Pharmacokinetics

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Abstract

The process that a drug tablet goes through, once ingested into the human body, can be modeled by Fick’s first law, the Noyes-Whitney equation, and the Michaelis-Menten Kinetic equation. The route a solid drug tablet takes on its way through the body consists of five main processes: dissolution, absorption, distribution, metabolism, and elimination.
1 Introduction

Pharmacokinetics is the study of how drugs move through the human body. Pharmacokinetics consists of four main pathways: absorption, distribution, metabolism, and elimination. Depending on how a drug is administered is dependent on the pathway that the drug takes. If a drug is ingested orally through a tablet, liquid, suspension, or a capsule then more factors need to be considered like the disintegration of the drug and the rate of dissolution. If a drug is received through an IV infusion, or an IV bolus the process begins at the absorption pathway. In this essay the process a solid drug tablet takes through the human body will be looked at.

The following image shows a brief outline of the different pathways a drug tablet will take on it’s route through the human body.

2 Dissolution

Once a solid drug tablet is ingested, it travels through the GI track where it is disintegrated and then dissolved. The rate that it takes for a tablet to dissolve is called drug dissolution; this process can be modeled by the Noyes-Whitney Equation. As seen in the diagram below the drug tablet is first reduced to granules and then to small particles through disintegration. During all three of these phases dissolution occurs. The more the body breaks the tablet down the
better the rate of dissolution. As the body breaks down the drug tablet some
of the molecules gain positive or negative charges making them ions. These
ions are excreted through the body or taken to another location for further
use. These ions will not diffuse across the membrane and into the bloodstream.
Also, if there is any food or other drugs present in the stomach it can interfere
with the rate the tablet is disintegrated and the rate of dissolution. If the solid
drug tablet is the rate determining step relative to absorption, then complete
dissolution can be assumed.

2.1 Assumptions

- Dissolution only occurs in the last phase, small particles.
- Complete dissolution.
- None of the molecules have a positive or negative charge.
- No drugs are present in the body.
- No food is present in the stomach.
- Entire drug tablet dissolves.
2.2 Noyes-Whitney Equation Derivation

- $M =$ amount of drug dissolved (mg)
- $t =$ time (min)
- $D =$ diffusion coefficient of the drug (cm$^2$/min)
- $A =$ surface area of drug (cm$^2$)
- $h =$ thickness of the membrane (cm)
- $\frac{dM}{dt} =$ rate of dissolution (mg/min)
- $C_s =$ Saturation solubility of drug (mg/L)
- $C =$ concentration of drug in bulk solution (mg/L)
- $V =$ volume of drug in bulk solution (L)
- $V_s =$ volume of drug in the stomach (L)
- $R =$ constant (mg/L)
- $c =$ the concentration of drug (mol/cm$^3$)
- $J =$ diffusion flux (amount of substance that will flow through a small area during a small time interval) (mol/cm$^2$*min)
- $C_{total} =$ Total concentration of solution (mg/L)
- $M_{total} =$ Total amount of solution (mg)
- $V_{total} =$ Total volume of solution (L)

$$(1/A) \left( \frac{dM}{dt} \right) = J$$

$$J = -D \frac{\partial c}{\partial t}$$

Set these two equations equal to each other.

$$(1/A) \left( \frac{dM}{dt} \right) = -D \frac{\partial c}{\partial t}$$

The following equation can be substituted in for the partial derivative.

$$\frac{\partial c}{\partial t} = \frac{(C - C_s)}{h}$$

$$(1/A) \left( \frac{dM}{dt} \right) = \frac{D(C - C_s)}{h}$$

Multiply the equation by negative one.

$$(1/A) \left( \frac{dM}{dt} \right) = -\frac{D(C_s - C)}{h}$$

Next, both sides can be multiplied by $A$ to get the Noyes-Whitney Equation.

$$\left( \frac{dM}{dt} \right) = -\frac{(D \times A(C_s - C))}{(h)}$$

It can be assumed that

$$C_s - C < 0$$

because the amount of drug to be dissolved will be greater than the saturation solubility of the stomach. It is also known that

$$M = C + C_s$$
\[ \frac{dM}{dt} = \frac{dCs}{dt} + \frac{dC}{dt} \]

