APPLICATION OF CAPILLARY ACTION WATER-SOLUBLE DRUG DELIVERY

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ABSTRACT

This project intends to study and simulate a water-soluble drug working mechanism in the capillary which consists of a permeable membrane on its wall. Due to the capillary action, the drug will dissolve into the water. The system would require high precision as many parameters involved such as concentration, location, time, etc.[1] The model of this process will be demonstrated through COMSOL, with a constant flux and inlet velocity of the drug, to study the concentration changes of the drug in the drop over time.

KEYWORDS

Capillary action, water-soluble drug, capillary, COMSOL, concentration

INTRODUCTION AND BACKGROUND

The field of drug delivery has advanced dramatically in the past few decades. Drug delivery systems indicate the technologies that carry drugs into or throughout the body, such as swallowing a pill or injecting the vaccine [2]. Figure 1 shows different routes for drug delivery.

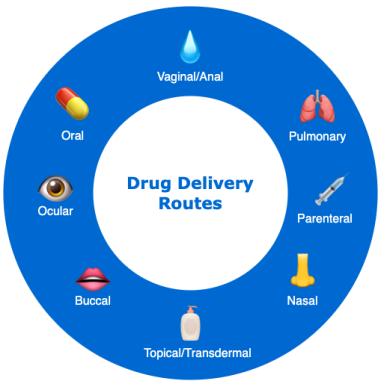

Figure 1. The presentation of different drug delivery routes.

From the principle of capillary action in drug delivery, the drug delivery system can also be described as the drug held by material, because of the capillary action, is packed and protected from degradation and allows it to travel wherever it needs to go in the body [2].

SIGNIFICANCE AND INNOVATION

Different routes of delivering medications into a patient's body during treatment face different challenges. Oral drug delivery systems have drug waste. It is difficult to maintain the integrity of protein molecules until it reaches the absorption site. Retaining and releasing the drug in the target absorption site is another obstacle [3]. Other drug delivery systems face barriers to protecting the drug from degradation. These inefficiencies in drug release control lead to side effects that drugs interact with healthy organs or tissues along the way it travels in the body, and this can limit the ability to treat many diseases. A more controlled drug delivery system could not only reduce the side effects but also reduce doses and costs.

Thus, we could see that the process of drug delivery requires high precision when it comes to the release location, timing, concentration, and amount of the drug to be administered. This is where COMSOL simulation can be very helpful, as it allows for the modeling of these aspects of the drug delivery system. Since when it comes to drug delivery, ensuring that the proper dosage of the drug administered is the key, we choose to focus on the concentration of the drug delivery system in this report.

METHODS

There are multiple ways how to target and deliver the drug to different parts of the body. This project focuses on the drug-delivery system based on the principle of capillary action. The capillary action describes the interaction between liquid and material, which can retain and control the release of drugs that are dissolved/dispersed in the liquid [4]. That is to say, because of the capillary, the drug held by some material is packed and protected from degradation and allows the package to travel through the body and release the drug at the target location.

The simulation intends to focus on the concentration change of the drug over time when passing the permeable membrane, thus other parameters, variables, and processes are controlled and simplified. Since the drug-delivery system happens in a micro regime, the Reynolds numbers are small (1 and below), viscous force dominates and the inertial force can be neglected. In this simulation, the gravity force on the droplet is also neglected. Since viscous forces dominate, resulting in a smooth velocity field, a constant velocity is assumed when the droplet travels through the permeable membrane. The volume of water is also assumed to be fixed. When the droplet travels along the capillary, the drug is relatively stable in the water. Figure 2. shows the basic model of the water-soluble drug droplet.

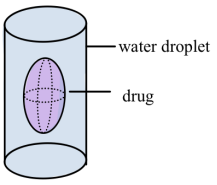

Figure 2. Model of the water-soluble drug droplet.

