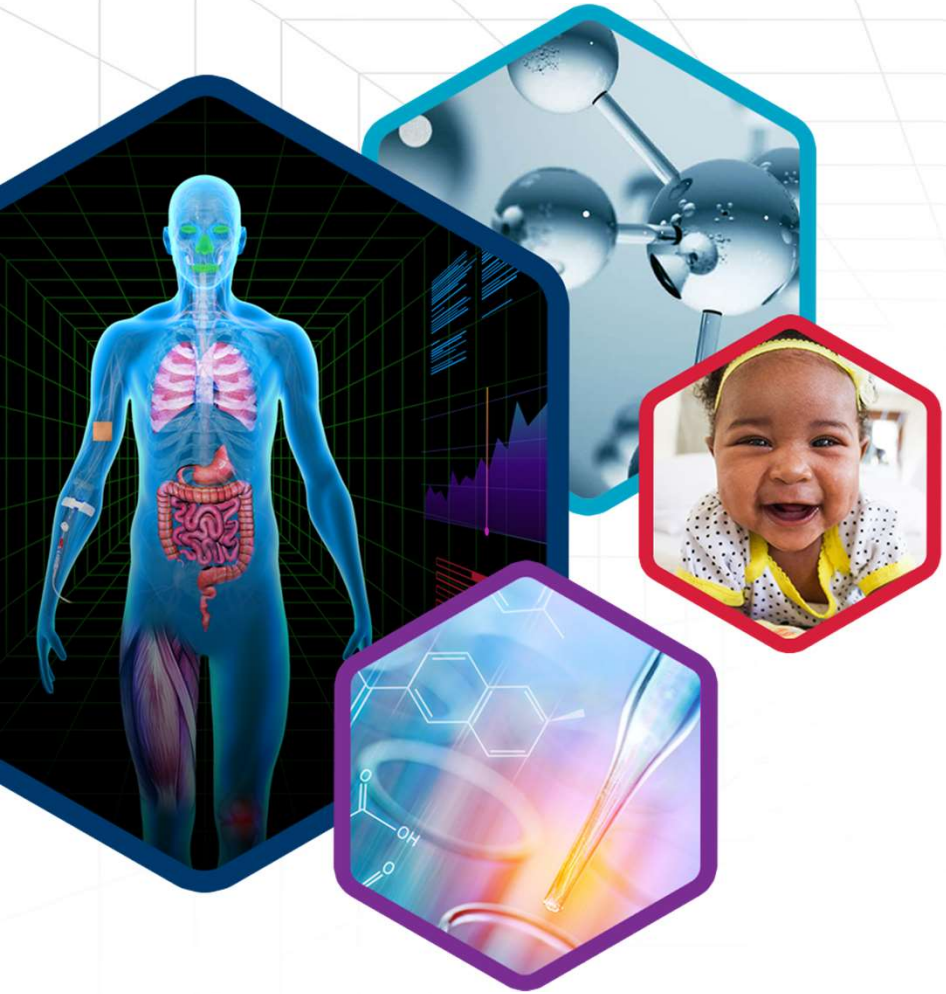

SimulationsPlus

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Challenges and opportunities in the development of IVRT and IVIVC of complex injectable formulations

Xavier Pepin

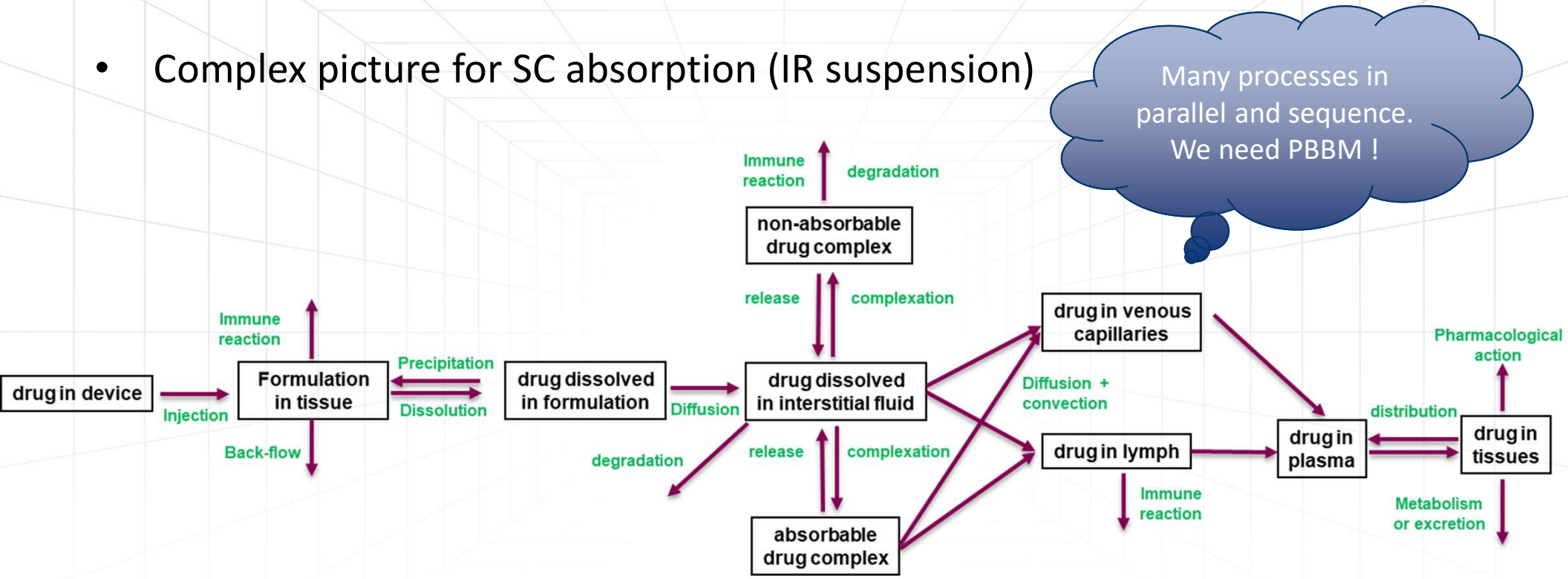
June 29, 2022

Outline

- Subcutaneous physiologically based modeling : A complex picture
- Case studies
  - Exenatide subcutaneous formulations : From ‘simple’ IR solution to extended-release microspheres
  - IVIVC: challenges with the IVR method and opportunities to use PBPK
  - Towards more mechanistic release models for PLGA spheres
    - Piroxicam : effect of particle size
- Take home messages

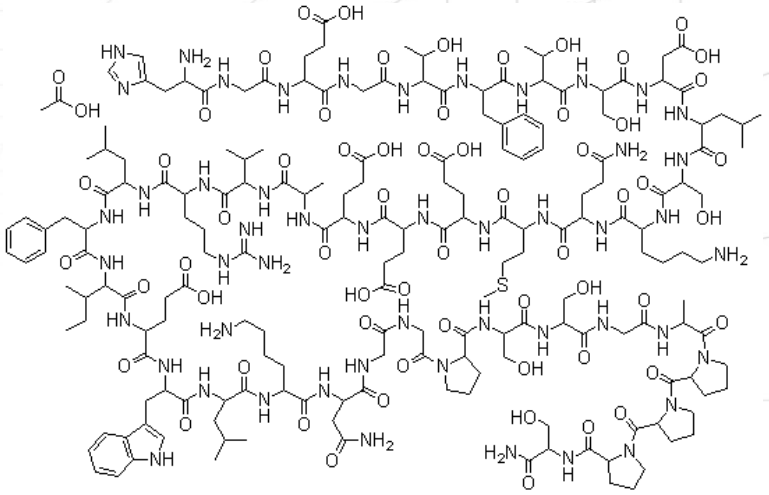
Phenomena leading to SC absorption

- Complex picture for SC absorption (IR suspension)



Exenatide

- 39 AA peptide
- MW: 4186.6, log P = -1.1[A] B:P=0.631
- fu,p not determined. Taken at 99%[B]
- Highly soluble and hydrophilic
- IV infusion in HV from study 2293-111
- IR formulation (Byetta®) = 250 ug/mL
- MR formulations (Bydureon® and Bydureon Bcise®)
  - Bydureon = 2 mg/0.85 mL PLGA extended release microspheres



His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2

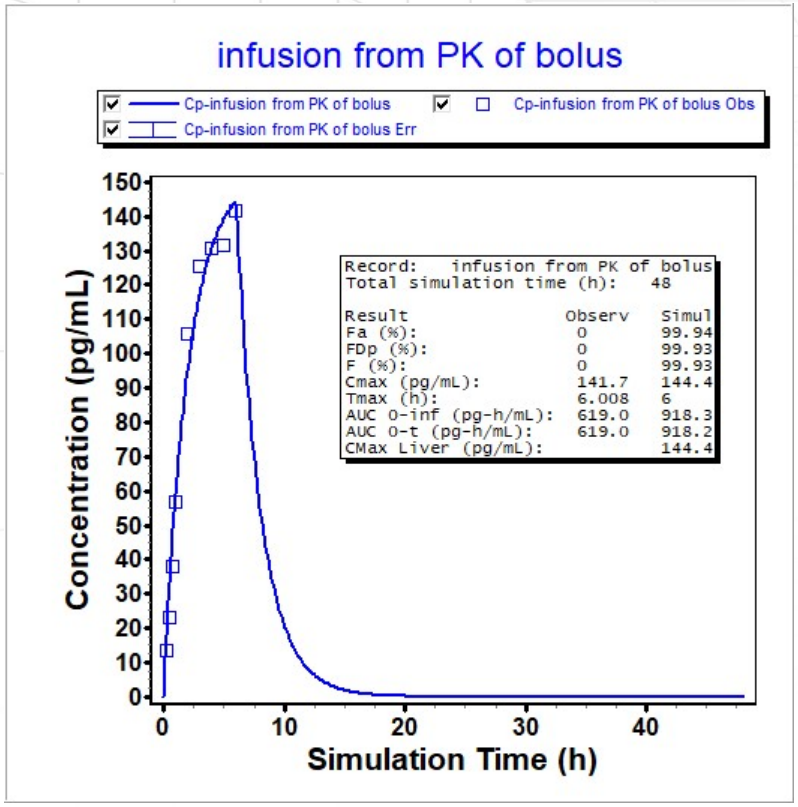
A: Menzel, C.;Holzeisen, T.;Laffleur, F.;Zaichik, S.;Abdulkarim, M.;Gumbleton, M.;Bernkop-Schnürch, A., In vivo evaluation of an oral self-emulsifying drug delivery system (SEDDS) for exenatide. J Control Release 2018, 277, 165-172. DOI: 10.1016/j.jconrel.2018.03.018.

