The BV Droplets Down Under: From Model Emulsions to Drug Delivery

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UniSA

Windsurfing in the Bristol Channel


Definitely not the Bristol Channel!

Memories of those good old days at Bristol in the late 80's with Brian as your supervisor

Civilised with a high level of decorum

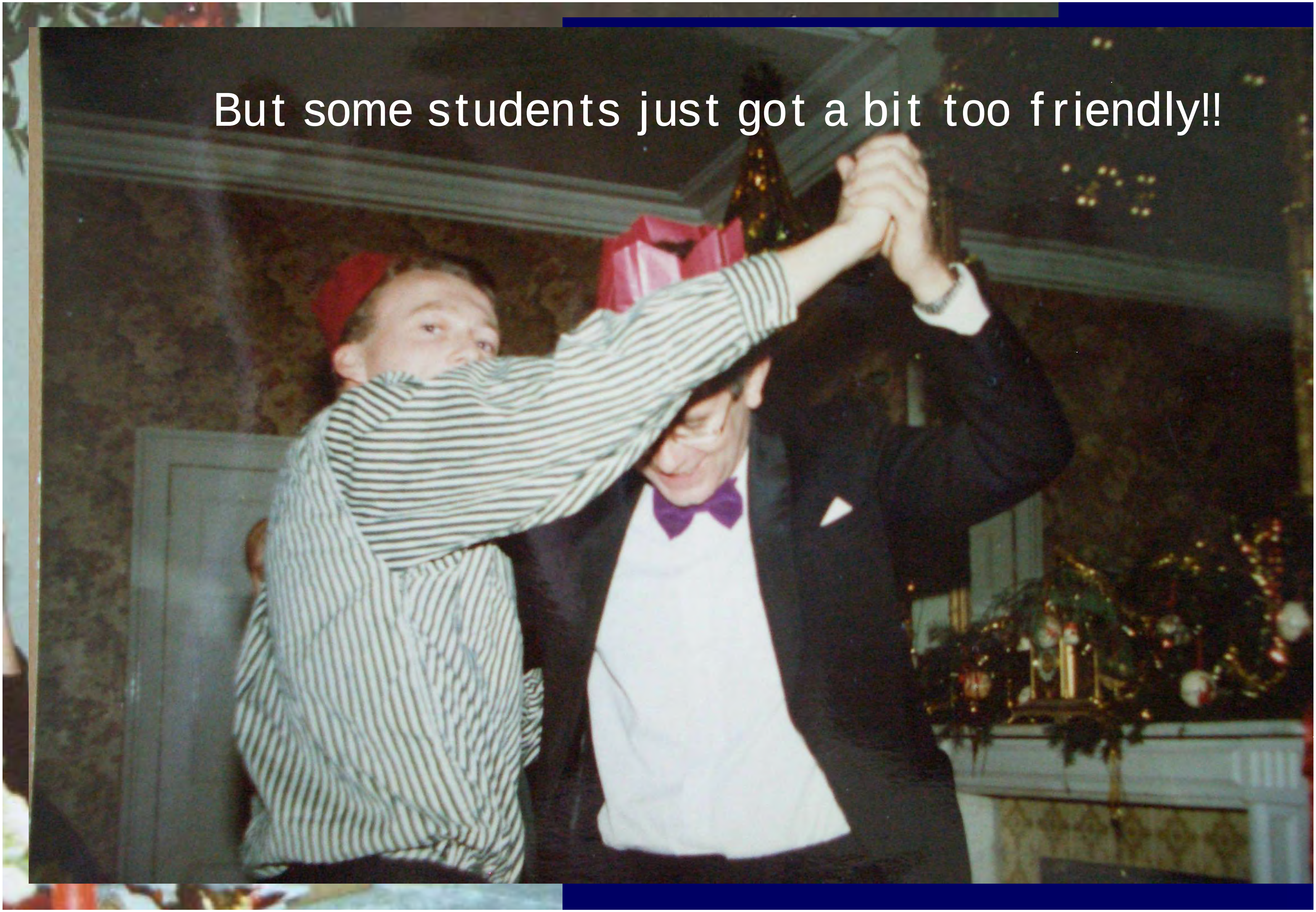
The BV Birthday – Always a Special Day……..

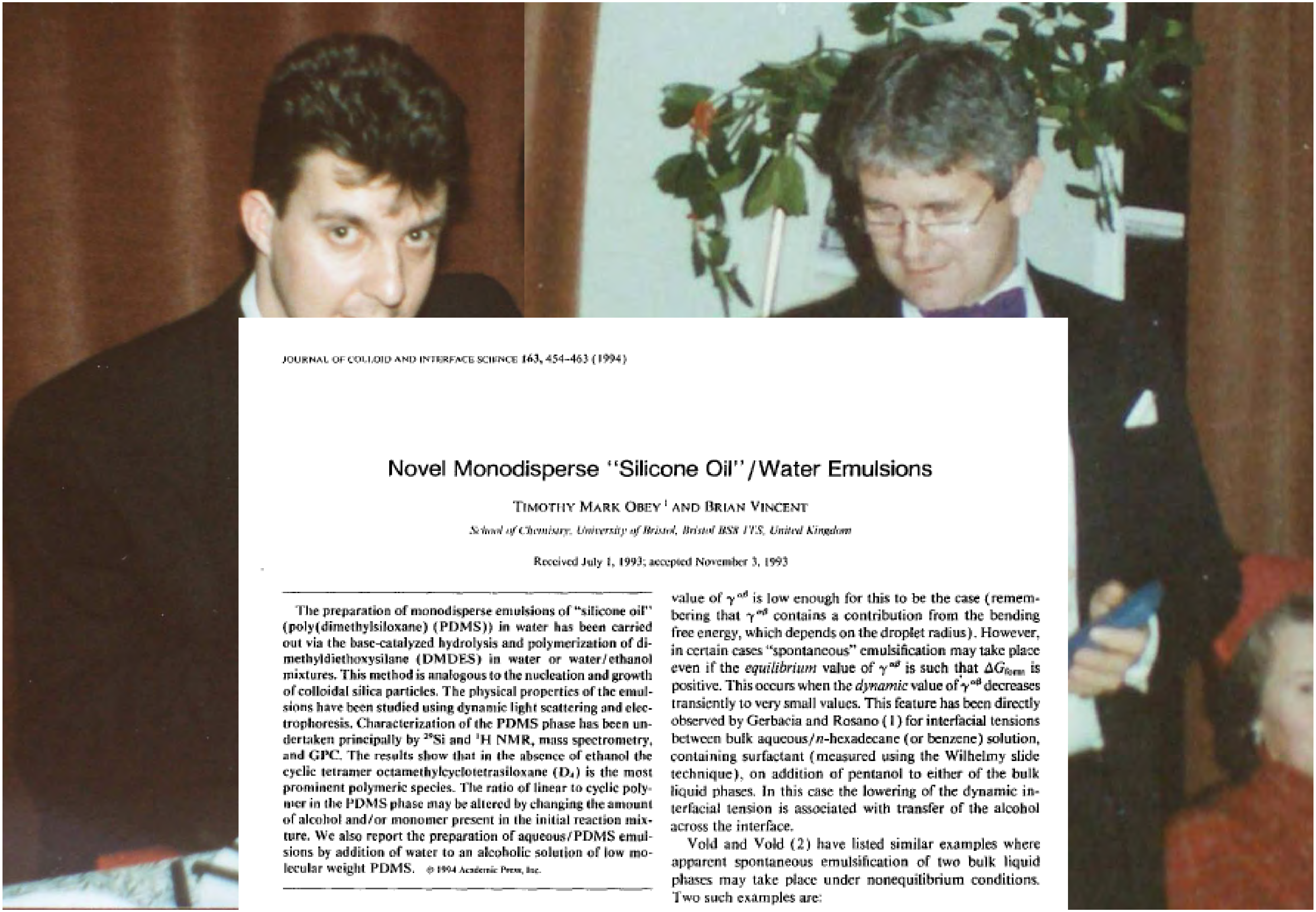
Kick a few students into a Mini Bus

Treat him like a King and make him the centre of attention


Feed him a nice big cake

But some students just got a bit too friendly!!





JOURNAL OF COLLOID AND INTERFACE SCIENCE 163, 454–463 (1994)

Novel Monodisperse "Silicone Oil"/Water Emulsions

TIMOTHY MARK OBEY[1] AND BRIAN VINCENT

School of Chemistry, University of Bristol, Bristol BS8 1TS, United Kingdom

Received July 1, 1993; accepted November 3, 1993

The preparation of monodisperse emulsions of "silicone oil" (poly(dimethylsiloxane) (PDMS)) in water has been carried out via the base-catalyzed hydrolysis and polymerization of dimethyldiethoxysilane (DMDES) in water or water/ethanol mixtures. This method is analogous to the nucleation and growth of colloidal silica particles. The physical properties of the emulsions have been studied using dynamic light scattering and electrophoresis. Characterization of the PDMS phase has been undertaken principally by ^{29}Si and ^{1}H NMR, mass spectrometry, and GPC. The results show that in the absence of ethanol the cyclic tetramer octamethylcyclotetrasiloxane (D_4) is the most prominent polymeric species. The ratio of linear to cyclic polymer in the PDMS phase may be altered by changing the amount of alcohol and/or monomer present in the initial reaction mixture. We also report the preparation of aqueous/PDMS emulsions by addition of water to an alcoholic solution of low molecular weight PDMS.

value of $\gamma^{\alpha\beta}$ is low enough for this to be the case (remembering that $\gamma^{\alpha\beta}$ contains a contribution from the bending free energy, which depends on the droplet radius). However, in certain cases "spontaneous" emulsification may take place even if the *equilibrium* value of $\gamma^{\alpha\beta}$ is such that ΔG_{form} is positive. This occurs when the *dynamic* value of $\gamma^{\alpha\beta}$ decreases transiently to very small values. This feature has been directly observed by Gerbacia and Rosano (1) for interfacial tensions between bulk aqueous/*n*-hexadecane (or benzene) solution, containing surfactant (measured using the Wilhelmy slide technique), on addition of pentanol to either of the bulk liquid phases. In this case the lowering of the dynamic interfacial tension is associated with transfer of the alcohol across the interface.

Vold and Vold (2) have listed similar examples where apparent spontaneous emulsification of two bulk liquid phases may take place under nonequilibrium conditions. Two such examples are:

ELSEVIER

Colloids and Surfaces
A: Physicochemical and Engineering Aspects 123–124 (1997) 183–193

COLLOIDS AND SURFACES A

Inorganic "silicone oil" microgels

Michael I. Goller, Timothy M. Obey, Declan O.H. Teare, Brian Vincent *, Matthias R. Wegener

School of Chemistry, University of Bristol, Bristol BS8 1TS, UK

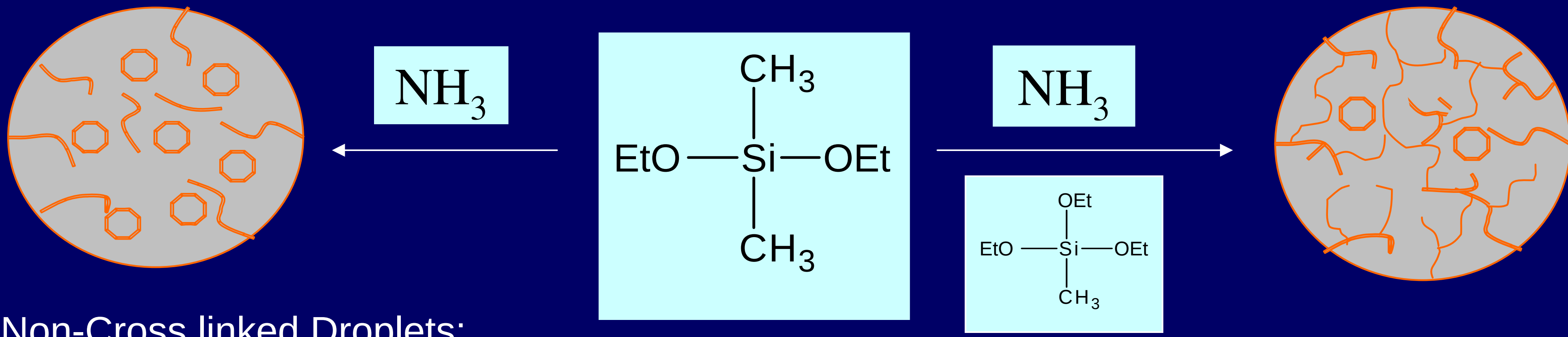
Received 18 July 1996; accepted 26 July 1996

Abstract

We report investigations into the stability, morphology, internal microstructure and swelling behaviour of polydimethylsiloxane oil-in-water emulsions (1 vol.% monomer; 1 vol.% NH_3 solution; 25°C) prepared using mixtures of difunctional (dimethyldiethoxysilane (DMDES)) and trifunctional silane monomers. Both methyltriethoxysilane (MTES) and 3-aminepropyltriethoxysilane (APTES) are potential cross-linkers owing to their trifunctionality. The addition of MTES leads to major changes in various properties of the PDMS droplets. Transmission electron microscopy was used to observe the transition between liquid droplets ([MTES]<50 vol.%) and solid particles ([MTES]>50 vol.%). The particles showed significantly reduced swelling in *n*-heptane in comparison with the liquid droplets. This restriction on swelling indicates the formation of internally cross-linked particles. ^{29}Si nuclear magnetic resonance (NMR) and mass spectroscopy demonstrated increased incorporation of trifunctional material in PDMS polymers as the MTES concentration was raised. The chemical structure of the trifunctional monomer was shown to be important, as ^{29}Si NMR suggests that APTES does not polymerize with DMDES but may reside in the aqueous continuous phase as a cationic oligomer. The presence of ethanol during particle formation causes enhanced particle swelling. The particle size of the swollen particles, however, falls steeply as the concentration of ethanol is reduced. Overall the data suggest the formation of cross-linked microgels at high MTES concentrations.

Keywords: Cross-linking; Emulsions; Microgels; Polydimethylsiloxane; Swelling

BV's PDMS Droplets



Non-Cross linked Droplets:
Viscous & deformable
(η < 5 $mNm^{-2}s$)

Cross linked droplets
Deformability control:
viscous to viscoelastic

- Highly monodispersed (~1μm in diameter)

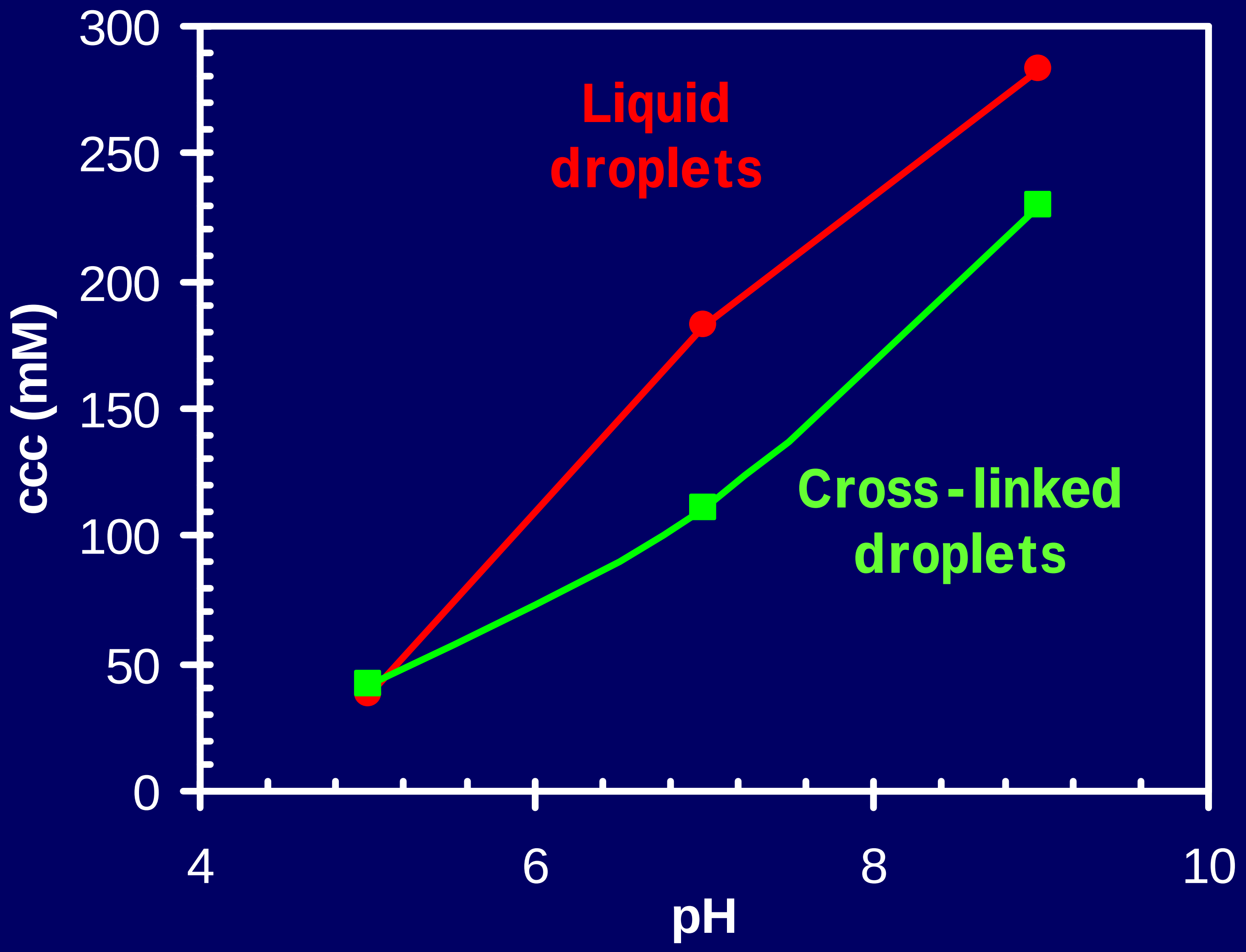
- Emulsifier free, negatively charged with IEP ≈ pH 2.5

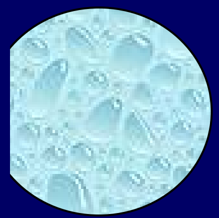
T. M. Obey & B. Vincent, *J. Colloid Interface Sci.*, **163** (1994) 454.
M. I. Goller *et al.*, *Colloids Surf. A:*, **123-124** (1997) 183.

The BV Droplets – an excellent model colloid with controllable deformability

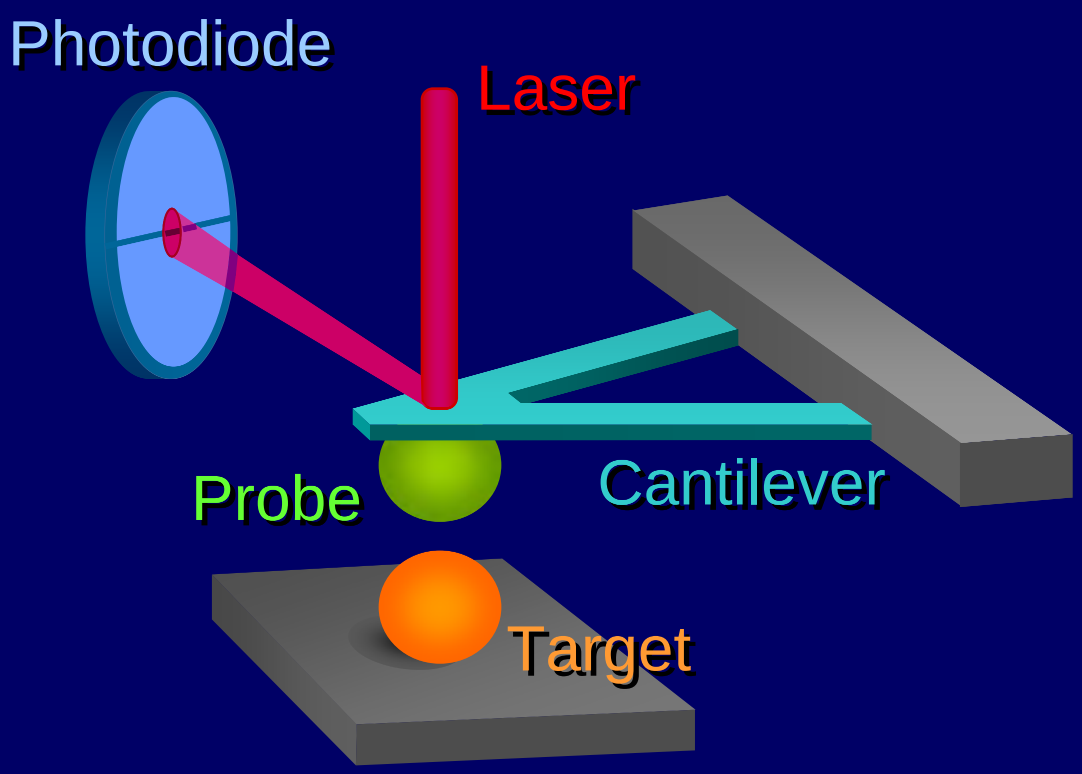
- Interaction forces of the BV droplets
- Rheological studies on concentrated emulsions of the BV droplets
- Block copolymers at the BV droplet - water interface
- Nanoparticles at the BV droplet - water interface
- Molecular transport across the BV droplet - water interface.

