Translating the effect of product manufacturing variants from in vitro to the clinic: Current possibilities and gaps for extended release formulations

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University of Maryland, Baltimore, USA

Disclaimer: Views expressed here are mine and does not necessarily reflect the opinion of any of the collaborators

Predicting Oral Drug Absorption

Broadly categorized into two approaches

IVIVC

- When PBBM model cannot fully capture the controlling mechanisms
- More biomimetic (complex) *in vitro* experiment to capture the likely *in vivo* formulation behaviour coupled with *in vivo* disposition model
- In vitro to in vivo relationship can be established by deconvolution and convolution methods
- Current common practice for ER/CR/MR formulations

IVIVE

- When PBBM model can (is expected to) capture the controlling mechanisms reasonably well
- Well-defined and complimentary *in vitro* experiments informing the biomimetic (complex) modelling to parameterize and validate/verify the predictive power of the model
- Would require mechanistic models of excipient interaction, polymer erosion, swelling, diffusion into the PBBM & suitable *in vitro* experiments

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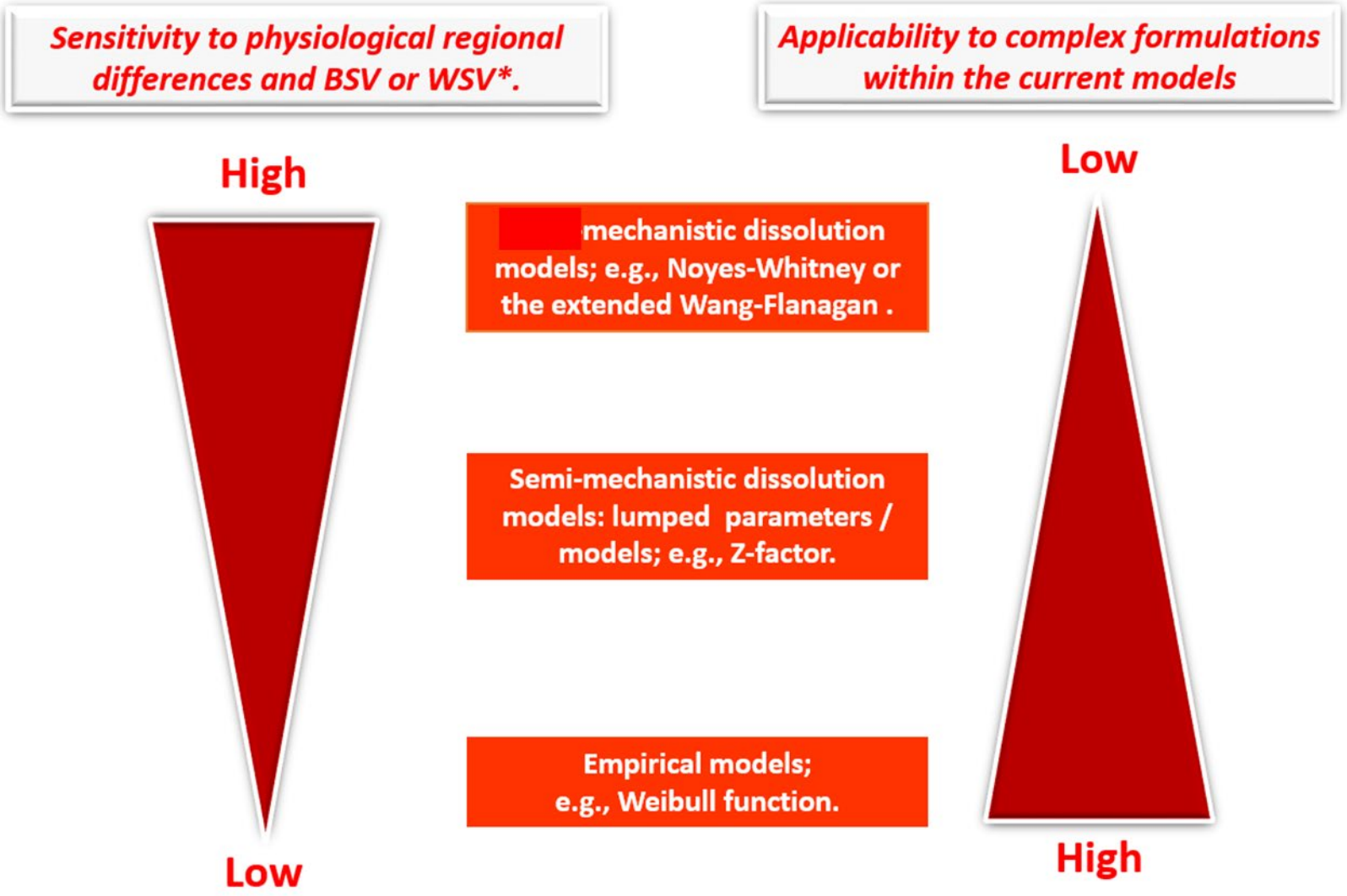
Predicting Oral Drug Absorption of Drug Products: Current Status



*BSV, WSV – Between, Within Subject Variability

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Case Studies

1. IVIVC to support ER formulation optimization
2. Convolution Based population IVIVC approach
3. Mechanistic modelling of enteric coated pellet formulations

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Case 1. IVIVC for ER formulation Development

Extended Release formulation with two polymer and dosage strength combinations to be evaluated (5 variants)

Questions to be answered

- Better IVIVC understanding via PBBM modelling?
- Does PBBM add to understanding of *in vivo* release?
- Is there added value of using individual subject data?

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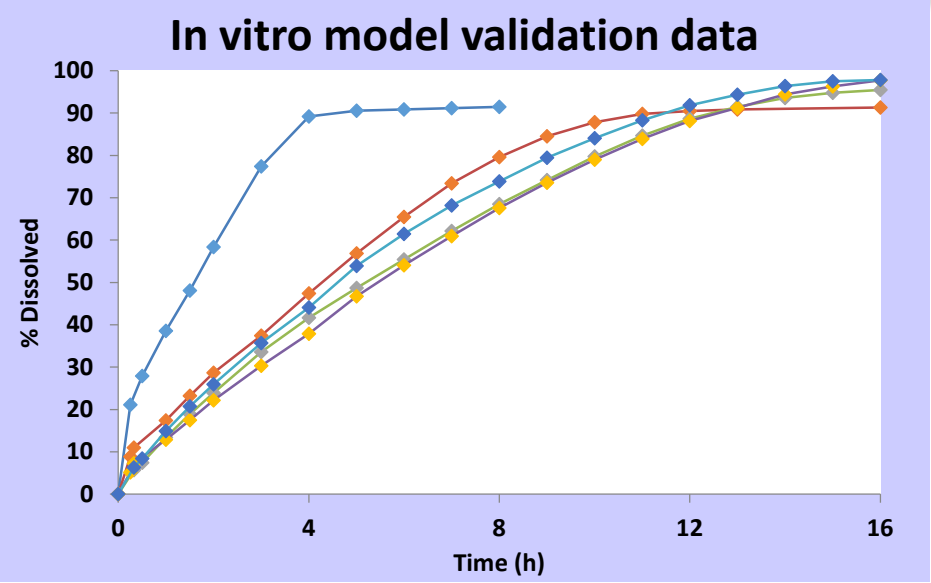
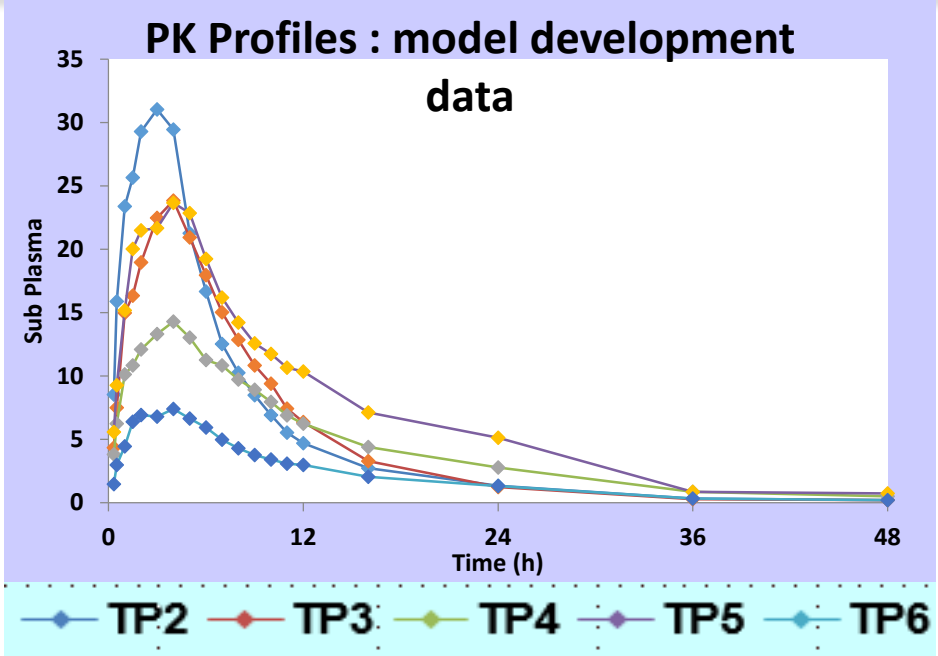
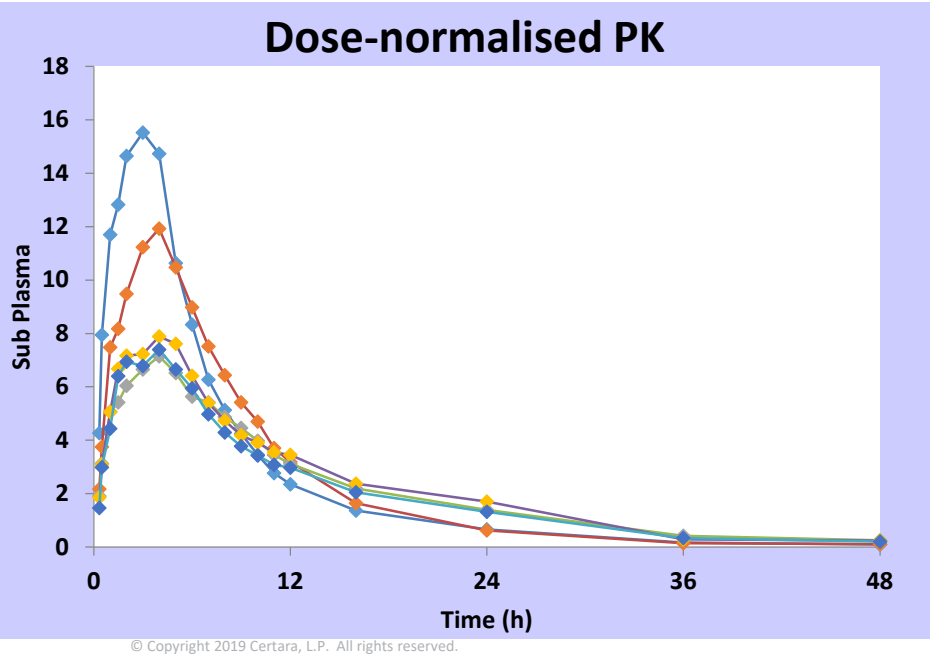
Exploratory Analysis – *in vitro* dissolution and *in vivo* PK data