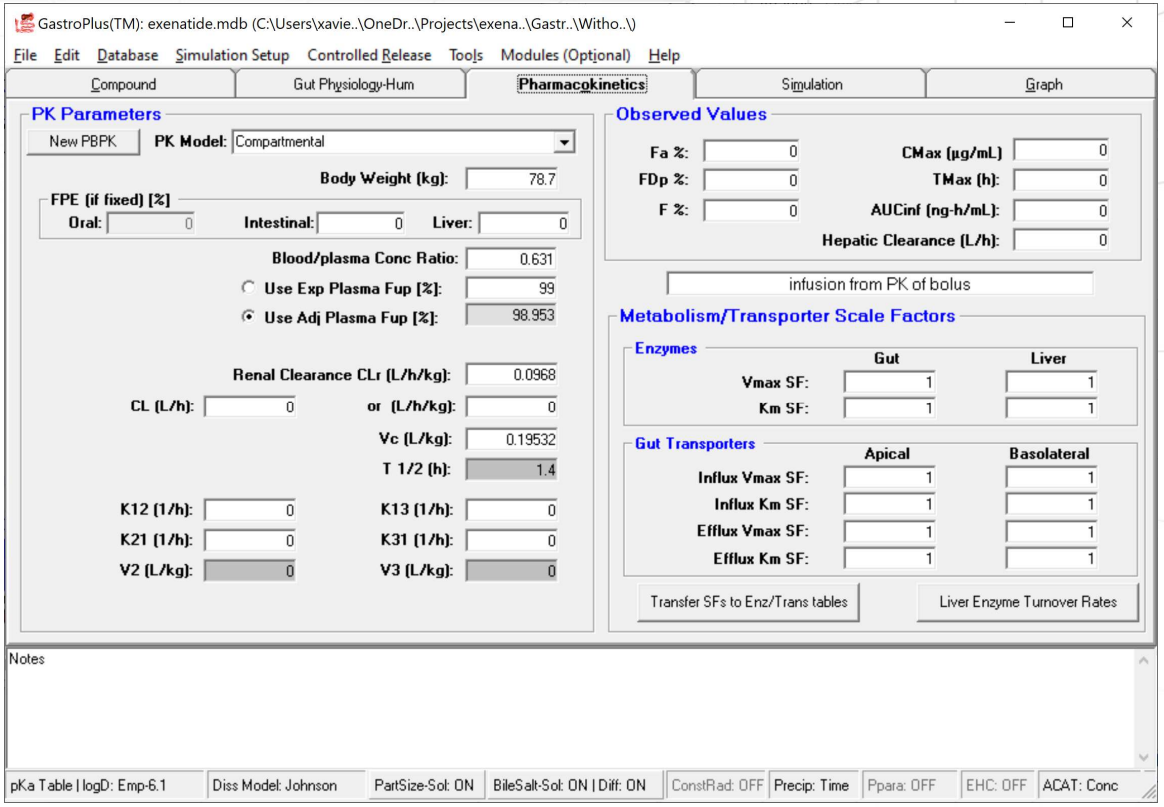
B: Plum, A.;Jensen, L. B.;Kristensen, J. B., In vitro protein binding of liraglutide in human plasma determined by reiterated stepwise equilibrium dialysis. Journal of Pharmaceutical Sciences 2013, 102, 2882-2888.

C: Degn, K. B.;Brock, B.;Juhl, C. B.;Djurhuus, C. B.;Grubert, J.;Kim, D.;Han, J.;Taylor, K.;Fineman, M.;Schmitz, O., Effect of Intravenous Infusion of Exenatide (Synthetic Exendin-4) on Glucose-Dependent Insulin Secretion and Counterregulation During Hypoglycemia. 2004, 53, 2397-2403. DOI: 10.2337/diabetes.53.9.2397.

PK parameters for IV

- IV disposition from Study 2293-111[A]

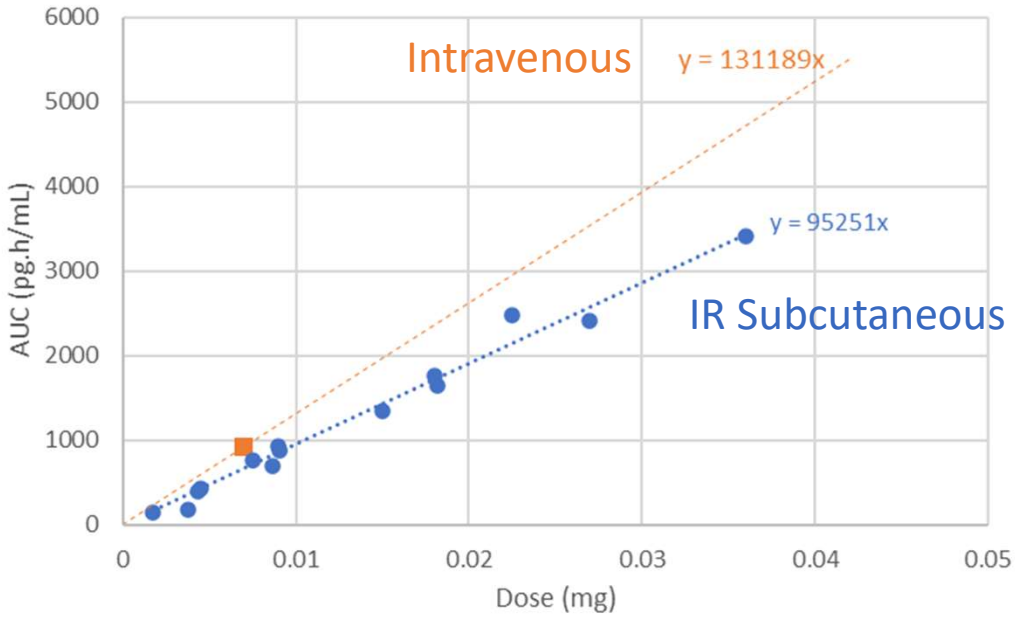




A: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021773_Byetta_biopharmr.PDF

Analysis of dose ranging studies

- Immediate release SC : 2293-101, 2293-102, 2293-104, 2293-110 (ascending dose studies)
- Intravenous infusion : 2293-111

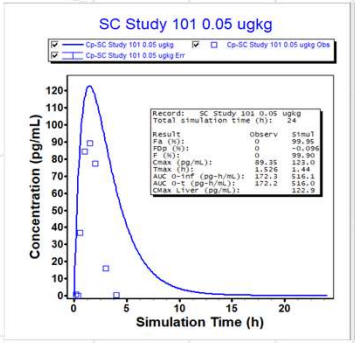


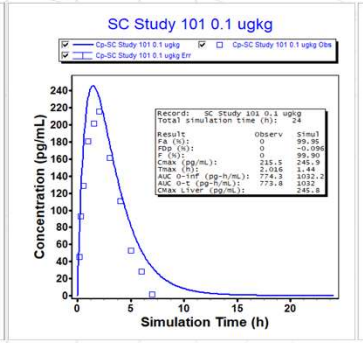
Intravenous clearance : 7.6L/h
F estimated from all SC injections = 72± 6%

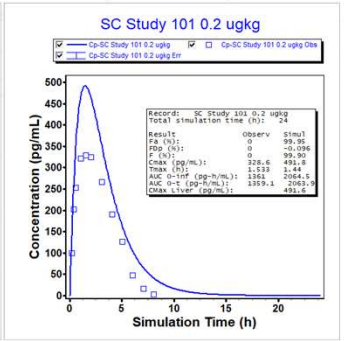
A: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021773_Byetta_biopharmr.PDF

