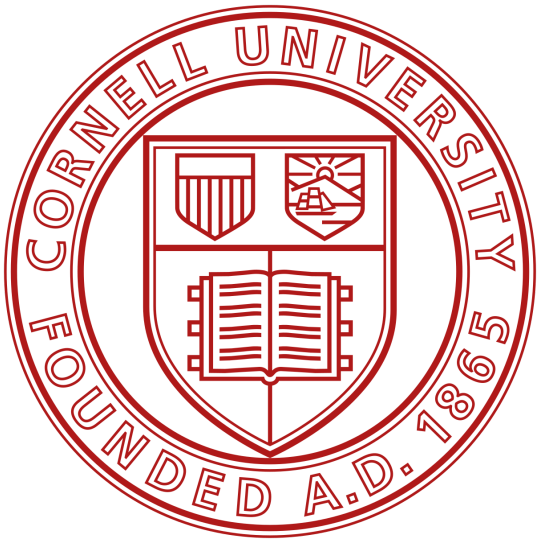

Drug Release Simulation of Swelling and Deformation in HPMC Tablets

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Keywords: Drug Diffusion, Extended Release, HPMC, Water Absorption, Tablet Geometry

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1.0 Executive summary

In this project, we aim to develop a comprehensive mathematical model to describe drug release kinetics from hydroxypropyl methylcellulose (HPMC) matrices, polymers commonly used in controlled drug delivery systems. HPMC facilitates sustained drug release by swelling upon water absorption, enabling gradual diffusion of the drug over time. However, this release process involves multiple interdependent mechanisms: water diffuses into the matrix, causing it to swell, while the drug simultaneously diffuses outward. Many existing models oversimplify these processes, often neglecting either diffusion or swelling, leading to inaccurate predictions. Such inaccuracies can result in overdosing or underdosing, compromising therapeutic outcomes, and reducing the ability to tailor release profiles to patient-specific needs.

To address this, our model integrates both diffusion and swelling mechanisms to more accurately capture the dynamics of drug release from HPMC matrices. The system is modeled using COMSOL Multiphysics® 6.0, with the drug tablet represented as a 2D axisymmetric geometry approximating a thin cylinder. As water diffuses into the matrix, it causes the polymer to swell axially, expanding the cylinder and facilitating drug diffusion out of the system. By applying conservation of mass through one-dimensional mass transfer equations, we simulate both water uptake and drug release, coupling these processes to model the resulting axial expansion. This swelling is represented as a moving boundary condition driven by water absorption.

Initial results revealed notable discrepancies between our model and experimental data. Without implementing a ramping function, the model predicted an unusually slow release profile, with only 20 percent of the drug released in eight hours, compared to the 80 percent observed experimentally. Additionally, the predicted axial expansion reached three times the initial height, whereas experimental data showed only a two-fold increase. While some of this deviation can be attributed to inherent model limitations, these do not fully explain the exaggerated early-stage expansion seen within the first two hours. As such, refining the model to better capture the physics of axial swelling remains a priority.

Despite these deviations, the model successfully captured key qualitative trends, lending confidence to its use for comparative analysis. To investigate how tablet geometry affects drug release, we simulated four cylindrical configurations: RxL, Rx2L, 2RxL, and 2Rx2L, each differing in radius and length. We analyzed the surface area to volume (SA to Vol) ratio across these geometries. Tablets with higher SA to Vol ratios (RxL and 2RxL) released approximately 98 percent of the drug within three to eight hours. In contrast, those with lower ratios (Rx2L and 2Rx2L) released only 68 percent and 66 percent, respectively. These findings indicate that drug release is inversely correlated with tablet length, while changes in radius have a comparatively

minor effect. Thus, diffusion path length appears to be a more dominant factor than surface area in determining release rate.

2.0 Introduction

Approximately 60% of Americans live with at least one chronic condition [1], often resulting in a need to routinely take medication repeatedly at an increased rate for a prolonged period, which can be tedious for the patient, lowering patient compliance. This increases the risk of user error from the patient, which can lead to either underdosing or overdosing, both of which can be dangerous for the patient. These challenges emphasize the need for improved drug delivery systems that reduce the frequency of dosing while having consistent therapeutic effects.

One promising solution to address these challenges is the development of extended-release drug formulations. Extended-release drugs are designed to release their active ingredients gradually, allowing for less frequent dosing and improved patient compliance. A commonly used approach to achieving controlled drug release is the use of hydrophilic hydroxypropyl methylcellulose (HPMC) matrices in tablet formulations [2]. The tablet is prepared by mixing the polymer and drug, followed by compression into a solid form. When the tablet is exposed to water or gastrointestinal fluids, the outer layer of the tablet absorbs water, causing the HPMC to swell and form a gel-like barrier. The drug dissolves within this swollen layer and diffuses through it at a controlled rate, with the rate of diffusion governed by the polymer viscosity and drug solubility. This controlled release mechanism helps maintain consistent drug levels in the bloodstream, reducing dosing frequency.

Despite the effectiveness of HPMC matrices in controlled drug release, challenges remain in optimizing drug release profiles for specific therapeutic applications. Current research often overlooks variations in drug properties, such as solubility, and the molecular characteristics of the polymer, which can significantly impact release rates. This study aims to address these limitations by investigating HPMC-based tablets, focusing on optimizing shape, size, and properties. We will analyze drug delivery time, tablet volume changes, and diffusion rates over time to improve release control.

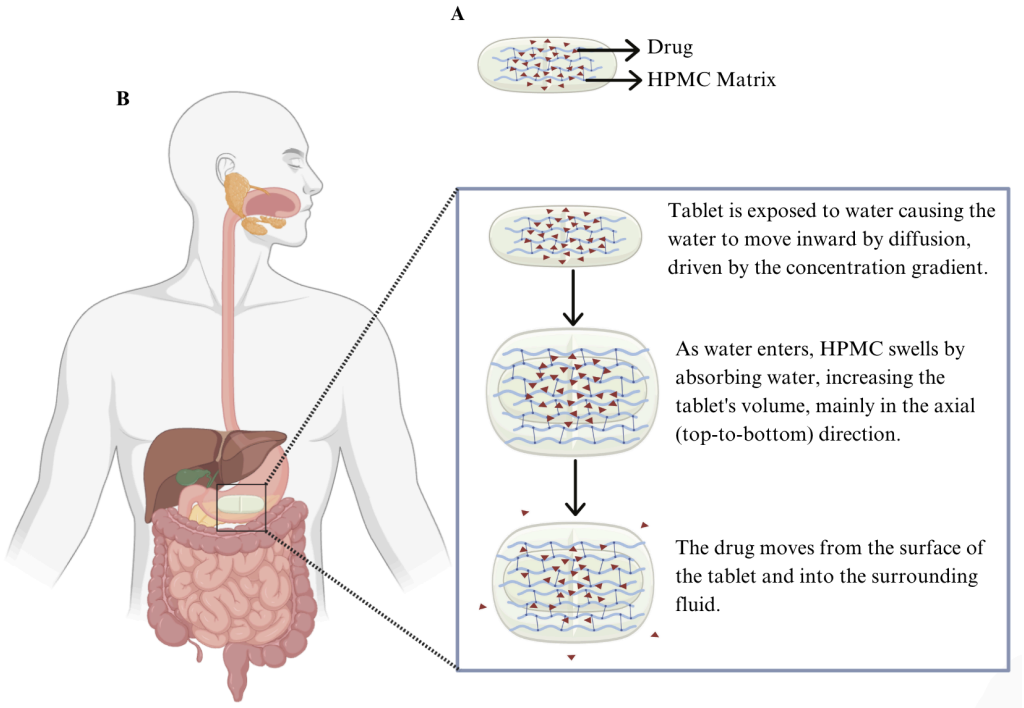


Figure 1: Extended-release formulations using HPMC matrix (Figure not to scale). Part A shows that the polymer (HPMC) is in a solid, non-swollen state, and the drug is trapped inside the polymer matrix. Part B depicts drug release from an HPMC tablet through water-driven swelling and diffusion, enabling controlled release under sink conditions.