- IVIVC seems likely but expect issues with TP3
- TP-4/5/6 appears difficult to discriminate
  - ✓ May need some investigation with *in vitro* experiment or mechanism of release from formulation or *in vivo* data

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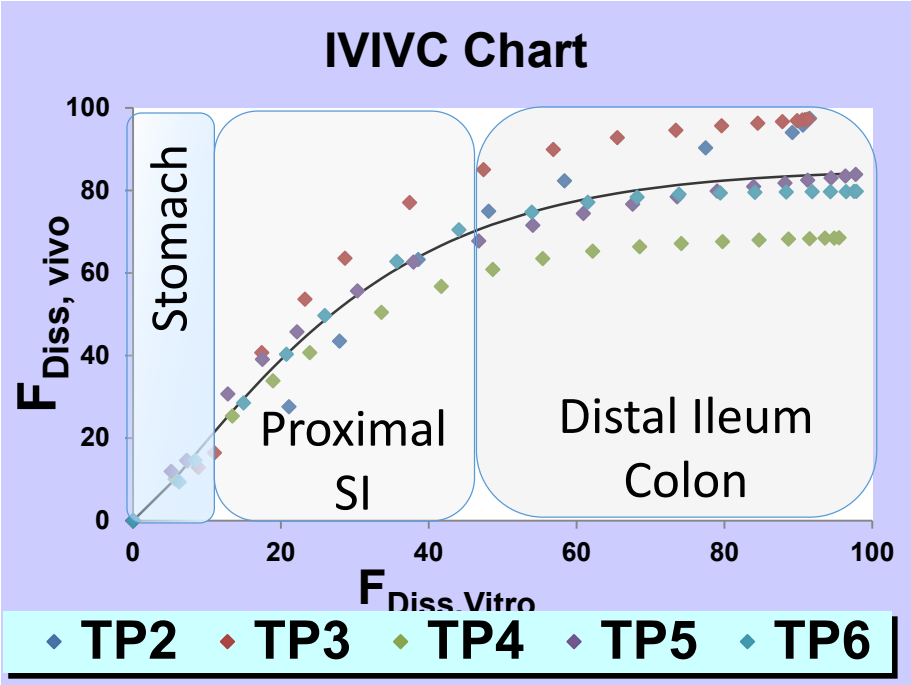
Two Stage Sequential IVIVC Approach – Mean PK data

- Deconvolute (estimate) *in vivo* dissolution profile from PK data
- Identify and verify, if any, (predictive) relationship between *in vivo* and *in vitro* dissolution



Predictive Performance

Formulation	AUCtlast			Cmax		
	Obs	Pred	%PE	Obs	Pred1	%PE1
TP2	241.83	183.53	24.11	31.02	28.54	8.01
TP3	226.69	171.37	24.41	23.84	18.15	23.86
TP4	201.54	168.29	16.50	14.29	16.13	-12.93
TP5	325.09	250.48	22.95	23.67	22.50	4.96
TP6	96.49	85.07	11.84	7.40	8.44	-13.99
Overall Internal			19.96			12.75

- Extent of release/dissolution *in vitro* and *in vivo* is significantly different and formulation dependent
- TP2/3 and TP4/5/6 have different excipients and hence release mechanisms
- There is poor correlation for release/dissolution in colon

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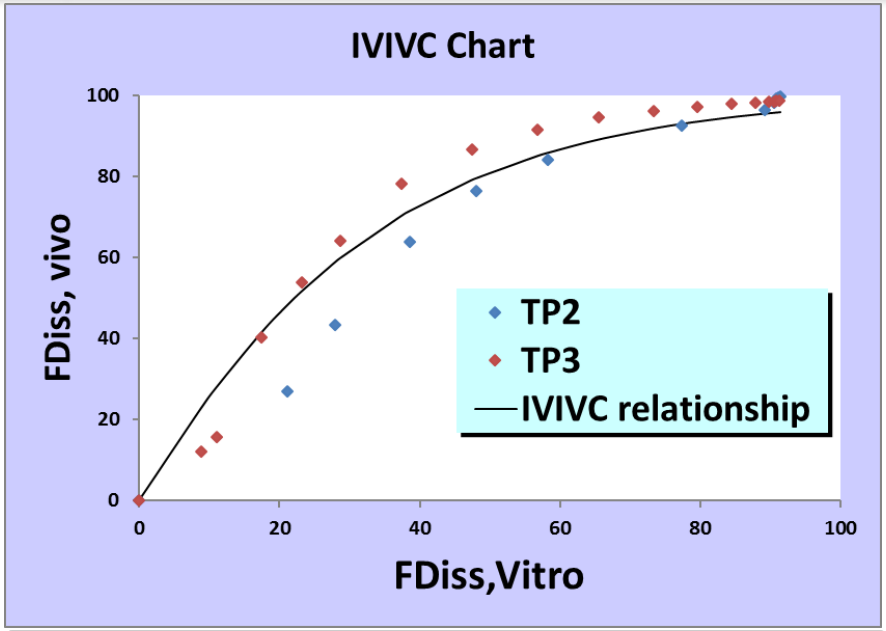
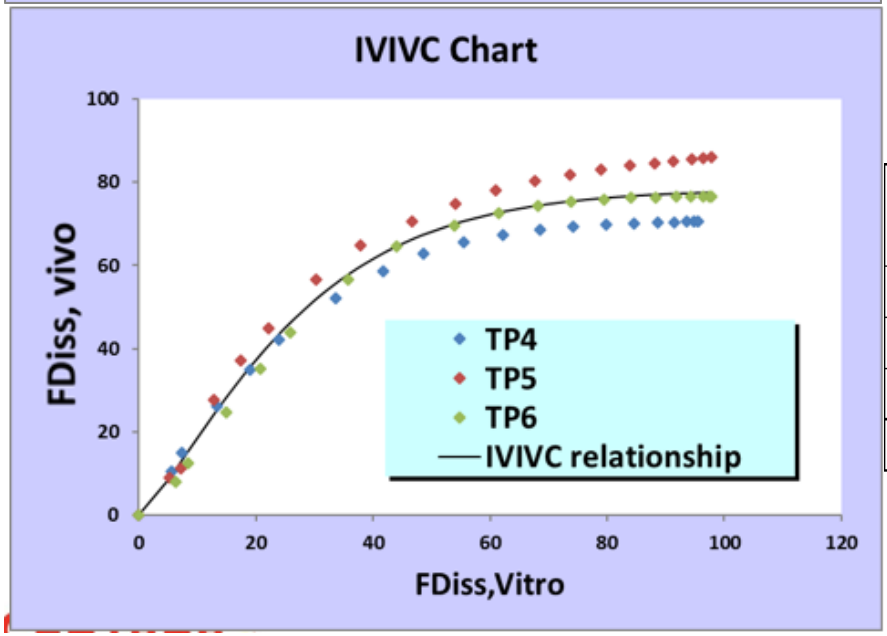
Two Sets – TP2/TP3 & TP4/5/6 – Sequential Two Stage IVIVC



Formulation	AUCtlast			Cmax		
	Obs	Pred	%PE	Obs	Pred1	%PE1
TP2	241.82	209.12	13.52	31.02	31.75	-2.33
TP3	226.69	195.59	13.72	23.84	20.78	12.82
Overall Internal			13.62			7.58

- Separating formulations by excipient group improved the IVIVC
- However, it is still nonlinear in the Distal SI/Colon region for all formulations



Formulation	AUCtlast			Cmax		
	Obs	Pred	%PE	Obs	Pred1	%PE1
TP4	201.54	155.91	22.64	14.29	15.31	-7.19
TP5	325.09	231.99	28.64	23.67	21.39	9.64
TP6	96.49	78.78	18.35	7.40	8.00	-8.06
Overall Internal			23.21			8.30