The model of the device is illustrated in Figure 3. Since a fixed volume of water and drug are assumed, in the COMSOL, we customize the geometry and material of capillary and droplet. The liquid water has a density of

1000 kg/m^3 and a viscosity of 10^{-3} Pa*s. The reminder of the capillary is filled with air, with a density of 1.25 kg/m^3 and a viscosity of 2x10^{-5} Pa*s. The capillary is clarified as a long vertical tube with a length of 1.5 mm. The drug-containing droplet is simplified as an eclipse, with a semi-major axis of 0.15 mm. In the COMSOL simulation, the initial position of the bottom of the droplet is set up at z = 1.0 mm, and the permeable membrane starts at z = 0.8 mm and ends at z = 0.6 mm. However, the permeable part of the capillary is not visible because it will be defined as a function applied to the boundary. The direction of motion of the droplet is from top to bottom of the capillary tube. At the initial position, the droplet is assumed to be stationary, and when it is released from the position, it travels down and accelerates to a constant velocity before reaching the permeable membrane. The diffusion coefficient of the drug in the water is $5\times10^{-9} m^2/s$. As the surface of the droplet is exposed to the membrane, its velocity is set to be a constant velocity to study the concentration change over time.

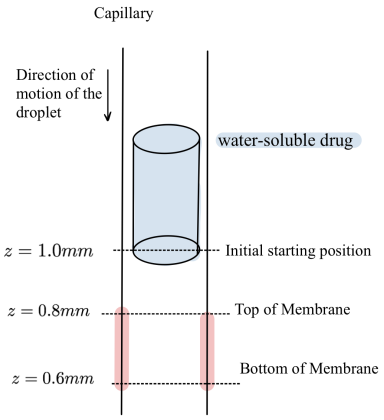

Figure 3. Model of the capillary with permeable membrane and water-soluble drug droplet at the initial position (t=0).

The simulation is a time-dependent study, addressing the modules of Laminar Flow (SPF) and Transport of Diluted Species (TDS). Since the model variables are set to track drug dose and drop location, a rectangle function is defined that is one at the region corresponding to the permeable membrane and zero anywhere else. The Navier Slip boundary condition is used on the walls along which the contact line moves, and a pressure constraint is applied at the outlet. In the Fluid-Fluid interface, the water-air surface tension coefficient is set as 70 mN/m at human body temperature. The contact angle before entering the permeable membrane is 135°, the exiting contact angle increases to 157.5°, and an equation is directly defined as $\frac{3}{4}\pi \times (1 - rect(z)) + \frac{7}{8}\pi \times (rect(z))$ which will make the contact angle vary when passing through the permeable membrane.

Transport of diluted species physics is added to model the process when the solute transport in the droplet and it ensures the drug transport occurs only in the liquid domain. For the drug to flow into the droplet, a boundary condition is added. The expression (1) ensures flux only enters the droplet as it passes the permeable membrane.

$$J0, c = rect(z) * 0.001[mol/(m^2 * s)] \quad (1)$$

Finally, set up the parametric sweep in the study. The time sweep range is from 0s to 10s with a time step of 0.5s. The constant velocity when the droplet enters the permeable membrane is 0.0002 m/s. A stop condition is also added to prevent the droplet from leaving the geometry. More detailed steps of the COMSOL setup are listed in Appendix A.

Results

As can be seen in Fig 4, the water-soluble droplet is stationary at the initial position of z = 1.0 mm, and the color of the droplet is maintaining a green, which means the concentration of the drug in the droplet is 0.

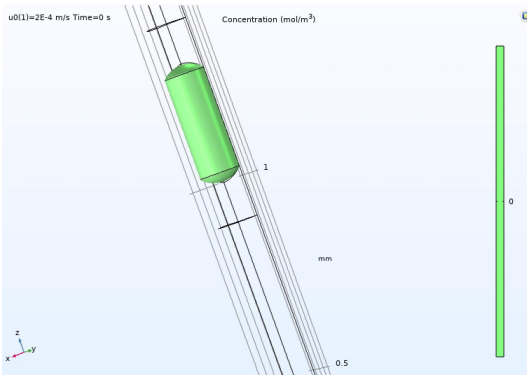

Figure 4. droplet concentration at the initial position (z=1.0 mm, t = 0s).

After 0.5s, the droplet moves for 0.1 mm, thus the droplet only arrives at the position at z = 0.9 mm, which does not enter the permeable membrane region. The concentration of the drug is illustrated in Fig 5.

