Welcome to Module 9!

- **Today's Pre-Module Playlist**
  - science fiction – Smallpools
  - Electric Feel – MGMT
  - Love Is Alive – Louis the Child

- **BMES General Board Applications**
  - Applications are out now!
  - Highly encourage you all to apply!
  - Recording of Board Panel Q&A
- **Upcoming BMES Events**
  - Azzur Infosession Wednesday Week 2
    - April 7th at 6 PM PST
    - Biotech Consulting
  - Codexis Infosession Wednesday Week 3
    - April 14th at 6 PM PST
    - Sustainable Manufacturing & Biotherapeutics

Announcements

BMES Cell Team

Spring 2021

Spring Quarter Cell Team

	Mon	Tues	Wed	Thurs	Fri
Week 1 (3/29-4/2)					
Week 2 (4/5-4/9)		Module 9: Drug Delivery Methods	**Labster Modules 5-6 (Homogenization and Cell Culture Basics) Assigned**	Independent Projects (Finalize Independent Project Groups)	
Week 3 (4/12-4/16)		Module 10: Wet Lab Applications to Medical Devices	**Labster Modules 7-8 (RNA Extraction and CRISPR) Assigned**	Independent Projects (Finalize Independent Project Topics)	

- **This quarter's focus: independent projects**
  - You will be presenting projects **Week 9** during Demo Day
  - We will let you know as soon as the date is finalized
- **2 final modules and 3 journal clubs**
  - We will organize a meeting time with those 3 groups over Slack
- https://docs.google.com/spreadsheets/d/1pcUlX9FAxrTHfGLIfCZx_0xVOVx6tgag2dbCGjc-g9Y/edit?usp=sharing

BMES Hackathon!

- **UCLA's first biomedical hackathon**
  - April 16-17 (end of Week 3)
  - Teams of 3-6 (don't have to have a full team to sign up!)
    - **Open to ANY college student**
  - 3 project prompts
    - COVID-19 (measuring lung capacity)
    - Medical (stroke after effects)
    - Non-Medical (machine learning)

- http://bmes.seas.ucla.edu/biohack.html

Module 9: Drug Delivery Systems

BMES Cell Team

Spring 2021

Outline

- Drug Processing Crash Course
    - ADME
    - Bioavailability
    - Toxicity
- Drug Delivery Systems
    - Oral
    - Respiratory
    - Intravenous
    - Intramuscular
    - Transdermal

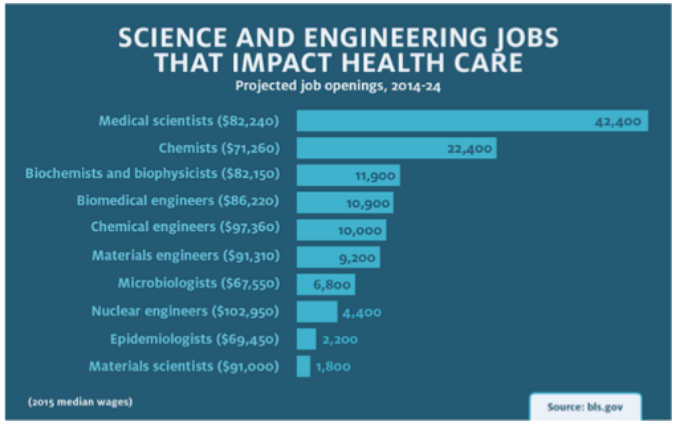
https://www.oecd.org/health/health-systems/pharmaceuticals.htm

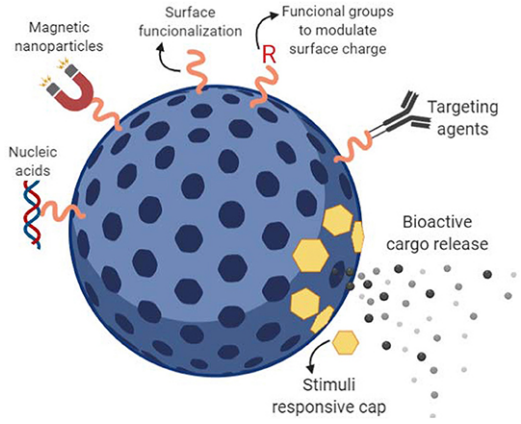
Why is drug delivery important?

- **Understanding drug processing is important for the pharma industry**
  - **1 in 7 biomedical engineers work for a pharmaceutical company**
  - The problems you will be solving will involve modifying drug delivery

- **Drug Delivery is a key factor in treatment efficacy**
  - **Ineffective drug delivery is a key barrier to marketability**
  - Product success depends on good drug absorption and excretion

- **Drug Delivery Systems are not a huge part of the BE core curriculum**
  - **Topic I have found to be important in my professional experience**
  - Area where I think there needs to be more engineering innovation





https://www.frontiersin.org/articles/10.3389/fbioe.2020.00079/full https://work.chron.com/places-employ-biomedical-engineers-26781.html

Real Life Example: Why is drug delivery important?

Karuna Therapeutics – KARXT

Xanomeline
MUSCARINIC AGONIST

Human PoC in double-blind, placebo-controlled trials in schizophrenia and Alzheimer's

Trials enrolled over 800 patients including 68 patients for ≥ 1 year

Exclusively licensed from Eli Lilly

Trospium Chloride
MUSCARINIC ANTAGONIST

Does not meaningfully cross the blood brain barrier, limiting effects to the peripheral tissues.

No known metabolic overlap with xanomeline

Generic drug for overactive bladder used since the 1960's

effective
but
nasty side effects

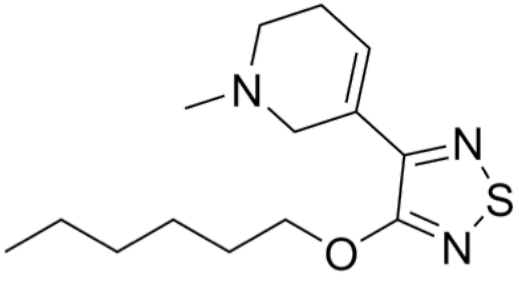
can block
nasty side effects

https://karunatx.com/programs/#karxt

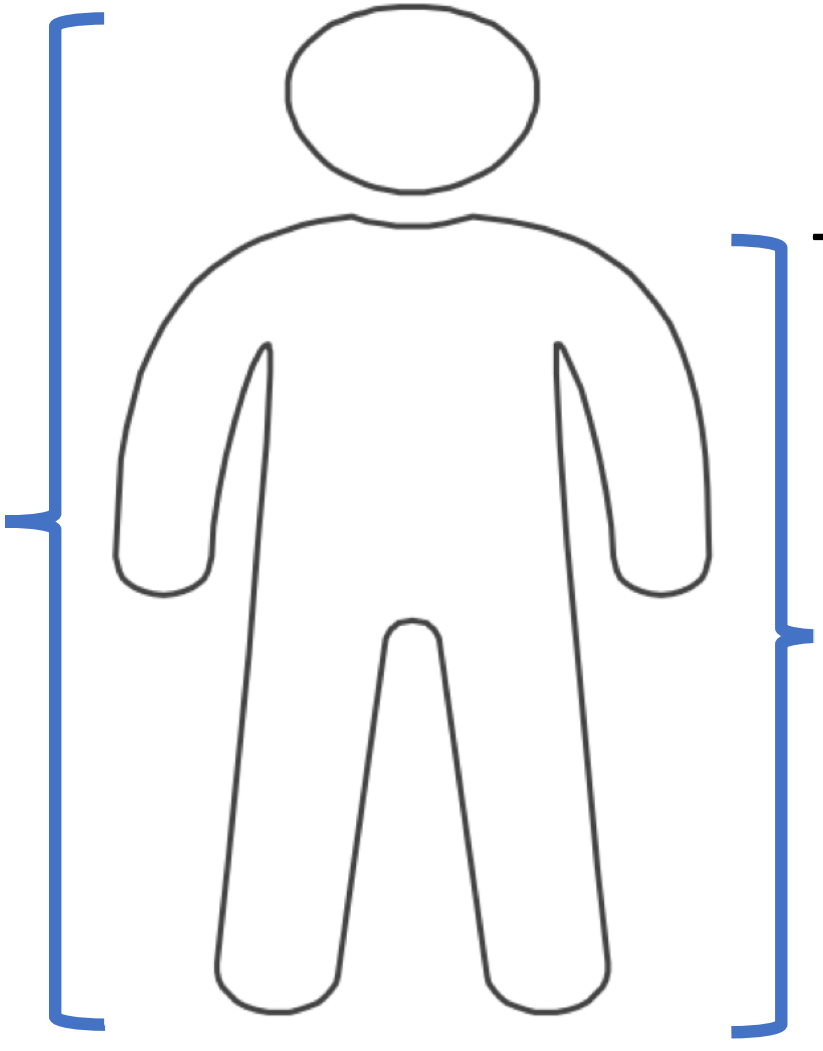
Real Life Example: Why is drug delivery important?

Karuna Therapeutics – KARXT

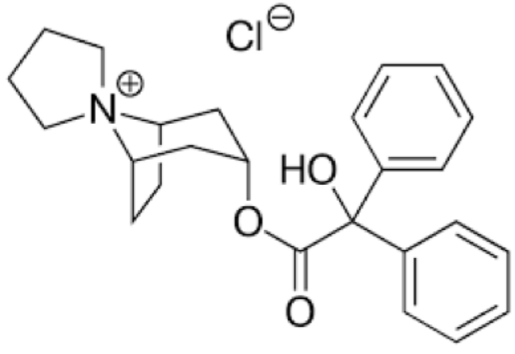
Xanomeline (X)



- Small
- Lipophilic
- Can cross BBB



Trospium Chloride (T)



- Large
- Ionic
- Can’t cross BBB

X can yield therapeutic effects in brain and T blocks side effects everywhere else!

https://karunatx.com/programs/#karxt

Real Life Example: Why is drug delivery important?

