Pharmacokinetics I: Administration & Absorption

PHC 721

Winter 2022

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Pharmacokinetic Processes (ADME)

Dosage Form:
Solid (e.g., Tablet), Liquid (e.g., Drop), Semisolid (e.g., Ointment), Inhalation (e.g., Aerosol)

Route of Administration:
Local (topical, deeper tissues) or Systemic (e.g., oral, nasal, parenteral)

Passage across biological membranes:
Passive Diffusion, Filtration, Active Transport

Absorption

Solution

DRUG

Capillary Bed

DRUG-Plasma Protein ↕ Free DRUG

Bloodstream

Heart

Distribution

DRUG

Tissue Reservoirs

Receptor ↔ DRUG

Site of Action

Capillary Bed

DRUG-Plasma Protein ↕ Free DRUG

Bloodstream

Metabolism

Free DRUG

Metabolites

Bloodstream

Excretion

Biotransformation
(Liver, Kidney, Intestine, Lungs, Plasma)

Urine, Bile, Air, Sweat, Saliva, Breast Milk

Dosage form such as tablets, liquid, semisolid, and inhalers. Now, the pending on the dosage form, different **routes of drug administration** are suitable or appropriate. The two major types: **local and systemic**. In your practice, you will be frequently using local route for deeper tissues, because this is how local anesthetics are administered. As far as systemic routes, the oral is the most common. We also talked briefly about features of parental routes, meaning subcutaneous intravenous. Those are the routes of administration.

The first step is the passage through biological membranes. Passage across biological membranes involves various processes. But by far, the most common is the passive diffusion, which you can probably understand. For example, active transport you need to have the specific molecule transporter that would be recognizing the drug, but the drug is the exogenous substance. So, most commonly, the drugs are basically passively diffusing through the membranes. We'll discuss the conditions that need to be melt in order for the drug to pass through the membranes.

Next step is very important in order for any drug to actually pass through them across the membranes. It needs to first go to solution. If the drug cannot go to solution, which is why it cannot be administered and cannot be absorbed and we cannot minister it. Now we are getting to the first step. Absorption is actually **absorption to the systemic circulation**. You probably remember from your cardiovascular Physiology class…The only part of the circulation that allows exchange with the outside world mean on the outside of the circulation are capillaries. So the drug is absorbed to the capillaries. Once it's absorbed, it's first in the freeform, but most drugs bind to some extent~ at least plasma proteins. We'll spend quite a bit of time here discussing the consequences of drug binding to plasma proteins. There are different proteins that bind drugs, what are the consequences of drug availability, and metabolism and so on.

So we have the drug in the circulation in the bloodstream. Now, the next important piece is the role of the heart surface process. As I already said, this is the process of absorption so one more comment here. We are here at this big picture… the passage through biological membranes because the drug is injected directly to the systemic circulation. But, it still doesn't make that drug easily available at whatever tissues because it needs to pass through the membrane from the circulation to the side of action. But first, the **drug in solution gets through biological membranes to the systemic circulation**.

Next is a big role of the heart. I will talk about the consequences of congestive heart failure. For example, on drug distribution, because now the with the bloodstream, thanks to the heart, the drug can be distributed throughout the body, specifically to the side of action, to the receptor. There's another place where the drug usually resides that would call tissue reservoirs. The drug is distributed throughout the body. It gets to the receptor where it actually acts, but also often gets the posited in tissues. We'll talk about the consequences on the volume of distribution and the availability of the drug. We have the drug acting at the receptor, so the role of the drug for the body ends there, but the drug is around and is circulating through the body.

The next step of the process is **metabolism**. Drug gets metabolized in several organs. Most important organ, of what we call also biotransformation, is the liver, but also the kidney, and the intestine, and lungs. Some drugs are metabolized in the plasma. This also includes some local anesthetics that we will discuss later. This is the metabolism.

The final step is **excretion**. Metabolites was the made in those organs of future biotransformation. They get back to the systemic circulation that excluded. There are several organs of excretion, but the most important is the kidney. Again, we'll talk about the consequences of kidney failure and liver failure metabolism and excretion, getting rid of the drug. We need to remember those are foreign chemicals that the body needs to dispose of somehow. We will also talk about excretion through the bio and also air because the lungs are also important organ of excretion. We'll briefly talk about the breast milk because it has consequences for nursing mothers. Again, this is just a big picture and overview of pharmacokinetic processes. In this first session, we'll talk about absorption, focus on passage through biological membranes and so on.

Drug Dosage Forms

Dosage form is a product suitable for administration of a drug (single dose) to a patient:
Drug (active ingredient) + Other substances (excipients, diluents, preservatives, etc.)

Solid Dosage Forms:
Powders, Tablets, Capsules,
Lozenges, Suppositories
…and Pills


Liquid Dosage Forms:
Injections,
Elixirs, Drops, Suspensions,
Lotions


Semisolid Dosage Forms:
Ointments, Pastes, Creams,
Gels

Inhalations:
Gases, Volatile Liquids,
Aerosols


The definition of the dosage form is product suitable for administration to a patient as a single dose and each dosage form consists of active ingredient which is the actual drug and other substances, such as vehicle to deliver the drug, preservatives added to extend the life of the drug, and so on.

The most common dosage form is the solid dosage forms because the most common route of administration is the oral administration. But you also see here, the powders included in the solid dosage forms. Those are for administration, the intrarectal administration. Those are commonly used solid dosage forms. I wanted to tell you a story about one more form that's commonly used in your language, but actually this dosage form is not commonly used anymore. Those are pills. We often refer to pills when we actually mean tablets or capsules, so I wanted to tell you a short story about pills…

YOUTUBE video [Victorian Pill-Rolling Machine (circa 1860)]

The reason I would mention the pill is the study specific dosage form because I wanted to also help you review a piece of neuroscience Parkinson's disease. One of very characteristic features is the pill rolling tremor. This is the name of the tremor as you saw the patient was walking here. Their fingers where moving like for pill rolling. The name comes from the times when the actual pharmacist would make the pills by hand, so I showed you the running machine under previous slide. But actually, the pill would be of an aid by pharmacist by hand. The movement of the fingers will be very similar to what Parkinson's disease patients present in their tremor.

Then, very briefly examples of other dosage forms:
- Liquid dosage forms are injections and so on
- Semisolid dosage forms and such as ointment, pastes, creams, gels
- Inhalations: this one is also very much relevant to dentistry when you think about inhalation anesthesia for example

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NEXT SLIDE
Routes of administration has 2 major routes local and systemic.