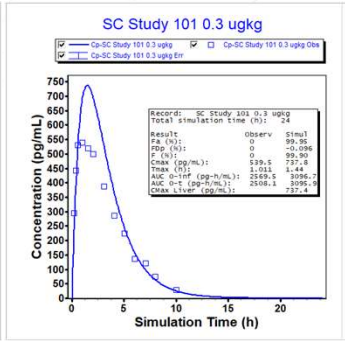
Prediction of PK profiles

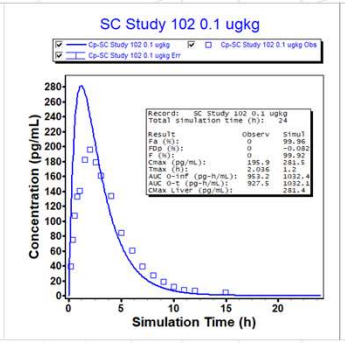
- Base model- no in situ clearance

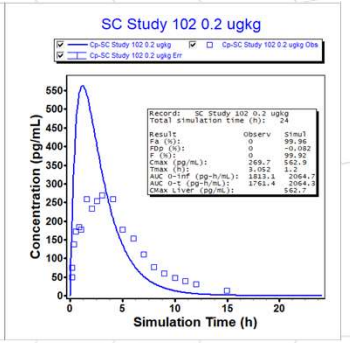


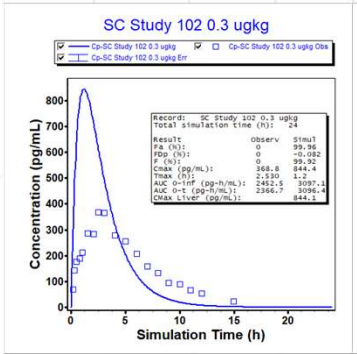


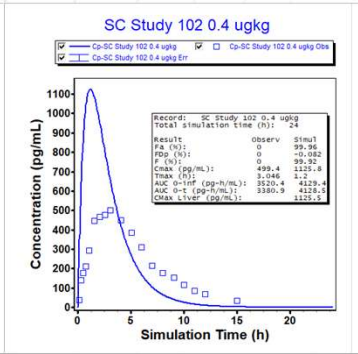


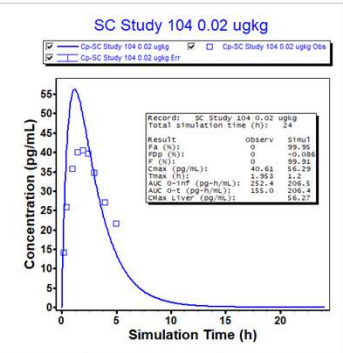


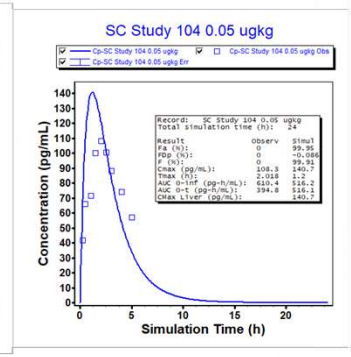


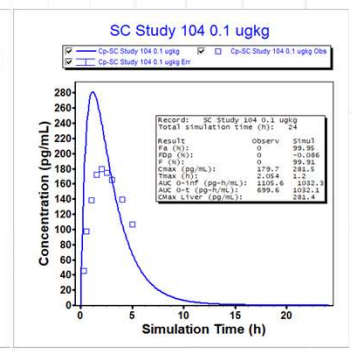












Prediction of PK profiles

- Base model- no in situ clearance

$AUC_{0\text{-}inf}$

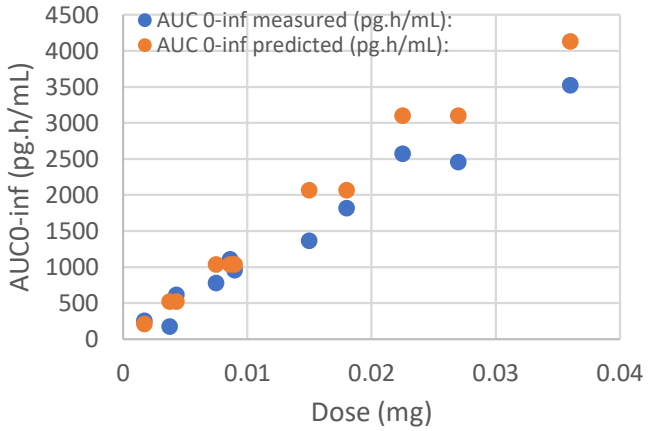
AFE	AAFE
1.2	1.3

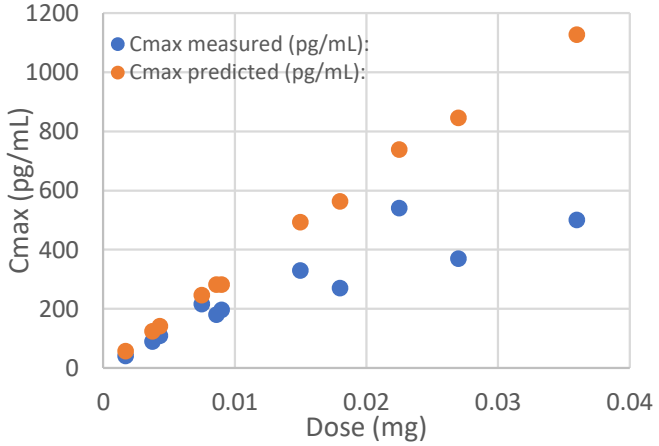
C_{max}

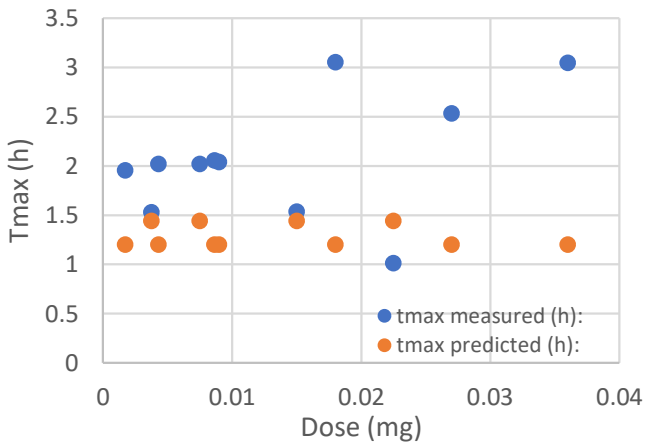
AFE	AAFE
1.6	1.6

t_{max}

AFE	AAFE
0.6	1.6







Overprediction of C_{max} and AUC

T_{max} underpredicted but right ballpark

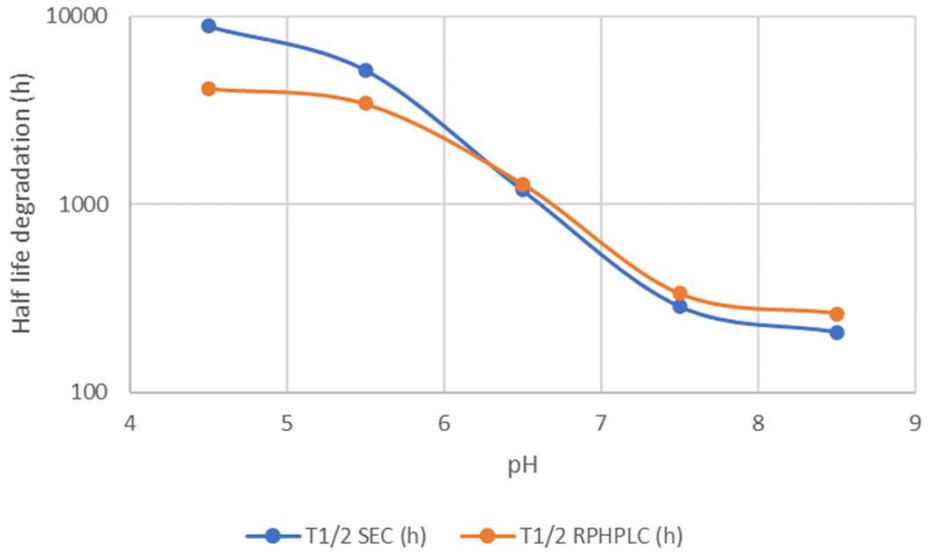
AFE = Average Fold Error = $10^{\frac{\sum Log\left(\frac{Predicted}{Measured}\right)}{n}}$, AAFE = Absolute Average Fold Error = $10^{\frac{\sum Log\left(\left|\frac{Predicted}{Measured}\right|\right)}{n}}$

Potential explanation of over-prediction

- Chemical degradation
- Metabolism
- Binding to cell surfaces or ECM
- Physical degradation (precipitation)
- Oligomerization (dimers)
- Slow diffusion of dimers in the ECM

Exenatide chemical degradation

- pH dependent degradation (chemical and formation of aggregates)
- Evidences by SEC and reverse phase HPLC



Unlikely explanation for the IR formulations ($t_{1/2}$>100h)

A: Benet, A., et al., The Effects of pH and Excipients on Exenatide Stability in Solution. Pharmaceutics, 2021. 13(8). https://doi.org/10.3390/pharmaceutics13081263

Potential explanation of over-prediction

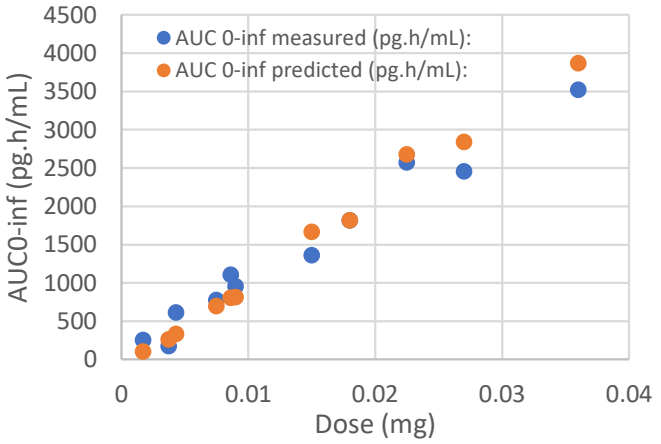
- Metabolism
  - Not a major substrate to DPP-4 or other peptidases
  - Attempt to simulate first pass degradation with constant in situ clearance