3.0 Problem Statement and Design Objectives

3.1 Problem Statement

Some complications can arise with the use of extended-release drugs, such as dose dumping or incomplete drug release. For this reason, it is important to have models that accurately depict how the drug is released into the body. To achieve specific drug release profiles, creating a model to demonstrate drug diffusion physics across various factors is necessary, as modelling the system through COMSOL Multiphysics® 6.0 allows for further understanding of release profiles for a wide range of differing drug geometries and molecules. This study aims to address these limitations by investigating HPMC-based tablets, focusing on optimizing shape, size, and properties. We will analyze drug delivery time, tablet volume changes, and diffusion rates over time to improve release control.

3.2 Objectives

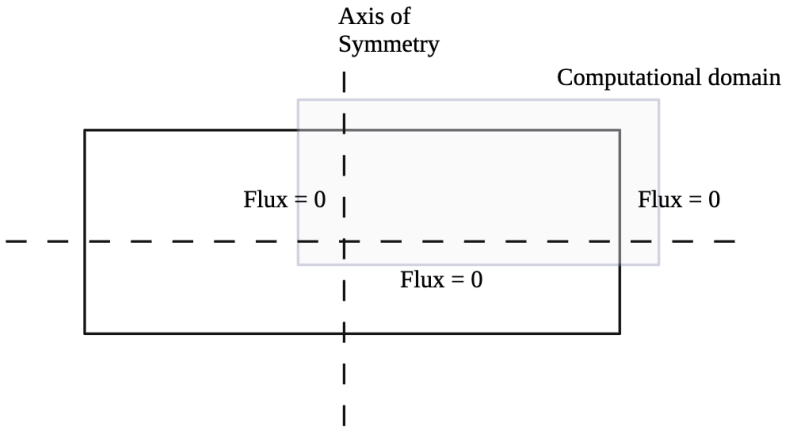
- Determine the change in length of the drug tablet throughout the extended-release process as water is absorbed by the polymer
- Determine the rate of water absorption and drug molecules across the homogenous polymer-drug mixture over time
- Compute the time for full drug delivery and water absorption through COMSOL Multiphysics® 6.0 implementation to determine when the drug has reached its equilibrium state
- Examine the influence of tablet sizing on drug release profiles

4. Methodology

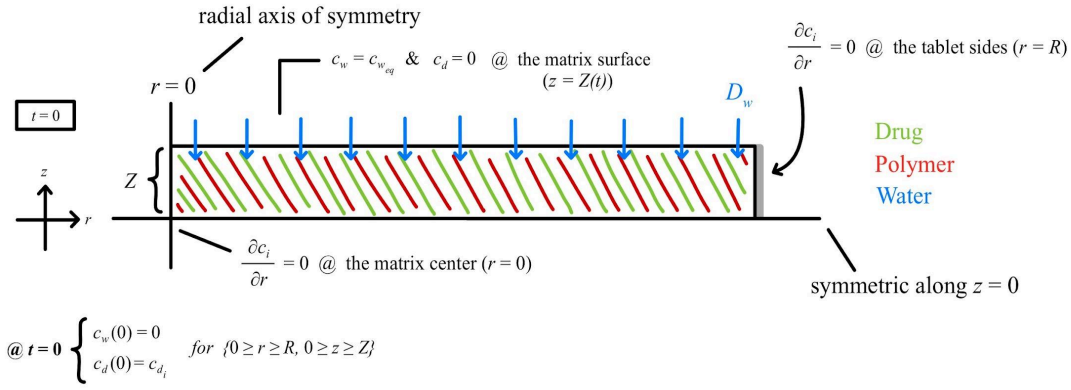
4.1 Physical Model Description

To study controlled drug release, a **2D axisymmetric cylindrical geometry** was used to model a hydrophilic matrix tablet composed of a homogenous HPMC/polymer mixture. Given the cylindrical symmetry, the model focuses on a quarter segment to reduce computational load while preserving accuracy, assuming uniform behavior across all quadrants. The tablet is initially dry and submerged in water, which acts as the surrounding medium. Upon hydration, water diffuses into the matrix, initiating **polymer swelling**, predominantly in the axial direction [3]. The surface of the tablet in contact with water is assumed to **instantly reach equilibrium water concentration**, with negligible radial swelling due to geometric proportions.

(A)



(B)



(C)

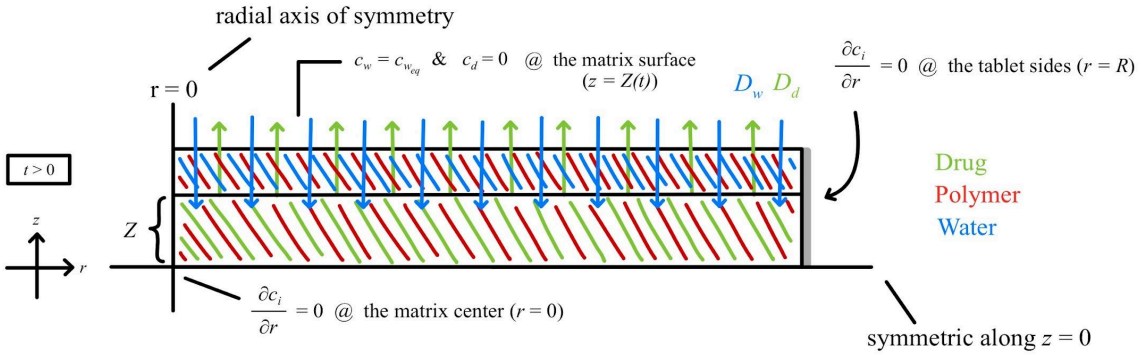


Figure 2: Schematic of the HMPC tablet model. Part A shows the section of the 2D plane modeled for the table. Part B shows the model at t=0. Part C shows the model at t>0.

4.2 Mathematical Model

To find the average total time for complete drug delivery, the key challenge is measuring the drug concentration leaving the tablet. Utilizing the law of conservation of mass, we conduct a mass balance across the tablet's surface boundary. This provides us with the concentration of both HPMC and water in the system at each time step. The governing equations that describe the diffusion of the drug and water in the system, modeled through **1D mass diffusion**, (eq 1 & eq 2)

For drug diffusion, the equation is:

$$\frac{\partial c_d}{\partial t} = \nabla(D_d \nabla c_d) \qquad (1)$$

For water diffusion, the equation is:

$$\frac{\partial c_w}{\partial t} = \nabla(D_w \nabla c_w) \tag{2}$$

where c_d and c_w represent the concentrations of the drug and water, respectively, as functions of time, and D_d and D_w are the diffusion coefficients for the drug and water. These 1D mass diffusion equations govern how drug and water molecules diffuse within the tablet over time. In environments such as the stomach, where convection is typically faster than diffusion, we simplify the model by neglecting convection, as diffusion is the rate-limiting step. This significantly reduces the complexity of the calculations without compromising accuracy. Furthermore, these equations do not include a source term, as there is no moving boundary or generation of mass within the system.