Local is very much relevant to your profession. 2 subtypes: **topical** and **deeper** tissues. As far as topical drugs, agents can be applied on the skin or the nasal or oral mucosa. Here, the examples are antibiotics, antifungal agents that you will be applying sometimes for your patients' surfaces. The deeper tissues, the most relevant for you is for administration of local anesthetics, injections to TMJ and so on.

- *For local routes, the assumption is that the most drug stays in the place where you administer it. We cannot exclude systemic absorption. There is always some fraction of the drug will get absorbed. Because if you put that on the tissue, tissue has vasculature in it, so some drug may be absorbed, but they are formulated. The dosage form is prepared the way that the absorption is either minimal or is there but very slow.*

Systemic routes is for absorption into the bloodstream.
1. Most common (and actually the most common) route of all when you look at all medication is the **oral ingestion**. Several important features of this route include: it's safe, convenient, doesn't require assistance, economic because does not need to be sterile. All drugs that are sterilized for administration in the parenteral route basically the cost is much higher.
2. Another route for systemic is the **sublingual**. Those are only selected. There are more routes that I'm presenting here, but those are the most relevant to dentistry. For sublingual, sometimes you will be administering to your patient. Anxiolytic, for example, like benzodiazepine, triazolam, this would be for sublingually. It's much faster absorption than through the GI tract, and also bypasses some processes that would decrease drug bio availability (we'll talk about this later), decrease basically the amount of the drug if you apply orally. Sublingually is basically absorption directly to the circulation.
3. And now **inhalation** also important for dentistry because of inhalation and anesthetic, like isoflurane. I mentioned this on the previous slide, but we will also talk about this a little bit more later.
4. Finally **parenteral** route and **subcutaneous** intra muscular, intravenous. Intravenous would be your IV sedation. You would be using that.

Routes of Drug Administration

I. LOCAL (Selected)

(for localized and accessible sites of action; minimal/slow systemic absorption)

1. **Topical:** skin or nasal mucosa (Analgesics, Antibiotics, Corticosteroids);
   DENTAL EXAMPLES: Antibiotics/Antifungals; Antiseptic mouthwashes; Hemostatics
2. **Deeper Tissues:** around a nerve, intraarticular
   DENTAL EXAMPLES: local anesthesia, TMJ injections

II. SYSTEMIC ROUTES (Selected)

(for absorption into bloodstream & distribution via circulation)

1. **Oral Ingestion** (safe, convenient, economic – noninvasive/no assistance, need not be sterile);
2. **Sublingual** (avoids destruction by gastric acid and intestinal/hepatic enzymes)
   DENTAL EXAMPLE: Triazolam (Oral Sedative);
3. **Inhalation** (rapid onset & rapid elimination)
   DENTAL EXAMPLE: Isoflurane (Inhalation Anesthetic);
4. **Parenteral**
   - **4A. Subcutaneous** (rich innervation $\Rightarrow$ non-irritant drugs only);
   - **4B. Intramuscular** (mild irritants acceptable; avoid in patients taking anticoagulants);
   - **4C. Intravenous** (only aqueous solutions; fast/reliable–in emergencies)
     DENTAL EXAMPLE: Midazolam (Anxiolytic-Sedative)

Passage Across Biological Membranes

Passive Diffusion – Influence of pH

Nonelectrolytes (Unionized) ⇒ **Lipid-Soluble** ⇒ **Cross Readily**
Strong Electrolytes (Ionized) ⇒ **Water-Soluble** ⇒ virtually **No Passive Diffusion**

Most Drugs are **Weak Electrolytes**, i.e. their ionization is **pH-dependent**

$$pH = pK_a + \log \frac{[A^-]}{[HA]} \text{ or } \frac{[B]}{[BH^+]}$$

$[A^-]$ **or** $[BH^+]$ – concentration of ionized drug (weak acid or weak base)
$[HA]$ **or** $[B]$ – concentration of unionized drug (weak acid or weak base)
pK_a – negative logarithm of acidic dissociation **constant**

When pH = pK_a ⇒ drug is 50% ionized *(log must be 'zero' ⇒ [ionized] : [unionized] ratio = 1)*

1 scale change in pH causes a 10-fold change in ionization

pH increased by 1
⇓
pH = pK_a + 1
⇓
pH = pK_a + $\log_{10}$ 10
⇓
$[A^-]$ / [HA] = 10, i.e. >90% ionized (weak acids)
[B] / $[BH^+]$ = 10, i.e. <10% ionized (weak bases)

pH reduced by 1
⇓
pH = pK_a - 1
⇓
pH = pK_a + $\log_{10}$ 0.1
⇓
$[A^-]$ / [HA] = 0.1, i.e. <10% ionized
[B] / $[BH^+]$ = 0.1, i.e. >90% ionized

↑ Ionization ⇒ ↓ Membrane Permeability

By far, the most common way that the drugs used to pass through biological membranes is passive diffusion. Very important role of pH of tissues on both sides of the membrane.

So first key pieces of information are that if we're dealing with the drugs that are non electrolytes, they're unionized. Those are lipid soluble, so they can easily pass passively across the membrane, through the lipid portion of the biological membrane.

On the other hand, if the drug is strongly ionized. It's strong electrolyte. Then, it's water soluble. As you know, in this case, there's no passive diffusion. Fortunately, most drugs are prepared the way that they are weak electrolytes. It means that their ionization is pH dependent.

Understand of Henderson hasselbach. I hope you are all familiar with this equation for acid and for bases.

When the pH = pKA for a drug, it means that the drug is 50% ionized. It's straight from the equation and I actually even explained here why.

One thing I wanted you to realize how strong the effect of the pH is. If you increase pH by 1 so from 7 to 8, please realize that 1 is not happening ever in the body, we have our physiological pH of the blood 7.4 (normal), so 7.8 would be already dangerous. We are talking about 7.4 to 8.4, I say even 7.8 would be dangerous/deadly for the body. Actually in general, the body deals better with acidification than alkylation by increasing the pH. With diabetes, they have pH of the blood even 6.9 or 7.0, so it's .4 difference down from normal (=7.3 or 7.4), but going up above 7.6, it's really bad and dangerous.

This is just for simplicity here. I'm increasing pH by one. You will see what happens with the proportion of the drug that gets ionized. We are adding one to this pH. **When you increase pH by 1, there is more than 90% of the drug becomes ionized for weak acid. For weak bases, there would be less than 10% of the drug will be ionized** because it's all dependent on their start pKA.

If you're a **reduce pH by 1**, using the same equation. You have the opposite situation **for weak acid, less than 10% of the drug being ionized and more than 90% being ionized for weak bases**. Again, you need to translate those numbers to what happens for crossing. Respect to the crossing, the membranes, the drug that's highly ionized, such as weak acid, when you increase pH, the membranes become impermeable to this particular drug. Opposite for the bases, reducing pH basically eliminates the ability of the drug to cross the membrane. One scale change in pH causes 10 fold change in ionization, so it's a huge effect.

