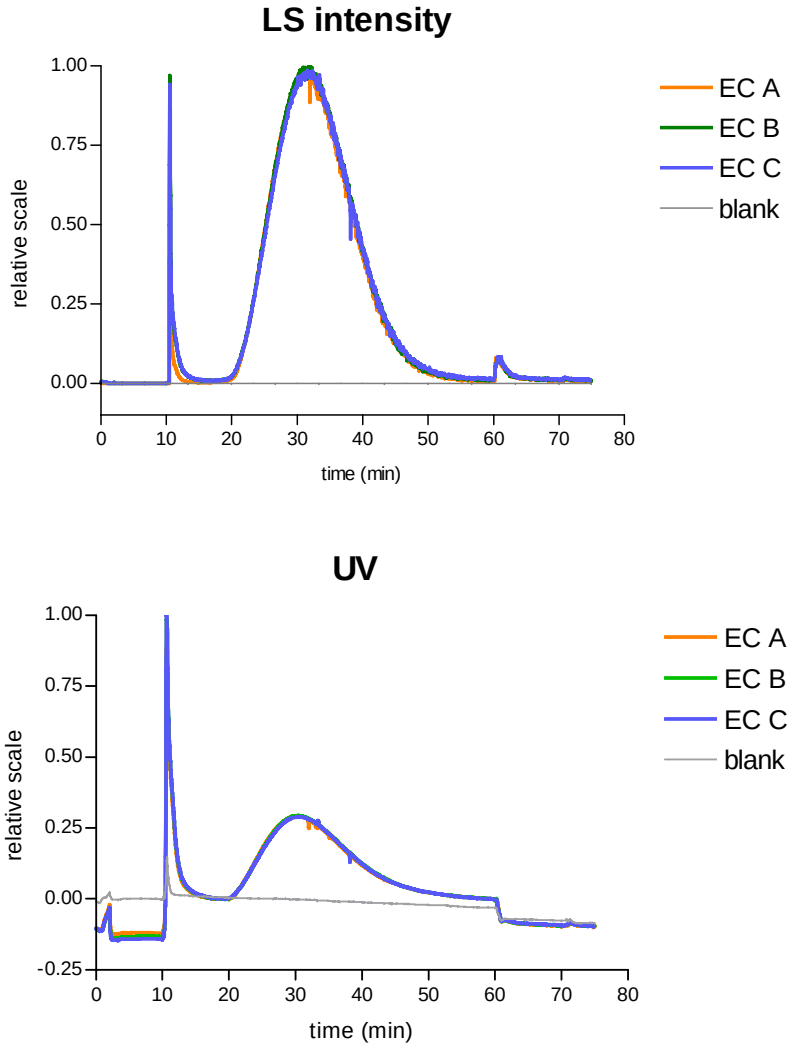
Fractionation of aq. Meltrex dispersions

Characterisation of the main fraction



	EC A	EC B	EC C	Mean	Stdev
Rn (nm)	55.3 (2%)	55.4 (2%)	54.9 (2%)	55.2	0,26
Rw (nm)	73.3 (1%)	73.7 (1%)	72.6 (1%)	73.2	0,56
Rz (nm)	144.6 (2%)	145.5 (1%)	139.2 (1%)	143.1	3,41

Fractionation of aq. Meltrex dispersions



Acknowledgements

- Abbott GmbH & Co. KG, Ludwigshafen
- The Norwegian Research Council, Oslo
- German Academic Exchange Service DAAD, Bonn

- M. Mägerlein
- J. Rosenberg
- B. Liepold
- P. Hölig

- G.E. Flaten
- S. Hupfeld
- A. Bauer-Brandl