Formulate me t**e**nder - Tackling formulation design @ Janssen

Kristof Kimpe – September 11th, 2019

J&J Changing the trajectory of health for humanity

CONSUMER

Motrin · TYLENOL · Neutrogena · Dr.Ci:Labo · Aveeno ACTIVE NATURALS · BAND-AID · Benadryl · NEOSPORIN · nicorette

ZYRTEC · Johnson's baby · LISTERINE · Rogaine · RoC · NeoStrata · Visine Sterile · DOKTOR MOM · Lactaid Enjoy Dairy Again! · NicoDERM

SUDAFED · Clean & Clear · Imodium · LE PETIT MARSEILLAIS · OGX beauty pure and simple · Lubriderm · BENGAY · Carefree · Benylin

MEDICAL DEVICES

MENTOR® PART OF THE Johnson&Johnson FAMILY OF COMPANIES · ETHICON PART OF THE Johnson&Johnson FAMILY OF COMPANIES · ASP · Johnson&Johnson VISION

STERILMED · CERENOVUS PART OF THE Johnson&Johnson FAMILY OF COMPANIES · Acclarent PART OF THE Johnson&Johnson FAMILY OF COMPANIES · Biosense Webster a Johnson&Johnson company · DePuy Synthes COMPANIES OF Johnson&Johnson

PHARMACEUTICALS

Tremfya™ (guselkumab) · Invokana canagliflozin tablets · Stelara (ustekinumab) · Remicade INFLIXIMAB · Zytiga abiraterone acetate · INVEGA TRINZA® paliperidone palmitate extended-release injectable suspension 273 mg, 410 mg, 546 mg, 819 mg · imbruvica (ibrutinib) capsules · Erleada (apalutamide) 60 mg tablets

Xarelto rivaroxaban tablets · Sirturo bedaquiline 100mg tablets · Simponi ARIA golimumab for infusion · DARZALEX (daratumumab) injection for intravenous infusion 100 mg/5 mL, 400 mg/20 mL · ONCE-MONTHLY INVEGA SUSTENNA paliperidone palmitate extended-release injectable suspension 39mg, 78mg, 117mg, 156mg, 234mg · PREZISTA (darunavir) tablets · Symtuza · Opsumit macitentan tablets 10 mg · Tracleer
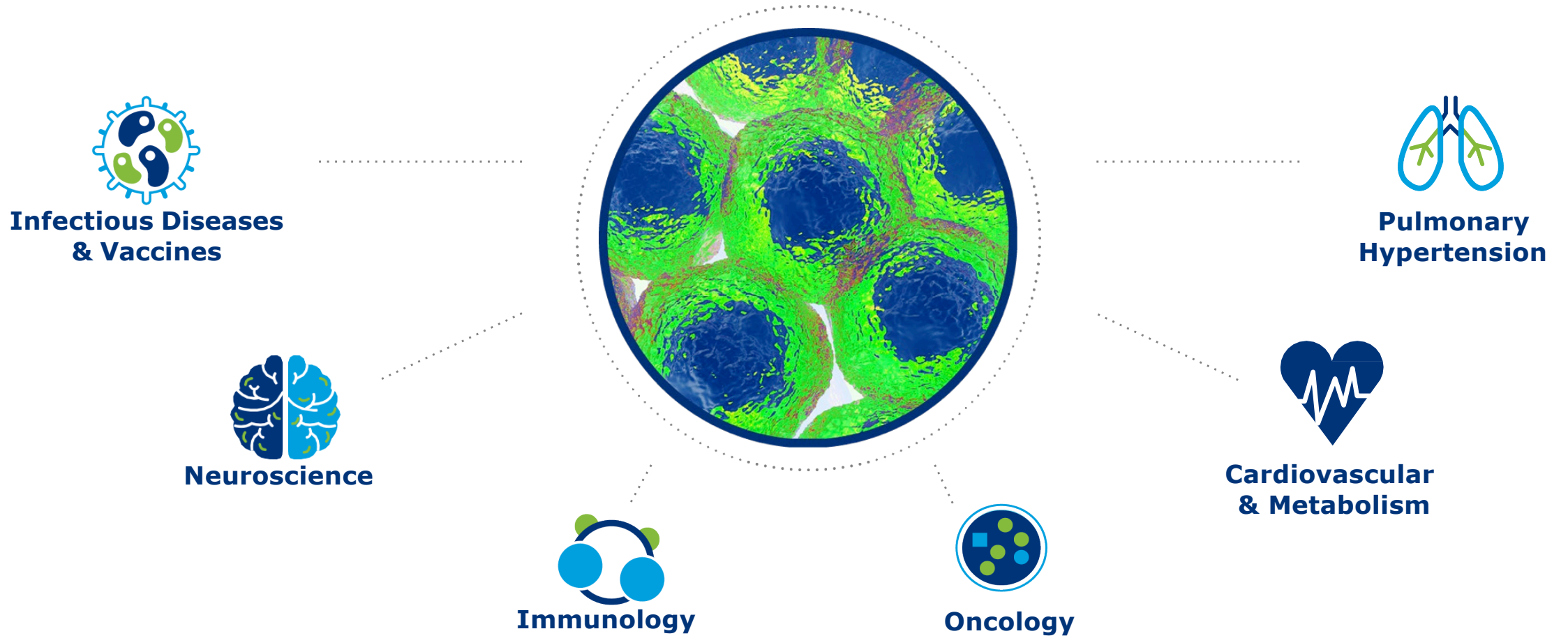
Source: Super Deck Johnson & Johnson Innovation – JLABS(accessed November 2018)
In EU Remicade and Simponi are marketed by MSD, Xarelto by Bayer

Our focus areas

We are developing treatments for patients in **six important therapeutic areas of healthcare**

Infectious Diseases & Vaccines

Pulmonary Hypertension

Neuroscience

Cardiovascular & Metabolism

Immunology

Oncology

Janssen and J&J in Belgium

Merksem

Janssen Pharmacology Unit

Beerse 1

Janssen
- R&D
- Supply Chain
- Liquids & Creams
- Parenterals
- Distribution Center
- General Services

Mechelen

Actelion

Beerse 2

Janssen-Cilag NV
Commercialization of all medicines in Belgium

Beerse 2

Consumer GCO

La Louvière

Janssen European Distribution Center

Olen

Janssen

Diegem

J&J Medical NV
- J&J Medical NV
- GMED bvba
- J&J Corporate Functions
- European Logistics Center
- One MD Regional Office

Courcelles

J&J European Distribution Center

Geel

Janssen Supply Chain
- API/Small Molecules

● Janssen
● Johnson & Johnson

Building the foundation for a robust drug product

Nasal spray

Beads in capsule

Solid dispersion in tablet

Injection

Keeping up appearances?

What makes a good formulation?

DP is made → DP lies on the shelf → DP is administered → DS gets absorbed → DS is eliminated

Stage	Q n°	Question
DP is made	1	Enabling formulation design needed?
DP lies on the shelf	2	Chemical and physically stable?
DP is administered	3	Does the DS release from DP?
DS is administered	4	Does the DS remain dissolved during GI transit time? Does it crash out?
DS gets absorbed	5	Quid permeability?
DS gets absorbed	6	Quid first pass (gut / hepatic)
DS is eliminated	7	Half life?

Enabling needed?

- Depends on the (projected) dose
- Depends on the solubility of the compound
  - Polymorphism!
  - FaSSIF medium @ 37°C
- Depends on the permeability
  - In vitro permeability assessment

Amidon GL, Lennernäs H, Shah VP, and Crison JR, 1995, A Theoretical Basis For a Biopharmaceutics Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability, Pharm Res, 12: 413-420

J.M. Butler, J.B. Dressman - The Developability Classification System: Application of Biopharmaceutics Concepts to Formulation Development – J. Pharm. Sci., 99, 2010, pg 4940

Dose number & permeability

- Dn = Dose / (S_{FaSSIF})*500mL

- In vitro permeability translated to human permeability

- When dose number is high: enabling

- When dose number is medium
  - Particle size reduction
  - Wetting agents (e.g. SLS, DOSS)
  - Salt formation?
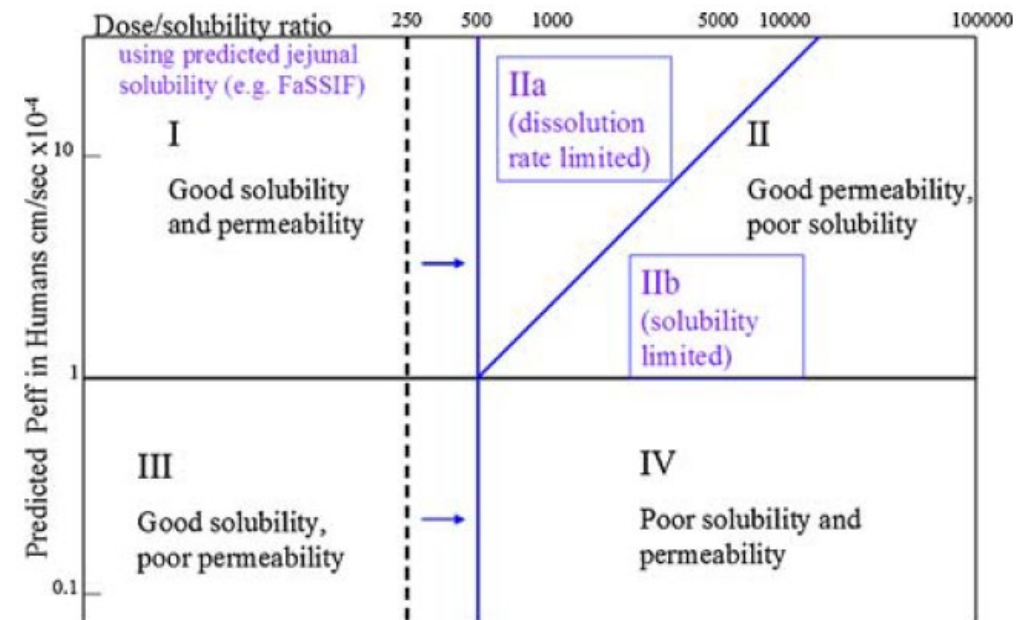
DCS 2 – now what?