Increasing ionization decreases membrane permeability —> this is one big piece that I wanted you to remember.

Passage Across Biological Membranes

The Partition Coefficient, Log*P*

Lipophilicity is a critical physical property of a drug because it impacts such processes as:

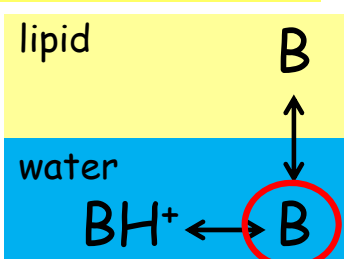
- Solubility - Passage across membranes - **A**bsorption,
- **D**istribution (including sequestration in tissues/organs and Blood-Brain Barrier penetration),
- Ligand recognition by the Target Protein, **M**etabolizing Enzymes (CYP450), etc.,
- Routes of clearance for drug **E**xcretion

The most commonly used measure of lipophilicity is:

$$\text{Partition Coefficient } (P) = \frac{\text{Concentration of neutral (un-ionized) solute in lipid}}{\text{Concentration of neutral (un-ionized) solute in water}}$$

P is determined by: **pK_a of the drug** & **pH of the body fluids**

$$\text{Log}P = \text{Log}\frac{[B]_{lipid}}{[B]_{water}}$$



'Shake-Flask' method with spectroscopy

Log*P* > 0 ⇒ Lipophilic

Log*P* = 0 ⇒ equally partitioned

Log*P* < 0 ⇒ Hydrophilic

Besides pH, another critical piece in pharmacokinetics is the **partition coefficient**, also known as **logP**. You maybe recognize logP in our first session when I was giving an overview of what pharmacokinetics is about. I gave an example of pharmacokinetic properties described for Propranolol and log P was included there. It's important for us to understand and be able to interpret different logP values.

LogP is a measure of lipid solubility or lipophilicity of drug. This property of the drug is really critical because it affects acid. I gave some examples for absorption, distribution, metabolism and excretion at all levels of pharmacokinetics of drug. log P or lipophilicity play a critical role because when we look at the pharmacokinetic properties, you will see the logP value of that.

What's logP we say partition coefficients along P partition coefficient is actually P, but presented as logarithm of P. Position coefficient P is the ratio of the concentration of the neutral solute (non-ionized) in lipid over the concentration of the solute in water. How much of the specific drug goes to lipid fraction and how much to water fraction. Fractions here is determined experimentally, but is determined by meaning depends on pKA of the drug and pH of the body fluids.

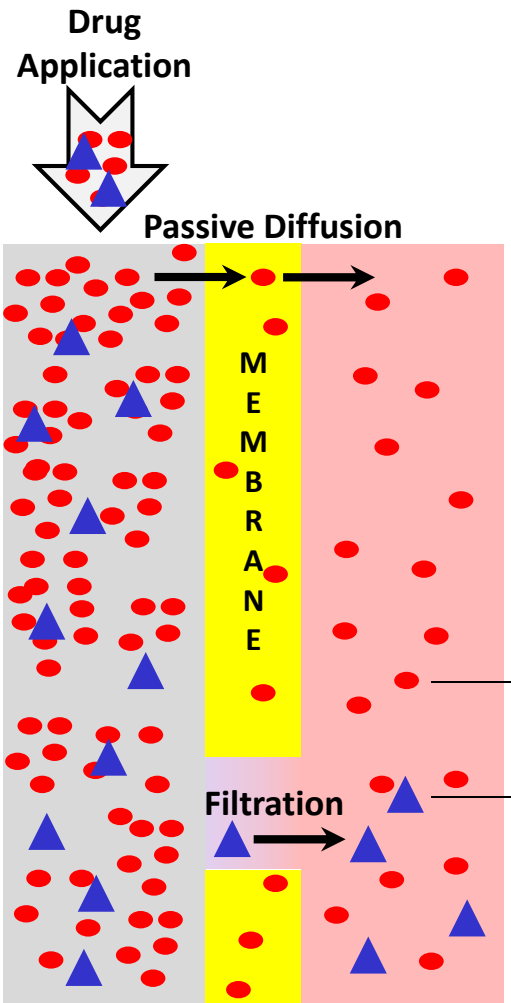
The method of establishing partition coefficient (most common) is the shape flask method. With spectroscopy, you measure the concentration of the drug. Basically that is this lipid water bilayer, you add the drug, you shake it with a nice form of the drug, and you measure in the lipid layer and in the water layer. Now here you have is the logarithm of this will be actually logP, logarithm of this ratio of the concentration of the drug in the lipid and in the water.

- **LogP >0**, the drug is **lipophilic** because they'll be basically higher concentration in the lipid, so drug is lipophilic.
- **LogP =0** is equally partitioned because when you have the same concentration in the lipid layer and in the water layer. There will be a logarithm 1, which is zero.
- **LogP <0** it means that the drug is **hydrophilic**.

Here might think **greater logP is better for the drug** versus what I said at the beginning that the lipophilicity is critical for all those processes. But, the story is a little bit more complex because you **cannot have the logP being too high** because then the drug will not go to solution.

As I said that the beginning, it's critical that the drug is able to go to solution in order to pass through membranes. This famous lipinski rule of five are several five spare as far as their molecular features of the drug, the types of bonds and everything is like multiplication of five. Among those rules for the ideal drug, before oral absorption is the role that the drug should have a **logP <5** because if a drug has too high logP (meaning too high velocity), it will not go to solution. If the logP <0, it is hydrophilic, too hydrophilic to pass through biological membranes. So we get the some middle ground but around **~5 is very good. If the logP is ~3 or 4 or so, it's also great**. We talk about logP of drugs, specifically your local anesthetics, because logP is also critical feature there for the action.

Passage Across Biological Membranes



Passage **increases** when:
- Molecular size ↓
- Degree of ionization ↓ ⇒ Lipid solubility ↑
- Concentration gradient ↑
- *Tissue inflammation (paracellular spaces widen)*

A drug will become
less ionized (**more lipid-soluble**)
at a **pH similar to its own pH**

Lipid-soluble (unionized) Drug

Non-Lipid-soluble (ionized) Drug

Here is my cartoon of the membrane and two processes playing role passive diffusion. For drugs that are ironized, not lipid soluble, the body has to lose filtration. Again, the passive diffusion is absolutely the number one way that the drugs get to the body will get absorbed.