Prediction of PK profiles

- Model with 0.0001 L/h in situ clearance

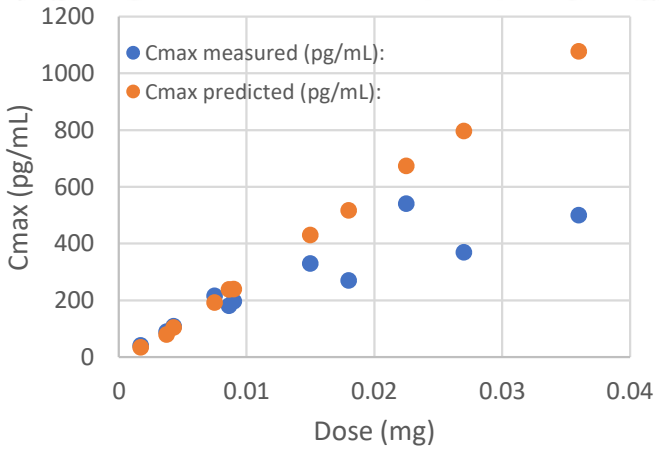
$AUC_{0\text{-inf}}$

AFE	AAFE
0.9	1.3



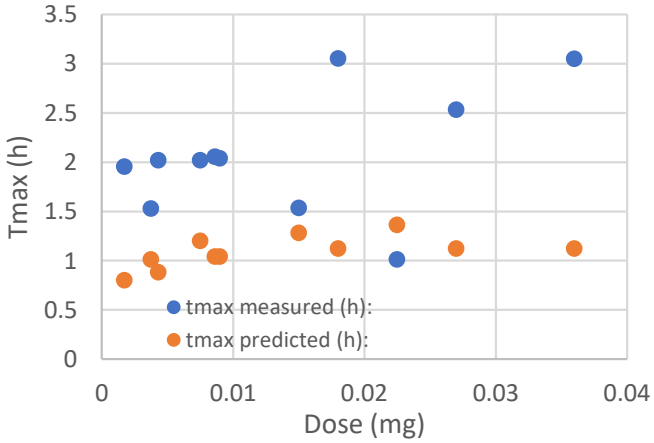
C_{max}

AFE	AAFE
1.3	1.4



t_{max}

AFE	AAFE
0.5	1.9

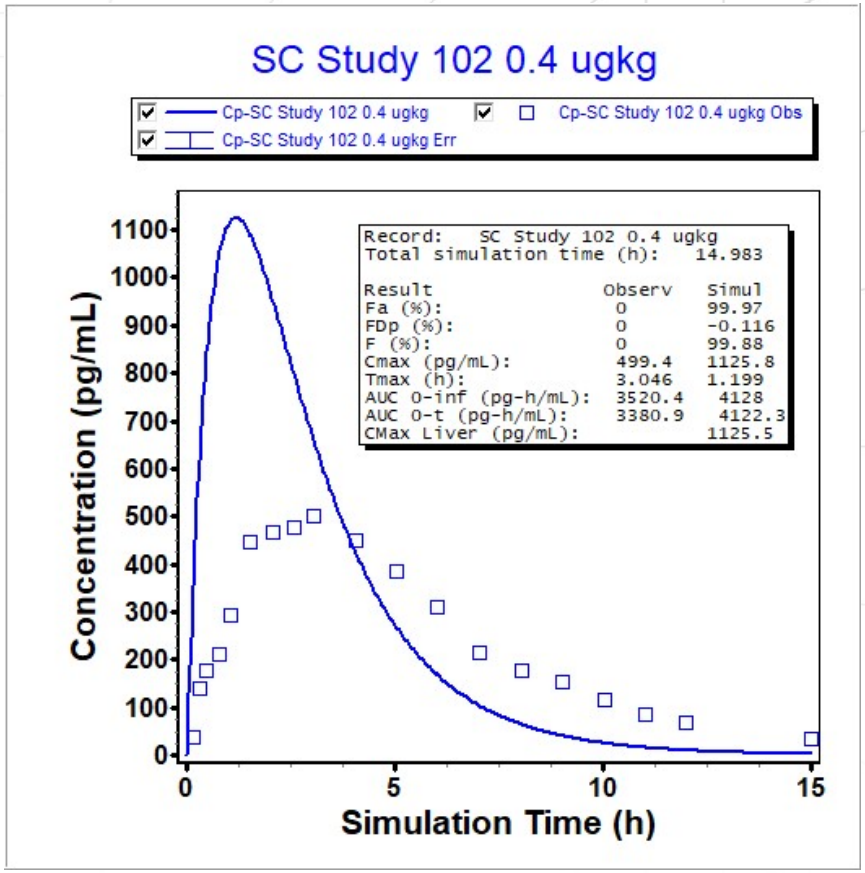


Improved prediction of C_{max} and AUC
T_{max} underprediction is worse

Local clearance does not help with profile prediction

Potential explanation of over-prediction

- *Chemical degradation*
- *Metabolism*
- Physical degradation (precipitation)
- Binding to cell surfaces
- Oligomerization (dimers)
- Slow diffusion of dimers in the ECM



Exenatide binding to cell surfaces

- Exenatide binds to liposomes as monomer and dimer [A]
- Study 102, 0.4 µg/kg, solution concentration 250 µg/mL, BW 90 kg, injection volume = 144 µL

$$S_{max} = V_{inj} \times \frac{\theta_{cell}}{RCS} \times \frac{6}{d_{adipocyte}}$$

144 µL

0.86

0.13

100-123 µm

$$S_{max} \approx 465 - 572\ cm^2$$

Monomer

Exenatide Molecular hydrodynamic radius	1.03	nm
Molecular surface area	3E-18	m2
Surface area available for binding	0.0465	m2
Molecules of exenatide bound	1E+16	
Mass of exenatide bound	9.70E+01	ug
Mass of drug injected	36	ug injected
Binding capacity	269.5	% of mass injected

Dimer

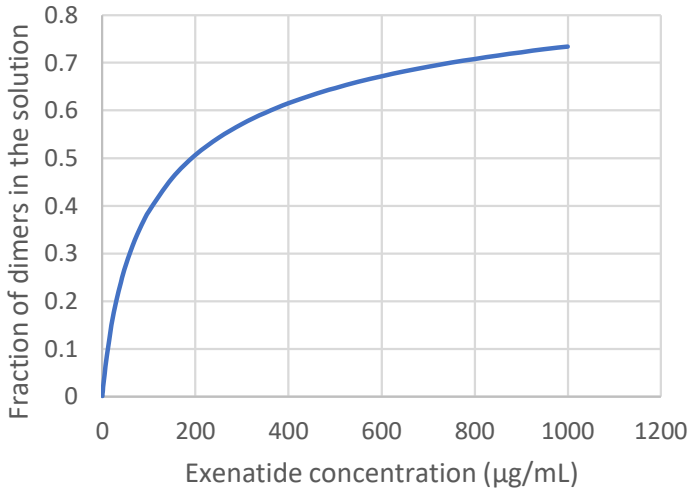
Dimer radius	10	nm
Dimer surface area	3E-16	m2
Surface area available for binding	0.0465	m2
Molecules of exenatide bound	3E+14	
Mass of exenatide bound	2.06E+00	ug
Mass of drug injected	36	ug injected
Binding capacity of cells	5.72	% of mass injected

A: Stulz, A., et al., Primary and Secondary Binding of Exenatide to Liposomes. Biophysical Journal, 2020. 118(3): p. 600-611. https://www.sciencedirect.com/science/article/pii/S0006349519344285

V_{inj} = volume injected, θ_{cell} = Cellular fraction in tissue, $d_{adipocyte}$ = diameter of adipocyte, RCS : relative concentration of formulation in depot

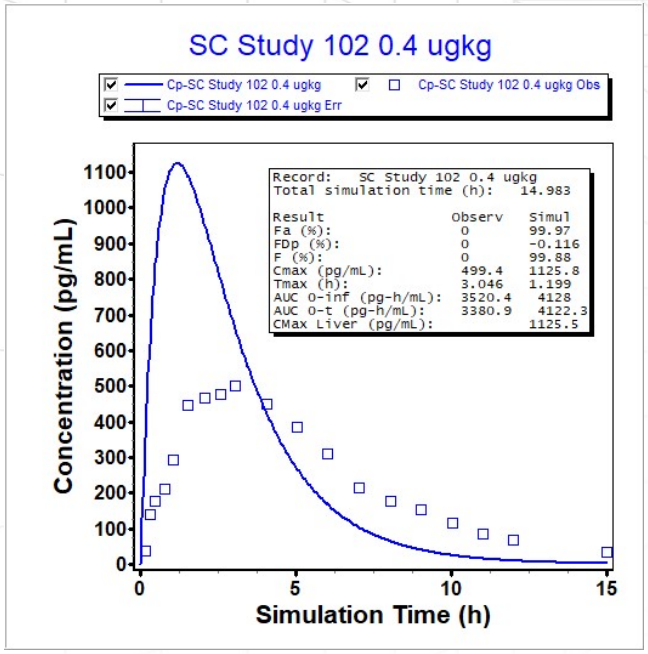
Exenatide oligomerization and diffusion

- Dimer formation with a K_d= 46 µM [A]
- $P + P \leftrightarrow PP,\ K_d = \frac{[P]^2}{[PP]}$
- At 250 µg/mL approx. 55% dimer
- 17% of the monomer and 32% of the dimer would be expected to be cleared by the lymph
- Dimer diffusion coefficient through ECM = 0.054 m^2/s compared to 0.124 m^2/s for the monomer [B]

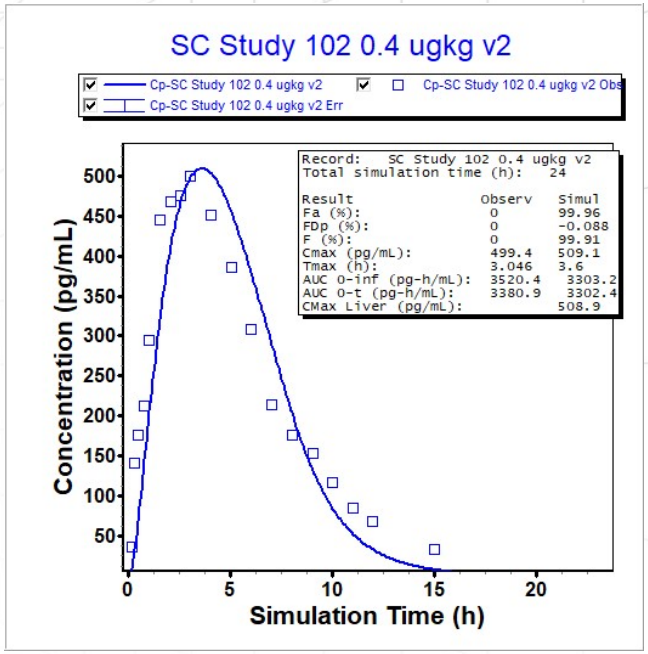


A: Stulz, A., et al., Primary and Secondary Binding of Exenatide to Liposomes. Biophysical Journal, 2020. 118(3): p. 600-611. https://www.sciencedirect.com/science/article/pii/S0006349519344285
B: Levick, J.R., FLOW THROUGH INTERSTITIUM AND OTHER FIBROUS MATRICES. Quarterly Journal of Experimental Physiology, 1987. 72(4): p. 409-438. https://doi.org/10.1113/expphysiol.1987.sp003085