Karuna Therapeutics – KARXT

Drug Delivery Challenges

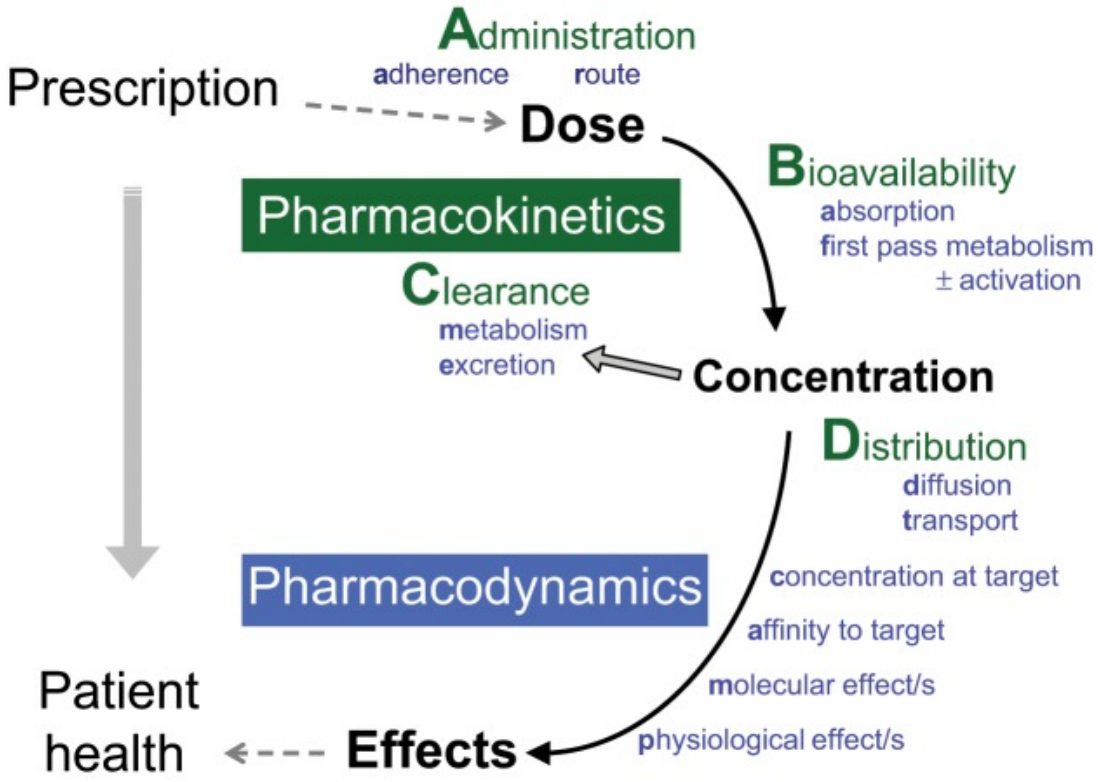
- **Two drugs have different pharmacokinetic profiles**
    - Different absorption timelines
        - T absorbed later than X
    - Differences in level of absorption
        - More X absorbed than T
- **Can cause side effects that lead to non-compliance**
    - Big problem with many current pharmaceutical regimens for patients with psychosis
- **Must find a drug delivery method that best aligns metabolic processing of X and T in order to reduce side effects of X**

https://karunatx.com/programs/#karxt

Drug Processing Crash Course

- Drug formulation focuses on understanding the product's pharmacokinetics

- **Definition:** Pharmacodynamics (PD) is what the drug does to the body. Pharmacokinetics (PK) is what the body does to the drug.



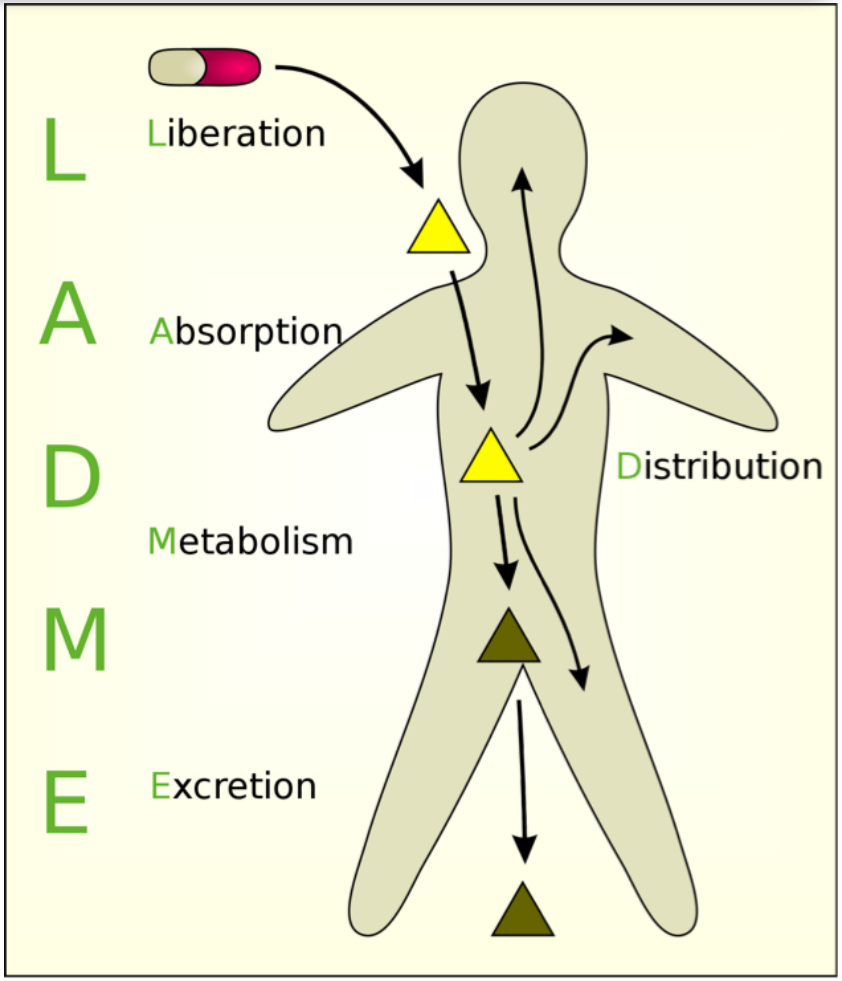
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4110820/

ADME

- **Definition:** Pharmacokinetics revolves around drug absorption, distribution, metabolism, and excretion (ADME)

- **Absorption**
  - Uptake of drug
- **Distribution**
  - Transfer of drug in the body
- **Metabolism**
  - Breakdown of drug
  - Deactivation
- **Excretion**
  - Removal of drug/metabolites

- Sometimes Liberation and Toxicity are added to this acronym

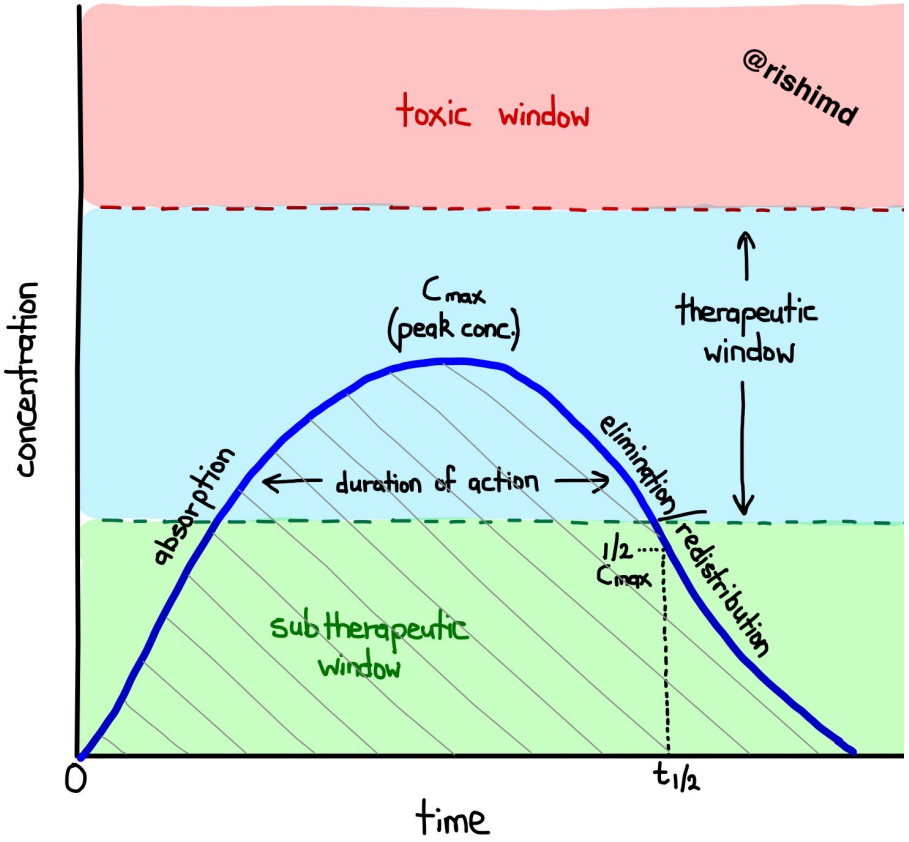


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4110820/

Pharmacokinetic Models

- **Definition:** Pharmacokinetic models depict drug concentration in the body over time and can be used to obtain drug ADME.

