Drug Absorption

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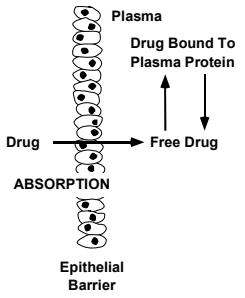
Definition of Drug Absorption



Drug absorption is the movement of the drug from its site of administration into the bloodstream.

Definition of Bioavailability

Bioavailability (F) is the fraction of administered drug that reaches the systemic circulation.

Bioavailability is 1 (100% absorption) for intravascular drug administration and usually less than 1 for oral drug administration.

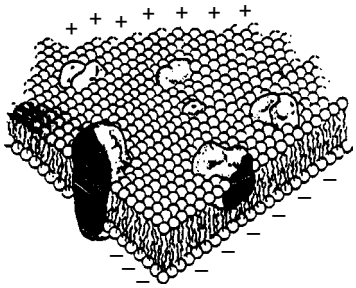
Drug Bioavailability is a key factor in the onset of drug Action.

Model of Membrane Structure

Lipid-Globular Protein Mosaic Model of Membranes

Outside - High Ca^{2+} and Na^{+}, positive charge

Diffusion
Filtration
Carrier-Mediated
Receptor-Mediated
Endocytosis



Inside - Low Ca^{2+} and Na^{+}, high K^{+}, negative charge

Fick's Law of Passive Diffusion

DIFFUSION RATE = - DAK (Cout-Cin) / ΔX

Diffusion Constant (D) is inversely proportional to drug's weight.

Area (A) of the membrane.

Lipid partition coefficient (K), a measure of lipid solubility.

Cout - Cin is concentration gradient across membrane (downhill).

ΔX thickness of membrane.

Henderson-Hasselbach Equation

pH = pKa + log Base[A^- ; B] / Acid[HA; BH^+]

weak acids = [HA ↔ H^+ + A^-] Acid is a proton donor

weak bases = [B + H^+ ↔ BH^+] Base is a proton acceptor

H-H equation is used to calculate the percent ionization of a drug in cellular compartments of different pH.

Understanding how changes in pH alter the ionization of drugs is very important since unionized drugs cross membranes.

Percent Ionization of Aspirin [Stomach]

pKa of Aspirin [weak acid] = 3.4 (50% HA and A- at pH 3.4)

pH stomach = 1.4 pH blood = 7.4

pH = pKa + log $(A^-)/(HA)$ [H-H equation]

pH - pKa = log $(A^-)/(HA)$

1.4 – 3.4 = - 2 log of 0.01= -2 (stomach)

A^- / HA= 0.01/ 1 so HA is 100 fold greater than A^-

HA moves from the stomach into the blood (good absorption)

Percent Ionization of Aspirin [Blood]

Stomach (pH=1.4) Blood (pH=7.4)

pH - pKa = log $(A^-)/(HA)$

7.4 – 3.4 = 4 log of 10,000 = 4 (blood)

A^- / HA= 10,000/ 1 so A^- is 10,000 fold greater than HA

Stomach		Blood	[Blood/Stomach]
A- + HA	↔	HA + A^-	
[.01] + [1]		[1] + [10,000]	10,000/1

Aspirin is readily absorbed from stomach into blood.

Percent Ionization of Codeine [Stomach]

CODEINE (weak base) pKa = 7.9

Stomach pH=1.9 Blood pH =7.4

pH - pKa = log(B)/(BH^+) [H-H equation]

1.9 - 7.9 = -6 log 0.0000001 = -6 [Stomach]

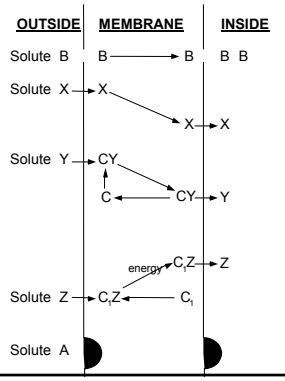
B/ BH^+ = 0.000001/1 so BH^+ is 1,000,000 fold greater than B.

Little B (codeine) is absorbed into the blood (poor absorption)..

Percent Ionization of Drugs

pH	Weak Acids % ionization of aspirin		Weak Bases % ionization of codeine	
3 units > pKa	99.9%	log [A^-/HA = 1000/1]	0.1%	log [B/BH^+ = 1000/1]
2 units > pKa	99%	log [A^-/HA = 100/1]	1%	log [B/BH^+ = 100/1]
1 unit > pKa	90.9%	log [A^-/HA = 10/1]	9%	log [B/BH^+ = 10/1]
pH = pKa	50%	log [A^-/HA = 1/1]	50%	log [B/BH^+ = 1/1]
1 unit < pKa	9%	log [A^-/HA = 1/10]	90.9%	log [B/BH^+ = 1/10]
2 units < pKa	1%	log [A^-/HA = 1/100]	99%	log [B/BH^+ = 1/100]
3 units < pKa	0.1%	log [A^-/HA = 1/1000]	99.9%	log [B/BH^+ = 1/1000]

Membrane Transport Processes



Filtration

Passive Diffusion

Facilitated Diffusion

Active Transport

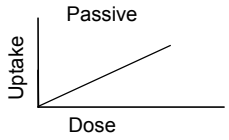
Receptor-Mediated Endocytosis

Site-Specific Drug Delivery

Radioactive Iodine to treat thyroid disorders.