Deformable BV droplets are more colloidally stable





Interaction forces on the BV droplets determined using colloid probe atomic force microscopy (AFM)



Potential from PD

↓

Deflection of cantilever

↓

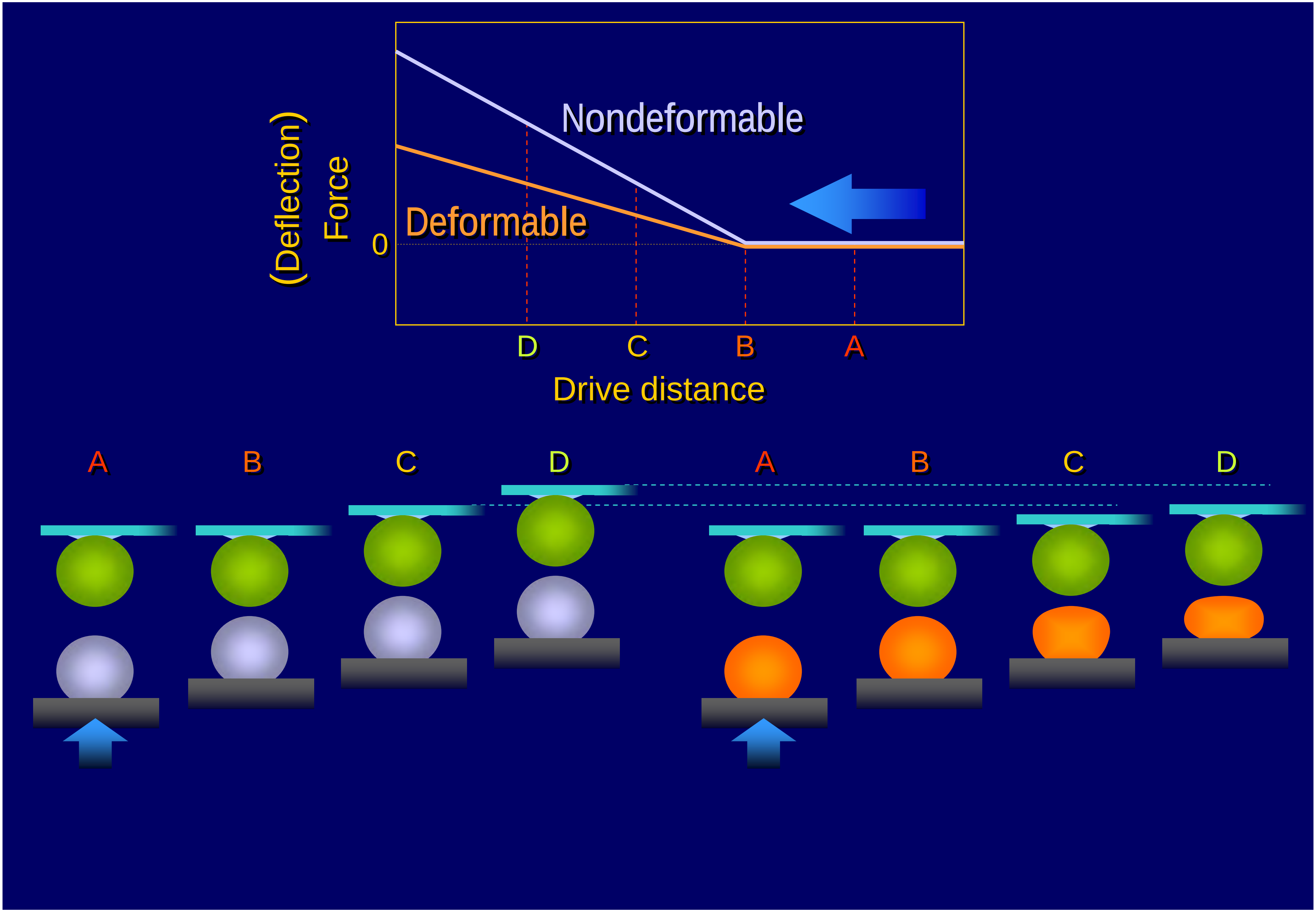
Interdroplet forces

Hooke's Law

$$F = -k_c\, x$$

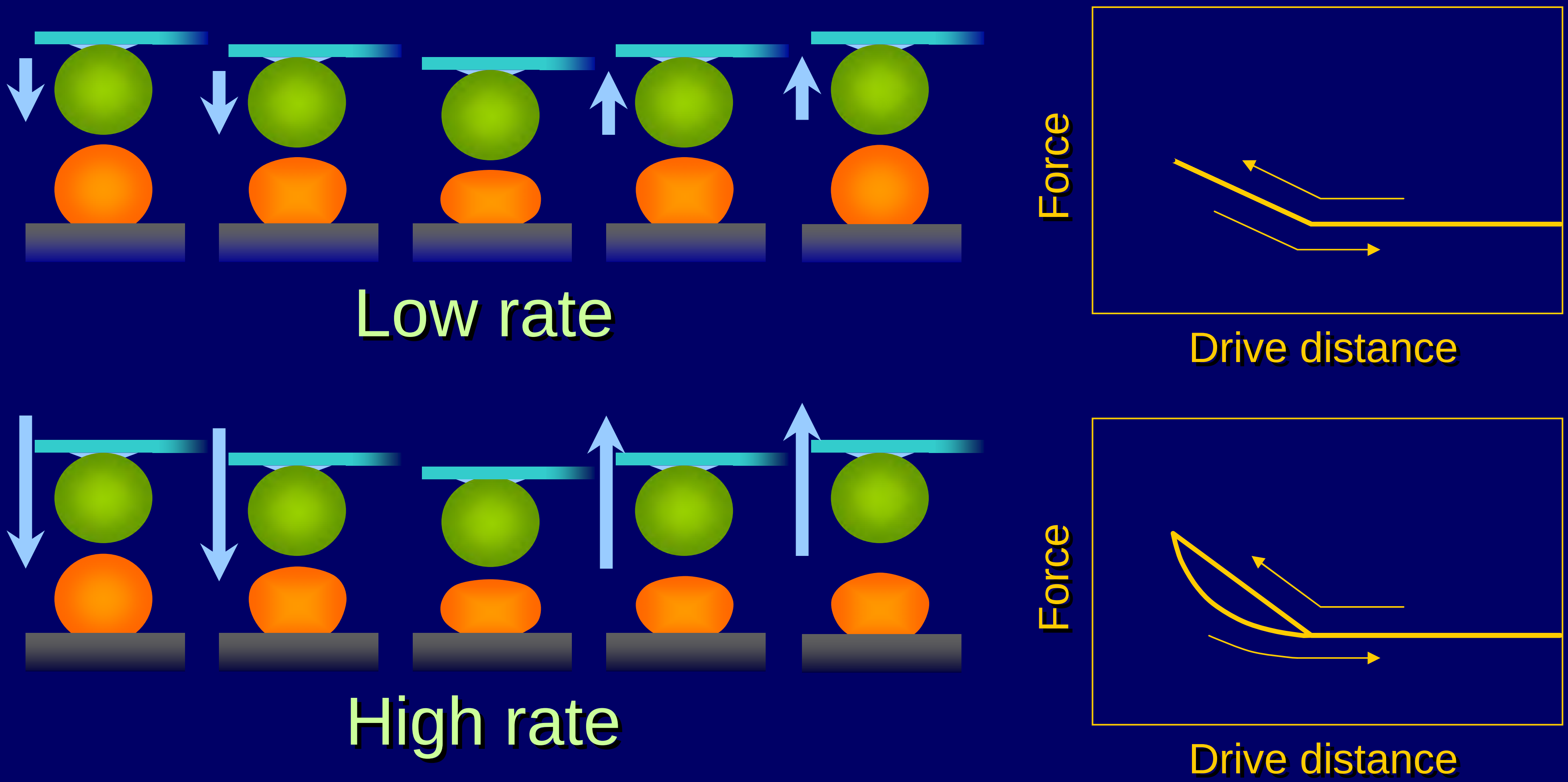
k_c: spring constant of cantilever

x : deflection of cantilever

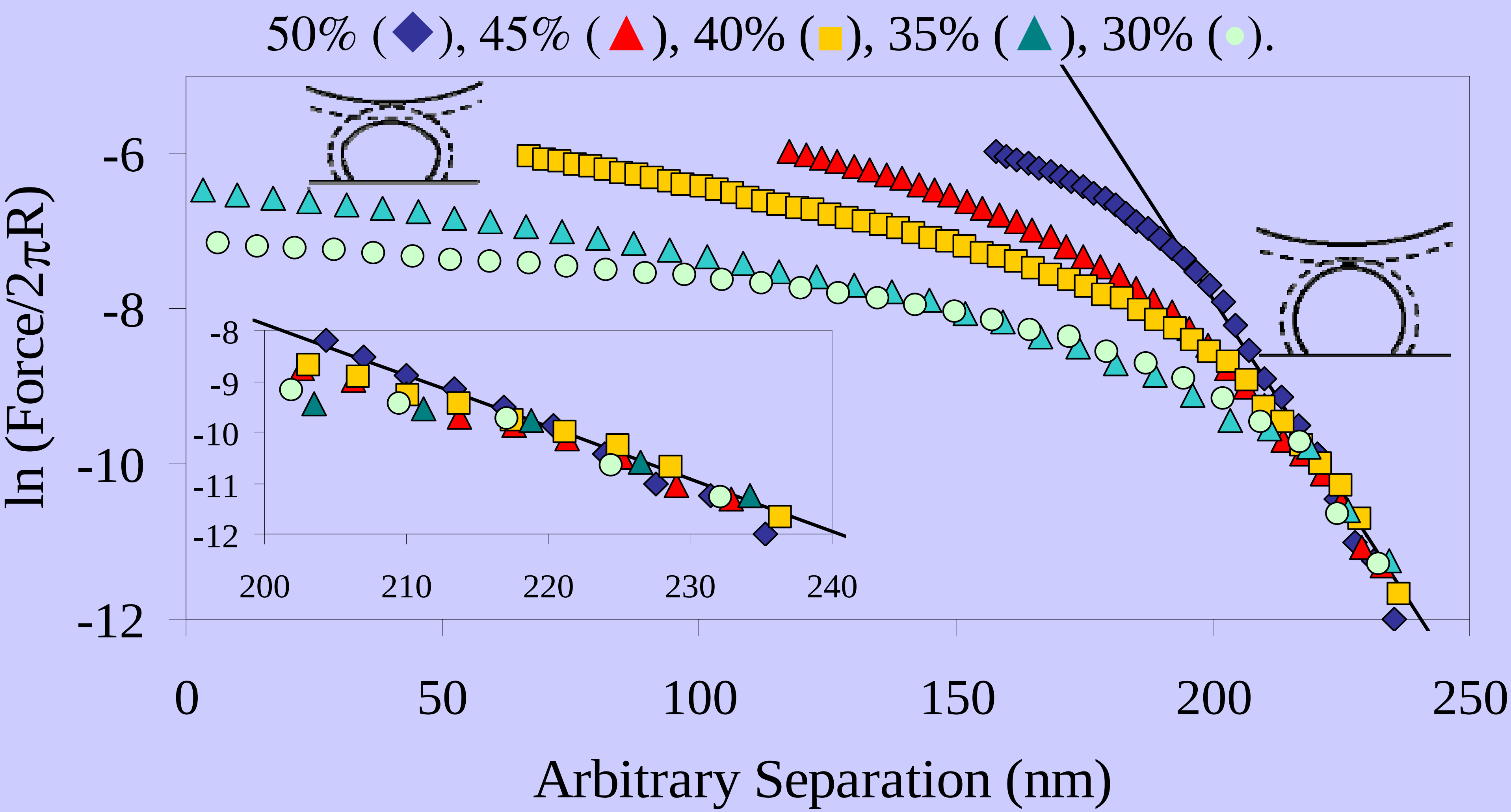


Nondeformable
Deformable
Force
(Deflection)
0
D
C
B
A
Drive distance
A
B
C
D
A
B
C
D

Approach Rate Dependence

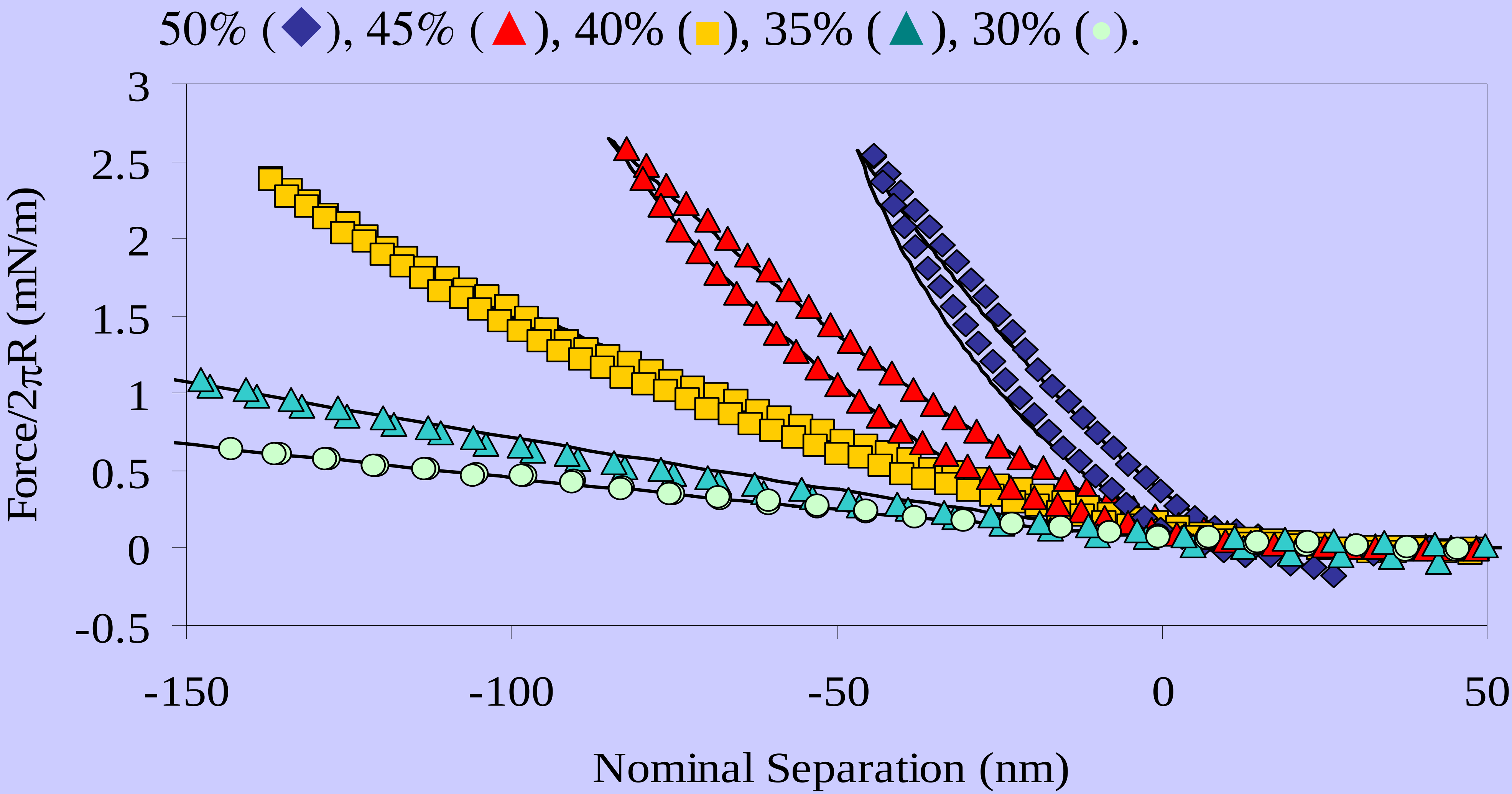


Interaction Forces between BV Droplets and AFM colloid probe



Gillies and Prestidge, *Langmuir*, 21, 12342-12347, 2005

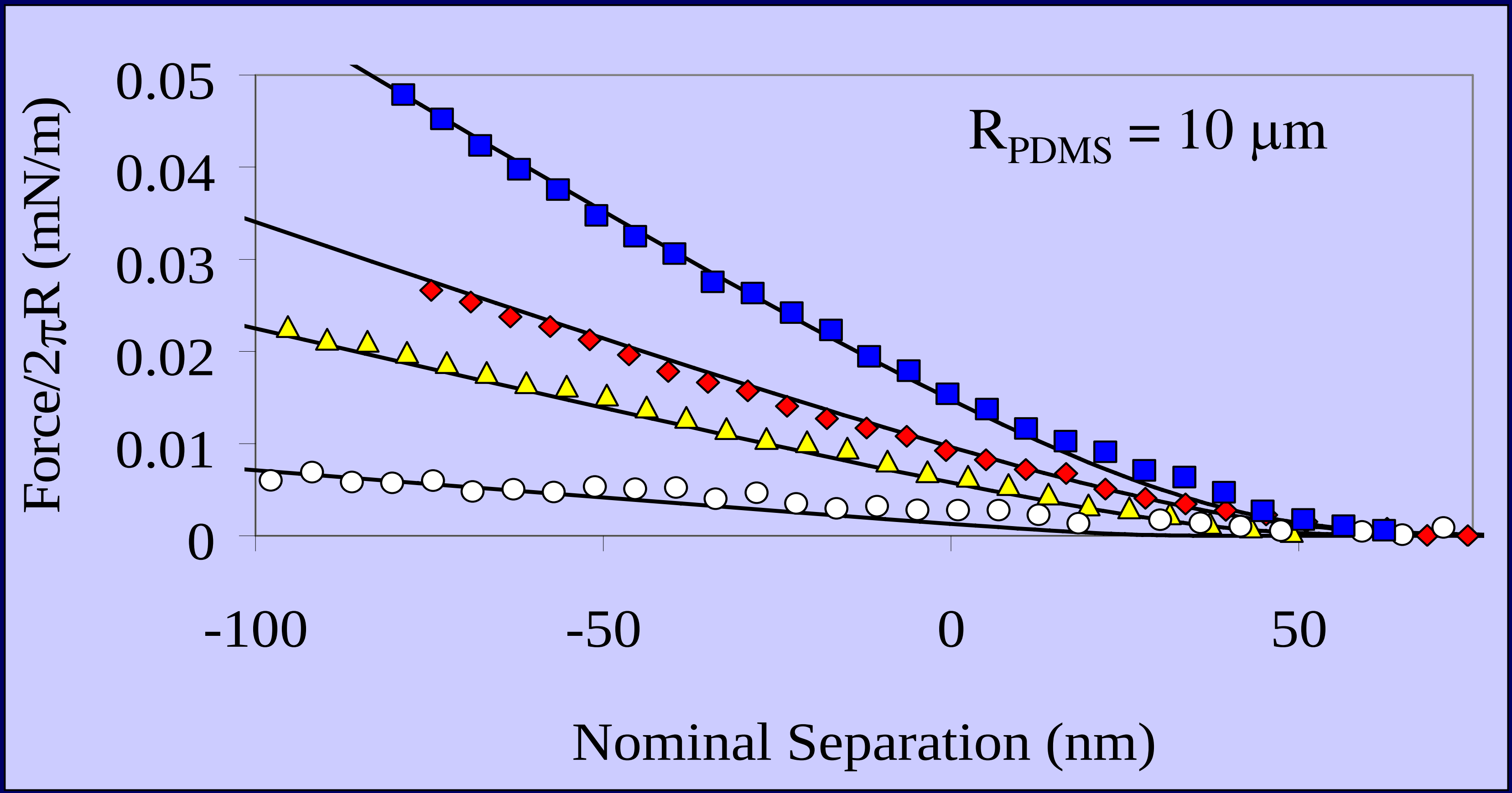
Deformation & Hysteresis- influence of cross-linking:



Gillies and Prestidge, *Langmuir*, 21, 12342-12347, 2005

Liquid-like BV Droplets: Influence of Surfactant (SDS)

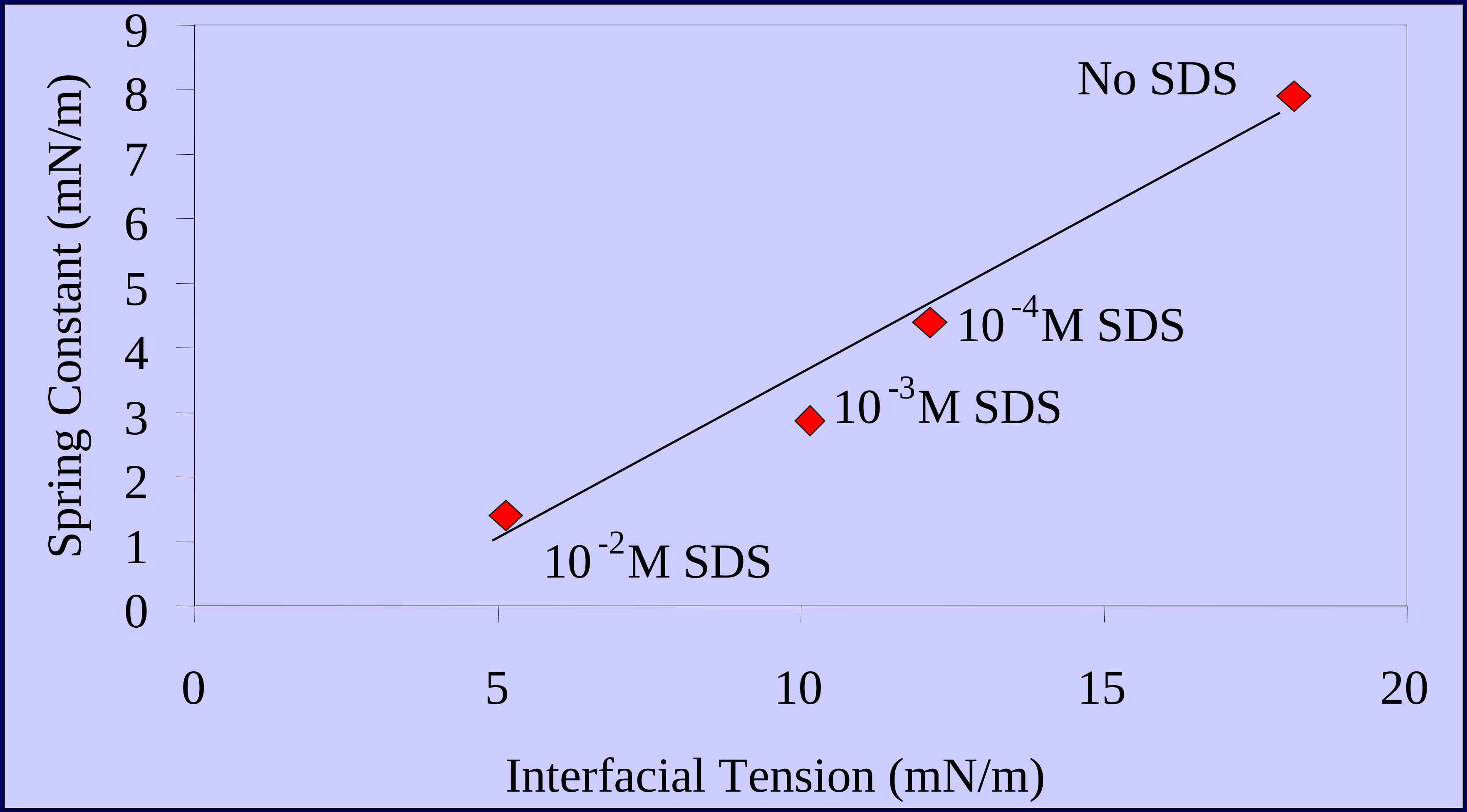
(■) No SDS (◆)10^{-4}M (▲)10^{-3}M (●)10^{-2}M



GS Gillies, CA Prestidge, *Adv. Colloid Interface Sci*, 108-109, 197-205, 2004.