- Particle size reduction possible?
  - Dissolution rate ~ PSD
  - Jet milling feasible?
  - Structural disorder?
 - Quid powder flow?
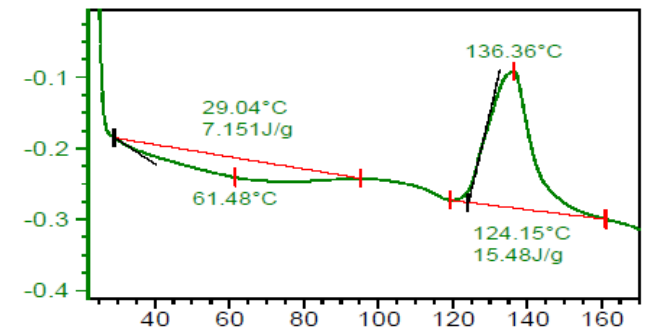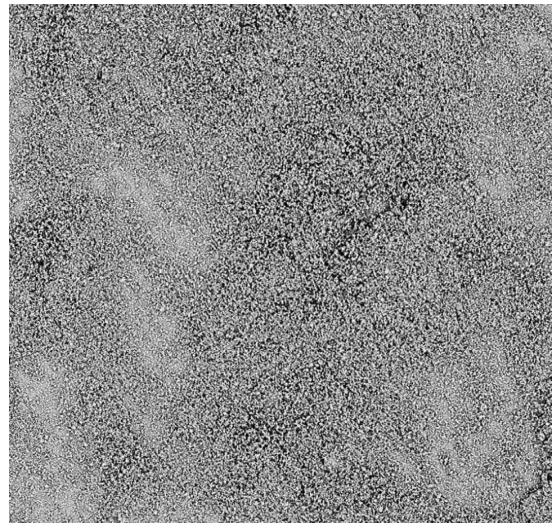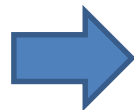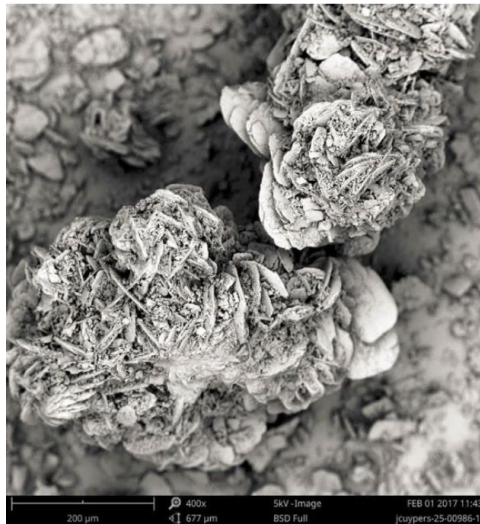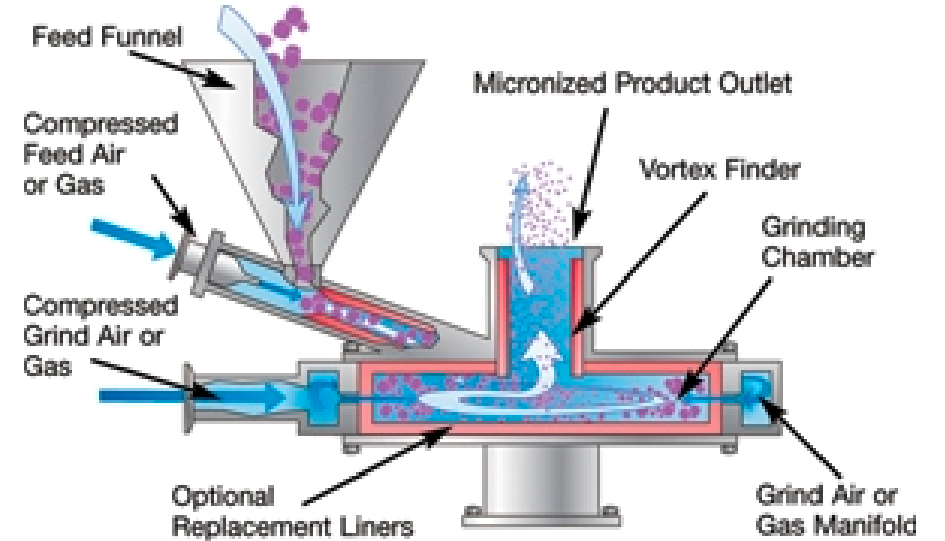
Salt formation possible?

- Take advantage of higher intrinsic dissolution rate
- Does compound have a suitable pKa?
  - What is pHmax for a given counterion?
  - What is risk of disproportionation during shelf life?

$$S_T = [BH^+]_s \left(1 + \frac{K_a}{[H_3O^+]}\right)$$

$$pH_{max} = pK_a + \log \frac{[B]_s}{\sqrt{K_{sp}}}$$

$$S_T = [B]_s \left(1 + \frac{[H_3O^+]}{K_a}\right)$$

Log Solubility vs pH

Solid state: Salt form

Solid state: Free base
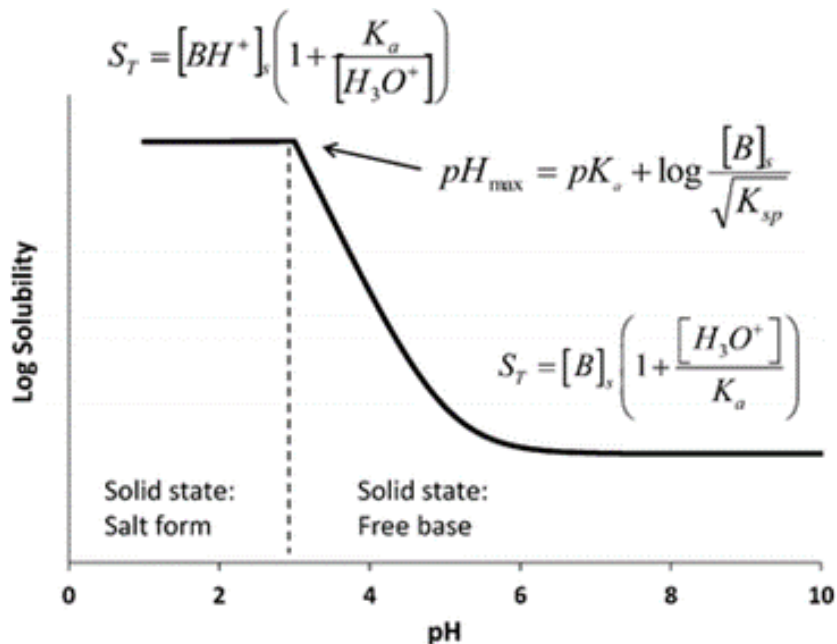
	Base pKa
Very strong	14
Strong	9.5-14
Weak	4.5-9.5
Very weak	**0-4.5**
Extremely weak	< 0

Salt considerations

- Counter ion determines the solubility product Ksp of the salt, i.e. the aqueous solubility. High solubility (desired) -> low pHmax (undesired)!

- E.g. sertraline: HCl and mesylate salt showed 100% salt disproportionation, while the benzoate salt showed only partial salt disproportionation: the reason is the high pHmax of benzoate due to its relatively low solubility .