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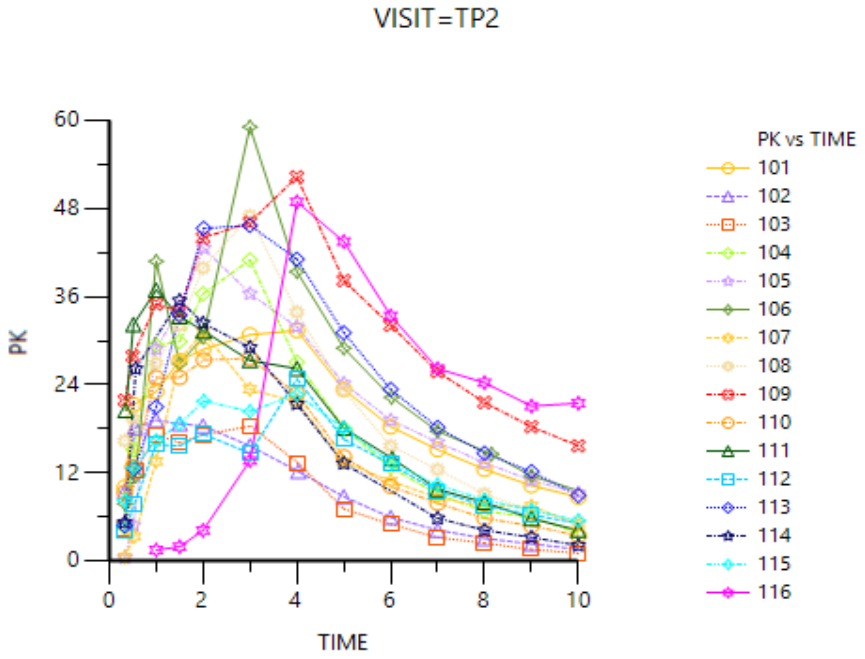
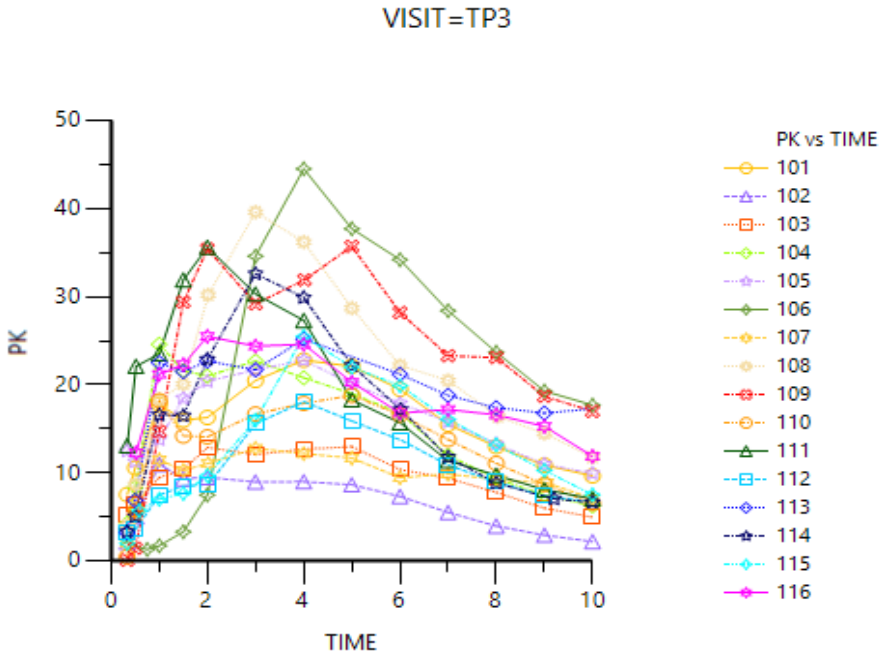
Population PK Data – Exploratory Analysis





- Fast is not the fastest and Slow is not the slowest in all subjects
- Rank Order of Mean PK is not retained at individual subject levels
  - Inter-individual variability
  - Inter-occasion variability
    - ✓ Formulation aspects
    - ✓ Physiology aspects

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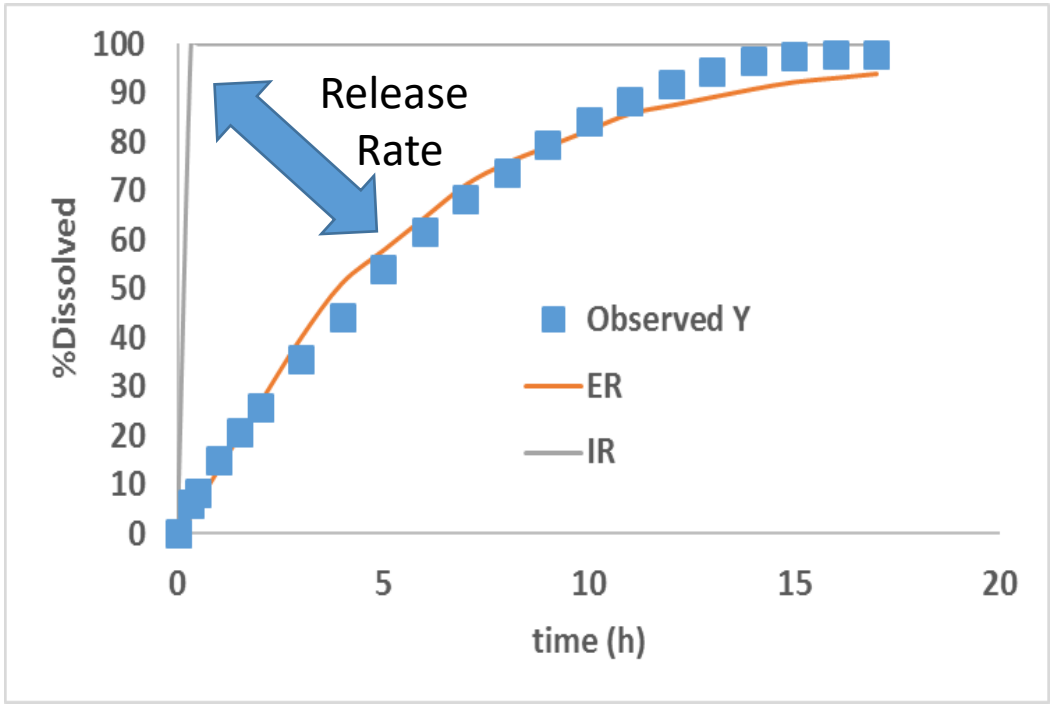
Population IVIVE for CR formulation – A New Approach

- Calculate Release Rate from *in vitro* dissolution profiles with SIVA

Solubility data [DRUG] => Dissolution Data [FORMULATION SPECIFIC]



Deconvoluting release rate from ***in vitro*** dissolution profile to re-convolute with ***in vivo*** **PBPK** model

IVIVE can account for any **differences in solubility/ dissolution *in vitro* and *in vivo*.**

However, currently polymer behaviour *in vivo / in vitro* are not typically modelled mechanistically in PBBM platforms

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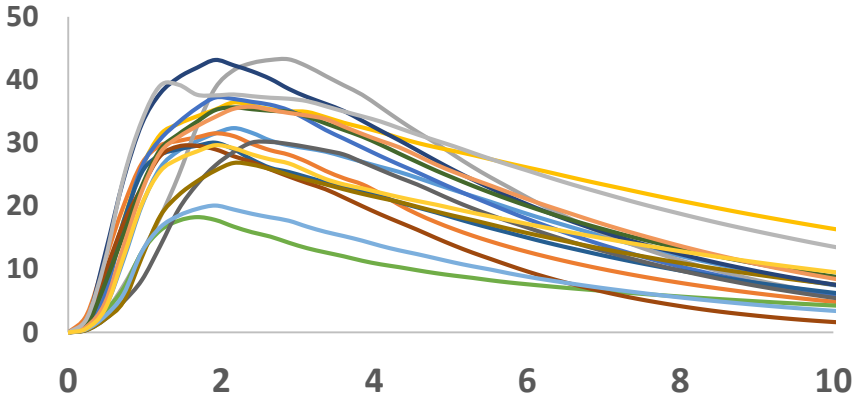
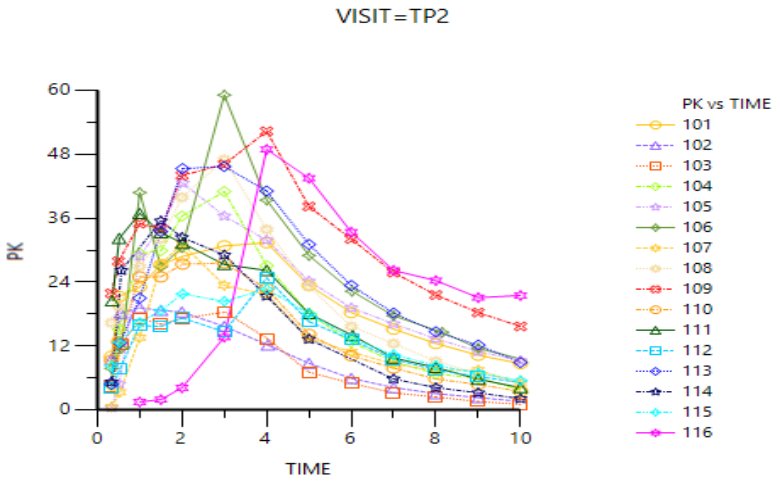
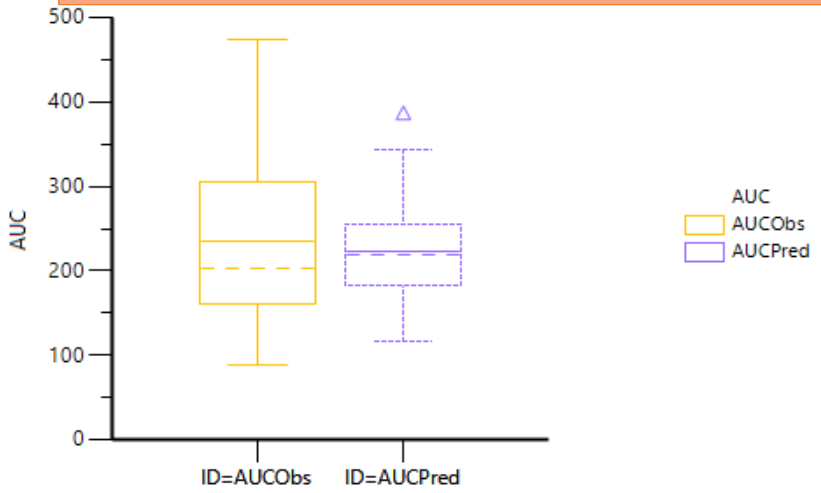
Virtual BE Between Clinical and IVIVE Simulated Profiles

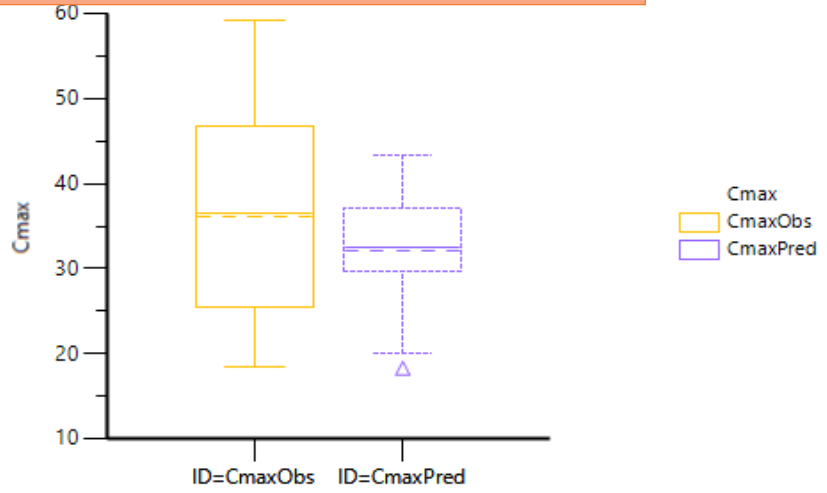
Assumed 10% CV for *in vivo* release rate and extent





16 virtual individuals in PBPK vs 16 clinical subjects (i.e., parallel design)





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Population IVIVE vs. Mean IVIVC Results