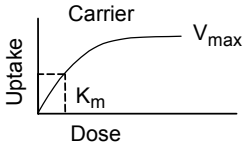
Liposome entrapped drugs taken up by liver and spleen.

Kinetics of Transport Processes



Linear Kinetics
Filtration
Passive Diffusion

Saturation Kinetics
Facilitated Diffusion
Active Transport
Receptor-Mediated
Endocytosis



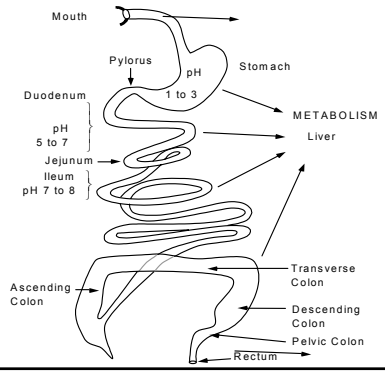
Enteral Drug Administration

Drug absorption from mouth throughout gastrointestinal tract.

Advantages: safe, economical

Disadvantages: slow onset, noncompliance, low bioavailability

Enteral Routes of Drug Administration



Sublingual
Rapid Onset
By-pass Liver
Few Drugs

Oral
Acid Media
Food
Metabolism
Degradation
Low Bioavail.

Rectal
Low Bioavail.
Few Drugs

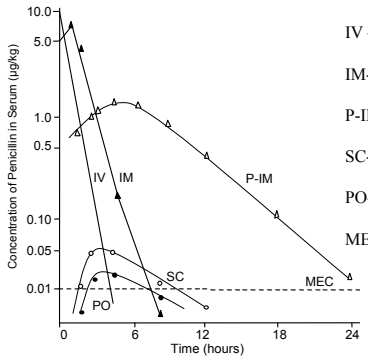
Parenteral Drug Administration

Drug administration to various sites by injection techniques.

Advantages: compliance, rapid onset of action, high bioavailability, avoid first-pass liver effects.

Disadvantages: expensive, more dangerous

Route of Drug Administration Alters Bioavailability



IV – intravascular

IM- intramuscular

P-IM- IM drug salt

SC- subcutaneous

PO-oral

MEC- Minimum Effective Concentration

Intravascular Drug Administration

Intravascular (IV) [drug administered into venous blood]

Rapid and complete delivery, no absorption problems (100%)

Fastest rate of drug delivery and onset of action

Intravascular Drug Administration

Flexible rate of drug administration

No way to stop response to drug **(no recall)**

Some problems with IV route: **anaphylaxis and infection.**

Intramuscular Drug Administration

Intramuscular (IM) [gluteus maximus,vastus lateralus, deltoid]

Rapid absorption and onset of action. **[lower rate in elderly]**

Uptake of drug is rapid or slow depending on drug solubility.

Intramuscular Drug Administration

Good blood flow to muscle sites enhances drug uptake.

Drug uptake from all muscle sites is similar in men

Women have slower uptake from gluteus maximus

Pain and limited volume (4-5 ml) are disadvantages.

Subcutaneous Drug Administration

Subcutaneous (under the skin)

Uptake is similar to IM but rate is slower and more erratic

Administer sustained release drugs (**disulfiram)**

Pain and tissue damage are disadvantages

Parenteral Drug Administration

Intra-arterial (into arterial blood)

Difficult technique; used for local tissue effect

Intrathecal (into spinal column)

Difficult and dangerous technique (spinal injury)

Useful for CNS infections and spinal block (childbirth)

Other Routes of Drug Administration

Intraperitoneal (into peritoneal cavity)

Drug administration to laboratory animals but not humans.

Topical (applied to the skin as transdermal patch)

Limited to potent, lipid soluble compounds such as **nitroglycerin** for angina and **scopolamine** for motion sickness.

Absorption may be **increased in elderly** due to thinning of dermal layer.

Intranasal Drug Administration

Intranasal (into nasal cavity)

Rapid uptake of decongestants, hormones and cocaine.

Pulmonary Drug Administration

Limited to gaseous and volatile compounds **(general anesthetics)**

Rapid and efficient absorption of many drugs

Passive diffusion across alveolar membrane.

Large surface area and good blood flow enhance drug uptake

Pulmonary Drug Administration

Blood/air partition coefficient (λ) influences onset of action

Methoxyflurane has a high λ (12) and the onset of action is slow.

Nitrous oxide has a low λ (0.5) and the onset of action is rapid.

Onset of drug action is inversely proportional to λ