SimulationsPlus

BO Session C : Modeling approaches to integrate dissolution in PBBMs

M-CERSI workshop

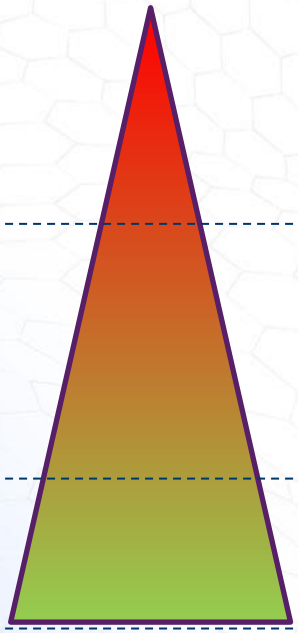
2023 August 29

Outline

- Different models to fit dissolution
  - Assumptions for each model
  - Use for IR formulation fitting
  - Main equations
- Important drivers of dissolution
  - How DS and DP CQAs can influence shape of profile
- How to choose a dissolution method and how to choose fitting strategy ?
- Take home messages

Dissolution integration: How methods compare

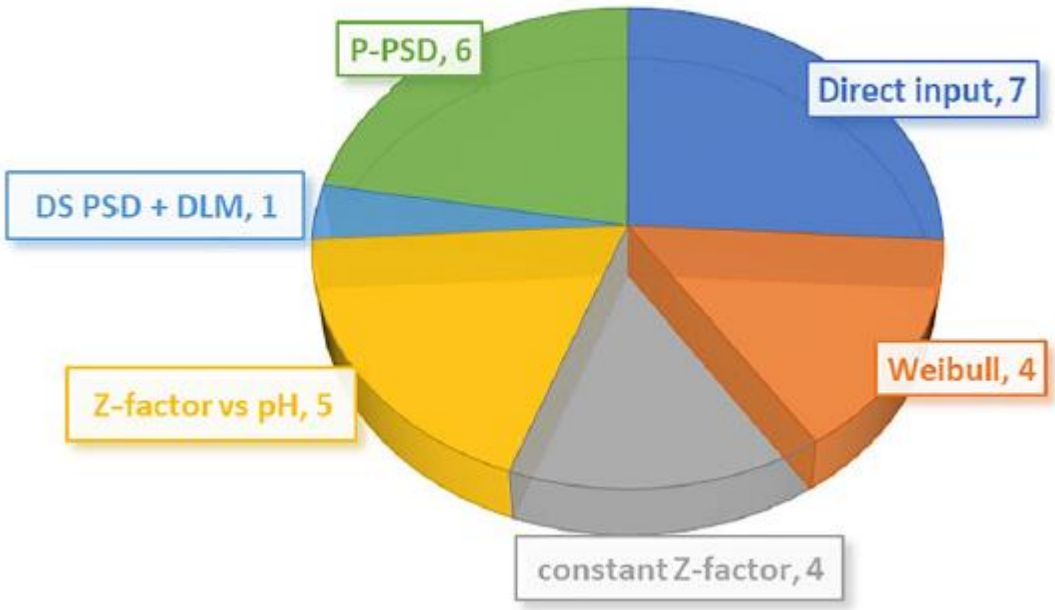
Less Mechanistic

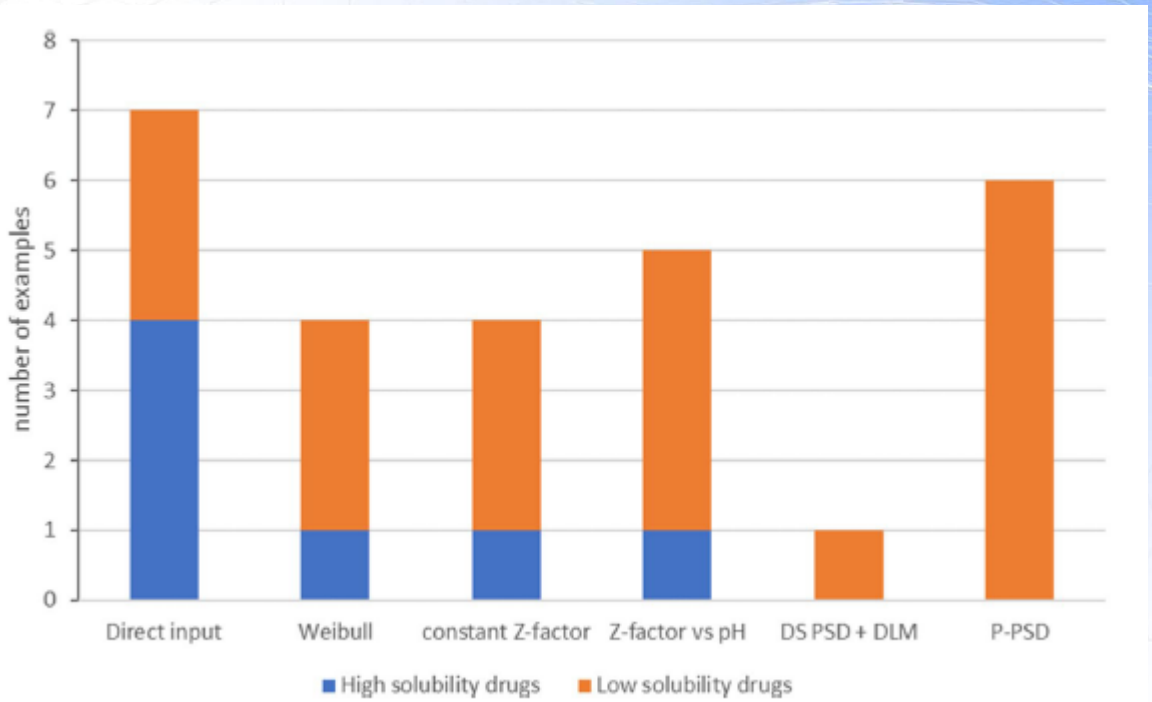


More mechanistic

	Assumptions/conditions of use
Direct input	Solubility/dose/volume is not limiting dissolution, hydrodynamics in vitro is not impacting release Formulation controls release (e.g. MR or eroding formulations)
Weibull fit	
Z-factor vs pH	Z-factor should not depend on pH, Check inputs if it does. Could mask issue with pH-dependent wettability. Cannot use with surfactants since lumped factor
Fixed z-factor	
P-PSD	A DP batch specific 1-10 bin PSD which represents the DS particles available for dissolution after product disintegration

IR Dissolution integration: literature



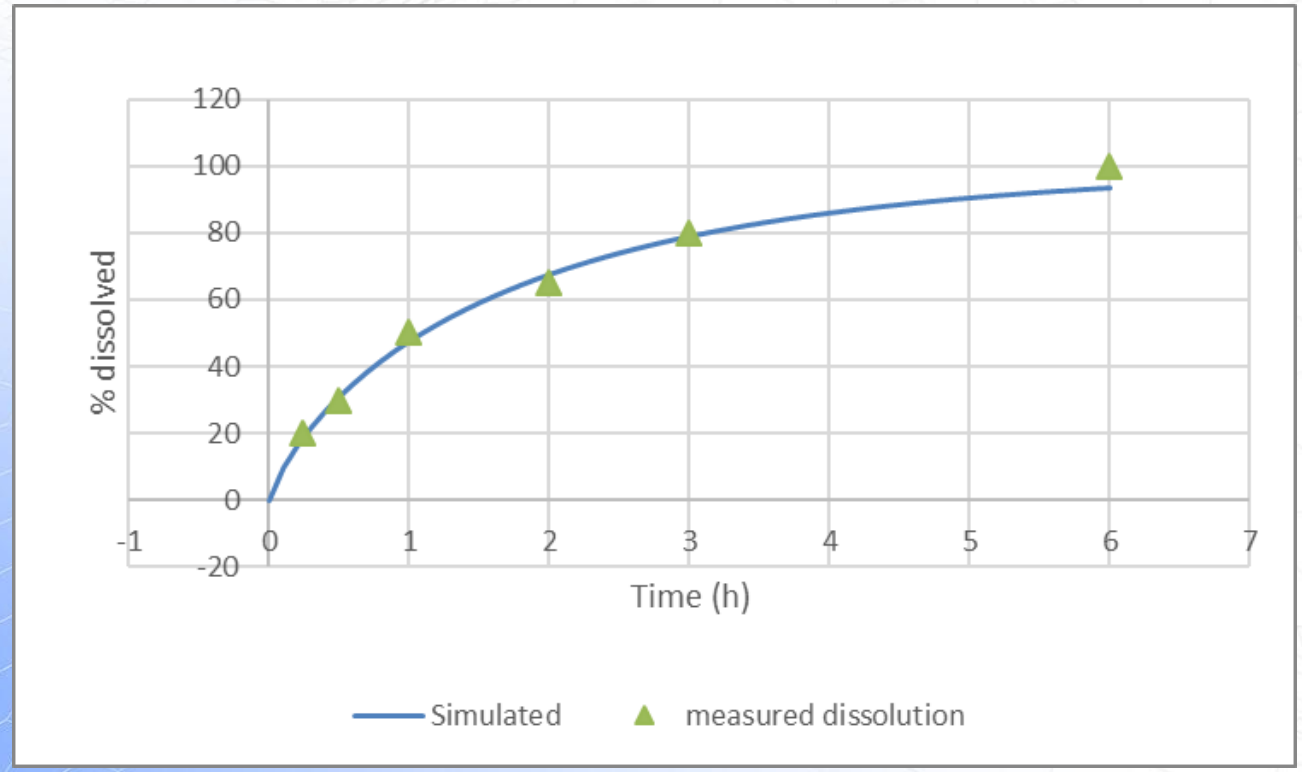


(1) Anand, O.; Pepin, X. J. H.; Kolhatkar, V.; Seo, P. The Use of Physiologically Based Pharmacokinetic Analyses—in Biopharmaceutics Applications - Regulatory and Industry Perspectives. *Pharmaceutical Research* ***2022. DOI: 10.1007/s11095-022-03280-4.***

Weibull equation

>V9.7 : up to three phase-Weibull

$$P\%(t) = P_{max} \times \left(1 - \exp\left(-\frac{(t - t_{lag})^b}{A}\right)\right)$$



Max % dissolved	100
Lag time (h)	0
A parameter	1.54986
b parameter	0.799337
t1/2diss (min)	66
t80%diss (min)	188

Simple to fit to dissolution data
With 3 phases all profiles matched
Fill missing points

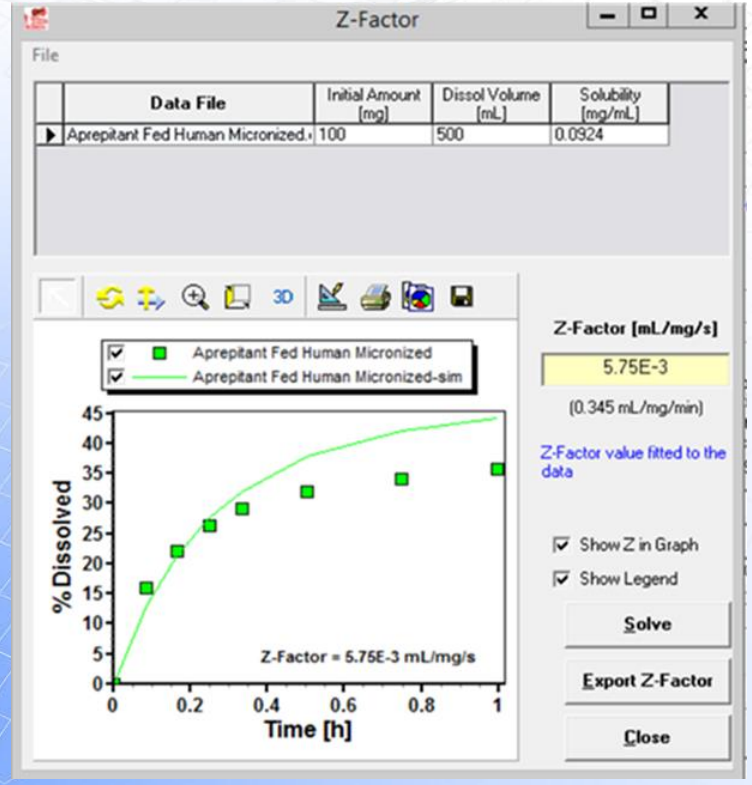
Is not mechanistic.
Imposes release over time

Z-factor-Takano

Takano, R., et al. (2006). "Oral absorption of poorly water-soluble drugs: computer simulation of fraction absorbed in humans from a miniscale dissolution test." Pharm Res 23(6): 1144-1156.

$$\frac{dX_{d,vitro}(t)}{dt} = \frac{3D}{\rho h r_0} \times X_{0,s,vitro} \times \left(\frac{X_{s,vitro}(t)}{X_{0,s,vitro}}\right)^{2/3} \times \left(C_s - \frac{X_{d,vitro}(t)}{V_{vitro}}\right)$$

$$= z \times X_{0,s,vitro} \times \left(X_{s,vitro} \times \left(\frac{X_{s,vitro}(t)}{X_{0,s,vitro}}\right)^{2/3} \times \left(C_s - \frac{X_{d,vitro}(t)}{V_{vitro}}\right)\right)$$



$$z = \frac{3D}{\rho h r_0}$$

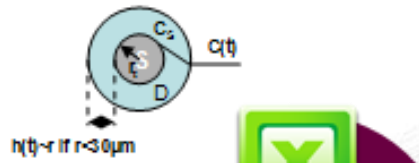
Z groups particle size, diffusion and thickness of UWL and drug density.