The diffusion of the drug is directly influenced by the water concentration within the polymer matrix. As water concentration increases, the drug diffusion becomes easier due to the higher availability of solvent. The drug diffusion coefficient as a function of time is modeled by:

$$D_d(t) = D_{d,eq} e^{(-\beta_d(1-\frac{c_w}{c_{w,eq}}))} \tag{3}$$

Similarly, the water diffusion coefficient is modeled as:

$$D_w(t) = D_{w,eq} e^{(-\beta_w(1-\frac{c_w}{c_{w,eq}}))} \tag{4}$$

In these equations, $D_{d,eq}$ and $D_{w,eq}$ are the equilibrium diffusion coefficients for the drug and water, respectively, while β_d and β_w are constants that control the rate of change in the diffusion coefficients as the water concentration approaches equilibrium. These equations describe how diffusion coefficients evolve as the system progresses toward equilibrium, which is essential for accurately simulating the drug release process.

By incorporating these diffusion equations, we can track how the drug moves through the system and how the tablet's structure changes over time. Specifically, as the polymer absorbs water, it expands, and the tablet’s boundary shifts. This expansion is modeled using the following equation for polymer expansion

$$\Delta L = \frac{1}{\pi R^2}\left(\frac{c_{w,total} M_w}{\rho_w}\right) \quad (5)$$

With the radial dimension of the tablet remaining fixed (as per the assumptions), the volume change is entirely manifested as a change in the axial direction. Using conservation of mass, we can directly relate the concentrations of water and drugs to the physical space they occupy, allowing us to model the moving boundary due to water absorption. This equation links the absorption process to the physical expansion of the tablet.

Through the use of these governing equations, we can calculate the percentage of drug delivered over time and track the polymer's maximum water absorption. The water absorption percentage is determined by the extent to which the polymer reaches its equilibrium water concentration, causing the tablet to expand axially.

However, the model has certain limitations. It assumes a zero-flux condition in the radial direction, meaning that drug diffusion is confined to the axial direction. Consequently, for tablets with a width much larger than their length, the model will not accurately represent the real-world scenario. Additionally, the model does not account for the effects of shrinking due to polymer and drug diffusion, which could affect the accuracy of the simulation under different conditions.

4.3 Numerical Implementation

The simulation was implemented using COMSOL Multiphysics® 6.0. A boundary system with deformed geometry was used to model the swelling behavior of the tablet. A mixed mesh approach was applied, incorporating prescribed mesh-free deformation to accommodate the anisotropic expansion of the matrix. The Transport of Diluted Species physics module was employed to simulate the diffusion of water and drug molecules within the polymeric matrix. The coupled multiphysics system integrates water diffusion, swelling, and drug transport dynamics, and is solved using time-dependent analysis. The study is conducted for 8 hours for a timestep of 6 minutes.

4.4 Assumptions

To simplify the physics within our model, the following assumptions are made.

- Due to the assumption of a soluble drug, the species is considered to dissolve instantaneously, leaving diffusion as the primary factor influencing drug transport. The drug concentration at the surface is assumed to be zero, which represents a **perfect sink**

condition, meaning that as soon as the drug reaches the surface, it is immediately carried away by the surrounding fluid (such as in the stomach).
    - This impacts our model as there is no drug build-up on the surface of the tablet, allowing us to correlate the amount of diffused drug equal to the amount of drug delivered into the system. Additionally, this assumption allows us to neglect dissolution and convection physics within the drug diffusion process.
- Ideal water absorption
    - The surface of the tablet in contact with water has instantaneously absorbed the maximum amount of water, equal to the water equilibrium concentration.
- The system is fully submerged in water
    - This impacts our model as our initial parameters are specifically the diffusivity constants between HPMC and water– altering the fluid within the system will require these input parameters to change.
- Geometry shrinking due to drug diffusion and polymer erosion is negligible.
    - This impacts our model by simplifying the physics for our moving boundary, allowing us to model it through correlating the change in volume due to water absorption to the amount of drug diffused. If the geometry was simultaneously shrinking, this method would be incorrect, hence requiring simplification
    - Polymer erosion is negligible, leading to diffusivity constants being constant over time, instead of diffusion through polymer increasing as time continues
- Flux on the sides of the tablet is assumed to be zero due to negligibly thin side geometry.
    - Axial expansions greatly exceed radial expansion (due to significantly larger surface area in the axial dimensions), thus allowing polymer swelling in the radial direction to be neglected ($\frac{dR}{dt} = 0$)
    - This has a small impact on results due to diffusion through end caps not being modelled, and although negligible, will have a larger impact for larger length: radius ratios
    - Due to the proportions of our geometry, this assumption is acceptable. However, if the ratio of R:L were to decrease, this assumption would no longer be valid, and there must be flux on the right-most edge of the tablet. Since the tablet is modelled axisymmetrically across the radial and axial directions, the left edge of the COMSOL Multiphysics® 6.0 geometry (located at r=0) will still be a no-flux condition due to the symmetrical geometry being revolved around it.

4.5 Boundary Conditions and Initial Conditions

The boundary conditions at the outer surface of the matrix (z = Z(t)) are defined as (eq. 6 and 7)

$$c_d = 0 \quad (6)$$

$$c_w = c_{w_{eq}} \quad (7)$$

Since the tablet is fully submerged in water, the outermost polymer layer is continually replenished by the surrounding medium. As a result, the water concentration at the surface is assumed to instantly reach a constant equilibrium value $c_{w_{eq}}$. The drug concentration at the surface is assumed to be zero due to the comparatively rapid diffusion of drug molecules relative to the relaxation or erosion of polymer chains. This fast outward diffusion prevents any drug accumulation at the boundary.

A zero-flux condition is applied at the midline and axis of symmetry (z=0), meaning that no material enters or leaves from the middle. This is because the model is axisymmetric, resulting in zero concentration gradients at the center. In other words, the water and drug concentrations remain unchanged at the center.

At the Tablet Sides (r=R), Zero-flux boundary conditions are also applied at the radial boundaries. This assumption reflects the negligible radial expansion of the tablet during the dissolution process. As such, material transport through the sides is considered insignificant and is excluded from the model.

Initial conditions

The tablet is dry at the initial time t=0, and the drug is evenly distributed throughout the entire matrix. For all radial positions($0 \geq r \geq R$) and axial positions, the drug concentration is at its initial value, denoted as (eq 8)

$$c_d(0) = c_{d_i} \quad (8)$$

representing the uniform distribution of the drug throughout the tablet. In contrast, the water concentration is initially zero throughout the tablet, with (eq 9)

$$c_w(0) = 0 \quad (9)$$

indicating that no water has penetrated the tablet at the start of the process.

3.5 Input Parameters

Below is a table listing the input parameters' values used in the model, including their values, units, and sources. These parameters are used throughout the study to calculate and simulate the dissolution process of the tablet.