Initially it can assume that

\[ \frac{dC}{dt} = 0 \]

This can be assumed because the amount of drug in the stomach is so much less than the concentration of the drug in bulk solution so C won’t be effected by much. This allows \( \frac{dC}{dt} \) to drop out of the equation. The equation can then be rewritten as

\[ \frac{dM}{dt} = \frac{dCs}{dt} \]

dCs/dt can then be substituted in for dM/dt in the Noyes-Whitney Equation.

\[ (\frac{dCs}{dt}) = -(D * A/h)(Cs - C) \]

The variable Cs can then be brought to the other side.

\[ \frac{dCs}{dt} + (D * A/h)Cs = (D * A/h)C \]

Next, an integrating factor can be found

\[ e^{\int (D * A/h) \, dt} \]

\[ e^{(D * A/h) * t} \]

Now that an integrating factor has been found the integral can be set up.

\[ \int (e^{(D * A/h) t} * Cs)' = \int ((D * A/h) * C * e^{(D * A/h) t}) \]

\[ e^{(D * A/h) t} * Cs = C * e^{(D * A/h) t} + R \]

\[ Cs = (C * e^{(D * A/h) t} + R) * e^{-(D * A/h) t} \]

The initial condition

\[ Cs(0) = 0 \]

can be used to find the constant R. R is found to equal -C. This can be substituted in

\[ Cs = C - C * e^{-(D * A/h) t} \]

Finally, if the C is factored out the final differential equation is found.

\[ Cs = C(1 - e^{-(D * A/h) t}) \]

Since D,h,A,V, and C are constants the following values will be used to solve the above differential equation:

\[ A = 2500 \]
\[ D = 0.000000175 \]
\[ h = 0.0125 \]
\[ C = 0.00021 \]

From this graph it can be seen that the concentration of the drug in solution plateaus at $2.1 \times 10^{-4}$ which is equal to the given C value. This is the total amount that can be dissolved into the stomach because that is the total amount of drug available. This value of C acts as an asymptote. The graph will approach this value. This graph shows that there was complete dissolution.
2.3 Sink Conditions

When a system is said to be under sink conditions, this means that the concentration of the drug that is inside the stomach has already reached its saturation solubility. The stomach won’t dissolve anymore drug until what has been dissolved is sent out of the stomach into the small intestines to be absorbed into the bloodstream. Once this occurs the stomach will then continue to dissolve more drug until that saturation max is met. This process insures the complete dissolution of the drug.

The Noyes-Whitney Equation:

\[
\frac{dM}{dt} = -\frac{(D \ast A(Cs - C))/(h)}
\]

When the system is under sink conditions, it can be assumed that

\[
dCs/dt = 0
\]

It is still known that

\[
M = C + Cs
\]

so

\[
dM/dt = dCs/dt + dC/dt
\]

Initially it is being assumed that

\[
dCs/dt = 0
\]

This allows \(dCs/dt\) to drop out of the equation. The equation can then be rewritten as

\[
dM/dt = dC/dt
\]

\(dC/dt\) can then be substituted in for \(dM/dt\) in the Noyes-Whitney Equation.

\[
(dC/dt) = -(D \ast A/h)(Cs - C)
\]

The variable \(C\) can then be brought to the other side.

\[
dCs/dt - (D \ast A/h)C = -(D \ast A/h)Cs
\]

Next, an integrating factor can be found

\[
e^\int -(D \ast A/h)dt
\]

\[
e^{- (D \ast A/h) t}
\]

Now that an integrating factor has been found the integral can be set up.

\[
\int (e^{-(D \ast A/h) t} \ast C)' = \int -(D \ast A/h) \ast Cs \ast e^{- (D \ast A/h) t}
\]
\[ e^{-\left(\frac{D \cdot A}{h}\right)t} \cdot C = C_s \cdot e^{-\left(\frac{D \cdot A}{h}\right)t} + R \]
\[ C = (C_s \cdot e^{-\left(\frac{D \cdot A}{h}\right)t} + R) \cdot e^{\left(\frac{D \cdot A}{h}\right)t} \]
\[ C = C_s + R \cdot e^{\left(\frac{D \cdot A}{h}\right)t} \]