Impact of dimer release on PK

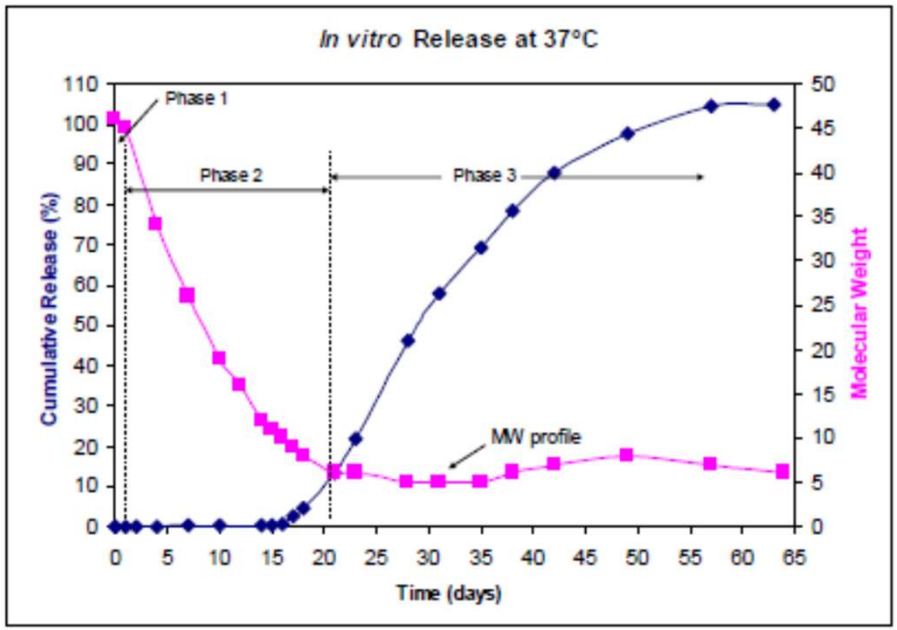


Move to “SQ suspension”
10 nm radius
20% bound to cells
Reduced diffusion coefficient
No metabolism
Reduced solubility for monomer



Modelling ER formulations

- Bydureon mechanism of release [A]



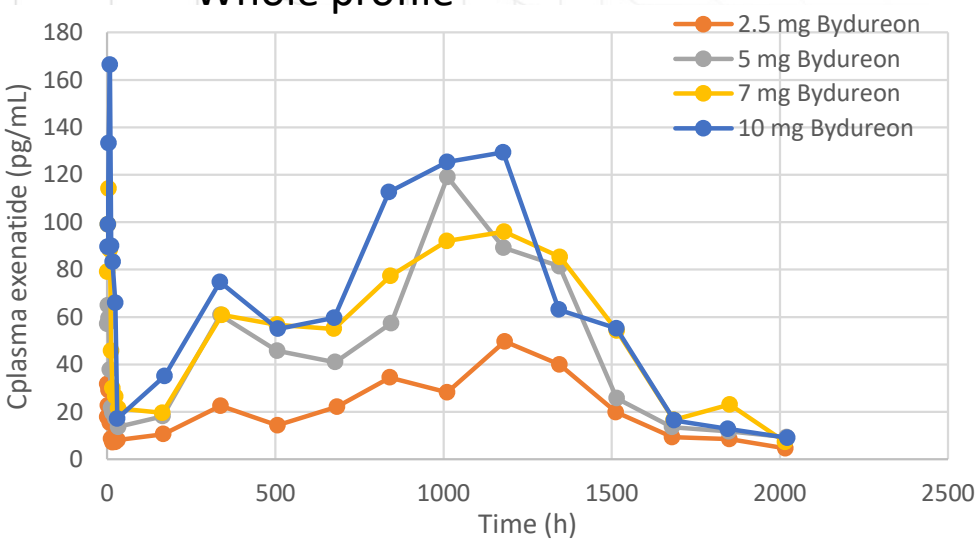
1. Initial release of loosely bound surface exenatide,
2. Hydration phase where the polymer begins to be hydrolyzed providing for a controlled manner for exenatide release, and
3. Extended-release phase as the polymer matrix erodes

A: https://www.tga.gov.au/file/1010/download

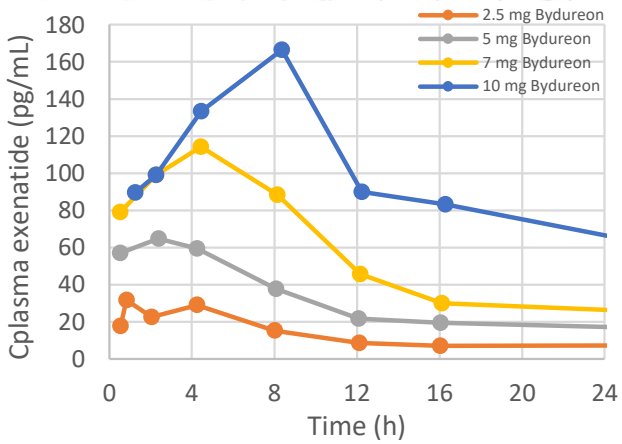
Modelling ER formulations

- Bydureon PK, study 2993LAR-103 [A]

Whole profile



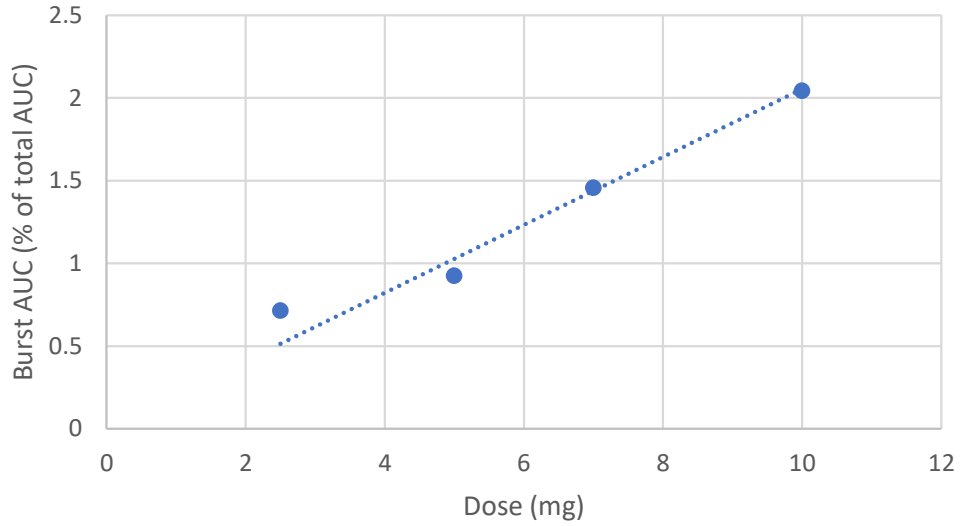
Burst release



A: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022200Orig1s000ClinPharmR.pdf

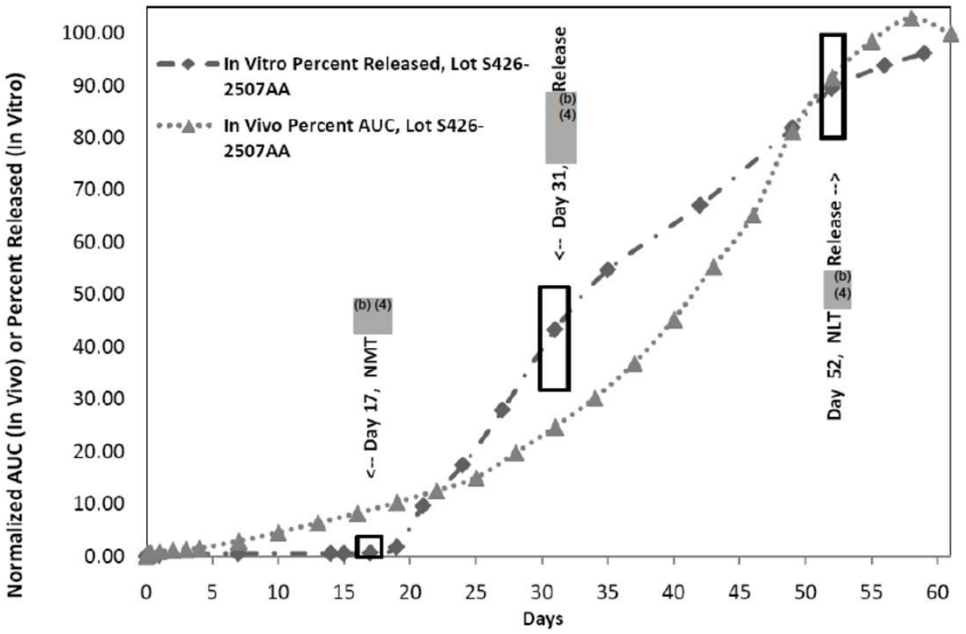
Burst release

- Loosely bound drug (less than 2% of the total AUC)