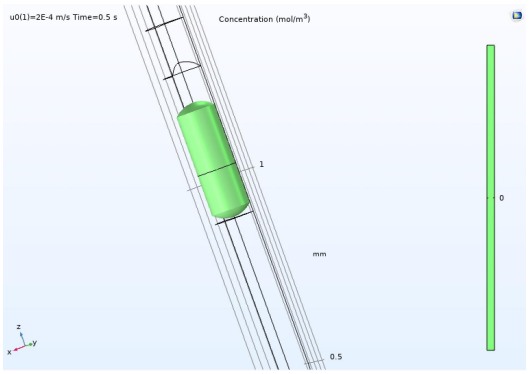

Figure 5. droplet concentration at t = 0.5s (z = 0.9mm).

At t = 1s, the bottom of the droplet reaches z = 0.8 mm, and thus starts to enter the permeable membrane. From Figure 6, the concentration at the bottom of the droplet can be seen changing from 0 to $25 \times 10^{-5} mol/m^3$ and more. The color at the bottom of the droplet changed from dark blue to green, yellow, and dark red, where different colors represent different concentration magnitudes in the droplets.

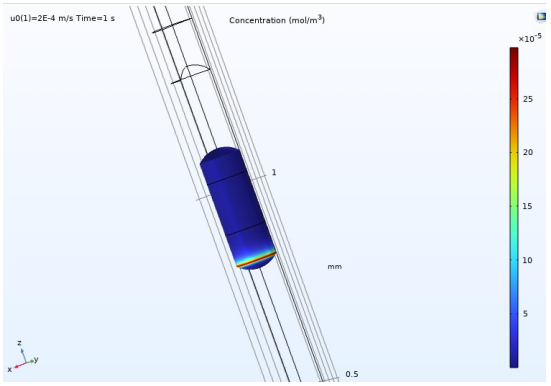

Figure 6. droplet concentration at t = 1s (z = 0.8 mm).

Figure 7 to 12 shows the concentration change of droplet from t= 1.5s to t = 4s, with a time increase of 0.5s. It can be seen that the concentration change of the drug in the droplet starts at the bottom and gradually moves to the middle and finally at the top of the droplet. This is because the bottom of the droplet is the first place having contact with the permeable membrane. The contact angle starts to change and causes the drug to dissolve in the water, and as the contact area with the permeable membrane increases, more and more drugs start to dissolve in the water. And as Fig 9 to Fig 12 indicates, when the droplet passes over the bottom of the permeable membrane, the concentration of the drug starts to decrease. It is due to the absorption of the membrane which absorb part of the drug in the droplet.

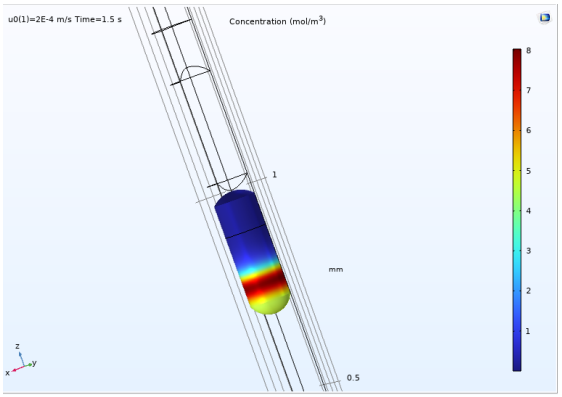

Figure 7. droplet concentration at t = 1.5s.

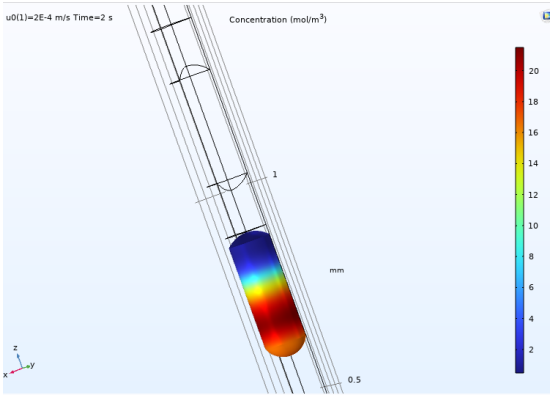

Figure 8. droplet concentration at t = 2s.

