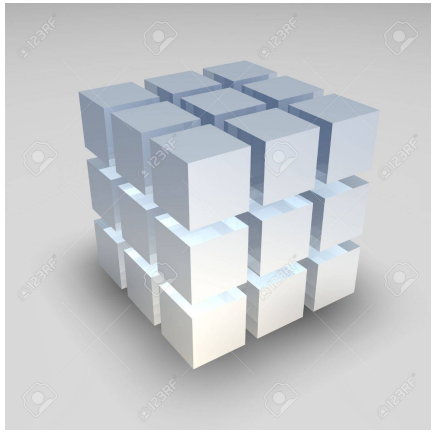
Week 9 problem solving

+ equations, + applications

Kinetics, diffusion, dissolution

Dissolution rate of drug crystals

- The Rate is proportional to the **total surface area** of drug *micro-crystals*
- *Individual area per mass depends on Crystal* ***habit*** (shape)
- **Cubes** have the **smallest surface area** per given volume
  - lowest dissolution rate
- Breaking the same amount of substance into **smaller particles** increases the total surface area,
- For cubes: ***Total_Area = Total_Volume/OneCubeEdgeLength***
  - Increased dissolution rate for smaller ones
  - For arbitrary shape micro-crystals:
    - Calculate surface ***a***rea and volume of each microcrystal (***v***)
    - Divide the fixed total Volume by the single-crystal volume
      - $N = V_{tot} / v$
    - Multiply the ***Total_Area = a*N***
    - Dissolution rate is proportional to the total surface area



Dissolution rate of crystals

- **Q:** Three formulations are used to deliver **equal amounts** of the same drug.
  - ❖ Formulation **X** consists of cubic microcrystals of size 1μm×1μm×1μm
  - ❖ Formulation **Y** features cubic microcrystals of size 0.1μm×0.1μm×0.1μm
  - ❖ Formulation **Z** contains needle-like, elongated microcrystals of size 100μm×0.1μm×0.1μm
- Rank the formulations in the order of increasing dissolution rate:
  - A. X < Y < Z
  - B. X < Z < Y
  - C. Y < X < Z
  - D. Y < Z < X
  - E. Z < Y < X
  - F. Z < X < Y
- **Solution:**

	X	Y	Z
Xtal dimensions	1μm × 1μm×1μm	0.1μm × 0.1μm × 0.1μm	100μm × 0.1μm × 0.1μm
Volume per xtal	V	$0.001 \times V$	V
SA per xtal	$A = 6\mu m^2$	$0.01 \times A$	$\approx 40\mu m^2 \approx 6.66 \times A$
# of xtals	N	$1000 \times N$	N
Total SA	$A \times N$	$10 \times A \times N$	$\approx 6.66A \times N$

- **Answer:** X < Z < Y

Drug absorption in the GI tract

- Let us make the following assumptions:
  The surface area of the stomach is ~0.1 m^2 and that of the intestine is ~100 m^2.
  The pH in the stomach and the intestine is 2 and 7, respectively (simplification)
- **Q:** An acidic drug with the pK_A of **4** is taken orally, dissolves in the stomach and spends ~ 1hr in the stomach and ~4 hrs in the intestine as it moves through the GI tract. What percentage of the drug is absorbed in the stomach? What percentage is absorbed in the gut?
- ***Hint:*** *only neutral drug species are absorbed efficiently*
  A. 100% in the stomach, negligible in the gut
  B. 80% in the stomach, 20% in the gut
  C. 50/50
  D. 80% in the gut, 20% in the stomach
  E. 100% in the gut, negligible in the stomach
- **Solution:**

	10^{pKa-pH}	Fraction neutral	Time	Area	Total absorbed assuming flux J
Stomach	$10^{4-2} = 100$	~1	1 hr	0.1 m^2	$J \times 1 \times 1 \times 0.1 = 0.1\ J$
Intestine	$10^{4-7}=0.001$	~0.001	4 hrs	100 m^2	$J \times 0.001 \times 4 \times 100 = 0.4\ J$

- **Answer:** 80% in the gut, 20% in the stomach

Rates of reactions, K

	0th order	1st order	2nd order
Rate law (*how fast?*)	Fixed time	Exponential decline	
Integrated rate law (*extent of the reaction after the given time elapsed*)	$[A] = [A]_0 - k_0 t$	$[A] = [A]_0 e^{-kt}$	
Units of ***k***	M s^{-1}	s^{-1}	$M^{-1}s^{-1}$
Half-life $t_{½}$	$t_{1/2} = A_0 / 2k_0$	$t_{1/2} = \ln(2)/k$	
Examples	Degradation, dissolution at infinite dilution	Elimination, isomer conversion, radioactive decay	1:1 protein-ligand binding