Solubility goes down

pHmax goes up
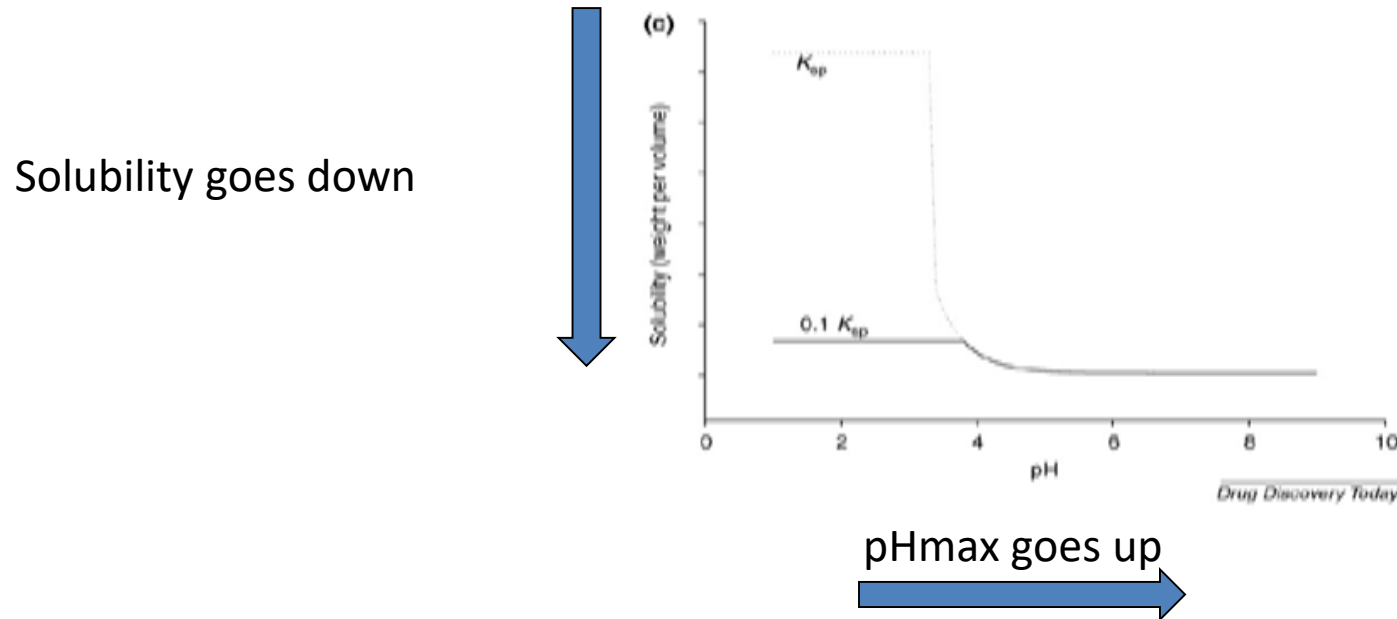
- Y.-L. Hsieh, W. Yu, Y. Xiang, W. Pan, K.C. Waterman, E.Y. Shalaev, S.L. Shamblin, L.S. Taylor, Impact of sertraline salt form on the oxidative stability in powder blends, Int. J. Pharm., 461 (2014) 322-330.
- N.K. Thakral, R.J. Behme, A. Aburub, J.A. Peterson, T.A. Woods, B.A. Diseroad, R. Suryanarayanan, G.A. Stephenson, Salt Disproportionation in the Solid State: Role of Solubility and Counterion Volatility, Mol. Pharm., 13 (2016) 4141-4151.

# Unstable salts?

- ## Low to very low pHmax

  - ### As solid:

    - Use neutral excipients
    - Or, if salt of base: acidic excipients, e.g. citric acid, to lower "environmental pH"
    - Moisture control

  - ### As liquid: dose in non-aqueous medium, e.g. oil

N.K. Thakral et al, Int. J. Pharm. Sci. – 520, 2017 pg 228-240

Average Plasma vs time (n=3)
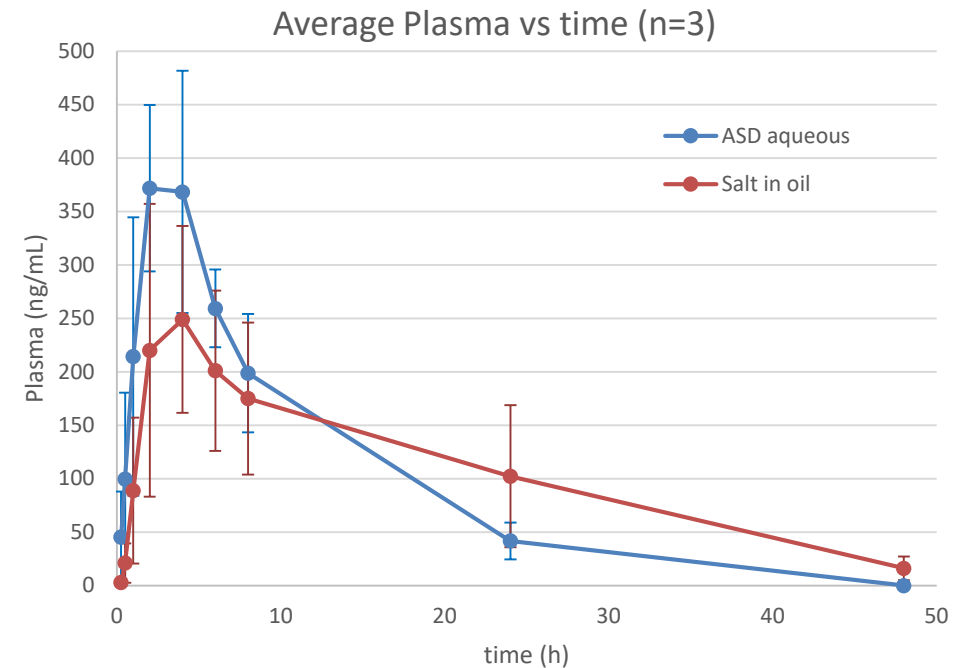
- NHP
- Cmax lower than solid dispersion
- Higher plasma levels at longer timepoints
- AUC values ~ equal