Population IVIVE (n=16, PBPK vs Clinical)

Form ID	AUClast*			Cmax*		
	Obs	Pred	%PE	Obs	Pred	%PE
TP2	235.70	222.10	5.77	36.52	32.52	10.95
TP3	225.36	216.76	3.82	25.51	21.10	17.28
TP4	198.91	204.09	-2.61	15.25	17.00	-11.45
TP5	323.71	311.39	3.81	27.13	26.03	4.05
TP6	91.76	106.49	-16.05	8.37	9.22	-10.15
Overall Absolute %PE			6.41			10.77

Mean PK data IVIVC

Formulation	AUCtlast			Cmax		
	Obs	Pred	%PE	Obs	Pred1	%PE1
TP2	241.83	183.53	24.11	31.02	28.54	8.01
TP3	226.69	171.37	24.41	23.84	18.15	23.86
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TP6	96.49	85.07	11.84	7.40	8.44	-13.99
Overall Internal			19.96			12.75

*** Mean of 16 virtual or real subjects for PBPK and clinical study, respectively**

Investigate formulations *in vitro* under more bio-relevant conditions

Develop more mechanistic models of polymer erosion/release

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Case 2. Convolution Based IVIVC Approach

- PK profiles exhibited non-smooth PK curves
  - Challenging to estimate/deconvolute *in vivo* dissolution

- A novel convolution based approach was applied
  - ✓Disposition model was verified with oral solution and IV PK
  - ✓ 1:1 IVIVC was assumed *a priori* (*in vitro* dissolution is *in vivo* dissolution)
  - ✓Clinical trial (age, gender, dosage regimen, sampling times) was simulated with *in vitro* dissolution data for ER products
  - ✓BE between simulated and observed PK data was carried out
  - ✓BE indicates that assumption of existence of IVIVC was correct
  - ✓Validation was carried out by %PE

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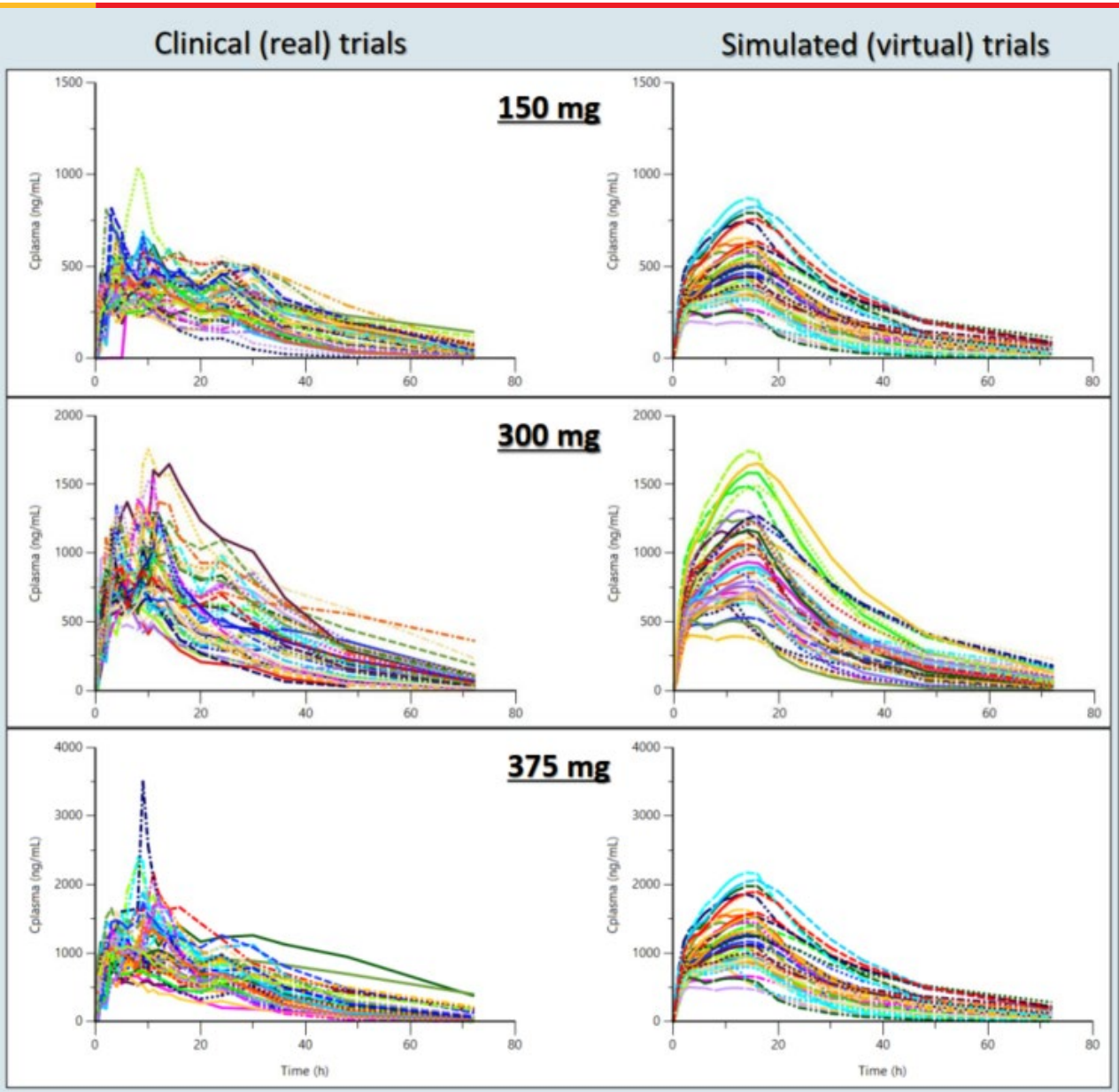
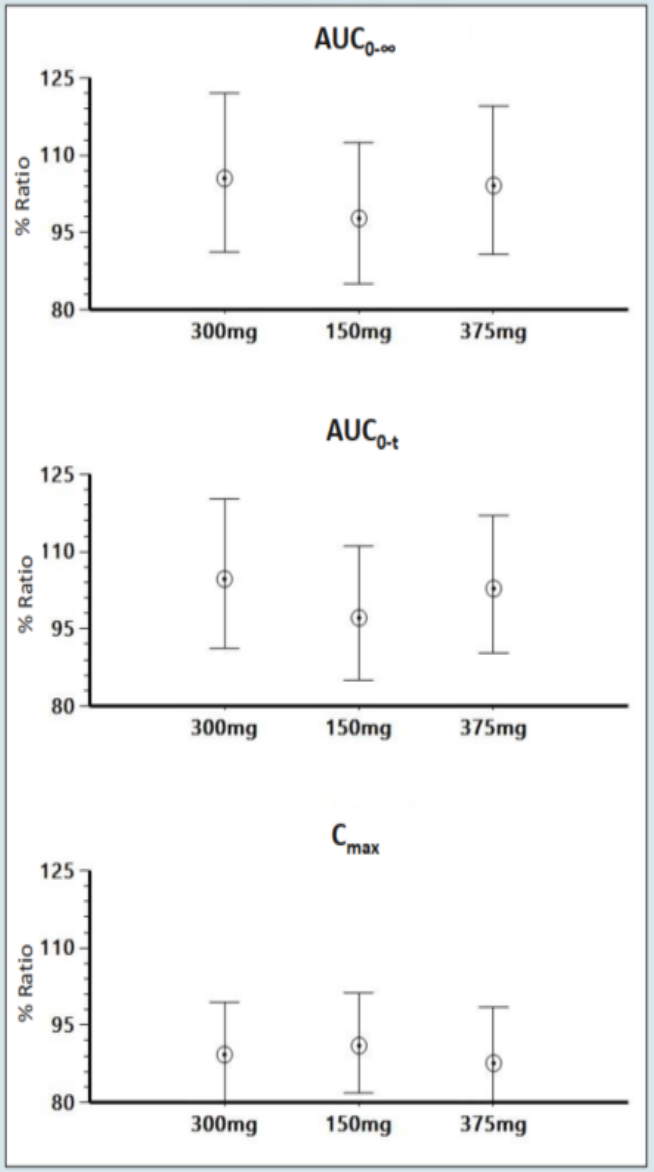
Virtual BE – Simulated vs Clinical PK





Oggianu *et al*. 2018

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Validation of IVIVC

Dosages	PK Parameter and units	Clinical			Simulated			% Prediction Error (%PE)		
		Mean	Median	GeoMean	Mean	Median	GeoMean	Mean	Median	GeoMean
300mg ER (N=42)	$AUC_{0-\infty}$ *(ng/ml*h)*	30598.04	27786.18	28447.65	32519.97	31992.85	30018.16	**-6.28**	**-15.14**	**-5.52**
	AUC_{0-t} *(ng/ml*h)*	28777.90	26922.41	27108.70	30554.15	30082.43	28381.19	**-6.17**	**-11.74**	**-4.69**
	C_{max} *(ng/ml)*	1069.32	996.55	1036.29	975.28	915.42	925.48	**8.79**	**8.14**	**10.69**
150mg ER (N=44)	$AUC_{0-\infty}$ *(ng/ml*h)*	16326.32	15417.47	15391.18	16361.54	15996.31	15045.36	**-0.22**	**-3.75**	**2.25**
	AUC_{0-t} *(ng/ml*h)*	15442.02	15266.33	14657.16	15383.26	15041.28	14238.35	**0.38**	**1.47**	**2.86**
	C_{max} *(ng/ml)*	527.62	515.60	510.00	490.14	457.71	464.29	**7.10**	**11.23**	**8.96**
375mg ER (N=44)	$AUC_{0-\infty}$ *(ng/ml*h)*	38324.91	36953.94	36124.29	40902.93	39990.36	37612.65	**-6.73**	**-8.22**	**-4.12**
	AUC_{0-t} *(ng/ml*h)*	36286.85	34632.22	34613.12	38457.14	37603.01	35595.05	**-5.98**	**-8.58**	**-2.84**
	C_{max} *(ng/ml)*	1400.94	1280.00	1324.35	1225.36	1144.27	1160.73	**12.53**	**10.60**	**12.35**
Average absolute % PE	$AUC_{0-\infty}$ *(ng/ml*h)*							**4.41**	**9.04**	**3.96**
	AUC_{0-t} *(ng/ml*h)*							**4.18**	**7.26**	**3.46**
	C_{max} *(ng/ml)*							**9.48**	**9.99**	**10.67**

Oggianu *et al*. 2018

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Case 3. Modelling Release from Enteric Coated Tablets and MUPS

Esomeprazole Formulations

Table 1
Commercial PPI products included in the study.

