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Model based design of controlled release drug delivery systems

Aditya Pareek, Praduman Arora, Venkataramana Runkana

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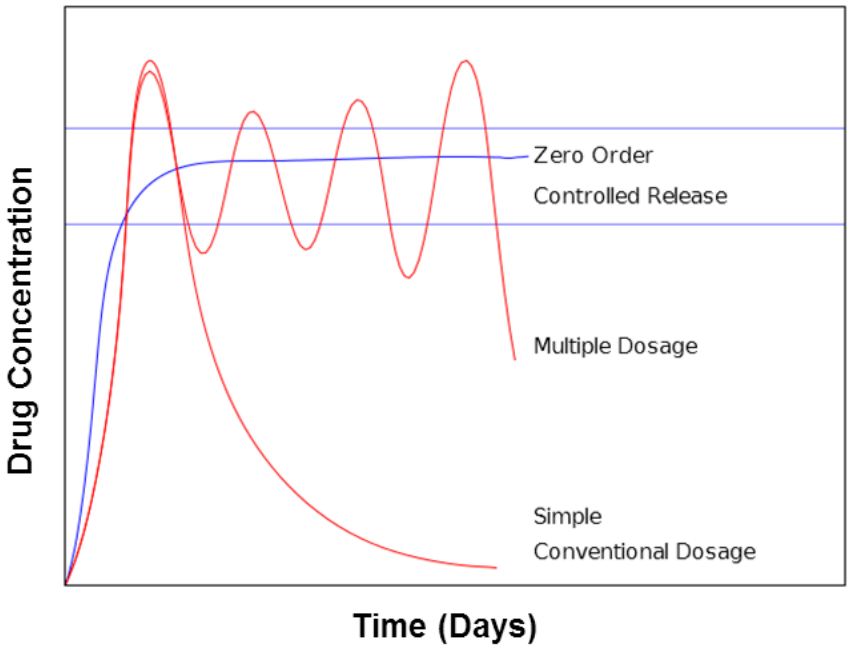
Why we need controlled drug delivery?

Limitations of conventional delivery

- Low bio-availability
- Frequent dosage leading to poor patient compliance
- Steady state concentration unattainable

Advantages of controlled drug delivery

- Maintains therapeutic drug level for prolonged periods of time
- Achieves predictable release rates
- Reduces dosing frequency and increase patient compliance
- Deploys to a target site and thus limits side effects



Novel drug vehicles are being developed to achieve this target.

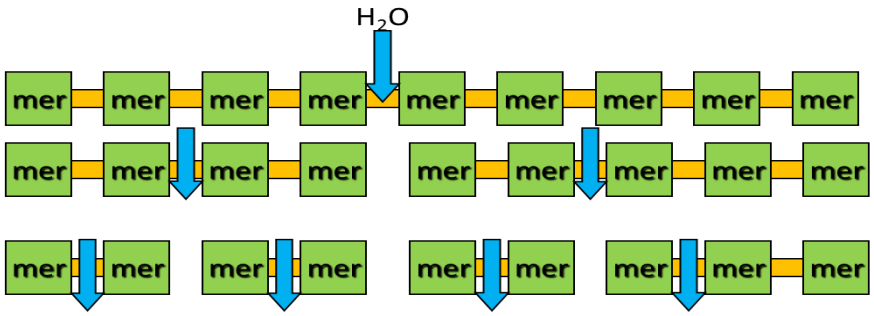
Controlled Drug Delivery Systems

- Polymer Hydrogels
- Environment responsive hydrogel (pH, Glucose, Temperature)
- Polymer particles (Chitosan, PLGA (Poly (Lactic-co-Glycolic Acid))
- Inorganic nanoparticles (Silica, Gold)
- Micro needles, Carbon nanotubes
- Vesicular systems: Liposomes, Solid Lipid Nanoparticles
- Micro-emulsions, Nano-emulsions
- These drug carriers along with new potential routes of drug administration (Transdermal, Subcutaneous, Ocular) are being utilized to achieve controlled and targeted drug delivery

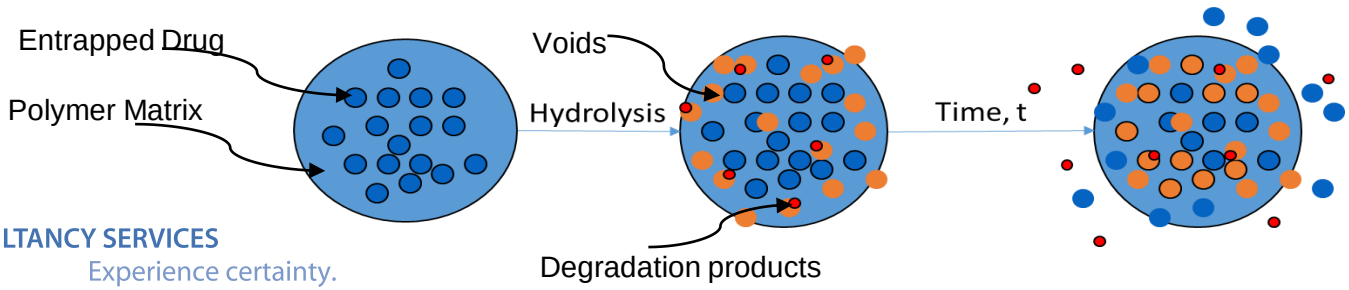
Biodegradable polymers as potential DDS

- Biodegradable polymer degrades into smaller biocompatible compounds and ultimately to CO_2, N_2 and H_2O
- This property allows synthesis of drug loaded polymer particles that can protect and thus release drug over extended period of time in vivo
- E.g. PLGA (Poly(lactic-co-glycolic Acid), Polyanhydride, Polycaprolactone