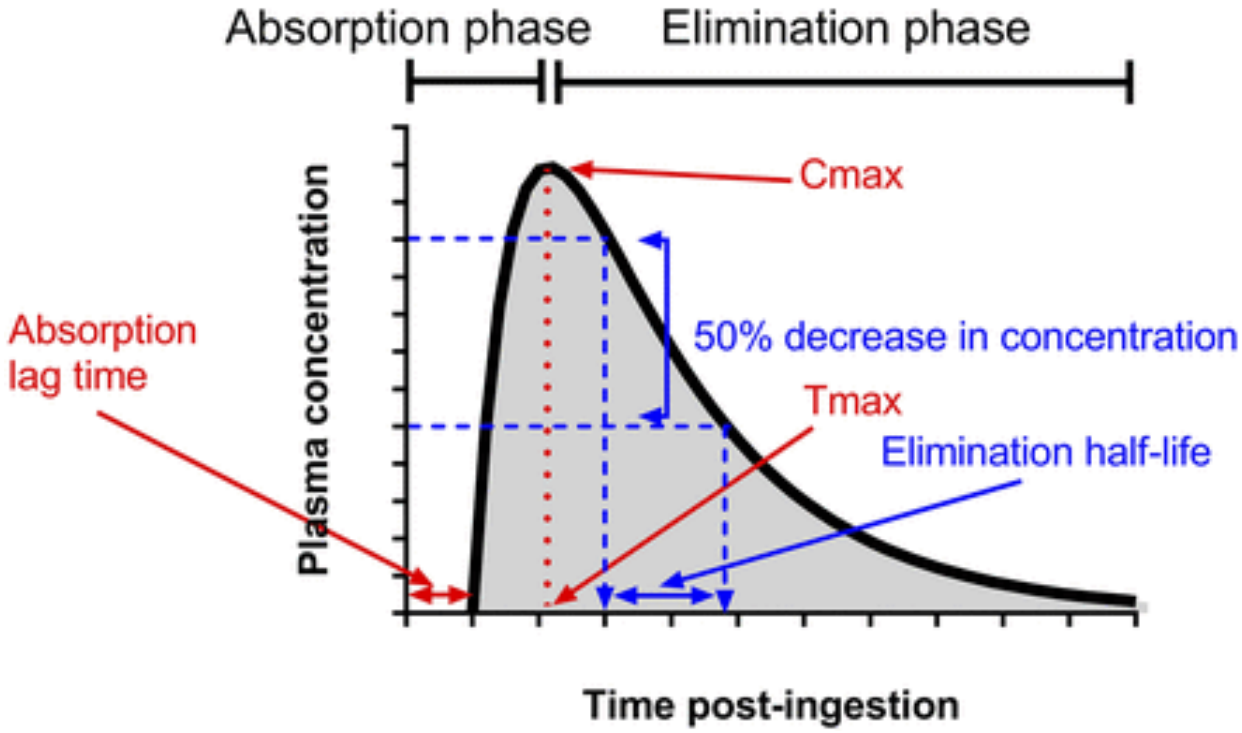
- **Cmax** is the maximum concentration of drug in the blood
- Want Cmax to be within the **therapeutic window**
  - High enough to be effective
  - Low enough to be non-toxic
- The **duration of action** is the length of time the drug is effective



Ideal PK Model

https://rk.md/2020/pharmacokinetics/

Pharmacokinetic Models



- **tmax** is the time it takes to reach Cmax
    - Marks the end of the absorption phase
- Typically, the **absorption phase** is much shorter than the **elimination phase**
- **Lag time** between drug dosing and an increase in drug plasma concentration
    - Drug must be absorbed into the bloodstream
    - Lag time varies with drug delivery method

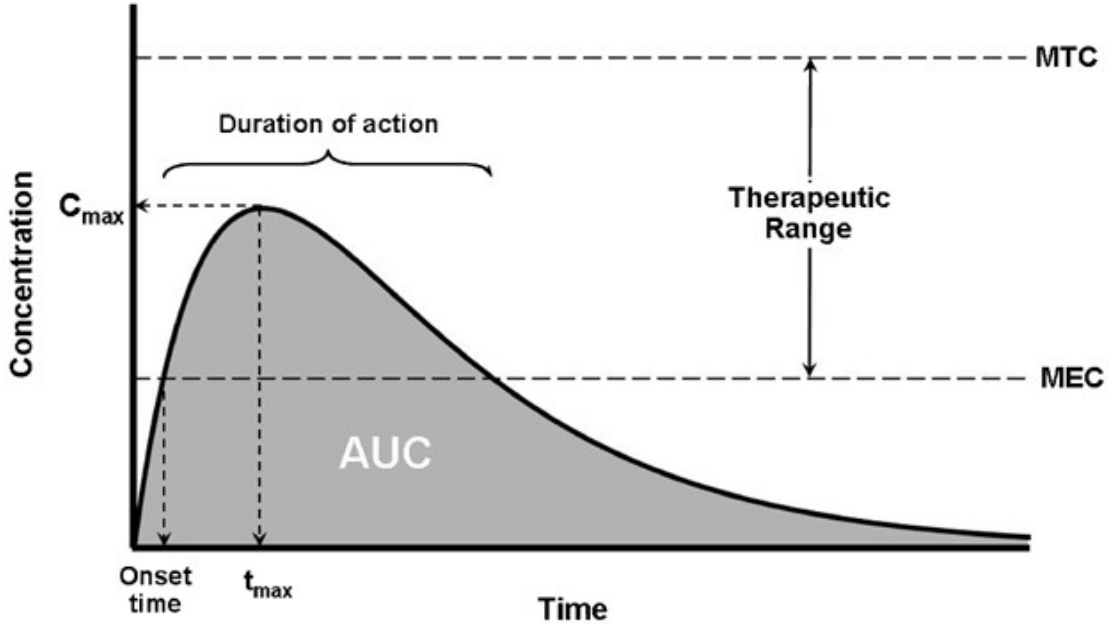
https://cjasn.asnjournals.org/content/13/7/1085

Bioavailability

- **Definition:** Bioavailability is the proportion of delivered drug that is able to circulate in the bloodstream and yield a therapeutic effect.

- Bioavailable drug = drug in dose – drug metabolized by body

- Calculated using the area under the curve (**AUC**)

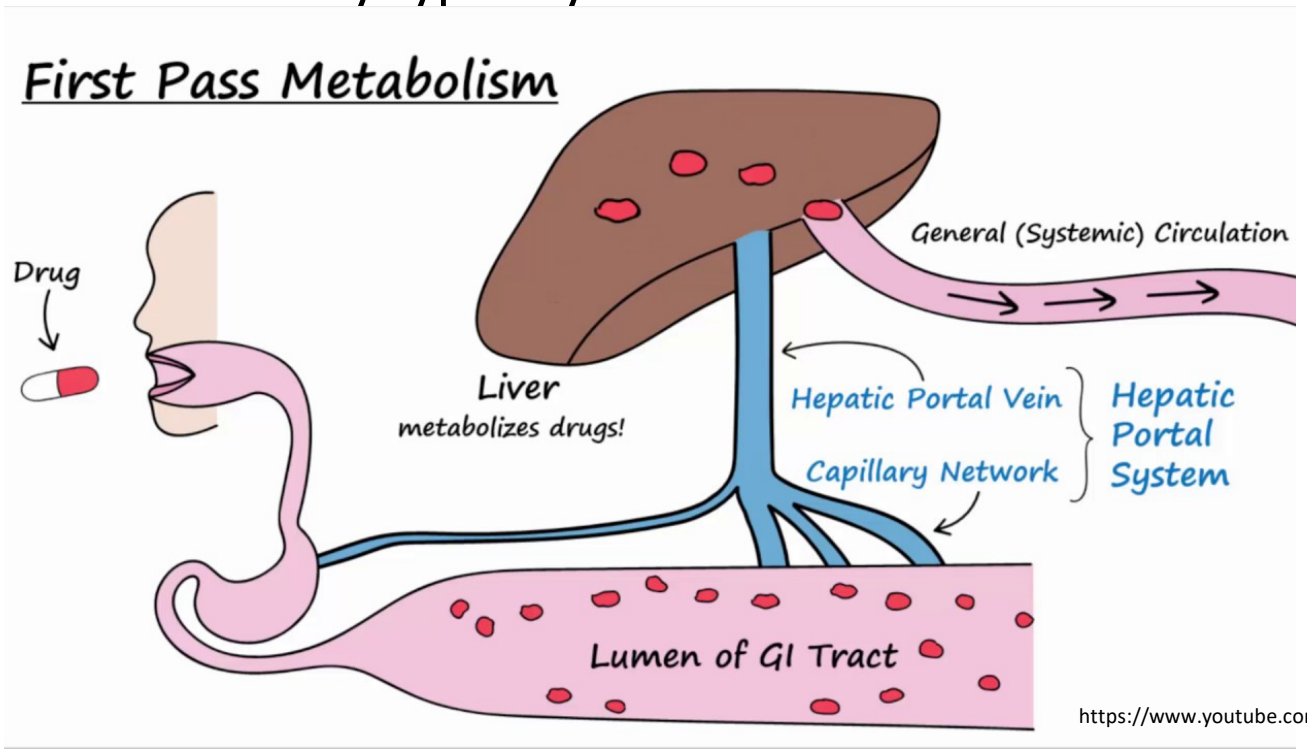


http://gim.unmc.edu/dxtests/roc3.htm

Bioavailability

- **Bioavailability is calculated based on how much of the drug makes it into the bloodstream**
    - Different drug delivery methods result in different metabolism pathways before reaching the blood → different bioavailability

- Example: Intravenous vs. Oral
    - Intravenous Bioavailability = 100%
    - Oral Bioavailability typically < 1%