Brand name	Strength	Formulation	Enteric coating	Manufacturer
Esomeprazole				
Nexium	10 mg	Gastro-resistant granules for oral suspension, sachet	Methacrylic acid–ethyl acrylate copolymer (1:1) 30% dispersion	AstraZeneca
Emozul	20 mg	Gastro-resistant pellet-enclosed capsule	Methacrylic acid–ethyl acrylate copolymer (1:1) 30% dispersion	Consilient Health Ltd.
Actavis	20 mg	Dispersible tablet containing gastro-resistant pellets (MUPS tablet[a])	Methacrylic acid–ethyl acrylate copolymer (1:1) 30% dispersion	Actavis Group PTC

Table 2
Particle size of multiparticulate products.

Brand name	Formulation	Particle size	
		Sieve method, μm (% weight)	Laser diffraction (X_{50}) (μm)
Esomeprazole			
Emozul	Pellet-enclosed capsule	1400–2000 (100%)	n/a
Nexium	Granules (sachet)	n/a	648
Actavis	MUPS tablet	500–710 (21%); 355–500 (75.23%); 250–355 (3.77%)	494

Liu & Shokrollahi 2015

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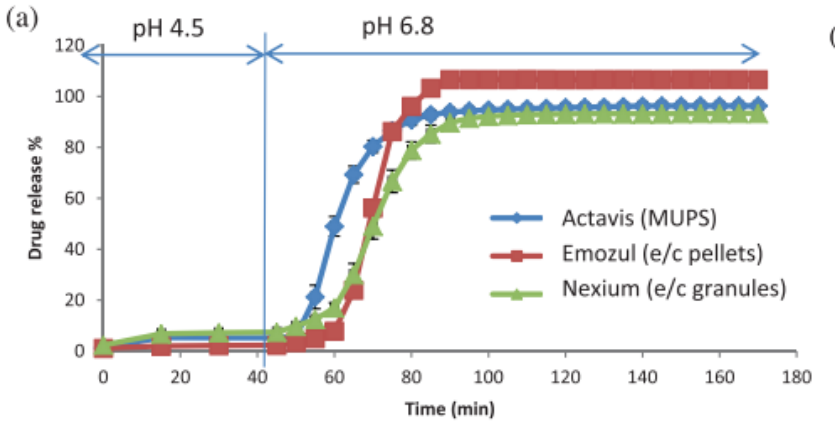
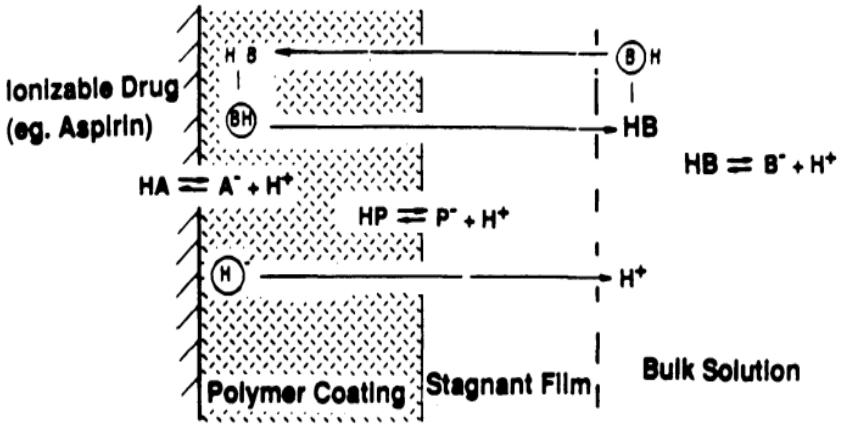
Esomeprazole Formulations

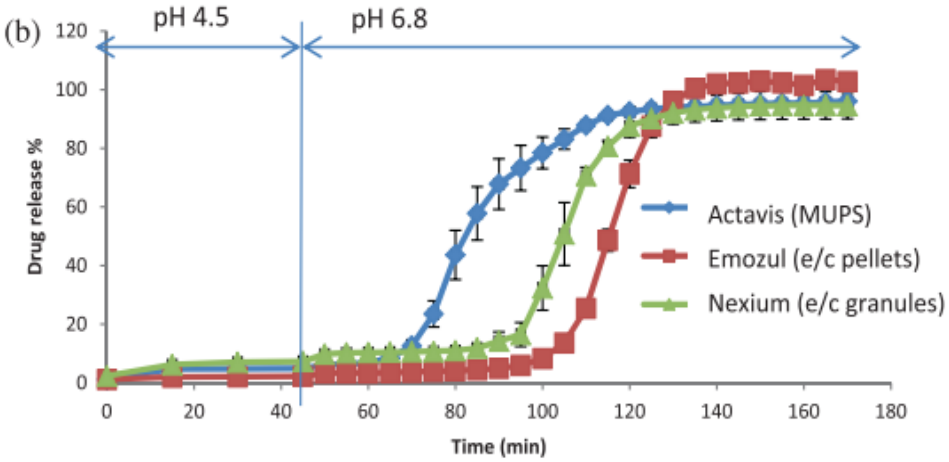
pH 6.8 Phosphate buffer (50mM)





pH 6.8 Bicarbonate buffer (5mM)

Ozturk et al. 1988



Liu & Shokrollahi 2015

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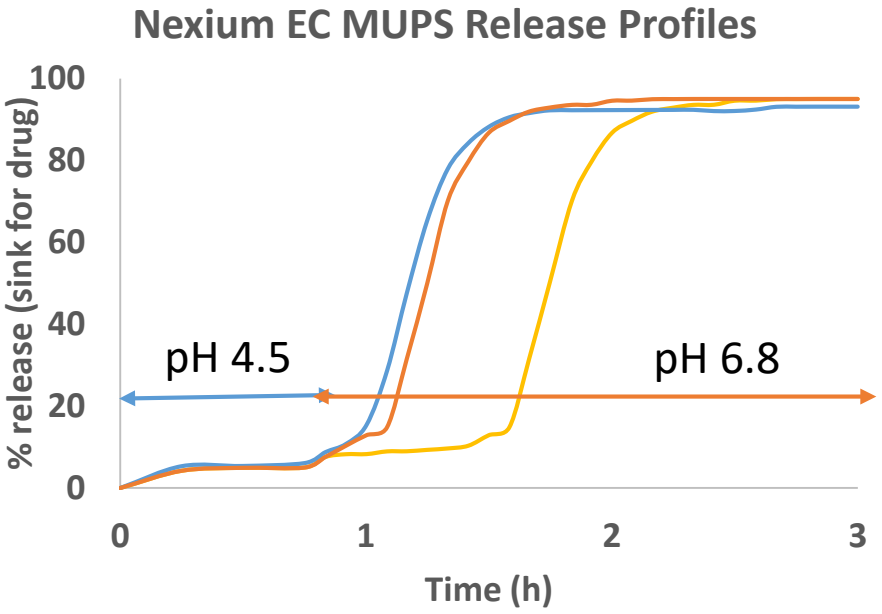
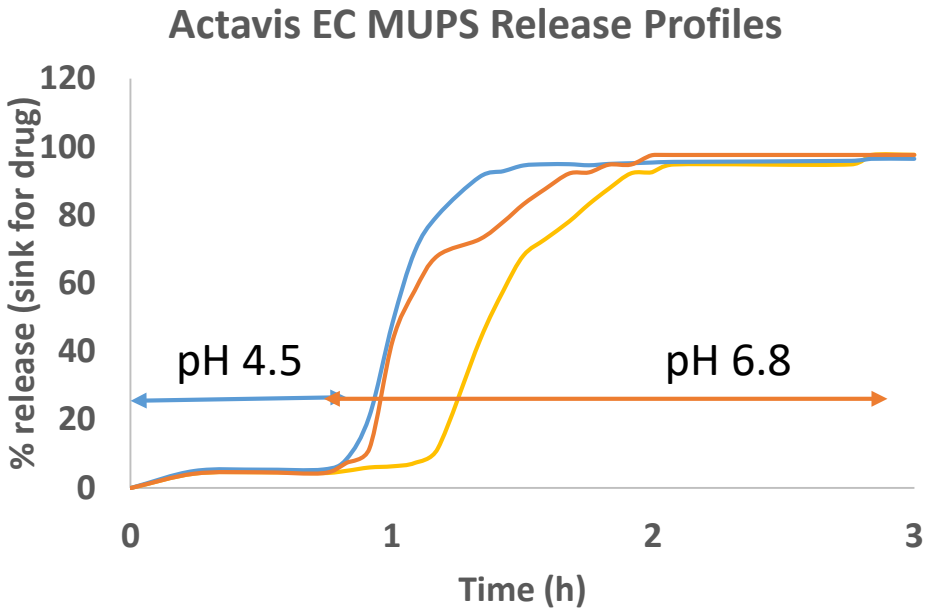
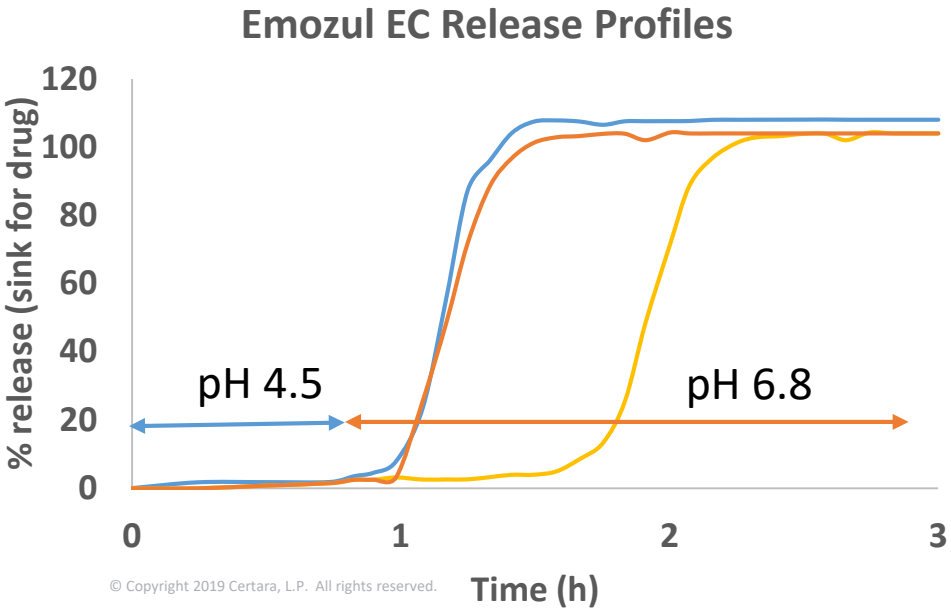
Esomeprazole Formulations