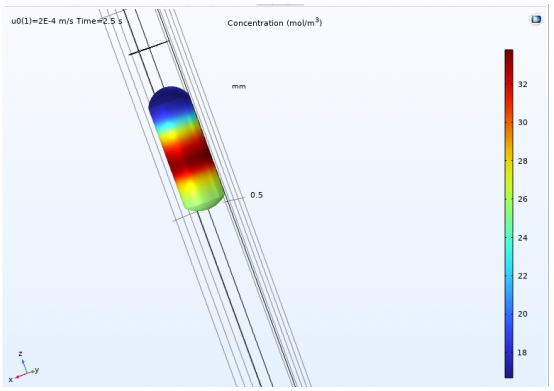

Figure 9. droplet concentration at t = 2.5s.

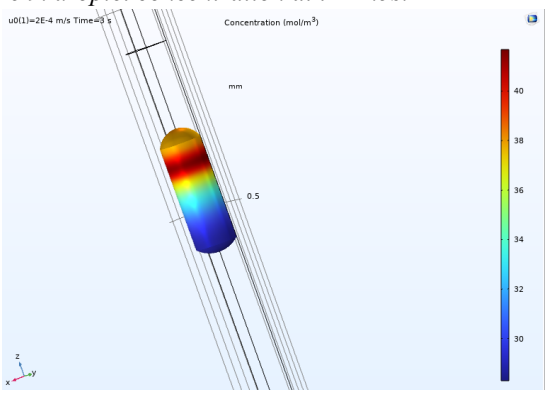

Figure 10. droplet concentration at t = 3s.

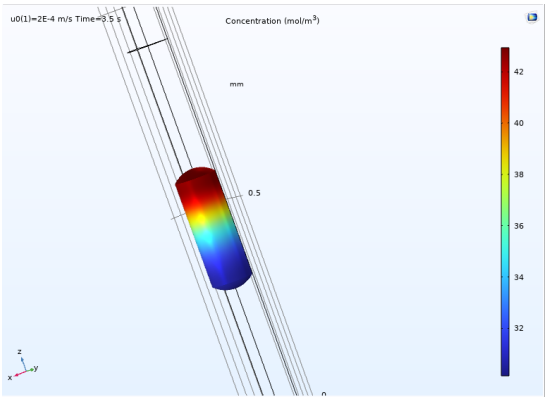

Figure 11. droplet concentration at t = 3.5s.

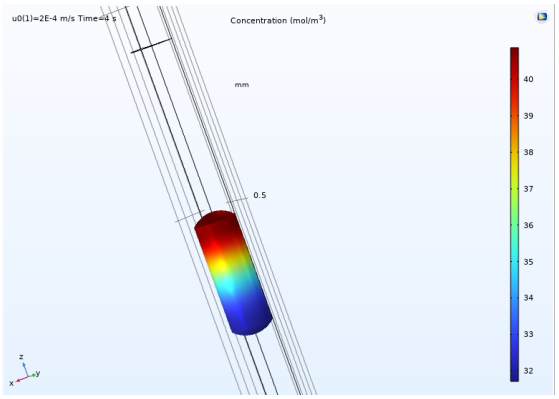

Figure 12. droplet concentration at t = 4s.

Figure 13 shown below examines the relationship between the total amount of the drug that has diffused into the droplet and time. When the droplet is traveling at a

speed of 0.0002 m/s, the drug concentration increases with an s-shaped profile. There is a steady increase between 3 and 6 seconds. It is when the droplet's surface is in contact with the membrane.

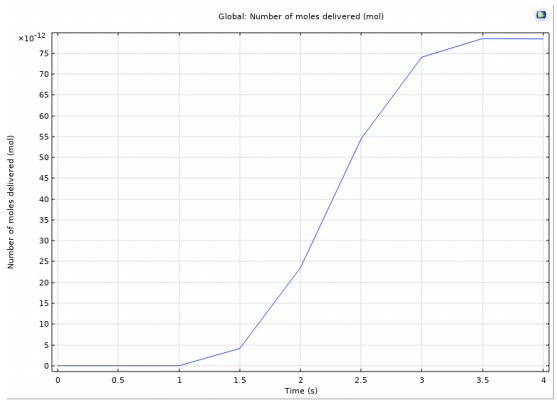

Figure 13. The number of moles delivered as a function of time.