The initial condition
\[ C(0) = 0 \]
can be used to find the constant \( R \). \( R \) is found to equal \(-C_s\). This can be substituted in
\[ C = C_s - C_s \cdot e^{\left(\frac{D \cdot A}{h}\right)t} \]
Finally, if the \( C_s \) is factored out the final differential equation is found.
\[ C = C_s(1 - e^{\left(\frac{D \cdot A}{h}\right)t}) \]

Since \( D, h, A, \) and \( V_s \) are constants the following values will be use to solve the above differential equation:
\[ A = 2500 \]
\[ D = 0.000000175 \]
\[ h = 0.0125 \]
\[ C = 0.00021 \]

By looking at the above graph, it can be seen that the concentration of the drug tablet is decreasing with time. This is because it is dissolving into the stomach. In actuality, the stomach will not dissolve the full drug tablet. The stomach has a saturation solubility and will only hold a certain concentration of a drug. This means that only a portion of the drug can dissolve in a given amount of time. Once that amount has been reached is when the sink conditions occur and the stomach will get rid of it’s concentration into the bloodstream, before dissolving more. The stomach will approach it’s asymptote of \( C_s \), which is not shown in the above graph.

### 2.4 GI Track

After the drug is dissolved in the stomach it then proceeds to the small intestines to be absorbed into the bloodstream.

In order for the dissolved drug to be processed through the body, it will first undergo absorption, distribution, metabolism, and finally elimination.
3 Absorption

When a drug is being absorbed into the bloodstream there are three types of ways it can be transported across a membrane. First is active transport; this requires an input of energy, ATP, by the cell. It allows the drug to go from a low concentration to a high concentration. Second is simple diffusion; this will only allow small, uncharged molecules across. Last is facilitated diffusion; this requires a carrier protein, and will only allow large, uncharged molecules or small, charged molecules across. Both simple and facilitated diffusion transport the drug from an area of high to low concentration in which no energy is required. These are both given the name passive diffusion.

This process can be modeled by Fick’s First Law.
3.1 Assumptions

○ No charged particles.
○ All of the drug tablet is absorbed into bloodstream.
○ The drug is transported by passive diffusion.
○ The drug travels from high to low concentration.
○ Assume steady state diffusion.
○ Constant thickness of membrane.
○ No previous drugs are present in the bloodstream.

3.2 Fick’s Equation Derivation

● D= the diffusion coefficient (cm$^2$/min)
● c= the concentration of drug (mol/cm$^3$)
● x= thickness of the membrane (cm)
● J= diffusion flux (amount of substance that will flow through a small area during a small time interval) (mol/cm$^2$*min)
● M=amount of drug in the body (mg)
● t=time(min)
● A=surface area of membrane(cm$^2$)
● dM/dt=rate of diffusion (mg/min)
● Ch=concentration of drug in small intestines (mg/L)
● Cl=concentration of drug in blood (mg/L)
● Vl=volume of drug in blood (L)
● Vh=volume of drug in small intestines (L)
● R=constant(mg/L)

In the diagram below it can be seen that the concentration of the drug in the small intestines will diffuse across the membrane and into the blood where there is a concentration of the drug in the blood.

\[
\frac{1}{A}(dM/dt) = J
\]
\[ J = -D \partial c/\partial t \]

Set these two equations equal to each other.

\[ (1/A)(dM/dt) = -D \partial c/\partial t \]
\[ \partial c/\partial t = (Ch - Cl)/x \]

This can be substituted in for the partial derivative.

\[ (1/A)(dM/dt) = -D(Ch - Cl)/x \]

Next, the negative sign can be distributed through the equation.

\[ (1/A)(dM/dt) = -D(Ch - Cl)/x \]

Next both sides can be multiplied by A to get the Fick’s Equation.

\[ (dM/dt) = (-D * A(Ch - Cl))/(x) \]

Since the derivation of this equation is the same as the Noyes-Whitney equation, except with different variables, the final integrated equation can be skipped to.

\[ Cl = Ch(1 - e^{(D*A/x*Vl)*t}) \]

In this graph it can be seen that the maximum amount of drug dissolved into the stomach is the maximum amount of drug that can be absorbed into the bloodstream.