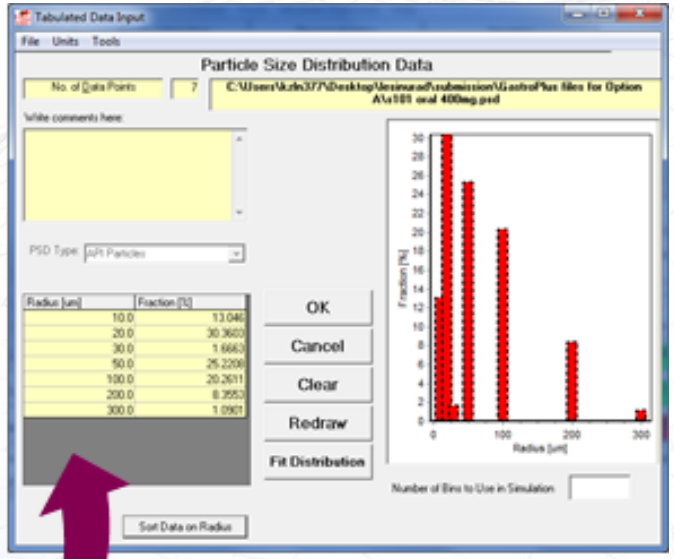
Simple to fit to dissolution data
Mechanistic (dose, pH, volume)

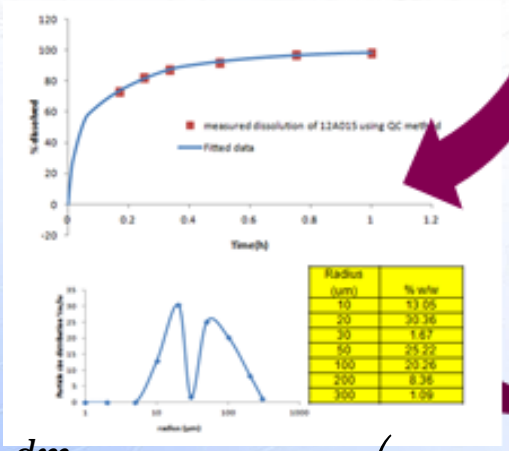
May not match all profiles (multimodal)

Cannot differentiate diffusion of micelles from free drug
Cannot integrate hydrodynamics over time
Particle size constant (OK for early stages)

P-PSD : Different tools available







$$\frac{dm_{solid}}{dt} = -A(t) \times \left(f_u \times \frac{D_u}{h_u(t)} + \frac{1 - f_u}{f_u} \times \frac{D_b}{h_b(t)} \right) \times \left(C_{S,u} - C_u(t) \right)$$

$$f_u = \frac{C_u(t)}{C(t)} \qquad \frac{h_b}{h_u} = \sqrt[3]{\frac{D_b}{D_u}}$$

1- Use of one dissolution data to extract the P-PSD

2- Verification that P-PSD is predictive of other dissolution conditions for same batch

3- Use of P-PSD as input in PBPK model

Simple to fit to dissolution data
Mechanistic (dose, pH, volume, surfactant)

Basic model comprises hydrodynamics with Johnson assumption

a: https://doi.org/10.1016/j.ejpb.2019.07.014

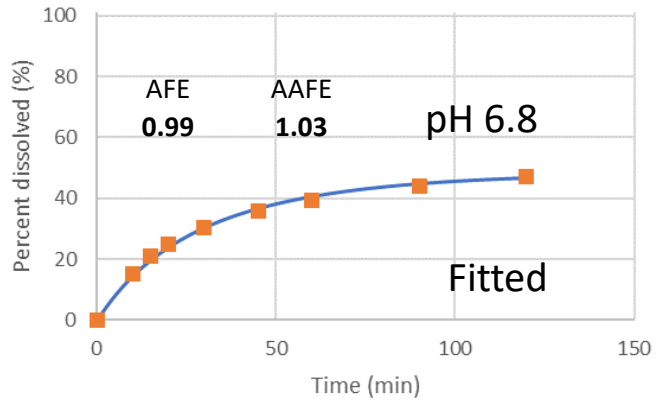
Commonalities and differences in dissolution fitting

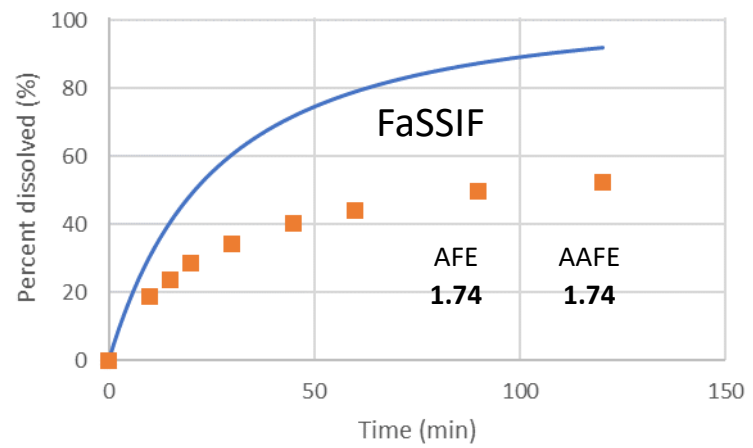
Method	Equation	Comments	Reference
Noyes-Whitney (1897)	$\frac{dm_{solid}}{dt} = -A(t)\frac{D}{h} \times (C_S - C(t))$	UWL assumption around particles	https://www.ncbi.nlm.nih.gov/pubmed/16920290
Johnson (1989)	$\frac{dm_{solid}}{dt} = -\frac{D(1+2s)}{\rho h r_t s} \times (C_S - C(t)) \times m_{solid,t}$	Particles can be cylindrical	https://doi.org/10.1016/0378-5173(89)90069-0
Wang Flanagan (1999)	$\frac{dm_{solid}}{dt} = -\frac{3D}{\rho} \times \frac{1}{r_t} \times \left(\frac{1}{r_t} + \frac{1}{h}\right)(C_S - C(t)) \times m_{solid,t}$	Spherical particles only	https://doi.org/10.1021/js980236p
Takano (2006)	$\frac{dm_{solid}}{dt} = -\frac{3D}{\rho h r} \times m_{solid,0} \times \left(\frac{m_{solid,t}}{m_{solid,0}}\right)^{2/3} \times (C_S - C(t))$	Particle size constant during dissolution Lumped parameter which does not differentiate micelles	https://www.ncbi.nlm.nih.gov/pubmed/16715363
Gamsiz (2010)	$\frac{dm_{solid}}{dt} = -\frac{A(t)}{h} \times \left[D_u\left(C_{S,u} - C_u(t)\right) + D_b\left(C_{S,b} - C_b(t)\right)\right]$	Shrinking particles during dissolution Flux of unbound and bound drug explicit but same UWL	https://www.ncbi.nlm.nih.gov/pubmed/20963629
Pepin (2019)	$\frac{dm_{solid}}{dt} = -A(t) \times \left(f_u \times \frac{D_u}{h_u(t)} + \frac{1-f_u}{f_u} \times \frac{D_b}{h_b(t)}\right) \times \left(C_{S,u} - C_u(t)\right)$ $f_u = \frac{C_u(t)}{C(t)}$ $\quad \frac{h_b}{h_u} = \sqrt[3]{\frac{D_b}{D_u}}$	Shrinking particles Immediate partitioning of drugs to micelles at the surface Flux of unbound and bound drug explicit Different UWL for free and micelle bound drug Shrinking particles during dissolution	https://doi.org/10.1016/j.ejpb.2019.07.014

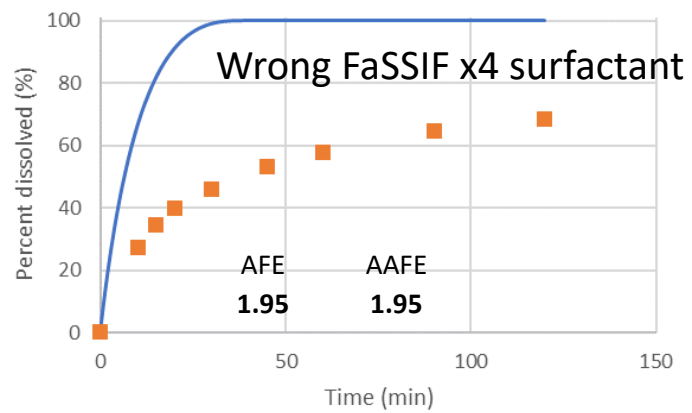
Z-factor vs P-PSD for surfactant media

Acalabrutinib capsule batch L0505009

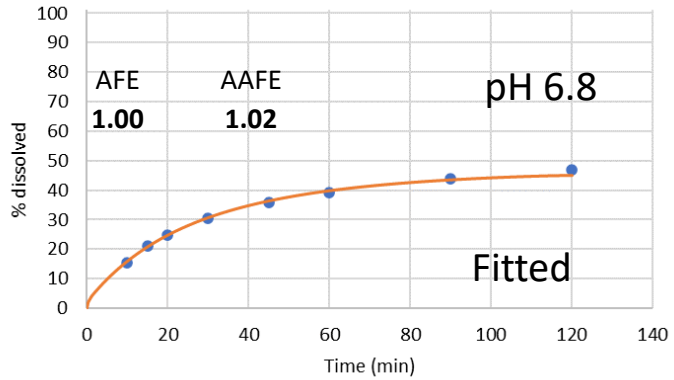
Z-factor

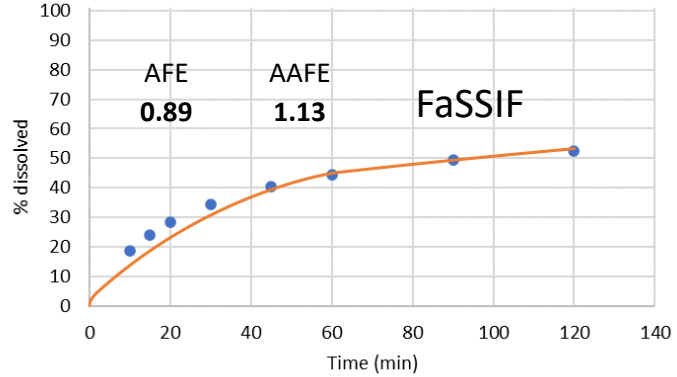


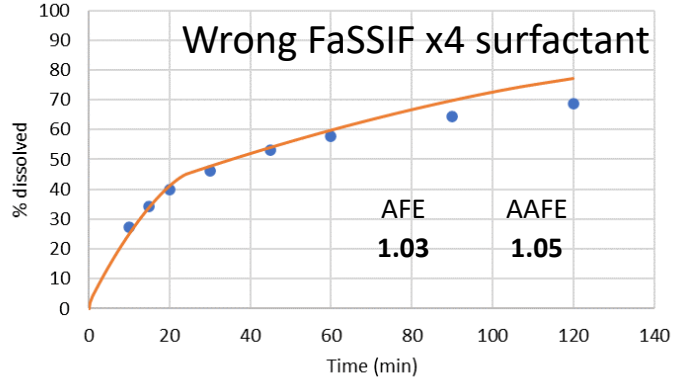




P-PSD







Total apparent solubility in surfactant media + Z-factor fitted without surfactant → over-estimation of the dissolution rate

Diffusion coefficient is part of Z-factor but changes with medium micelle concentration

Outline

- Different models to fit dissolution
  - Assumptions for each model
  - Use for IR formulation fitting
  - Main equations

- Important drivers of dissolution
  - How DS and DP CQAs can influence shape of profile

- How to choose a dissolution method and how to choose fitting strategy ?

- Take home messages

Important drivers of Dissolution

Dissolution happens when there is a different chemical potential between the drug as a solid and the drug in solution = dynamics

$$\frac{dm_{solid}}{dt} = -A(t)\frac{D}{h} \times (C_S - C(t))$$

1897-Noyes-Whitney
https://www.ncbi.nlm.nih.gov/pubmed/16920290

Mass variation ($kg.s^{-1}$)

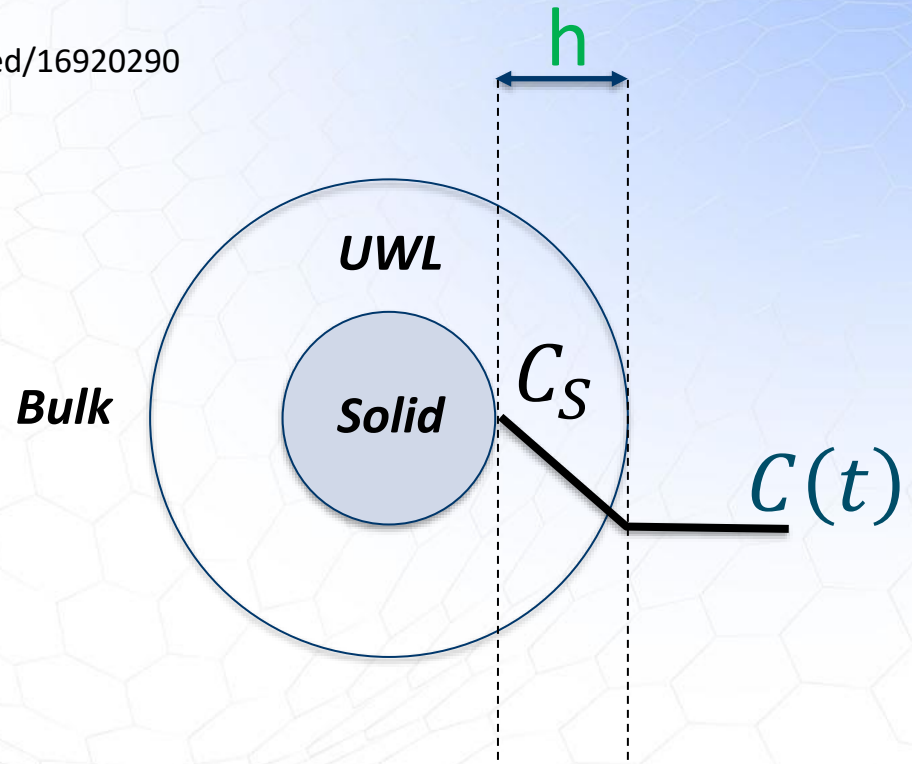
Surface area available for dissolution (m^2)

Diffusion coefficient ($m^2.s^{-1}$)

Thickness of the unstirred water layer (m)

Drug solubility ($kg.m^{-3}$)

Drug concentration in the bulk of the medium ($kg.m^{-3}$)



$A(t)$ Surface are available for dissolution

$$\frac{dm_{solid}}{dt} = -A(t)\frac{D}{h} \times (C_S - C(t))$$

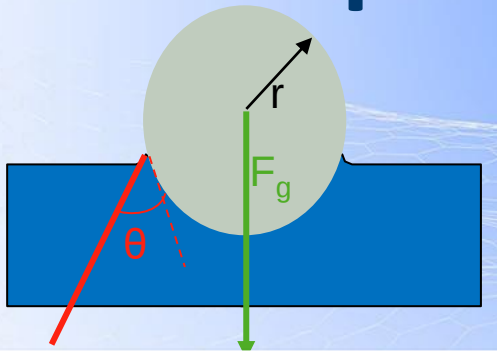
What surface to consider

- Capsule opening, tablet disintegration → Time correct data prior to fitting
- Wettability : pre-requisite
- → Excipients play a role to help the wetting (wicking and wetting agents help, lubricants or lipidic matrixes can delay wetting), wet granulation can improve wettability
- During dissolution surface changes with time as particles shrink
- Manufacturing process plays a role
  - Attrition can create more surface
  - Over-granulation or compression can “hide” drug inside granules