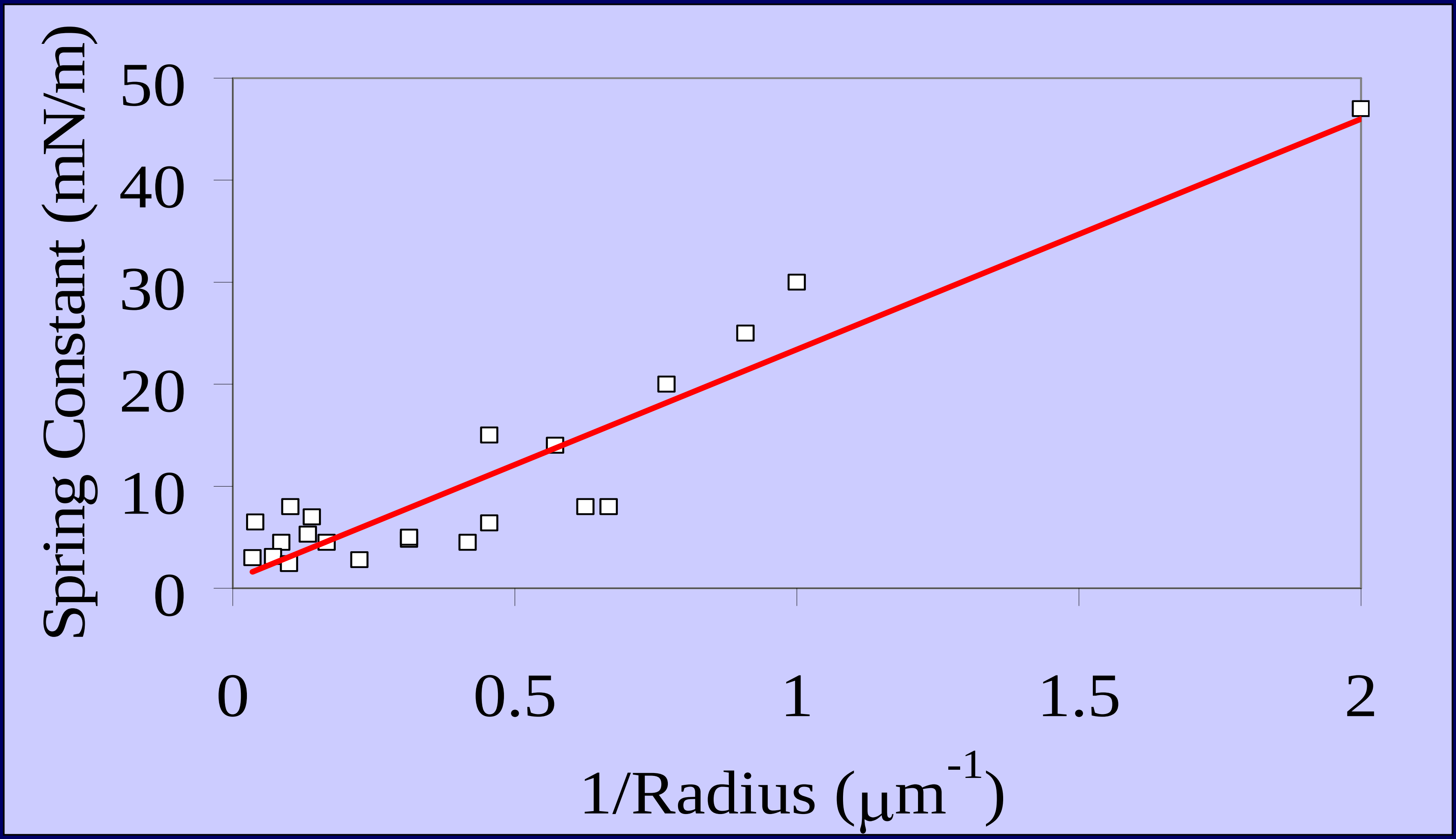
Spring constant controlled by interfacial tension

$R_{PDMS} = 10\ \mu m$



GS Gillies, CA Prestidge, *Adv. Colloid Interface Sci*, 108-109, 197-205, 2004.

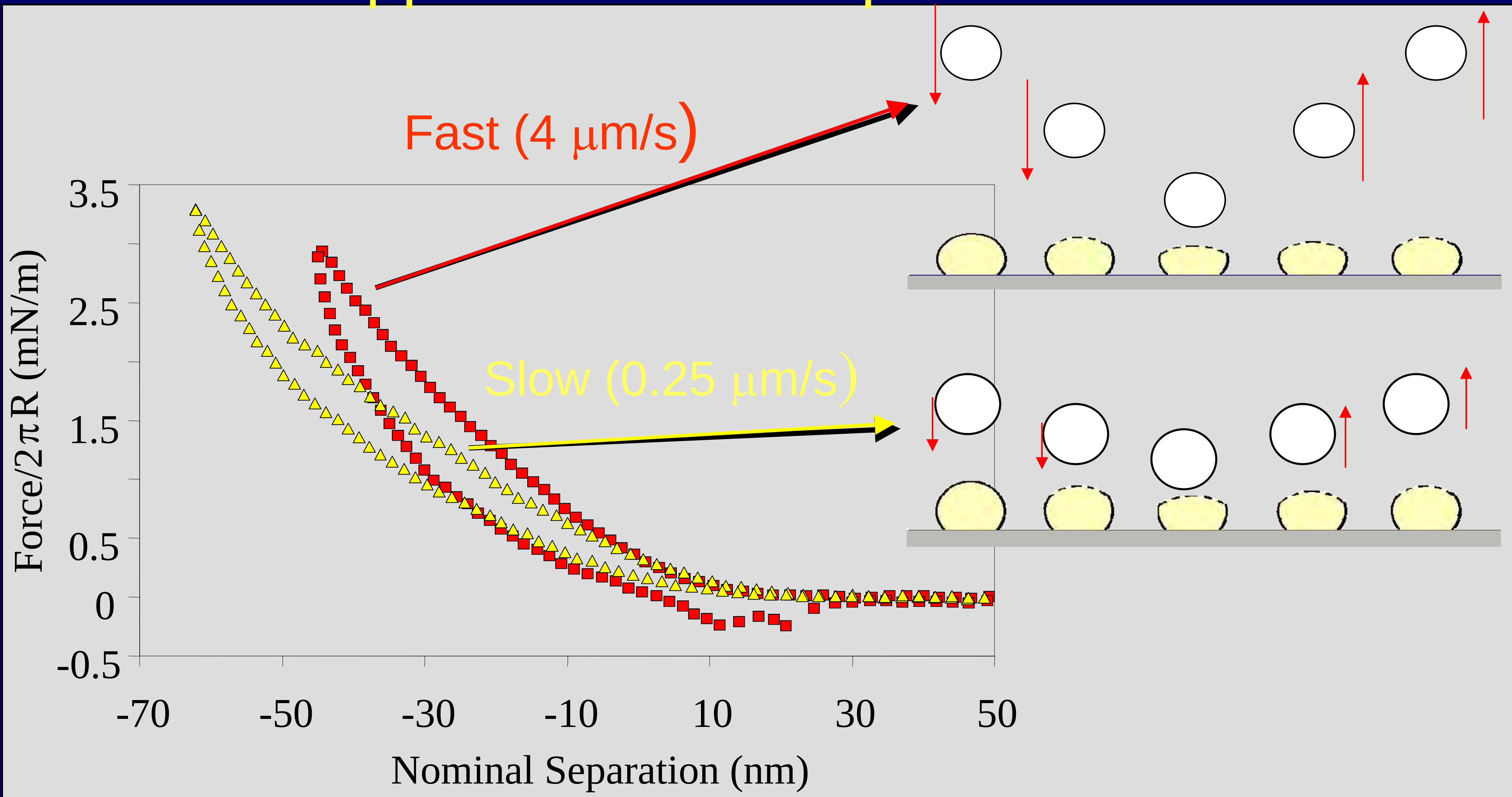
Liquid-like BV Droplets: Influence of size



Laplace pressure controls spring constant

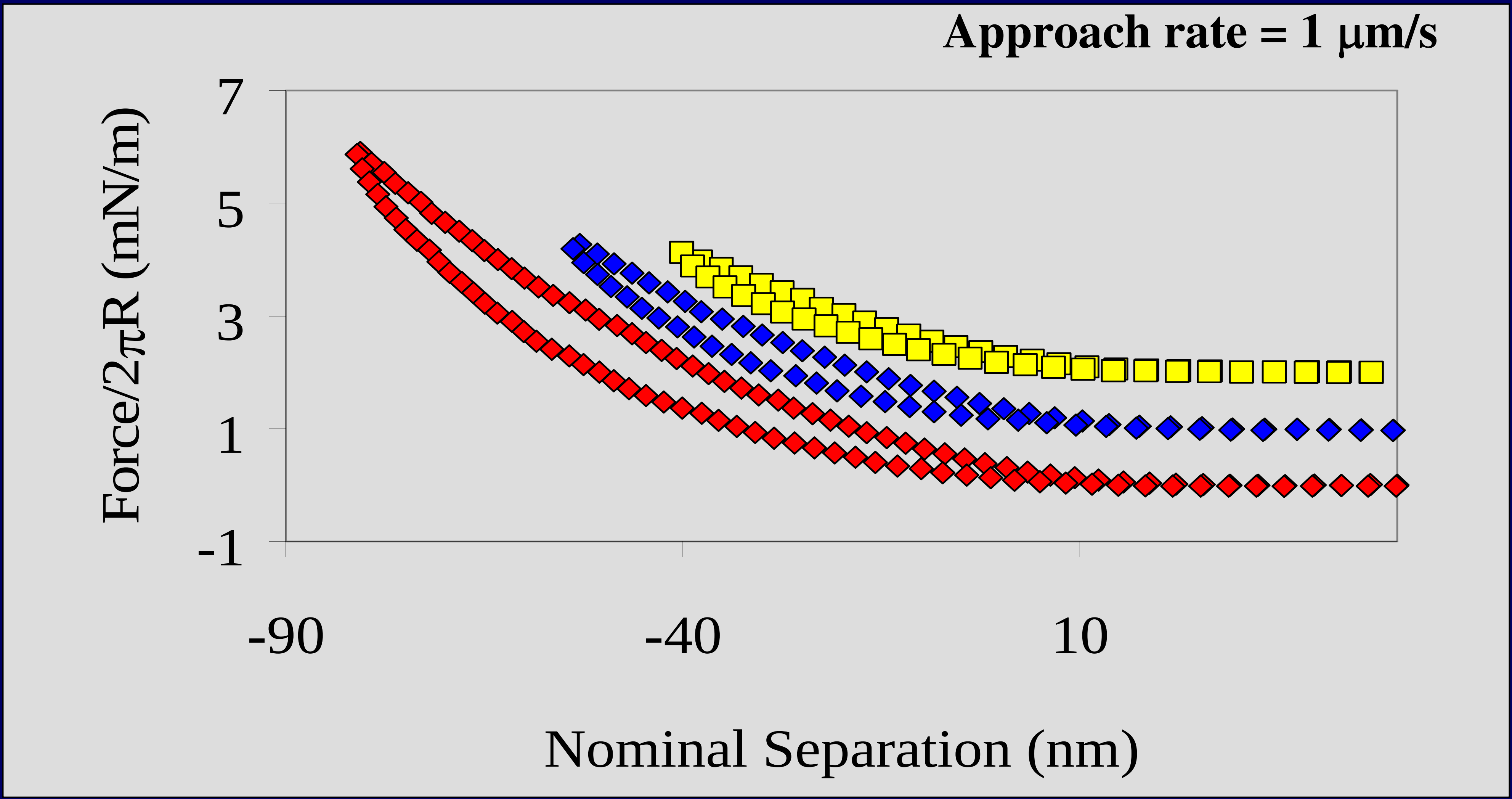
GS Gillies, CA Prestidge, *Adv. Colloid Interface Sci*, 108-109, 197-205, 2004.

Cross-linked BV Droplets: Approach Rate Dependence

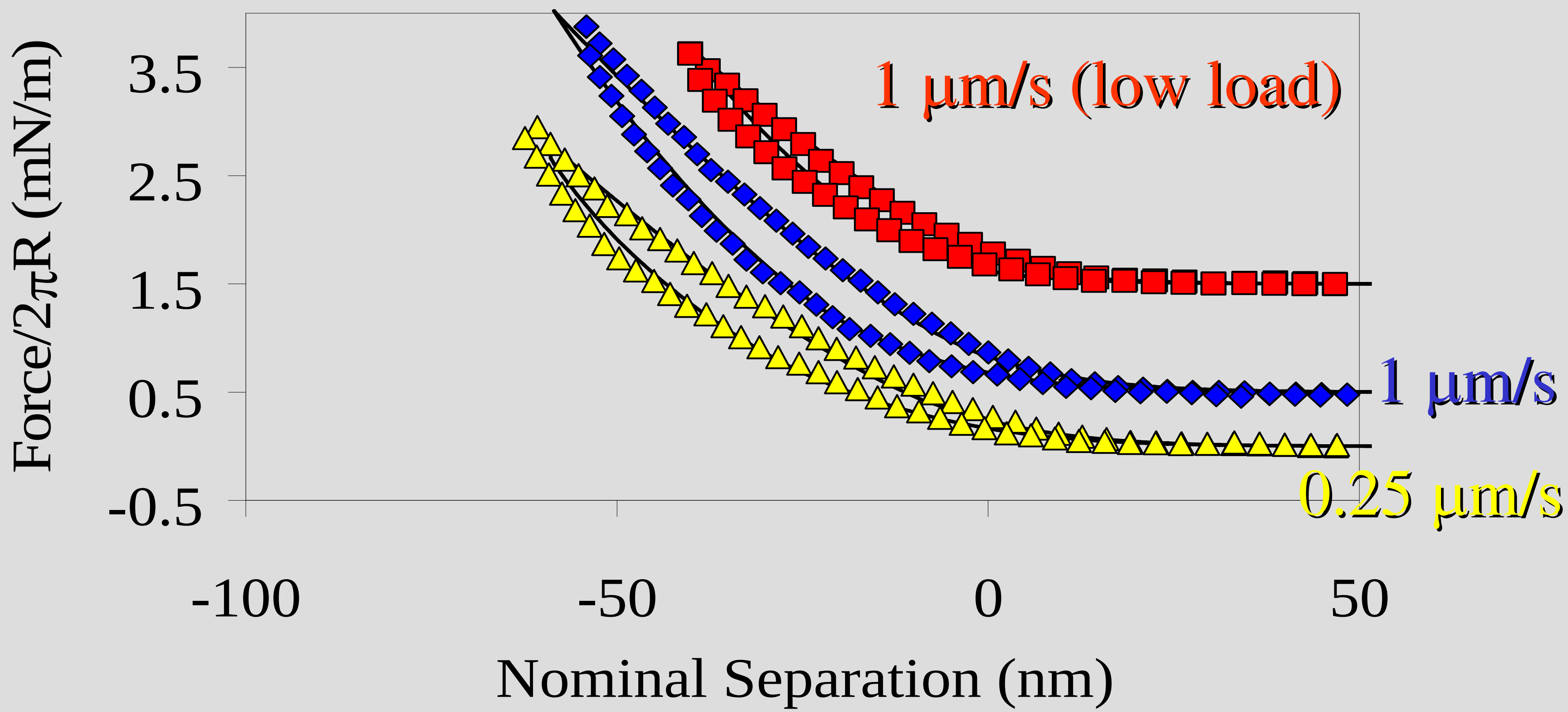


Gillies and Prestidge, *Langmuir*, 21, 12342-12347, 2005

Cross-linked BV Droplets: Load Dependence



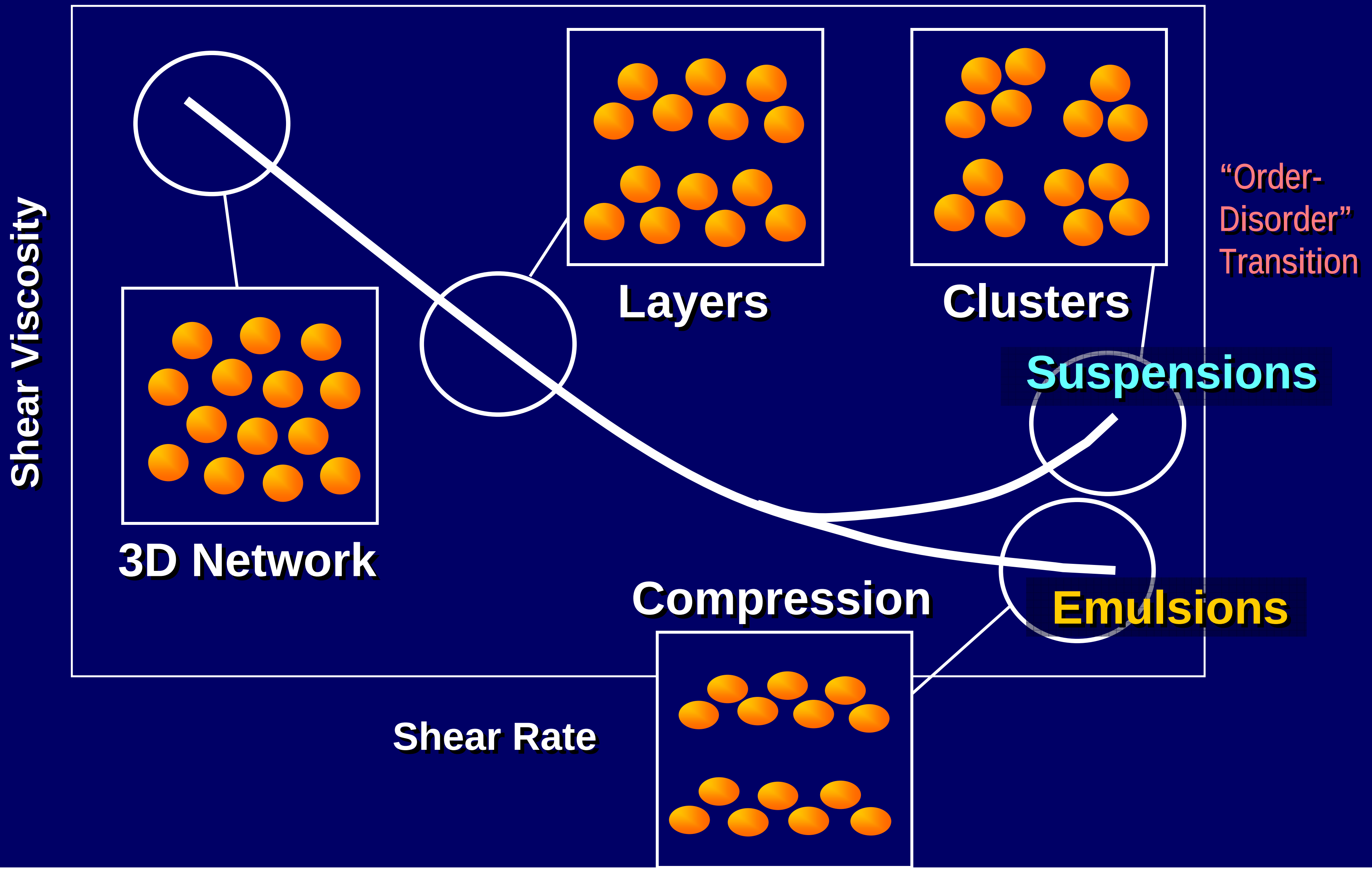
Nano-Rheology of a BV Droplet



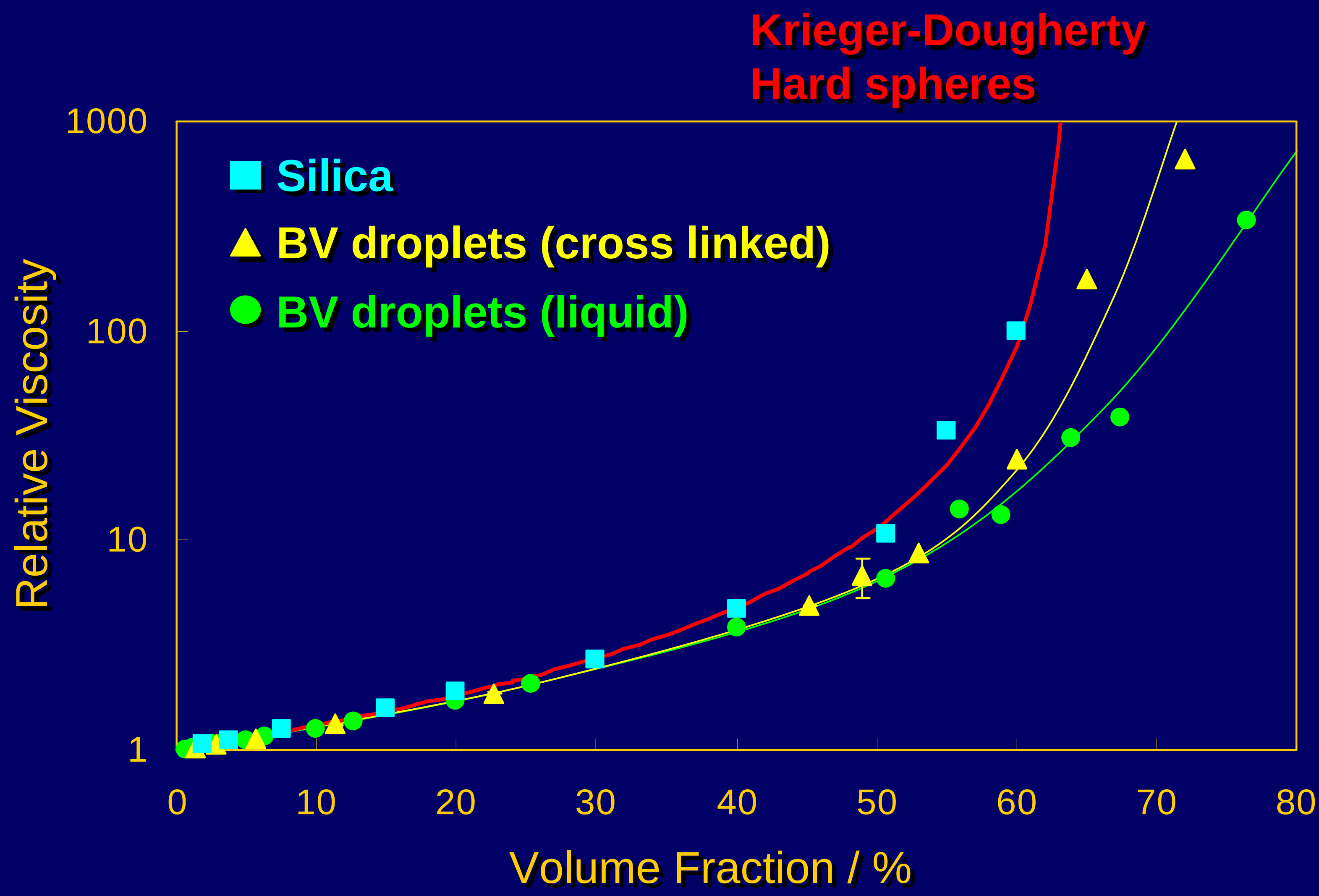
E_0 = 1.2 MPa, E_∞ = 0.8 MPa and τ = 0.12 s