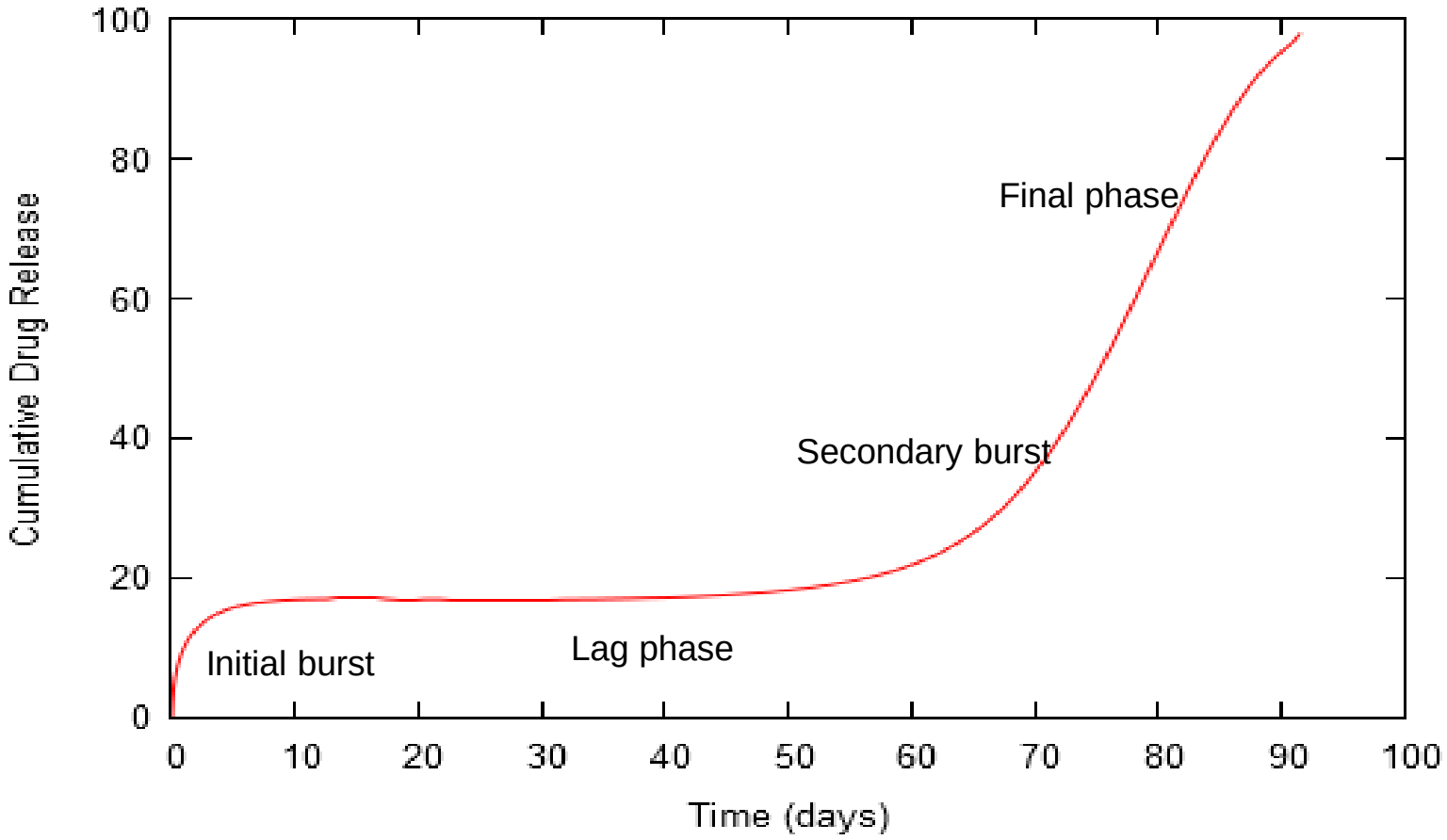
Polymer degradation (Hydrolysis)