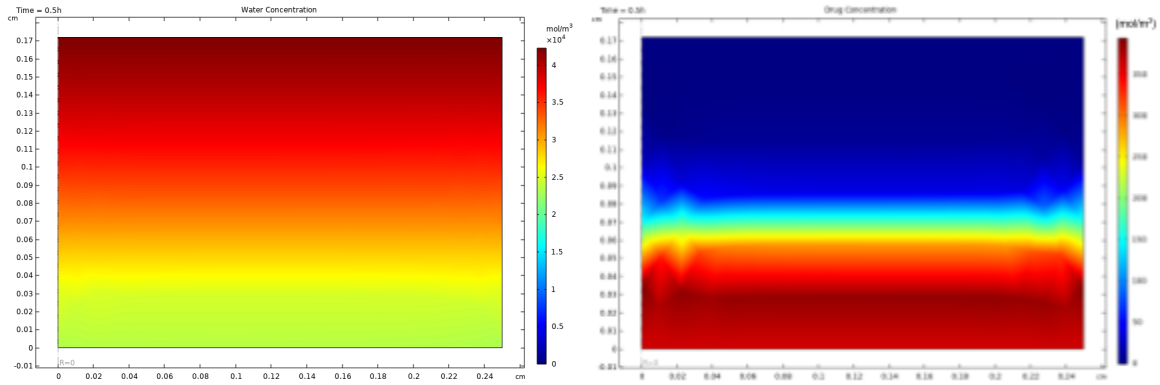
Table 1: Input parameters used in the simulation model

Parameter	Definition	Value	Units	Source
$c_{w_{eq}}$	Concentration of water at equilibrium	0.042286	$[\frac{mol}{m^2}]$	Siepmann et al. (1999) [4]
$\beta_w(\beta_1)$	Concentration dependent diffusivity constant for water	2.5	[-]	Siepmann et al. (1999) [4]
$D_{w_{eq}}(D_{1_{eq}})$	Diffusion coefficient of water within the fully swollen tablet	$5.6 * 10^{-6}$	$[\frac{cm^2}{s}]$	Siepmann et al. (1999) [4]
$D_{d_{eq}}(D_{2_{eq}})$	Diffusion coefficient of propanol hydrochloride within the fully swollen tablet	$6.3 * 10^{-7}$	$[\frac{cm^2}{s}]$	Siepmann et al. (1999) [4]
$\beta_d(\beta_2)$	Concentration dependent diffusivity constant for propanol hydrochloride	9.5	[-]	Siepmann et al. (1999) [4]
$c_d(0)$	Initial propanol hydrochloride concentration	0.00036849	$[\frac{mol}{m^2}]$	Siepmann et al. (1999) [4]
M_w	Molar mass of water	18.02	$[\frac{g}{mol}]$	PubChem [5]
ρ_w	Density of water	1	$[\frac{g}{mL}]$	PubChem [5]

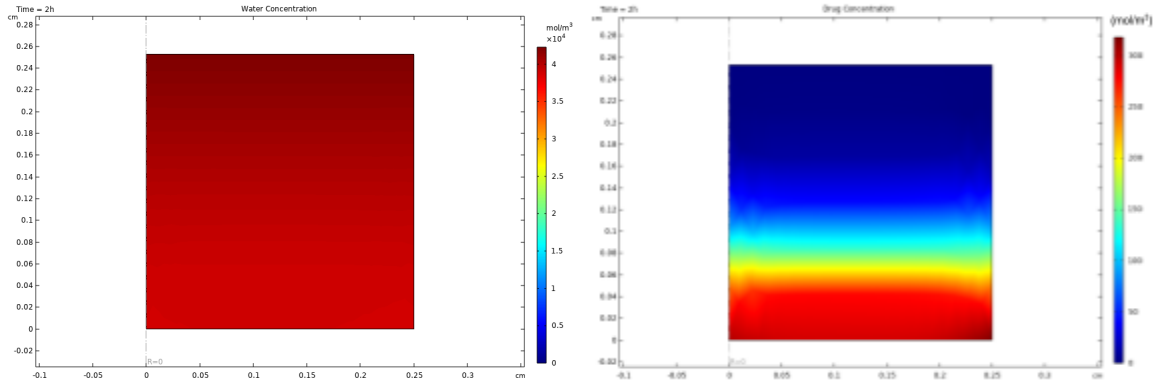
5.0 Results and Discussions

5.1 Mesh convergence

The percent of drug released holds the most weight in terms of relevance to real-life applications, thus, we have decided to use this as our reference variable. With the drug release tending to plateau around the 3-hour mark, we have chosen to use the 2-hour mark as a testing point for comparing results. Figure 5d. helps justify this reference point, because even though the tablet is almost completely saturated by the 2-hour mark, as shown in Figure 3c, in nearly a quarter of the tablet, a significant amount of the drug is still yet to be released.



3a. 3b.



3c. 3d.

Figure 3. 3a. Water Concentration Profile (0.5 hr), 3b. Drug Concentration Profile (0.5 hr), 3c. Water Concentration Profile (2hr), 3d. Drug Concentration Profile (2hr)

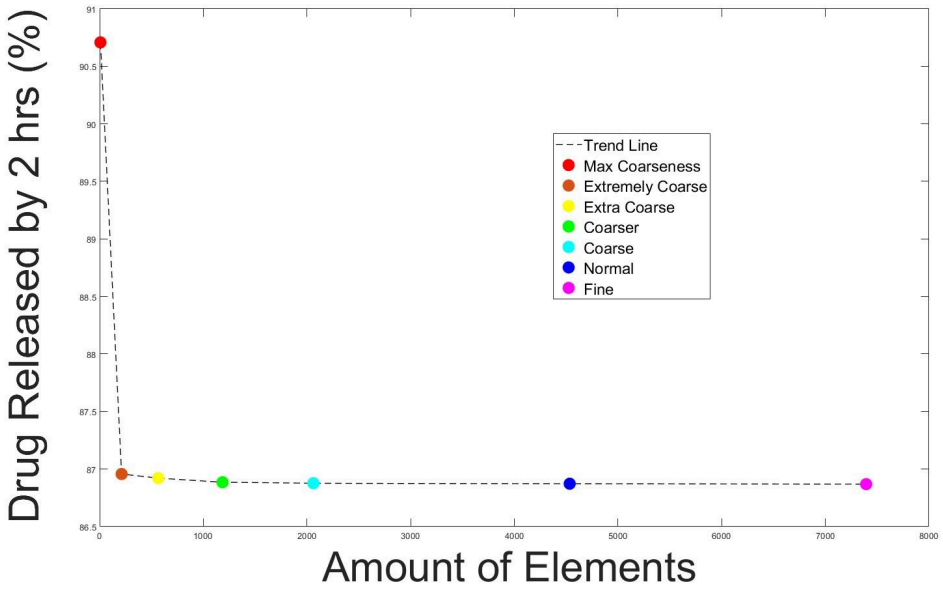


Figure 4. Mesh Resolution on Model Accuracy

As visible in Figure 4, meshes composed of more than 1,000 elements show virtually identical values at this time. For coarser meshes, with element counts in the magnitude of the hundreds range, a very slight change in drug release can be noticed. With the "Extremely Coarse" mesh (212 elements) only showing a drug release 0.12% higher in comparison to the "Coarser" mesh (1186 elements), we deemed this difference to be statistically insignificant, with a variation of this scale unlikely to hold any real-world significance. On the extreme side, the coarsest mesh we were able to manually generate consisted of only 8 elements, where at the 2-hour mark, a 3.75% difference in drug release was present, which was deemed large enough to impede model accuracy. Ultimately, the "Extremely Coarse" preset was chosen for the final mesh, as the substantially reduced running time of this solution can enable more simulations to be carried out, thus allowing for a larger, more expansive set of scenarios to be investigated.