Gillies and Prestidge, *Langmuir*, 21, 12342-12347, 2005

Rheological studies on concentrated emulsions of the BV droplets

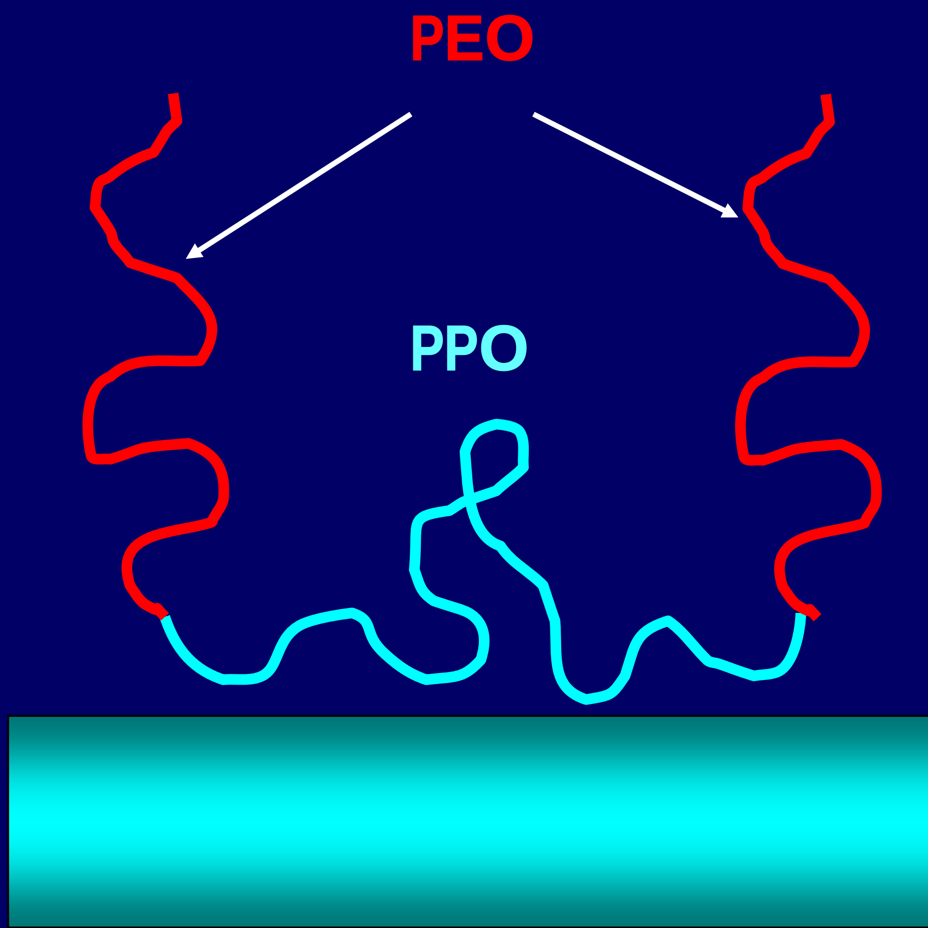


Viscosity versus volume fraction

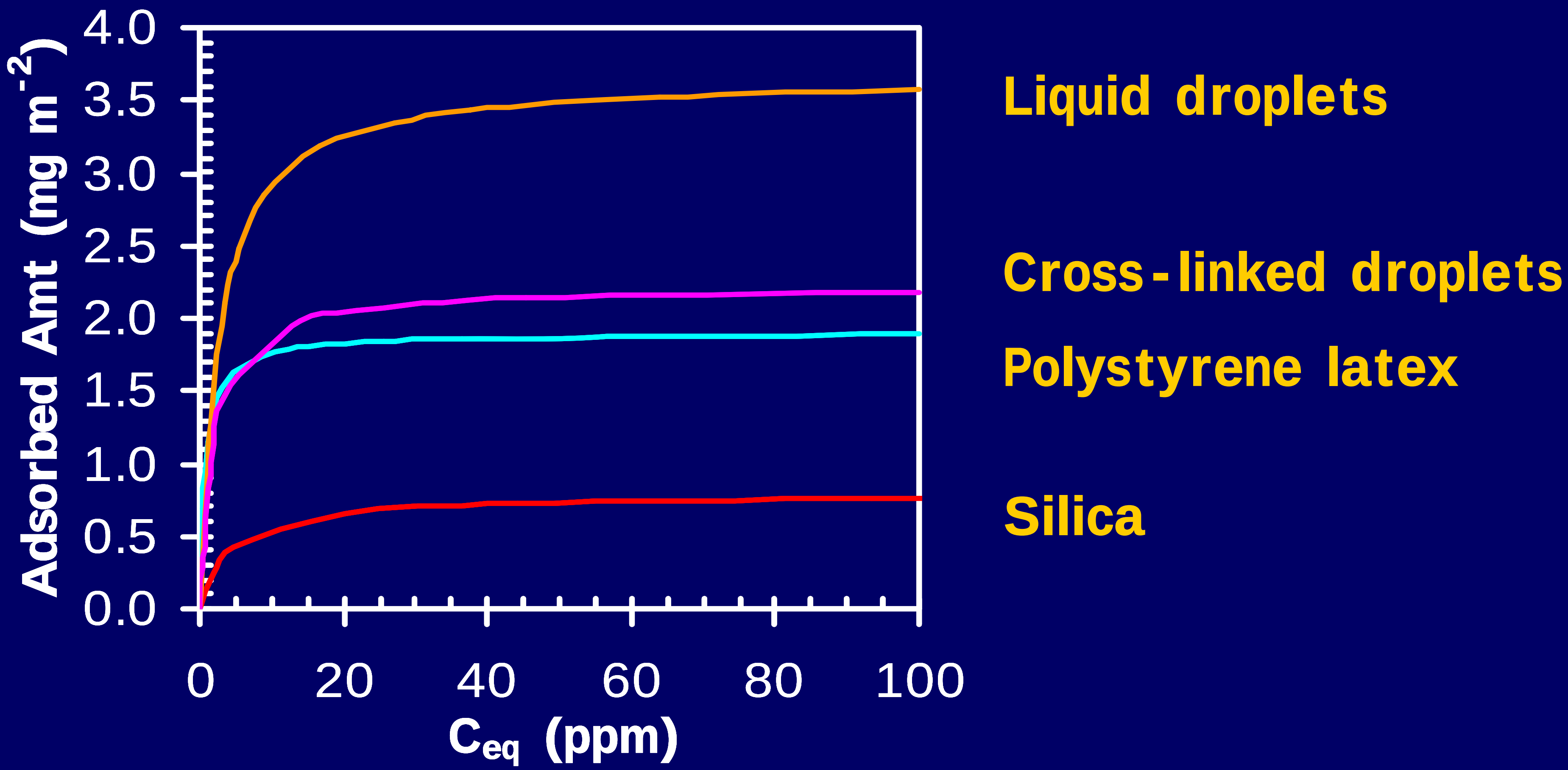


Saiki, Prestidge and Horn, *Colloids and Surfaces A*, 299, 65-72, 2006.

PEO-PPO-PEO Copolymers at the BV droplet - water interface

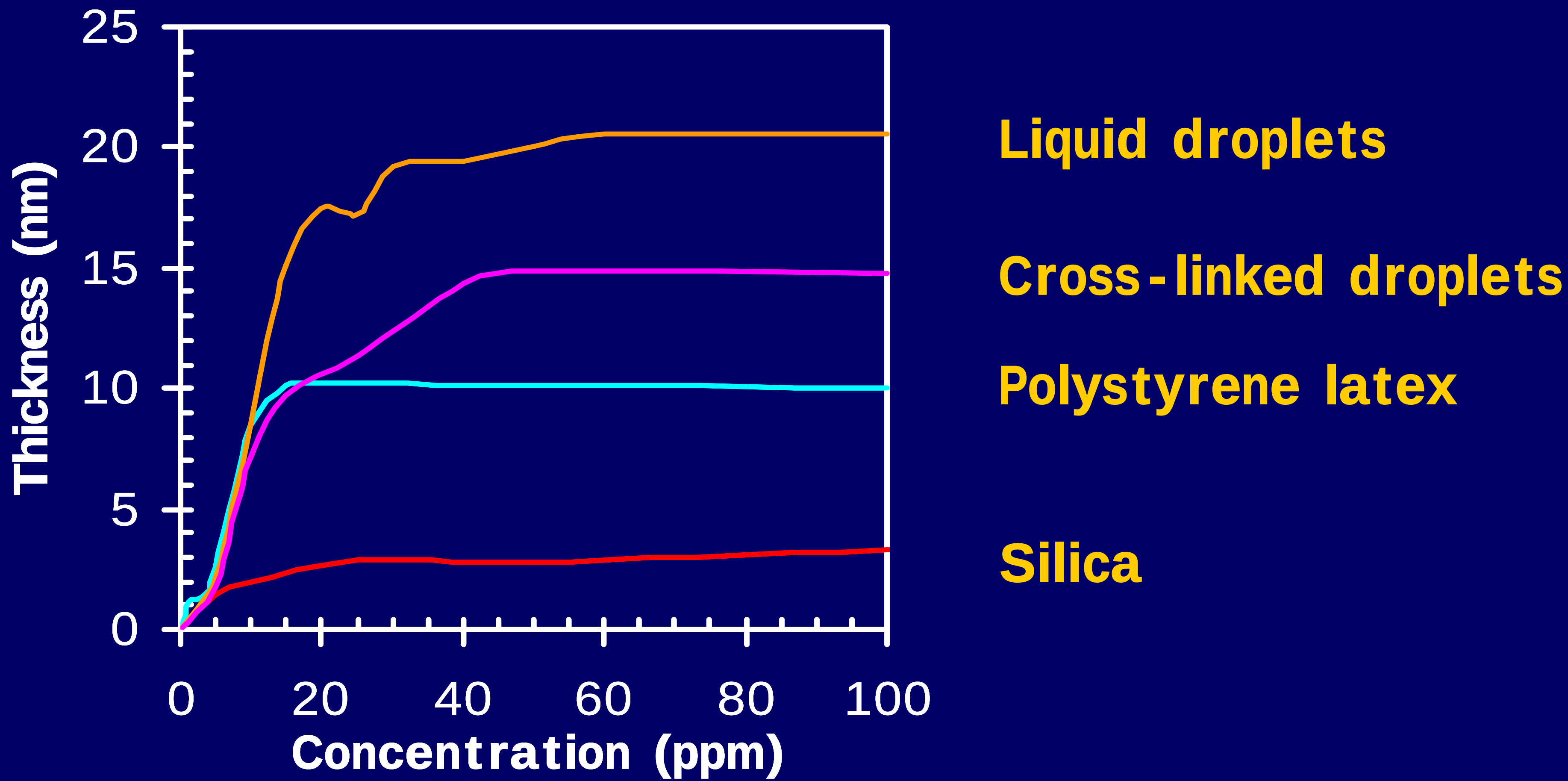


Adsorbed Amount of F108



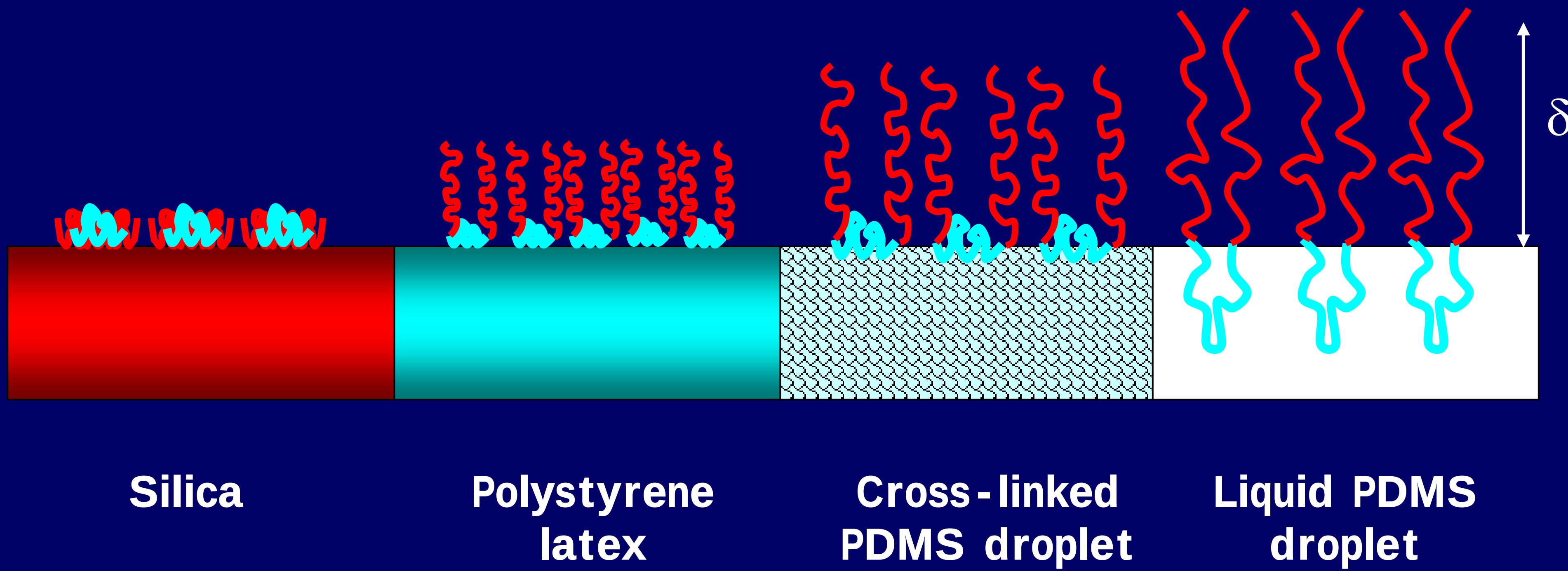
Prestidge, Barnes and Simovic, *Adv. Colloid Interface Sci* , 108-109, 105-118, 2004.

Adsorbed Layer Thickness of F108

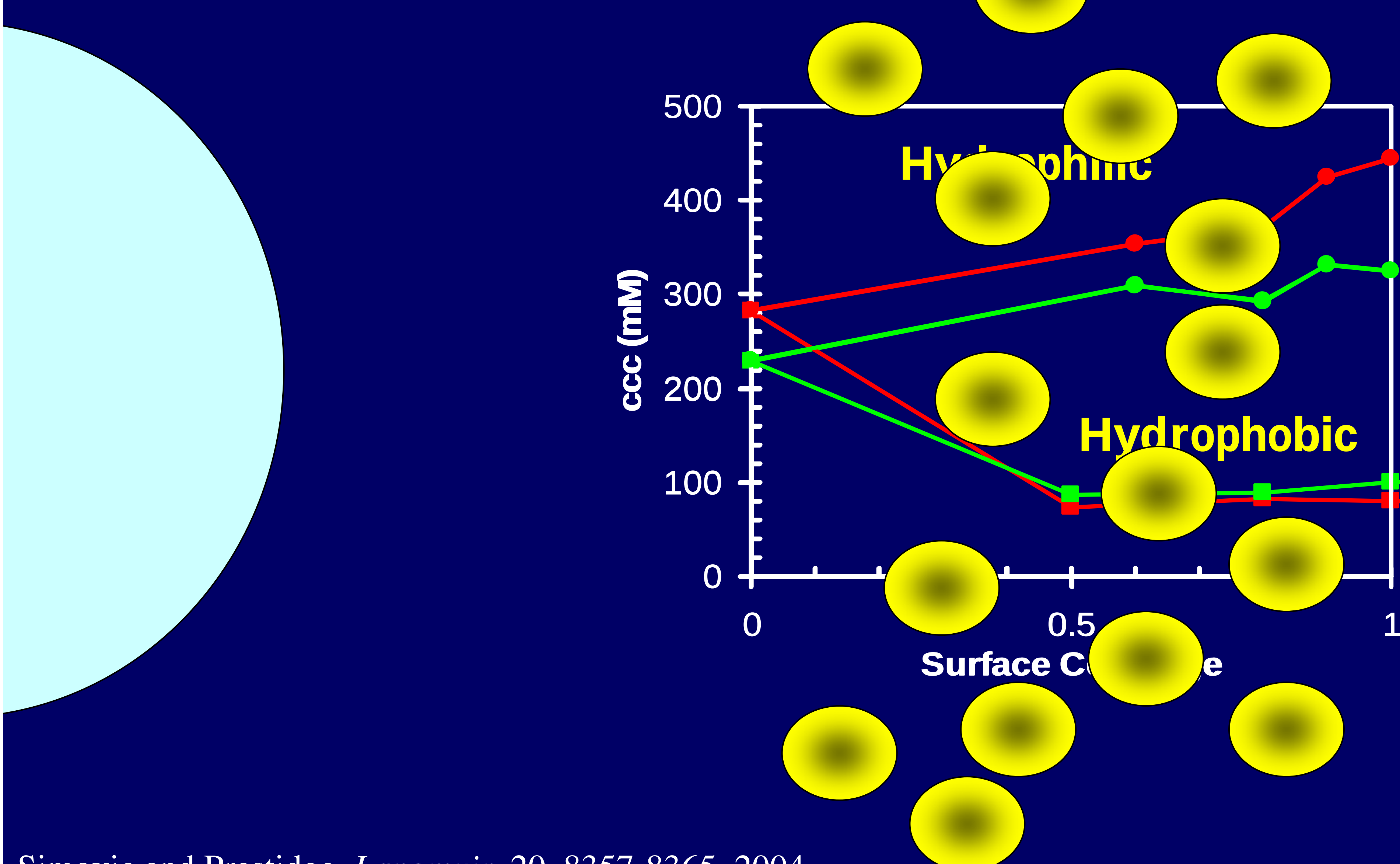


Prestidge, Barnes and Simovic, *Adv. Colloid Interface Sci* , 108-109, 105-118, 2004.

PEO-PPO-PEO Copolymers

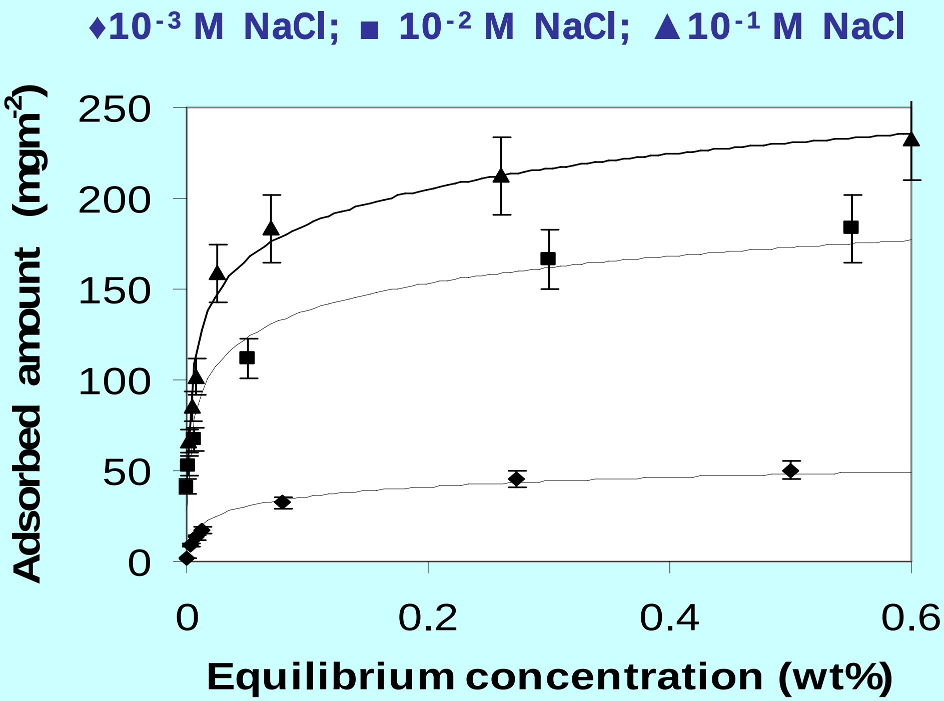


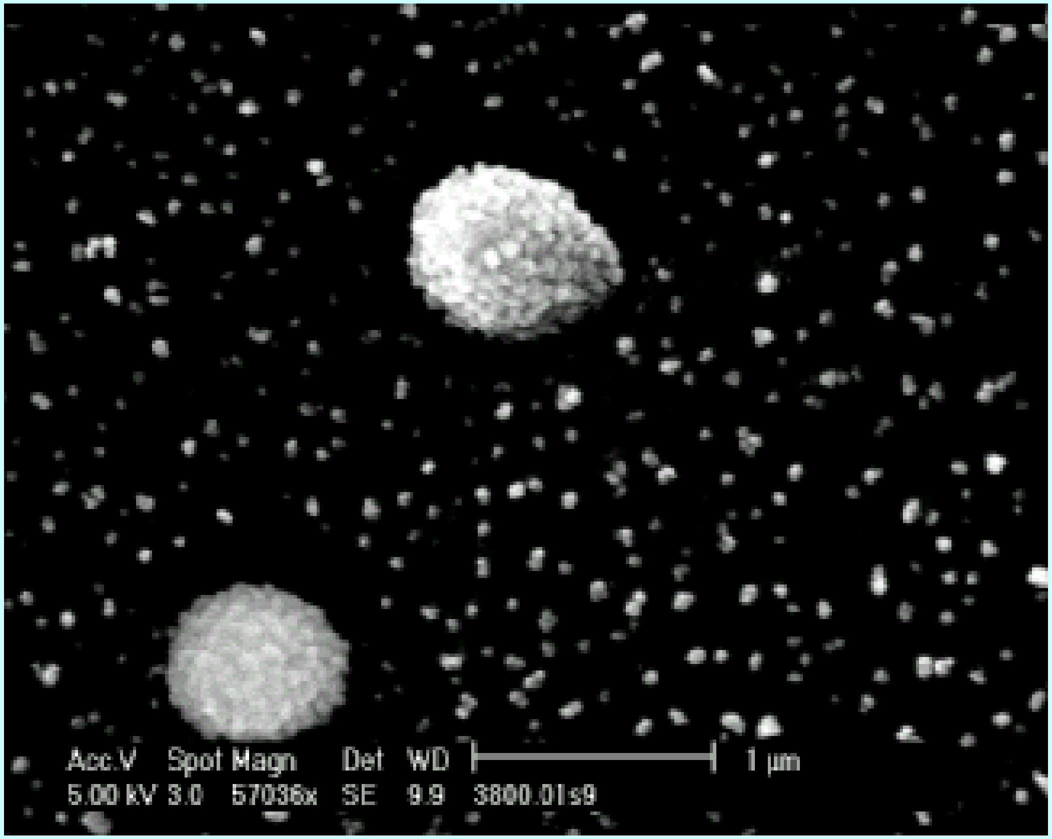
Nanoparticles at the BV droplet - water interface



Simovic and Prestidge, *Langmuir*, 20, 8357-8365, 2004.