Passage increases when the molecular size of the drug decreases. When the **ionization decrease, its solubility increases**. This will help the passage concentration gradient driving force for the drug. Higher concentration of the drug you apply, you expect more the drug to get see the cell because of the concentration difference on both sides of the membrane.

One additional feature that is beyond the physical chemical properties of the drug and the membrane is the tissue inflammation. We will talk about this when we talk about meningitis, the role of inflammation of meningitis in getting drugs to the central nervous system, what blood brain barrier is. We will briefly talk next session. Blood brain barrier prevents the drugs getting to the CNS, but during inflammation, the paracellular spaces hidden. The drugs that normally don't get to the brain can get there. There's also plays a role in your treatment although tissue inflammation for action of local anesthetics has a little different layer there of features. Because this is about pH, that tissue inflammation associated with decreased pH. Decreased pH also prevents some local anesthetics from getting to the site of action. So we need to use specific local anesthetic with specific pKa. We'll discuss all those relationships later.

Again the most important role for you to remember. It's highlight in gold: **a drug will become less ionized, more lipid soluble, more membrane permeable at a pH similar to its own pH**, so related to the pKa.

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NEXT SLIDE

After the first solid dose of physical chemistry and basic principles that governed the movement of drugs, let's test what we just discussed and thinking about specific drugs and biological processes…

Here going back to the effects of pH, first the distinction of acidic drugs and basic drugs. When we are dealing with the **acidic drugs such as aspirin, they are largely unionized at gastric pH because gastric pH is acidic**. Acidic drugs when they are close to their own pH, as we've said, the drug is largely unionized. Unionized is good for membrane permeability, **so acidic drugs are absorbed from the stomach**. The truth is that most absorption actually happens from the intestine because of the large surface area of the intestine much greater than the stomach. But, still a significant proportion of acidic drugs get absorbed around the stomach because they're unionized at low pH.

On the other hand, **basic drugs such as codeine** and other drugs from your list of common use drugs, this would be **ionized because it's bases would be ionized in the stomach**. So it doesn't get absorbed from the stomach, **only from the intestine.**

Now let's look at cartoon to explain the concept of ion trapping. The phenomenon of iron trapping is important for you to understand. You have the yellow portion of this box in the stomach. Yelow is like your corresponding to their low pH would be more yellow. This pH in the stomach is between 1 and 3.
Now you have the **anesthetic drug, largely unionized.** This is why I put a big H in large font. It shows you that large great concentration of the drug is unionized. It is in equilibrium with the ionized form, but there is small proportion is ionized. **When the drug moves from the stomach to the mucosal cell, mucosal cell in the gastric mucosal at the pH is much higher than in the stomach**. It goes from 3 to 7, so it's huge change in pH. The pH is much higher than the pH or pKa of this acidic drug. Now the **drug becomes ionized** because the pH is farther from its own pH. Now the drug becomes ionized. When it's ionized, it **cannot move through the membranes.** The drug becomes trapped in the cell. It's thought that excess of the process of moving out of the mucosal cell is much slower, prevents an easy escape.

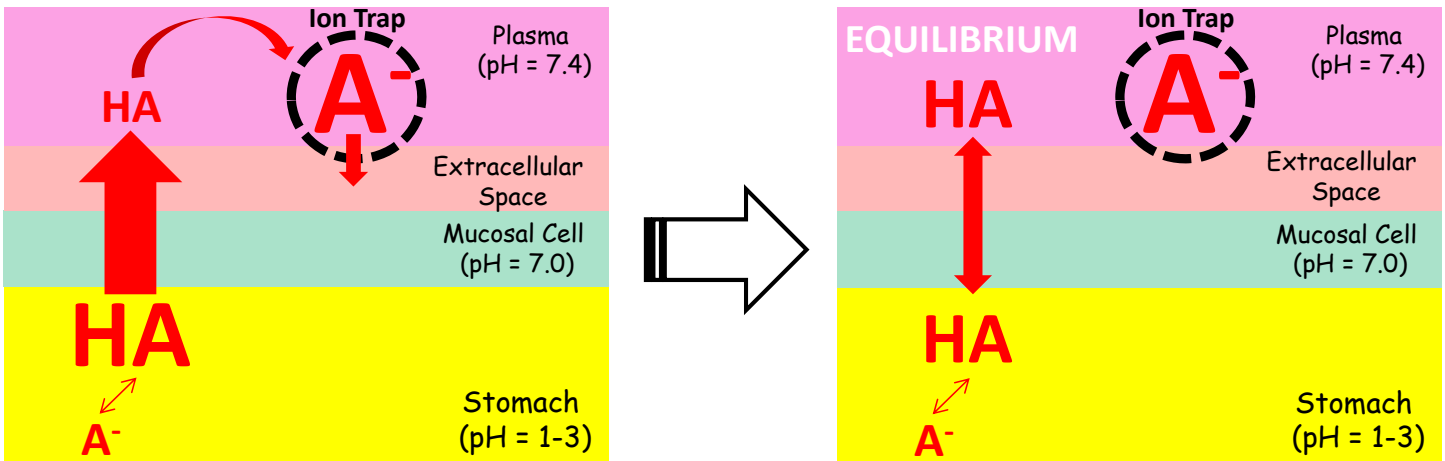
This actually phenomenon is thought to contribute to the gastric mucosal damage caused by aspirin. Aspirin is acidic, so if it stays in the mucosal cell longer than an average drug that's less acidic. Basically, it can cause mucosal damage. It's one of the many thoughts on the mechanisms of drugs damaging the gastric mucosa. So, obviously the role of prostaglandin, blocking there and so on. This is one of the concepts and is thought that could contribute, but in general, the concept of ion trapping is important for you to understand.

- In plasma, you also have the situations that the drug is at much higher pH than its own. It becomes ionized. When it's ionized, it cannot move out of the membrane.
- One more is **toxicology application** of this effect of pH because the acidic drugs are ionized and higher pH.
    - With more alkalized solution (if you alkalize~meaning increase pH of urine), the acidic drug will not be absorbed back in the kidney tubules, so will be faster excreted. When you have the acidic drug, if you want to get rid of it faster, you want to increase the pH of the urine, so alkalize it.
    - If you have basic drugs that have high pH, you want them to be now in more acidified urine, so they will be again more ionized, and more easily excreted because less easily absorbed through the membranes.

Passage Across Biological Membranes

Effects of pH

- **Acidic drugs** (e.g., Aspirin) are largely unionized at gastric pH ⇒ **absorbed from the stomach**
- **Basic drugs** (e.g., Codeine) are largely ionized in the stomach ⇒ **absorbed from the intestine**



- Unionized acidic drugs cross the gastric mucosal membrane to encounter a higher pH ⇒ revert to the ionized form, which prevents their easy escape (the **Ion Trapping** phenomenon). *This phenomenon may contribute to gastric mucosal cell damage caused by Aspirin.*

- Acidic drugs are ionized more in alkaline urine ⇒ do not back diffuse in the kidney tubules ⇒ are excreted faster. Basic drugs are excreted faster if urine is acidified. Toxicology applications.