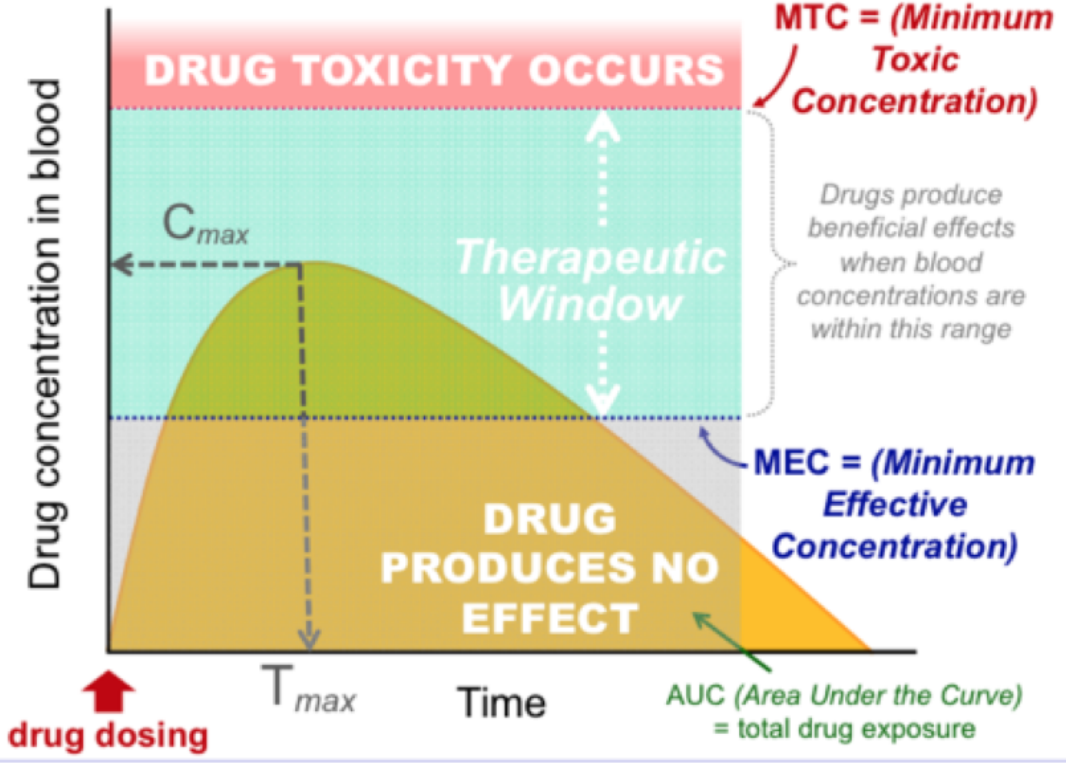


https://www.youtube.com/watch?v=BQQns7RAUzA

Toxicity

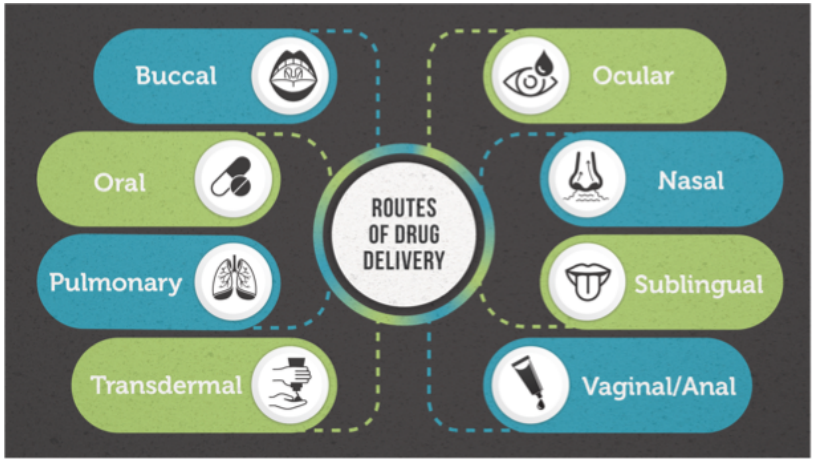
- **Definition:** Drug Toxicity is the damage that the drug can cause to the organism

- **At high enough doses, all drugs are toxic**
- It is imperative to keep drug dose low enough so that the patient does not experience toxic side effects
- Drug toxicity occurs above the **minimum toxic concentration (MTC)**
- Cmax must be below MTC
- Effective **clearance** of drug reduces the likelihood of side effects

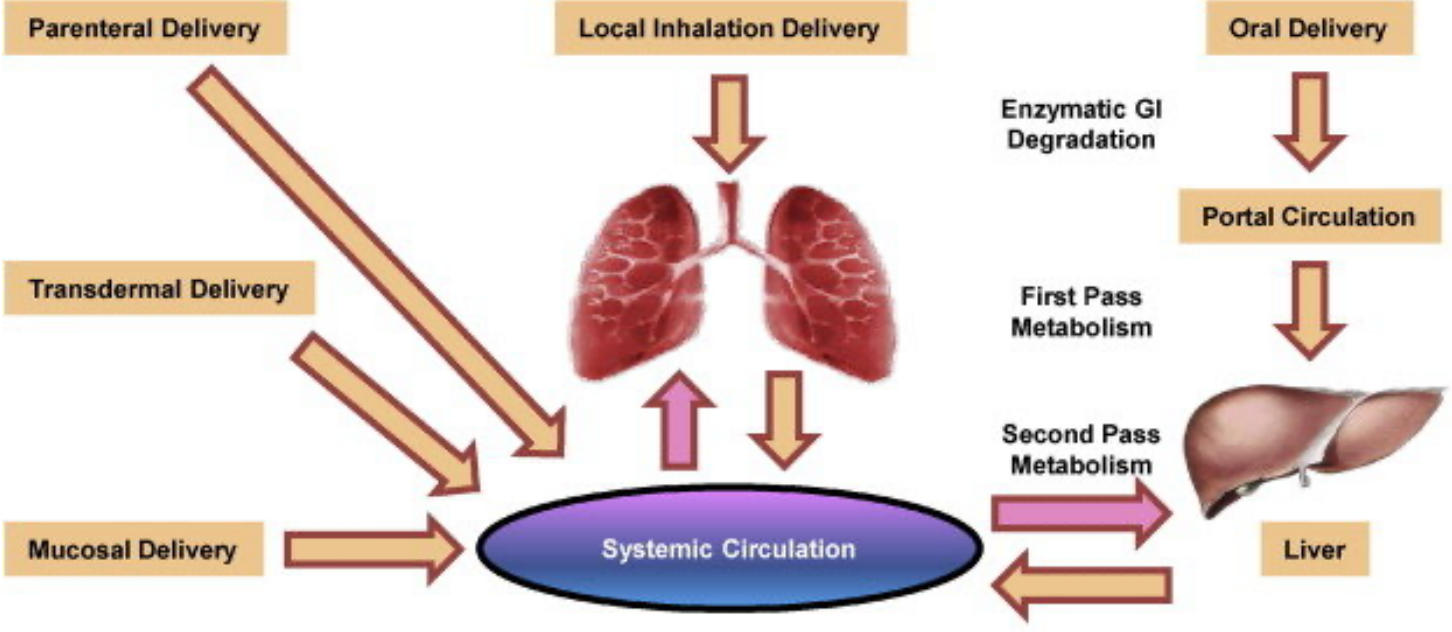


Types of Drug Delivery Mechanisms

- The method of drug delivery is selected based on the:
  - Target tissue
  - Frequency of dosing
  - Structure of the drug
  - Drug metabolism within the body



- Many different routes for drug delivery:



Oral

Oral Drug Delivery Cheat Sheet

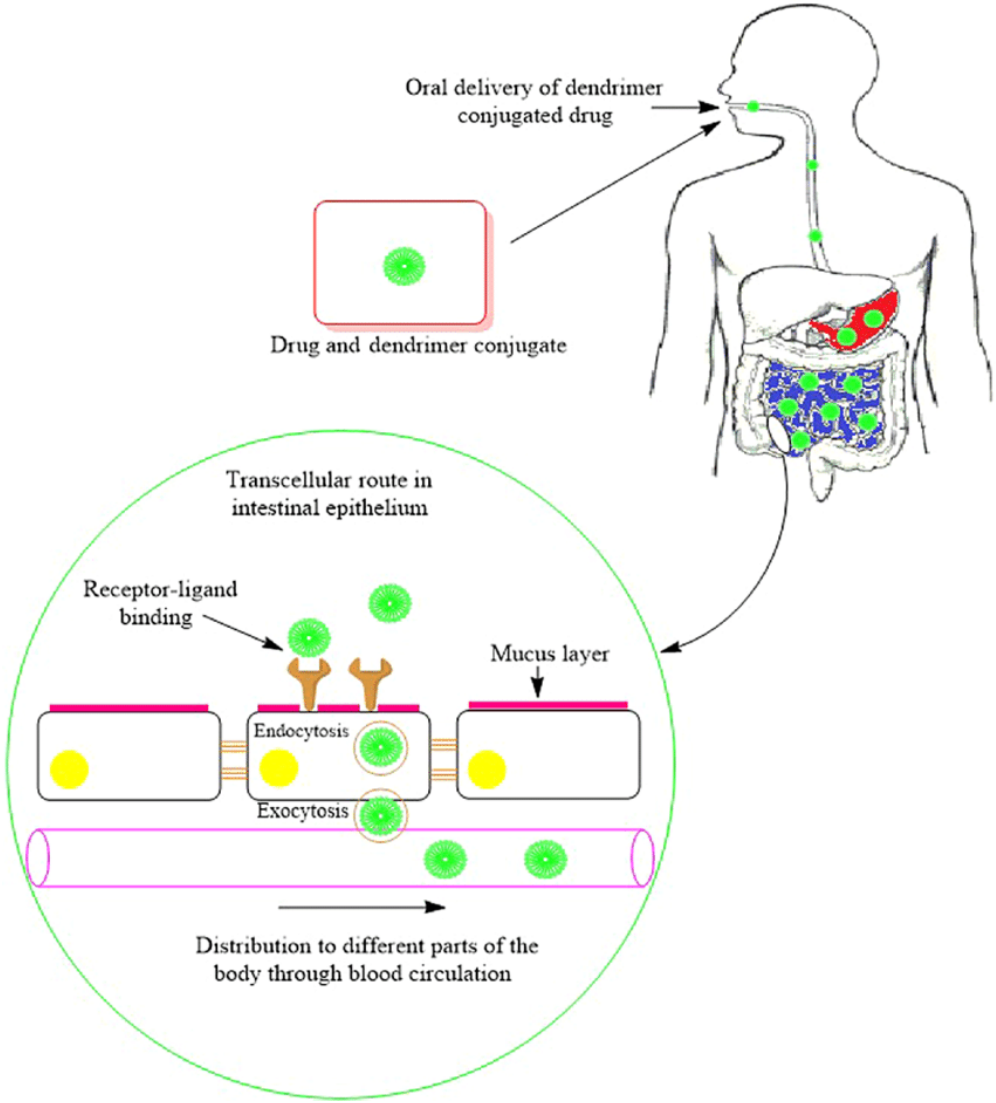
Systemic (all tissues)