Drug Release

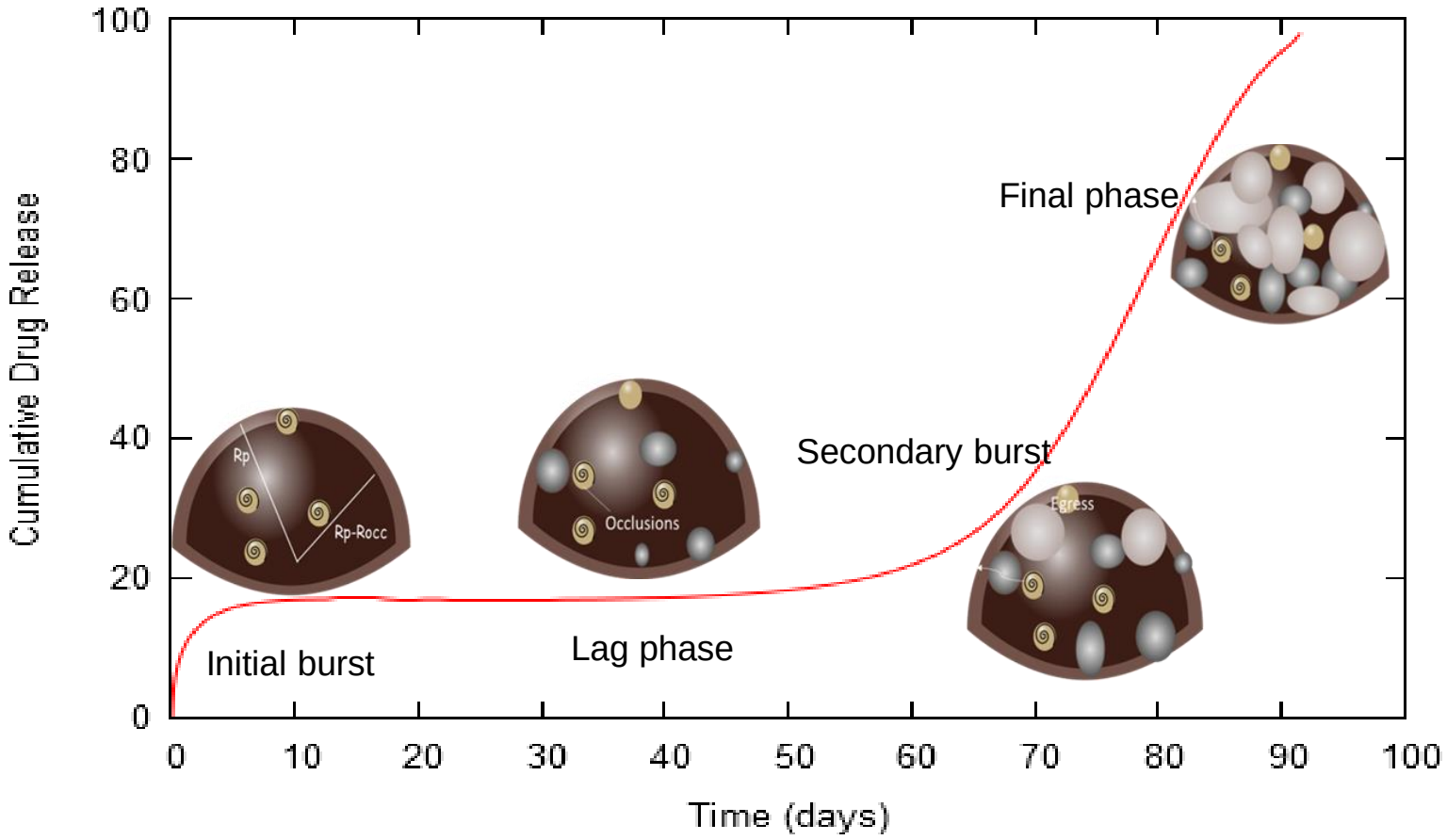


Typical Drug Release Profile



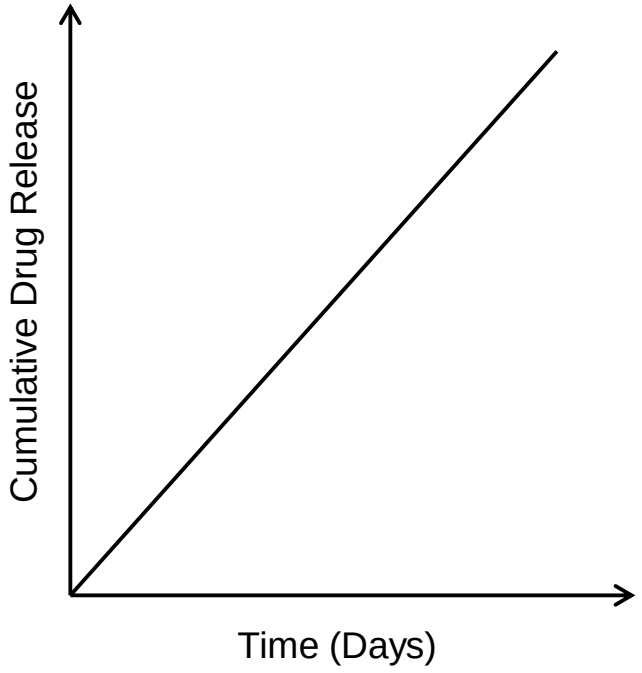
Duvvuri S. et al., Pharm Res, 2006, 23(1). 215-223