Biorelevant implication

Red = solution
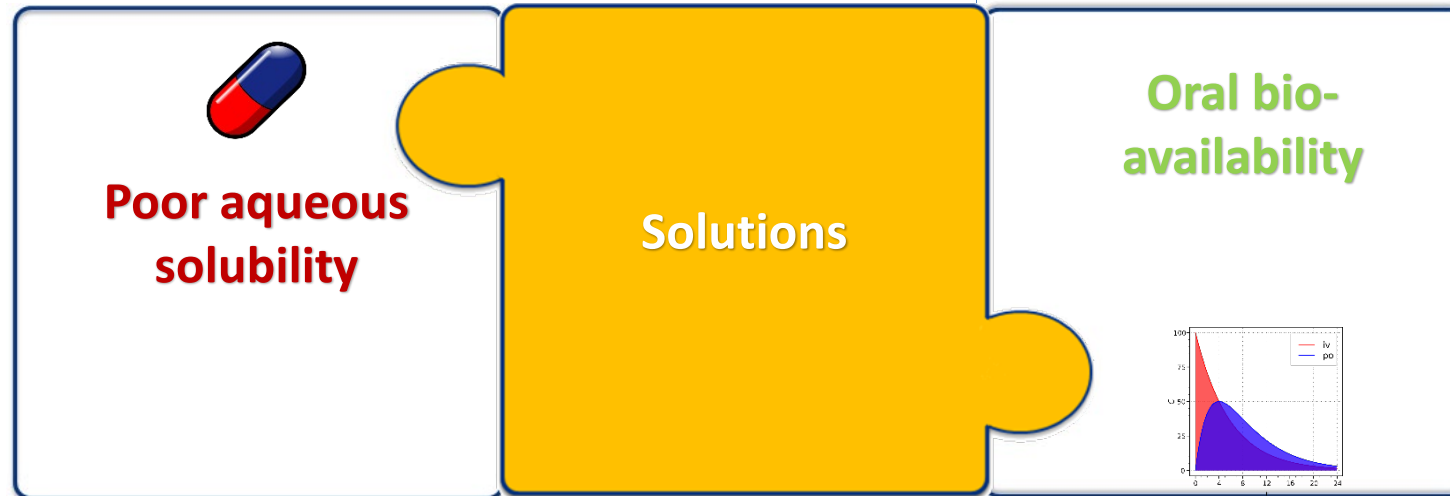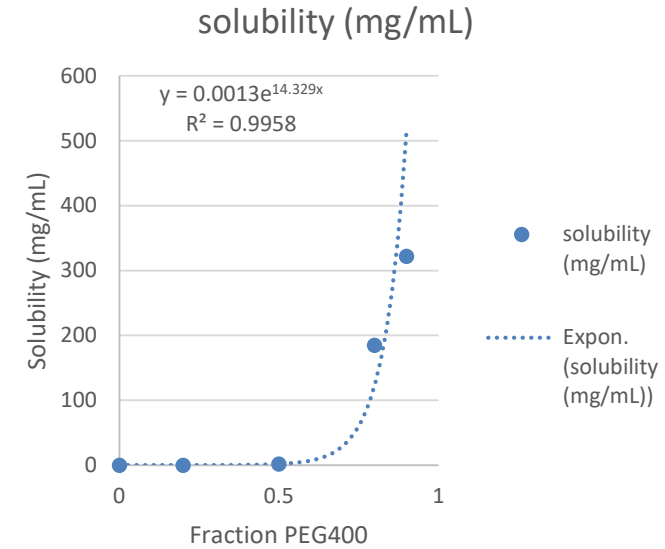Purple = aq. Suspension
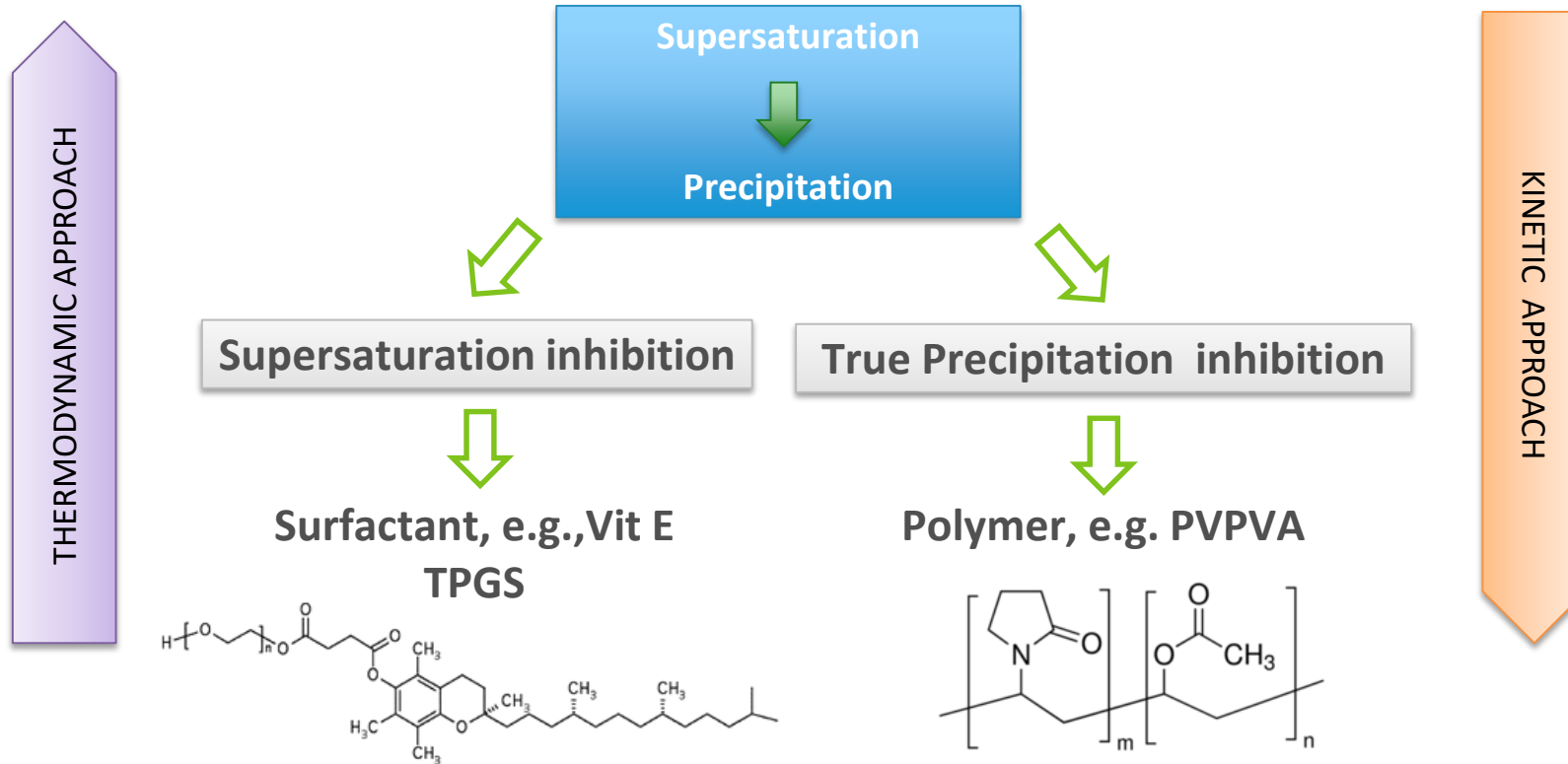Blue = LCT suspension

Gastric residence time
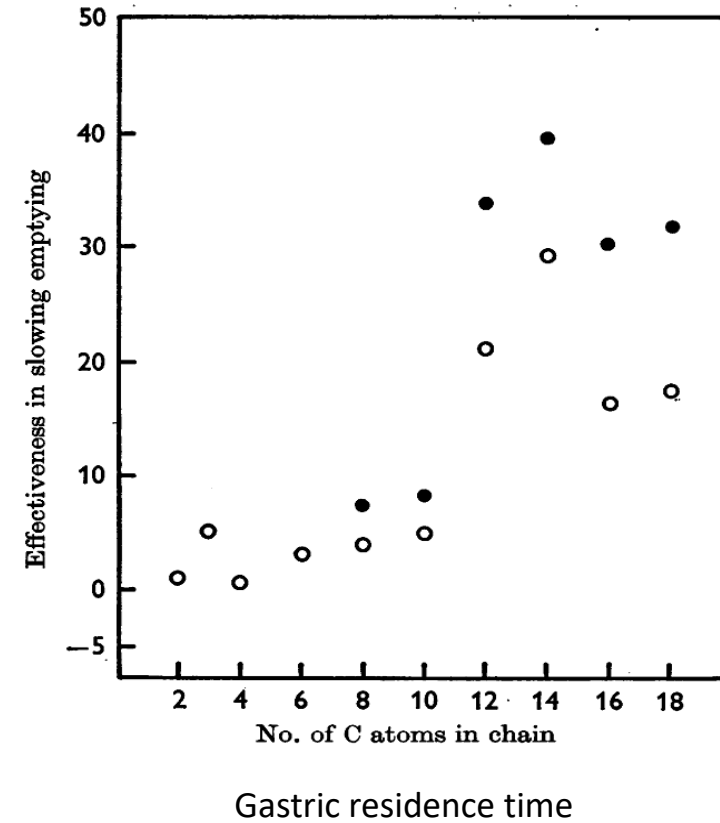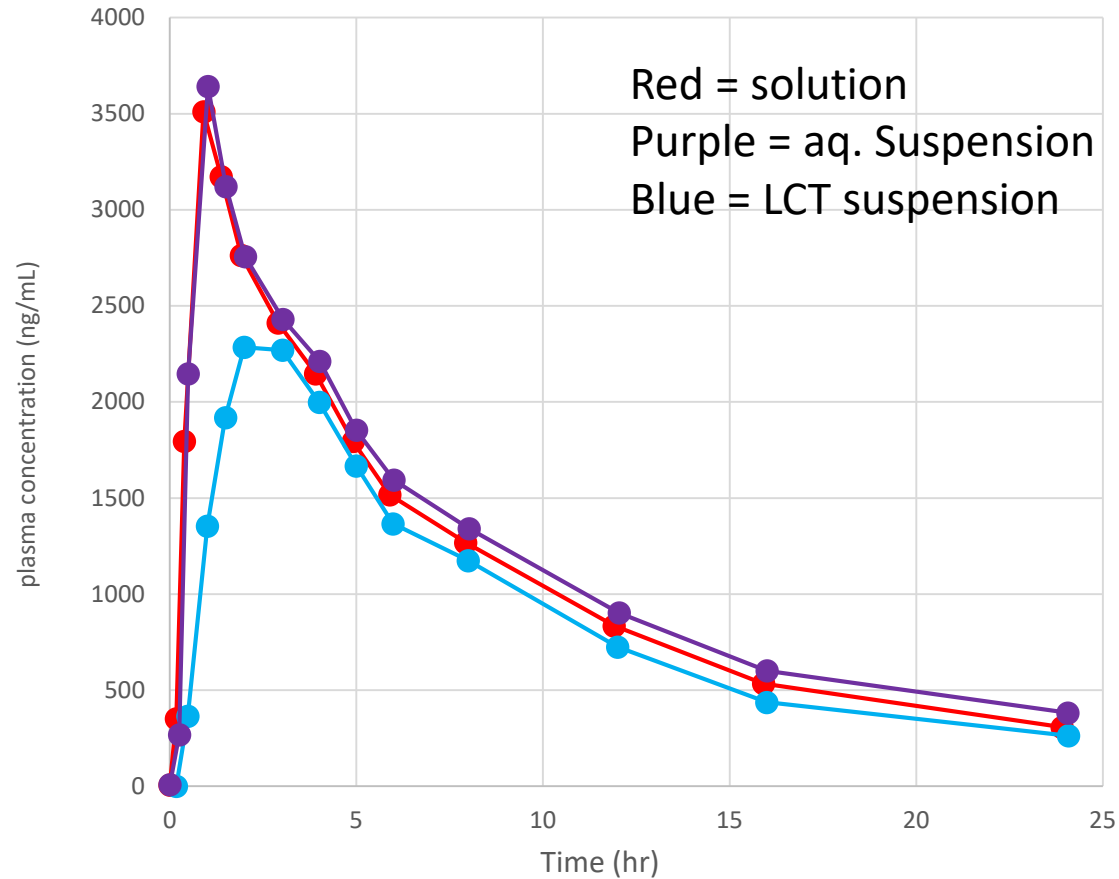
A relation between the chain length of fatty acids and the slowing of gastric emptying. **al, J.N. Hunt et.** 1968, J. Physiol., Vol. 194, pp. 327-336.
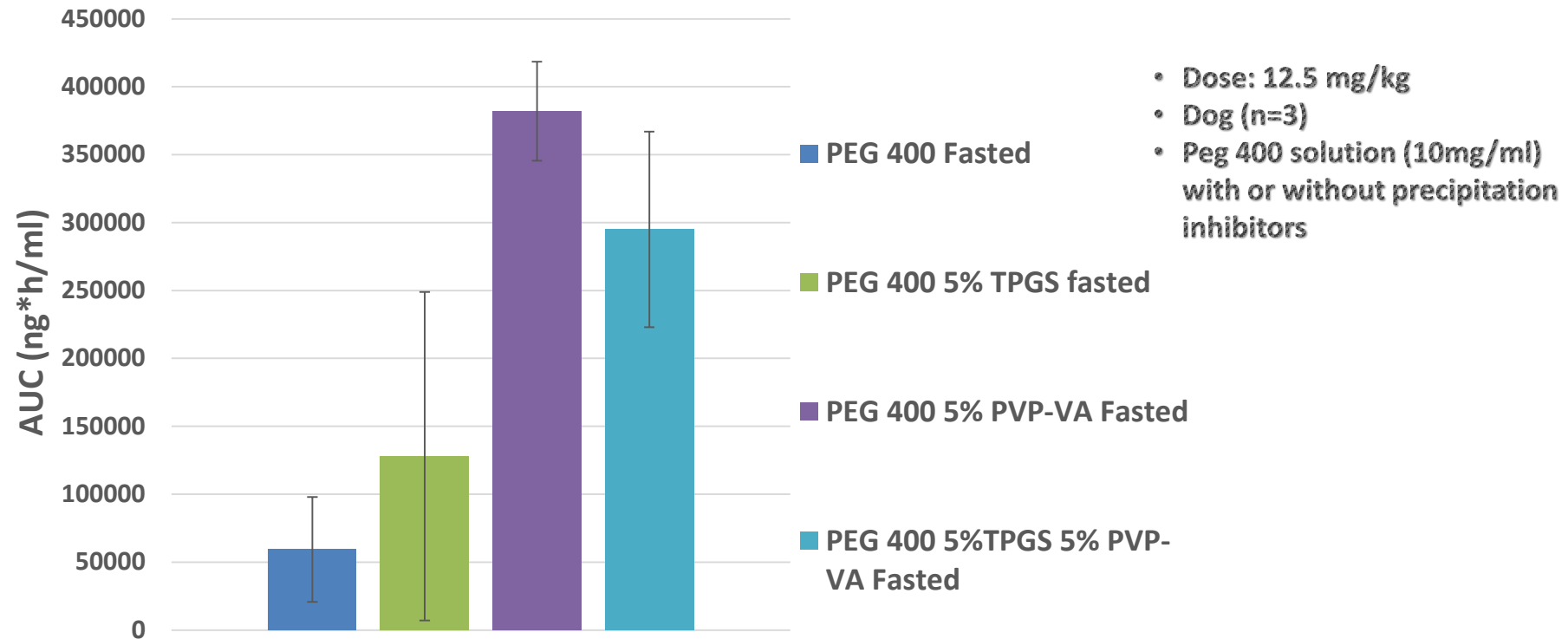
DCS2 -> Co-solvents?