Absorption

Absorption is the transfer of drug from its site of administration into the circulation.

Factors Affecting Absorption – All Routes of Administration

(except INTRAVENOUS - 100% availability)

- Passage across membranes

- Influence of pH - Ionization status: ↓ ionization ⇒ ↑ lipid solubility ⇒ ↑ absorption

- Influence of concentration: ↑ drug concentration ⇒ ↑ concentration gradient ⇒ ↑ absorption

- Aqueous solubility (rate of dissolution of drugs given in solid form)

- For poorly water-soluble drugs (e.g., Aspirin), dissolution controls absorption

- Area of absorbing surface

- ↑ area ⇒ ↑ rate of absorption

- Vascularity of the absorbing surface

- ↑ blood flow ⇒ ↑ drug removal from the site ⇒ ↑ concentration gradient ⇒ ↑ absorption

- Diffusion of drugs across capillaries is dependent on the rate of blood flow through them rather than on lipid solubility of the drug or pH of the medium.

- Other factors, unique to individual routes of drug administration:

Oral Ingestion, Parenteral Injection (Intravenous, Intramuscular & Subcutaneous)

Absorption is the transfer of drug from the site of administration into the circulation. Absorption is affected by many factors. It's almost never 100% of the drug gets absorbed, except for one route. All routes of administration have to deal with passage through the membranes. There's one exception, which is intravenous route, where you inject the drug directly to the circulation. By definition, the absorption is a transfer to the circulation, you don't have the process of transfer, the drug is already in the circulation for the intravenous route. All other routes are affected by factors that can decrease the absorption.

First group of factors are related to specifically passage across the membranes: the influence of **pH** and influence of **concentration**.

- **If you decrease ionization, you increase lipid solubility, increase drug absorption.**
- **higher the concentration of the drug, greater the concentration gradient, so greater absorption.**

Besides that, we are talking about the drug that's in solid form. It first needs to go to solution. If the drug is poorly water **soluble**, then that dissolution getting to solution controls absorption. The rate at which the drug gets to the liquid form is the limiting factor that limits absorption.

Another one already mentioned too, when I talked about the aspirin. Absorption from the stomach versus the intestine the area. The **surface area that absorbs the drug matters**. Greater the area, greater rate of absorption. It's pretty straightforward. When I was talking about aspirin, we say a significant proportion is absorbed from the stomach, but still a lot of it is absorbed from the intestine because of the significantly larger surface area.

One more general factor that applies to all routes of administration, again, all except intravenous, would be **vascularity**. Highly vascularized surface will have the greater rate of absorption. It depends on the blood flow. Here is critical role of the heart because when you have the greater blood flow, the drug is removed on the side of the capillary much faster. The concentration gradient is greater because if it's quickly removed from the place where you can subscribe to the circulation, the concentration of the drug drops. Then, the gradient across the membrane increases. This increases absorption and the rate as far as the capillaries, the diffusion is dependent on the rate of blood flow. As I mentioned already, congestive heart failure when the rate of the blood flow decreases because it would be dependent on the pressure difference. When the rate decreases, the absorption decreases. Those are the general factors that affect absorption.

Now we will briefly talk about other factors that are actually specific to individual routes of administration oral ingestion and some parenteral injections.

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NEXT SLIDE

First factors that affect absorption of drugs after oral administration.

- One important factor is food. In general, presence of food delays gastric emptying. so retards absorption. Also, some specific influences of specific components of food that can affect absorption. Tetracyclines, for example, a group of antibiotics, absorption would be inhibited by calcium from milk. Prescribed tetracycline to your patients, you advise them not to take them with some dairy product.
- Another one is degradation by acid and digestive enzymes in general. This can be prevented by preparing enteric coated tablets that they don't get dissolved until they get to their intestine.
- One group of factors are actually over medication that the patient is taking
    - Antibiotics, for example, will wipe out the natural microflora. This will have an effect on what's known as internal hepatic cycling of drugs. Some drugs are basically taken by bio and excreted to their intestine, and then taken back. They are cycling through the system. We'll talk about them therapeutic cycling, but here the issue is that antibiotics can destroy the GI flora that actually enables the reabsorption of the drug from the GI tract, so influence of other medication.
    - Another example example of the influence of medication is when the patient is treated with anticholinergic drugs or opioids that decrease gut wall motility. This would actually compromise the absorption.
    - Another example is not just drugs, but elderly patients also have decreased GI track motility.
    - Another drug-inducing affecting the absorption is the mucosal damage caused by some medication, methotrexate, for example. It's hemo therapeutic. This also would alter the absorption.

Absorption

Factors Affecting Absorption - Oral Ingestion

- *Food:* Presence of food delays gastric emptying and dilutes the drug ⇒ retards absorption; Certain drugs form poorly absorbed complexes (e.g., Tetracycline with Calcium from milk);

- *Degradation by acid and digestive enzymes:* Certain drugs are degraded in the GI tract (e.g. Penicillin G by acid)
  ⇒ enteric coated tablets (acid-resistant coating) and sustained release preparations (also minimize irritation).