5.2 Experimental validation

For axial expansion, both the experimental data and the model (without ramping) show an increase in axial expansion over time. This relationship is expected due to matrix swelling as water diffuses in. However, the increase in axial expansion for the model without ramping is disproportionately faster than the experimental, plateauing at a significantly higher value as well. To combat this issue, a ramping function was incorporated to give the rate of axial expansion a

more linear profile and prevent drastic changes in expansion speed. Though the model with ramping still initially increases faster than the experimental data, similar to the model without ramping, the linear profile eventually lowers this rate, making the overall increase significantly less in comparison to without ramping. The model with ramping also plateaus at a value close to the experimental data.

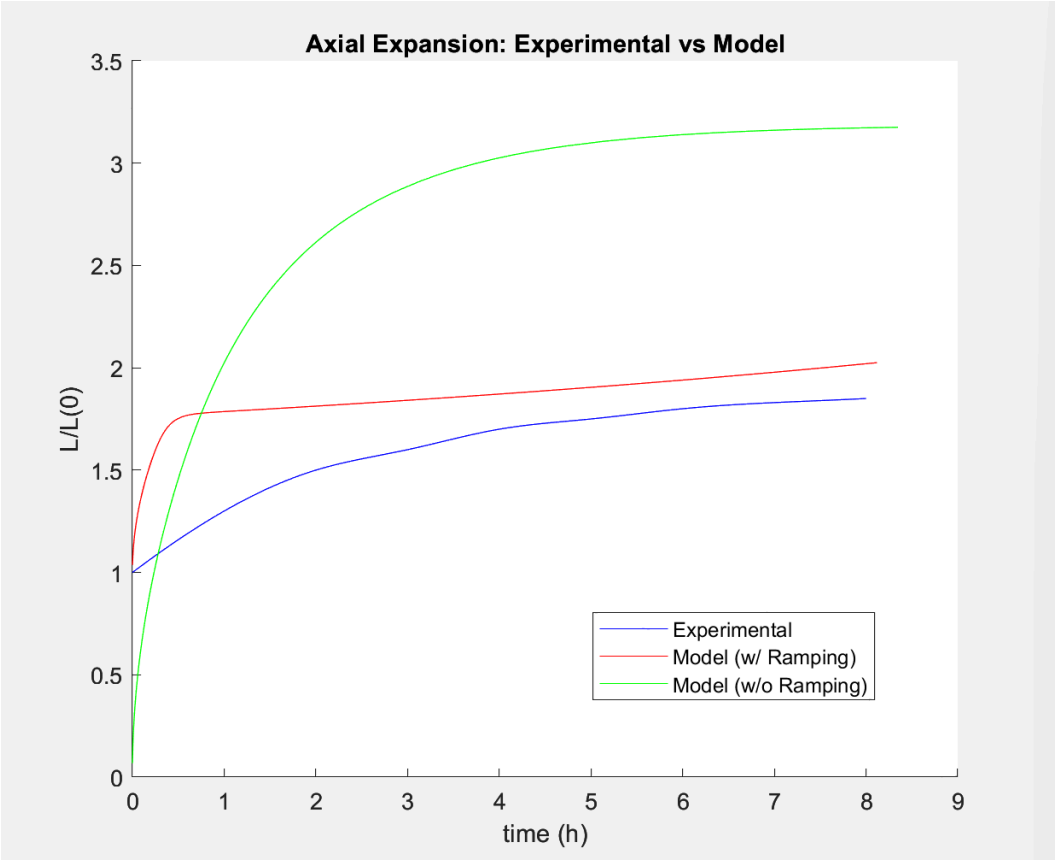


Figure 5. Axial Expansion Validation

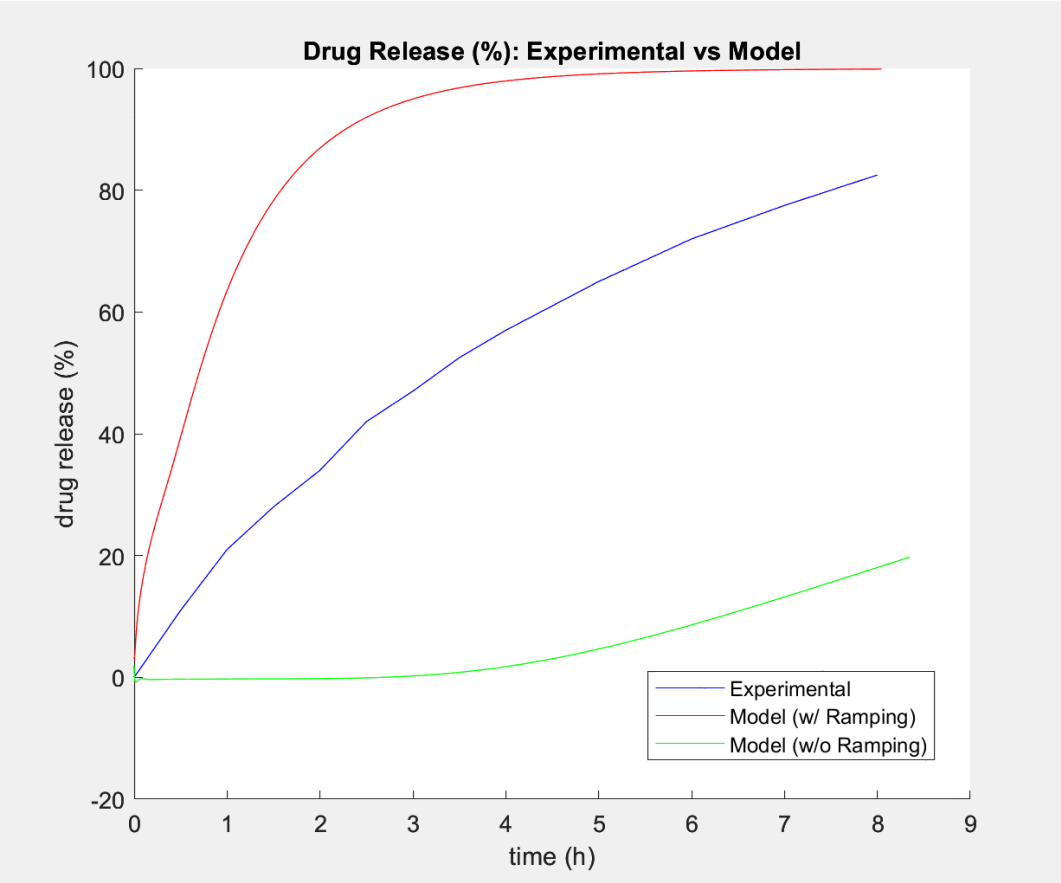


Figure 6. Drug Release Validation

The rate of drug release is directly affected by the speed of axial expansion, because as the tablet grows in length, the drug molecules must diffuse across an increasingly farther distance before they can reach the edge of the system. The model implemented in this study originally resulted in disproportionally fast axial expansion towards the beginning of the simulation, compared to the rate of drug diffusion at this time. This resulted in the tablet reaching its fully expanded length in an unreasonably short amount of time, which greatly exaggerated the period for the drug to fully be released. As a result, the rate of drug release stalls out in the beginning, as while the tablet is still expanding, the speed of drug diffusion is greatly outmatched by the rate of expansion. With this extensive delay, only 20% of the drug can leave the system by the end of the 8-hour period, where this significant deviation from expected results raises concerns of model invalidity. Though the ramping function on the axial expansion did enable a more realistic drug release profile, it simultaneously brought along its inaccuracies as well. With the beginning of the simulation being most affected, the expansion rate was hindered to the point where the speed of drug diffusion greatly outweighed the length of the tablet, allowing a significant portion

to travel the needed distance to escape the tablet. Experimental data, as visualized through Figure 6, display a much more gradual drug release profile compared to the numerical model, where the full extent of the drug is released by the 5-hour mark. The intention of the HPMC matrix, and extended release drugs in general, is to allow for a consistent and evenly distributed drug release rate, ideally allowing the drug to last an entire 24 hours, so that the medication only needs to be taken once per day. This is where the utility of the model falls short, as the entirety of the drug is depleted in less than a quarter of its intended time.