Reaction rate: 1st order

- **Q:** Thalidomide undergoes spontaneous conversion from (+) form to (-) form and vice-versa. For example, the half-life of initially pure (+)Thalidomide in human plasma is 11.5 minutes. Estimate the **rate constant** for the reaction of conversion of (+)Thalidomide into (-)Thalidomide in human plasma.
- **Hints:**
  - Enantiomer conversion is 1st order; hence constant $t_{1/2}$
  - Asks for rate constant (***k***), not rate ($d[A]/dt = -k[A]$)

A. $11.5\ \text{min}^{-1}$
B. $8.33\ \text{min}^{-1}$
C. $0.001\ \text{s}^{-1}$
D. $\ln 2\ \text{s}^{-1}$

- **Solution:**
  - $t_{1/2} = 11.5\ \text{min} = 690\ \text{s}$
  - The rate constant is $k = \ln 2 / t_{1/2} = \ln 2 / 690 \sim 0.001\ \text{s}^{-1}$

- **A:** $0.001\ \text{s}^{-1}$

Reaction rate etc.: 1st order

- **Q:** Iodine-131 decays with the half life of 8 days. At the time of calibration, the activity in the vial is 100 mCi. What will be the remaining activity after 32 days?

A. 96 mCi
B. 31.25 mCi
C. 25 mCi
D. 6.25 mCi

Ci is a **Curie** unit of radiation
It is 3.7 x 10^{10} Bq (disintegrations or nuclear transformations per second).
A Ci is emitted by 1 g of radium-226.

- **Solution 1:**
  - The rate constant is $k = \ln 2 / t_{1/2} = \ln 2 / 8$ days = 0.0866 d^{-1}
  - $[A] = [A]_0 e^{-kt} = 100 \text{ mCi} \times e^{-2.7726} = 100 \text{ mCi} \times 0.0625 = 6.25 \text{ mCi}$
- **Solution 2:**
  - After 8 days, the remaining activity will be 50 mCi
  - After 16 days, 25 mCi
  - After 24 days, 12.5 mCi
  - After 32 days, 6.25 mCi
- **A:** 6.25 mCi

Rates vs equilibrium in reversible reactions

- In a reversible reaction, two rates:
  One for **forward** reaction: $\boldsymbol{k_f}$
  Another for **reverse** reaction: $\boldsymbol{k_r}$
  Two half-live times depending where one starts
- At equilibrium, [A]$\boldsymbol{k_f}$ = [B]$\boldsymbol{k_r}$

$$K_{eq} = \frac{k_f}{k_r}$$

- A bimolecular reaction of drug-target binding:
  k_f = $\boldsymbol{k_{on}}$ (kinetic association constant, not to be confused with equilibrium association constant)
  k_r = $\boldsymbol{k_{off}}$ (kinetic dissociation constant, not to be confused with equilibrium dissociation constant)
  Equilibrium dissociation constant $K_d = \frac{k_{off}}{k_{on}}$
  Important parameter: drug ***residence time***

$$\tau = \frac{1}{k_{off}}$$

Equilibrium vs rates in a reversible 1st order reaction

- **Q:** The reversible reaction of drug A binding to its target is characterized by k_{on}=8×10^6 M^{-1} min^{-1} and the equilibrium dissociation constant K_d=0.5 nM. Find k_{off} and the drug residence time τ at the target.
  - *A.* k_{off} = 0.004 min^{-1}, τ = 4hr 10 min
  - *B.* k_{off} = 0.12 min^{-1}, τ = 500 sec
  - *C.* k_{off} = 1.6×10^{16} min^{-1}, τ = 6.25×10^{-15} min
  - D. Impossible to tell
- **Solution:** use $K_d = \frac{k_{off}}{k_{on}}$ and $\tau = \frac{1}{k_{off}}$

  $k_{off} = K_d \times k_{on}$ = (0.5×10^{-9} M) × (8×10^6 M^{-1} min^{-1}) = 4×10^{-3} min^{-1} = 0.004 min^{-1}

  τ = 1/k_{off} = 1/0.004 = 250 min
- **Answer:**

  k_{off} = 0.004 min^{-1}, τ = 4hr 10 min

  This is a **long-residence-time** drug

  Often a desirable feature in pharmacology: the target is inhibited for many hours after the dose, regardless of plasma concentration decrease