- Co-solvents can be explored

- However, upon dilution, the solvent power decreases exponentially

- Can we "enable" cosolvents?

solubility (mg/mL)

$y = 0.0013e^{14.329x}$
$R^2 = 0.9958$

- solubility (mg/mL)

...... Expon. (solubility (mg/mL))

Fraction PEG400

Poor aqueous solubility

Solutions

Oral bio-availability

Yalkowski, Samuel. Solubility and solubilization in aqueous media. New York - Oxford : Oxford university press, 1999.

Enabling cosolvents

Enabled solutions performance in vivo (Fasted Dog)

- Dose: 12.5 mg/kg
- Dog (n=3)
- Peg 400 solution (10mg/ml) with or without precipitation inhibitors

Legend:
- PEG 400 Fasted
- PEG 400 5% TPGS fasted
- PEG 400 5% PVP-VA Fasted
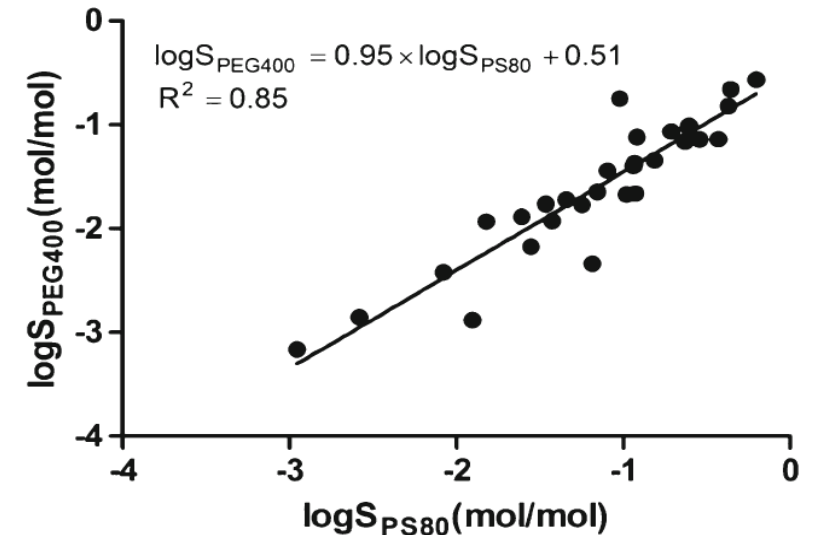- PEG 400 5%TPGS 5% PVP-VA Fasted

Y-axis: AUC (ng*h/ml)

DCS 2 -> Lipid based?

- LogP of API is important
  - In vivo partitioning and solubilisation ratio
    - **Log(SR)** = 2.27 + 0.75*LogP (e.g. fasted vs fed)
    - Risk of in vivo crash out (upon dilution with water)
- Modified dose number for lipids (caveat for pH)?

$$-D_n = \frac{Dose}{S_{FeSSIF} \times 500mL}$$

- PEG400 solubility as early predictor (high HLB)
  - Many lipids are ethoxylated
- API modification?
  - Lipophilic salts -> improved properties?
  - Prodrugs?

$logS_{PEG400} = 0.95 \times logS_{PS80} + 0.51$
$R^2 = 0.85$

Estimation of the increase in solubility of drugs as a function of bile salt concentration. J.B. Dressman et.al, 1996, Pharm. Res., Vol. 13, pp. 163-167
Computational prediction of drug solubility in lipid based formulation excipients. L.C. Persson et.al, 30, 2013, Pharm. Res., pp. 3225-3237

DCS 2 -> Lipid based?

- Can we obtain high solubility in lipid based vehicles?
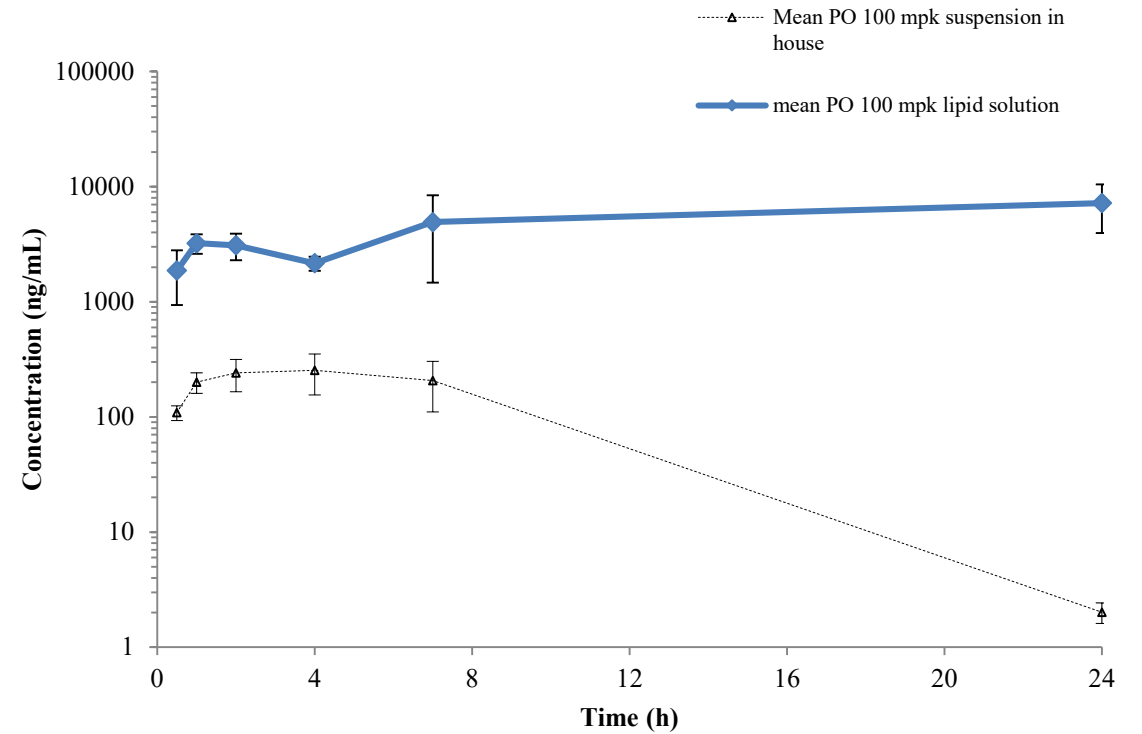
Long chain Triglycerides (LCT)		Safflower oil Castor oil Olive Oil Soybean oil Sesame oil
Long chain mono/diglycerides LC M/D		Maisine 35-1 Glycerol MonoOleate / Peceol
Medium chain triglycerides (MCT)		Miglyol 812 Captex 355 EP Labrafac CC/Labrafac™ Lipophile WL1349
Medium chain mono/di glycerides (MCM/D)		Imwitor 742 / Capmul MCM EP
Propylene glycol esters (water insoluble surfactant) low HLB		Lauroglycol 90 Capmul PG-12 Capryol 90 / Capmul PG-8 Capryol PGMC Softigen 767
Polyoxyglycerides (water dispersible surfactant) high HLB		Labrafil M1944CS / Acconon AKG-6 Labrafil M2125CS Labrafil M2130CS Gelucire 44/14 Acconon MC8-2 / Labrasol Kolliphor RH40 / Cremophor RH40 Kolliphor EL / Cremophor EL