Frequent dosing (~daily)

High Compliance

First Pass Metabolism in Liver

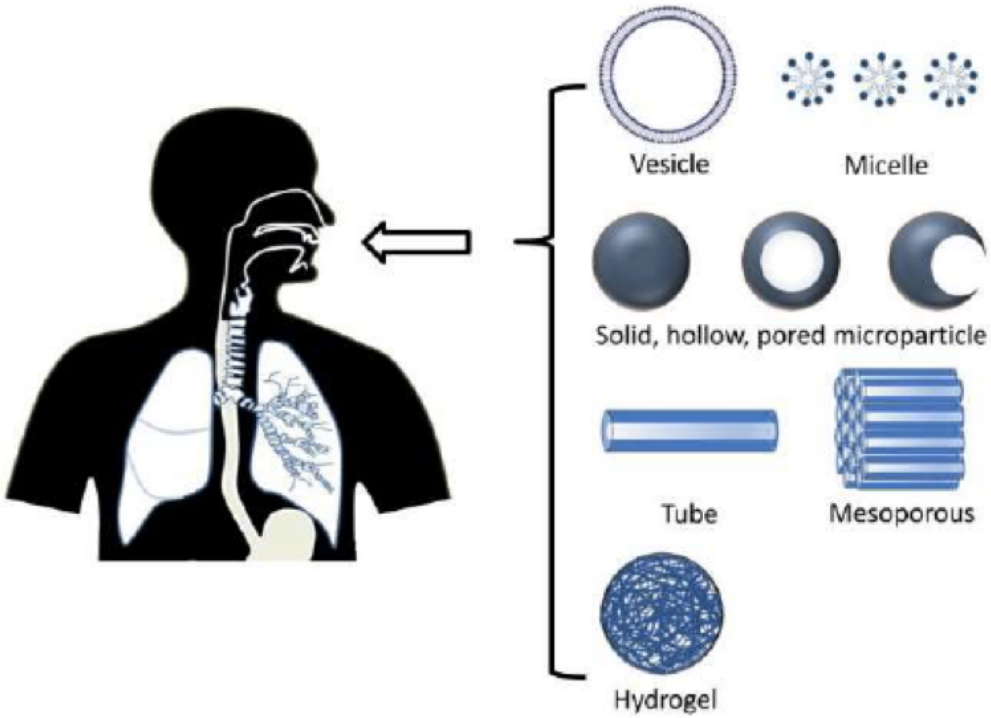
Low Bioavailability

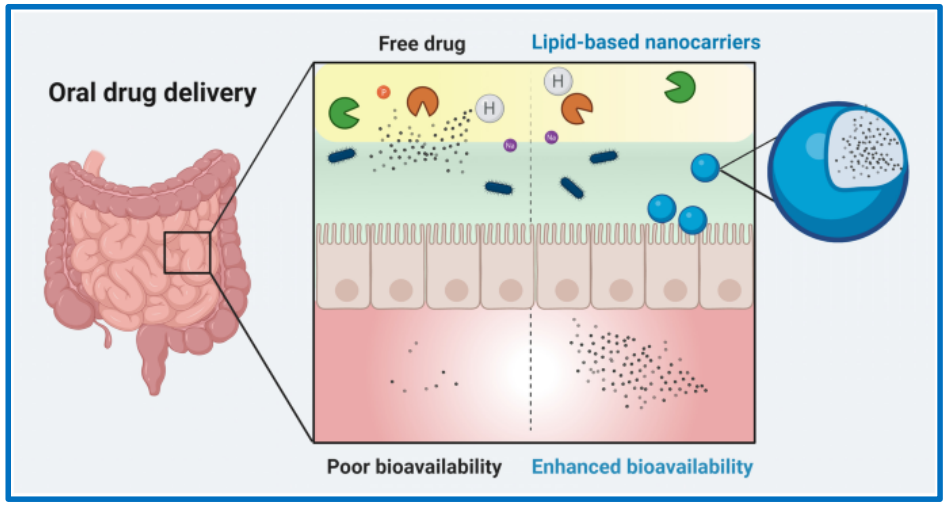


https://www.researchgate.net/figure/Schematics-Diagrammatic-Uptake-Mechanism-of-Various-Drug-through-Oral-Route-f0010_fig1_305873761

Oral

- Encapsulation techniques are used to enhance the bioavailability of drug and increase the duration of action





https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.researchgate.net%2Ffigure%2FSchematics-Diagrammatic-Uptake-Mechanism-of-Various-Drug-through-Oral-Route-f0010_fig1_305873761&psig=AOvVaw0Bplier8diZvu24kH_CRne&ust=1617833538118000&source=images&cd=vfe&ved=0CA0QjhxqFwoTCNDdgt3R6u8CFQAAAAAdAAAAABAJ

Respiratory

Respiratory Drug Delivery Cheat Sheet

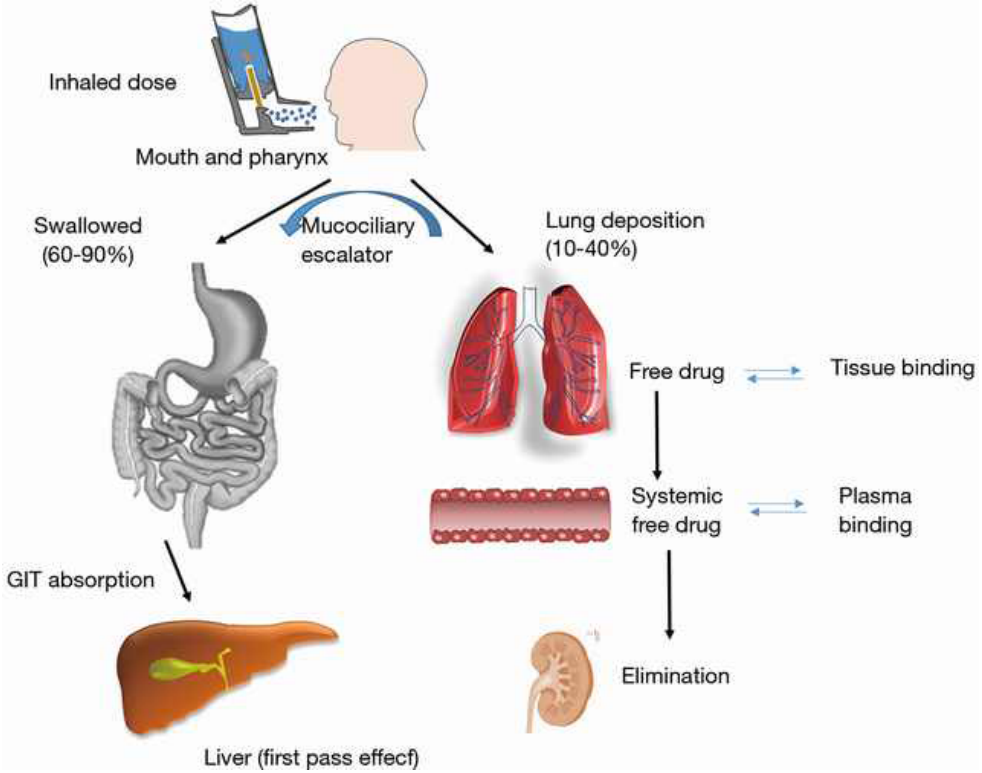
Pulmonary System

Frequent dosing (~daily)