Adsorption of hydrophilic silica nanoparticles to Droplets



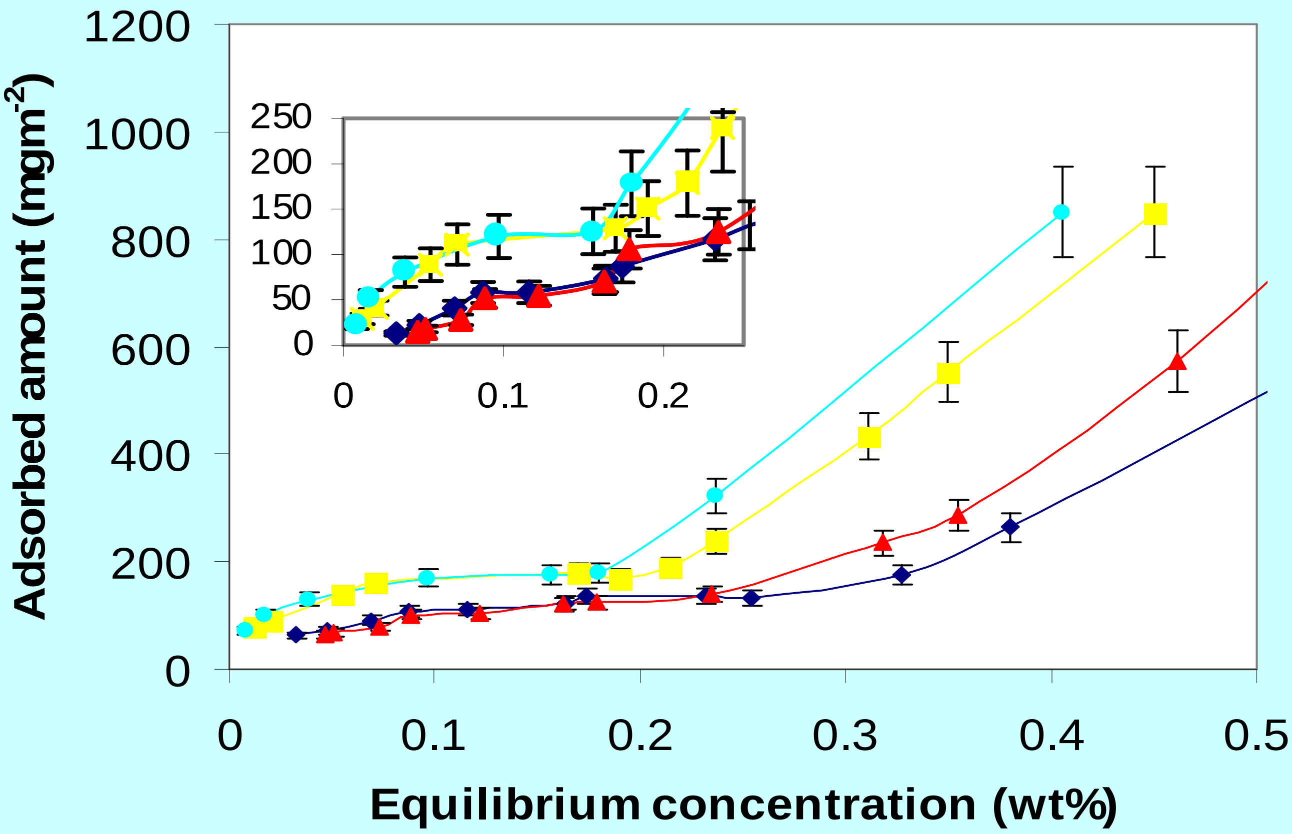


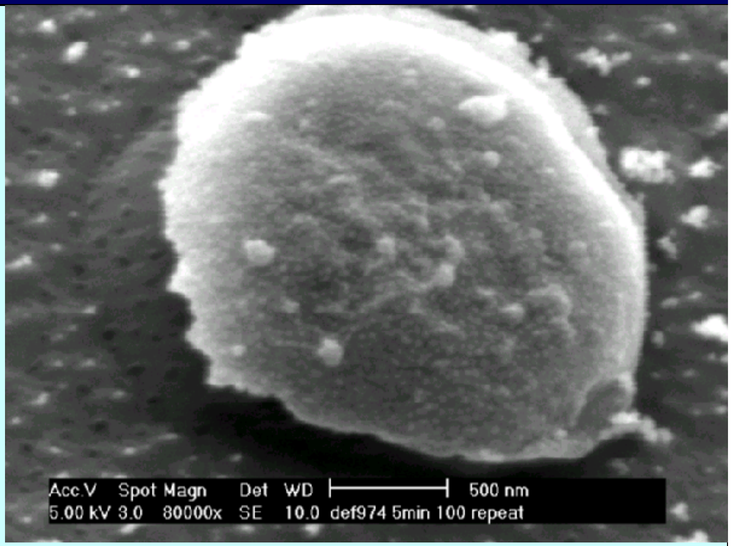
$h = a\,(1/\theta^{1/2} - 1)$ h- lateral separation
a-particle diameter
θ-plateau fraction coverage

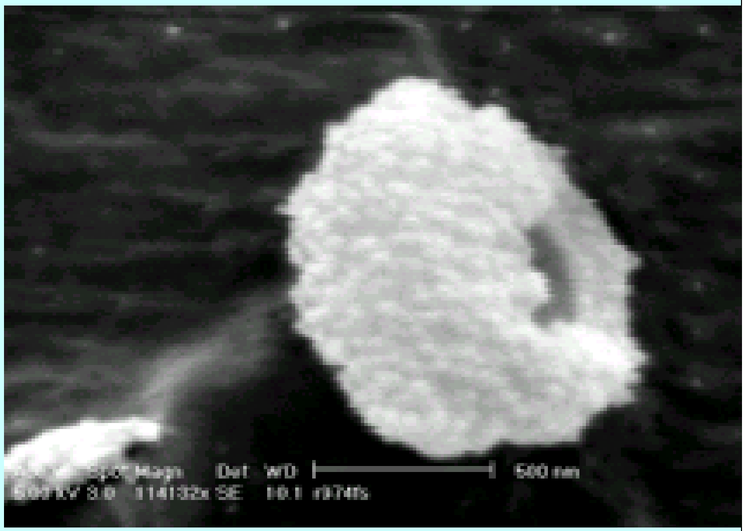
Simovic & Prestidge, *Langmuir 19 (2003) 3785-3790*

Adsorption of hydrophobic silica nanoparticles (10-4 M NaCl)

pH: ♦ 9; ▲ 7; ■ 5; • 4





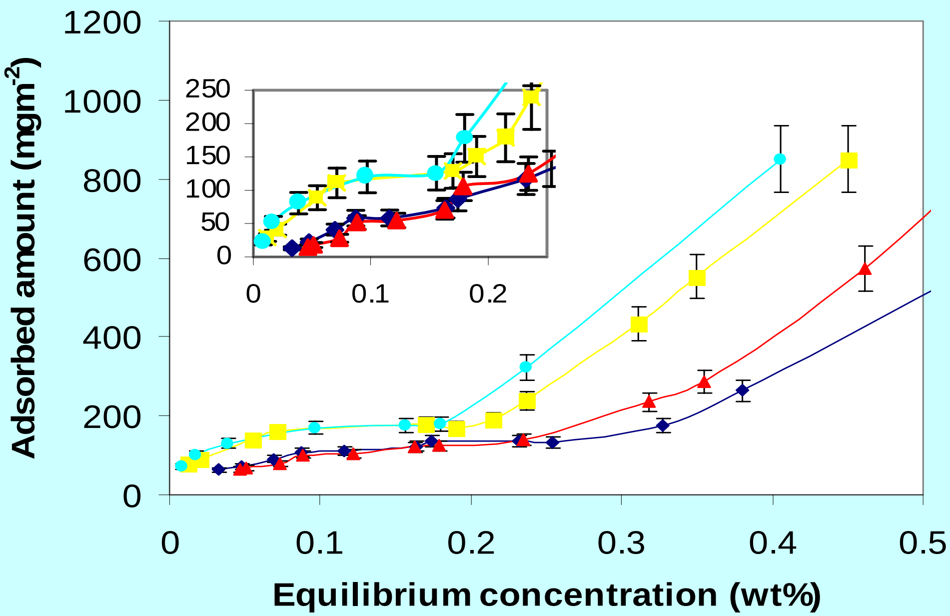


Simovic & Prestidge, *Langmuir 19 (2003) 8364-8370*

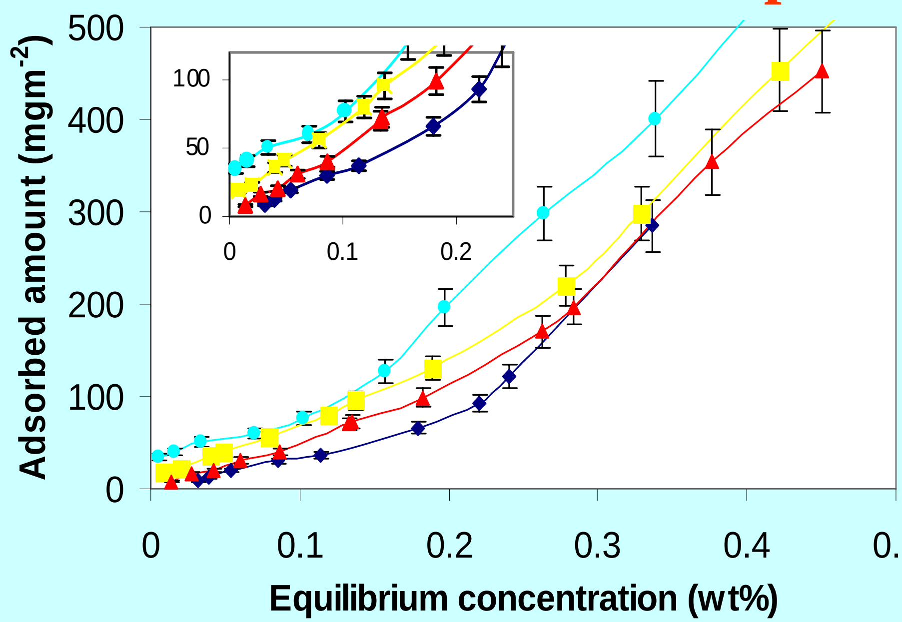
Adsorption of hydrophobic silica nanoparticles (10-4 M NaCl)

pH: ♦ 9; ▲ 7; ■ 5; • 4

Liquid BV Droplets



Cross-linked BV Droplets



- Multilayer adsorption
- Strong pH dependency
- Adsorption *affinity* is greater for liquid droplets

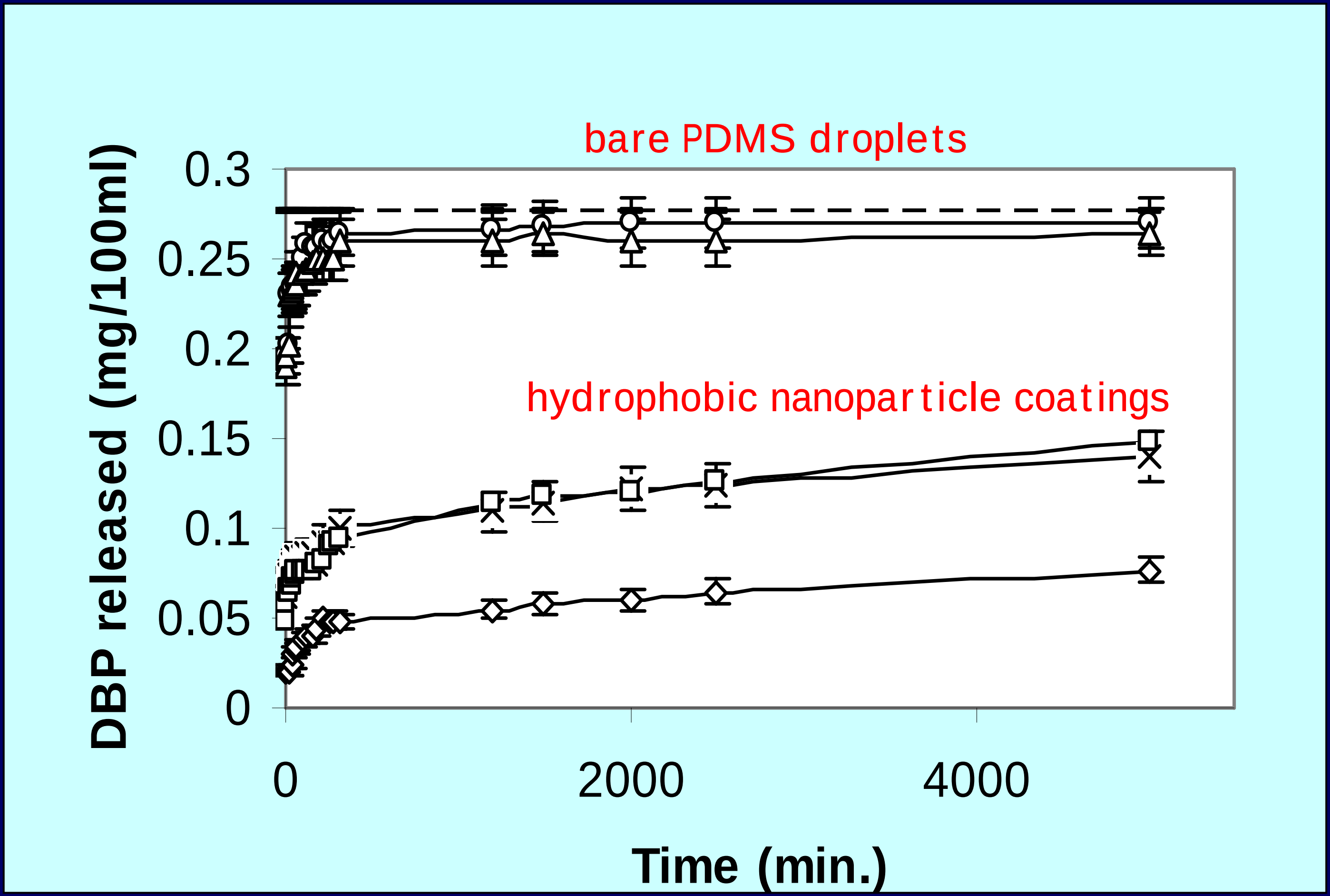
Simovic & Prestidge, *Langmuir 19 (2003) 8364-8370*

Molecular transport across the BV droplet-water interface

Dibutyl phthlate (DBP)

USP rotating paddle method
+ ultracentrifugation
+ HPLC analysis

DBL release from BV Droplets: low loading levels – 0.28mg/100ml



Activation Energy

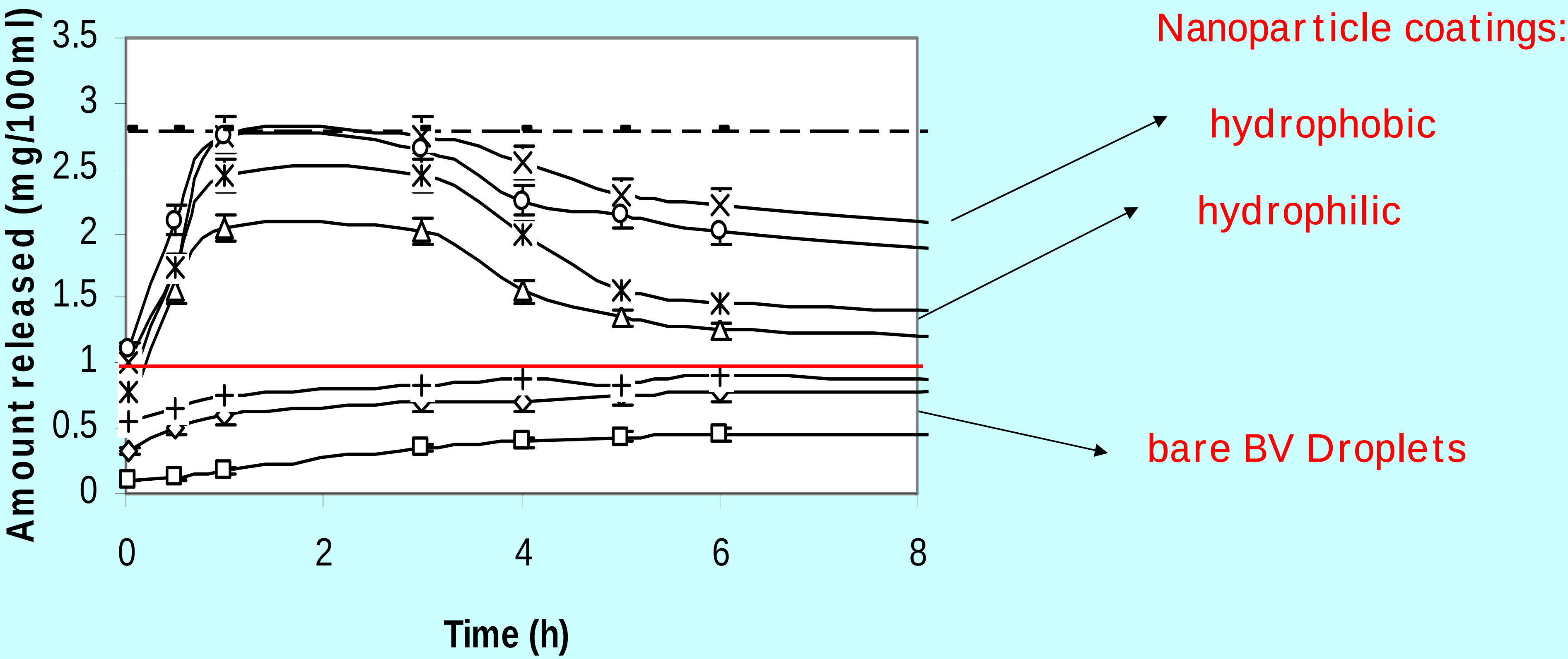
~580 kJmol^{-1}

Pluronic F-68
Activation energy for release = 52.8 kJmol^{-1}

Washington et al. J. Controlled Release 33 (1995) 383-390

Prestidge & Simovic: *Int. J. Pharmaceutics*, **324**, 92-100, 2006.
European J. of Pharmaceutics and Biopharmaceutics, 66, 39-47 2007

DBL release from BV Droplets: high loading levels – 2.8mg/100ml



Prestidge & Simovic: *Int. J. Pharmaceutics*, **324**, 92-100, 2006.
European J. of Pharmaceutics and Biopharmaceutics, 66, 39-47 2007

Towards Drug Delivery

1. Drug incorporation into lipid vehicle

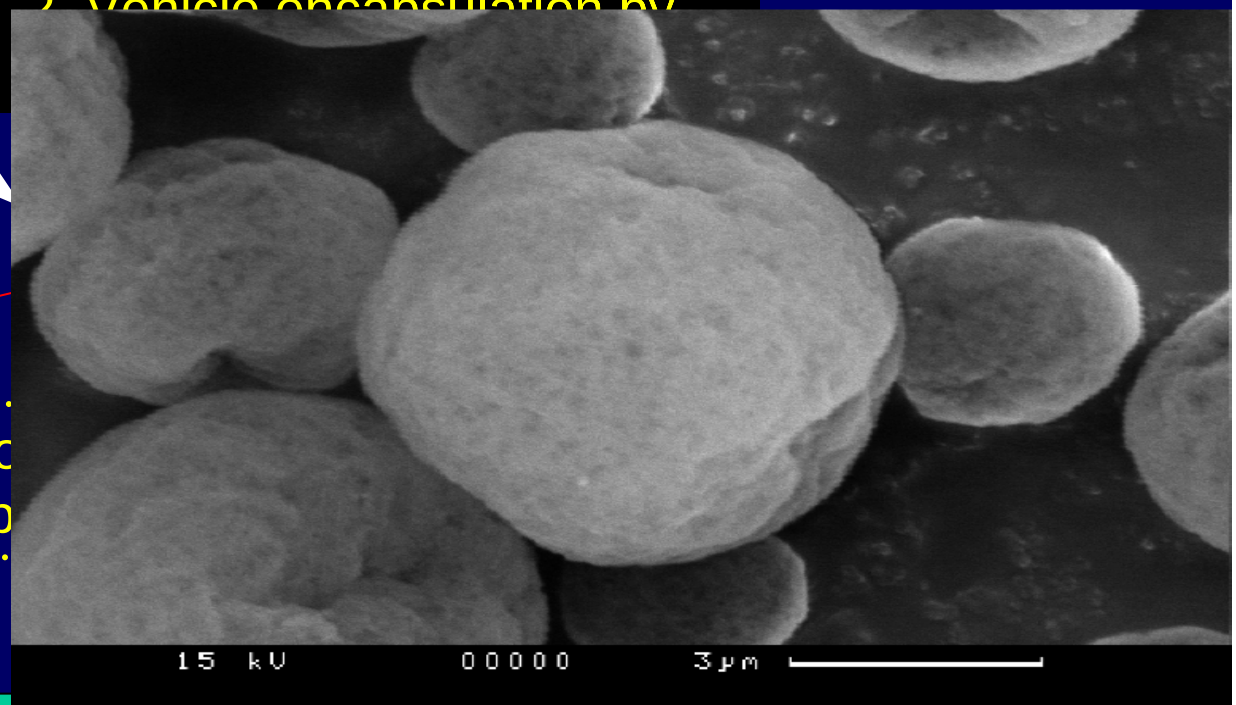
Lipophilic drug

Vehicle (oil droplet)

2. Vehicle encapsulation by

Hydrophilic silica nanoparticles (~ 50 nm)

Wet co
drop



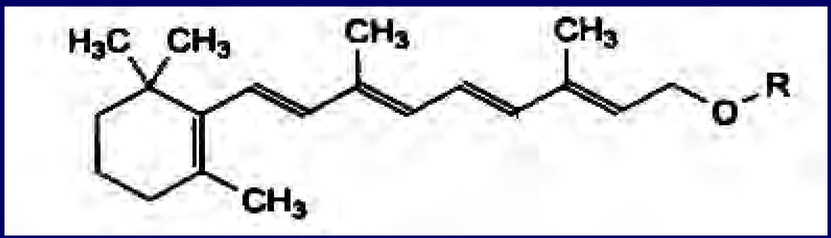
(for storage)

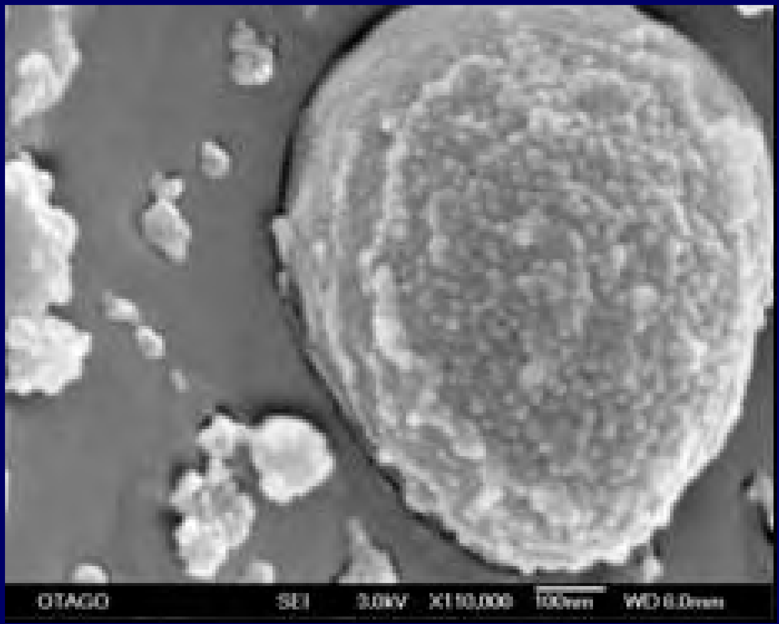
Dermal Delivery

Oral Delivery

Improved Photo-stability of Vitamin A in Nanoparticle Coated Emulsions

All-trans Vitamin A (Biopotency: 100%) —*Isomerisation* / *UV light*→ 9-cis Vitamin A (Biopotency: 24%)