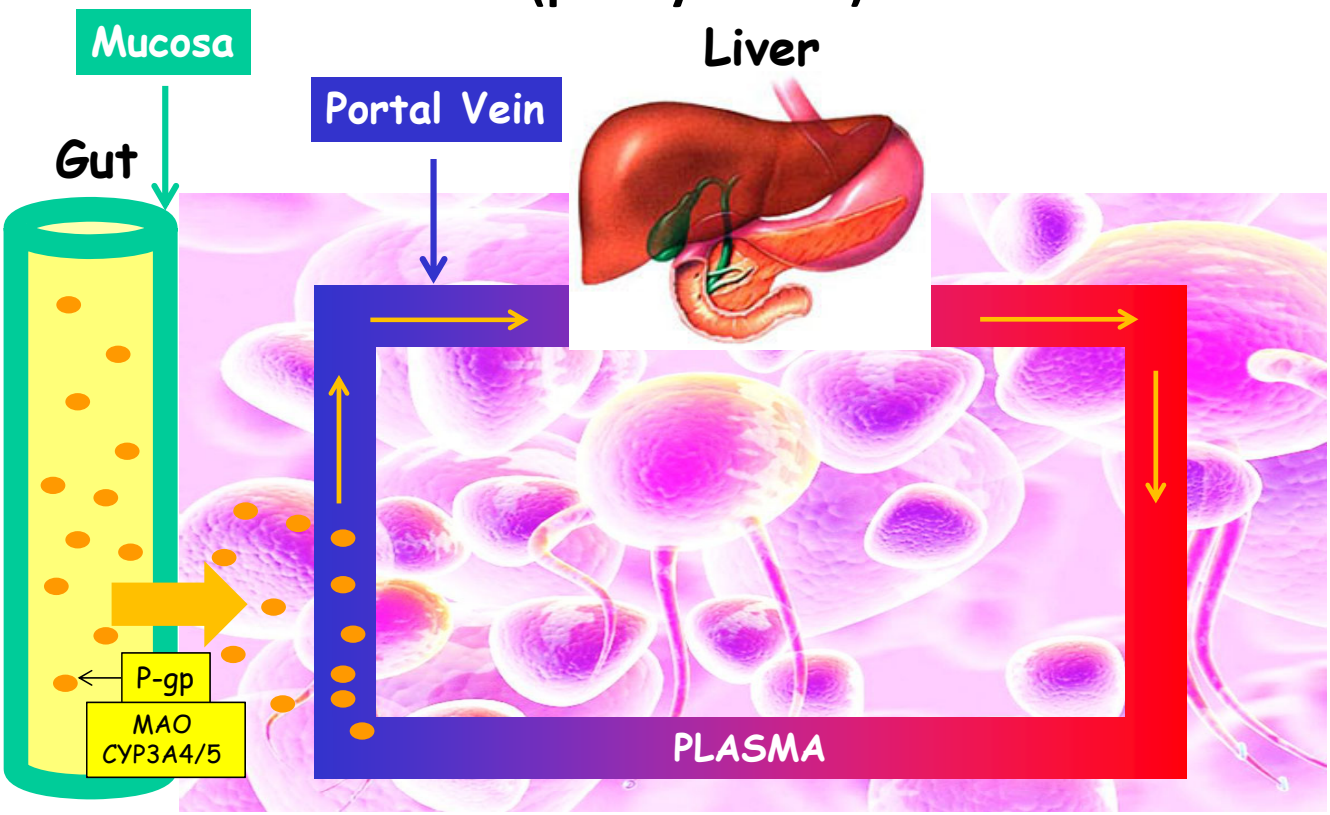
- *Other factors:*
  - Antibiotics ⇒ altered GI flora ⇒ effect on enterohepatic cycling of Oral Contraceptives

  - Decreased gut wall motility (e.g., Tx w/ Anticholinergics, Opioids) ⇒ compromised absorption

  - Drug-induced mucosal damage (e.g., Neomycin, Methotrexate) ⇒ altered absorption

Absorption

First-Pass (pre-systemic) Metabolism



A **first pass** of high drug concentration through the liver can significantly reduce the quantity of drug reaching the systemic circulation (e.g., Opioid Analgesics, Antibiotics).

Besides all the factors that affect orally administered drug absorption that I just summarized, I wanted to talk with you now about the very important phenomenon of first pass or pre-systemic metabolism. We will be coming back to this many times for many drug groups because it's really a factor that affects significantly drug availability so what's the first pass metabolism.

So here we have a gut. We're talking about the absorbed drugs already administered, absorbed from the GI tract. There is mucosa there. Here is the connection with the rest of the body, with the circulation, and the liver. Here we have the drug that gets to the gut and needs to pass through the mucosa. It passes through the mucosa to the interstitial fluid. First barrier are the enzymes already present in the GI tract mucosa. We got protein, MAO, monamine oxidase, and some cytochrome P450 enzymes, specific 3A4, 3A5. We'll talk about those enzymes soon, but there are there ready to chew on the drug. This is the first step of the pre-systemic metabolism, meaning metabolism that happens to the drug before the drug gets to the systemic circulation. This is actually a minor component that first pass metabolism.

Next, the drug is absorbed to the first system is the portal system from the GI tract through the portal vein. The drug goes through the liver before it gets to the systemic circulation. The liver keeps tabs like it's checking what's coming through to the body. Unfortunately, the drug gets metabolized already in the liver before it has a chance to get to the circulation and get to the receptor where it's supposed to act.

So the **first pass through the liver can significantly reduce the quantity of drug actually reaching the systemic circulation. This includes opioid, analgesics, antibiotics, and other drug groups that are important for you as well**.

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NEXT SLIDE

So now what are the characteristic features of drugs that are known that have high first pass metabolism meaning that are susceptible to this metabolism by either the enzymes in the gut or in the liver.

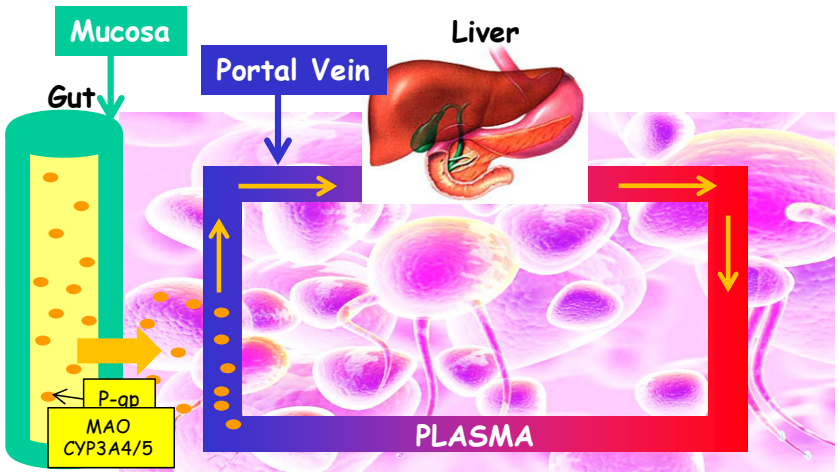
- When you have the **patient who has severe liver disease,** for example, the first pass mechanism will be less significant because the liver is not able to metabolize the drug as effectively. Then, you expect in such patients, more drug will be available, more drug will get to the systemic circulation.

- Same, if the **patient is simultaneously taking another medication** that also is metabolized by the liver, because we have the competition for the enzymes, there's less enzyme available to metabolize the specific drug, because it's used to metabolize another drug. Again, the oral bioavailability of the drug will be increased. The level of the amount of drug that gets to the systemic circulation also increase.