IVIVC – based on cumulative AUC

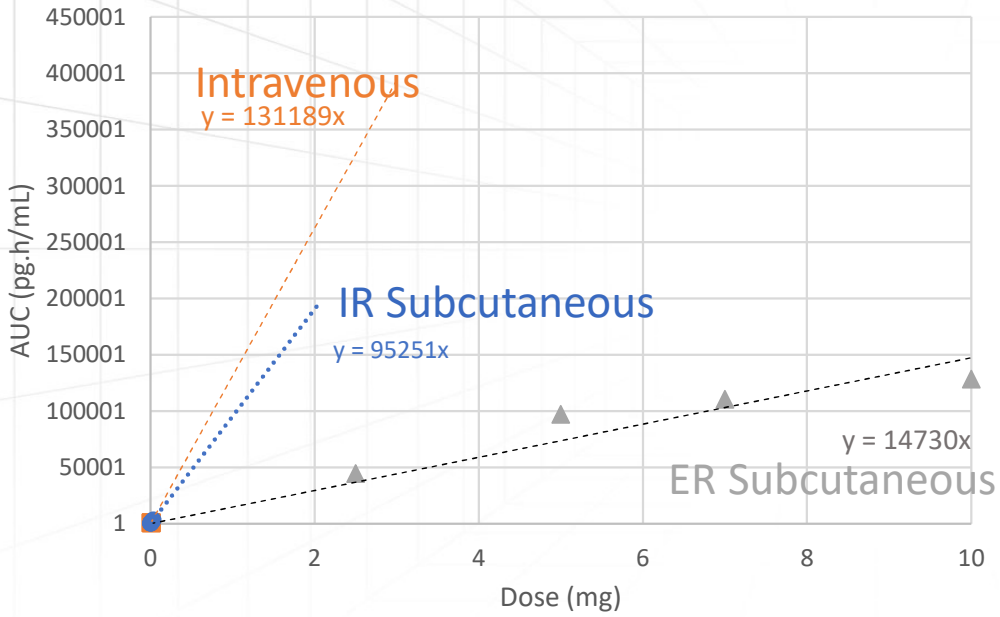
- Initial release phase in vivo is not captured in vitro during polymer hydration [A]
- In vitro test at 37°C, In vivo the temperature of the SC tissue is around 34°C



A: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022200Orig1s000ClinPharmR.pdf

Overall exposure of ER formulations

- Absolute bioavailability of Bydureon is low

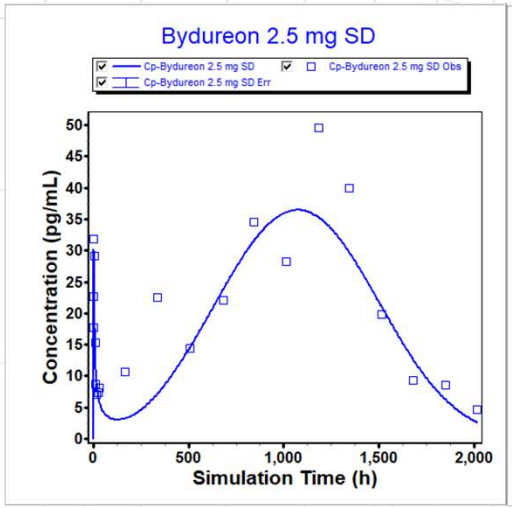


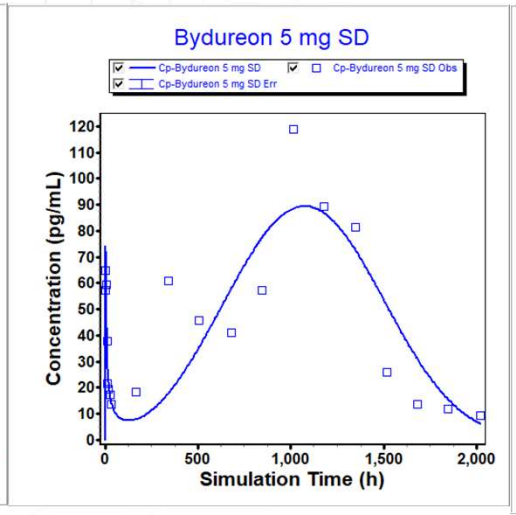
Intravenous clearance : 7.6L/h
F estimated from all SC Bydureon injections : 9.8% (10 mg) to 14.8% (5 mg)

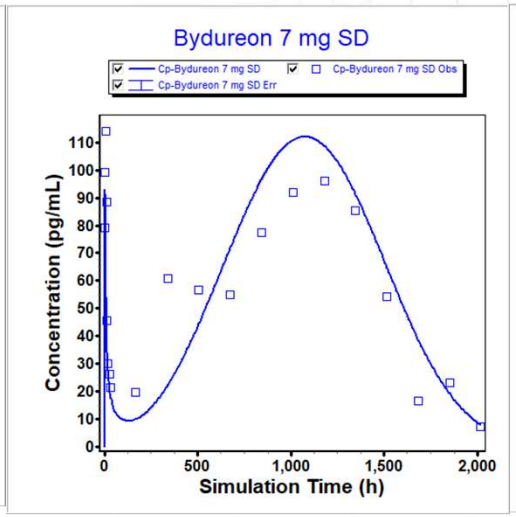
Cumulative AUC can be misleading since not all the drug is absorbed (or released ?)

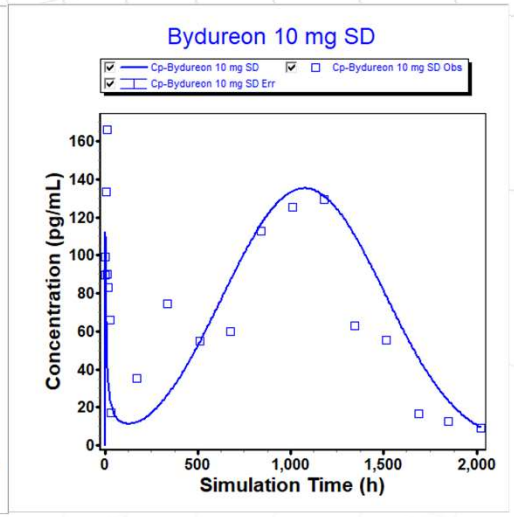
Simulating PK profile in GastroPlus

- Use of triple phase Weibull function
- Hypotheses : Similar and full release for all doses, increasing local clearance with dose (degradation)