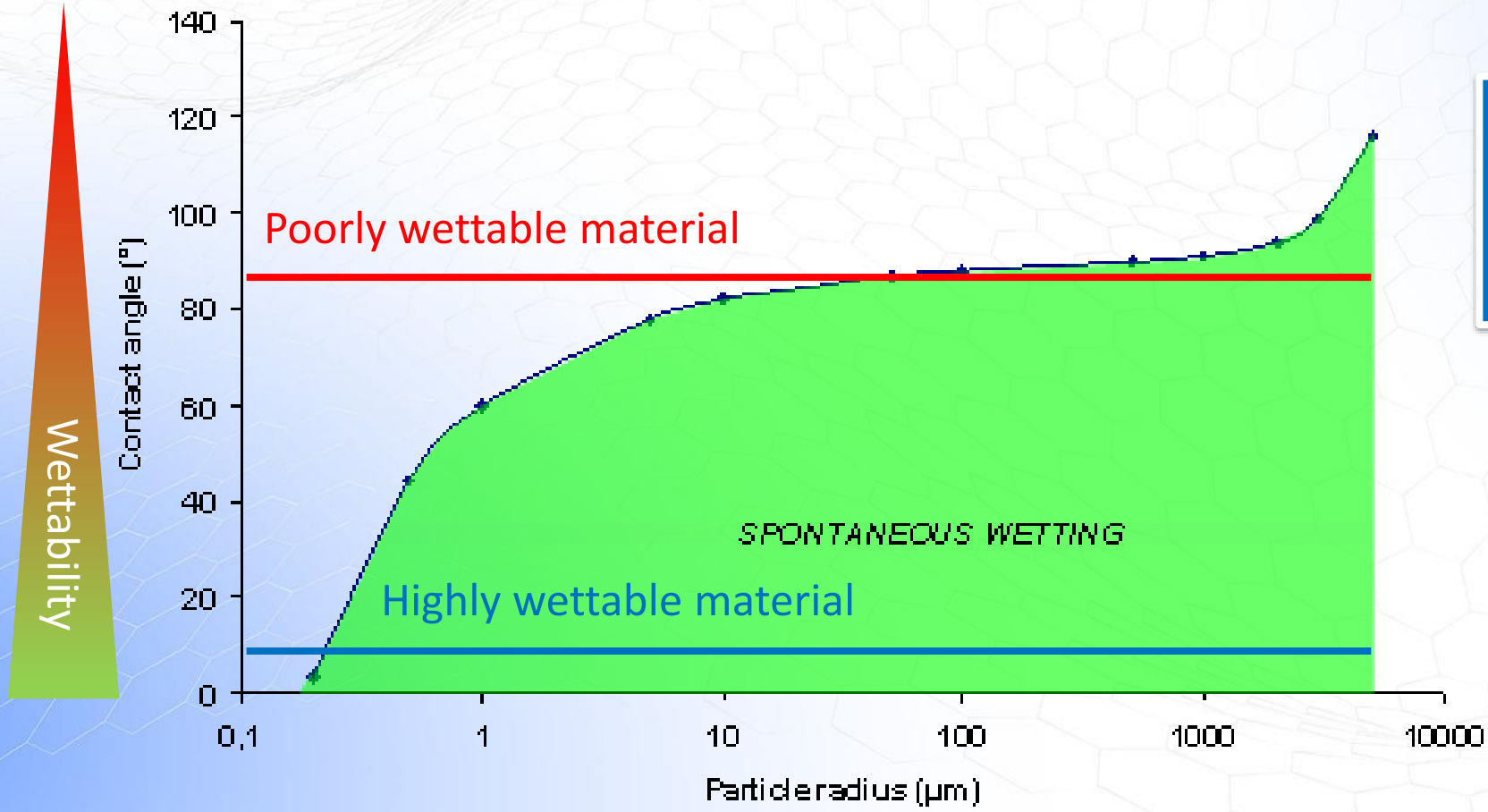
Difficult to predict DS particle size “available” for dissolution inside most solid dosage forms

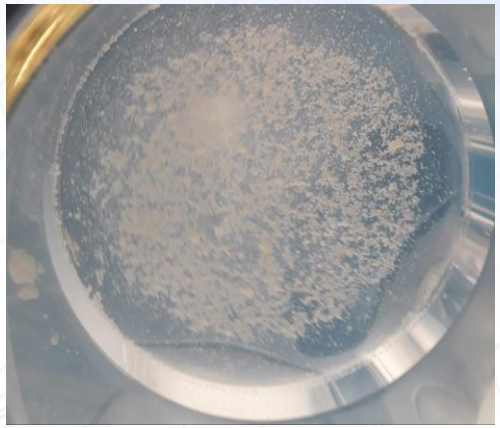
Wettability of drugs : not all particles are equal !

Limiting contact angle for spherical particle spontaneous wetting due to gravitation. ρS = 1.2 g/mL, ρL = 1 g/mL, ηL = 1 mPa.s

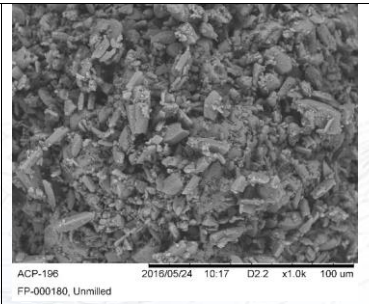
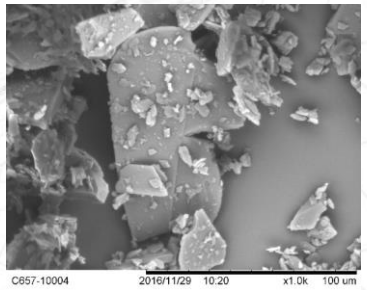
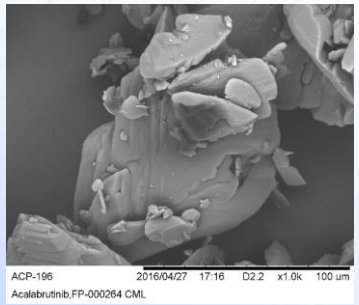
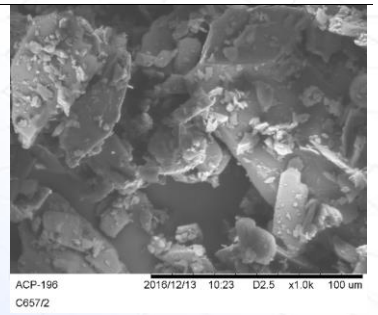
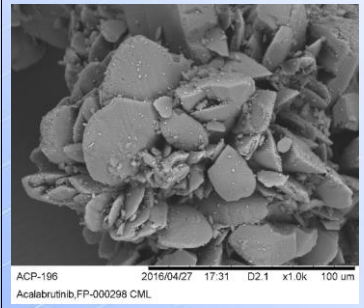
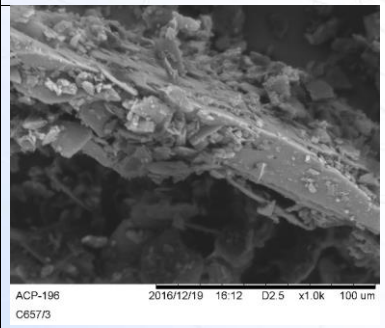


Size of particles determines spontaneous wetting
Small particles wet less easily than large particles

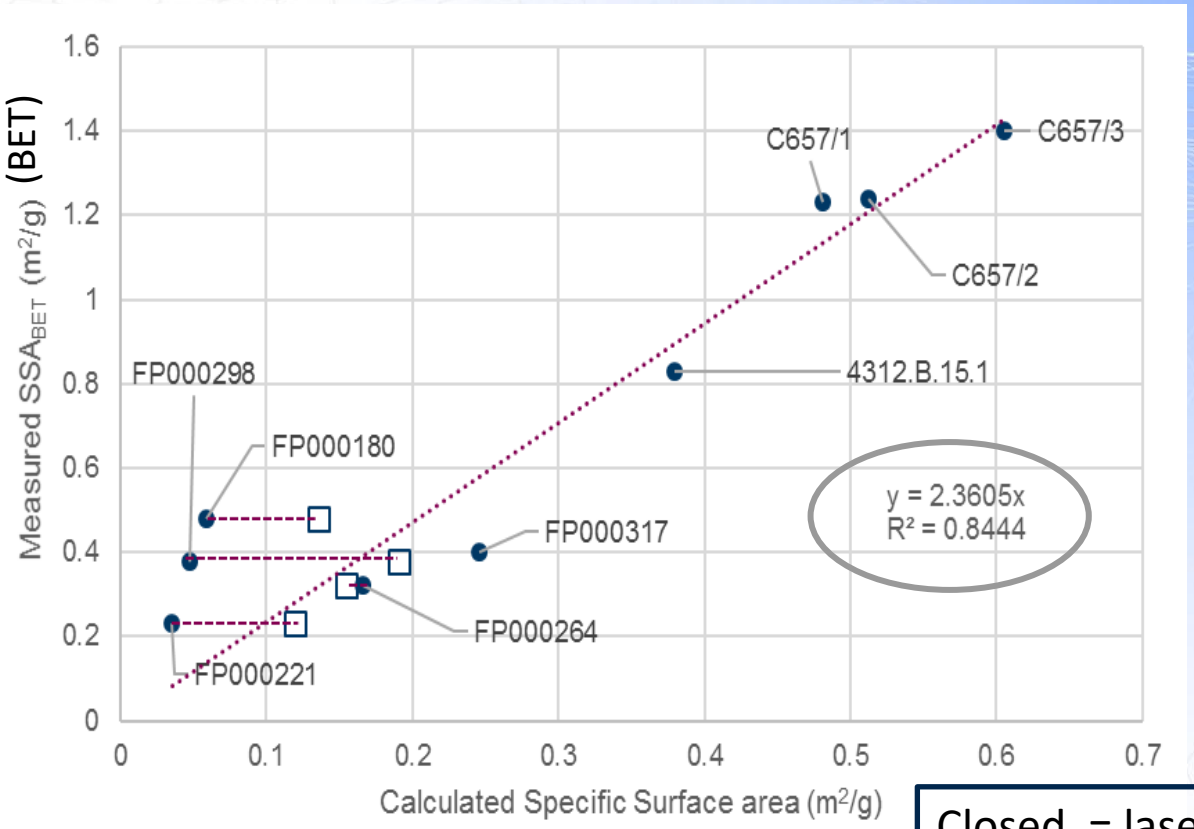




Different measures of drug surface area

FP000180		C657/1	
FP000264		C657/2	
FP000298		C657/3	

Laser under-estimates surface area esp. if particles are aggregated

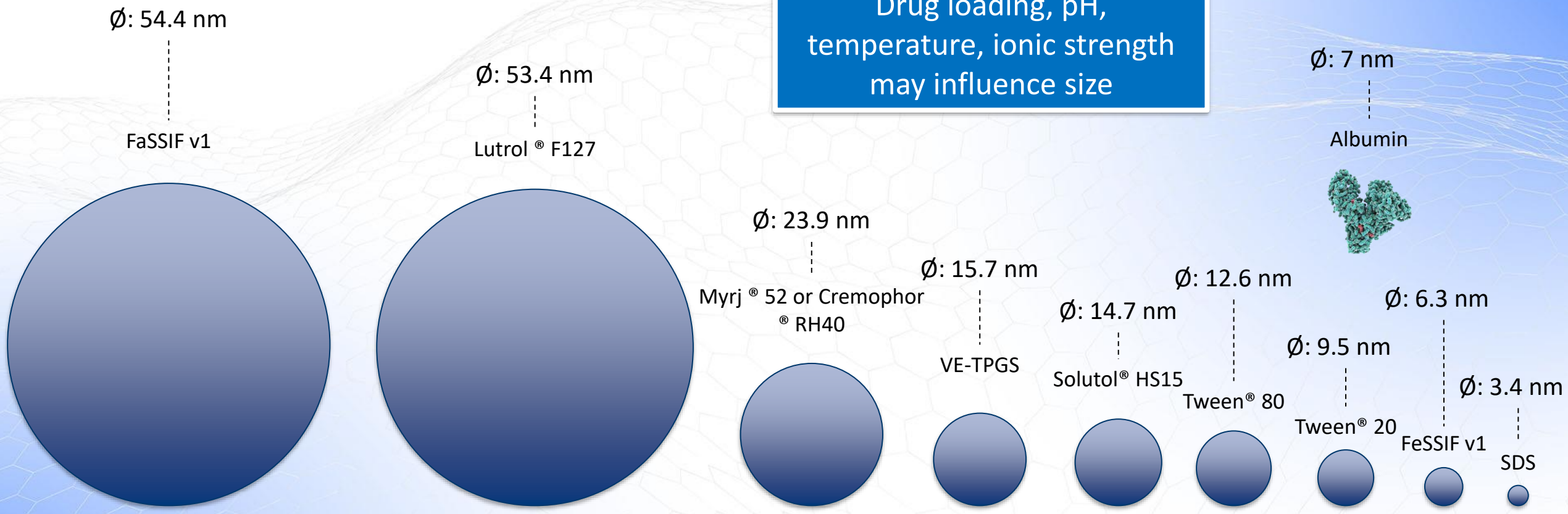


P-PSD shows "more" DS surface than laser diffraction

Closed = laser
Open = P-PSD (dissolution)

Diffusion Coefficient – in vitro and in vivo micelles

Drug loading, pH, temperature, ionic strength may influence size

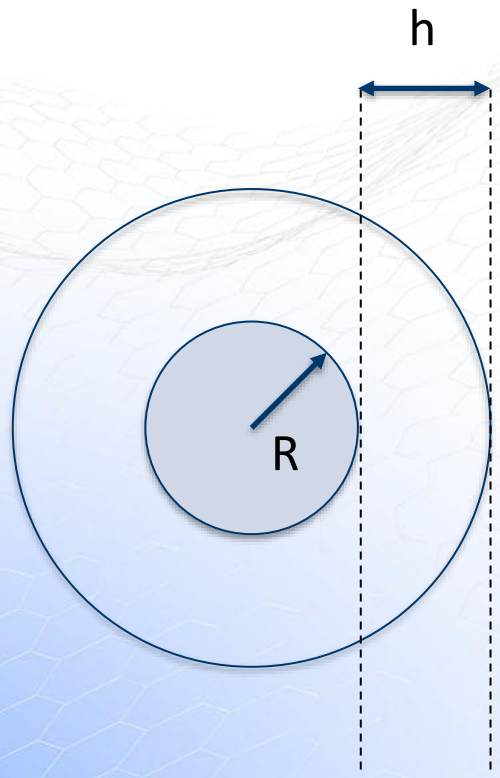


1. Nayem, J., et al., Micellar Morphology of Polysorbate 20 and 80 and Their Ester Fractions in Solution via Small-Angle Neutron Scattering. Journal of Pharmaceutical Sciences, 2020. 109(4): p. 1498-1508.
2. Okazaki, A., T. Mano, and K. Sugano, *Theoretical dissolution model of poly-disperse drug particles in biorelevant media. Journal of pharmaceutical sciences, 2008. 97(5): p. 1843-52.*
3. *Hammouda, B., Temperature Effect on the Nanostructure of SDS Micelles in Water. Journal of research of the National Institute of Standards and Technology, 2013. 118: p. 151-67.*
4. *Feng, S., et al., Predictive Modeling of Micellar Solubilization by Single and Mixed Nonionic Surfactants. J Pharm Sci, 2018. 107(8): p. 2079-2090.*

1.1 nm Ø unbound drug diffuses ≈ 50 or 4 times faster than when bound to FaSSIF or SDS respectively

