Biomaterials Lab

Statistical Modeling of Drug Release from Spherical Surface-Degrading Particle Batch

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Research question: Is it possible to create a tool that can help companies statistically determine acceptable theoretical batch parameters?

Introduction

1. Many medical devices utilize degradable drug-eluting microspheres to improve control over drug release and minimize systemic drug effects [1]. However, manufactured batches typically do not have size uniformity, which leads to a nonuniformity in drug release [2].
2. FDA strictly regulates drug dosing [3]. Companies must prove that their drug amounts deliver therapeutic effects, but it is difficult to control exact drug dosage in a nonuniform particle batch.
3. Solution: a computational template that statistically models the effects of mean and percent standard deviation on drug release
   - ➢ Conserve time, money, and material resources of companies and the FDA.

Methods

1. Mathcad File
   - ➢ Inputs: mean, % standard deviation
   - ➢ Outputs: Time for 60% drug release, Slope and Intercept (log scale)
2. JMP14: Design of Experiments and Statistical Analysis
   - ➢ 2n factorial experimental design
3. Excel: Data Comparison

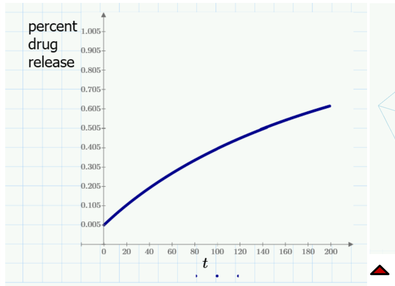


Figure 1: Graph for percent drug release until point of 60% drug release

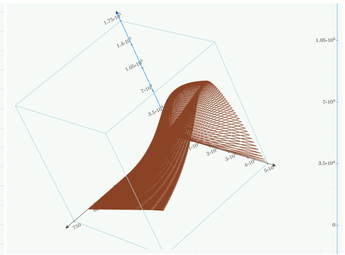


Figure 2: 3D visualization of dimensionalized drug release over time and radius

Assumptions:

1. Radius Distribution: Log-normal Probability Function

$$PDF = \frac{1}{x\sigma\sqrt{2\pi}} exp\left(\frac{-(ln\,x - \mu)^2}{2\sigma^2}\right)$$

1. Surface Degradation
   1. No drug diffusion

$$\frac{dr}{dt} = -b$$

2. Material uniformity: Nonporous, Spherical
3. Boundary Conditions
   1. All drug begins inside microparticle with maximum radius
   2. As time goes to infinity, all drug environment with radius = 0

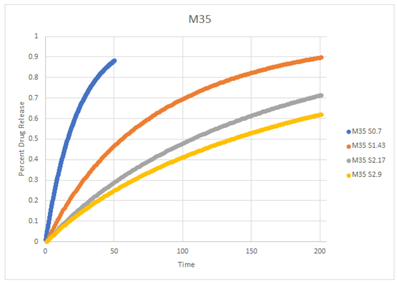


Figure 3: Excel graph for the radius mean of 35. Each curve represents a different value for standard deviation.

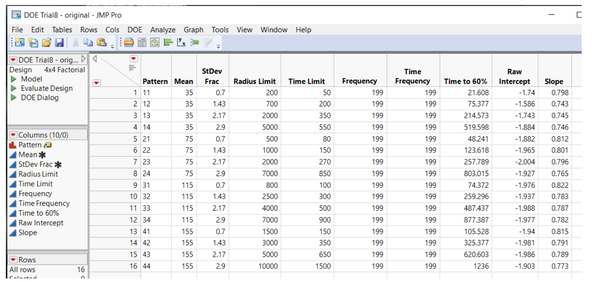
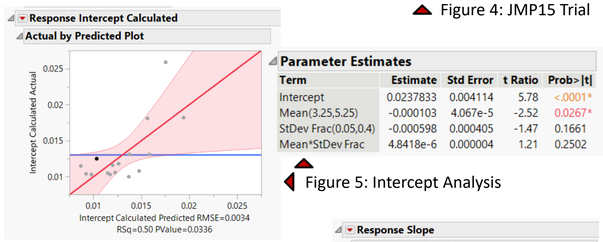


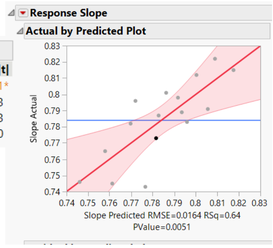
Figure 4: JMP15 Trial



Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	0.0237833	0.004114	5.78	<.0001*
Mean(3.25,5.25)	-0.000103	4.067e-5	-2.52	0.0267*
StDev Frac(0.05,0.4)	-0.000598	0.000405	-1.47	0.1661
Mean*StDev Frac	4.8418e-6	0.000004	1.21	0.2502

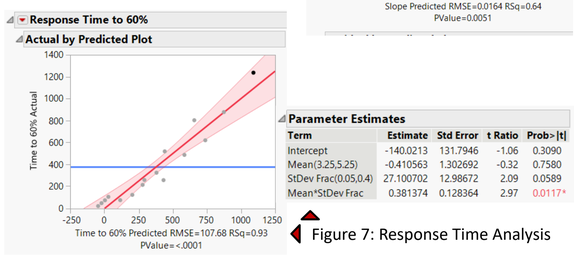
Figure 5: Intercept Analysis



Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	0.7955166	0.020082	39.61	<.0001*
Mean(3.25,5.25)	0.0001971	0.000198	0.99	0.3403
StDev Frac(0.05,0.4)	-0.003823	0.001979	-1.93	0.0773
Mean*StDev Frac	6.4298e-6	1.956e-5	0.33	0.7480

Figure 6: Slope Analysis



Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	-140.0213	131.7946	-1.06	0.3090
Mean(3.25,5.25)	-0.410563	1.302692	-0.32	0.7580
StDev Frac(0.05,0.4)	27.100702	12.98672	2.09	0.0589
Mean*StDev Frac	0.381374	0.128364	2.97	0.0117*

Figure 7: Response Time Analysis

Challenges:

1. Selected assumptions constrains ability to interpret data
2. Determining range/limits to adequately capture enough data
3. Program Syntax and limitations

Discussion:

1. Comparison and visualizations of experimental trials are shown in Excel.
2. Contrary to what was expected, results showed inconsistent presence of statistical significance.

Future Work

1. Analysis of other reasonable values for mean and standard deviation
2. Application to other distribution models (both radius distribution and drug release)
3. Application to randomly generated data
4. Comparison of results acquired from Mathcad to experimental data acquired from a wet lab
5. Translation of mathematical logic to other programs (Matlab, Wolfram Mathematica, etc.)

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References:
[1] Tzafriri A.R., Lerner E.I, Flashner-Barak M., et al. Mathematical Modeling and Optimization of Drug Delivery from Intratumorally Injected Microspheres. Clin Cancer Res. 2005;11:826-834
[2] Witschi C, Doelker E. Influence of the microencapsulation method and peptide loading on poly(lactic acid) and poly(lactic-co-glycolic acid) degradation during in vitro testing, J Controlled Release. 1998;51:327- 341.
[3] *Final Guidance for Industry - Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation* [PDF]. (2018, April). Silver Spring, MD: Food and Drug Administration. https://www.fda.gov/science-research/nanotechnology-programs-fda/nanotechnology-guidance-documents
[4] Poncelet De Smet B, Neufeld RJ. Control of mean diameter and size distribution during formulation of microcapsules with cellulose nitrate membranes. Enzyme Microb Technol. 1989;11:29- 37.

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