A Predictive Mechanistic Model of Drug Release from Acetalated Dextran Particles

Rebeca T. Stiepel[1], Erik S. Pena[2], Matthew D. Gallovic[3], Christopher J. Genito[4], Eric M. Bachelder[1], Kristy M. Ainslie[1,2,4]

[1]Division of Pharmacoengineering and Molecular Pharmaceutics, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599
[2]Joint Department of Biomedical Engineering, University of North Carolina at Chapel Hill and North Carolina State University, USA
[3]IMMvention Therapeutix, Durham, NC 27701
[4]Division of Microbiology & Immunology, University of North Carolina School of Medicine, Chapel Hill, NC 27599

UNC ESHELMAN SCHOOL OF PHARMACY

Introduction

Systemic administration of drugs with narrow therapeutic windows often results in inadequate dosing at the target site and/or negative off-target effects. Acetalated dextran (Ace-DEX) has been utilized as a microparticle (MP) drug delivery platform, allowing for triggered release in acidic environments, such as the endosome of phagocytic cells, tumor microenvironments, and sites of inflammation. Ace-DEX has tunable degradation rates based on cyclic acetal coverage (CAC). In this work, the effect of CAC on the release of various drugs from Ace-DEX MPs was evaluated *in vitro*. **The goal of this work is to develop a predictive mathematical model based on a combination of diffusion and particle degradation.** Initial results indicate accuracy of our model, even while varying polymer CAC, MP cargo, and environmental pH.

Background

Advantages of Particle Drug Delivery
Enhanced local delivery of drug
Reduced toxicity and other adverse effects
Can protect drug from degradation in the body
Controlled release of drug over time = less dosing

Advantages of Mathematical Modeling
Gain insight to the role of individual parameters and inputs
Predict the behavior of similar systems
Reduce future experimental trial and error
Aid in translation from *in vitro* to *in vivo* experiments

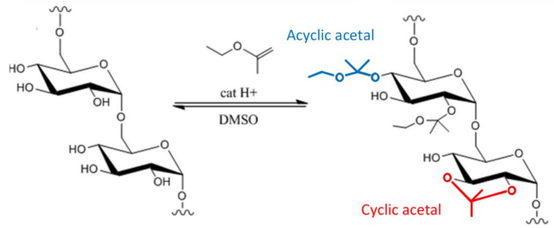


Figure 1: *Water-soluble dextran reacts with 2-ethoxypropene to form Ace-DEX, an acid sensitive polymer that is soluble in organic solvents. More cyclic acetal groups form as the reaction time increases. These acetal groups are more thermodynamically stable, making higher CAC Ace-DEX polymers more stable in aqueous environments.*

Acetalated Dextran (Ace-DEX)

- **Acid sensitivity** allows for triggered drug release in the phagosome or tumor microenvironment.
- Ace-DEX is **biocompatible** with pH-neutral degradation products.
- **Tunable degradation rate:** Reaction time during synthesis (Fig. 1) determines the ratio of cyclic to acyclic acetal groups, where a higher CAC results in a slower degradation.
- **Degradation Mechanism:** As a hydrophobic, non-reactive polymer, Ace-DEX is expected to degrade via surface erosion in aqueous buffers.

Methods

Experimental Methods

- **Particle Formation:** 20, 40, and 60 CAC Ace-DEX MPs were made by emulsion (Fig. 2). Paclitaxel (PTX), Rapamycin (Rapa), and Dexamethasone (DXM) loading were determined by high performance liquid chromatography (HPLC). Doxorubicin (DXR) and Resiquimod (R-848) loading were determined by plate reader fluorescence (ex/em: 480/580 and 260/370 respectively).

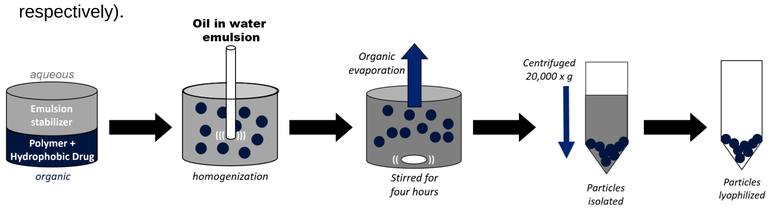


Figure 2: *Schematic of particle formation via homogenization.*

- **Drug Release and MP Degradation:** Drug release and MP degradation were evaluated in pH 5 and 7.4 buffer under sink conditions at 37°C. Drug release was determined via HPLC for PTX and Rapa and by fluorescence reading for DXR and R-848. Blank particle degradation was evaluated with a bicinchoninic acid (BCA) assay and imaged via scanning electron microscopy (SEM).