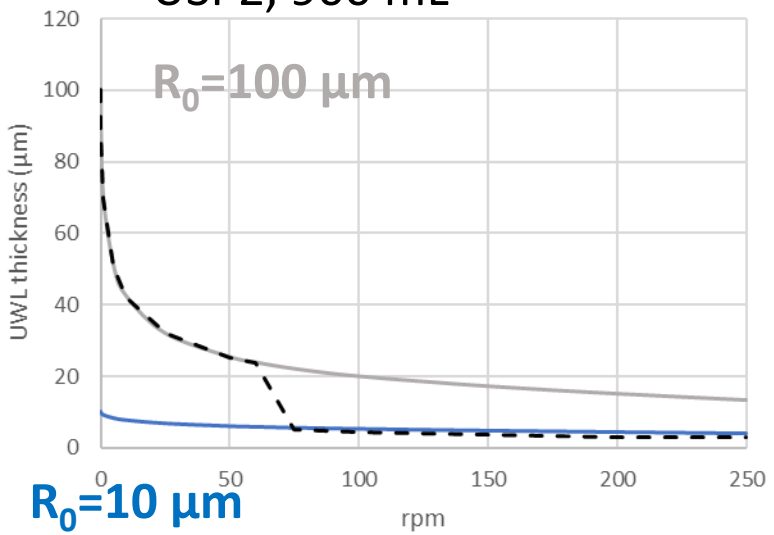
h Thickness of the unstirred water layer

$$\frac{dm_{solid}}{dt} = -A(t)\frac{D}{h} \times \left(C_S - C(t)\right)$$

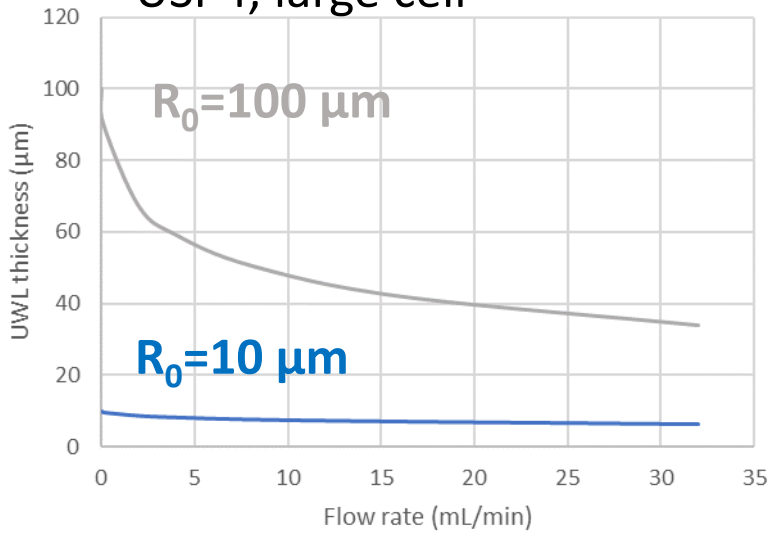


Default assumption h=Rs up to 30 µm then constant if Rs> 30 µm = low agitation conditions representative of in vivo hydrodynamics

USP2, 900 mL



USP4, large cell

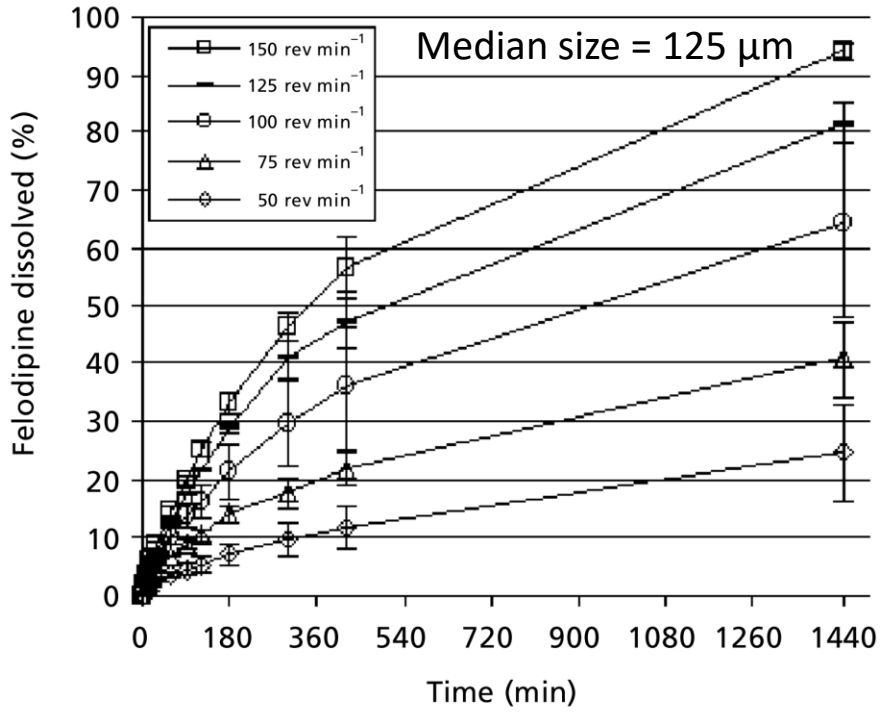


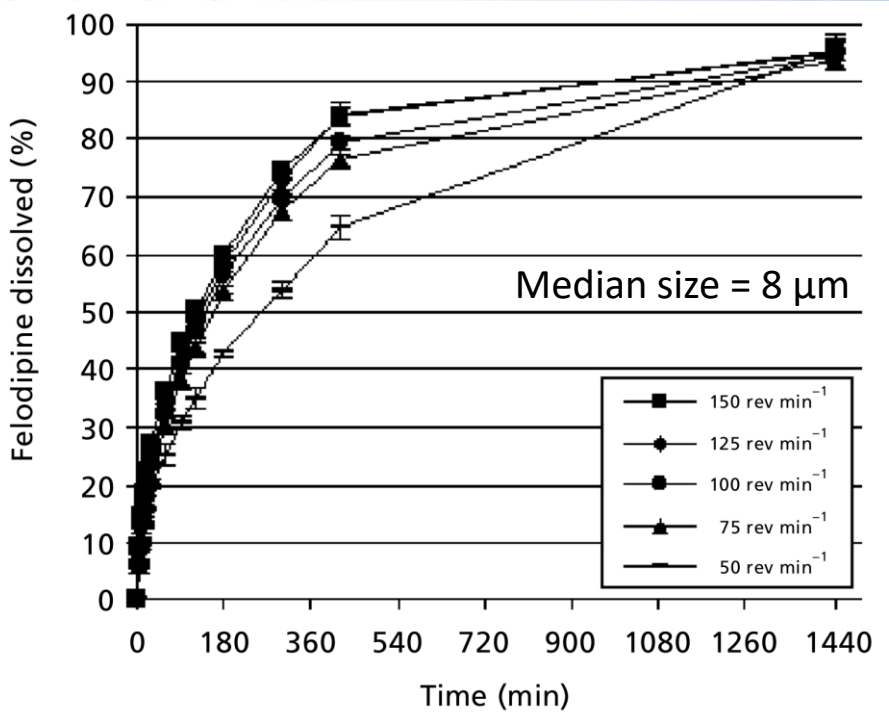
Hydrodynamics more important for large particles, e.g. pellets or eroding tablets

h Thickness of the unstirred water layer

$$\frac{dm_{solid}}{dt} = -A(t)\frac{D}{h} \times \left(C_S - C(t)\right)$$

10 mg felodipine suspension dissolution in USP2. 500mL simulated canine chyme [A]





Fitting (or prediction) of coarse particle dissolution needs to integrate variable UWL as function of agitation

Check that agitation does not influence dissolution prior to fitting with any other model

A: Scholz, A., et al., Can the USP paddle method be used to represent in-vivo hydrodynamics? J Pharm Pharmacol, 2003. 55(4): p. 443-51.

C_S Drug solubility

Surface pH: why is it important !

$$\frac{dm_{solid}}{dt} = -A(t)\frac{D}{h} \times (C_S - C(t))$$

Dissolution rate is influenced by the micro-environmental pH (surface pH) for drugs that ionize

- Below max pKa for bases
- Above min pKa for acids

In the bulk the pH is not changed (for large volumes)
In the vicinity of the drug surface, during dissolution, the pH is altered when acid-base reactions take place. This local pH determines the surface solubility which drives dissolution rate

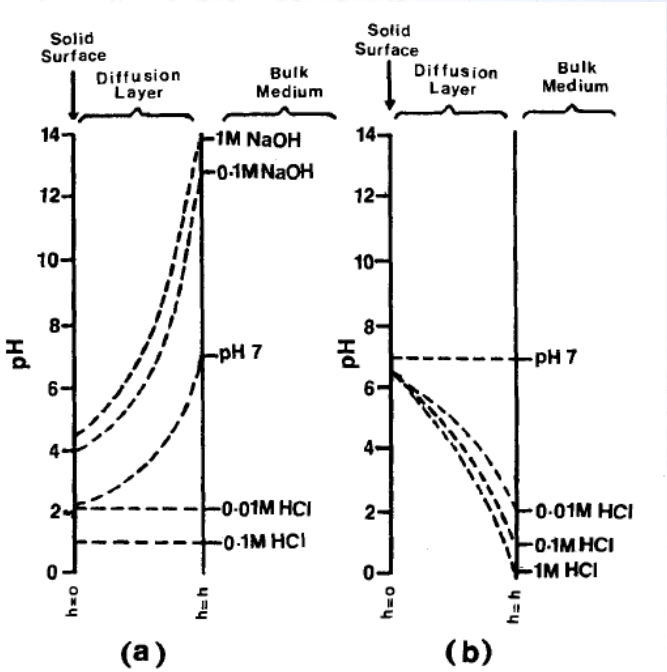
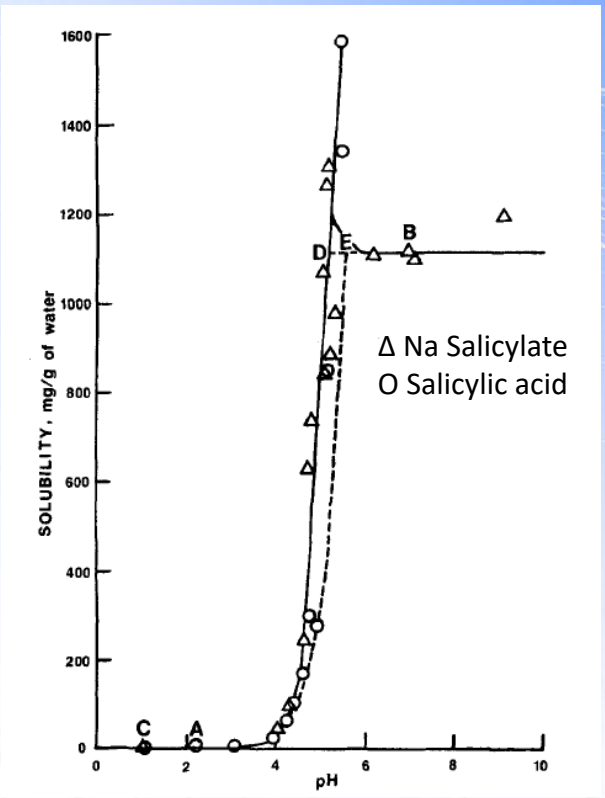
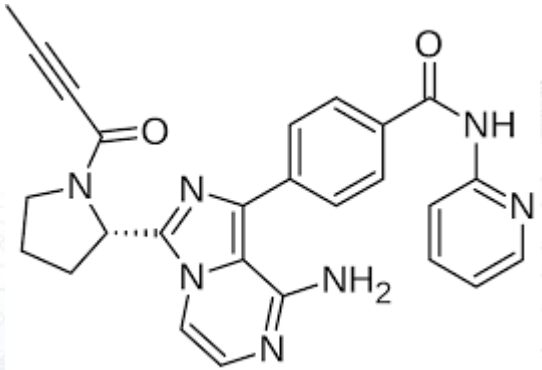


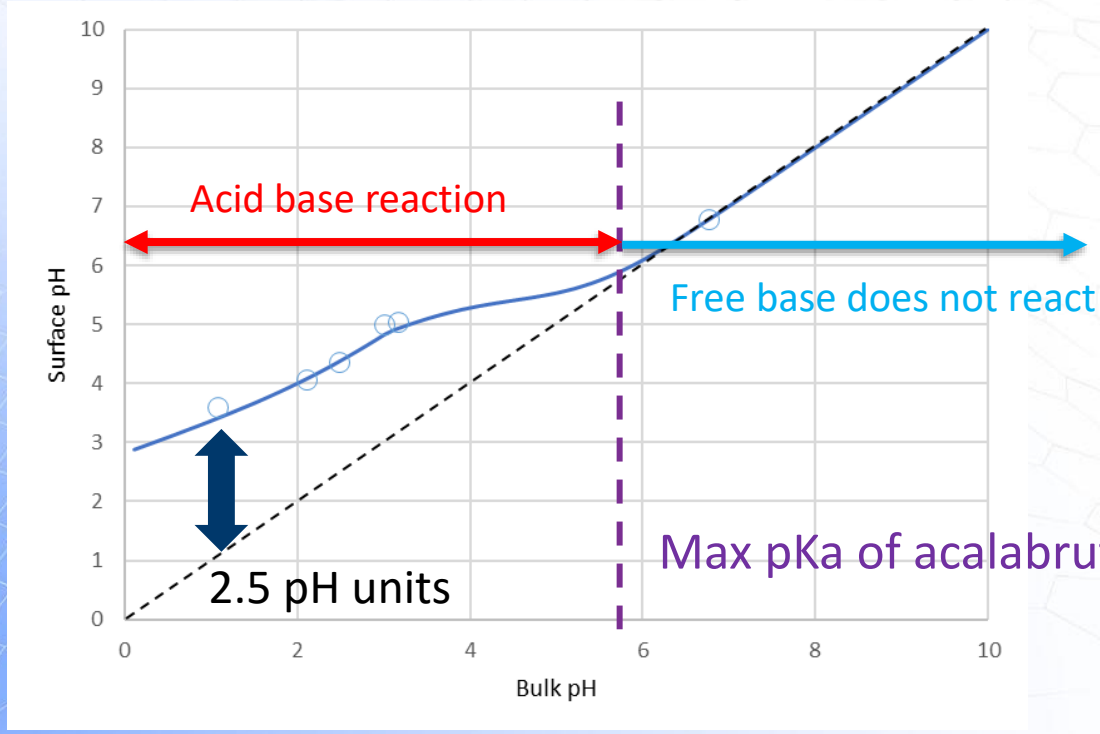
Figure 7—*Graphical representations of the buffering effect of (a) salicylic acid and (b) sodium salicylate in the diffusion layers of various media. The dotted lines are schematic.*



Serajuddin, A.T.M. and C.I. Jarowski, Effect of Diffusion Layer pH and Solubility on the Dissolution Rate of Pharmaceutical Acids and Their Sodium Salts II: Salicylic Acid, Theophylline, and Benzoic Acid. Journal of Pharmaceutical Sciences, 1985. 74(2): p. 148-154.