Schematic of phenomena involved during drug release

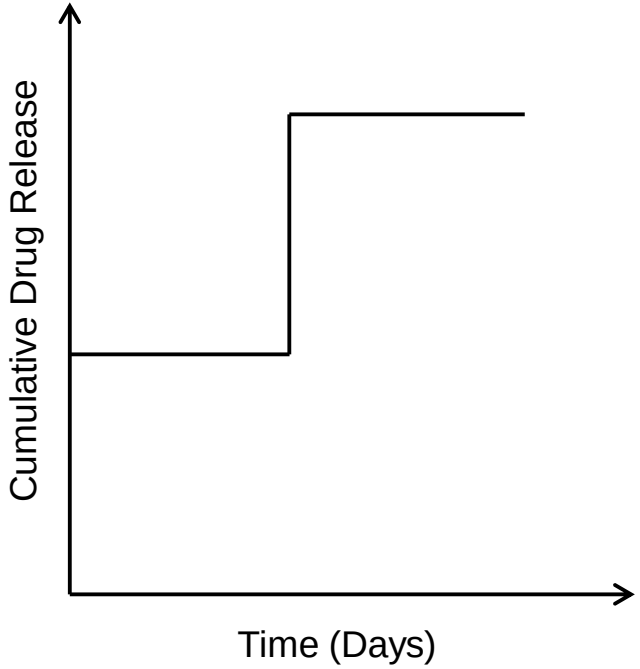


Ideal drug release kinetics

Zero Order Release



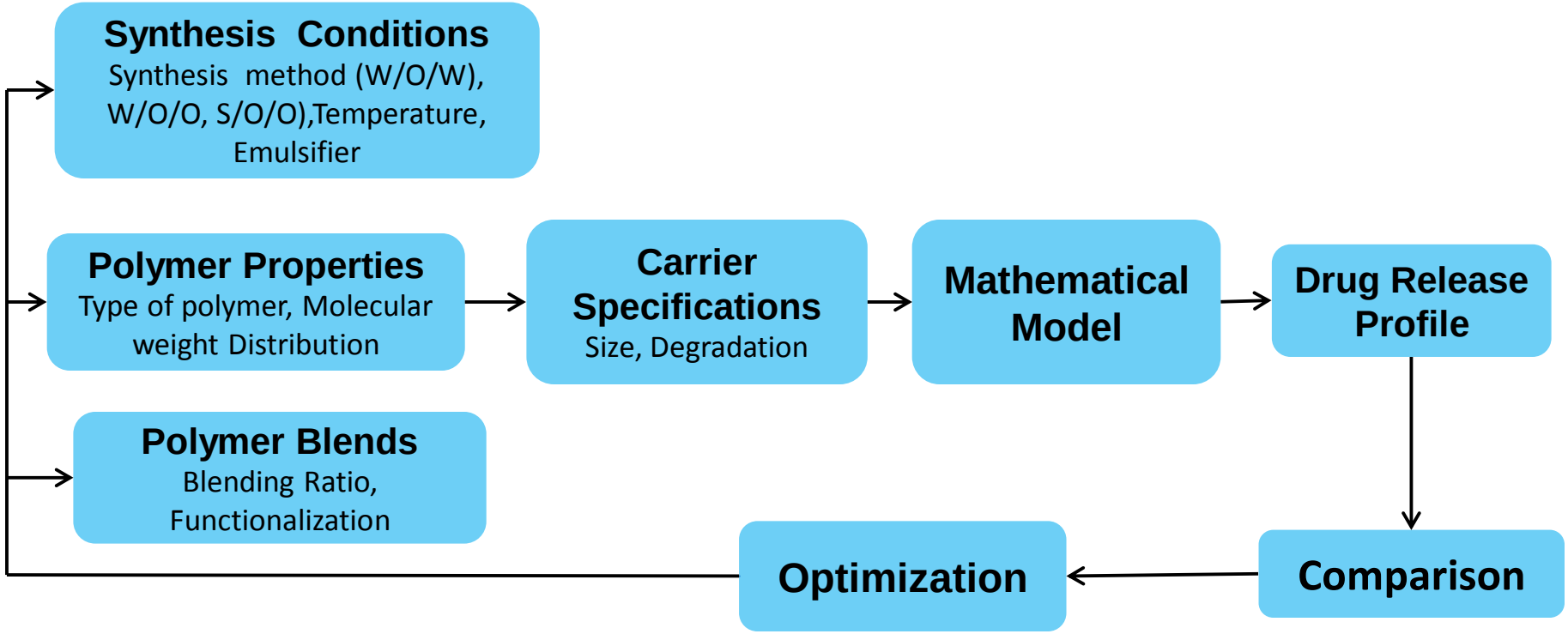
Pulsatile Release



What should be the specifications of a biodegradable particle to achieve a desired release profile?

Aim of this work

- Develop a mathematical model for controlled delivery of drugs with polymer particles as carrier



The model can thus help us reduce time, efforts and expenses by minimizing the requirement for design experiments.