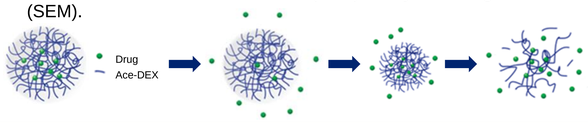


Figure 3: *Release mechanism over time involving simple diffusion, degradation mediated diffusion, and final particle degradation.*

Methods (continued)

Development of the Diffusion-Erosion Model

- Constitutive equations were developed based on the predicted release mechanism (Fig. 3)

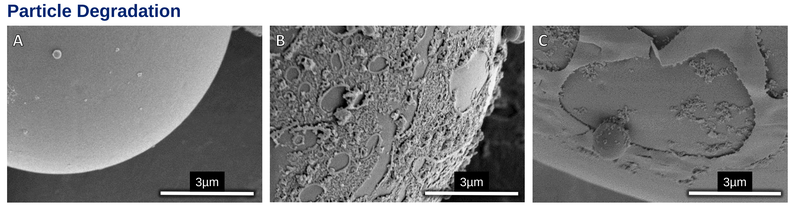
$$(1)\quad \frac{M_t}{M_{A0}} = \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left(-\frac{D_{AB}n^2\pi^2 t}{R^2}\right)$$

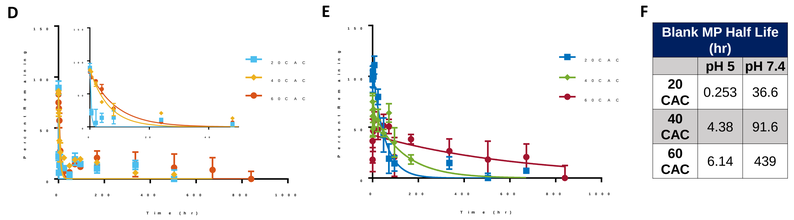
$$(2)\quad \frac{dR}{dt} = -k_{deg} * R$$

- M_t=mass of drug remaining in MPs at time t, M_{A0}=initial mass of loaded drug, R=total MP radius, D_{AB}=diffusion coefficient, k_{deg}=polymer degradation coefficient.
- **Equation 1** was developed from the continuity equation and Fick's Law at unsteady state to represent drug diffusion away from the MP.
- **Equation 2** represents the surface erosion of Ace-DEX MPs and follows first order degradation.
- Model simulations were done in MATLAB, and outputs were evaluated against drug release. D_{AB} was estimated by nonlinear fit of release curve data with weighted least squares for PTX, Rapa, DXR, and R-848 release, while all other parameters were determined empirically.
- Machine learning was employed to predict D_{AB} for DXM release. A neural network (NN) was developed to estimate D_{AB} from drug properties (polar surface area, logP, molecular weight), MP properties (polymer CAC, drug loading), and buffer pH.

Results

Particle Degradation





Blank MP Half Life (hr)		
	pH 5	pH 7.4
20 CAC	0.253	36.6
40 CAC	4.38	91.6
60 CAC	6.14	439

Figure 4: *Visualization of MP degradation and measurement of blank MP degradation rates at varied CAC levels. Representative SEM field of (A) 40 CAC MP surface at t=0 prior to pH 7.4 incubation, (B) MP surface at t=0.5h, and (C) MP surface at t=168h. Comparison of A, B, and C indicates surface erosion behavior over time. BCA assay results (data points) and nonlinear fit of one phase decay (lines) of 20, 40, and 60 CAC MPs in (D) pH 5 and (E) pH 7.4 buffer at sink conditions and 37°C demonstrate MP degradation kinetics. (F) Blank MP half lives determined via nonlinear fit of the one phase decay model.*

Drug-Loaded Particle Formulation and Diffusion Coefficient Estimates

Drug	Radius (µm)	Theoretical Loading	CAC	Encapsulation Efficiency	Loading (µg/mg)	D_{AB} (cm²/s) pH 5	D_{AB} (cm²/s) pH 7-7.4
PTX	1.34 ± 1.31	1%	20	94.0 ± 2.3%	9.40 ± 0.23	Not estimated	4.89E-13
			40	86.7 ± 2.4%	8.67 ± 0.24		2.13E-14
			60	87.8 ± 2.7%	8.78 ± 0.27		1.06E-13
		5%	20	85.2 ± 2.7%	42.58 ± 1.36		3.84E-13
			40	85.4 ± 2.8%	42.72 ± 1.39		3.86E-14
			60	87.3 ± 4.3%	43.67 ± 2.14		4.29E-14
Rapa	0.28 ± 0.20	1%	20	113.0 ± 6.7%	11.30 ± 0.67	6.74E-14	1.02E-14
			60	112.0 ± 8.0%	11.20 ± 0.80	7.93E-15	2.12E-16
R-848	0.17 ± 0.08	1%	20	8.5 ± 0.6%	0.85 ± 0.06	1.54E-13	6.09E-13
			40	9.6 ± 1.5%	0.96 ± 0.15	3.32E-14	9.95E-16
			60	9.3 ± 0.2%	0.93 ± 0.02	1.33E-14	2.08E-15
DXR	0.18 ± 0.09	1%	20	22.7 ± 0.8%	2.27 ± 0.08	4.79E-15	9.31E-16
			40	26.3 ± 0.1%	2.63 ± 0.01	1.28E-15	6.66E-16
			60	24.7 ± 3.5%	2.47 ± 0.35	1.62E-15	4.34E-16
DXM	0.19 ± 0.08	1%	20	19.23 ± 4.97%	1.92 ± 0.49	Not estimated	Predicted separately via machine learning
			40	14.56 ± 5.05%	1.46 ± 0.50		
			60	20.52 ± 3.14%	2.05 ± 0.31		

