-sheet no.4

-pharmacology

SO we previously had discussed about the drug discovery and studied its possible side effects ,assisted its kinetics and safety and now the drug should be manufactured in a suitable dosage form in order to be given to the patient!!

**THE ADMINISTARTION OF A DRUG** :is giving the drug to the patient ,either orally ,locally (topically ),rectally …etc !

-The drug has to be absorbed to the systemic circulation in order to be further distributed and transmitted to its site of action (where it is supposed to do its job and react )!for example if a drug was meant to affect the central nervous system ,was given orally ..then the drug should be 1st absorbed from the intestines toward the systemic circulation ..where it will further distribute in order to reach its site of action (the CNS) and play it’s role on it !

**#major divisions of pharmacology :**

1. **Pharmacokinetic division :**the process of absorption ,distribution, metabolism and excretion of a drug !
2. **Pharmacodynamics**:it means or study the mechanism by which **the drug do its action (how the drug produces its effect ) or in other words the mechanism of action of the drug on the body !**
3. **Pharmacotherapy or pharmacotherapeutics:** explains what the drug does to the body therapy (cure,control, diagnosis ,treat …etc) ,it also includes the side effects and the toxicity of a drug !
4. **Pharmacogentics : it discusses** the individual variation in responding to drug (how individuals may respond differently among the same drug ), we can realize that there is differences andvariations among individuals in reacting to a specific drug(the amount of dosage should be taken,if a specific dosage do it’s pharmacological role or not for example) due to the differences in the absorption of a specific drug … for example if we gave two males having the exact( age weight ….)a drug with a 500 mg dosage ,one has absorbed 400 mg for example and the other has only absorbed 200mg ..so you can realize that there is variation and differences between different individuals who have been given a same in responding to that drug based on their different absorption rates!

Another example to strengthen your understanding is that one male would say that 100 mg dosage of a drug is enough and he got better ,where as another would say that the same amount of the dosage of that drug isn’t enough and has made no changes and that he needed more …all these previous cases are due to the differences in absorption between different individuals .. and this what pharmacogentics is all about !

#now we will be discussing pharmacokinetic in more details :

-pharmacokinetics as we said previously IT ANSWERS THE QUESTION (WHAT THE BODY DOES TO THE DRUG ??) and the best definition of that term is a mathematical representation of the processes (absorption ,execretion,metabolism and distribution )

**IMPORTANT NOTEEE : BE AWARE OF THE DIFFERENCES IN MEANING BETWEEN :**

**Pharmacokinetics: what the body does to a drug where as pharamacodynamics includes the effect of the drug on the body !!**

Now let’s start with absorption :

What is the drug absorption ??

Simply it’s the passage of the drug from the site of administration to the systemic circulation, in order to distribute later and reach it’s site of action !

For example : a drug that is taken orally will 1st move to the GI TRACT and in order to reach its site of action it has to be absorbed to the systemic circulation first !

**###THE BEHAVIOR OF DRUG IN THE PLASMA:**

There is two things that you have to be familiar with regarding the behavior of drugs in plasma :

#1: the bioavailability >> it has to be determined before the approval of the drug !

***But what bioavailability of the drug means???***

-it’s simply the fraction of the given dose that gets into **the circulation**!!

For further understanding suppose **that 100 mg** of a drug is given orally for a patient and the drug’s bioavailability **is 50%,**how much of the drug will be absorbed to the systemic circulation???it’s simply **50** **mg** , suppose that the bioavailability **is 90%** how much will get into the systemic circulation ?**90 mg** !!

**VERY IMPORTAAANT NOTE :**

-THE ONLY DRUG THAT HAS A BIOAVAILABILITY OF 100% IS THE DRUG THAT IS TAKEN INTRAVENOUSELY (IV DRUG ) ,because **it’s directly** given and injected to the blood circulation with no loss (100% absorption to the blood flow ) so always keep in mind that if a drug of 100 mg is given to a patient through IV administration , the amount of it that will be in the systemic circulation is” 100 MG” and thus the bioavailability of other drugs that is given non intravenously wont exceed the 99.9% even if these drugs have an excellent bioavailability !!!!

SO AS A CONCLUSION : the only drug that has a bioavailability of 100% is that which is taken through IV injections ,and keep in mind that is for a drug that is orally administrated ,its bioavailaibility can’t exceed the 99.9%(thus it can’t be 100%) no matter what was its excellence degree !!!

***Now for a drug having a bioavailability of only 5% ,what will be the amount of drug absorbed to the systemic circulation ??***

-For example if we gave a patient a 100 mg dosage of a drug having only 5% bioavailability only 5 mgs of the 1oo will be absorbed to the systemic circulation ,but do you think this amount of drug is enough to do it’s pharmacological role ?or in other words is this drug with this low bioavailability effective enough?

**The answer is NO !!**

-**GENERALLY AND IN MOST CASES A DRUG** WITH A bioavailability of only 5% isn’t effective orally!But in some cases these 5 Mgs out of the 100 is all what we need from a drug to do its job!

>>To understand more, imagine that we took a 100 mg tablet(with 5%bioavailability ) for healing problems in the CNS for example ,only 5 mgs out of the 100 will be existing in the systemic circulation then this tiny amount has to pass through other membranes in order to distribute and reaches its site of action (the CNS in this example )and in general 5 mgs are NOT good enough to produce a pharmacological action on its site of action !!

**So as a conclusion** : in general and in most cases drugs with low bioavailability will be ineffective orally !! (I think we need to increase the dosage of such drugs to accomplish their purpose, or change the way of the administration ) !

#2 : protein binding :

Once the drug enters the circulation it will **not** exist in a free form only,but it will also bind to the plasma proteins (albumin or globulin )which is something very important pharmacologically !!