High Compliance

Small drug particles

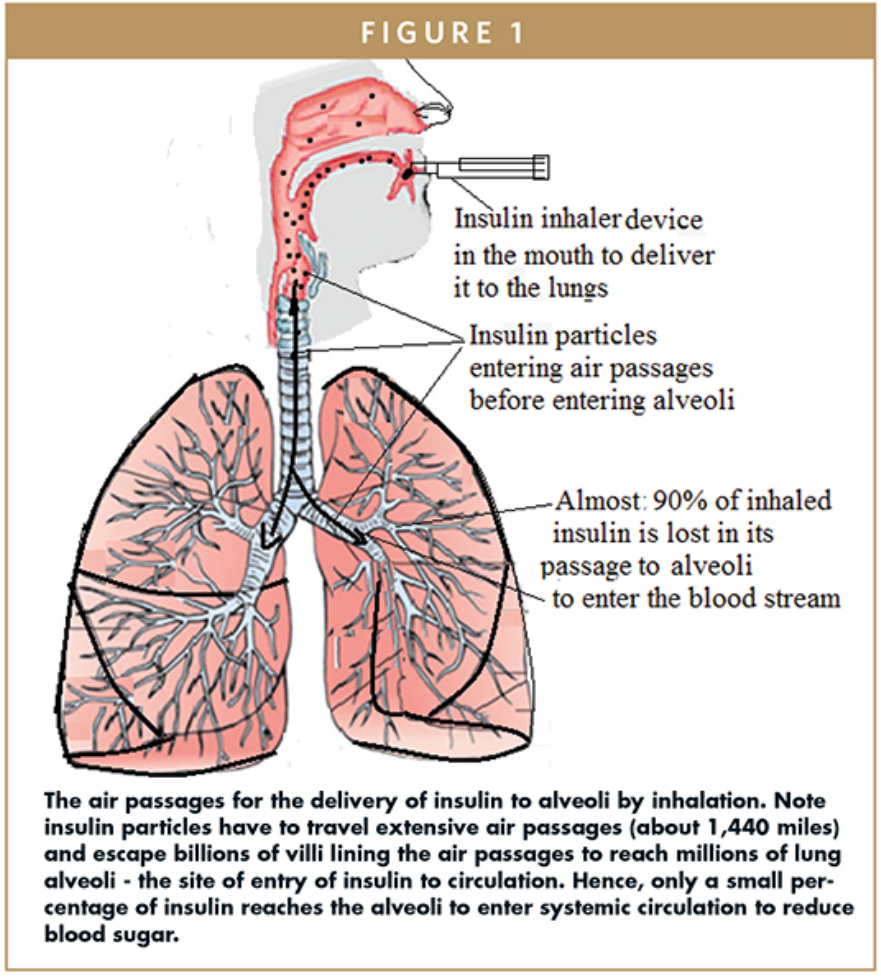
Low Bioavailability

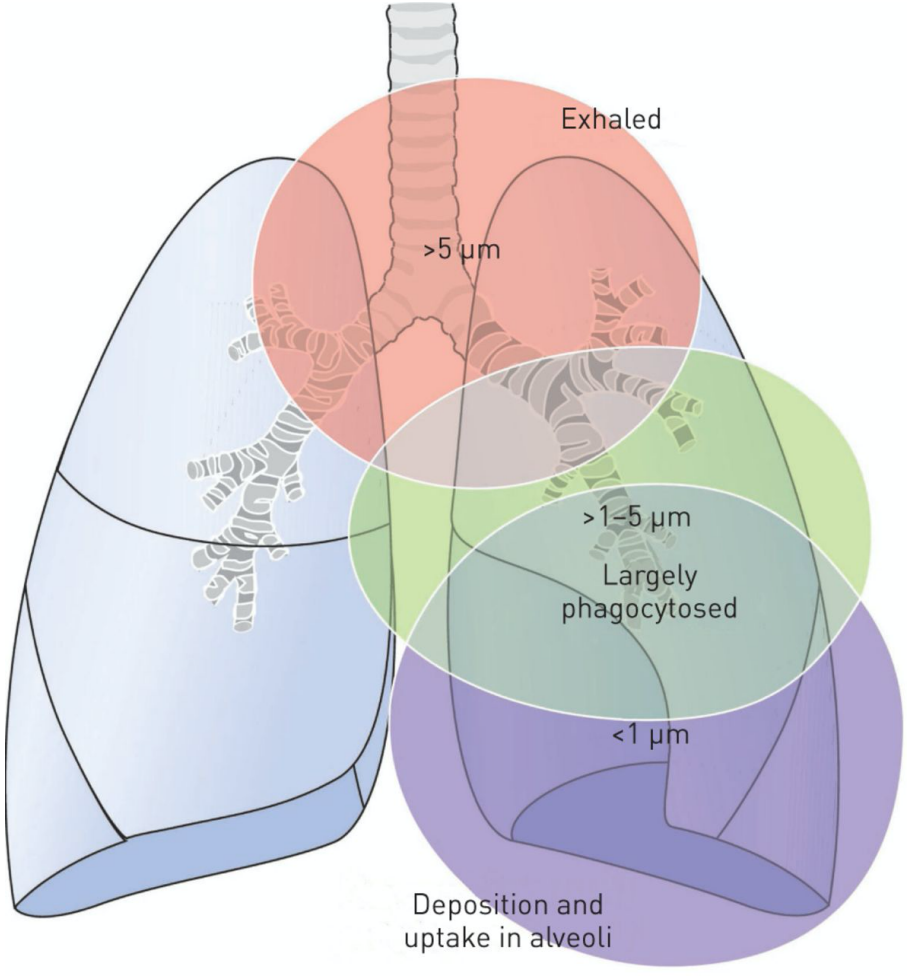


https://atm.amegroups.com/article/view/16842/html

Respiratory

- Encapsulation techniques are used to enhance the bioavailability of drug and increase the duration of action
- Not effective for delivering large proteins (ex: insulin)





Intravenous

Intravenous Drug Delivery Cheat Sheet

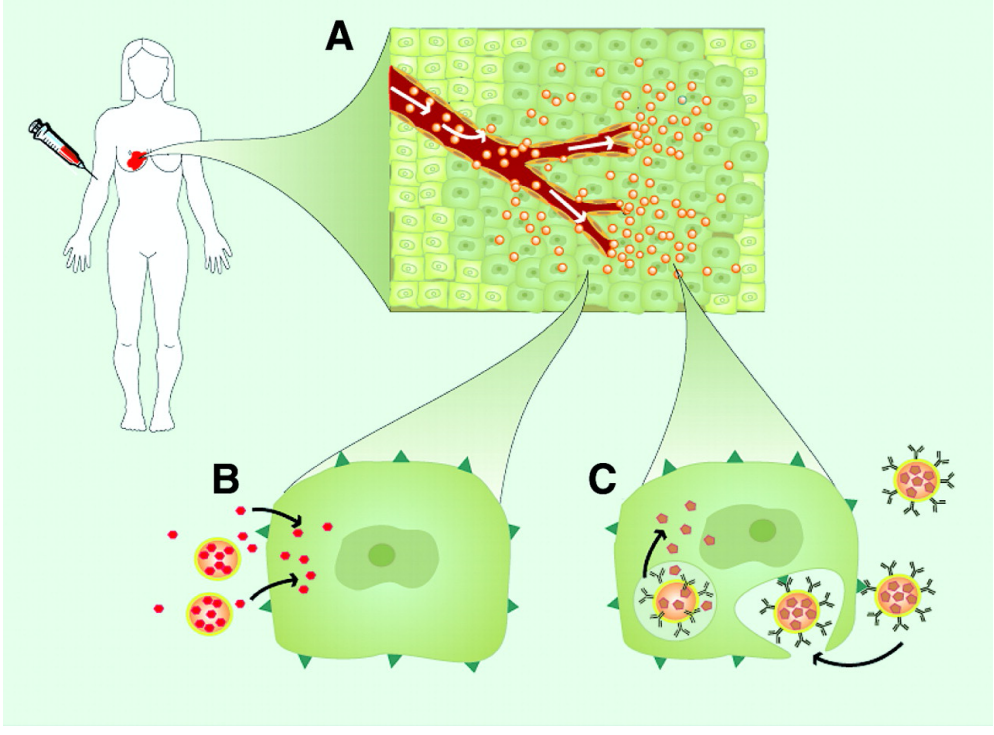
Systemic

Infrequent dosing (~monthly)

Lower Compliance

Hydrophilic drug particles

High Bioavailability



Intramuscular

Intramuscular Drug Delivery Cheat Sheet

Systemic

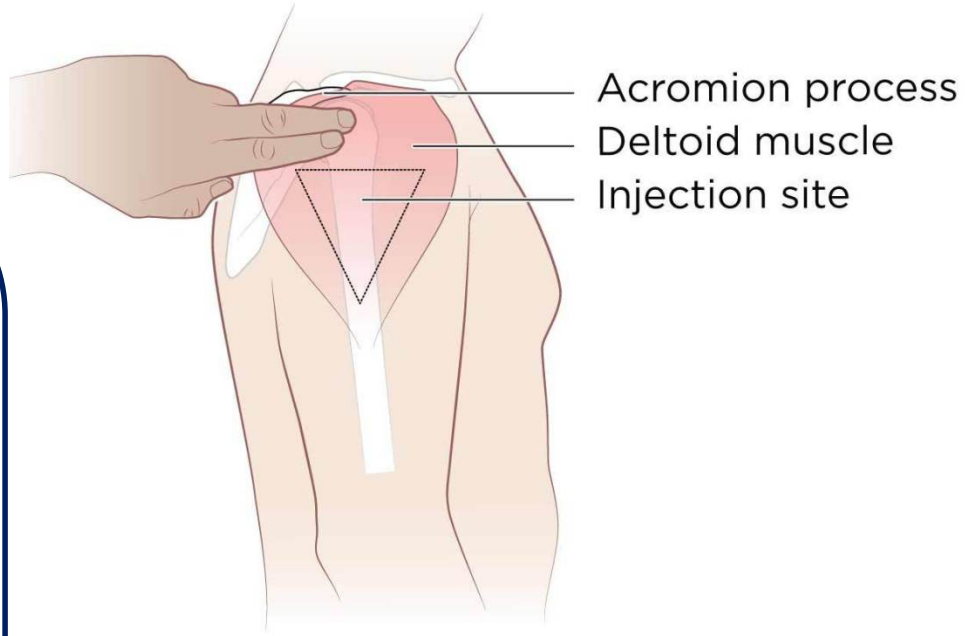
Infrequent dosing (~monthly)

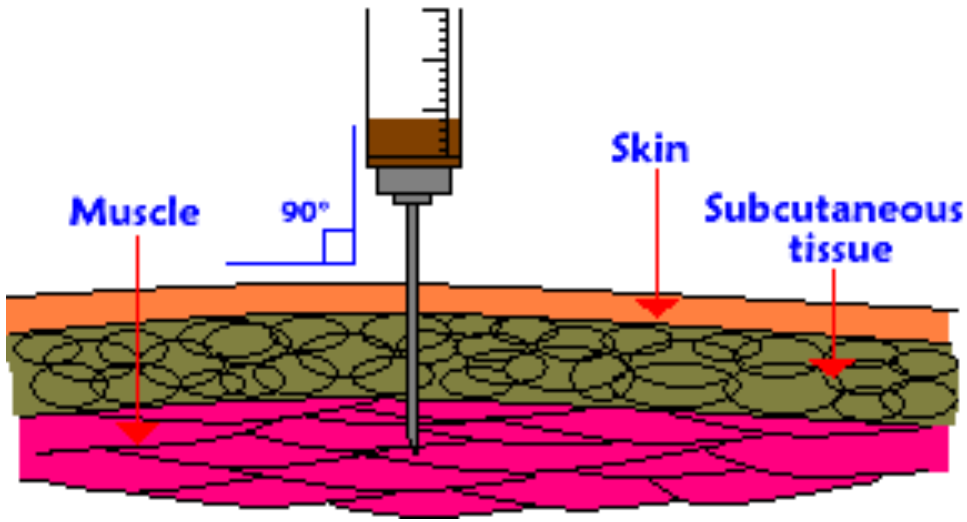
Lower Compliance

Hormones, Antibiotics,

Antibodies, and Vaccines

High Bioavailability





https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1118997/ https://www.healthcarejourney.com/q--a-for-virtual-ms-center/what-is-the-journey-of-an-intramuscular-injection