- Finally, we'll have specific session on pharmacogenetics, but I just wanted to mention already that **patients differ in their levels of enzymes and activity of hepatic enzymes**. This is genetically determined if the patient has a low rate of hepatic metabolism. This will also decrease the first pass metabolism, increase the availability of the drug. Those drugs that are characterized by this high first class metabolism are calculated to account for this first pass. So oral dose of such drugs is significantly higher than sublingual or parenteral dose. Because smaller fraction of the drug gets to the systemic circulation in the intact form, the concentration of the drug is increased to account for first pass metabolism. If the patient suffers from liver condition or has genetically determined lower rate than the normal concentration of the drug, that's recommended by the manufacturer may be too high.

Absorption

Characteristics of Drugs with High First-Pass Metabolism



1. Oral bioavailability of such drugs is **increased** in patients:

   A) with severe liver disease;

   B) concurrently taking another drug that competes in first-pass metabolism;

   C) with a low rate of hepatic metabolism (genetically-determined)

2. Oral dose of such drugs is substantially higher than sublingual or parenteral dose.

Absorption

Factors Affecting Absorption – Parenteral Injections

Intramuscular (i.m.) & Subcutaneous (s.c.): Drugs deposited directly in the vicinity of the capillaries ⇒ all pass readily. Absorption from s.c. site is slower than i.m. site.
Heat, Massage & Muscular Exercise ⇒ vasodilation ⇒ ↑ blood flow ⇒↑ absorption
Vasoconstriction ⇒↓blood flow ⇒↓absorption (e.g. adrenaline with local anesthetics, ice packs, tourniquets in an emergency)

Intravenous (i.v.): Drugs injected/infused directly into the bloodstream ⇒ bypassing absorption. Most i.v. drugs should be administered over a period of 1 minute (blood circulation time through the body) to avoid concentration spikes and allow discontinuance in case of untoward effects.

- **Parenteral Injections** are given when:

1) a rapid onset of effect is necessary (emergencies),
2) oral ingestion is precluded (patient's condition), or
3) oral BIOAVAILABILITY is low.

And now briefly about factors that affect absorption from parenteral and injections.

- First, as far as **intramuscular** and **subcutaneous**, muscles in general have great blood supply, a lot of vasculature there, highly vascularized. When you inject to the muscle, it's a great chance that is very close to the capillary, to the blood vessel there. So it's readily absorbed. The absorption is slower from the subcutaneous side because the tissue subcutaneous tissue doesn't have a lot of vasculature. That absorption is slower.
    - Some examples as far as how the blood flow affects the absorption: heat, massage, and muscular exercise. They all cause **vasodilation** in the muscles, increase the blood flow, increase absorption. This is why when you have the intramuscular injection, that is advised to massage the area, sometimes increase the temperature.
    - On the other hand, the **vasoconstriction** decreases the blood flow, decreases the absorption. This is actually what's used in your practice also you add adrenaline to local anesthetics. This is not intramuscular, but similar concept. By adding adrenaline, you constrict blood vessels, so you prevent the absorption. This is what you actually want.

- Intravenous is 100% availability because you bypass the absorption start. Most drugs should be administered as far as intravenous over a longer period of time, not as quick bolus, but over one minute. The entire blood is exchanged in one minute. There basically cardiac output of individual equals the entire blood volume. The heart processing the entire blood volume in one minute. By **spreading the intravenous injection over longer time, you avoid the concentration spikes. If something happens to the patient within the first few seconds when you apply, you can stop the administratio**n.

So what are the indications for parenteral injections in general:
1. First, when you want the very quick action of the drug, this would be mostly in the emergencies.
2. Sometimes you cannot apply the drug orally for some patient because of the patient condition. We will also talk about more specific analgesics that you can use either. If you cannot apply, if the patient cannot take the drug orally.
3. Finally if the drug has very low oral bioavailability. For all the reasons, we just presented most frequently is the first pass metabolism. In this case you want to avoid the oral application. You would choose the parenteral injection.

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NEXT SLIDE

Bioavailability definition. So you administer certain dose of the drug, whatever portion of the drug reaches the systemic circulation in the unchanged form is the portion that we care about. We consider this as drug being available biologically for the body.

Blue curve: the area under the curve for comparing the drug plasma concentration, how it changes with time after absorption. We'll talk about this in great detail when we get to the later portion of the pharmacokinetics in the last hour. Now very briefly, the time course of changes in plasma concentration for drug applied orally, you see the Cmax will be the maximum concentration reached after oral dose. The concentration increases relatively slowly and then decreases. The decrease is due to metabolism and excretion of the drug. The Tmax will be the time it takes to reach the Cmax. The area under the curve is the exposure of the body to the drug. This is for oral administration.

Red curve is what the time course of the plasma concentration looks like when you apply the drug IV, intravenously. You have much faster rise in the peak concentration. This will be the area under the curve for the IV.

Oral bioavailability is determined from those exposures. You compare the oral exposure to the intravenous exposure. It's basically the area under the curve. This is how it's calculated: area under the curve for oral over the area under the curve for IV. Then, you normalize it for the dose you applied for the patient because the oral dose is usually greater, so you need to basically normalize it. You get the fraction. This would be the bioavailability.

- Again, intravenous is 100% bioavailability.
- For intramuscular and subcutaneous, it is close to 100%, but still not exactly because there is some loss at the injection site.
- Binding of the drug to the tissues that for oral ingestion is definitely less than 100%. For most of the drugs, this would be incomplete absorption. First, the drug that's in solid form needs to be cut just needs to get disintegrated and get to the solution. Low water solubility will compromise absorption. And also, first pass metabolism in both intestine and the liver.

Absorption

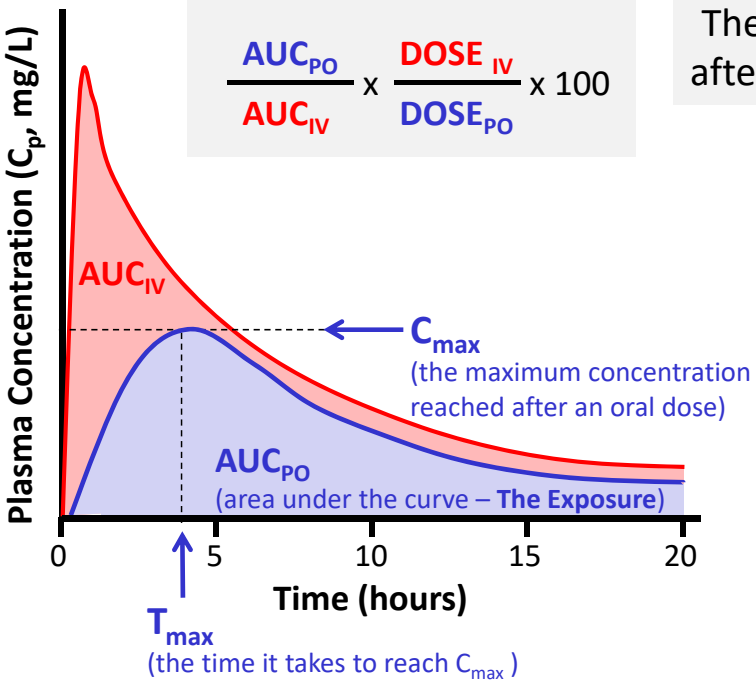
Bioavailability

Bioavailability (F) is the fraction of the administered dose of a drug that reaches the **systemic circulation** in the **unchanged** form.