Bicarbonate

Phosphate

Bicarbonate lag-time adjusted

Mainly the buffer system affected lag time rather than rate of dissolution of polymer

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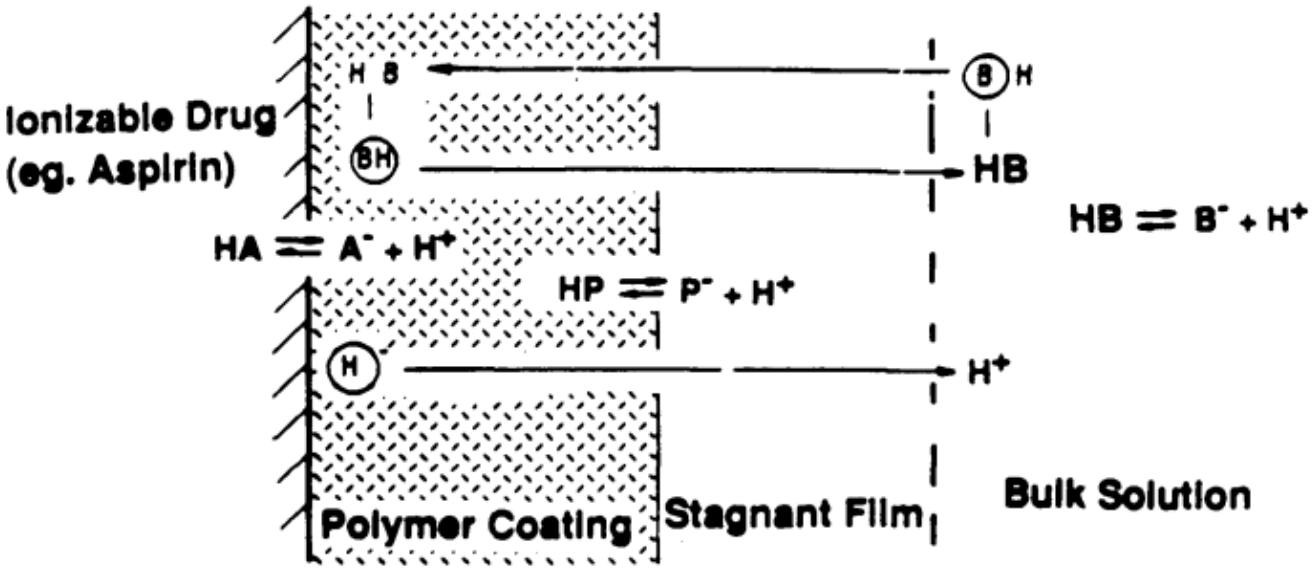
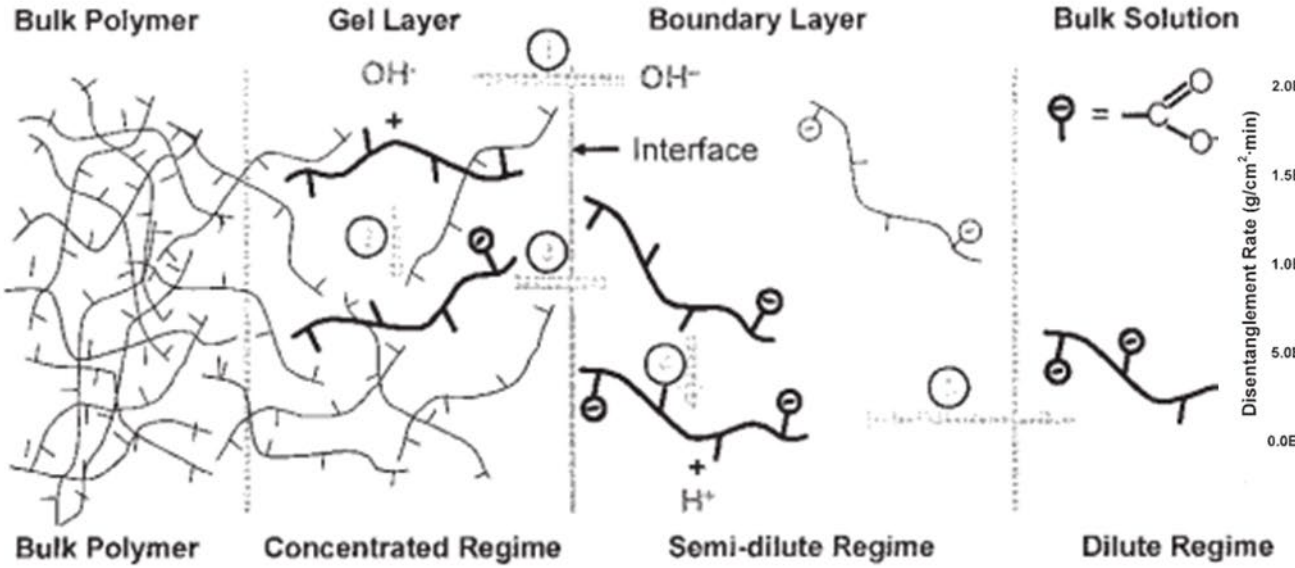
Polymer Erosion/Dissolution – Full Mechanism

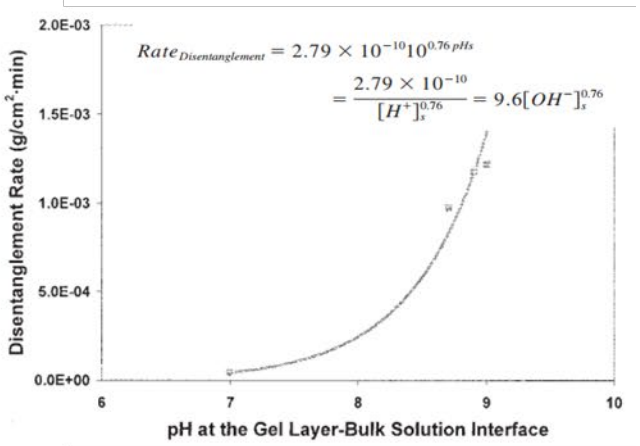


NO DELAY

Ozturk et al. 1988



Dis-entanglement Rate



Nguyen and Fogler 2004

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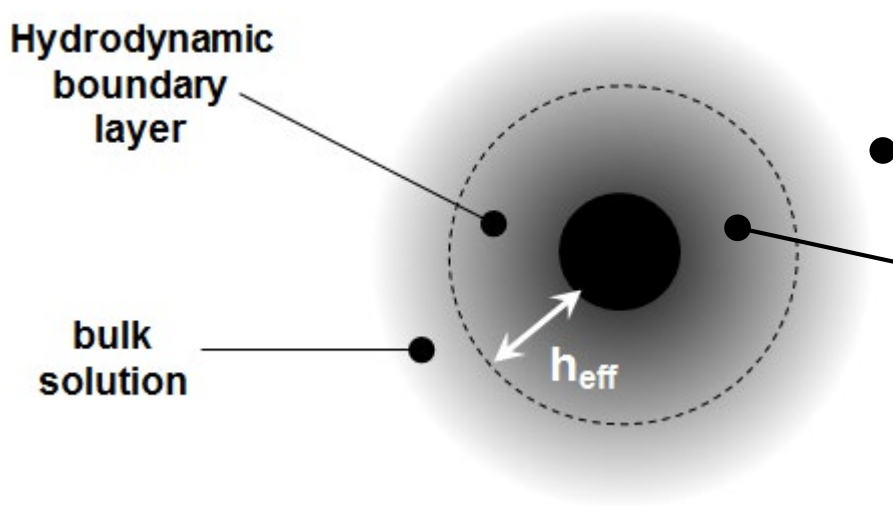
Surface Solubility and Surface pH Model

$$Dissolution\ Rate(t) = -N\frac{D_{eff}}{h_{eff}(t)} 4\pi\, a(t)\,(a(t) + h_{eff}(t))(S_{surf}(t) - C_b(t))$$

A. Bulk Luminal Fluid Solubility

B. Particle Surface Solubility



pH_{bulk}

$C_{bulk}(t)$

$pH_{surface}$

$[Buffer]_{bulk}$

$S_{surface}$

Surface pH Calculations (ionisable API)