Example with acalabrutinib





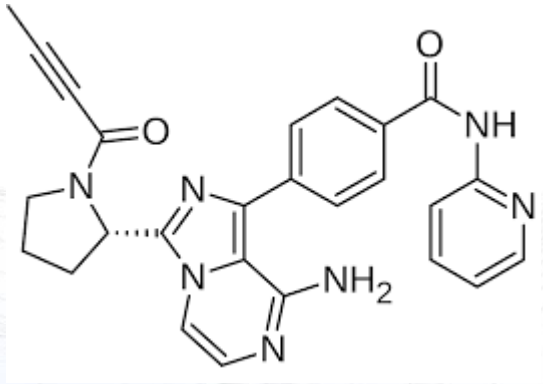
Acalabrutinib exhibits 2 pKas in the physiological range: 3.5(B), 5.8 (B)

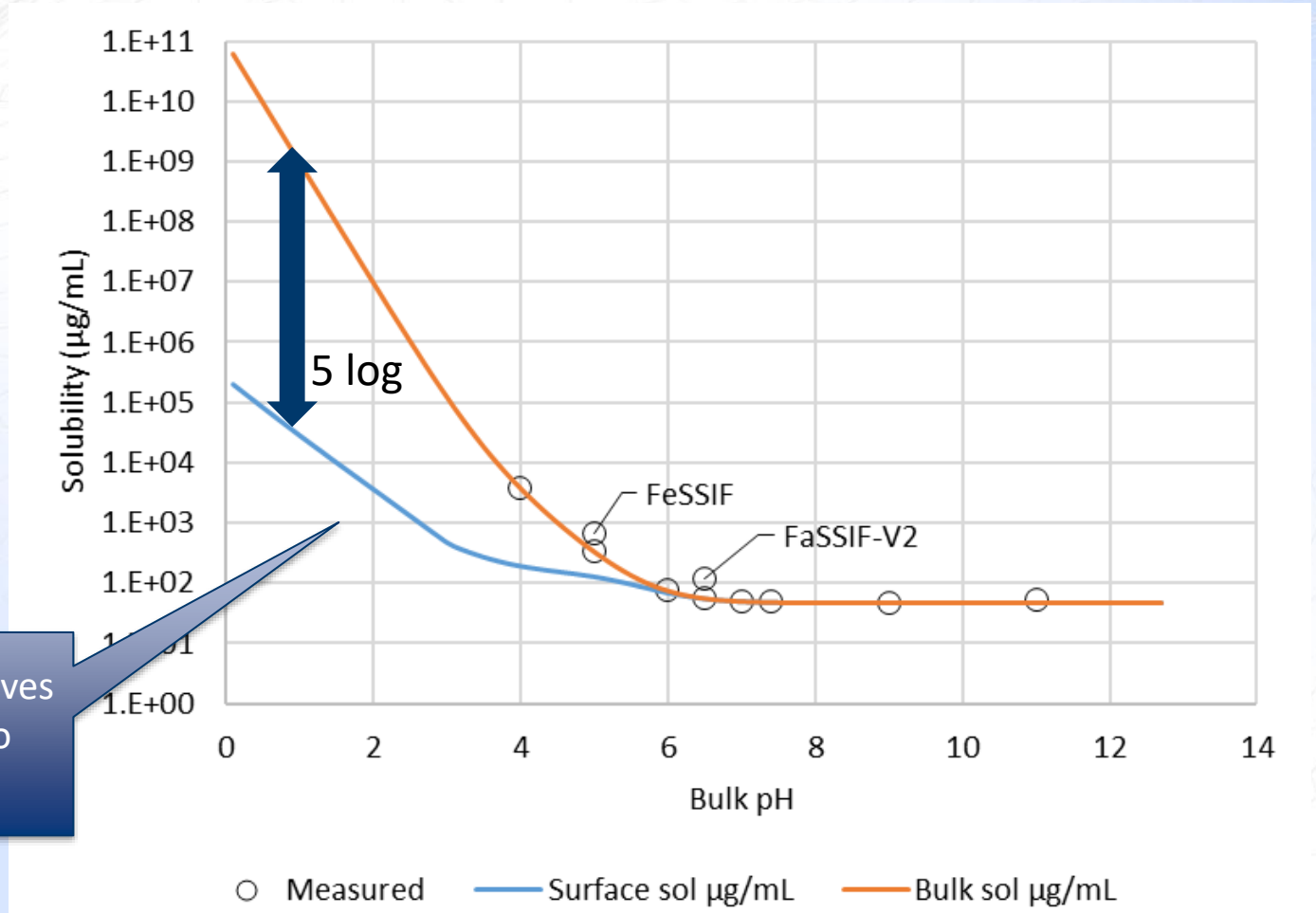
Intrinsic solubility = 48 ug/mL @ pH 9

Acid base reaction at the surface : surface pH > bulk pH during dissolution below pKas since the free base “consumes” protons from the bulk to ionize.

$$B + H^+ \leftrightarrow BH^+ + H^+ \leftrightarrow BH_2^{2+}$$

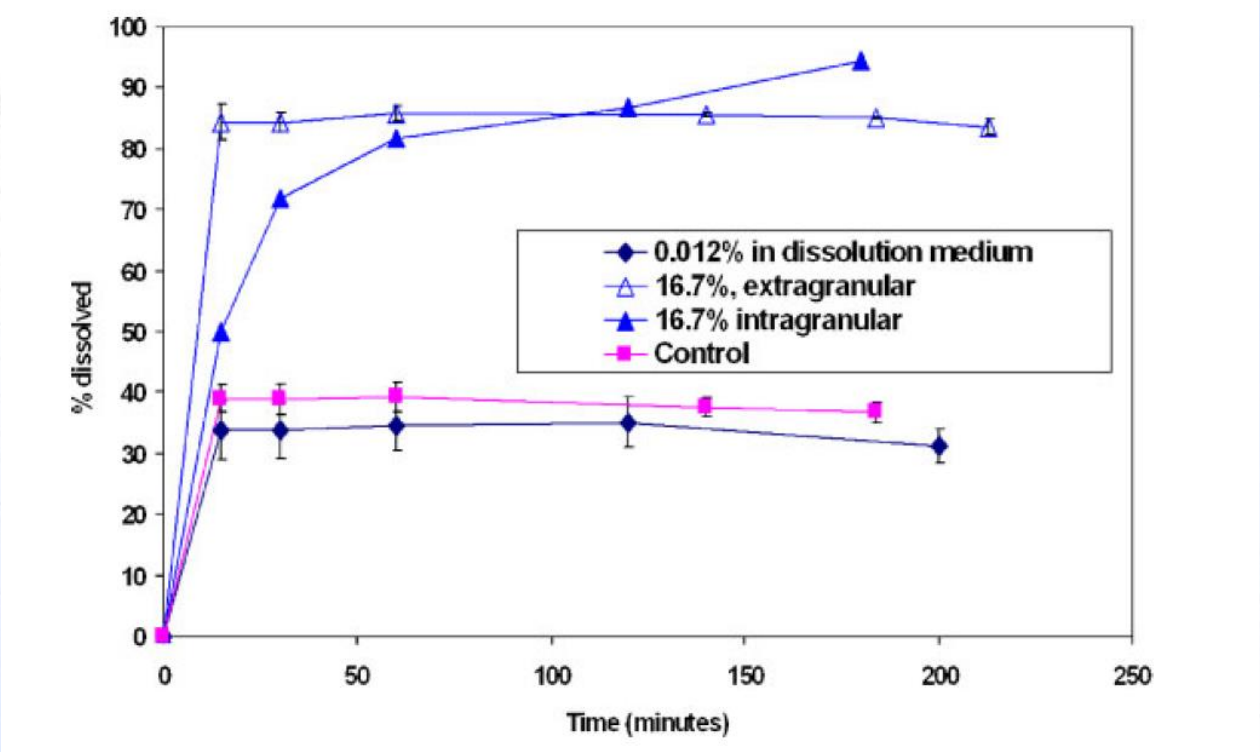
Surface vs bulk pH solubility profile





Surface solubility drives in vitro and in vivo dissolution

Surface pH can be influenced by excipients



Effects of tartaric acid on the dissolution profile of BMS-561389 tablets in acetate buffer, pH 5.5

Badawy SIF, Gray D, Zhao F, Sun D, Schuster A, Hussain MA. 2006. Formulation of solid dosage forms to overcome gastric pH interaction of the factor Xa inhibitor, BMS-561389. Pharm Res 23: 989–996.

Bulk concentration

$$\frac{dm_{solid}}{dt} = -A(t)\frac{D}{h} \times (C_S - C(t))$$

Will determine the end of the dissolution if C_S=C(t)
Plateau < 100% dissolved if dose > V x C_S

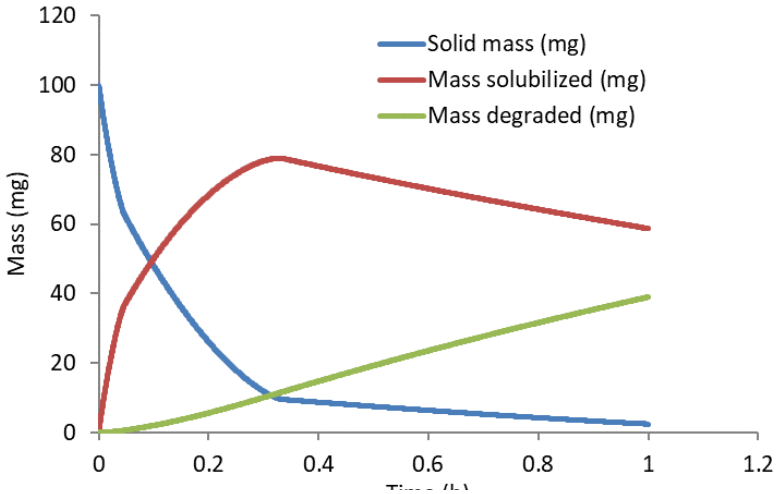
Plateau in dissolution does <u>not always</u> signify that an equilibrium is reached !

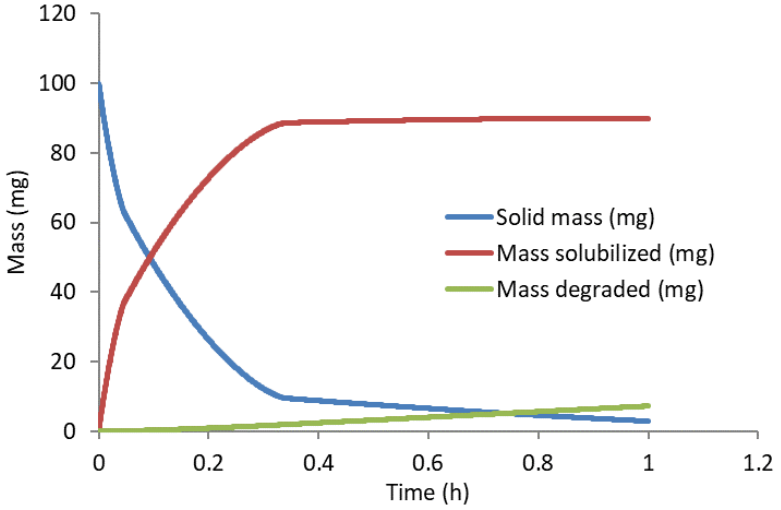
<u>Plateau could hide :</u>

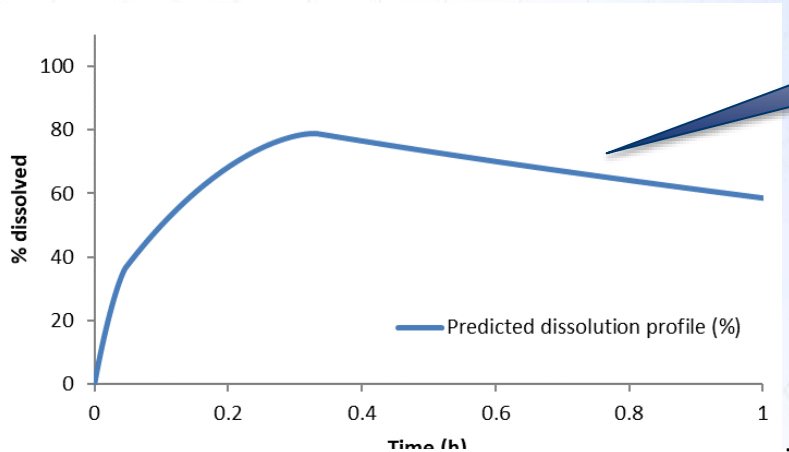
Chemical degradation
Presence of polymorphic impurity
Precipitation