Oral Bioavailability (%, F)

$$\frac{AUC_{PO}}{AUC_{IV}} \times \frac{DOSE_{IV}}{DOSE_{PO}} \times 100$$

Oral Bioavailability is determined from The Exposure (Area Under the Curve, AUC) after **oral (PO)** *versus* **intravenous (IV)** dose.



Intravenous ⇒ 100% Bioavailability

Intramuscular & Subcutaneous:
< 100% *due to loss at the injection site caused by drug binding, etc.*

Oral Ingestion: < 100%
due to:
1) incomplete absorption
(poor disintegration, low water solubility)
2) first pass metabolism
in intestinal wall/liver

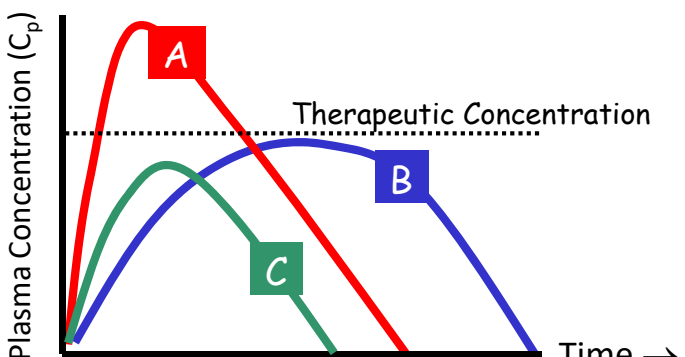
Absorption

Bioequivalence:

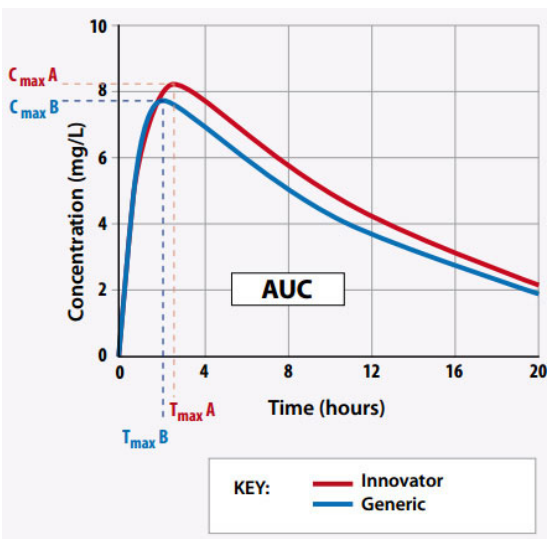
The absence of a significant difference in the **rate** and **extent**
to which the active ingredient (…) becomes available (…) when administered
at the **same molar dose** under **similar conditions** in an appropriately designed study.

U.S. Food & Drug Administration, Orange Book Preface, February 2020

*Formulations from different batches/different manufacturers may have the same amount of the drug (⇒ **chemically equivalent**), but yield different blood levels (⇒ **not biologically equivalent**).*
***IMPORTANT** for drugs with: 1) low safety margin, or*
2) the need for precise dosage control (e.g. Oral Hypoglycemics, Oral Anticoagulants)



Preparations **A**, **B**, and **C** contain the same amount of a drug, but are not bioequivalent. **A**, **B**–the same amount absorbed (exposure; AUC), but slower absorption of B ⇒ B may not produce therapeutic effect; **C**- absorbed to a lesser extent (lower exposure; smaller AUC) ⇒ lower bioavailability.



First the definition from the FDA, bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient of the drug becomes available when administered at the same molar dose under similar conditions. The rate and extent of availability of the drug needs to be similar, not significantly different when you administer it, at the same dose, under similar conditions. The last part definition is in an appropriately designed study so this definition refers to studies of drugs because the FDA is responsible for approving drugs on the US market.

So when the new drug is developed it needs to pass the test of bio equivalence. This is why we actually don't need to worry about this once the drug is approved on the market but it's important for you to be and aware of the fact.

Same chemical formulation coming from different batches of the same manufacturer (let alone different manufacturers), even though they had the same chemically amount of the drug, they seem to be identical. When applied to the patient can give different levels of the drug in the blood, so they are not biologically equivalent. This is particularly important when you are dealing with drugs with low safety margins. We're talking about the therapeutic window between the therapeutic dose and the toxic dose, or therapeutic index of the drugs. With low therapeutic index, when the toxic dose is low, meaning similar to the therapeutic dose, the drugs that need to be precisely controlled. Like oral hypoglycemics, because if the patient all of a sudden get more of a drug, because the drug is better absorbed, than they may end up with hypoglycemia and dangerous condition. Oral Anticoagulants also, blood has is the ion particles really high, meaning the time is really long. It's affected negatively calculation but anticoagulant patients receive to decrease the broad calculation, but only to a certain point. We'll talk about anticoagulant. Here is just example of drugs that there doesn't need to be precisely controlled.

So here I will show you an example time course of plasma concentration for three drugs. You have A, B, and C. You see the area under the curve seems very similar for A and B, but significantly lower for C. It means that that availability of drugs C is significantly lower. One more point is where the therapeutic minimum therapeutic concentration is.

Here we have the therapeutic concentration.

- Drug A seems to be fine. It's going to help the patient. Even though all drugs were applied at the same dose, A was absorbed very quickly and reached the peak that is above the minimum therapeutic concentration.
- Drug B was absorbed much more slowly. Being absorbed slowly, it didn't really reach the therapeutic concentration, may not be actually effective.
- Drug C has significantly smaller area under the curve. This tells you that the lower exposure, lower bioavailability as we talked on the previous slide. So the drug C has lower bioavailability, less of it got absorbed.

Drug B was absorbed much more slowly than drug A, but also didn't really reach therapeutic concentration. Those drugs are not bioequivalent.

Here is an example of curves submitted to actually FDA for approval when you have in red the innovator meaning the first drug in the group. Some other company, or even sometimes the same manufacturer applies again for approval of a different formulation of the same theoretically, the same drug. You can see that the area under the curve is very similar. This drug probably would get approved, but it needs to show curves like this in order to be approved as **bioequivalent**.