Subcutaneous

Subcutaneous Drug Delivery Cheat Sheet

Systemic

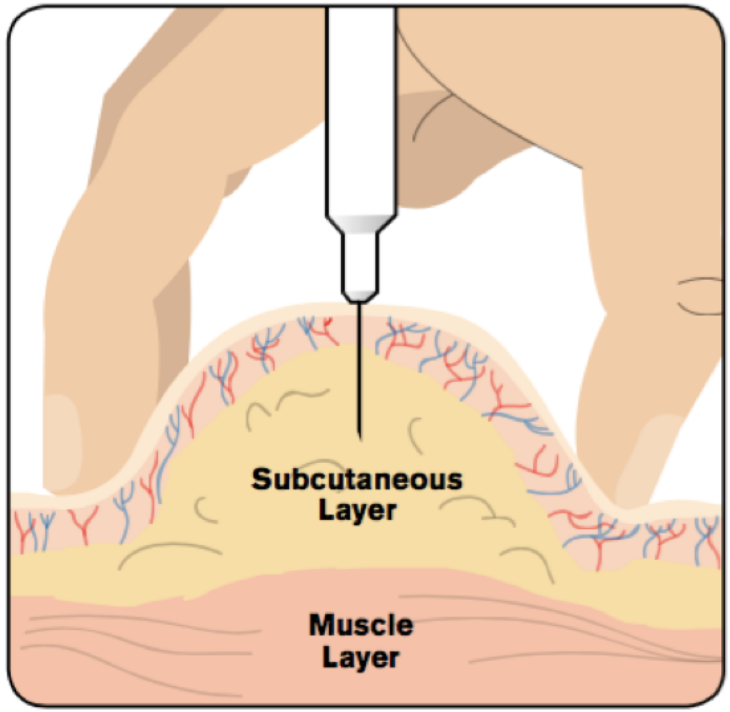
Infrequent dosing (~monthly)

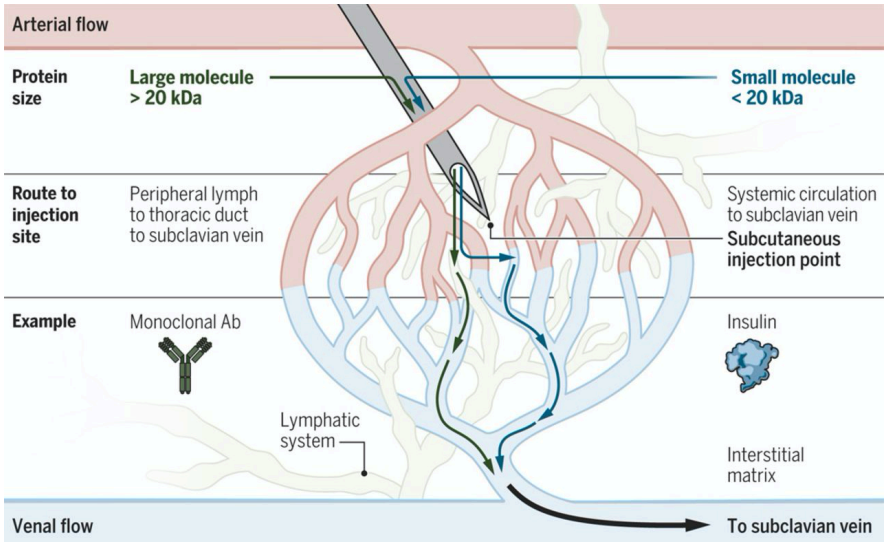
Slow, Sustained Delivery

Lower Compliance

Vaccines and Hormones

High Bioavailability

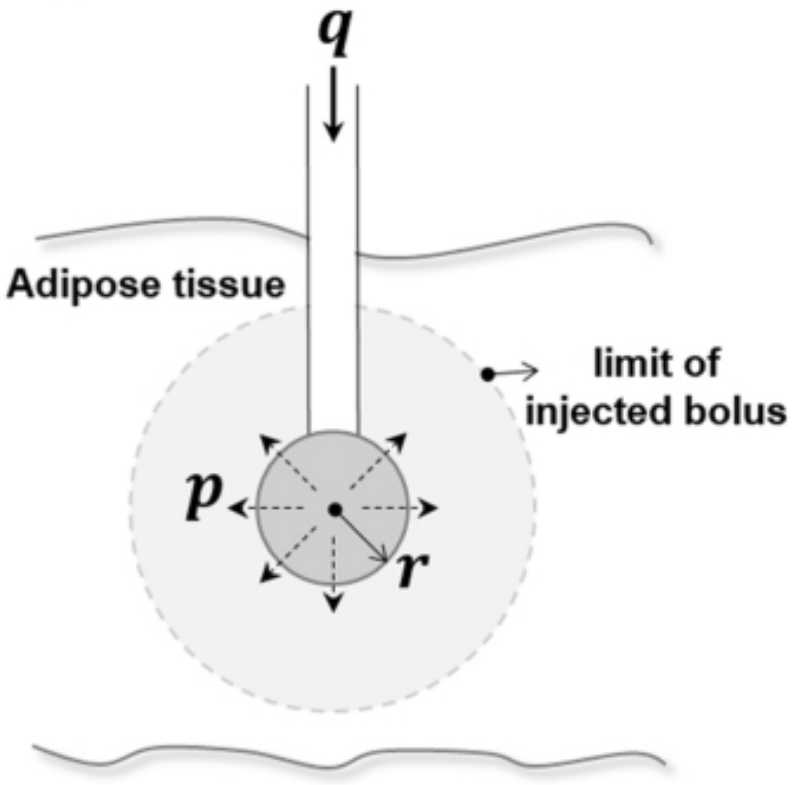




https://stm.sciencemag.org/content/9/405/eaaf9166.full https://epmonthly.com/article/the-right-route/

Subcutaneous

- Drug delivery into fatty tissue with few blood vessels allows for slow, continuous delivery that mimics natural organ release of drug molecules



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5575294/
https://www.trendhunter.com/trends/insulin-port

Transdermal

Transdermal Drug Delivery Cheat Sheet

Systemic

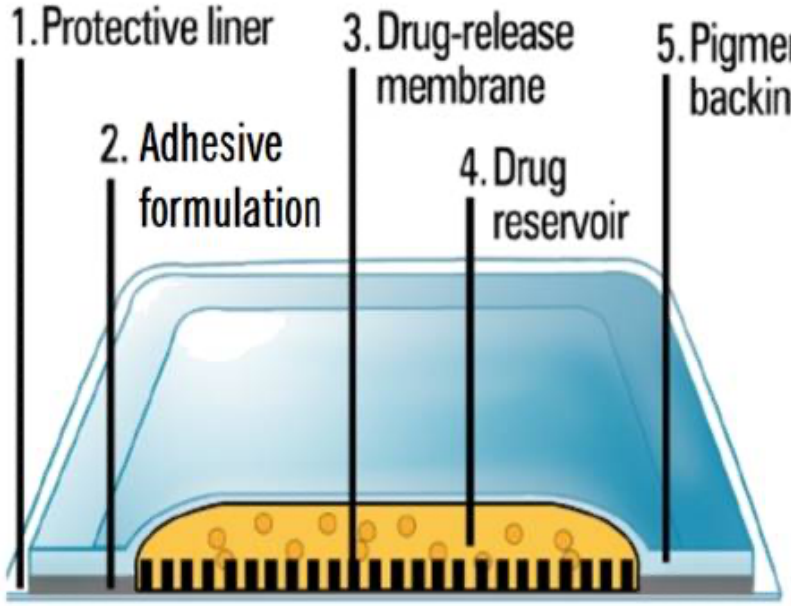
Infrequent dosing (~weekly)