5.3 Sensitivity analysis

The key input parameters to test within our model are varying the equilibrium concentration of water, the diffusion coefficients of HPMC and water, the diffusivity constants of water and HPMC, and the initial concentration of HPMC. The sensitivity analysis will be performed by independently varying each listed parameter by +/- 10% and analyzing the resulting data to confirm that the physics still behaves properly and uncertainty is low. The results of this analysis are shown in the graphs below.

Table 2: Values used for sensitivity analysis

Parameter	**Initial Value**	**-10%**	**+10%**
$c_{w_{eq}}$	0.042286 mol	0.038057 mol	0.046515 mol
$D_{w_{eq}}$ ($D_{1_{eq}}$)	$5.6 * 10^{-6}$ $[\frac{cm^2}{s}]$	$5.04 * 10^{-6}$	$6.16 * 10^{-6}$
$D_{d_{eq}}$ ($D_{2_{eq}}$)	$6.3 * 10^{-7}$ $[\frac{cm^2}{s}]$	$5.67 * 10^{-7}$	$6.93 * 10^{-7}$
$c_d(0)$	0.00036849 $[\frac{mol}{m^2}]$	0.000331641	0.000405339
$\beta_d(\beta_2)$	9.5	8.55	10.45
$\beta_w(\beta_1)$	2.5	2.25	2.75

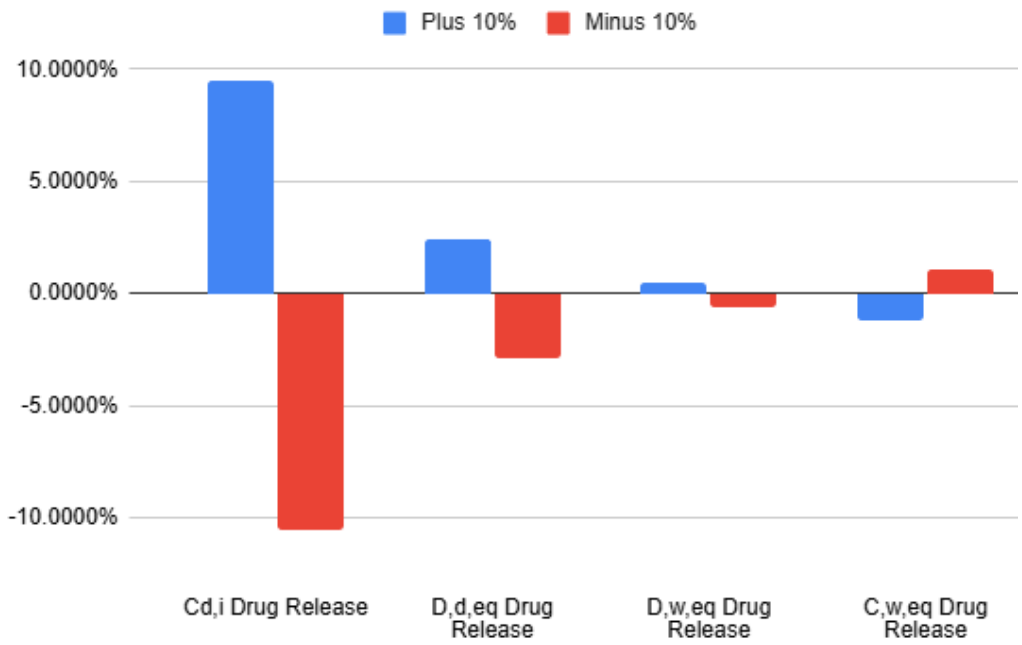


Figure 7: Sensitivity Analysis of Drug Release at 2 hours and Final Axial Expansion for relatively significant percent changes (greater than plus or minus 0.5%)

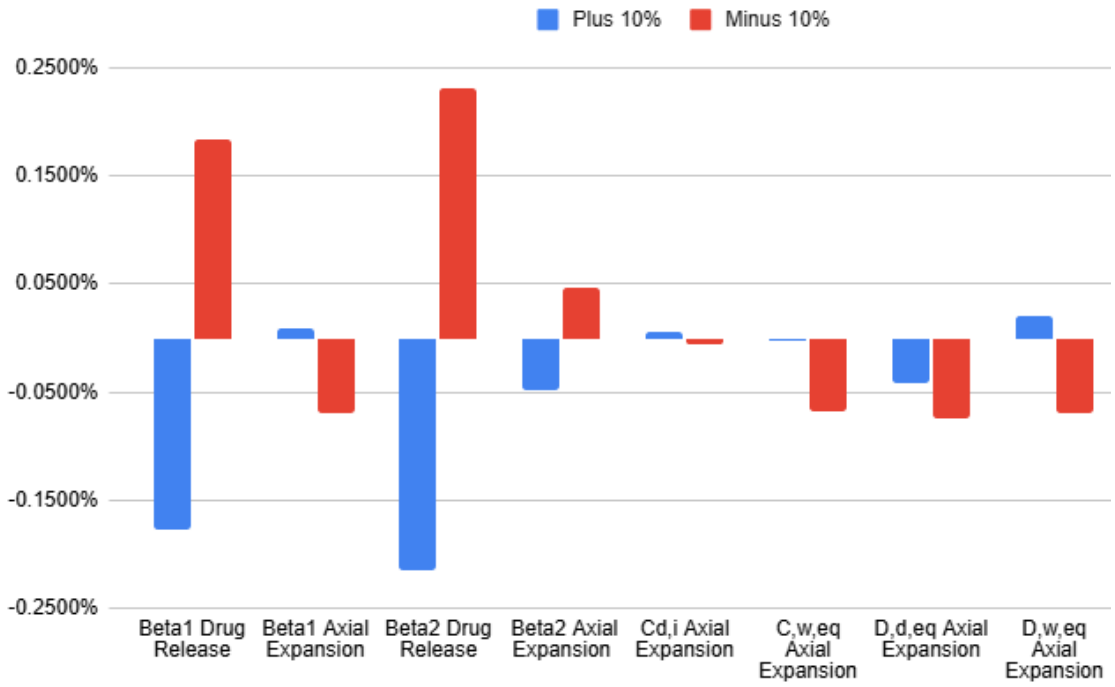


Figure 8: Sensitivity Analysis of Drug Release at 2 hours and Final Axial Expansion for relatively insignificant percent changes (less than plus or minus 0.5%)

The results of the sensitivity analysis fall in line with the expected physical outcome. As $\beta_w(\beta_1)$ increases, the water diffusion coefficient decreases proportionally, thus lowering the water and drug concentration at that given time. Within that same reasoning, lowering $\beta_d(\beta_2)$ results in a lower drug diffusion coefficient, thus having less drug released at a given time. As $D_{w_{eq}}$ ($D_{1_{eq}}$) and $D_{d_{eq}}$ ($D_{2_{eq}}$) are increased, the rate of diffusion is unaffected, while the equilibrium coefficient is, thus leading to a higher diffusion coefficient at any given time. $D_{d_{eq}}$ has a much more direct relationship with the drug released compared to $D_{w_{eq}}$ (as expected), thus leading to a larger uncertainty when varying this parameter. As $c_{w_{eq}}$ increases, the drug diffusion coefficient decreases, which causes less drug to be released at any given time. And finally, as the initial drug concentration is increased, drug release at a given time increases proportionally. This makes physical sense, as the rate of drug diffusion is unchanged, but there is more available drug to be diffused.