Free Acid API

$$HA \Leftrightarrow A^- + H^+$$

Local pH ↓

Solubility ↓

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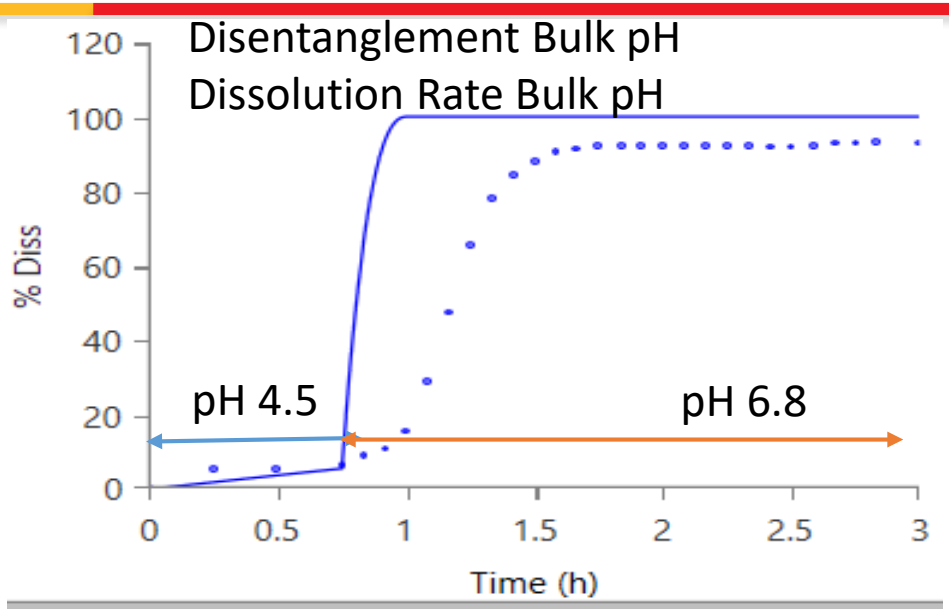
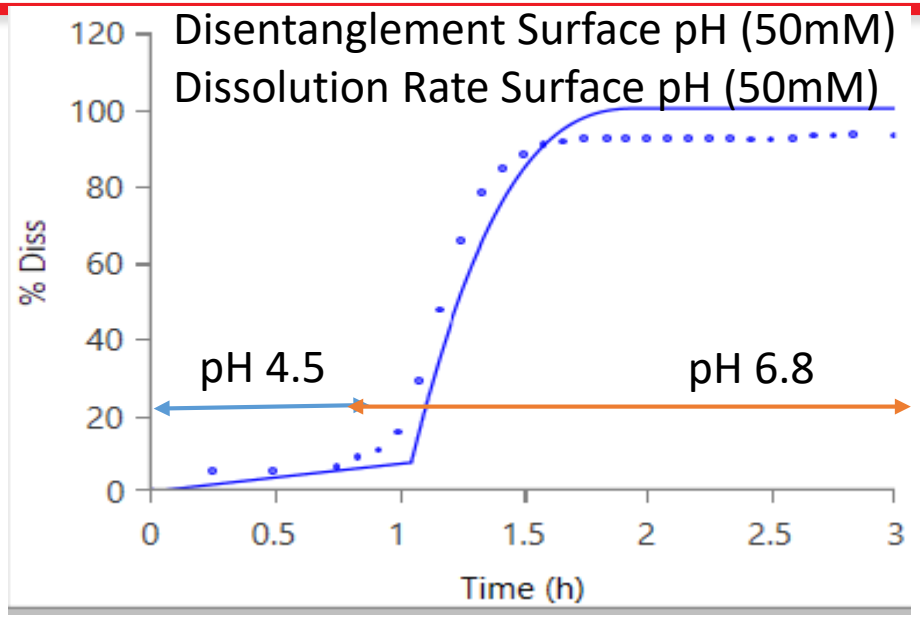
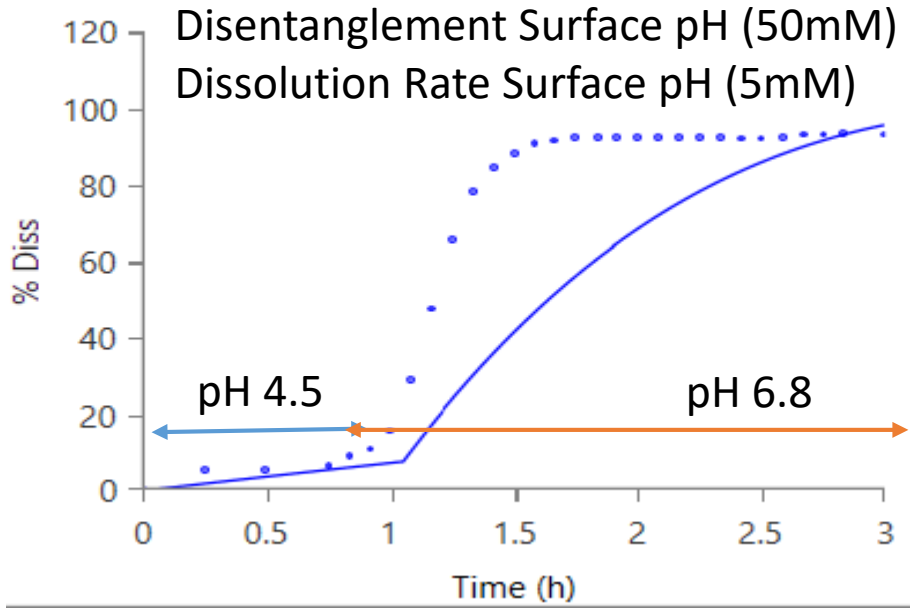
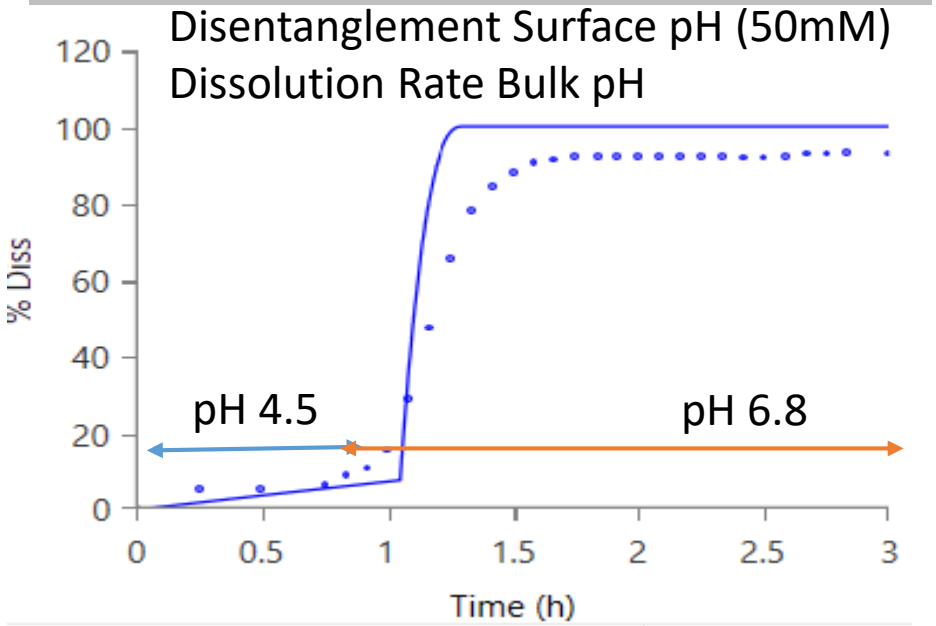
Nexium EC – Dissolution in Phosphate Buffer (50mM)









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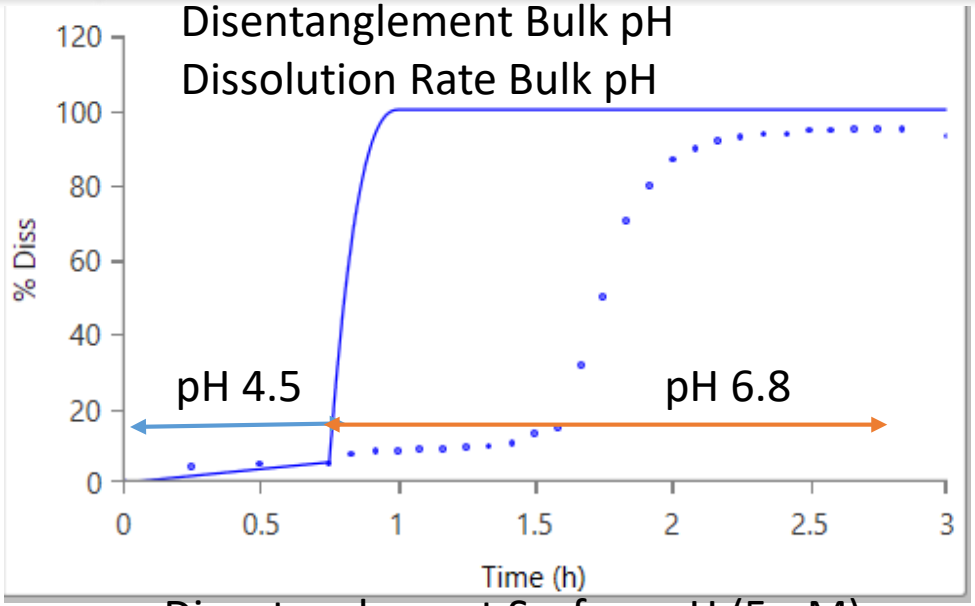
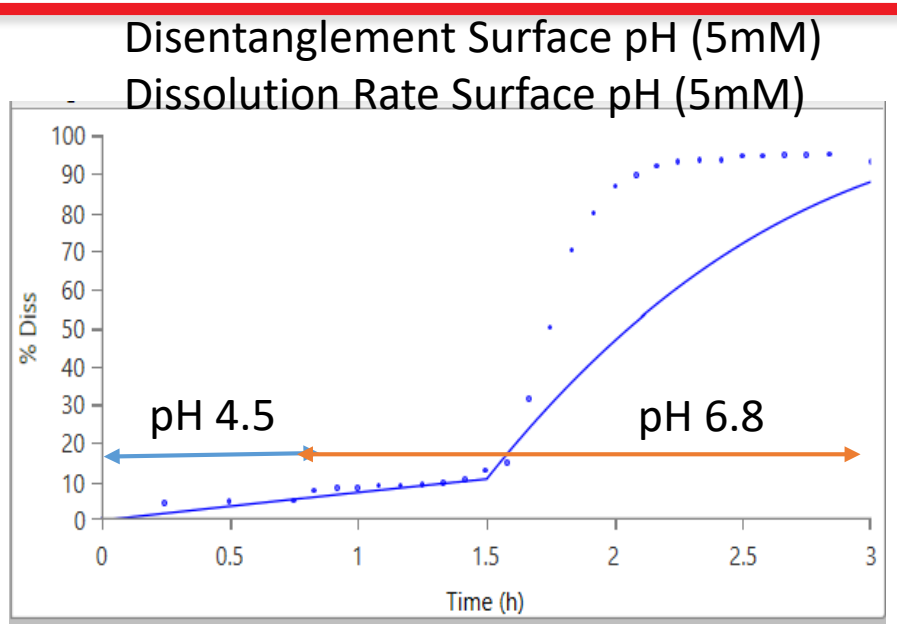
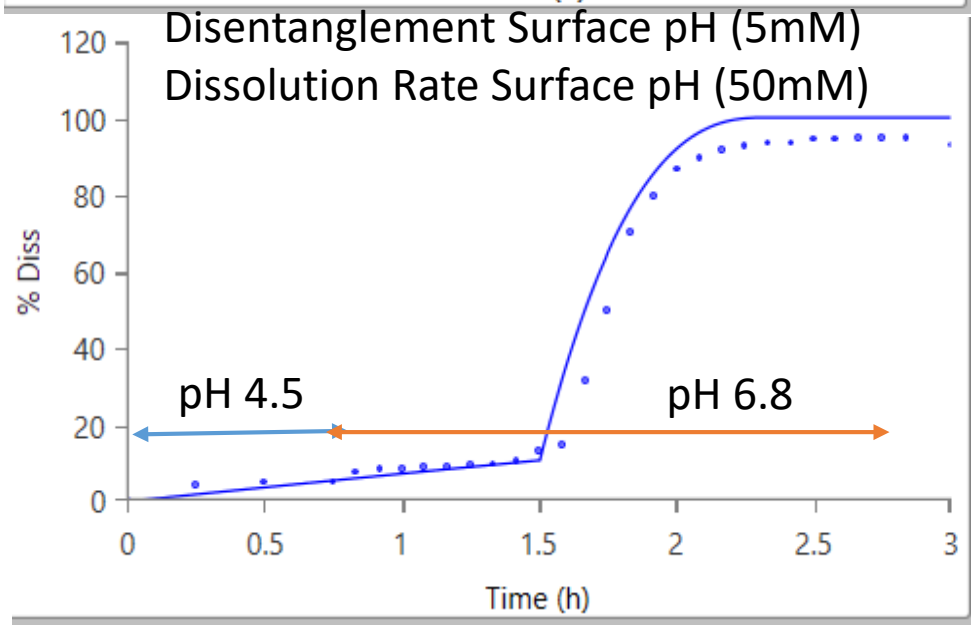
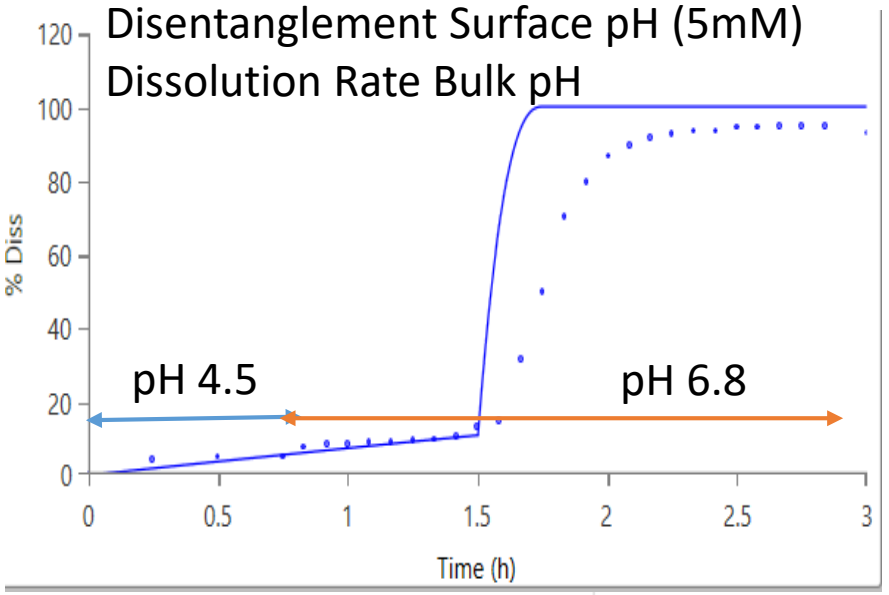
Nexium EC – Dissolution in Bicarbonate Buffer (5mM)