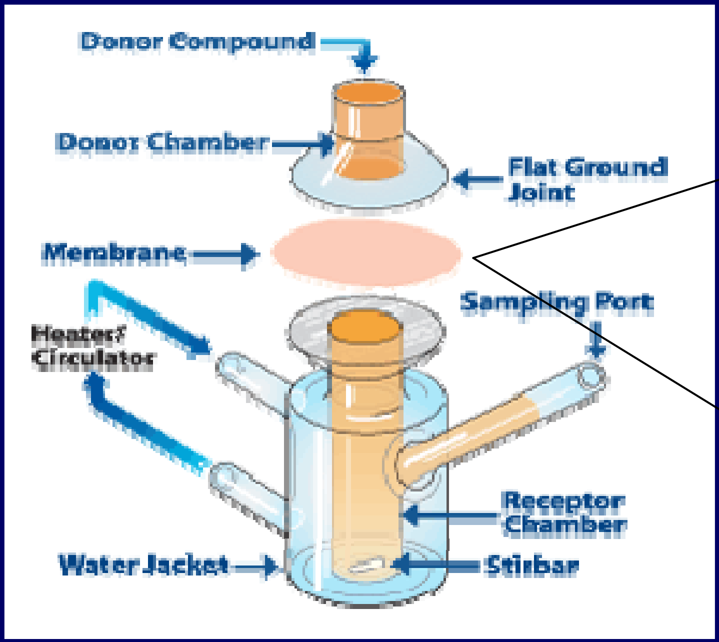


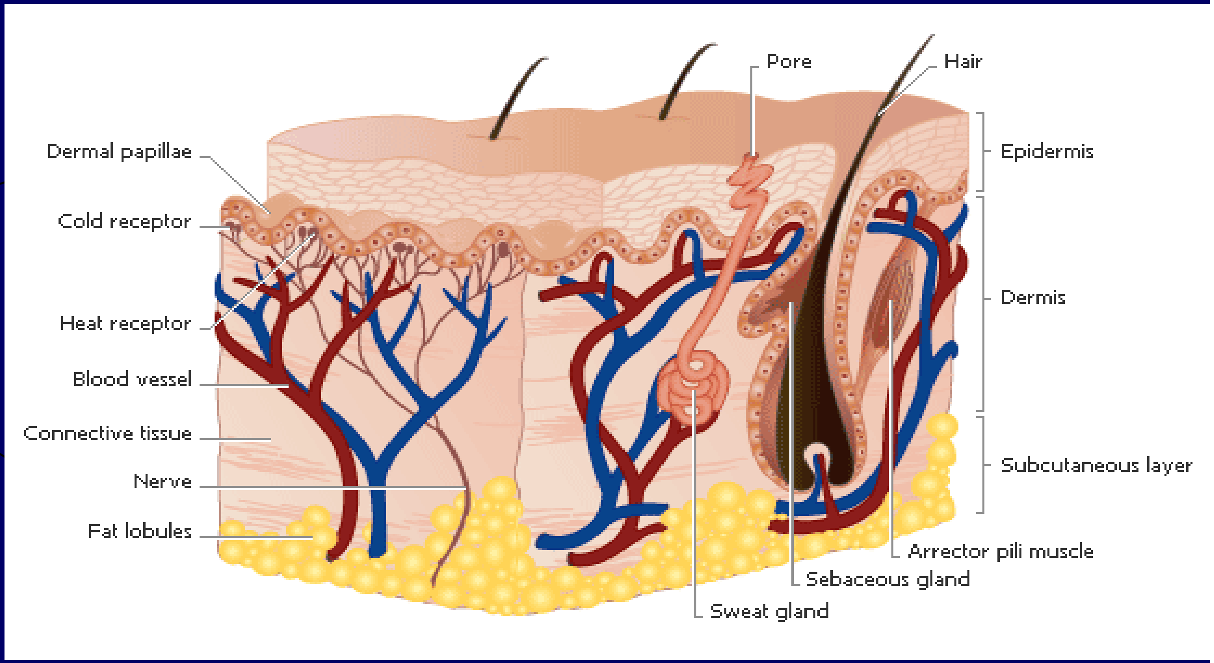


Formulation	k, min^{-1} ($\times 10^4$)	$t_{1/2}$ (day)
Control Emulsion	13.10	0.37
Nanoparticle coating A	0.91	5.27
Nanoparticle coating B	0.18	26.22

N. Ghouchi Eskandar, S. Simovic and C. A. Prestidge, *Phys ChemChem Phys*, 9 (48), 6426-6434, 2007.

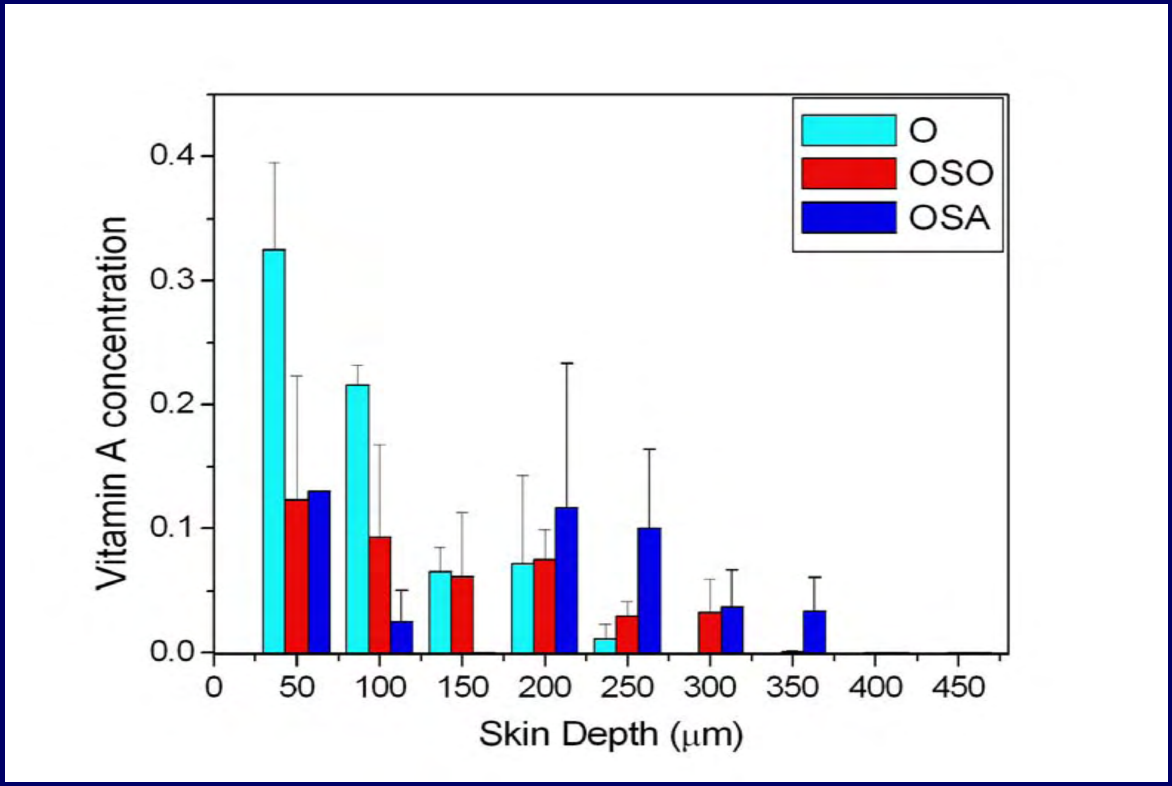
Delivery to the skin

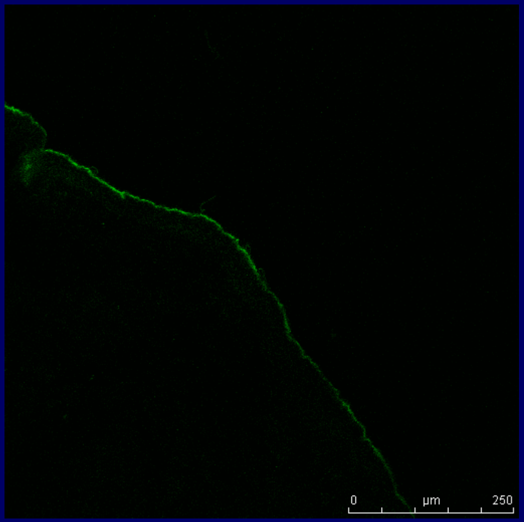


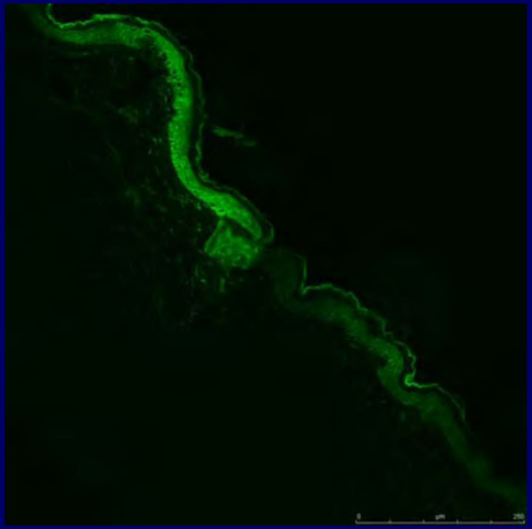


Schematic of a Static Franz Diffusion Cell

Nanoparticle coated droplets improve the skin penetration of Vitamin A





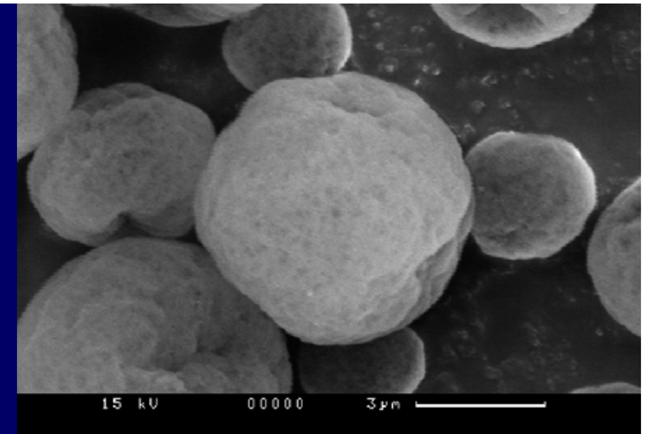


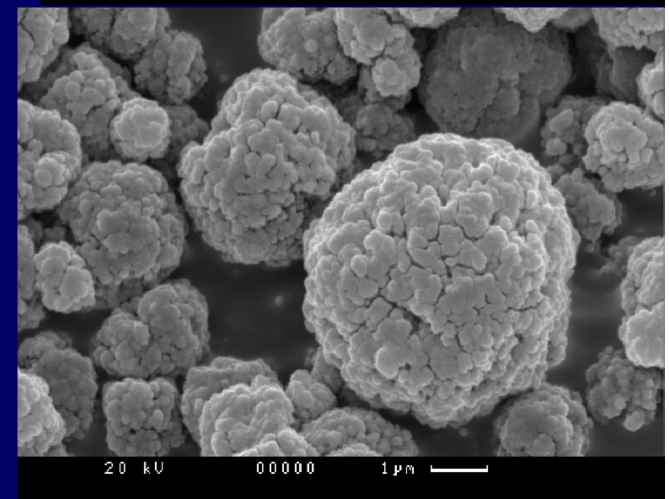
Dry capsules for oral delivery:

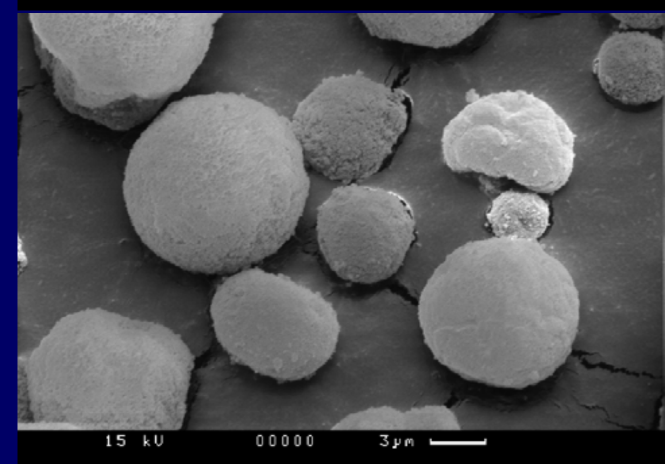
- Spray drying
- Freeze-drying
- Phase coacervation

Drying method + formulation composition controls:

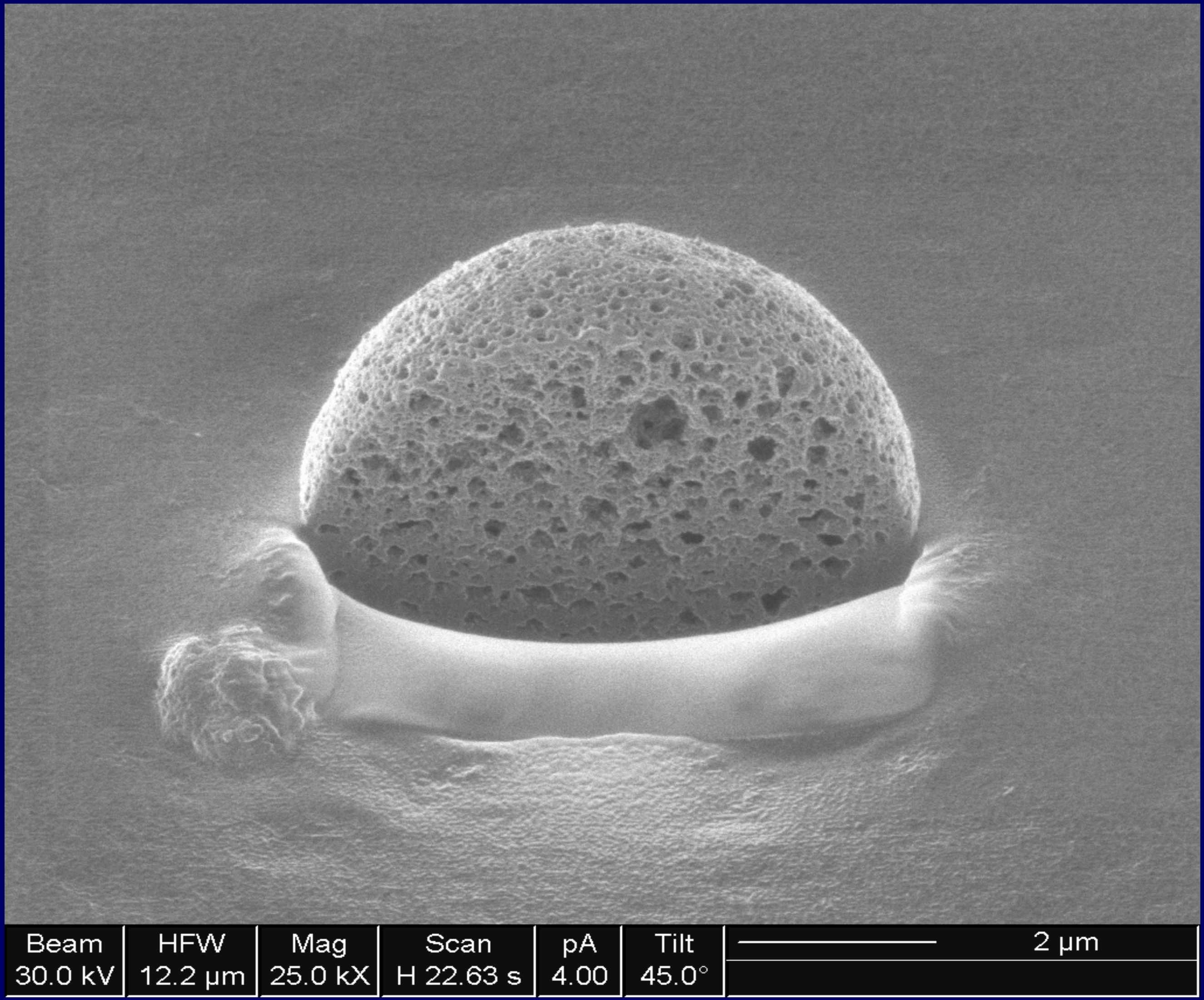
- Structure
- Stability
- Delivery characteristics



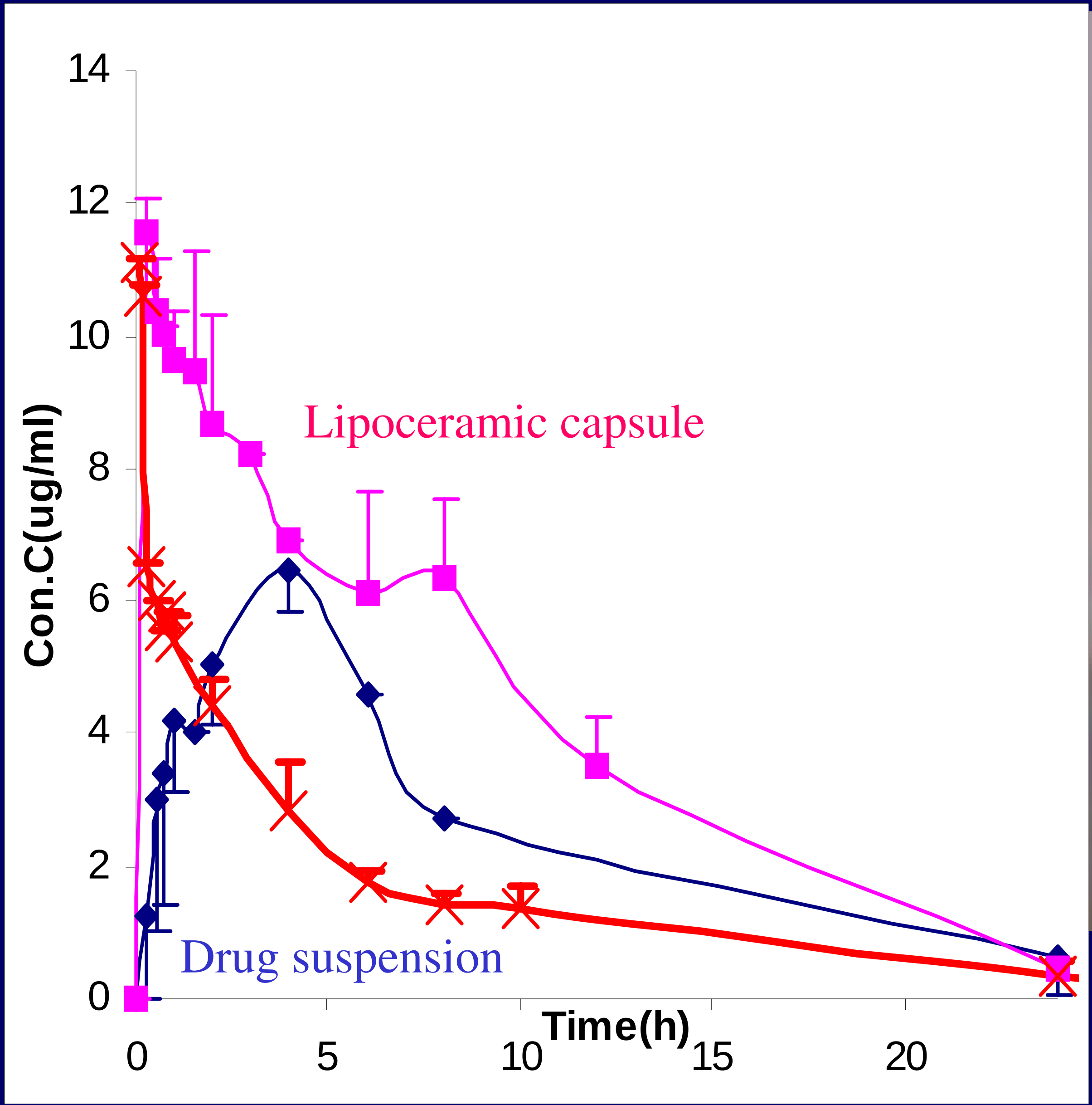


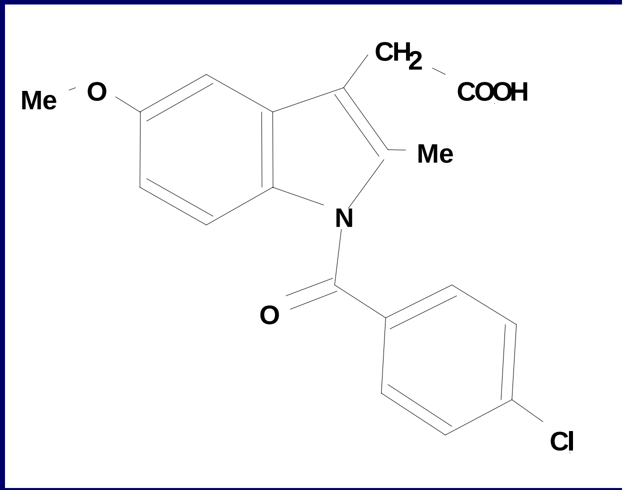


Internal structure of capsules is controllable and facilitates capsule performance



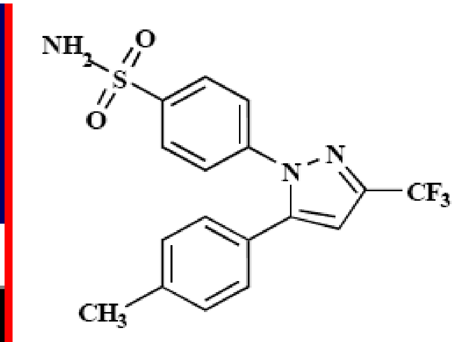
In vivo studies: improved oral delivery of poorly soluble drugs, e.g.indomethicin