Impact of chemical degradation

Bulk concentration is decreased over time, e.g. Rifampicin + Isoniazid at pH 2

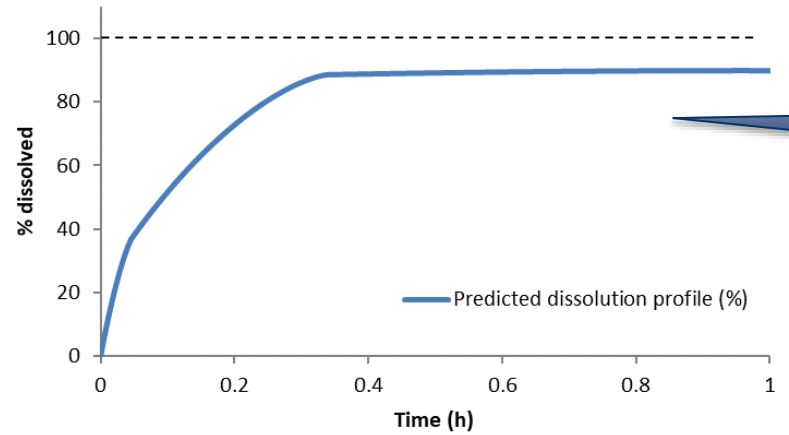






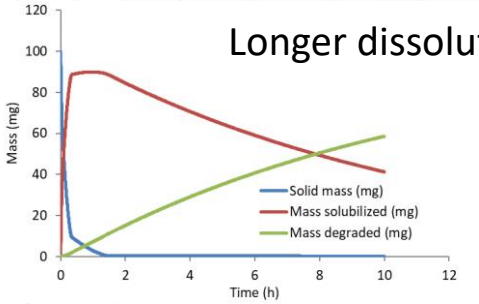
Rapid degradation = bell shape

This is <u>not</u> incomplete release



Slow degradation = plateau below 100%

Longer dissolution



Polymorph mixture

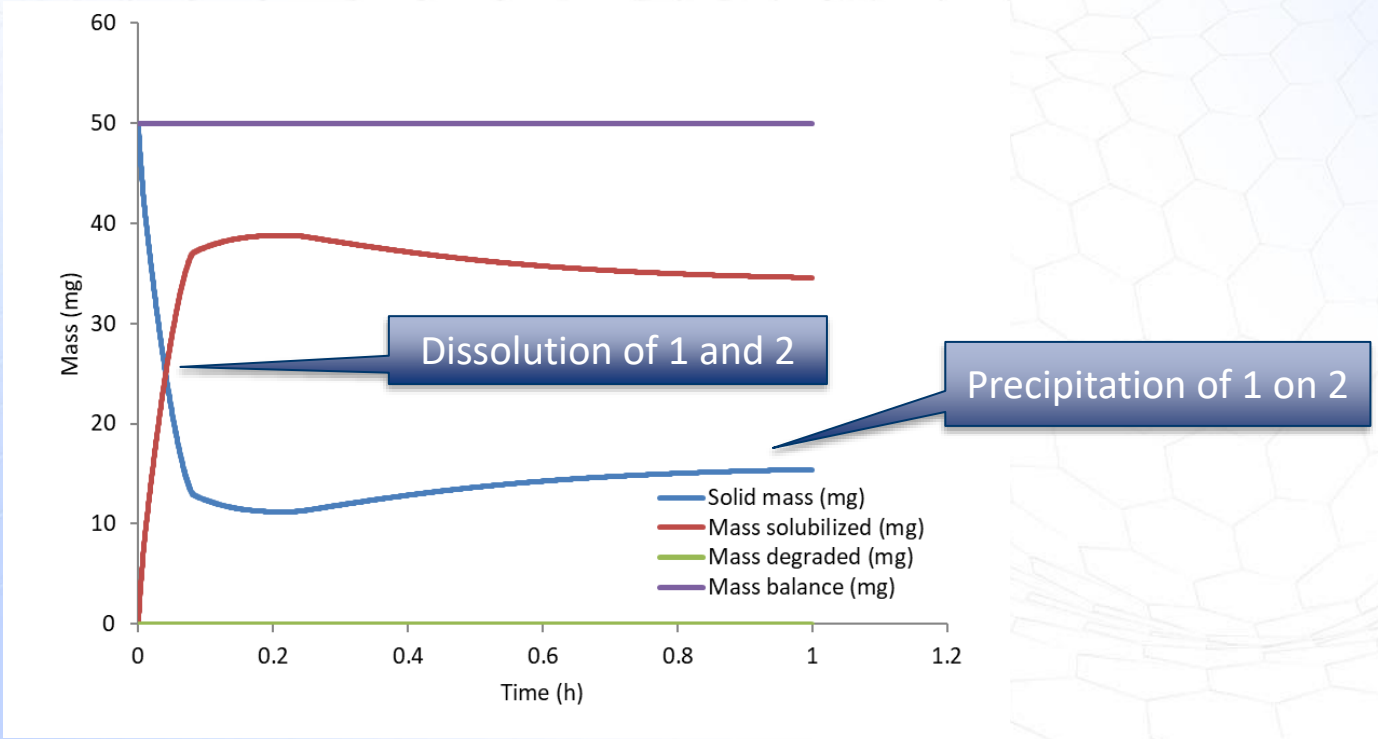
Two different solubilities C_{S1}, C_{S2}, same released moiety = same bulk concentration

$$\frac{dm_{solid}}{dt} = -A_1(t)\frac{D}{h} \times \left(C_{S1} - C(t)\right) - A_2(t)\frac{D}{h} \times \left(C_{S2} - C(t)\right)$$

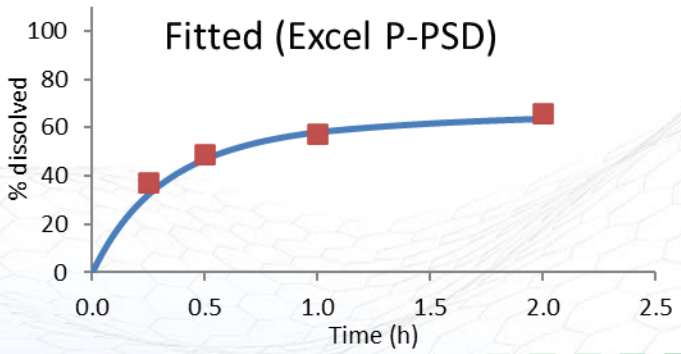
$C_{s1} > C_{s2}$

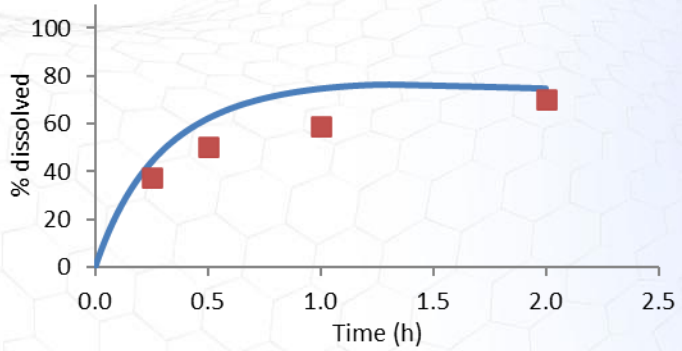
Polymorph 1 dissolves faster than polymorph 2

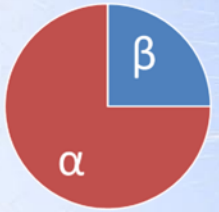
When $C_{S2} < C(t) < C_{S1}$ solute precipitates on polymorph 2



Rifaximin polymorph α and β mixtures [A]

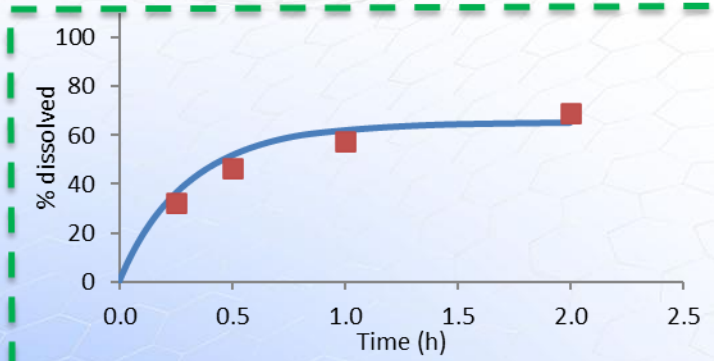


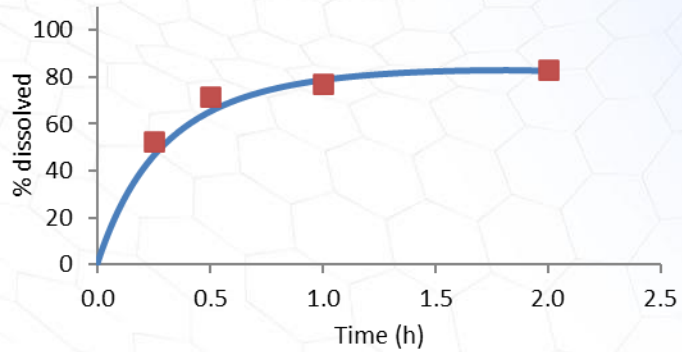


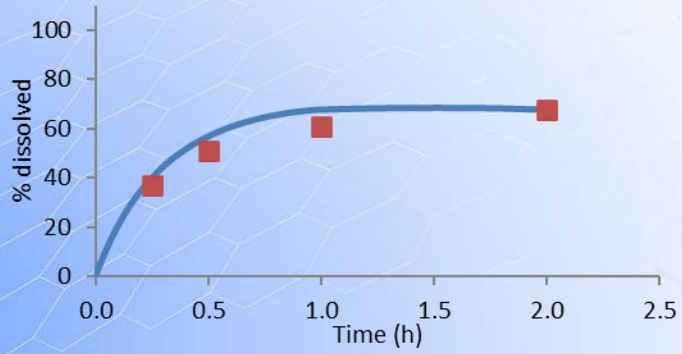


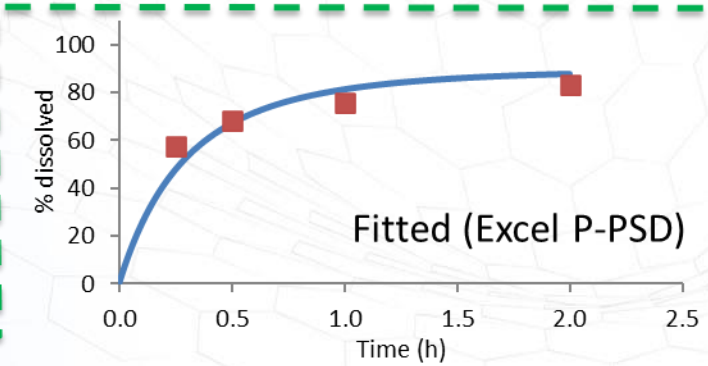
$C_S\alpha \approx 1.7 \times C_S\beta$

Predicted Excel P-PSD



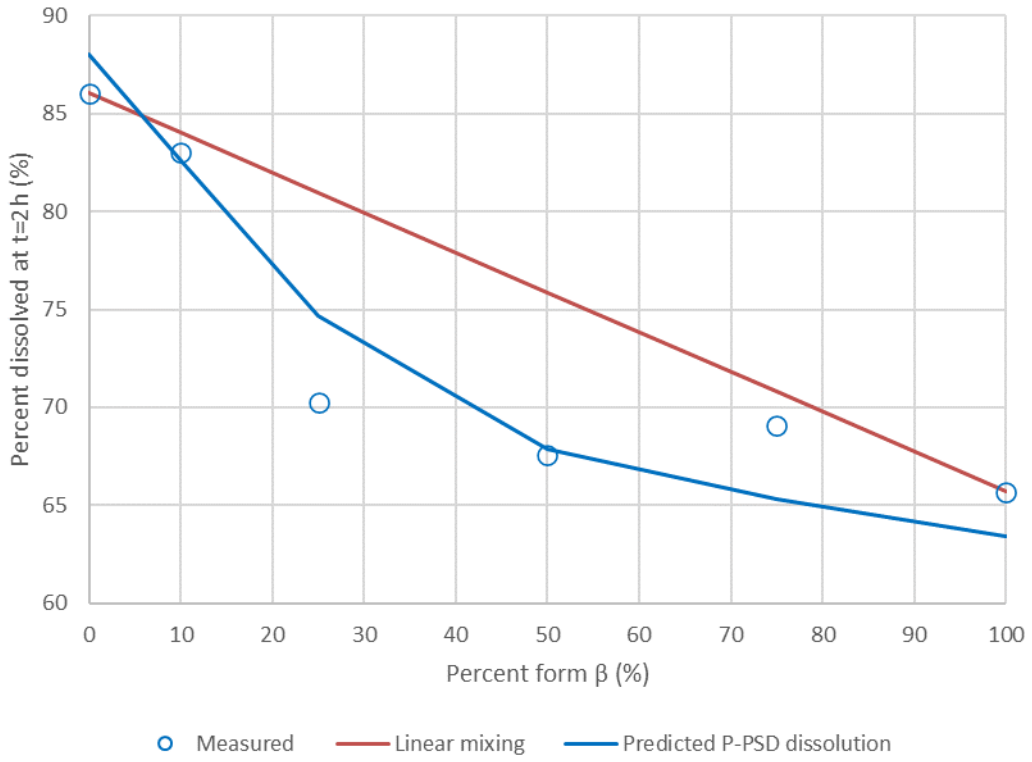






A: Dharani, S., et al., Development and Validation of a Discriminatory Dissolution Method for Rifaximin Products. J Pharm Sci, 2019. 108(6): p. 2112-2118.

Mixing law for rifaximin α and β



Extent of dissolution for polymorph mixtures does not always show linear relationship with impurity content

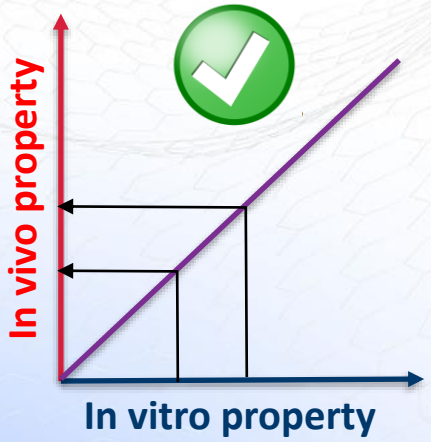
Outline

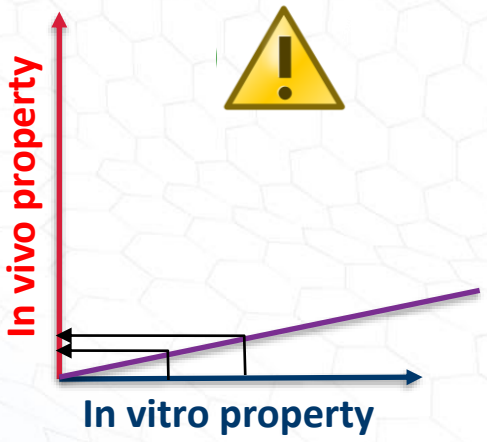
- Different models to fit dissolution
  - Assumptions for each model
  - Use for IR formulation fitting
  - Main equations
- Important drivers of dissolution
  - How DS and DP CQAs can influence shape of profile

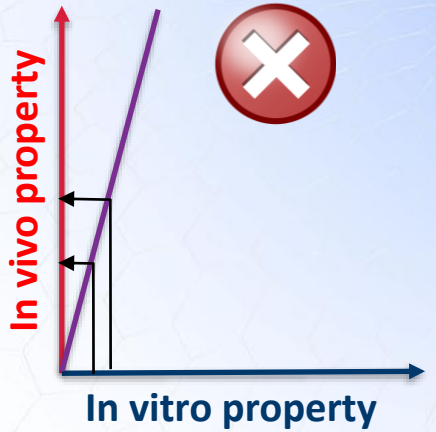
- How to choose a dissolution method and how to choose fitting strategy ?
- Take home messages

Choice of dissolution methods

Discrimination: changes in product in vitro performance are shown when CMA and or CPP are varied
Rank order: Changes in product in vitro performance align with in vivo behaviour







Right level : changes of in vitro properties translate to in vivo performance

Over discriminative: large changes in vitro translate to smaller changes in vivo

Under discriminative: small changes in vitro translate to larger changes in vivo

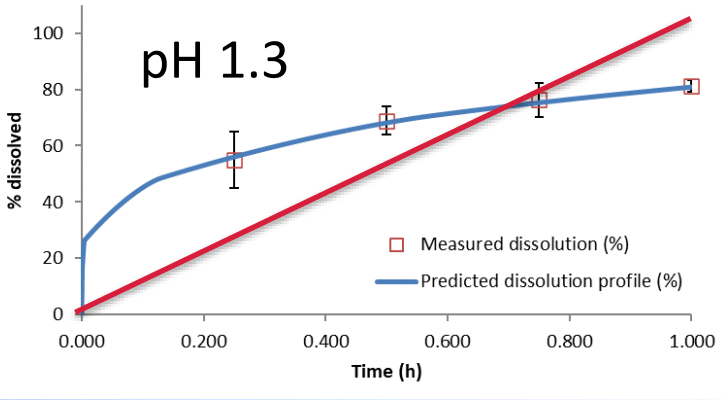
Both these methods may be clinically relevant and biopredictive