Formulation using LFCS

Formulation type	Excipients	Composition	Characteristics	Dispersion (size)
Type I	Oils without surfactants (e.g. tri- ,di-and monoglycerides)	100%	Non-dispersible in aqueous media; Solubilisation in the GI upon rapid digestion	Non-dispersible in aqueous media
Type II	Oils Low HLB surfactants	40-80% 20-60%	SEDDS without water-soluble components; readily dispersible in GIT	Opaque emulsion (200 nm-10 μm)
Type III	Oils, High-HLB surfactants, Cosolvents	20-80% 20-50% 0-50%	SEDDS/SMEDDS with water-soluble excipients; lower extent of digestion	Clear or bluish ultrafine dispersion (10-200 nm)
Type IV	Low HLB surfactants High-HLB surfactants, Cosolvents	0-20% 30-80% 0-50%	Formulation disperses typically to form a micellar solution	Transparent nano systems (2-10 nm)

Lipid formulation for oral administration of drugs: non-emulsifying, self-emulsifying and self-microemulsifying drug delivery systems. **CW, Pouton.** Eur. J. Pharm., Vol. 11, pp. Supplement 2: S93-S98.
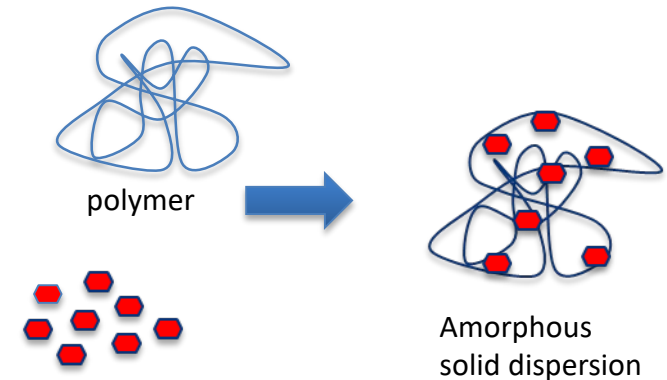
Illustration in rat

- Rat PO
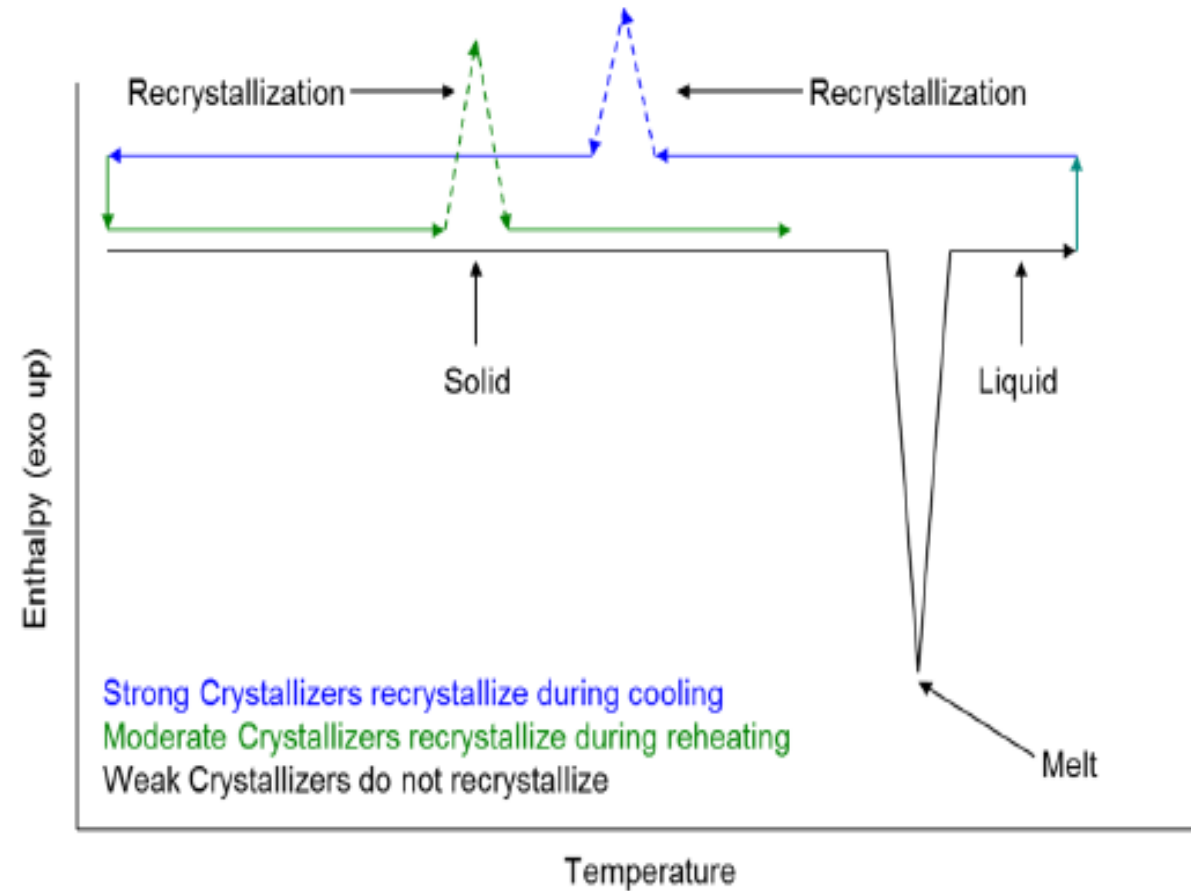- Crystallline suspension vs solution
- Type IV lipid based solution

DCS 2 -> ASD?

- Amorphous state -> increasing the apparent solubility
- Thermodynamically unstable
- Early predictors for kinetic stability
  - Tg of API, Tm
  - Glass forming ability of API
  - Precipitation behaviour of API
  - Tg as function of water content of ASD
  - DVS curve of amorphous API, ASD
- Manufacturing aspects
  - Solubility in organic solvents
 - Melting point, thermal stability

polymer

Amorphous
solid dispersion

Glass forming ability of the API

Assess feasibilty of ASD formulation by means of a DSC experiment

A classification system to assess the crystallization tendency of organic molecules from undercooled melts. **J.A., Baird.** 99, 2010, J. Pharm. Sci., pp. 3787-3806.
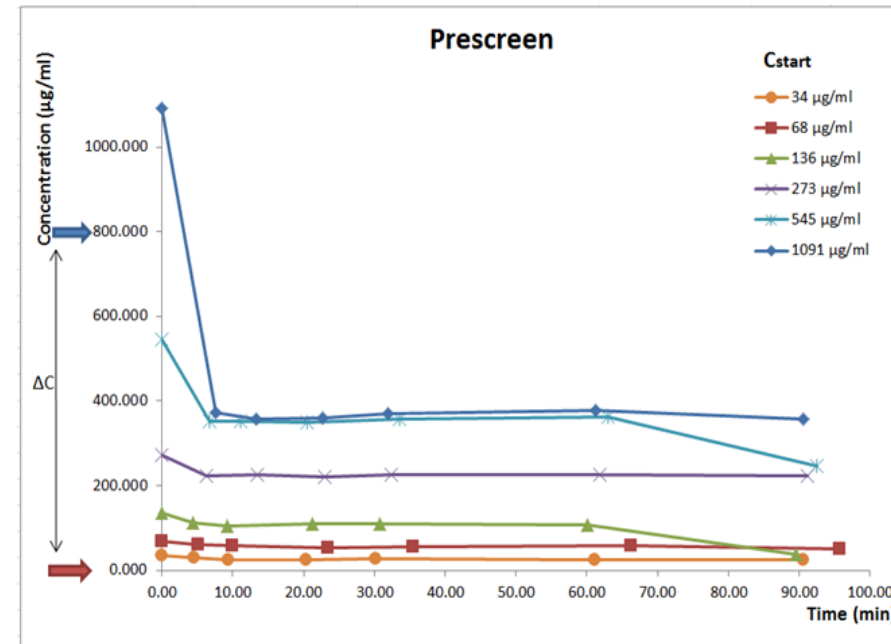
Precipitation behaviour of API