Table 1: *A summary of Ace-DEX MP formulations. CAC is determined by nuclear magnetic resonance (NMR). Encapsulation efficiency is determined via HPLC for PTX, Rapa, and DXM and via fluorescence reading for DXR and R-848. Diffusion coefficients are estimated through the diffusion-erosion model via nonlinear fit of release curve data with weighted least squares.*

Results (continued)

Drug Release Data and Model Output

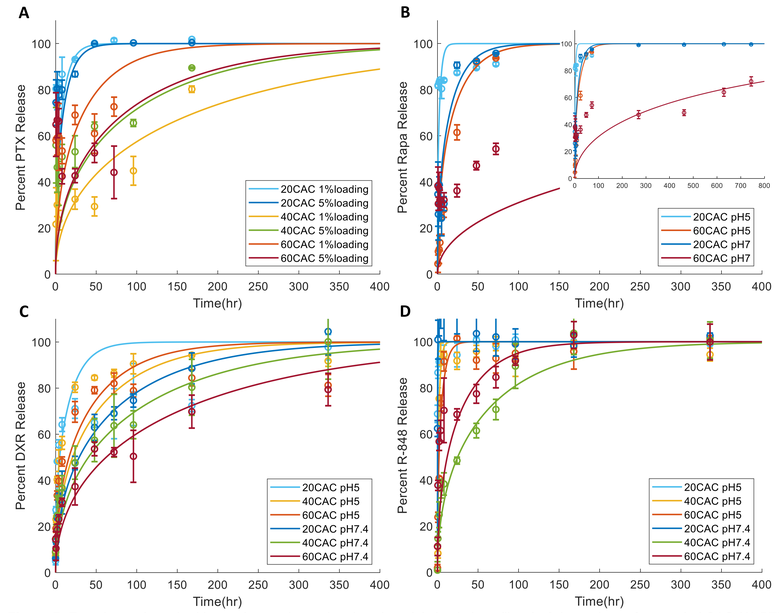
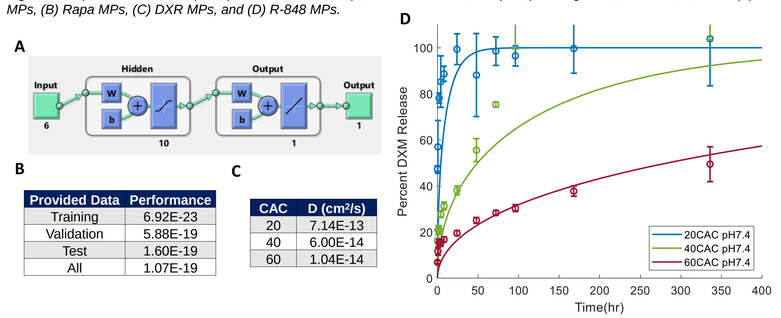


Figure 5: *Experimental results (data points and error bars) and model simulations (lines) of drug release from varied CAC (A) PTX MPs, (B) Rapa MPs, (C) DXR MPs, and (D) R-848 MPs.*



Provided Data	Performance
Training	6.92E-23
Validation	5.88E-19
Test	1.60E-19
All	1.07E-19

CAC	D (cm²/s)
20	7.14E-13
40	6.00E-14
60	1.04E-14

Figure 6: *A) NN structure and B) NN model performance values represented by MSE. Of the input and output data provided to develop the NN, 70% was randomly assigned as training data, 15% as validation data, and 15% as test data. C) NN predicted D_{AB} parameter values per CAC of DXM MPs at pH 7.4. D) DXM release experimental results (data points and error bars) and model simulations (lines) with NN predicted D_{AB} parameter values.*

Conclusions

- Ace-DEX MPs appear to degrade via surface erosion with a rate dependent on CAC and pH.
- Each drug demonstrated distinct release kinetics, likely influenced by varied drug properties.
- Our model was successful in fitting drug release behavior for various Ace-DEX MP systems.
- With training data from model fitting, a neural network machine learning algorithm was able to accurately predict diffusion coefficients for additional release curves with DXM.
- **With further work, this model can aid in the optimization of drug delivery kinetics of Ace-DEX formulations.**

Future Work

- Applications of the model are planned with additional cargos and geometries.
- *In vivo* experiments are planned with varied CAC MPs.

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References

1. Kauffman KJ, Do C, Sharma S, Gallovic MD, Bachelder EM, Ainslie KM. Synthesis and Characterization of Acetalated Dextran Polymer and Microparticles with Ethanol as a Degradation Product. *ACS Appl. Mater. Interfaces*, 2012, 4 (8), pp 4149–4155. DOI: 10.1021/am3008888.
2. Siepmann J, Elkharraz K, Siepmann F, Klose D. How Autocatalysis Accelerates Drug Release from PLGA-Based Microparticles: A Quantitative Treatment. *Biomacromolecules*, 2005, 6 (4), pp 2312–2319. DOI: 10.1021/bm050228k.