CONCLUSION

According to the analysis of the quantity of the drug in the droplet with time, as the drop passes by the permeable membrane, the drug dissolves into the water. Then there's a marked change in concentration. The drug concentration changes over time in the area of permeable membrane mostly exponentially.

For future work, we can also study other aspects affecting the precision, such as the relationship between the drug-delivering velocity and the final concentration of the drug in the droplet. The assumption is that by altering the droplet velocity, the number of moles delivered in the drop can be adjusted. It could be useful for finding the optimal velocity in order to administer a desired drug dosage in the target absorption site. Continuing advances in this area will help to facilitate the targeted delivery of drugs while mitigating their side effects at the same time.

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APPENDIX A

Protocol:

1. Open a new COMSOL File and define the following:
    a. Model Wizard > **2D Axisymmetric**
    b. Select Physics > Fluid Flow > Multiphase Flow > **Two-Phase Flow**
    c. Select Physics > Moving Mesh>**Laminar Two-Phase Flow, Moving Mesh**
    d. Study > General Studies > **Time Dependent**
2. Define Parameters:
    a. Model Builder > Global Definitions > **Parameters 1**

Name	Expression	Value	Description
u0	0.001[m/s]	0.001 m/s	Droplet velocity (m/s)

3. Create the Geometry:
    a. Model Builder > Geometry1 > Unit > **mm**
    b. Model Builder > right click Geometry > Rectangle (In the "Setting Window", set the following values)
        i. Rename as r1
        ii. **Width** = 0.05, **Height** = 1.5
        iii. **Layers**:

Layer name	**Thickness (mm)**
Layer 1	0.9
Layer 2	0.5

    c. Model Builder > right click Geometry > **Ellipse** (In the "Setting Window", set the following values)
        i. Rename as e1
        ii. a-semiaxis = 0.09
        iii. b-semiaxis = 0.15
        iv. Position: z = 1.15
        v. Object Type > Type > Curve
    d. Model Builder > right click Geometry > Booleans and Partitions > **Partition Objects** (In the "Setting Window", set the following values)
        i. Rename as par1
        ii. Select r1
        iii. Tool objects > Activate Selection > e1
4. Define Domains and Boundaries:
    a. In the "Definitions" toolbar > Nonlocal Couplings > **Integration**
        i. Right click and rename the Integration to "intop1"
        ii. In the "Settings window" set Input Entities: Domain 3
        iii. In the "Settings window" set Advanced: Clear the Compute integral in the revolved geometry check box.
    b. In the "Definitions" toolbar > Nonlocal Couplings > **Integration**
        i. Right click and rename the Integration to "intop2"
        ii. In the "Settings window" set Input Entities > Point: Point 4
        iii. In the "Settings window" set Source Selection > Advanced: Clear the Compute integral in revolved geometry check box
    c. In the "Definitions" toolbar > Local Variables > **Variables 1**
        i. In the "Settings window" set Variables section

Name	Expression	Unit	Description
n_abs	intop1(2*pi*r*c)		Number of moles delivered
z_pnt	intop2(z)	m	Position of top of droplet

    d. In the "Definitions" toolbar > More Functions > **Rectangle**
        i. In the "Settings window" set Parameters
            1. Lower limit = 6e-4
            2. Upper limit = 8e-4
        ii. Smoothing > Size of transition zone = 5e5
        iii. Plot
    e. In the "Definitions" toolbar > Moving Mesh > **Symmetry/Roller**
        i. Select Boundaries 1, 3, 5–7, and 10–14
        ii.
5. Define the Physics:
    a. Laminar Flow (SPF)
        i. Model Builder > Component 1 (comp1) > **Laminar Flow (SPF)**
        ii. Boundaries: 10–14
            1. In the "Settings window" for Wall, set the Boundary Condition section.
            2. Wall 2 > Wall condition list > **Navier slip**.
        iii. Add an **Inlet** Boundary (Inlet 1)
            1. Boundary: 9
            2. Select Boundary Condition: Fully developed flow
                a. Set Uav as u0*step1(t/1[

s]).

iv. Add an **Outlet** Boundary (Outlet 1)
1. Boundary: 2
2. Select Boundary Condition for the droplet surface and the contact point.