Precipitation curves via solvent shift
- E.g. Solvent shift to FaSSIF @ 37°C
- Prescreen to determine the right supersaturation level to enable screening of precipitation inhibitors
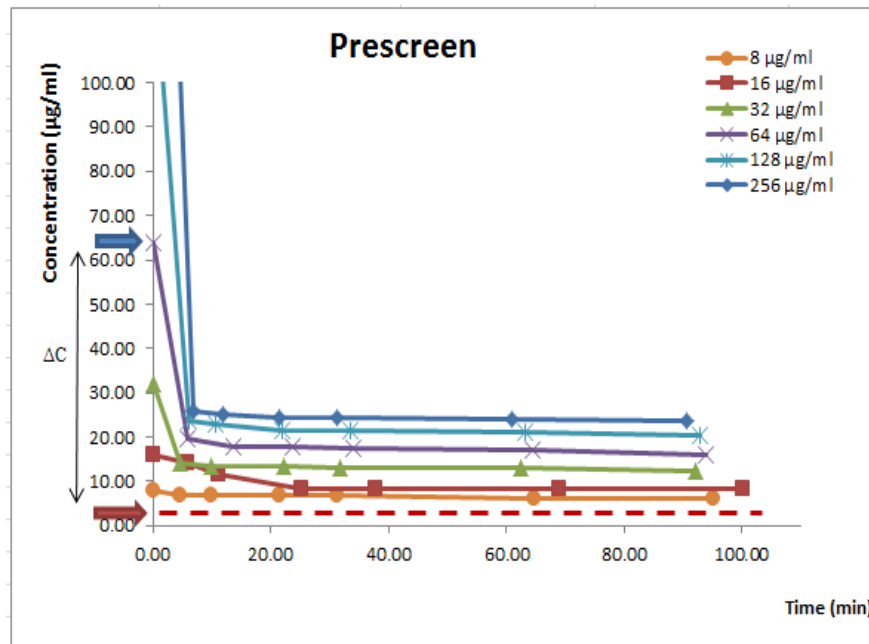

High supersaturations not feasible

High supersaturations are reached

ASD formation

- Conversion of crystalline to amorphous state

- Amorphous state can be stabilized by polymers, e.g.:

  - ## Cellulose based – enteric polymers

  - ## Polyacrylic acid based – enteric polymers

  - ## Cellulose based water soluble polymers

  - ## Polyvinylpyrrolidone based water soluble polymers

polymer

API

Amorphous solid dispersion
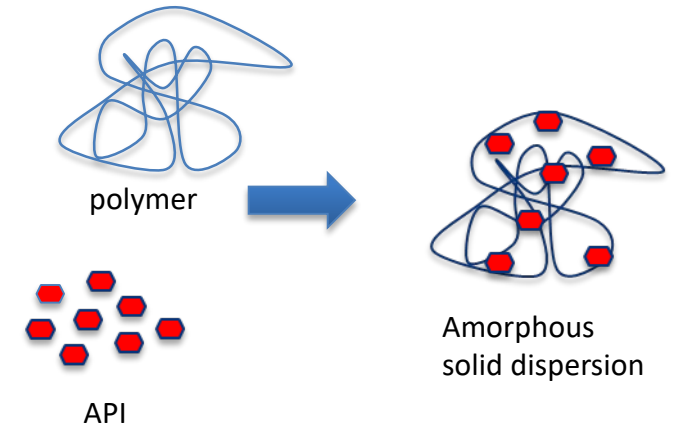
ASD's and moisture

- DVS provides data on water sorption behaviour.
  - $T_{g,dispersion,100\%RH} = T_{g,dispersion,dry} - 10\ °C \times$ extrapolated % wt. gain @ 100% RH
- Can be used to judge stability of aqueous suspensions of ASD's – e.g. with HPMCAS (enteric polymer)
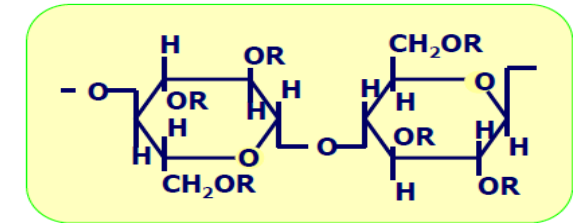
CAS; 71138-97-1, listed in JPE, USP/NF

R= -H, -CH$_3$, -COCH$_3$,
-COCH$_2$CH$_2$COOH
-CH$_2$CH(OH)CH$_3$,
-CH$_2$CH(CH$_3$)OCOCH$_3$,
-CH$_2$CH(CH$_3$)OCOCH$_2$CH$_2$COOH

Shin-Etsu company brochure

Effects of sorbed water on the crystallization of indomethacin from the amorphous state. **Andronis, Vlassios et al.**
1997, J. Pharm. Sci., Vol. 86, pp. 346-351.

ASD suspensions

- For preclinical dosing (rodents)
- Enteric polymer based
- Non-aqueous vehicles (e.g. vegetable oil) can be considered for water soluble polymers

Evaluation in mouse
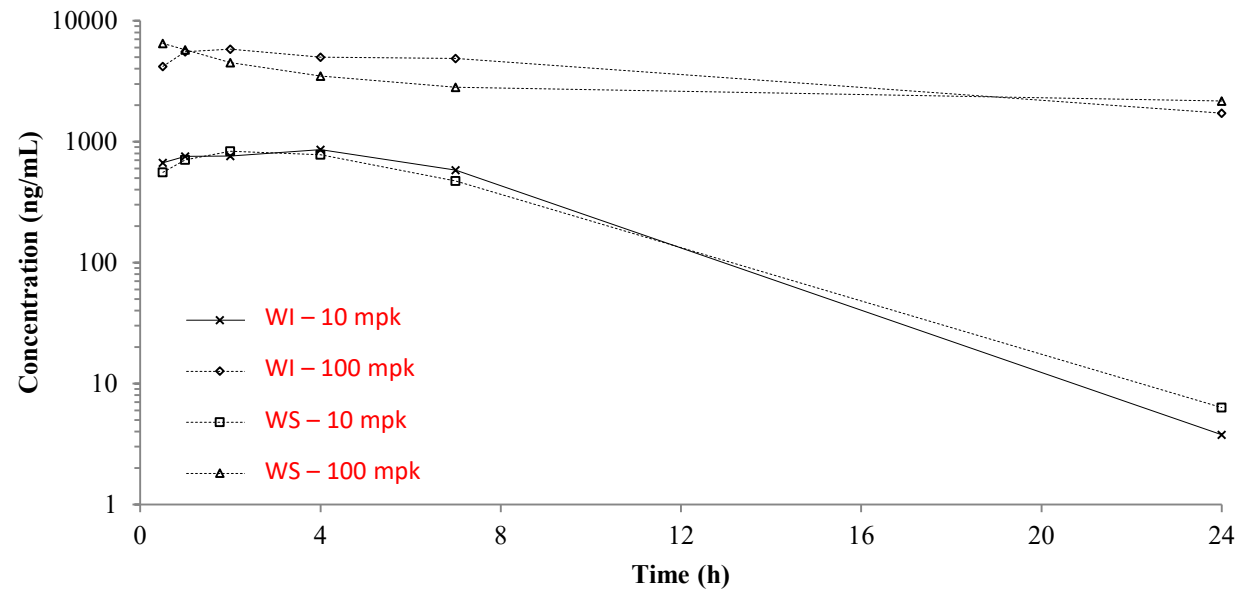
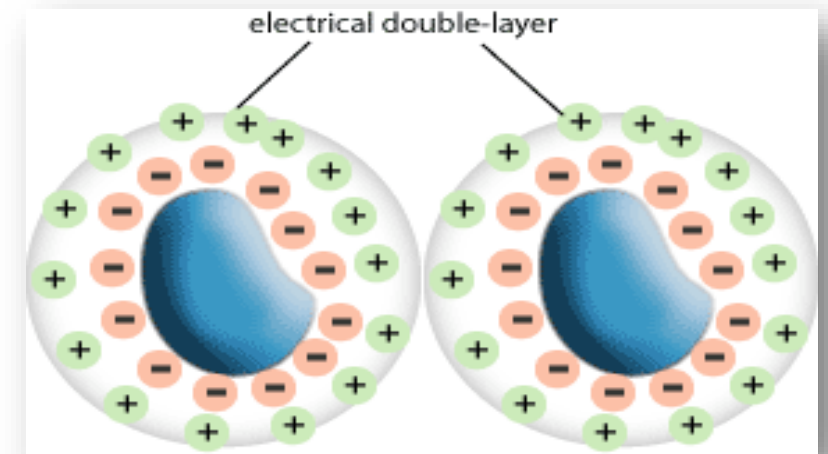HPMC **in oil** vs HPMCAS in aqua at 10 and 100 mpk