The parameters with the most statistical significance on the results of the model were all regarding their effect on drug release, and those parameters were $c_{w_{eq}}$, $D_{d_{eq}}$, $D_{w_{eq}}$, and $c_d(0)$. All the parameters only minimally affected the final axial expansion, with the largest effect being +/- 0.0735% after varying $D_{d_{eq}}$. The parameter with the greatest impact on the drug released is $c_d(0)$ followed by $D_{d_{eq}}$ and $c_{w_{eq}}$. These parameters all vary the drug released at a given time by at least 1%, which is statistically significant for drug delivery, as slight changes in dosage can lead to large physical ramifications. Thus, the parameters that must be the most accurate are the initial drug concentration, the drug diffusion equilibrium coefficient, and the water concentration at equilibrium.

5.4 Variation in Drug Release with Changes in Radius and Length

To achieve this, we analyzed four cylindrical tablet configurations by systematically varying the radius and length. The configurations studied include RxL (radius = 0.25 cm, length = 0.07 cm), Rx2L (radius = 0.25 cm, length = 0.14 cm), 2RxL (radius = 0.50 cm, length = 0.07 cm), and 2Rx2L (radius = 0.50 cm, length = 0.14 cm). These variations were chosen to isolate

the effects of increasing the length, radius, or both dimensions.

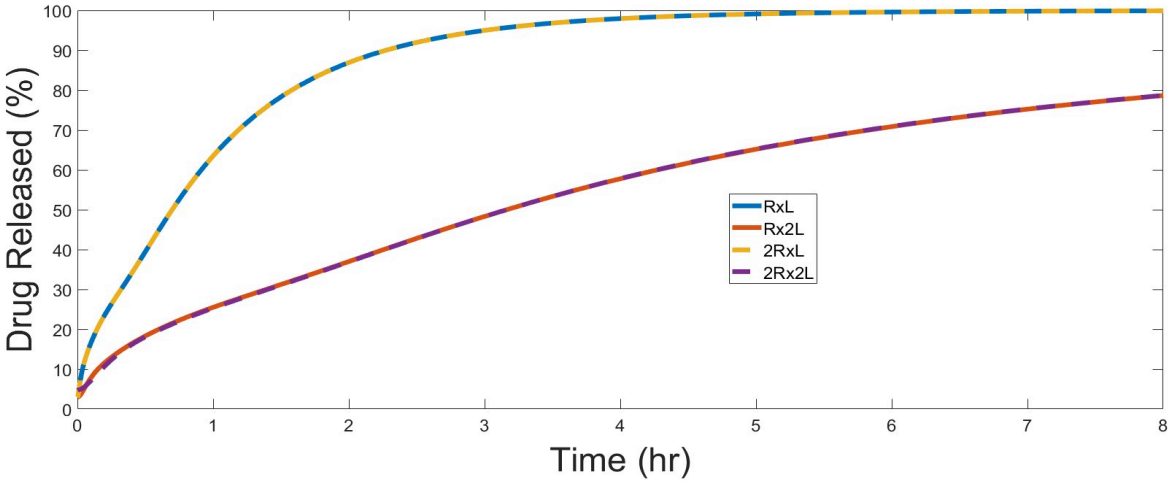


Figure 9: The plot shows the drug release profile over time for tablets of varying dimensions, where RxL (Blue): base size (R=0.25, L=0.07), Rx2L (Red): same radius, double the length (R=0.25, L=0.14), 2RxL (Yellow): double the radius, same length (R=0.5, L=0.07), 2Rx2L (Purple): double both radius and length (R=0.5, L=0.14).

The RxL and 2RxL groups release the drug more rapidly compared to Rx2L and 2Rx2L. This is likely because shorter tablets (smaller L) provide a shorter diffusion path and higher surface area-to-volume ratio, promoting faster release. RxL and 2RxL show the fastest release, nearing 100% by ~3 hours, suggesting increased surface area (due to larger R) greatly accelerates drug release. Rx2L and 2Rx2L both show much slower release rates and follow nearly identical profiles. This suggests that increasing length (L) creates a greater barrier to diffusion, dominating the effect of increased radius in 2Rx2L. The near overlap between Rx2L and 2Rx2L indicates that doubling the radius has minimal effect when the length is already doubled. It implies that the increased path length limits drug diffusion more significantly than the increased surface area facilitates it. The faster-releasing profiles (RxL, 2RxL) reach a plateau at ~100%, indicating complete release. The slower profiles (Rx2L, 2Rx2L) are still increasing linearly and reach around 70% at 8 hours, suggesting extended release or incomplete drug release within this time frame.

5.5 Effect of Surface Area-to-Volume Ratio on Drug Release

For each configuration, surface area and volume were calculated, and the corresponding SA:Vol ratio was derived. This ratio is a crucial parameter that significantly influences drug

release kinetics, making it central to understanding the performance of these tablets in drug delivery systems.

Table 3: Geometric parameters of cylindrical tablet configurations and their corresponding surface area, volume, and surface area-to-volume (SA:Vol) ratios.

Configuration	Radius (cm)	Length (cm)	Surface Area (cm^2)	Volume (cm^3)	SA:Vol Ratio
RxL	0.25	0.07	0.503	0.014	36.571
Rx2L	0.25	0.14	0.613	0.027	22.286
2RxL	0.5	0.07	1.791	0.055	32.571
2Rx2L	0.5	0.14	2.011	0.11	18.286