So far, in this process, a solid drug tablet has been orally ingested and dissolved in the G-I Track through dissolution until it became a solution. The drug has just finished diffusing across the membrane and into the bloodstream. Now that it is in the bloodstream it will be transported through the body by distribution.

\[ \text{Dissolution} \quad \rightarrow \quad \text{Absorption} \]

\[ SOLID \rightarrow \rightarrow \rightarrow \quad SOLUTION \rightarrow \rightarrow \rightarrow \quad BLOOD \]

\[ \text{G-I Tract} \quad \rightarrow \quad \text{Membrane} \]
Cl = Ch(1 - e^{(D'A/x*Vl)*t})

Concentration of Drug in Blood, Cl (mg/L)

0  50  100  150
0
1
2
x 10^{-4}

time (min)
4 Distribution

The main system of transporting nutrients to the human body’s tissues and organs is through the bloodstream. When the nutrients arrive at a cell that is deficient, it will create a concentration gradient between the cell and the blood vessel. The nutrients then will want to diffuse from the high concentrated blood to the low concentrated cell; delivering the proper nutrients to the body’s cells.

When a drug is introduced into the body’s bloodstream, the rate of distribution is dependent upon a number of factors. First, the tissues with the highest blood flow receive the drug first. Second, if the drug is attached to a plasma protein it can only go where the proteins go. Third, the drug can enter tissues that are highly lipid soluble. Lastly, distribution is dependant on the degree of the drugs ionization; unionized drugs can go anywhere they want. These four factors also determine where the drug will end up in the body.

This process requires both the use of Fick’s law and a new equation. Since Fick’s equation has already been modeled, it will be excluded from the calculations. In the process of distribution, Fick’s law comes into play when the drug has to diffuse from the blood into a deficient organ or cell.

Below is a diagram that shows the multiple paths a drug can take once in the bloodstream.

![Diagram](image)

4.1 Assumptions

- Assume a steady heart beat.
- The drug is distributed evenly throughout the body.
No charged particles.
No previous drugs present in the body.
No ionized particles.

4.2 Differential Equation

- Cp=drug concentration in blood plasma (µg)
- X=dose of drug in body (mg)
- Vd=volume of distribution of drug (L)
- R=constant (mg/L)

\[ Vd \times \frac{dCp}{dt} = \frac{dX}{dt} \]
\[ \int Vd \times \frac{dCp}{dt} = \int \frac{dX}{dt} \]
\[ Vd = \frac{X}{Cp} \]
\[ Vd = 36.3L \]

By the graph above it can be seen that the amount of drug in the bloodstream being distributed will decrease with time. Depending on what value is chosen...
for Vd, the volume of drug in the blood, depends on how long it will take for it to be eliminated from the body.

5 Metabolism

The goal of metabolism is to make the drug easier to excrete from the body. In the liver, the main site for metabolism, drugs are metabolized through oxidation, reduction, hydrolysis, conjugation, condensation, or isomerization. Most drugs metabolize in two phases. The first phase involves cleaving functional groups through oxidation, reduction, or hydrolysis. Phase two involves conjugation with an endogenous substance. In phase two of the metabolism, polar metabolites are formed and are quickly excreted by the kidneys in the form of urine. Those metabolites that are formed in phase one of the metabolism are not as readily excreted.

5.1 Assumptions

- No other drugs are present in the liver.
- All drug is metabolized.