Nanosuspensions

- Unstable system: prone to particle size growth

- Therefore needs:
  - Poor solubility in medium of interest
  - Temperature control
  - Selection of suitable stabilizer

Zhaohui, Wu et al, Shape control of inorganic nanoparticles from solution, nanoscale, 2016, 8, 1237
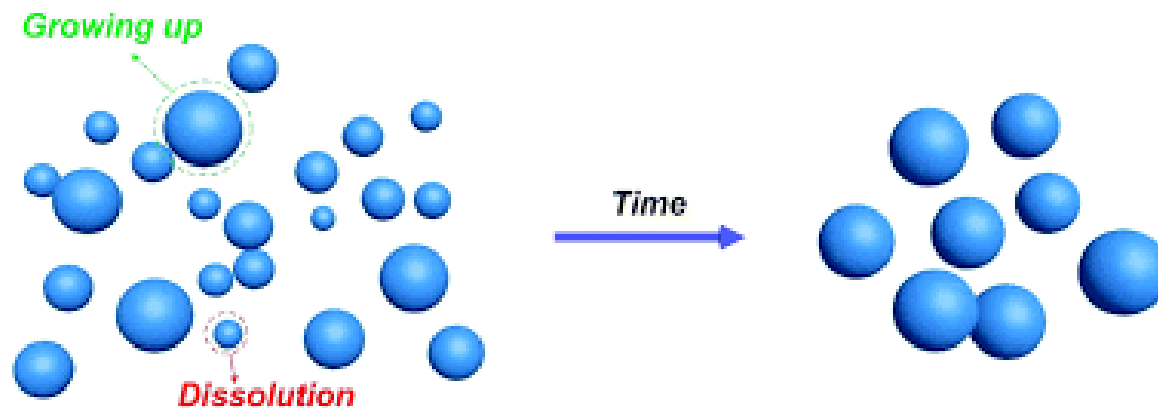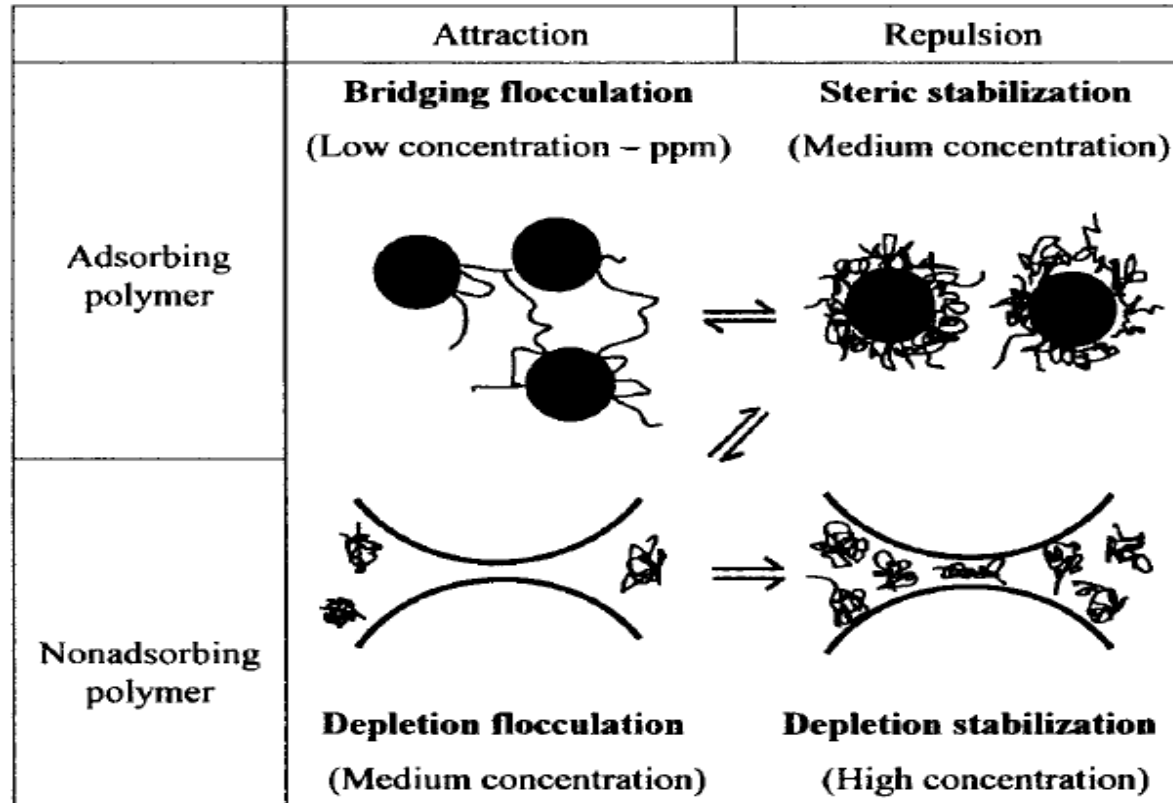
Stabiliser strategies: Electrostatic stabilisation

- Quid compound pKa?

  - Using buffer in the right pH range to impart charge on particle surface

- Adding a charged surfactant

  - E.g. DOSS (oral/parenteral) or SLS (oral only)

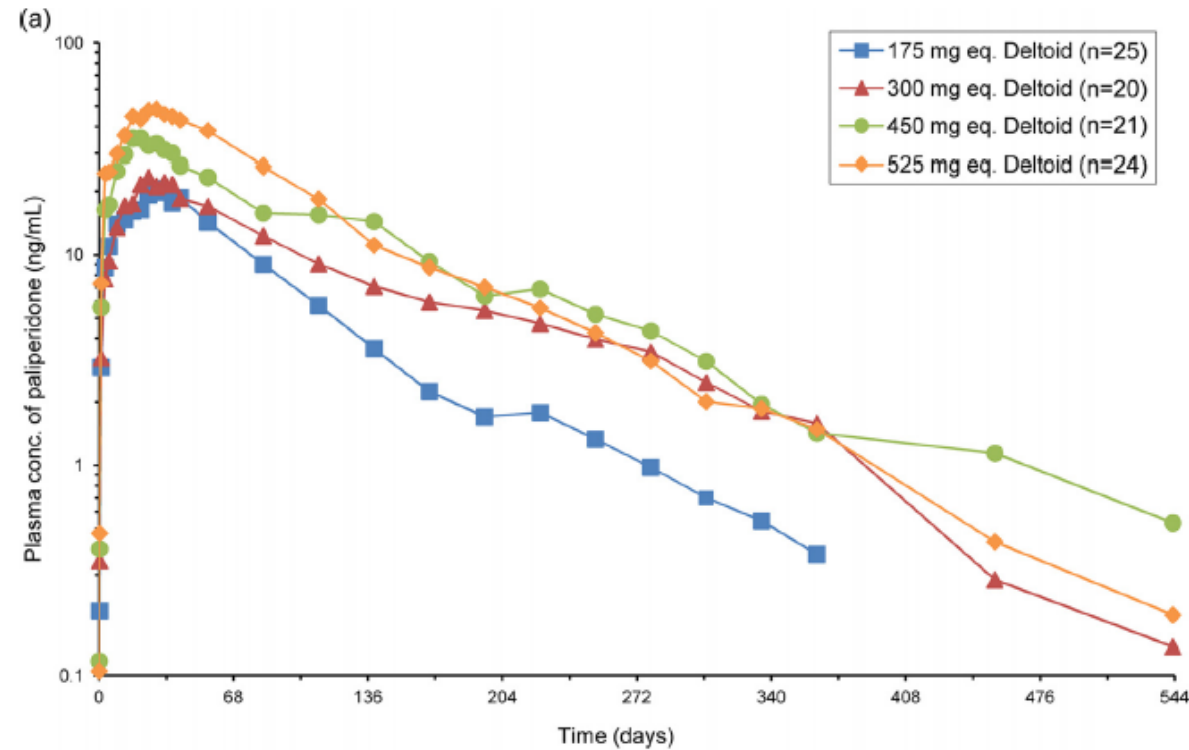 - Sodium deoxycholate: pH should be > 7 (pKa 6.5)

electrical double-layer

Stabilizer strategies: steric / depletion stabilisation

	Attraction	Repulsion
Adsorbing polymer	**Bridging flocculation** (Low concentration – ppm)	**Steric stabilization** (Medium concentration)
Nonadsorbing polymer	**Depletion flocculation** (Medium concentration)	**Depletion stabilization** (High concentration)

Adsorbing: e.g. HPMC, poloxamer
Non adsorbing: PEG4000

Schramm, L.L. Colloid stability - section 5.3. *Emulsions, foams and suspensions: fundamentals and applications.* s.l. : Wiley-VCH, 2005.

Invega trinza - PK elimination profile over time

Ravenstijn et al., 2016 J.ClinPharm. 2016, 56(3) 330–339

Conclusions

- Look at your API phys-chem profile
- Look at your formulation options
- Look for a match ☺
- Never (gonna) give (you) up!