Mathematical Model

Diffusive Drug Release (Fick's Law)

$$\frac{\partial C_A}{\partial t} = \nabla\left(D_{eff}\nabla C_A\right) \qquad D_{eff} = D\varepsilon(t)$$

Polymer Matrix Degradation (Pore Formation)

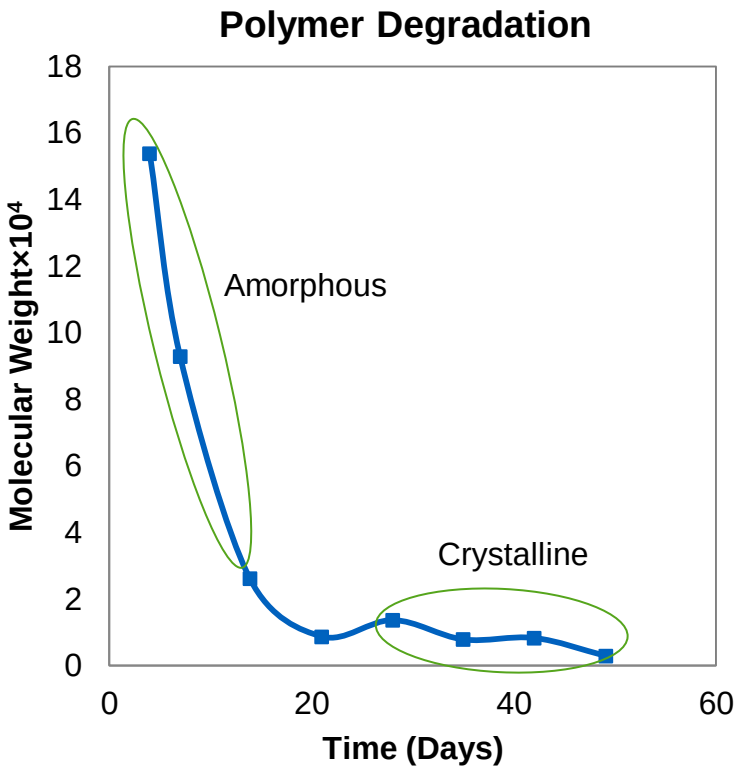
$$\varepsilon(t) = \frac{1}{2}\left[erf\left(\frac{t-\bar{\tau}}{\sqrt{2\sigma^2}}\right)+1\right]^{**}$$

$\varepsilon(t)$ is porosity of the polymer matrix.
$\bar{\tau}$ is the mean time for pore formation.
σ^2 is the variance in time required to form pores.

** Rothstein SN et al., J Mater Chem, 2008,18(16):1873–1880

Estimation of Degradation Parameters

- Degradation rate constant for the two phases was calculated by fitting $M_w = M_{w0} \exp(-k_i t)$
- τ_i was calculated using equation $\tau_i = \frac{-1}{k_i} \ln \left| \frac{Mw_r}{Mw_0} \right|$
- $\bar{\tau} = \frac{\sum_i \tau_i}{n}$; where, *i* = number of phases considered
- The variance, σ^2, was calculated for this τ_i distribution



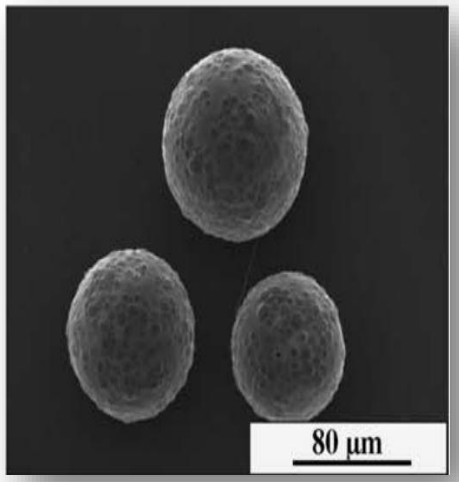
Grayson A. et al., J BioMater Sci Polym Ed, 2004, 15(10), 1281-1304.

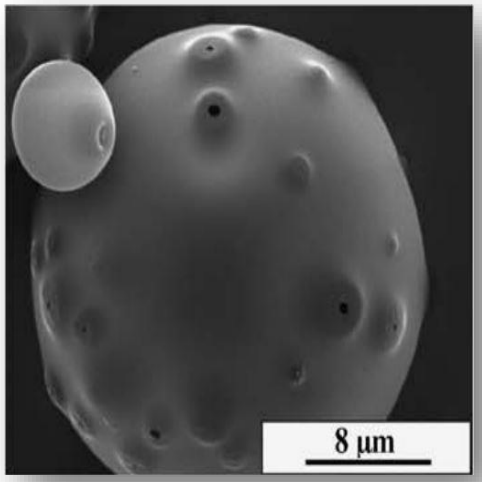
Estimation of Parameters

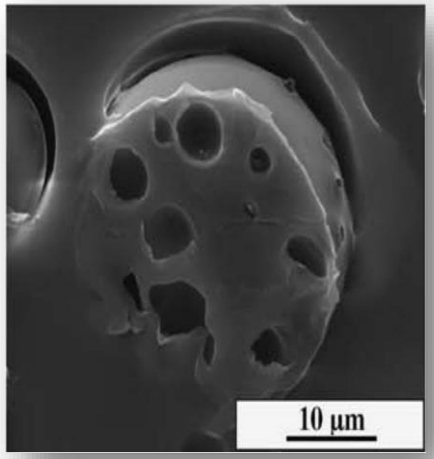
- Particle Radius (R_p) can be calculated by Particle Size Analyzer (DLS, SEM)