5.2 Michaelis-Menten Kinetics

- \( dC_p/dt \) = the rate of metabolism
- \( V_m \) = some maximum rate (mg/hr)
- \( C_p \) = the concentration of the drug in the blood (mg/L)
- \( K_m \) = Michaelis-Menton constant, the concentration at which the rate of metabolism is half the maximum \( V_m \) (mg/L)
- \( t \) = time (hr)
- \( R \) = constant (mg/L)

The following differential equation models the rate it takes for a drug to be metabolized in the body.

\[
dC_p/dt = -(V_m * C_p)/(K_m + C_p)
\]

This equation is separable so all the \( C_p \)'s are taken to one side.

\[
[(K_m + C_p)/C_p]dC_p/dt = -V_m
\]

This equation can then be integrated.

\[
\int [(K_m + C_p)/C_p]dC_p = \int -V_m * dt
\]
The integral can be simplified.

\[ \int [1 + (Km/Cp)]dCp = \int -Vm \cdot dt \]

By integrating the following equation results:

\[ Cp + Km \cdot \ln(Cp) = -Vm \cdot t + R \]

Where R is a constant. By using the following initial conditions R can be solved for. Let \( Cp=5 \) mg/L \( Km=4 \) mg/L \( Vm= 20.83 \) mg/hr at \( t=0 \) hr

\[ 5mg/L + 4mg/L \cdot \ln(5mg/L) = -20.83mg/hr \cdot 0hr + R \]

\[ 31.27mg/L = R \]

The differential equation can then be rewritten as:

\[ Cp + Km \cdot \ln(Cp) = -Vm \cdot t + 31.27mg/L \]

The equation can then be solved for t.

\[ t = (Cp + Km \cdot \ln(Cp) - 31.27)/ -Vm \]

Below is a graph of the differential equation.

The above graph shows that by the end of two hours all the drug has been metabolized and there is zero concentration of the drug in the bloodstream.

### 6 Elimination

Once a drug has been used to its full potential it is excreted from the body. The task of drug elimination follows five processes: conjugation, hydrolysis, oxidation, reduction, and finally excretion. Drugs can be excreted through salivary glands, lungs in a gas form, tears and sweat, milk, urine, and fecal matter.

### 7 Overall Process

Now that the process it takes for a solid drug tablet to go through the body has been modeled, aspirin will be used as an example.

This data was collected by the National Science Foundation. Starting with one gram of aspirin, it is absorbed into the bloodstream and then eliminated through the kidneys.
\[ t = \frac{(C_p + K_m \log(C_p) - 31.27)}{-V_m}, \quad V_m = 500, K_m = 4 \]
By the graph and data table it can be seen that in the first 15 minutes aspirin is being absorbed into the bloodstream. At the 15 minute mark, the graph reaches its maximum. This means that the amount of aspirin being absorbed and the amount that is being excreted are equal. From this point on, the amount of aspirin being excreted is greater than the amount being absorbed. As the amount of aspirin in the body decreases it is being distributed to different tissues and organs throughout the body. Once the tissues and organs are done using the aspirin they then send it back into the bloodstream where it is taken to the liver to be metabolized. After being metabolized it is sent to the kidneys to be eliminated through the body. This process takes place after the first 15 minutes until the three hour mark when no more aspirin should remain in the body.

Time (min): 0 15 30 45 60 75 90 105 120 150
Aspirin (g): 0 0.082 0.071 0.053 0.037 0.025 0.017 0.011 0.007 0.003

This data can be represented by:

\[ f(t) = 0.1 \sqrt{t} \times e^{(1-2t)} \]

By comparing the graph below to the one just discussed it can be seen how the graph should proceed for aspirin. By three hours almost all the aspirin should be eliminated from the body.
8 Conclusion

The figure below shows the overall process of a drug through the human body that we just described through mathematical equations. First, the drug tablet is ingested orally. Second, the drug travels through the body to the stomach where the Noyes-Whitney equation modeled how the drug is dissolved through disintegration and dissolution. Third, the dissolved drug travels through the GI track and enters the small intestines where it is absorbed through the membrane and into the bloodstream. This process was modeled by Fick’s First Law. Fourth, the drug is distributed through the body to various organs and tissues for desired functions. Fifth, the bloodstream takes the drug to the liver where it is metabolized. Here the drug is prepared for excretion. Lastly, the drug is excreted through the body by the kidneys in the form of urine.

9 Bibliography