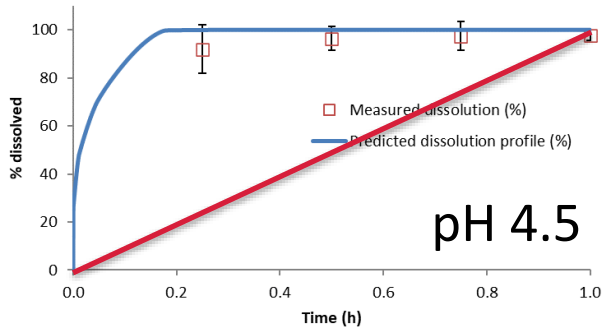
Choice of dissolution method for fitting

Choice of a discriminatory method

1-X method (Jesse Kuiper[A]): Dose / Volume = solubility of the drug

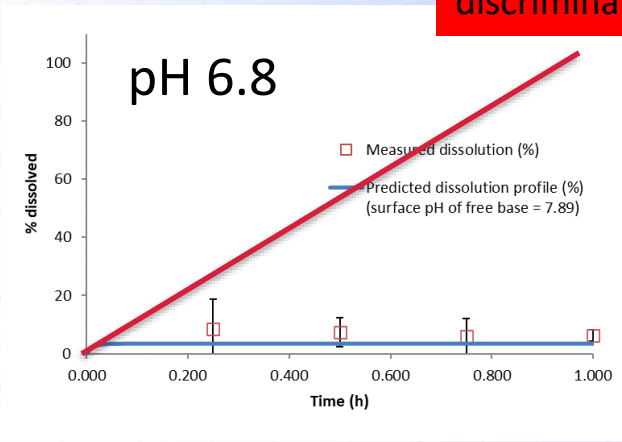
20%<all points<80% : best discrimination

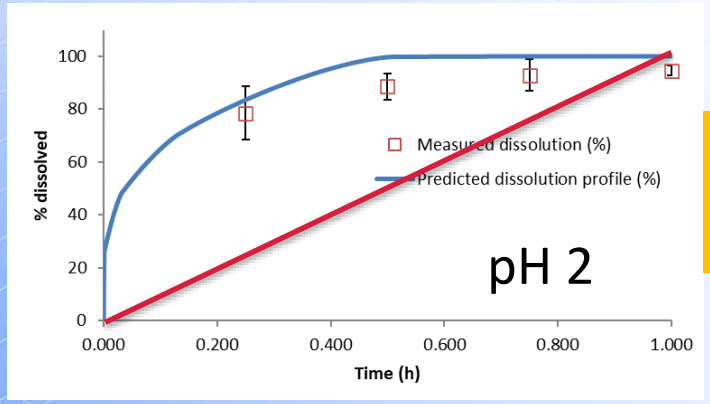




All points above 80% too high solubility = no discrimination

All points below 20% too low solubility = no discrimination





1 point below 80% not enough profile definition

A: Abend, A., et al., Dissolution and Translational Modeling Strategies Enabling Patient-Centric Drug Product Development: the M-CERSI Workshop Summary Report. The AAPS journal, 2018. 20(3).

Excel P-PSD Typical inputs to calculate dissolution

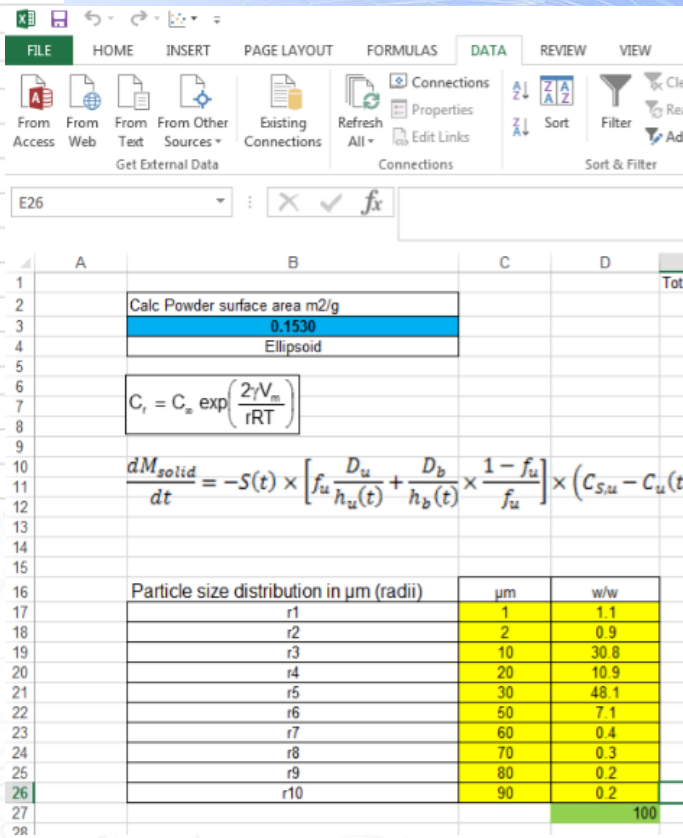
2	**Molecule**			
3	Viscosity of water	μ_L	6.85E-04	**Pa.s SF viscosity at T=..... 37**
4	Unbound drug hydrated radius	r_h	5.48677E-10	m
5	Diffusion coefficient of unbound drug	D_u	6.0465580E-10	m2.s-1
6	Avogadro n°	N_a	6.02214179E+23	-
7	Drug Molar weight	Mw	**500**	**g/mol**
8	True drug density	ρ_S	**1.2**	**g/mL**
9	Molecular volume	Mv	6.92E-28	m3
10	Molar volume	MolV	4.17E-04	m3
11	Boltzmann constant	k	1.3806504E-23	J.K-1
12	Gas constant	R_g	8.314472E+00	J.K-1.mol-1
13	Solubility in dissolution fluid w/o surfactants at at experiment temperature	$C_{s,u}$ @ T_{exp}	0.48500	**mg/mL or kg/m3 at T = ... 37**
14	Melting point	T_m	**473.15**	K
15	Solubility in dissolution fluid w/o surfactants at at reference temperature	$C_{s,u}$ @ T_{ref}	**0.485**	**mg/mL or kg/m3 at Tref =..... 310.15**
16	Tref for solubility	T_{ref}	**310.15**	**K**
17	Affinity for surfactant	k_{aff}	**0.0818**	**mg/mL/mM**
18	Concentration of surfactant in medium	C_{surf}	**0**	**mM**
19	Apparent solubility with surfactants	C_{total}	0.4850	**mg/mL**
20	Unbound fraction in solution	fu	1	-
21	Micelle radius	r_{mic}	**1.8**	**nm**
22	Diffusion coefficient of micelle-bound drug	D_b	1.41254E-10	**m2.s-1**
23	ratio of UWL thickness	h_b/h_u	0.615882306	

$$D = \frac{kT}{6\pi\eta R_h} \qquad R_h = \sqrt[3]{\frac{3 \times M_W \times 10^{-3}}{4\pi N_A \rho_S}}$$

$$S_{app} = S_{aq} + k_{aff} \times C_{surf}$$

$$f_u = \frac{S_{aq}}{S_{app}}$$

30				
31	**Dissolution conditions**			
32	Temperature	T	**37**	°C
33	Absolute Temperature	T	310.15	K
34	Drug mass administered	m_0	**100**	mg
35	Total dissolution time	t_{tot}	**1**	**hours**
36	Integration step	dt	**0.9**	**seconds**
37	number of steps	nsteps	4000	**steps**
38	Total volume of medium	V_L	**900.0**	**mL**
39	Degradation rate in solution	k_{deg}	**0**	**min-1**
40				

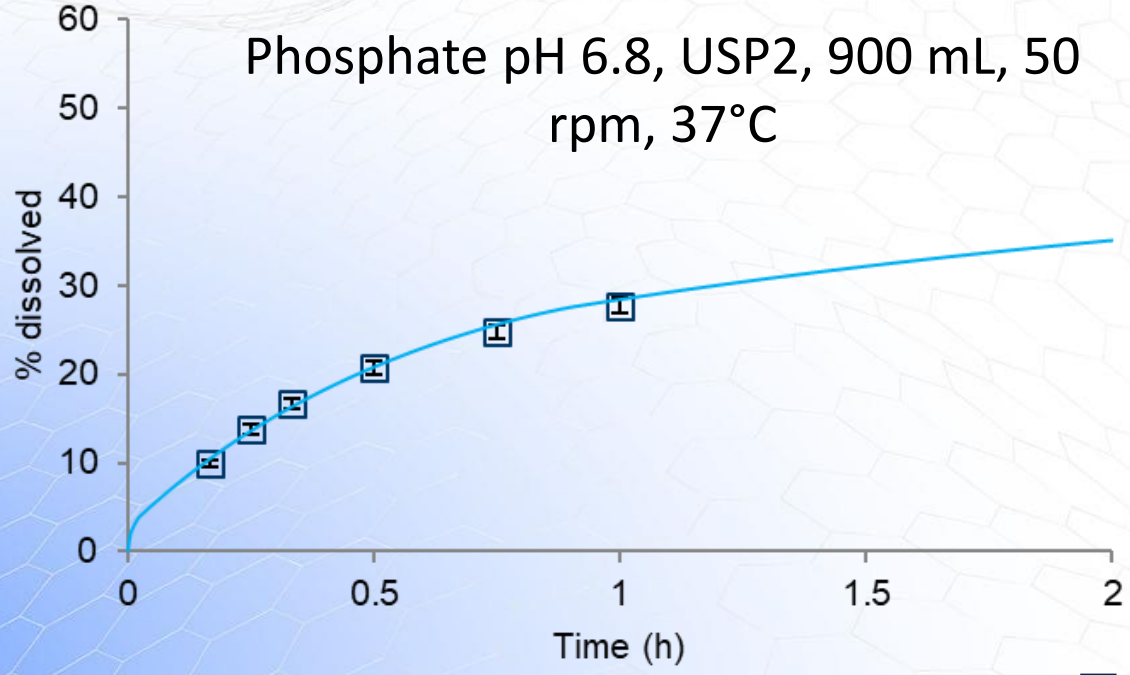


https://doi.org/10.1016/j.ejpb.2019.07.014

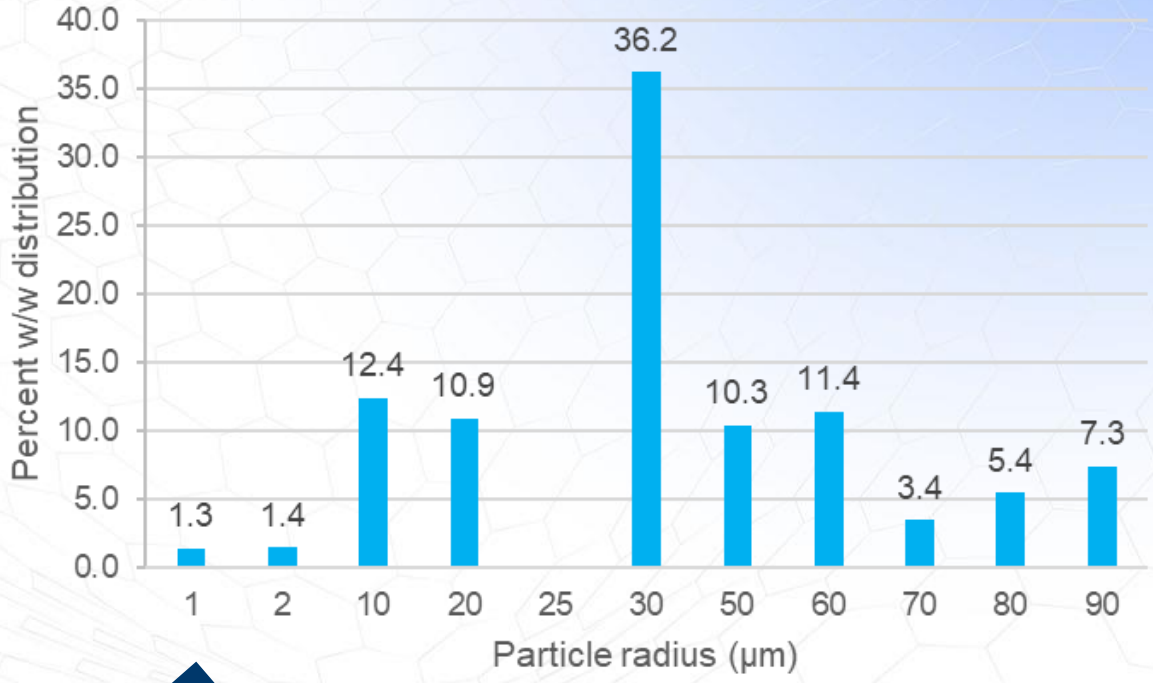
Example for P-PSD extraction

Step 1 : 100 mg acalabrutinib capsule batch W027180

Phosphate pH 6.8, USP2, 900 mL, 50 rpm, 37°C

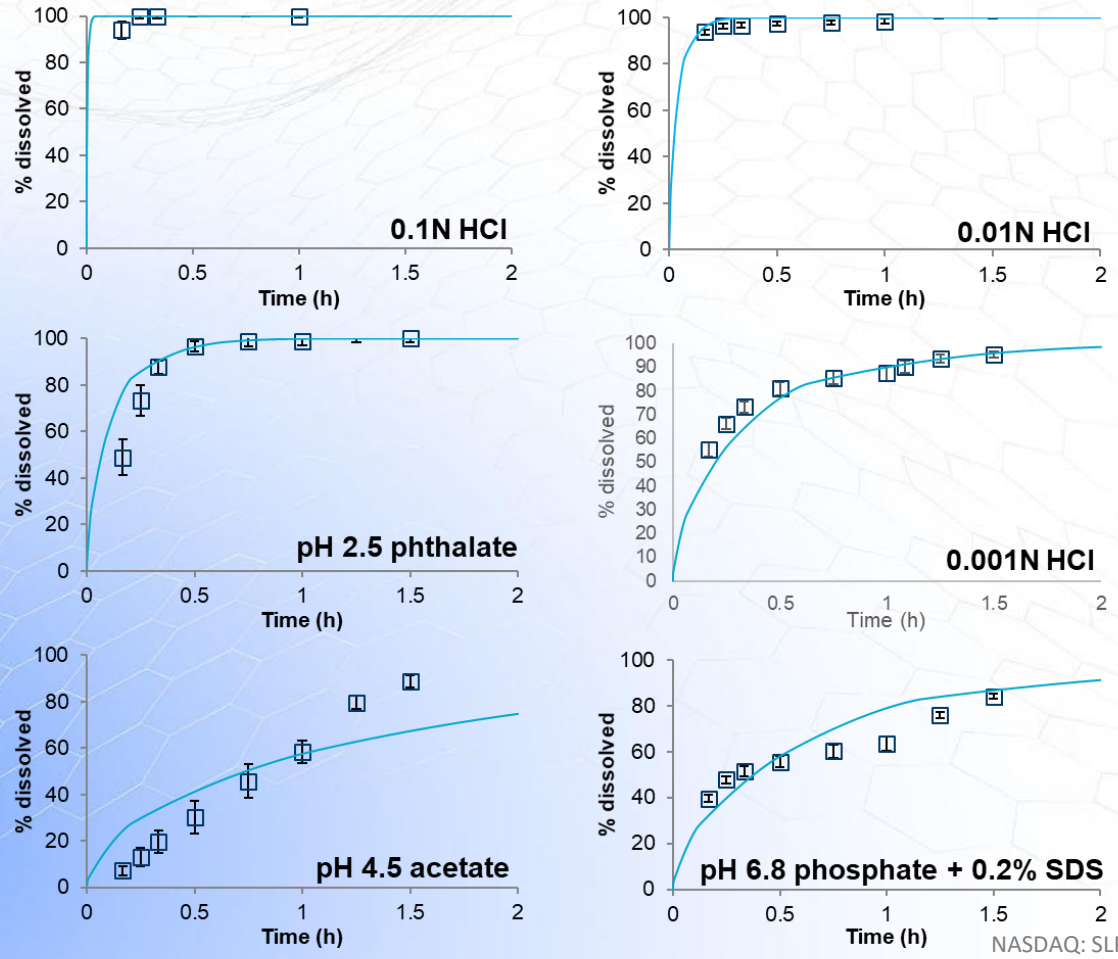


P-PSD for batch W027180



Example for P-PSD verification

Step 2 : Predicting other conditions for 100 mg acalabrutinib capsule batch W027180