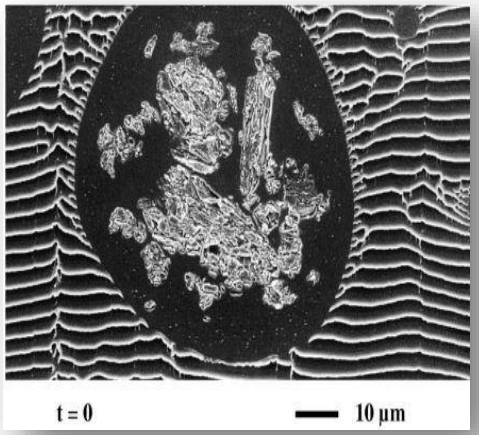
- Occlusion Size (R_{occ}) can be calculated by averaging the sizes of randomly selected occlusions, from Scanning Electron Microscope (SEM)

$$R_{occ} = \frac{\sum_i R_{occ_i}}{n}$$







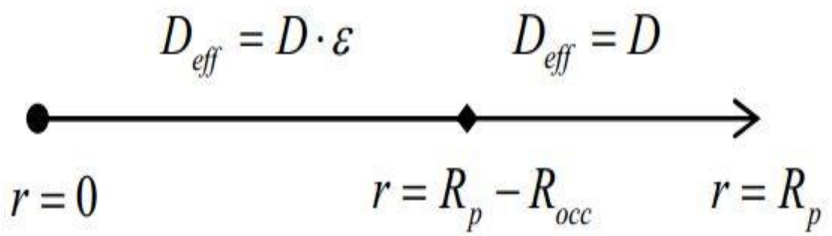


N. Faisant et. al, Eur J Pharm Sci,2002, 15(4), 355-366

D. Klose et. Al, Int J Pharm, 2006, 314(2), 198-206.

COMSOL Implementation

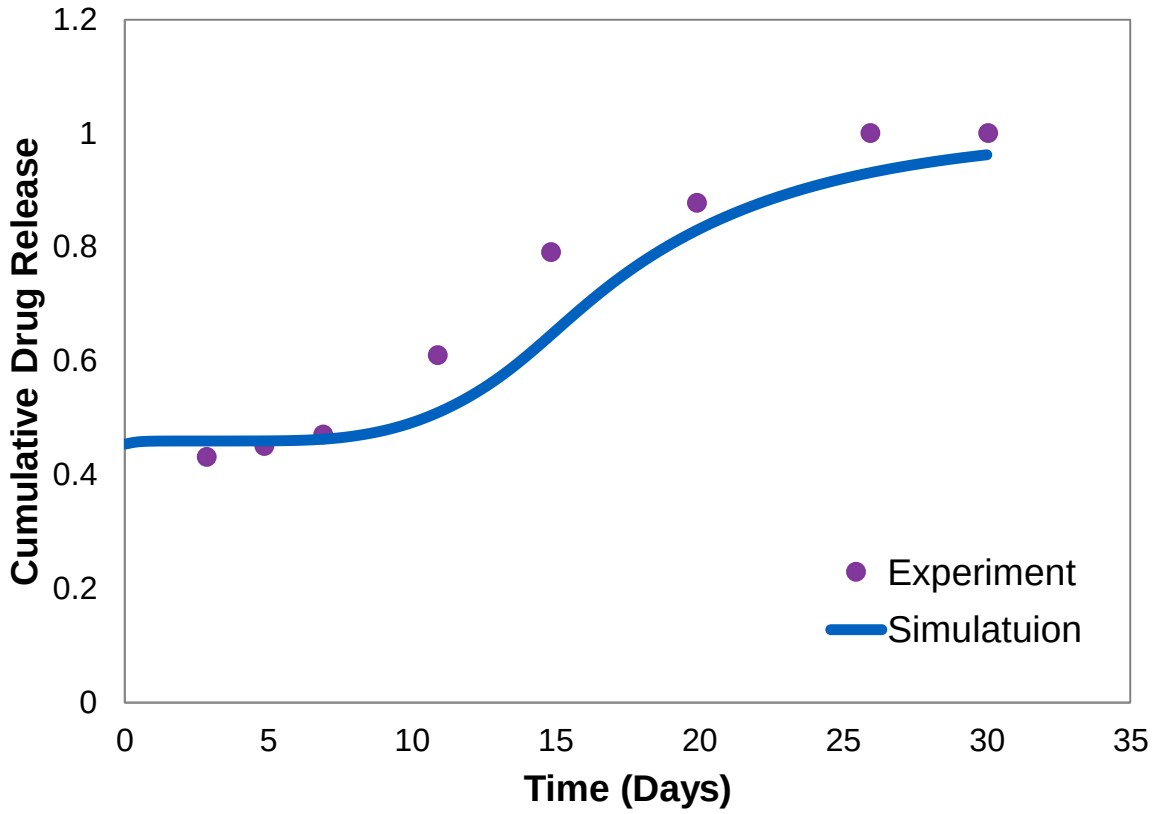
- A Spherical matrix is considered with radius R_p loaded uniformly with drug at concentration, C_{A_0}
- Due to spherical symmetry, the problem was solved in 1D
- Two subdomain are considered, so drug flow is either pore mediated or free-flowing
- Physics used: **Transport of Diluted Species (chds)**
- $\varepsilon(t)$ was defined as a variable to calculate porosity of the matrix
- A function $F(t) = 1 - V^{-1} \int \left(\frac{C_A}{C_{A_0}}\right) dV$ was defined to calculate cumulative drug release