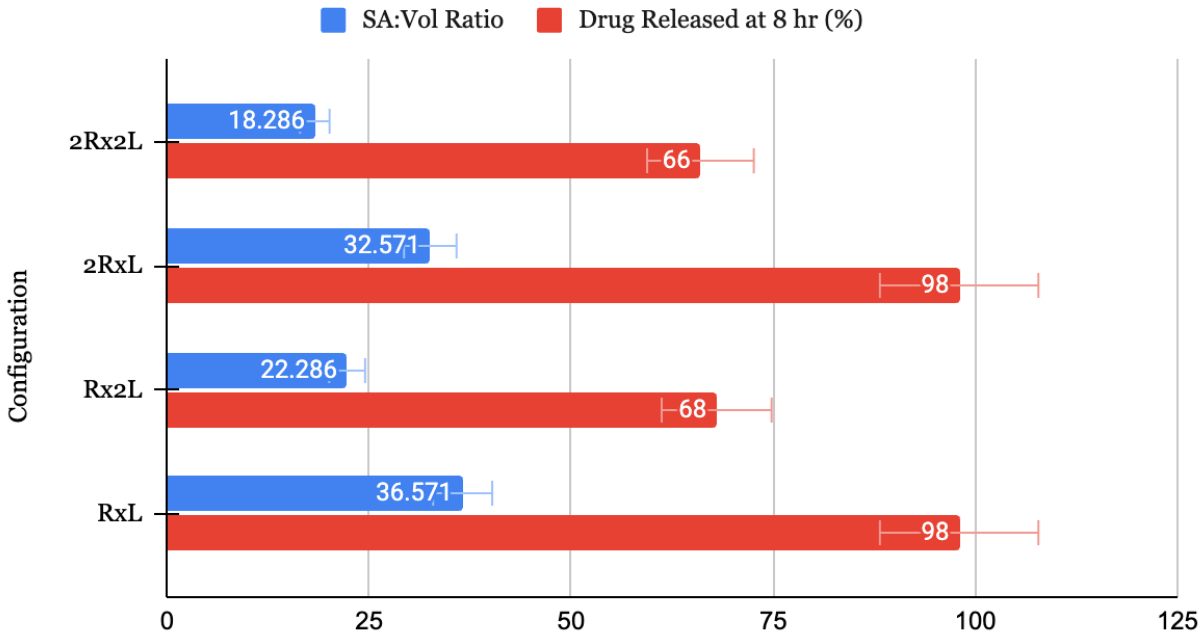


Figure 10: Surface area-to-Volume Ratio and drug released at 8 hr (%)

As shown in Figure 10, the smallest configuration, RxL (radius = 0.25 cm, length = 0.07 cm), achieves nearly complete release within 3 hours. In contrast, the largest tablet, 2Rx2L (radius = 0.50 cm, length = 0.14 cm), releases less than 70% of its drug content even after 8 hours.

Intermediate configurations follow a release pattern consistent with their SA:Vol ratios, confirming that increased surface exposure relative to volume enhances drug dissolution.

The drug release profiles reveal a strong correlation between SA:Vol ratio and the extent of drug release. Tablets with higher SA:Vol ratios, such as RxL (36.571) and 2RxL (32.571), released approximately 98% of their drug content. In contrast, configurations with lower ratios Rx2L (22.286) and 2Rx2L (18.286) exhibited significantly reduced release, at 68% and 66%, respectively. Notably, while RxL and 2RxL demonstrate similar high release percentages, their geometries differ, indicating that drug release may be more sensitive to the diffusion path length (i.e., the cylinder's length) than to surface area alone.

6.0 Conclusions and Design Recommendations

6.1 Conclusions

Ultimately, our results were unfruitful for our initial design objectives and goals. Our axial expansion not only does not follow the same behavioral trends as the experimental data, it also plateaus much later in the model, and shows a 1.5 times increase in expansion compared to experimental values. Within our drug release results, our model delivers most of the total amount of drug within the first three hours, compared to the experimental results, which deliver only fifty percent of the drug during that time. Thus, our model does not adequately reflect the experimental data shown with this system in the real world. This limitation is due to the lack of an accurate axial expansion formula, thus negatively influencing our drug diffusion rate. Several additional limitations in our model restrict its physical application, including assumptions contingent on a small length-to-width ratio, neglected polymer erosion, and perfect sink conditions contingent on a very soluble drug. By varying the size of the tablet, our findings further show the importance of optimizing both geometry and SA:Vol ratio in tablet design to achieve targeted release profiles, particularly in controlled-release or rapid-onset therapeutic applications. Higher SA:Vol ratios lead to faster and more complete drug release. While surface exposure is key, the similar release from RxL and 2RxL suggests that diffusion path length also influences release efficiency. Tablet design must therefore consider both geometry and SA:Vol balance.

6.2 Design Recommendations

Based on the findings from the simulation and analysis of HPMC-based drug delivery systems, several design recommendations can be made for optimizing future drug delivery tablets, particularly in terms of their geometry and drug release characteristics.

For further research, the existing cylindrical geometry in the model can be modified to simulate a spherical shape, providing a direct comparison of axial expansion rates between the two forms. This comparison will allow for a deeper understanding of how geometry influences swelling behavior, which is critical for optimizing drug release profiles. The spherical shape, with its uniform expansion properties, may offer advantages in terms of more controlled or efficient swelling behavior compared to the cylindrical shape [4]. Additionally, drug release kinetics in spherical HPMC matrices can be further explored using Fick's laws of diffusion and swelling-controlled release models. By assessing how geometry influences drug diffusion and release profiles, this analysis will provide valuable insights for improving the drug delivery system's effectiveness.

Furthermore, the polymer dissolution rate, which has previously been modeled mathematically, should be incorporated into future studies. The equation:

$$m_{dm}(t) = m_{dm}(0) - k_{diss} A_t t \tag{10}$$

with m_{dm} referring to the mass of the dry matrix (where $c_W = 0$) and A_t referring to the entire surface area of the tablet. From here, k_{diss} can be used to calculate the velocity of the boundary per unit surface area, which can be related to the overall volume change to find the individual rates of axial and radial expansion [4]. Currently, polymer dissolution is assumed to be negligible, but incorporating this factor into the model will help more accurately simulate the real-world behavior of the tablet.

Additionally, the current model assumes that expansion occurs only in the radial direction. However, in real-world scenarios, expansion happens in both the radial and axial directions. This limitation can be addressed in future research, where both directions can be factored into the model for a more accurate representation of the swelling behavior. Accounting for both radial and axial expansion will be particularly valuable for simulating tablets with significantly larger widths relative to their length. By incorporating this into future models, a more accurate simulation of such situations can be achieved, improving the understanding of how these geometries behave in practical drug delivery applications.

When working on optimizing the geometry and drug release kinetics, several constraints must be addressed during the design process. Ethical considerations are important to ensure that the drug delivery system doesn't introduce any unintended risks to patients. For example, excipients like HPMC need to be carefully evaluated for biocompatibility and possible adverse effects. Beyond that, the ethical aspects of clinical trials, ensuring informed consent, and making

the system accessible to all demographic groups need to be taken into account as part of the development. Health and safety are also top priorities; the release profile of the tablet must be predictable and controllable to avoid risks like under- or overdosing. It's also necessary to look into the long-term stability of HPMC-based systems, particularly in terms of how the matrix interacts with the drug and behaves in the body. Rigorous testing protocols are required to meet the necessary regulatory standards for both safety and efficacy. Social and political factors come into play as well, especially since the approval process for new drug delivery systems can be complex and costly. Regulatory hurdles, particularly in markets with strict approval processes like the U.S. FDA or European Medicines Agency, can slow down the introduction of new systems, making the process more challenging.

7.0 References

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8.0 Appendix

8.1- Sensitivity Analysis Results, Percent Change

	Beta1 Drug Release	**Beta1 Axial Expansion**	**Beta2 Drug Release**	**Beta2 Axial Expansion**	**Cd,i Axial Expansion**	**C,w,eq Axial Expansion**	**D,d,eq Axial Expansion**	**D,w,eq Axial Expansion**	**Cd,i Drug Release**	**D,d,eq Drug Release**	**D,w,eq Drug Release**	**C,w,eq Drug Release**
Plus 10%:	-0.1774%	0.0096%	-0.2146%	-0.0482%	0.0063%	-0.0023%	-0.0411%	0.0202%	9.5262%	2.4586%	0.4997%	-1.1978%
Minus 10%	0.1836%	-0.0687%	0.2301%	0.0459%	-0.0063%	-0.0669%	-0.0735%	-0.0700%	-10.5239%	-2.8708%	-0.6041%	1.0750%