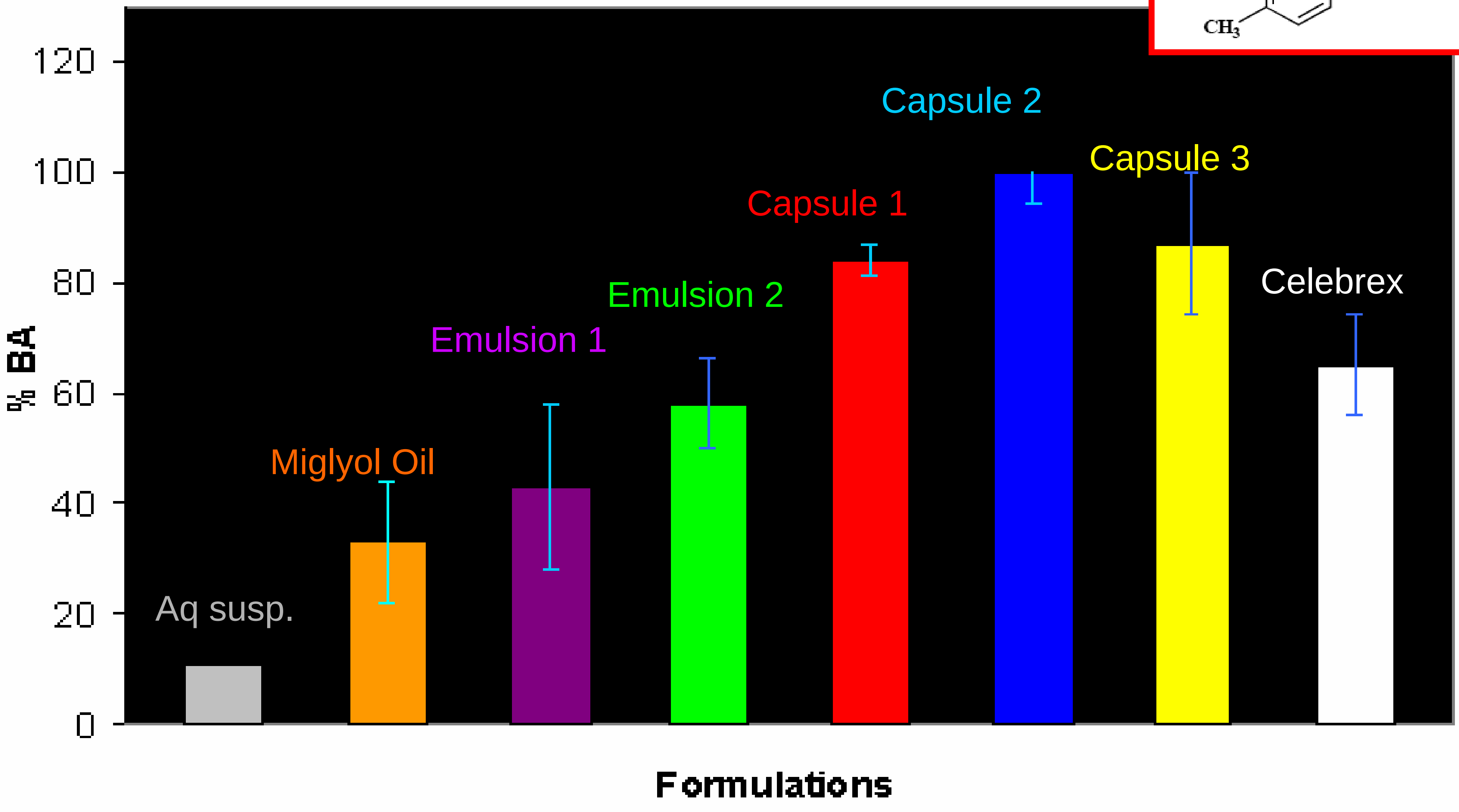




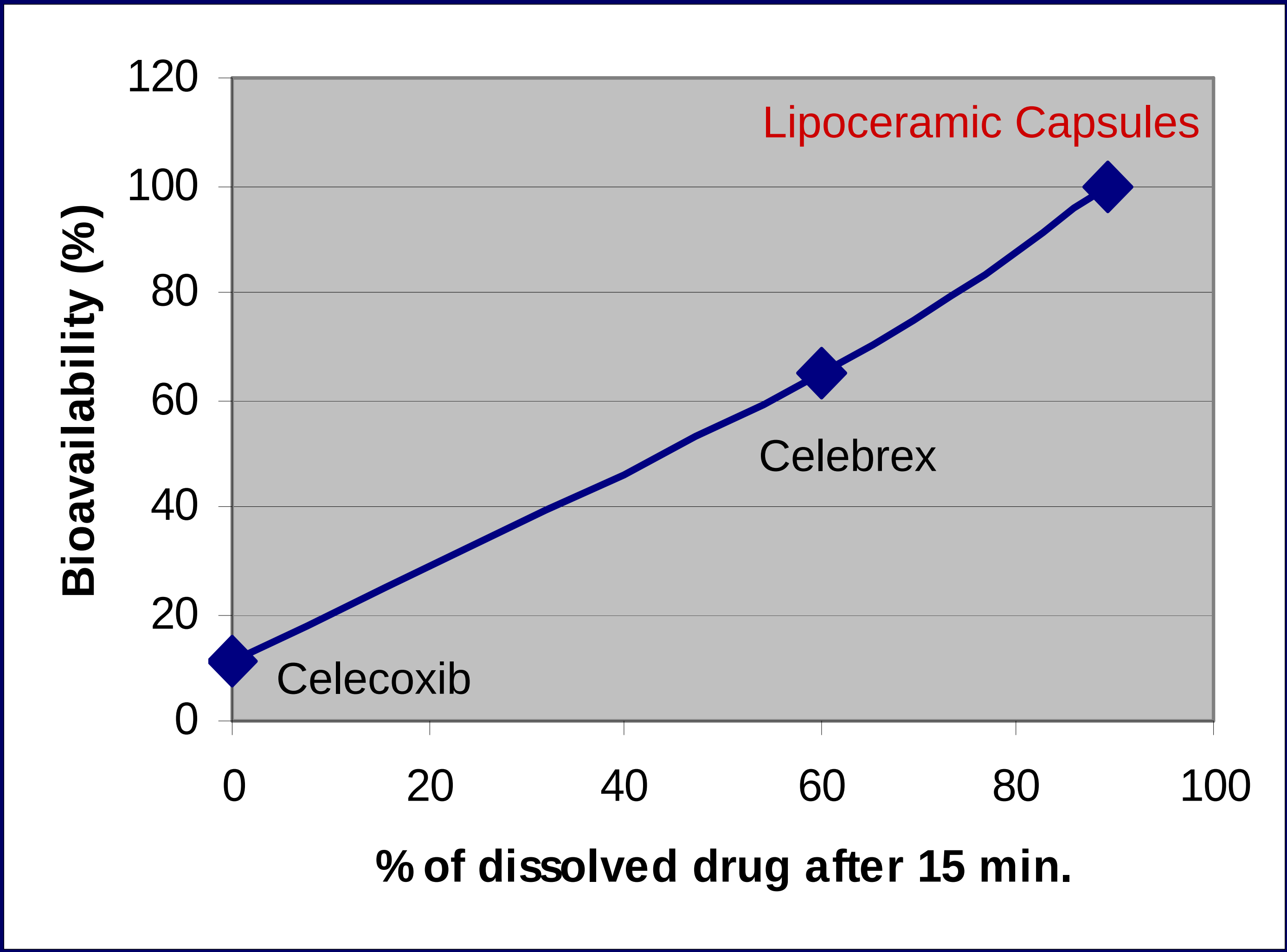
- Increased bioavailability
- Faster action

In vivo Bioavailability of Celecoxib



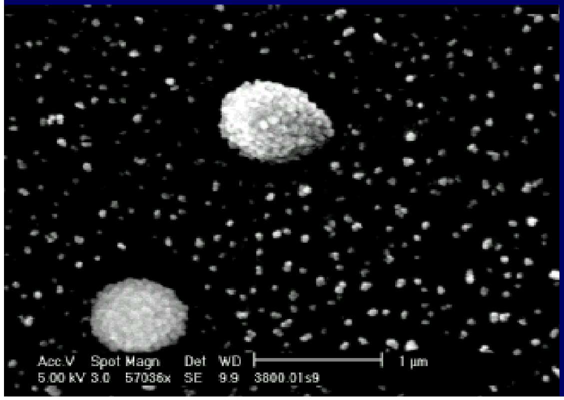


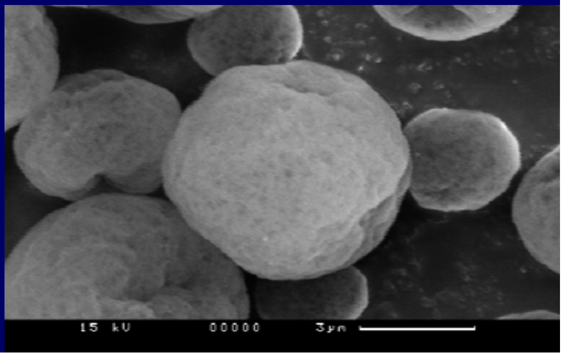
In-vitro / In-vivo Correlation



Concluding Remarks

- BV's monodispersed silicone emulsions are an excellent model colloid
- Investigations of the BV droplets have improved understanding of emulsion interfaces
- The BV droplets have inspired the development of new drug delivery systems based on emulsions and nanoparticles





Acknowledgements

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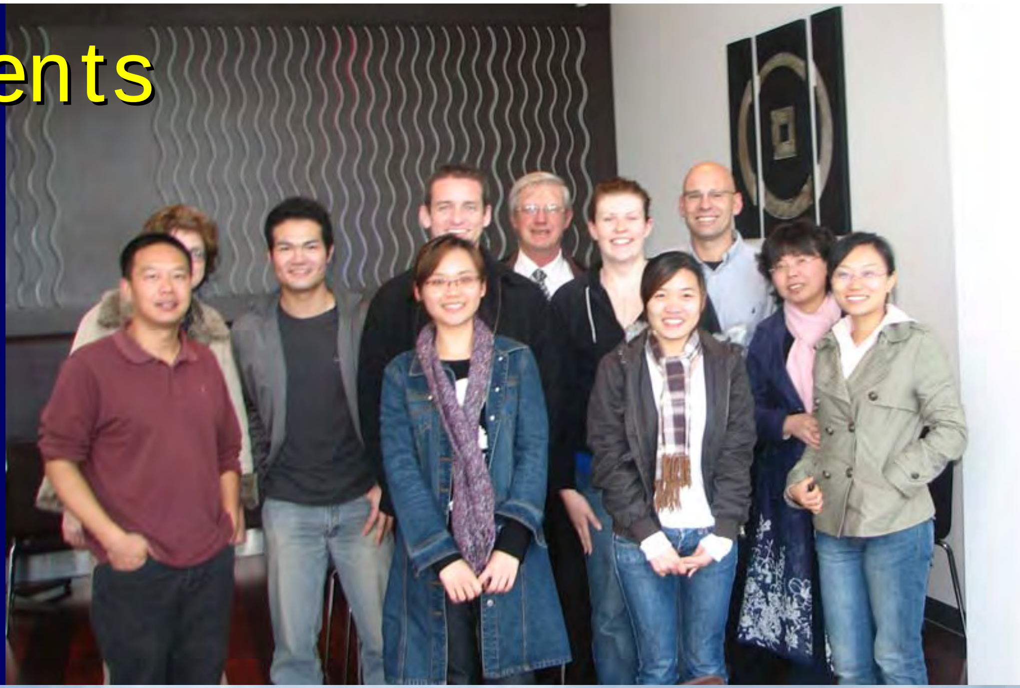
Dr Tim Barnes (polymer interaction)

Dr Spomenka Simovic (nanoparticle interaction)

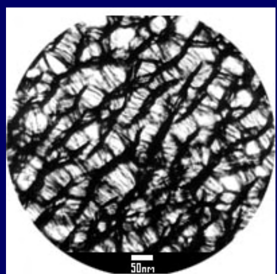
Angel Tan (oral delivery)

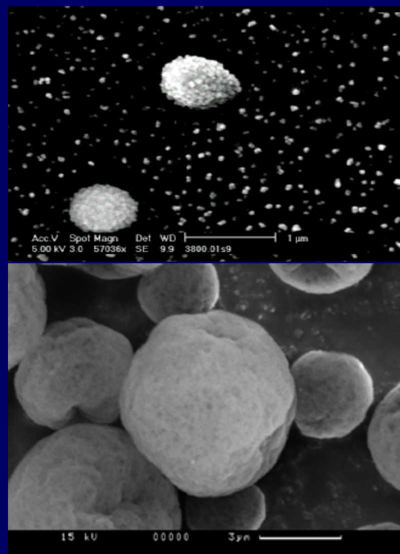
Nasrin Eskandar (dermal delivery)



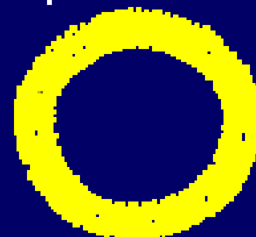
Nano-structured Drug Delivery Systems at the Wark

Mesoporous Particles

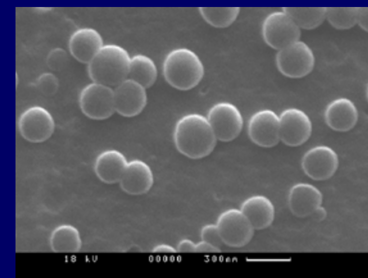




Liposomes

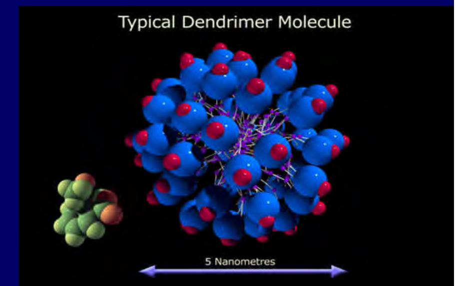


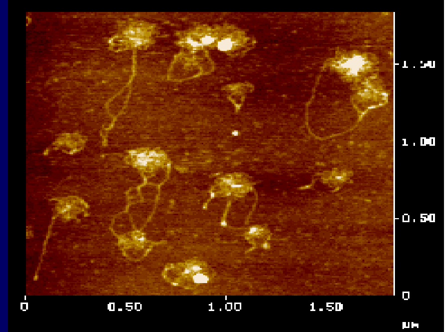
Emulsions + Micro/Nano Capsules



Nanoparticles

Dendrimers

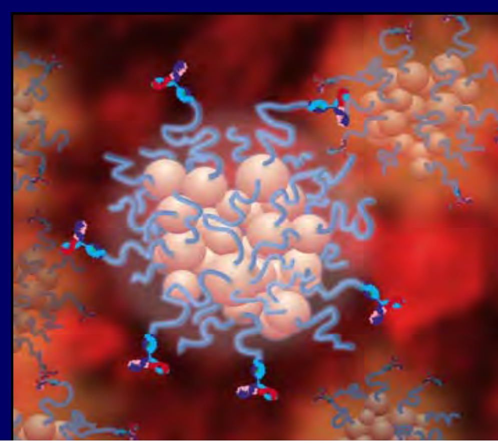


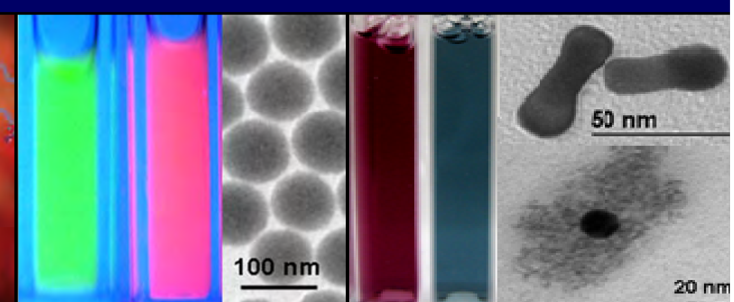


DNA-lipids

- Drug encapsulation
- Formulation stability
- Controlled release
- Improving bioavailability

- Controlled circulation
- Targeted delivery

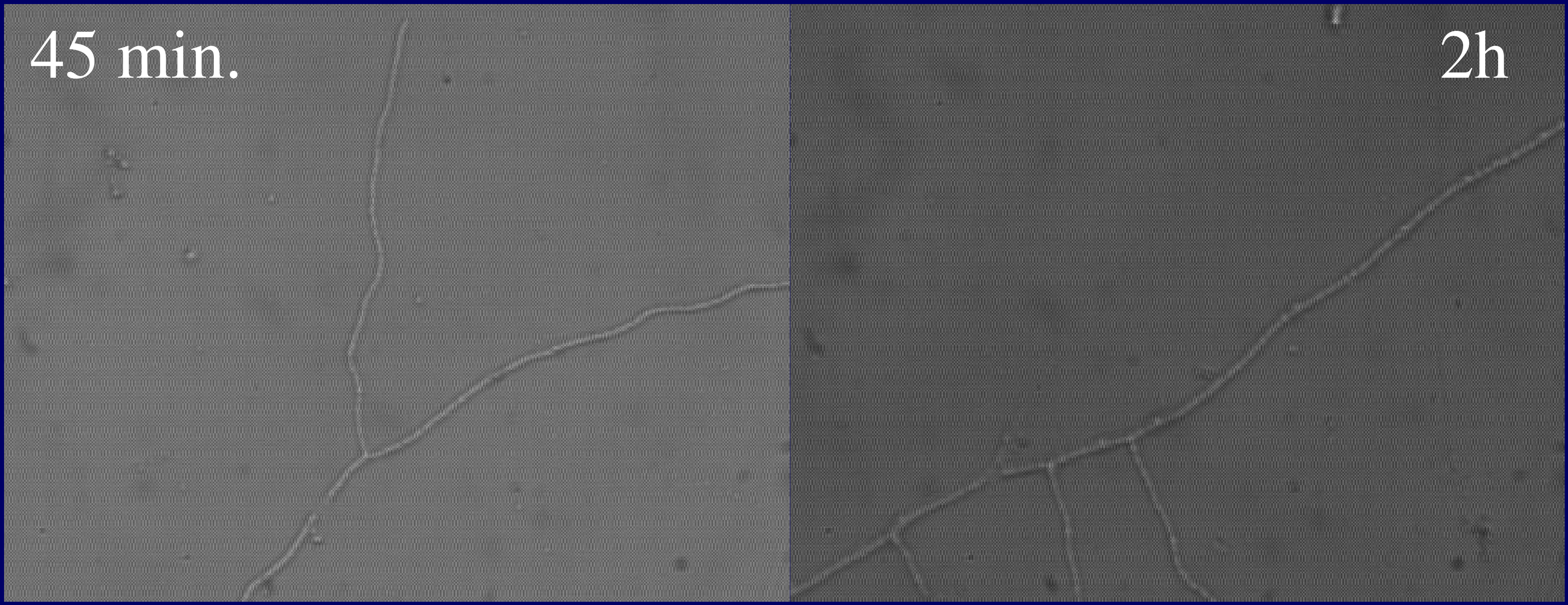




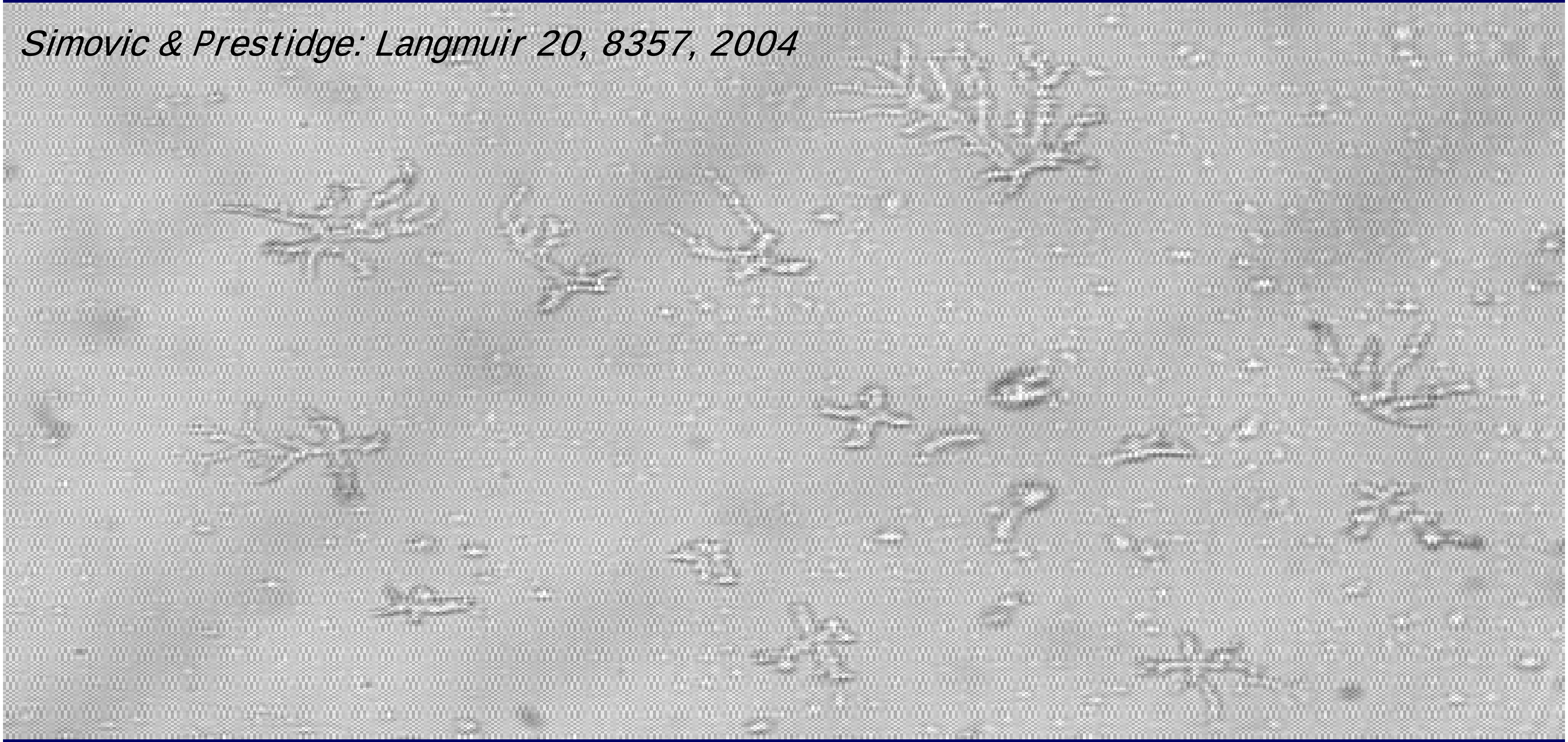
Functional Nanoparticle Research at the Wark™: Towards a new generation of diagnostic and therapeutic nanomaterials.