v. Add a **Fluid-Fluid Interface** (Fluid-Fluid Interface 1)
1. Boundaries: 15 and 16
2. Surface Tension coefficient list > User defined
3. Normal Direction > Reverse normal direction check box.

vi. Add a **Contact Angle** (Contact Angle 1)
1. Contact Angle > θw = 3*pi*(1-rect1(z/1[m]))/4+7*pi*rect1(z/1[m])/8
2. Normal Wall Velocity > Constrain wall-normal velocity check box.

b. Transport of Diluted Species (TDS)
i. Chemical Species Transport > **Transport of Diluted Species (TDS)**
1. Add to Component 1 in the window toolbar.
2. Domain Selection: Clear Selection. Then select Domain 3

ii. Component 1 (comp1)> Model Builder > Transport of Diluted Species (TDS) > Transport Properties 1
1. Convection > u list, > Velocity field (SPF).
2. Diffusion > Dc = 5E-9

iii. Physics > Boundaries > Flux
1. Rename as Flux 1
2. Boundary: 12
3. Inward Flux: Species c
4. In the J0,c = rect1(z/1[m])*0.001[mol/(m^2*s)]

6. Define the Materials:
a. Material 1 (mat1)
i. Model Builder > Component 1 (comp1) right-click on Materials > **Blank Material**
ii. Material Contents

Property	Variable	Value	Unit	Property group
Density	rho	1.25	kg/m³	Basic
Dynamic viscosity	mu	2e-5	Pa·s	Basic

iii. Domains: 1, 2, 4, and 5

b. Material 2 (mat2)
i. Model Builder > Component 1 (comp1) right-click on Materials > **Blank Material**
ii. Domain: 3
iii. Material Contents

Property	Variable	Value	Unit	Property group
Density	rho	1000	kg/m³	Basic
Dynamic viscosity	mu	1e-3	Pa·s	Basic

7. Add the Mesh:
a. Mesh 1
i. Mesh > Modify: Mesh > **Scale** (Scale 1)
1. Geometric Entity Selection: Boundary
2. Boundaries: 12, 15, and 16
3. Element: size scale = 0.5

ii. Right click on Mesh > Free Quad (Free Quad 1).
iii. Model Builder > **Size**
1. Element Size > Custom
2. Element Size Parameters > Maximum element size = 0.01
3. Minimum element size = 3E-5
4. Maximum element growth rate = 1.1
5. Curvature factor = 0.2

8. Study:
a. Study > **Parametric Sweep**
i. Study Settings > Add.

Parameter name	Parameter value	Parameter unit
u0 (Droplet velocity (m/s))	0.0002	m/s

b. Model Builder > right click study 1 > Study Steps > Step 1: **Time Dependent**
i. Study Settings > Output times = range(0,0.5,5).

c. Study > Show Default Solver > Model Builder > Solution 1 (sol1) > Right-click Time-Dependent Solver 1 > Stop Condition
i. Stop Expressions > Add

Stop expression	Stop if	Active	Description
comp1.z_pnt<0.0004	True (>=1)	√	Stop expression 1

ii. Model Builder > Time-Dependent Solver 1.
iii. Absolute Tolerance > Global method list > Unscaled.
iv. Time Stepping > Output: Clear the Store time derivatives

d. Model Builder > Study 1 > Compute

9. Results:
   a. Right click Results and add a new **2D Plot Group**
      i. Rename the plot as **Concentration (TDS)**
      ii. Data section > Parameter value (u0 (m/s)) list > 2.5E-4.
      iii. Time (s) list > 1.5
      iv. Concentration (TDS) > Plot
   b. Right click Results and add a new **1D Plot Group**
      i. Rename it as 1D Plot Group 2
      ii. Data section > Dataset list, > Study 1/Parametric Solutions 1 (sol2).
      iii. Parameter selection (u0) list > First.
   c. Right click 1D Plot Group 2 and choose Global
      i. Rename it as Global 1
      ii. y-Axis Data

Expression	Unit	Description
n_abs	mol	Number of moles delivered

iii. x-Axis Data > Axis source data list > Inner solutions
iv. Legends: Clear the Show legends