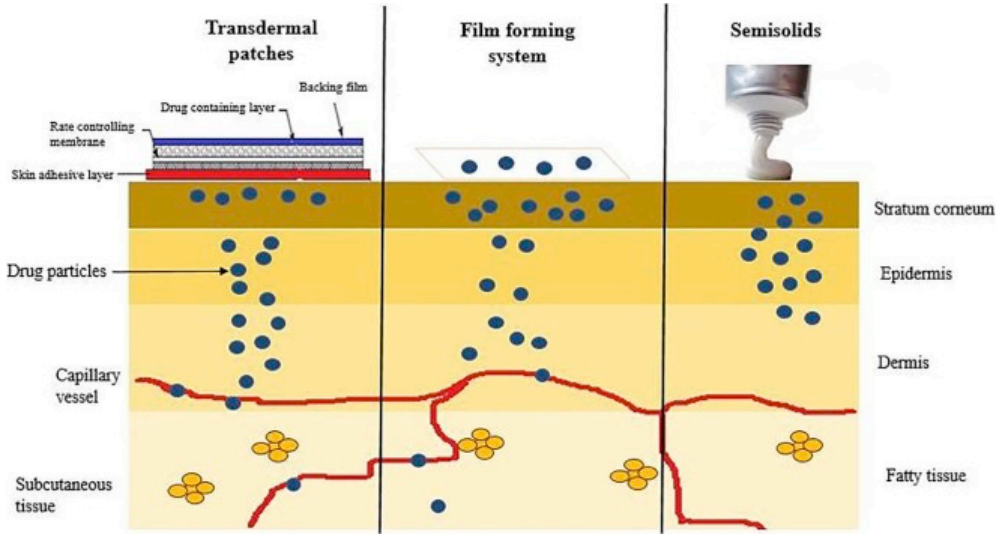
Slow, Sustained Delivery

Higher Compliance

Small, Lipophilic Drugs

High Bioavailability

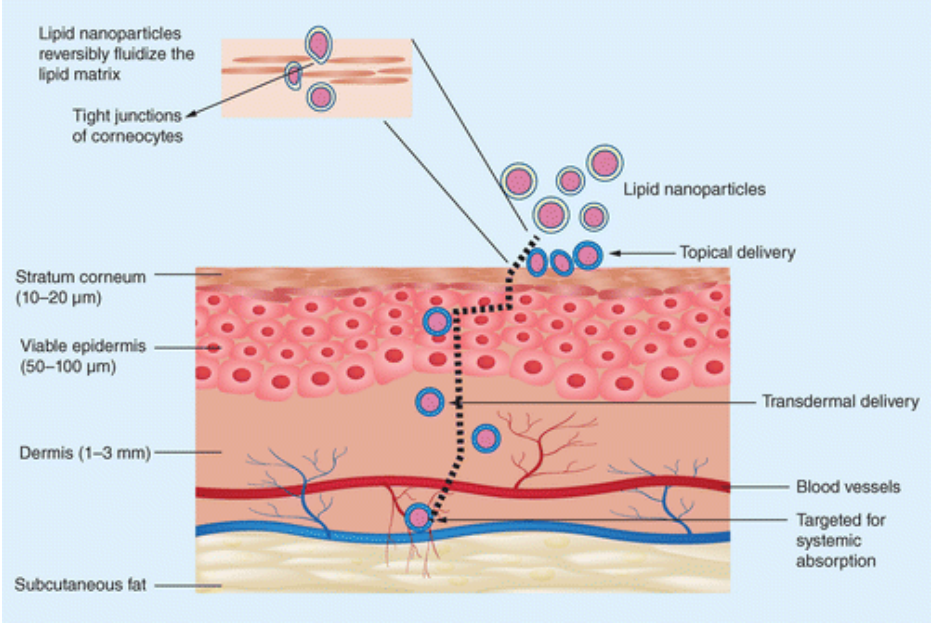


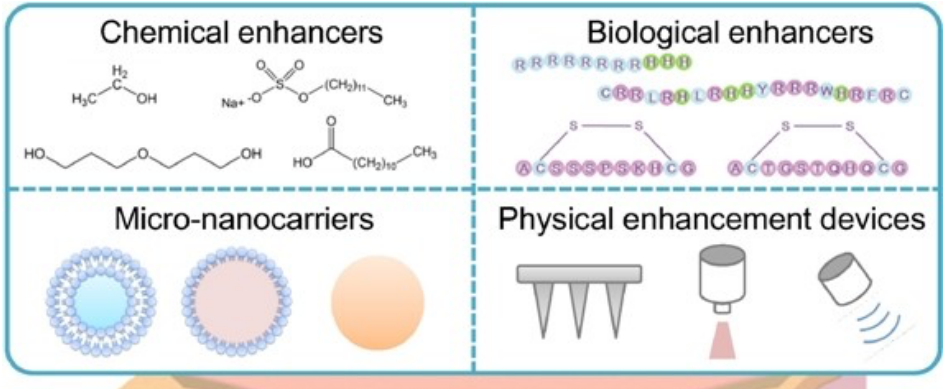


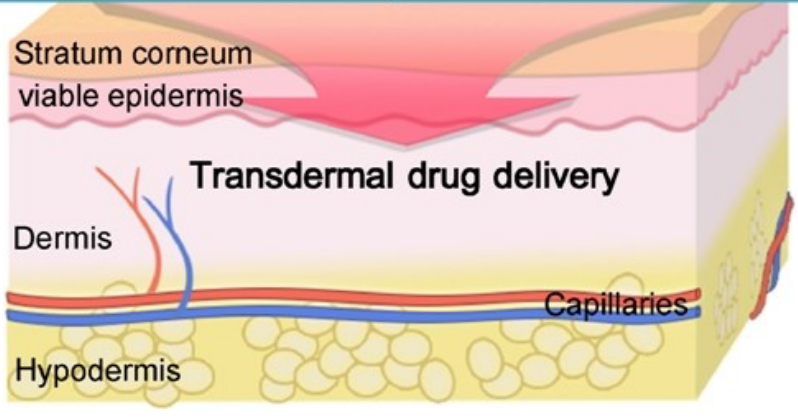
https://www.sciencedirect.com/science/article/pii/S1818087617301538

Transdermal

- The main barrier to transdermal drug delivery is the pore size in the **stratum corneum**, limiting successful delivery to small, lipophilic molecules
- Enhancement techniques (iontophoresis, ultrasonic treatment) are used to make these pores bigger and allow larger molecules through the skin

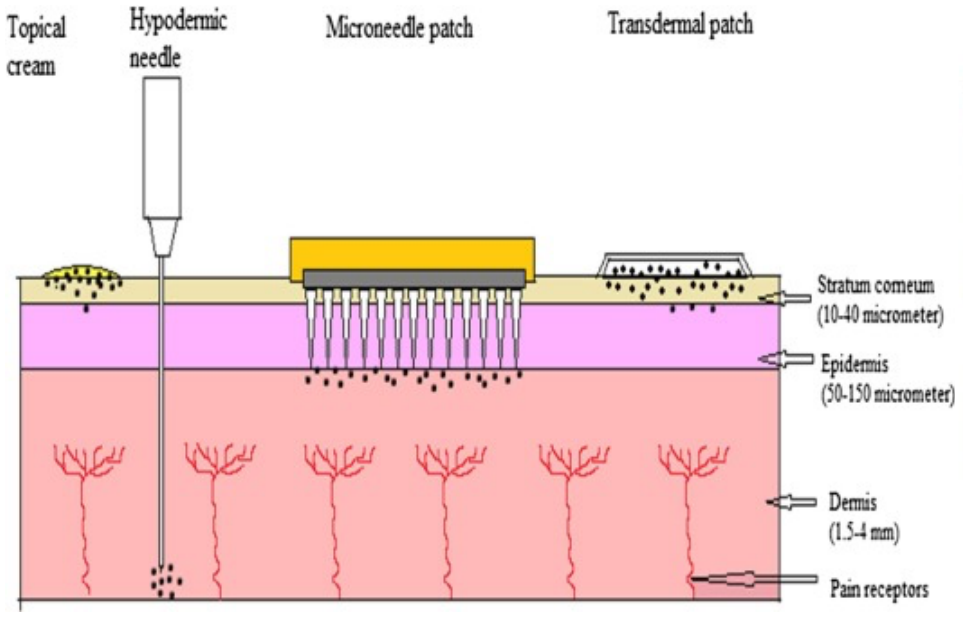


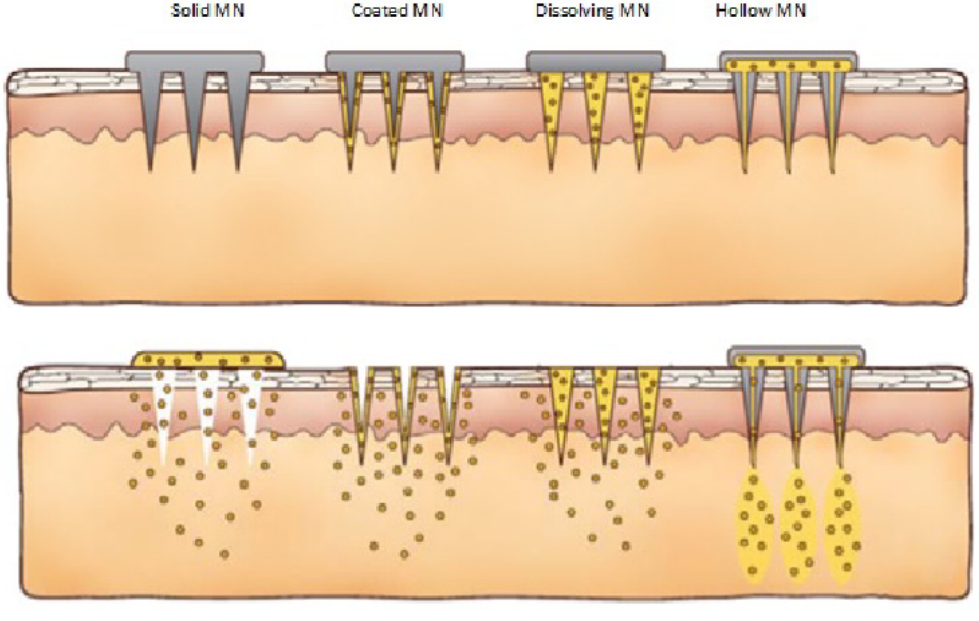




Combination Method: Microneedles

- Painless and effective transdermal drug delivery method
    - Needles are long enough to penetrate the stratum corneum
    - Needles are too short to hit pain receptors
- Limited by size of drug reservoir
    - Current patches hold a very small quantity of drug
    - More research is needed to enhance its dosage capacity





Module 9 Worksheet

BMES Cell Team

Spring 2021

Worksheet

- First part gets you familiar with pharmacokinetics vocabulary in the first half of the module
    - See slides on Cell Team website

- Seconds part gives you practice analyzing pharmacokinetic data
    - Assess the utility of 3 solid nanoparticle formulations in comparison to the free molecule Active Product Ingredient (API)
    - Use Google Sheets or Excel to do data analysis
    - See Protocol Discussion 1 Worksheet for a reminder of some of the commands you can use for this analysis

- Access Data Here:
    - https://docs.google.com/spreadsheets/d/1aD9m9y51YepugGBqTDPtqb2FWm0yOyKYFHxmhW_cJDo/edit?usp=sharing