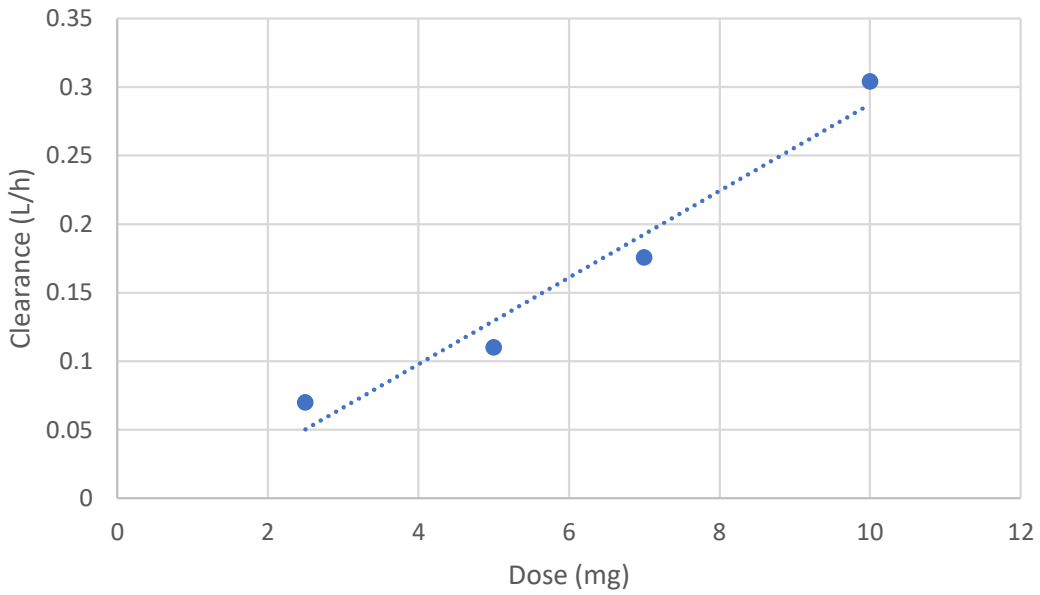




$AUC_{0\text{-inf}}$	C_{max}
AFE	**AFE**
0.94	**0.81**

In vivo degradation rate

- Local clearance



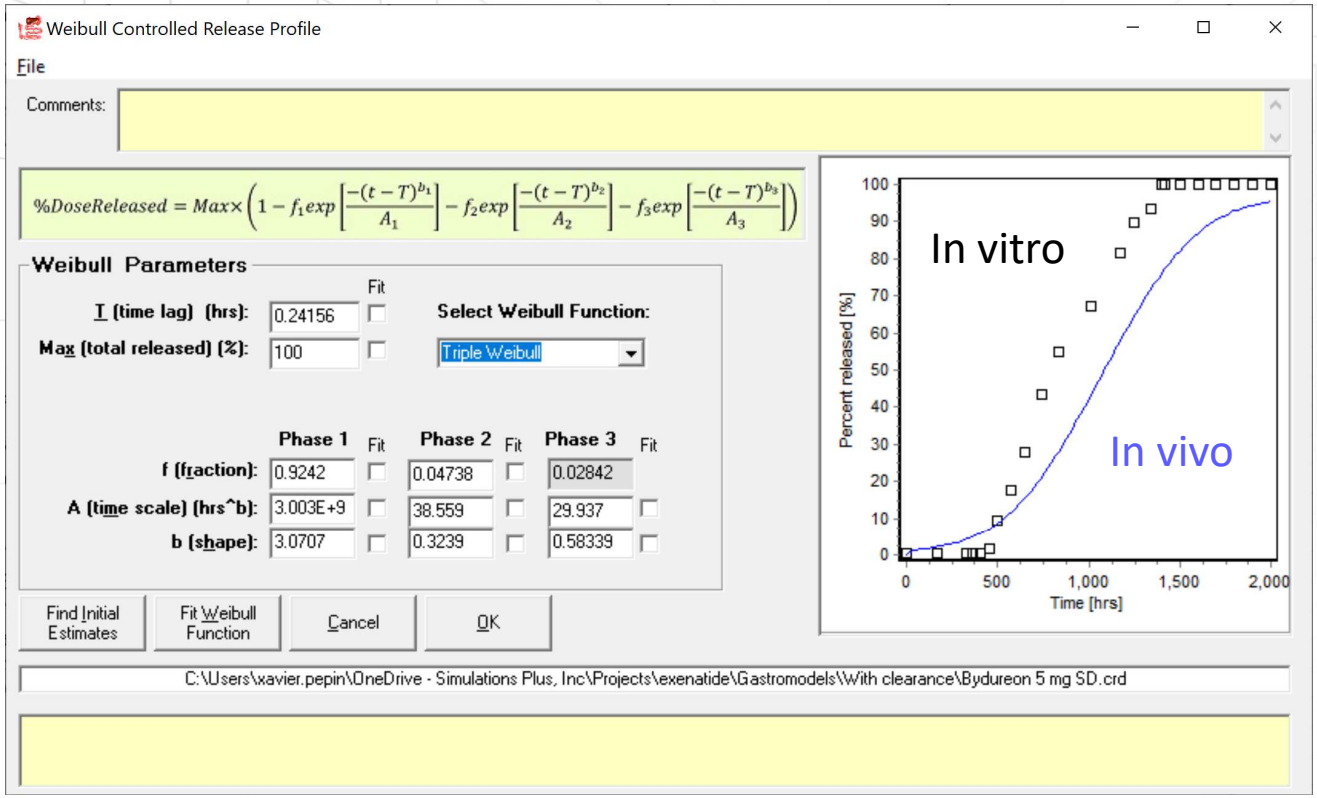
Local clearance increases with dose

Volume effect ? Volume of depot is a function of dose (degradation by self-catalysis, more enzymes mobilized)

Other explanations : lack of complete release (gell)

In vivo release for Bydureon

- Use of triple phase Weibull function



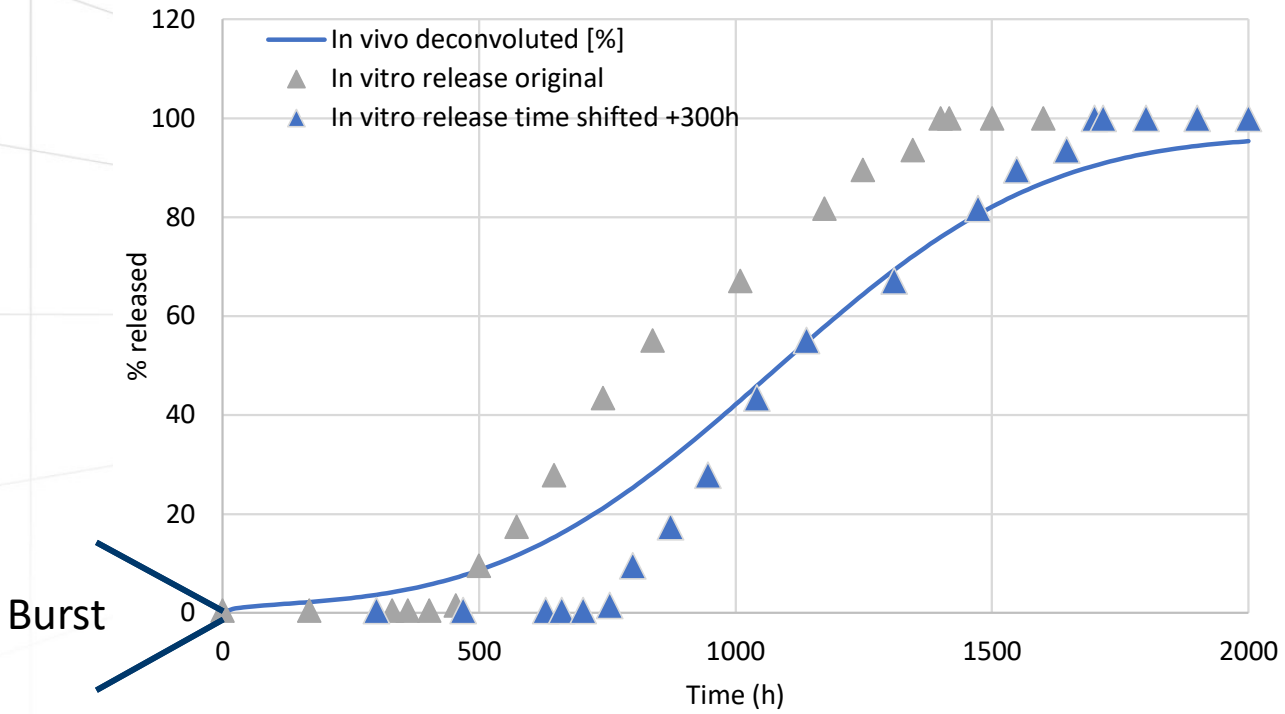
In vivo slower than in vitro release after hydration phase

Can we simply time shift to explain in vitro vs in vivo temperature differences (37 vs 34 °C) ?

PLGA is sensitive to temperature for hydrolysis

In vivo release for Bydureon

- In vitro in vivo correlation



Release rate post hydration phase in vitro matches in vivo release. In vivo release rate seems to apply regardless of dose

Hydration phase still not predicted in vitro. Injection stress, massage in vivo ?

Challenges to develop accelerated in vitro release methods

- Methods to accelerate IVR
  - Temperature
  - pH (solubility)
  - Solvent (solubility)

  } If rate controlling

- Challenges :
  - Make sure the release mechanism is not changed such that the biopredictive nature of the method is changed
  - Define time and release scaling with multiple variants which are clinically relevant. E.g. range of intrinsic viscosities for polymers or drug loading or size
  - Need to define and understand differences between in vitro and in vivo post release (degradation, adsorption, sink level, immune response…etc)
- Opportunities:
  - Rely on mechanistic deconvolution of clinical PK with PBBM : Serve as a blue print to define a biopredictive method

IVIVC for exenatide extended release ?

- Bydureon : IVIVC Study (BCB107)[A] failed on AUC and Cmax
  - Relative BA of bydureon to Byetta varied between 25% to 11%

Parameter Statistic	Treatment [1] Exenatide Once Weekly Formulation A (F17) (N = 21)	Exenatide Once Weekly Formulation B (F17) (N = 17)	Exenatide Once Weekly Formulation A and B (F17) (N = 38)	Exenatide Once Weekly Formulation C (F28) (N = 19)	Exenatide Once Weekly Formulation D (F30) (N = 20)
$AUC_{(0\text{-}last)}$ (pg·h/mL)					
Geometric Mean (SE) [2]	197,008 (19,975)	212,874 (25,518)	203,954 (15,654)	78,102 (6,987)	99,018 (9,881)
$C_{max(0\text{-}5h)}$ (pg/mL)					
Geometric Mean (SE) [2]	213.6 (33.4)	185.0 (14.6)	200.3 (18.6)	1392.4 (87.8)	128.5 (8.4)
$C_{max(0\text{-}last)}$ (pg/mL)					
Geometric Mean (SE) [2]	567.6 (91.9)	746.3 (175.3)	641.5 (88.5)	1392.4 (87.8)	203.3 (29.3)
$T_{max(0\text{-}5h)}$ (h)					
Median	2.0	3.0	3.0	3.0	3.0
Min, Max	1.5, 3.0	1.5, 4.0	1.5, 4.0	1.4, 4.1	1.5, 4.0
$T_{max(0\text{-}last)}$ (h)					
Median	961.0	960.0	960.7	3.0	780.1
Min, Max	2.0, 1680.9	3.0, 1320.0	2.0, 1680.9	1.4, 4.1	1.5, 1392.0
T_{last} (h)					
Median	1537.0	1535.9	1536.4	1391.9	1536.0
Min, Max	1177.0, 1753.0	1104.1, 1824.0	1104.1, 1824.0	1104.0, 1680.4	1152.2, 1896.0
Relative Bioavailability (%) [3]					
Mean (SD)	21 (7.5)	25 (13.3)	22 (10.5)	14 (8.5)	11 (5.2)

Abbreviations: AUC, area under the concentration-time curve; C_{max}, peak concentration determined as the maximum observed concentration during the sampling interval; Max, maximum; Min, minimum; QW, once weekly; SC, subcutaneous; T_{last}, time of last point with quantifiable concentration; T_{max}, time of peak concentration.

[1] Formulation A: single dose of exenatide once weekly AC2993-F17 Lot S426-2377CA 10 mg SC; Formulation B: single dose of exenatide once weekly AC2993-F17 Lot S426-2507AA 10 mg SC; Formulation C: single dose of exenatide once weekly AC2993-F28 8 mg SC; Formulation D: single dose of exenatide once weekly AC2993-F30 10 mg SC. Exenatide once weekly doses are nominal doses.

[2] Geometric Mean = exp(mean(log(X))); SE of Geometric Mean = Geometric Mean * SE of Mean(log(X)).