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Under-prediction of Dissolution Rate in Bicarbonate Buffer

pH 6.8 mHanks buffer was used (Liu & Shokrollahi 2015)

The mHanks buffer was adapted from Hanks' balanced salt solution composed of 36.9 mM NaCl, 5.37 mM KCl, 0.812 mM $MgSO_4 7H_2O$, 1.26 mM $CaCl_2$, 0.337 mM $Na_2HPO_4 2H_2O$, 0.441 mM KH_2PO_4, 4.17 mM $NaHCO_3$. A sufficient quantity of CO_2(g) was purged into the media to reach pH 6.8

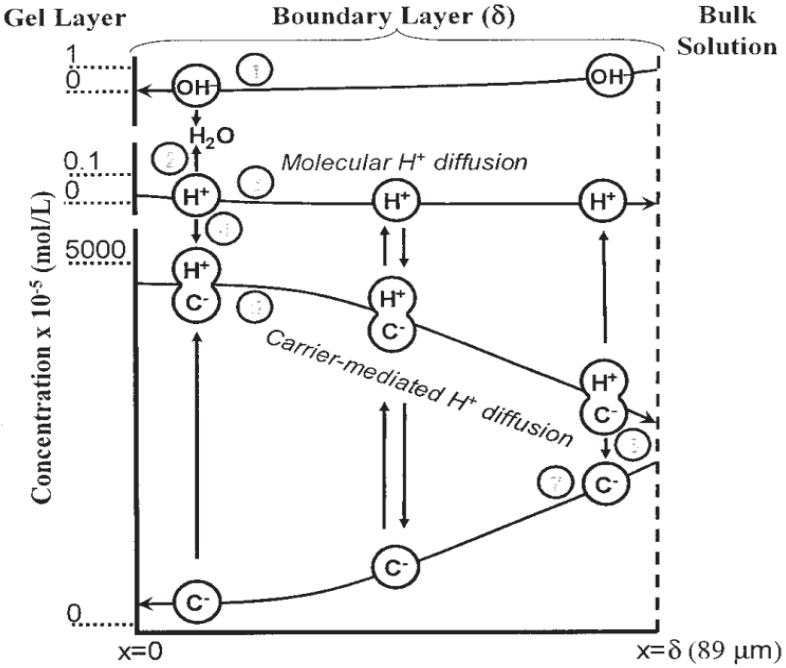

Figure 6. Mechanism of the faciliated diffusion of hydrogen ion in the boundary layer.

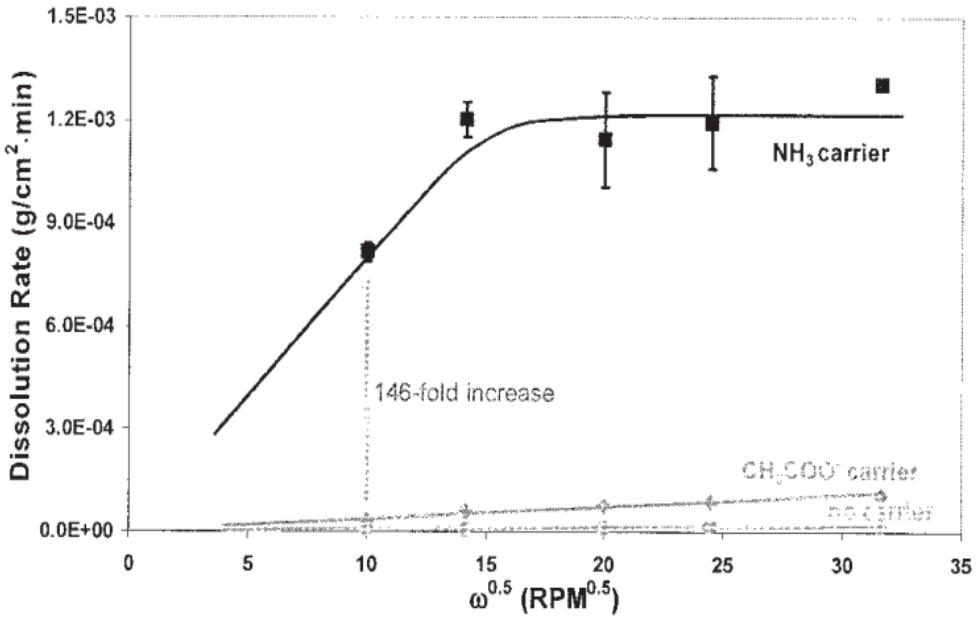

Figure 8. Facilitation effect of proton-carriers ([Carrier] = 0.5 mol/L, pH = 9).

Nguyen and Fogler 2004

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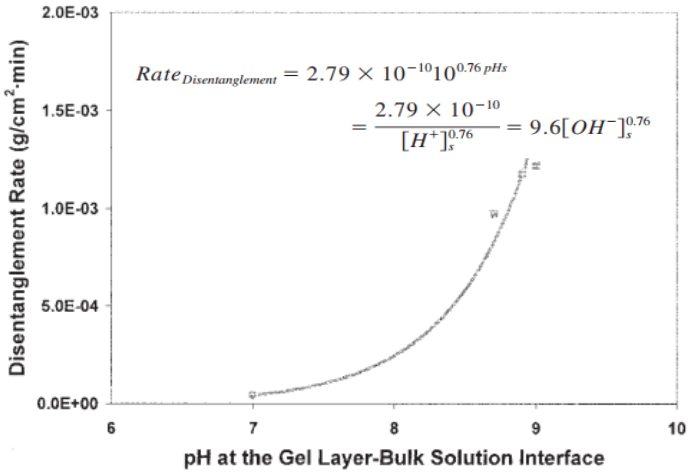
Findings from the Study

- Surface pH effect on disentanglement of polymer and the thickness of the enteric polymer coat are likely rate limiting steps rather than surface pH on polymer dissolution rate.
- Other proton carriers in the formulations play a role after disentanglement hence the rate of dissolution is almost the same in phosphate and bicarbonate buffers
- AND/OR – the thickness of polymer coat is formulation dependent and not correlated with size of granules



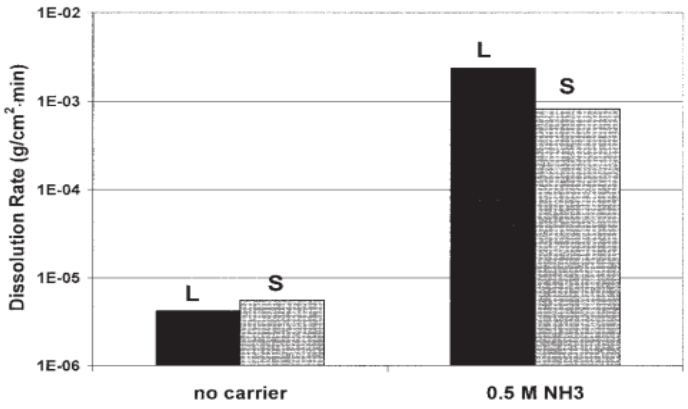


Figure 13. Effect of polymer acidity on the dissolution rate (pH = 9).

Nguyen and Fogler 2004

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Future Directions

- More mechanistic models for polymer erosion, swelling, diffusion and dissolution are needed
- Further understanding on how polymer combinations and interactions with other excipients impact release is needed
- Further research into how the polymers behave *in vivo* and relevant physiological parameters that contribute to variability
- Formulation simulations can be performed at the population level under a VBE framework to factor in the impact of variability
- More case studies spanning different drug and formulation types and polymer combinations are needed to understand and address the gaps

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Note: The Simcyp Simulator is freely available, following completion of the relevant workshop, to approved members of academic institutions and other not for -profit organizations for research and teaching purposes.

Questions?