Hydrophobic nanoparticles: restricted (limited) coalescence

Initial interfacial coverage in the range 0.7 and 0.9: chain structures



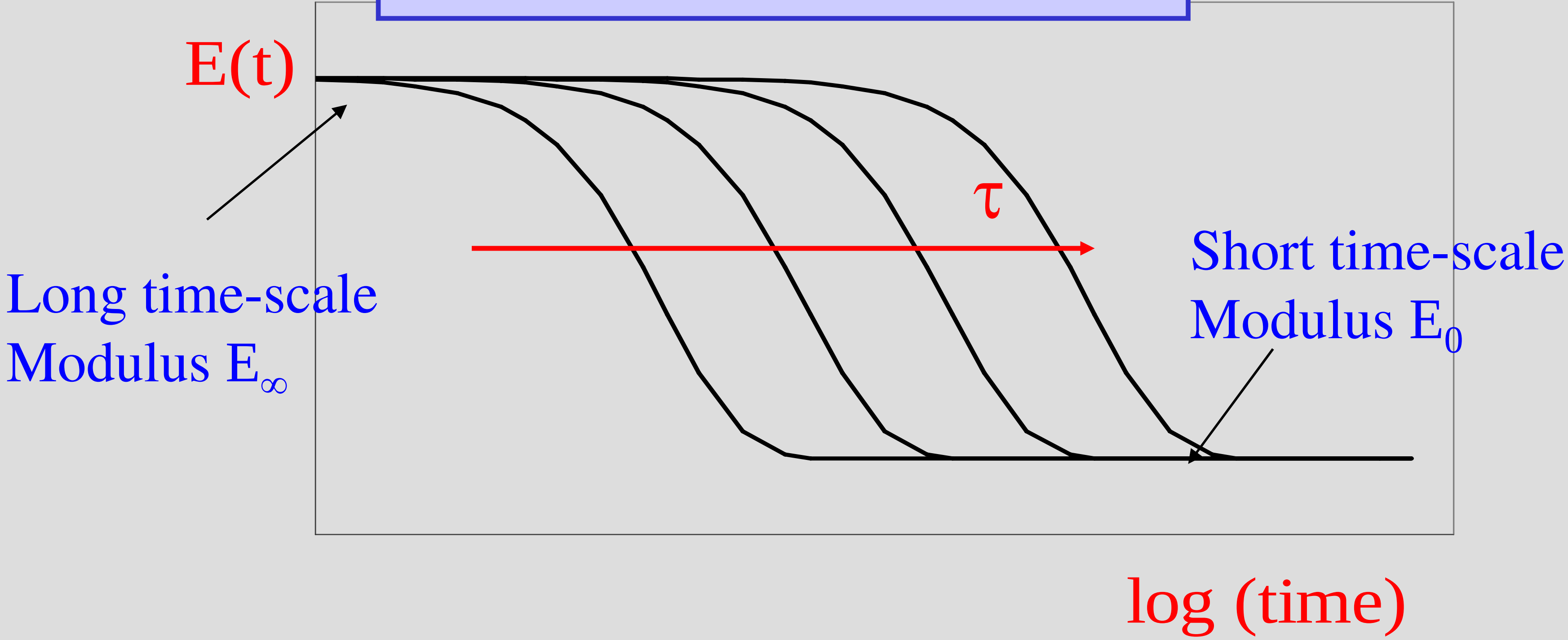
Initial interfacial coverage of hydrophobic nanoparticles of ~0.6: dendritic structures

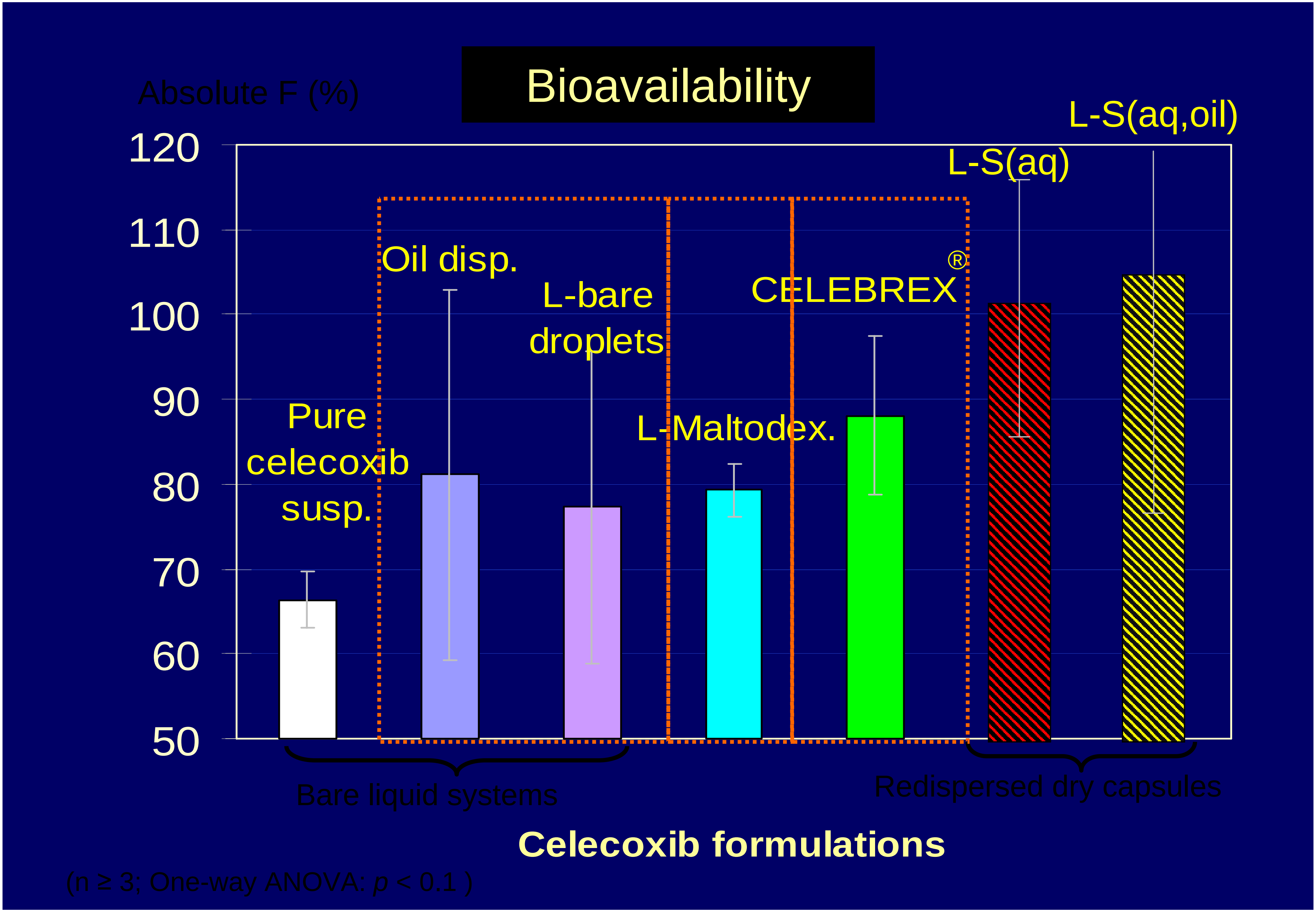


Data Analysis: Nano-Rheology

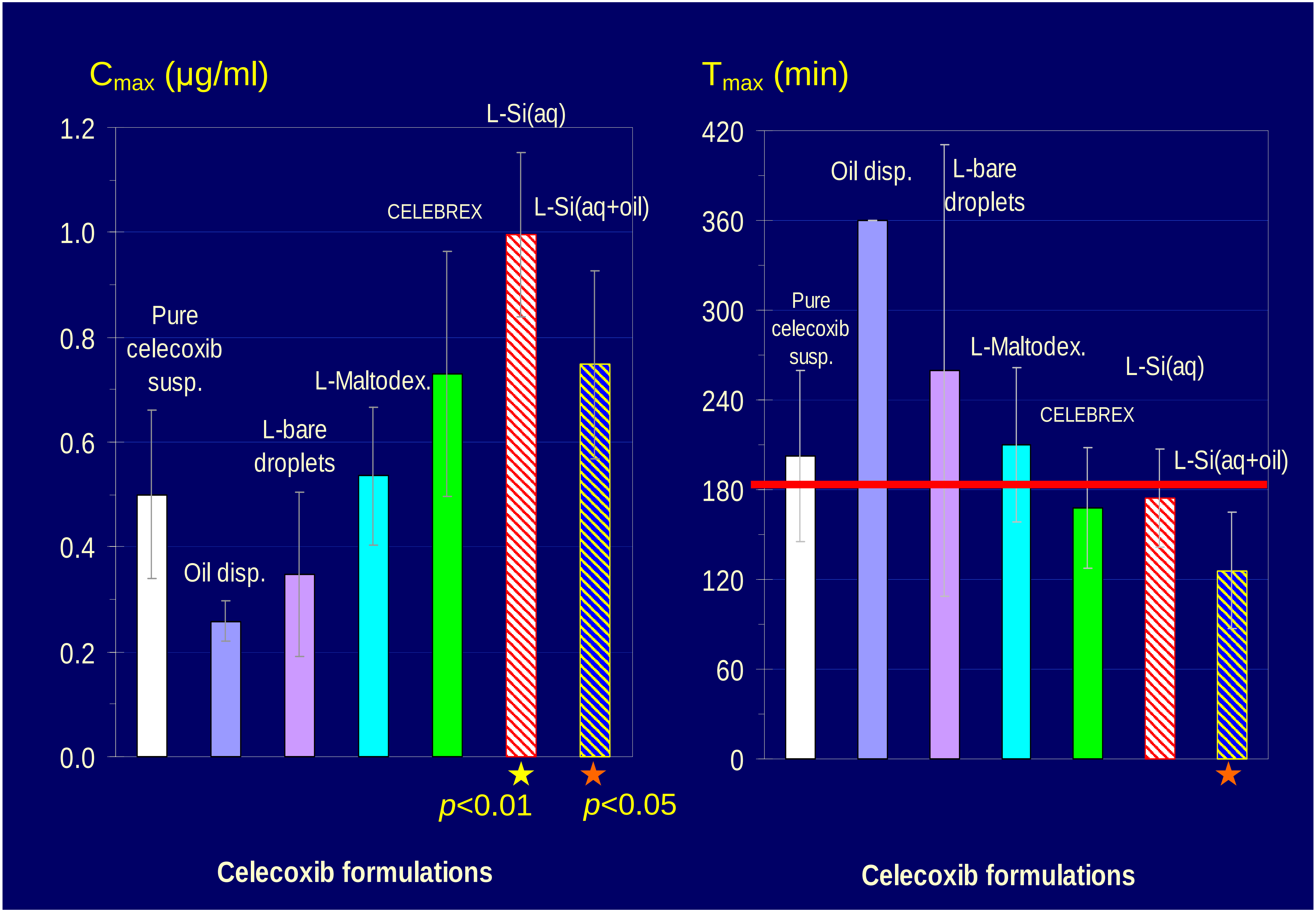
Viscoelasticity of a Sphere (Attard, *Phys. Rev. E,* 2001)

$$\frac{1}{E(t)} = \frac{1}{E_\infty} + \frac{E_\infty - E_0}{E_0 E_\infty} e^{-t/\tau}$$



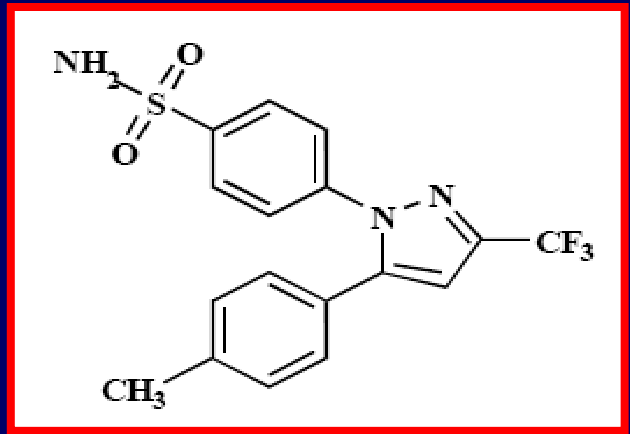


Bioavailability
Absolute F (%)
120
110
100
90
80
70
60
50
Pure celecoxib susp.
Oil disp.
L-bare droplets
L-Maltodex.
CELEBREX®
L-S(aq)
L-S(aq,oil)
Bare liquid systems
Redispersed dry capsules
Celecoxib formulations
(n ≥ 3; One-way ANOVA: p < 0.1)



Cmax (μg/ml)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Pure celecoxib susp.
Oil disp.
L-bare droplets
L-Maltodex.
CELEBREX
L-Si(aq)
L-Si(aq+oil)
p<0.01
p<0.05
Celecoxib formulations
Tmax (min)
420
360
300
240
180
120
60
0
Pure celecoxib susp.
Oil disp.
L-bare droplets
L-Maltodex.
CELEBREX
L-Si(aq)
L-Si(aq+oil)
Celecoxib formulations

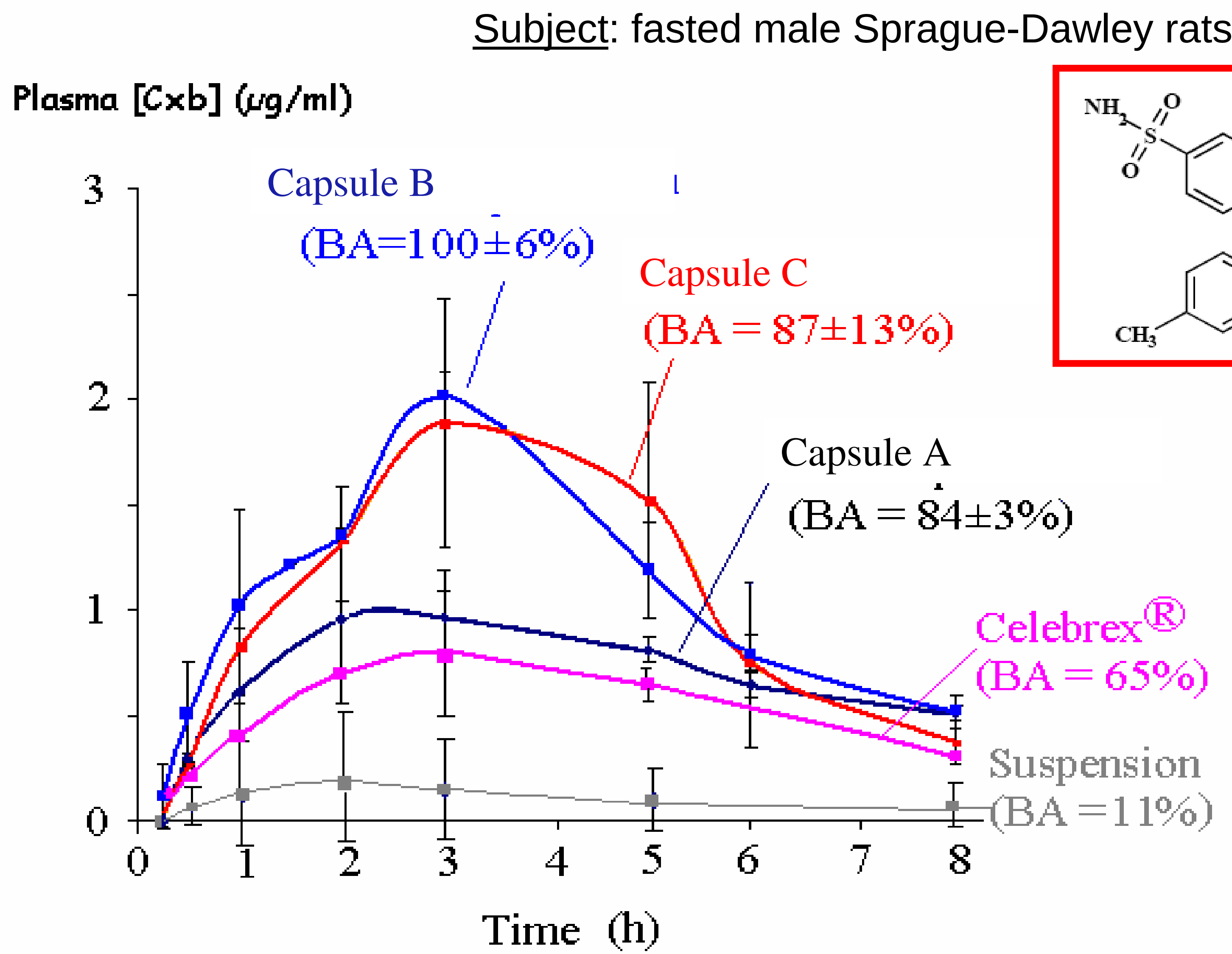
Model Drug: Celecoxib (BCS Class II drug)

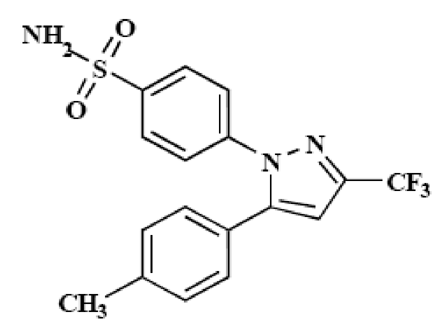


Indications:
Anti-inflammatory drug
→ primarily for rheumatoid arthritis & osteoarthritis

Celecoxib properties	Pharmaceutical limitations
► Hydrophobic (log *P* ≈ 3.5) ► Low solubility (7 µg/ml)	Incomplete & variable absorption; Excessive dose-dumping; No liquid formulation exists
► High T_{max} (3 h)	Slow onset of action (pain relieving)
► Cohesiveness; Low bulk density & compressibility; Poor flow properties	Difficult processing into solid dosage forms (tablets)

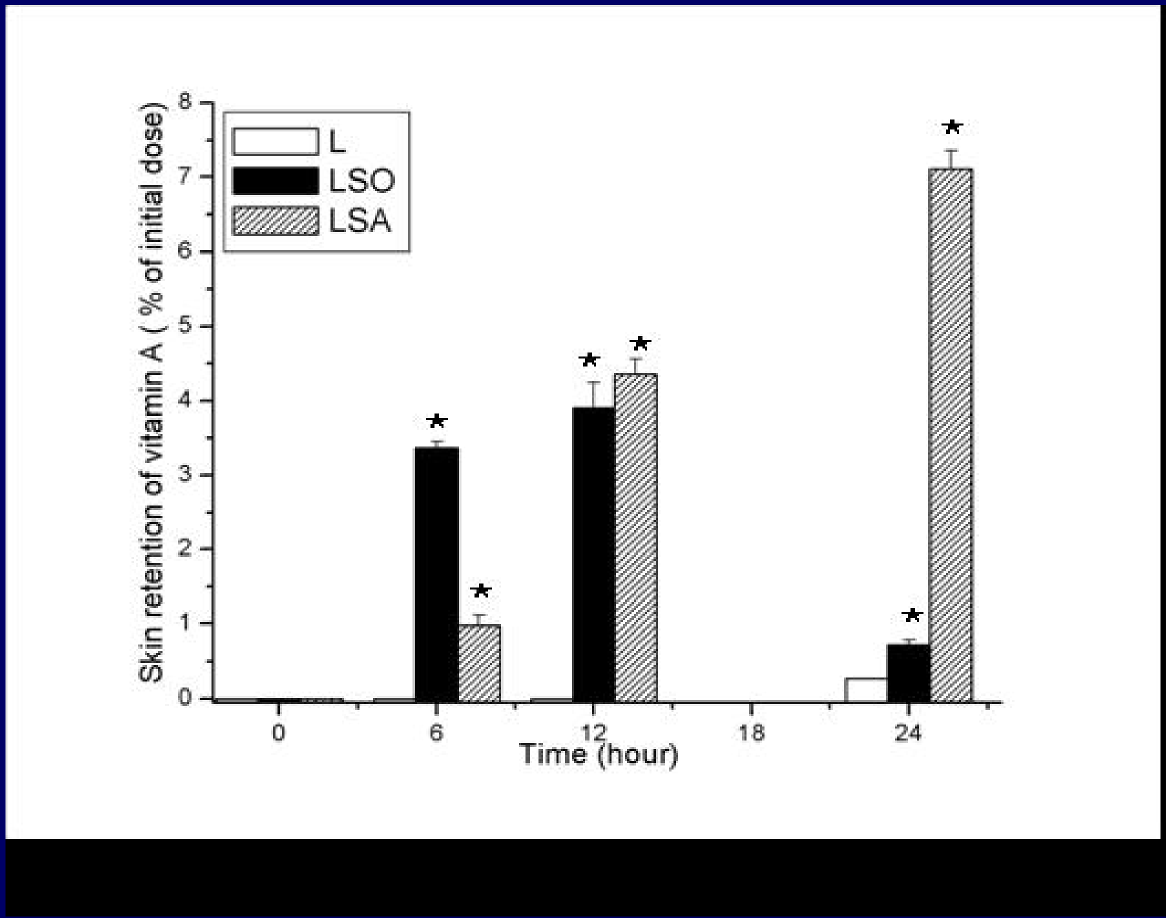
Celecoxib Pharmacokinetics: Bioavailability in Orally Dosed Rats



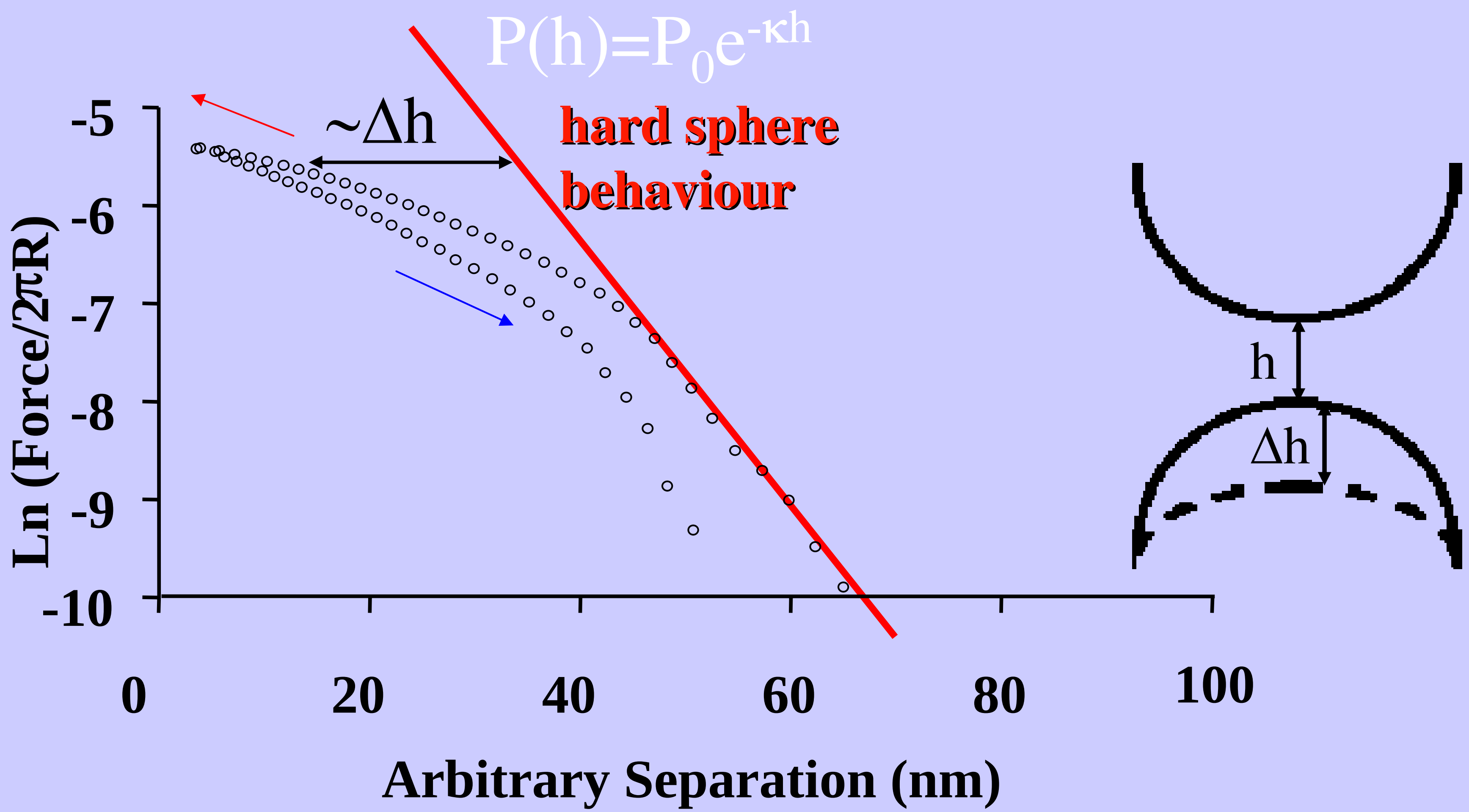


Ex-vivo delivery of Vitamin A to abdominal pig skin:

Nanoparticle coatings facilitate better skin delivery from emulsions



Crosslinked BV Droplets and a Silica Sphere



Nanoparticle coated emulsions facilitate better skin retention and less penetration of vitamin A in comparison with commercial products.

Topical delivery of vitamin A to upper layers of skin with minimum transport across the skin and minimal systemic exposure.