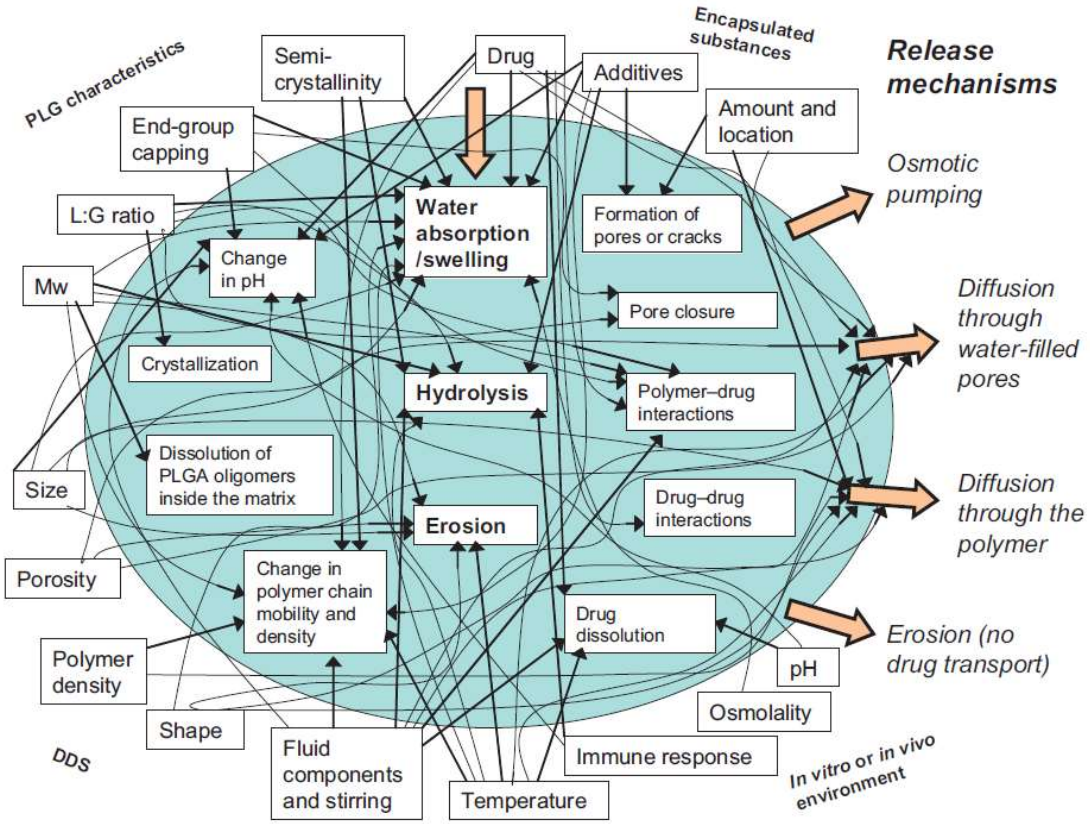
[3] Relative bioavailability (%) = 100 * ($AUC_{(0\text{-}last)QW}$ / $Dose_{QW}$) / ($AUC_{(0\text{-}inf)BYETTA}$ / $Dose_{BYETTA}$). The overall geometric mean of $AUC_{(0\text{-}inf)}$ BYETTA obtained from all available subjects was used for Subjects 101080, 101094, and 101095 who had exenatide once weekly data and no BYETTA data.

A: https://www.tga.gov.au/file/1010/download

Conclusions on modelling peptide absorption following sc administration

- Even IR solutions can be complex !
- Binding, oligomerization : Change absorption pathways, reduce diffusion coefficient and monomer solubility
- MR : Degradation rates of the drug (in the formulation or after release) should be considered, degradation of the polymer controls the onset of release. Need more external measurements to model complex mechanisms
- Immune response and inflammation can increase local volumes or add fibrous capsules around the depot

The complex nature of how different factors may affect drug release from PLGA matrices

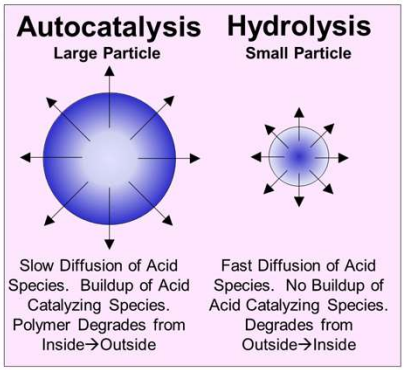


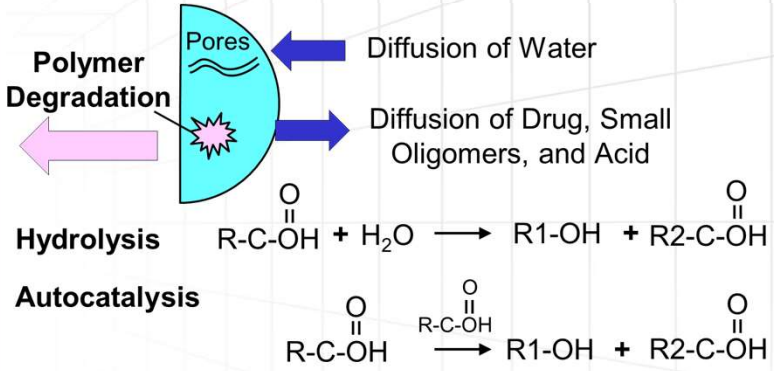
Fredenberg, International Journal of Pharmaceutics 415 (2011)

In vitro drug release : Model Extension

Additional mechanisms affecting the drug release from polymeric microspheres were derived and added to Model 2:

- Autocatalytic degradation
- pH-dependent solubility of API within the particle
- Water diffusion and reaction





Where *i* = Drug, Small Oligomer, Water, and Free Acid

C_D	Concentration of free drug in matrix
C_{ND}	Concentration of undissolved drug in matrix
R	Rate of degradation
S	Solubility
$D(r,t)$	Diffusion coefficient – radial/time dependent
D_o, A	Initial diffusion coefficient and exponential diffusion constant
$MW(r,t), MW_{ref}$	Molecular weight in particle and reference

$$\frac{\partial C_i}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 D(r)\frac{\partial C_i}{\partial r}\right) + R_i$$

$$\frac{\partial C_{ND}}{\partial t} = -k_{diss}(S - C_D)\left(\frac{C_{ND}}{C_{ND,o}}\right)$$

$$\frac{\partial C_D}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 D(r)\frac{\partial C_D}{\partial r}\right) + k_{diss}(S - C_D)\left(\frac{C_{ND}}{C_{ND,o}}\right)$$

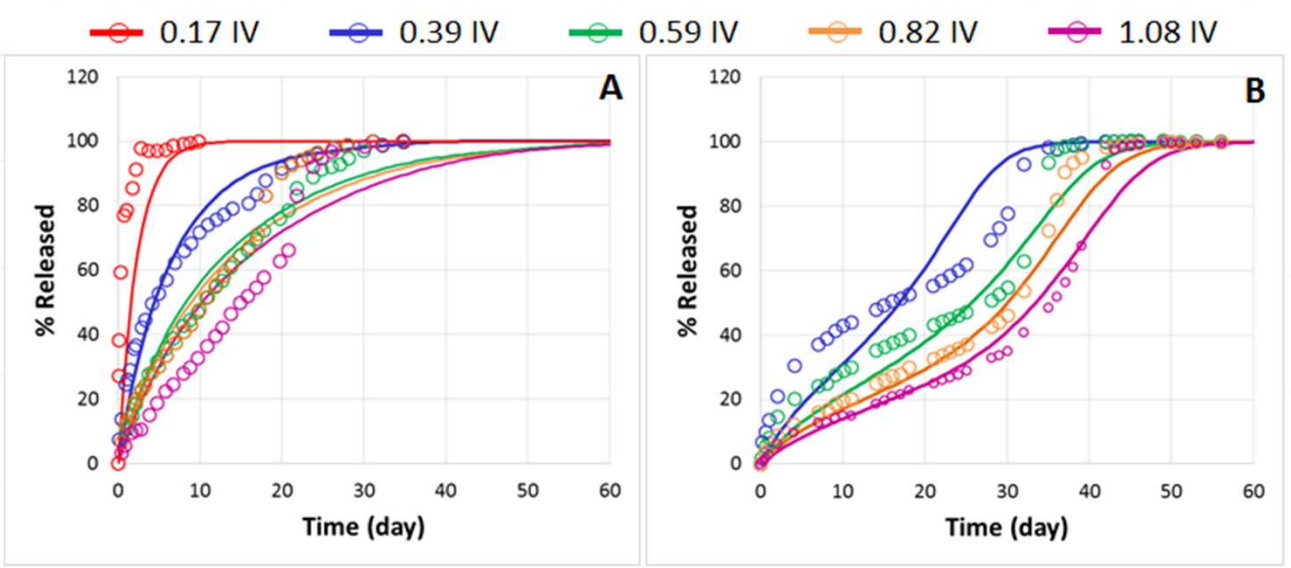
$$D(r,t) = D_o \times e^{-A\times\left(\frac{MW(r,t)}{MW_{ref}}-1\right)}$$

Mullin J. CRS 2017 Annual Meeting, Poster presentation

In vitro drug release : Model Extension

The expanded model showed potential to account for effect of particle size on API dissolution/release rate from LAI microsphere

Observed (points) and simulated (lines) dissolution profiles of piroxicam from several formulations with 10 micron (A) and 50 micron (B) particles with varying polymer molecular weights using the expanded model. The same set of parameter values was used to simulate the dissolution profiles of all formulations.



Observed data from: Raman et al. J Control Rel 2005, 103: 149-158

Take home messages

- Mechanistic in vivo drug release and its integration in PBBM/PBPK offers the possibility of greater IVIVC success rate for complex routes on administration/dosage forms
  - Mechanistic IVIVC surpasses classical approaches
    - Captures effect of size, intrinsic viscosity and polymer degradation
- Several factors need to be computed in addition to release
  - Effective depot size and fluid exchange in vivo
  - Local degradation (chemical or metabolic for the drug)
  - Binding to cells, extracellular matrix and proteins
  - Diffusion through the ECM
  - Oligomerization
- Cumulative AUC masks the… actual AUC
- Mechanistic models offer the choice of matrix and analyte
  - Locally active drug : Use of downstream metabolite
  - Link the in vitro performance to the in vivo exposure of the analyte of choice in relevant matrix
  - Recalculate active drug concentration at site of action

Thanks

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