Biomaterials Lab

Creation of a Computational File for Calculating Drug Release from Degradable Spherical Gel 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

- For better control over drug release, many medical devices utilize degradable drug-eluting particles to minimize systemic drug effects [1]. However, manufactured batches typically are not uniform in size, which leads to a nonuniformity in drug release [2].
- FDA strictly regulates drug dosing. Companies must prove that their drug amounts deliver therapeutic effects, but it is difficult to control exact drug dosage in a nonuniform particle batch.
- Solution: a computational file that statistically determines the effects of mean, standard deviation and percent standard deviation on drug release
    - Save the time and money of companies and the FDA.

	Pattern	Mu	Sigma	Intercept	Slope	Radius Limit	Time Limit	Frequency	Time Frequency	Time to 60%
1	11	3.5	0.05	-1.545	0.797	100	40	199	199	9.648
2	12	3.5	0.135	-1.436	0.763	200	80	199	199	16.884
3	13	3.5	0.22	-1.456	0.749	300	150	199	199	36.181
4	14	3.5	0.3	-1.435	0.741	500	300	199	199	70.854
5	21	4	0.05	-1.528	0.794	150	70	199	199	16.181
6	22	4	0.135	-1.422	0.758	250	150	199	199	30.905
7	23	4	0.22	-1.335	0.726	550	400	199	199	74.372
8	24	4	0.3	-1.374	0.728	1300	900	199	199	185.427
9	31	4.5	0.05	-1.606	0.805	200	100	199	199	27.638
10	32	4.5	0.135	-1.334	0.738	500	350	199	199	59.799
11	33	4.5	0.22	-1.293	0.71	1500	1100	199	199	193.467
12	34	4.5	0.3	-1.326	0.714	4000	3000	199	199	572.864
13	41	5	0.05	-1.53	0.792	400	200	199	199	47.236
14	42	5	0.135	-1.391	0.744	1000	600	199	199	120.603
15	43	5	0.22	-1.267	0.705	3000	2500	199	199	414.573
16	44	5	0.3	-1.296	0.713	8000	7000	199	199	1231

Figure 3: JMP14 Trial

Challenges:

- Determining acceptable values for DOE
- Determining range/limits to adequately capture enough data
- Program Syntax and limitations

Approach

- Create a Mathcad File
- Inputs: mean, standard deviation, % standard deviation
- Extract slope, intercept, and time for 60% drug release (log scale)
- Analyze statistical significance (DOE) using JMP14.

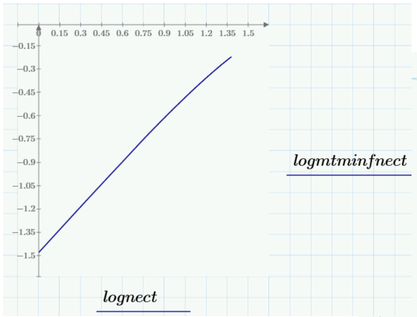


Figure 1: Log graph for trend of 60% drug release

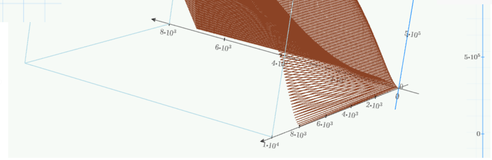
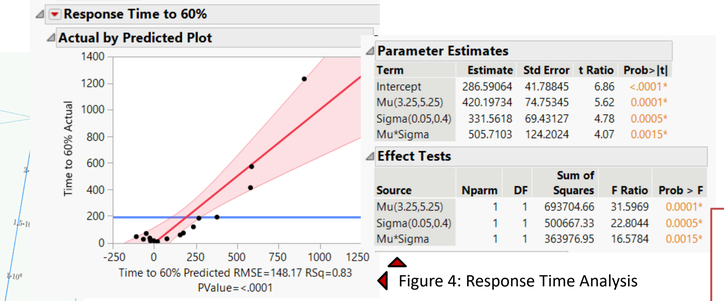


Figure 2: 3D visualization of drug release over time and radius



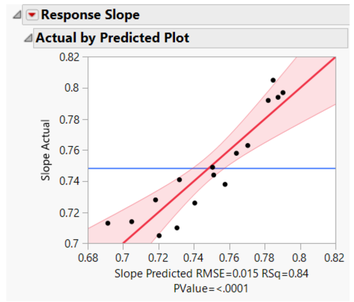
Parameter Estimates				
Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	286.59064	41.78845	6.86	<.0001*
Mu(3.25,5.25)	420.19734	74.75345	5.62	0.0001*
Sigma(0.05,0.4)	331.5618	69.43127	4.78	0.0005*
Mu*Sigma	505.7103	124.2024	4.07	0.0015*

Effect Tests					
Source	Nparm	DF	Sum of Squares	F Ratio	Prob > F
Mu(3.25,5.25)	1	1	693704.66	31.5969	0.0001*
Sigma(0.05,0.4)	1	1	500667.33	22.8044	0.0005*
Mu*Sigma	1	1	363976.95	16.5784	0.0015*

Figure 4: Response Time Analysis

Methods:

- Mathcad File:
    - Added text to relate file functionality to theory
    - Worked with graduate student to observe Mathematica and use of a different distribution curve
- Literature review for theoretical values
- JMP14



Parameter Estimates				
Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	0.7340428	0.004244	172.96	<.0001*
Mu(3.25,5.25)	-0.020522	0.007592	-2.70	0.0192*
Sigma(0.05,0.4)	-0.052122	0.007051	-7.39	<.0001*
Mu*Sigma	-0.014977	0.012614	-1.19	0.2581

Effect Tests					
Source	Nparm	DF	Sum of Squares	F Ratio	Prob > F
Mu(3.25,5.25)	1	1	0.00165470	7.3071	0.0192*
Sigma(0.05,0.4)	1	1	0.01237265	54.6372	<.0001*
Mu*Sigma	1	1	0.00031926	1.4098	0.2581

Figure 5: Slope Analysis

Discussion:

- Visual representations for calculations also included in file
- Did not end up using mean and standard deviation – used shape parameters instead
- Used 4 levels

Future Work

- Application to other distribution models
- Apply to randomly generated data
- Application to real data rather than theoretical
- Research more into other reasonable values for mean/standard deviation (theoretical)
- Utilize other programs

Acknowledgements:

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- Thank you to FURI for providing the opportunity to further explore this area of healthcare.

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] 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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