P-PSD able to reproduce the observed dissolution rates in other conditions of pH with and without surfactant

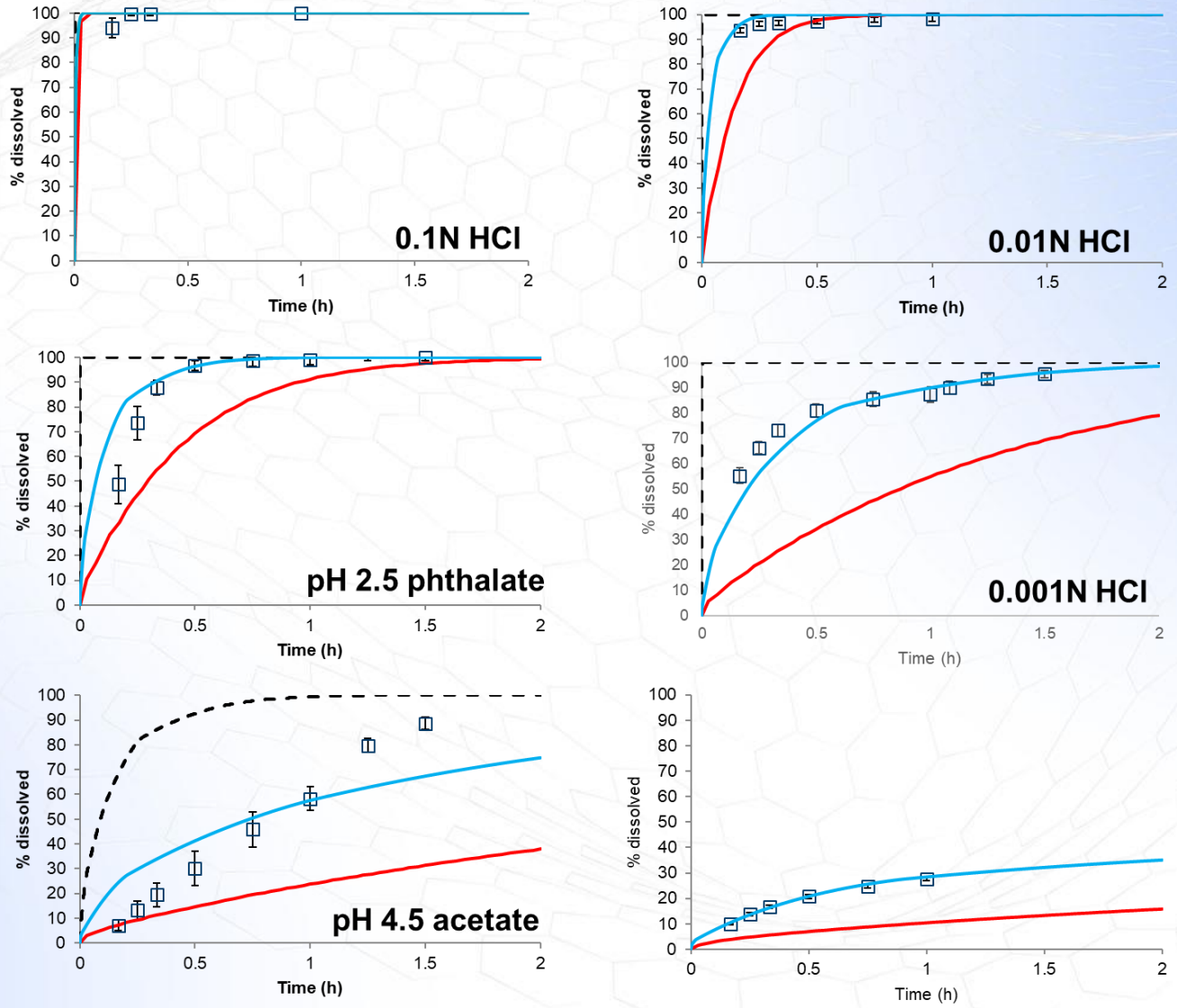
Use of surface pH
Different UWL thicknesses (if micelles)

Other alternatives to predict dissolution (DS-PSD or bulk solubility)

DS-PSD underestimates dissolution

Bulk solubility and P-PSD overestimates dissolution

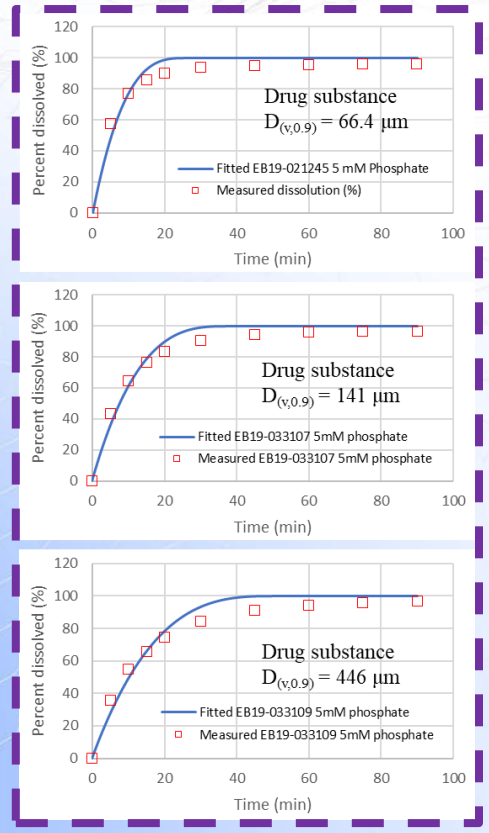
Surface solubility and P-PSD is the way forward !



100 mg capsule batch W027180

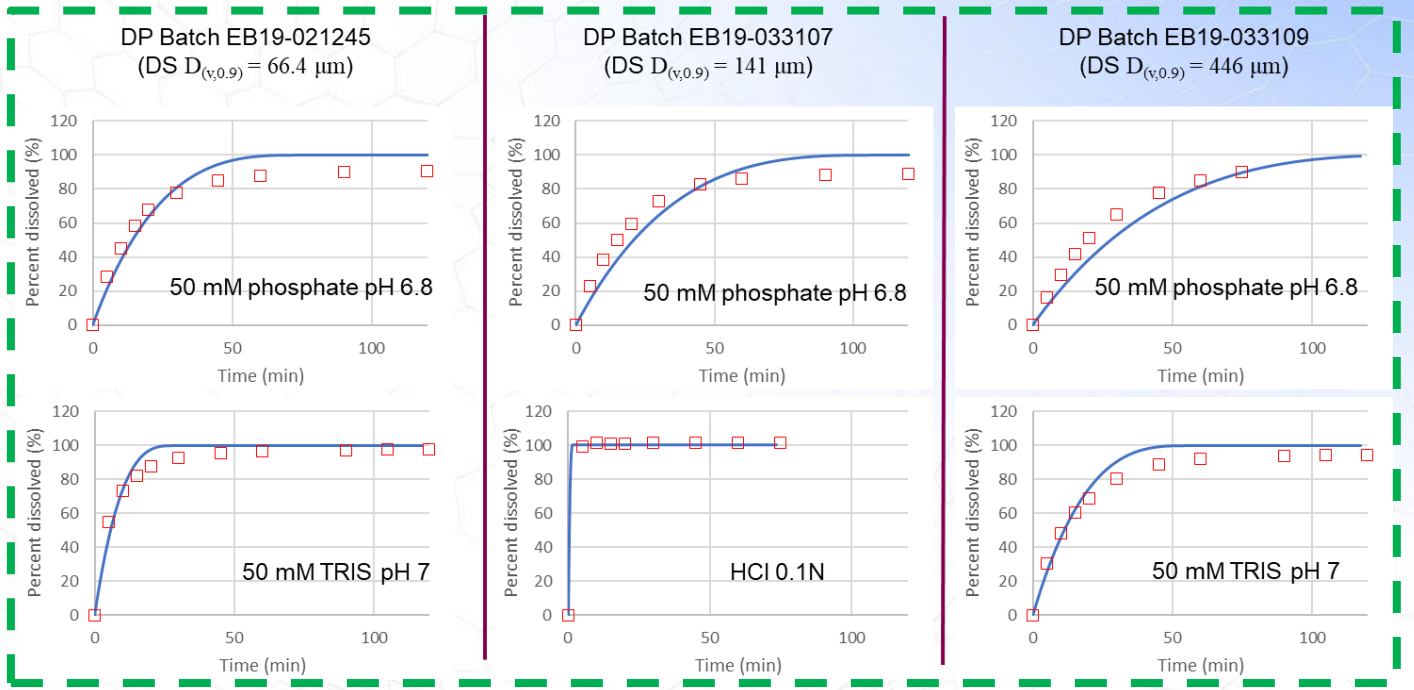
AFE and AAFE : Indicators of goodness of fit z-factor fitting of dissolution

1-QC dissolution method + z-factor fit



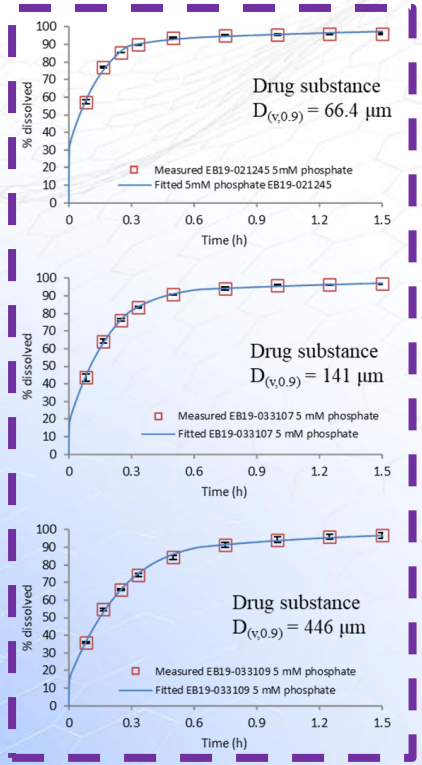
2-Z-factor verification: dissolution prediction in other media

AFE=0.96, AAFE= 1.12



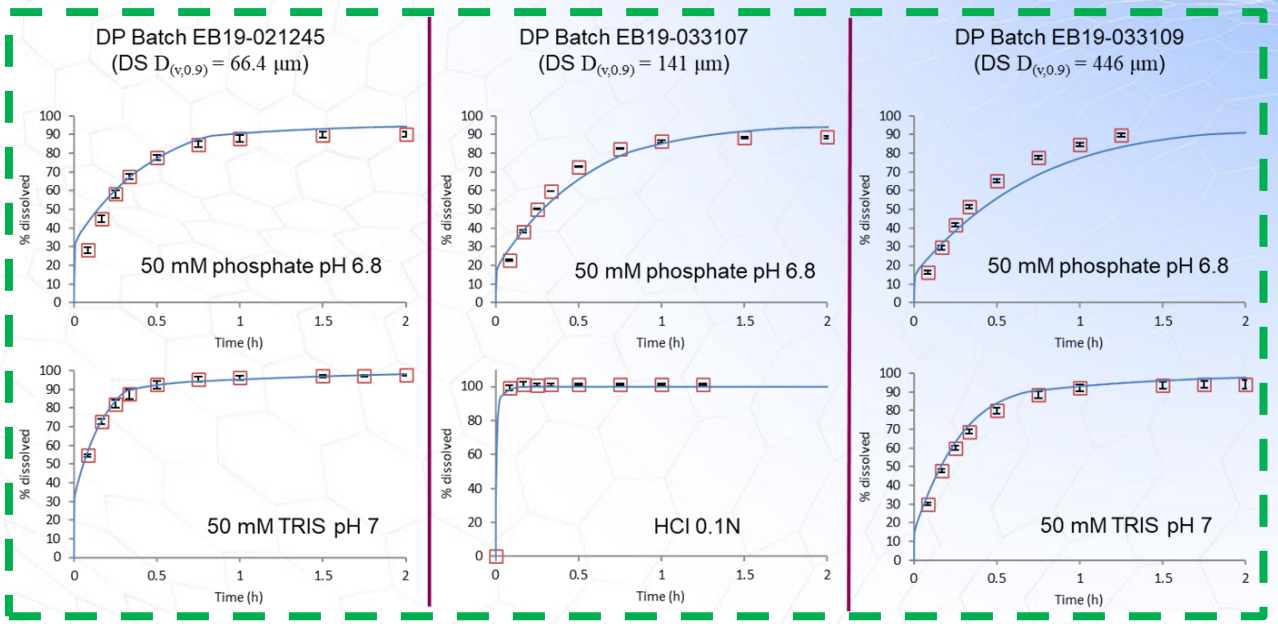
AFE and AAFE : Indicators of goodness of fit
P-PSD fitting of dissolution

1-QC dissolution method + P-PSD extraction



2-P-PSD verification: dissolution prediction in other media

AFE=1.02, AAFE= 1.06



Absolute prediction error during verification
P-PSD = 6% vs z-factor = 12%
P-PSD chosen

SimulationsPlus

Outline

- Different models to fit dissolution
  - Assumptions for each model
  - Use for IR formulation fitting
  - Main equations
- Important drivers of dissolution
  - How DS and DP CQAs can influence shape of profile
- How to choose a dissolution method and how to choose fitting strategy ?
- Take home messages

Take Home Messages

- DS measured laser diffraction is (generally) a poor predictor of drug product dissolution : Excipients, process, aggregation and shape of DS
- IR DP Dissolution fitting should be mechanistic
  - Translate across populations, prandial states, pH in stomach
  - Provide realistic within and between subject variability during VBE
- Prior to fitting dissolution data verify absence of:
  - Precipitation or degradation
  - Agitation effect
- Use the best fitting method if multiple choices
  - Use surface solubility when appropriate
  - Time correct dissolution data for capsule opening or disintegration times
  - AFE and AAFE can be used to screen and select methods across different dissolution conditions
  - Use a discriminant dissolution method to fit

If present, measure independently and integrate in model

Thanks