Boundary Conditions

Position	Condition
r = 0	$dC_A/dr = 0$
$r = R_p$	$C_A = 0$

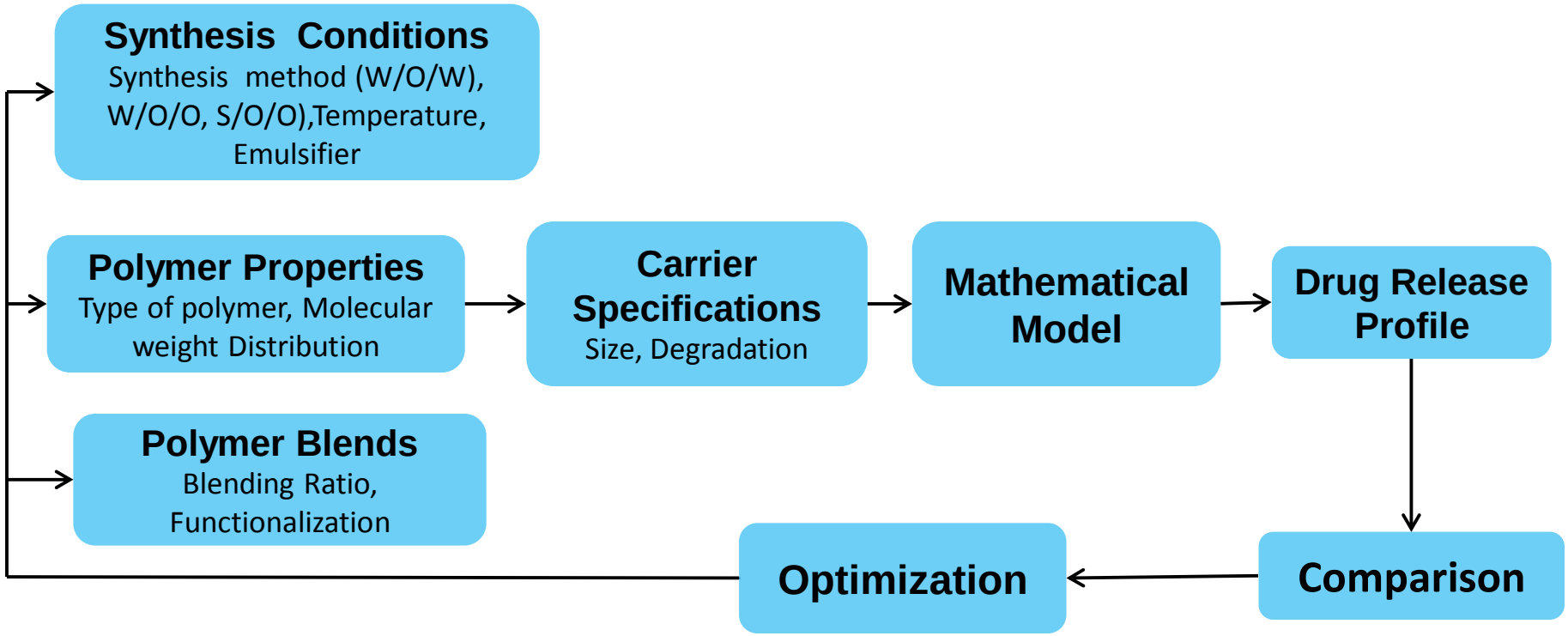
Model Validation



R_p = 3.7 µm
R_{occ} = 0.52 µm
Polymer:PLGA 50:50
Drug: Melittin (Anti-cancer Therapy)
Mw_0 : 9.5 kDa
τ = 13.32 days
σ^2 = 4.59 days^2

F. Cui et al.,J Control Release, 2005, 107(2), 310–319.

Optimizing the Design of Microparticles



Models for initial burst and lag period

We performed a large number of simulations and developed empirical models for two critical properties of release kinetics

Dependency of Initial burst on Occlusion and particle size:

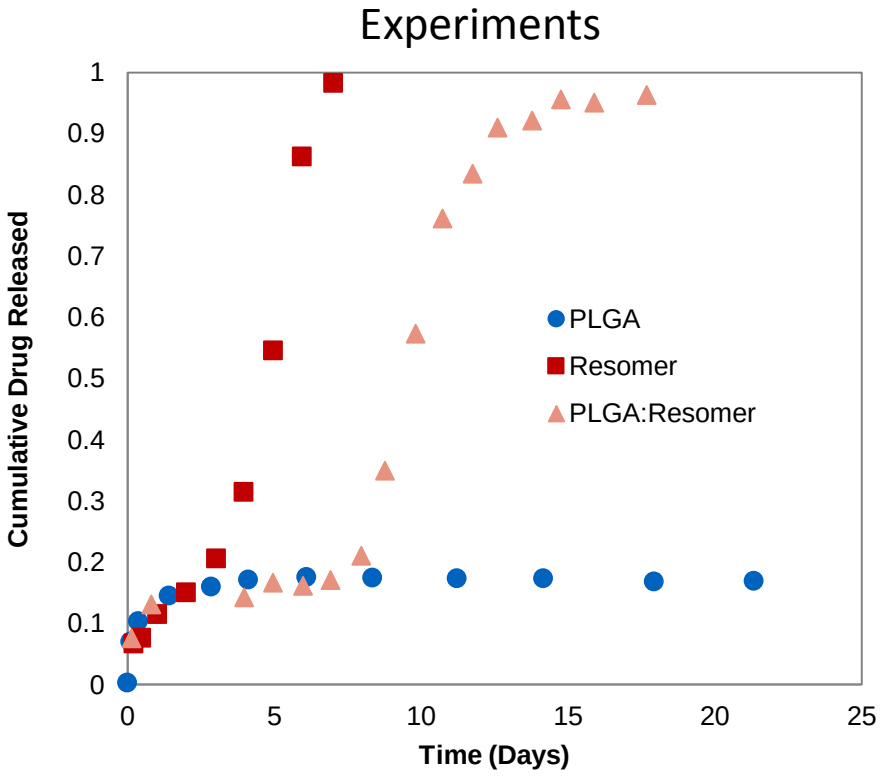
$$\textit{Initial Burst} = -5.06\left(1 - {R_{occ}}/{R_p}\right)^6 + 3.97\left(1 - {R_{occ}}/{R_p}\right)^3$$

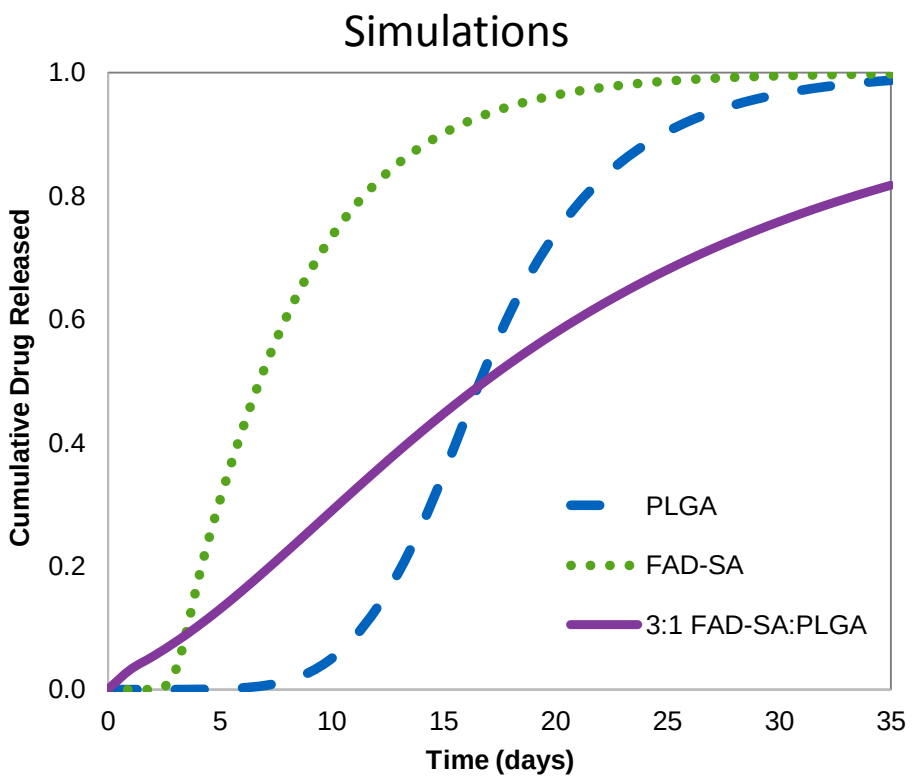
Dependency of Lag Period on τ and σ^2:

$$\textit{Lag Period}\ (d) = 0.92\tau - 0.36\sigma^2$$

These models give us a good initial guess of the specifications of a polymer particle required to achieve desired release profile

Optimizing Drug Release using Polymer Blends





Resomer® – Commercial poymer

FAD:SA – Poly(Fatty acid dimer:Sebacic Acid) Anhydride

A near Zero order release of insulin was achieved using a polymer blend of PLGA and Poly-anhydride

Duvvuri S. et al., Pharm Res, 2006, 23(1). 215-223

Summary

- A model to study drug release from biodegradable polymer was implemented in COMSOL
- The model was validated with relevant experimental data
- Simplified models were derived for initial burst and lag phase from simulation data obtained using the rigorous model
- These models were used to find specifications of a polymer particle required to achieve zero order release of insulin

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