**NOW LET’S** see what’s the functions or the consequences of the protein binding ???

1. It provides a reservoir(مخزن) for the drug
2. It represents a mean by which the drug could travel in the circulation ,as if it’s a carrier for the drug enables it to move through the blood and circulation !!
3. The third major point regarding the protein binding and its consequences is that it is a major site for drug interaction.

**\*Note** : A drug is made in it’s active form”the free form”(more specific drugs that are taken by oral administration such as tablets for example ) !

>>>what will actually happen after a free form tablet orally adminstarted enters our body ,and moves through our intestines reaching the systemic circulation ??

-Simply once the tablet(and drugs generally ) reaches the circulation it will exist in 2 forms :

* The free form (the active one ) is the form that crosses membranes >>thus is the one that reaches the site of action >>and produces a pharmacological action and do its role !
* The bound form :which is attached to the plasma proteins in the blood(systemic circulation)

For further understanding imagine that you are taking a tablet orally it will move through the body >>entering the blood>>attatchment of the drug to the plasma proteins >>and since the active form of the drug that is able to affect certain system is the free form ,a part of the drug should now dissociate from the protein in order to be able to cross membranes >>targeting the site of action >>then do it’s job >>it will then be excreted out of the body>>then another part of the drug will dissociate >>crossing different membranes and reaching it’s site of action >>do its action on the body >>then it will be excreted and eliminated out of the body and sooo on !

* **Important note that should be kept in mind**: the free form of the drug exist in a state of equilibrium between different compartments in the body including the site of action and it also moves freely !
* Now what rules the dissociation of the bound form of the drug thus changing into the free form (active one) ; is the concentration of the drug in different compartments!
* So when a drug concentration decreases (let’s assume that this low concentration is at the site of action)the equilibrium of the free form of the drug between different compartments should be maintained,so there will be sort of dissociation between the drug and the plasma protein ,then the free form produced will be then targeting the site of action and elaminated after doing its action ,and this will lead to drop in the plasma concentration of the freeform which will lead for more dissociation to occur for the maintenance of the equilibrium and these procedures(moving of the free form ,do it’s action and excretion ) will keep steady as long as the drug is available in its free form and easily dissociated from the plasma proteins ,and will continue till the amount of drug is all used up and consumed .
* **Important note** : always remember that the inactive form of the drug is the bound ,and as long as the drug is binding proteins it can’t do its action !
* The duration of action(DOA) of the drug depends on the extent of binding **;the stronger the extent of binding between the drug and the plasma proteins the more the time needed for the drug to do it’s action** (and this is mainly because almost the majority of a drug that have these strong binding properties will be in its inactive form ,thus the drug will remain more in plasma till part of it can dissociate and function on the site of action )
* When two drugs belong to the same category for example beta blockers, haveshown a differences in the duration of action of the drug on the body >>this may be due to the differences in the strength of binding between the drug and the protein in plasma!!

P.s :when we compare between different drugs in pharmacology each of these drugs should be listed under the same category ,for example (beta blockers include almost 40-60 drug)

* **So as a conclusion** the higher the extent of binding the longer the time needed for the drug to do it’s action...And the weaker the extent of binding the easier and faster the dissociation of the drug will be thus the shorter the time needed for the drug to function and do it’s role !!And the extent of binding has nothing to do on the efficiency of the drug (only affecting the duration )
* **For a pharmacological studies ,they care more about the concentration of the free form of the drug in the plasma rather than asking about the total concentration or level!**
* When pharmacologists made their kinetic studies on animals and humans they took the protein binding of the drug as an important major concept to be kept under consideration including information about the amount of the free form of the drug that is released each time, and for how long this binding will remain for a specific drug in comparison to another drug.
* So for each drug sort of calculations are required including the amount of the free form of the drug that targets its site of action and distributes out of the blood within a specific particular time , and according to many other things; the duration that is needed for each drug to do it’s action is determined .

#**PAY ATTENTION** THAT WHEN FDA MADE THEIR CALCULATIONS ON THE AMOUNT OF THE FREE FORM THAT SHOULD TARGET THE SITE OF ACTION EACH SPECIFIC PARTICULAR TIME IN ORDER TO MATCH THE DESIRED **Therapeutic** LEVEL OF THE DRUG ,, THEY MADE THEM AS FOR A DRUG GIVEN ALONE (single drug with no drug-drug interaction) ! keep that in your mind !

\*\*\*so all the previous calculations that were applied on a patient that is taking a single drug at specific time , but will they stay the same and not affecting the desired aim of treatment when another drug is administrated during the same time ?

The answer is absolutely NOO !

>>further explanation : so when giving a drug ,calculations have already taken including a single drug only (as a drug given alone ) and they include the extent of binding of that drug to the proteins of the plasma ,and the concentration of the free form in order to reach the therapeutic level at a specific time ,and according to these information that FDA has determined, the drug should be efficient enough and do its job well ,but when another drug enters the body these calculations including the 1st previous drug will change, interfering the final desired result of the drug !

>>imagine that we took two drugs A AND B , A is administered orally just before B , when the drug B is taken orally for example it will affect the extent of binding of the drug A to the plasma protein ,either by increasing the extent of binding of the drug A to the protein ;leading to a decreasing level of the free form of the drug A in the blood circulation >>less free form distributed to the site of action >>sub therapeutic level is reached so the level of the free form is not enough for the drug to apply its action on the site of action and reaching the desired effect won’t be accomplished (the drug A became not efficient regarding to the same dosage that were given without the interfere of another drug ‘DRUG B’)!Or drug B could weaken the extent of binding between the drug A and plasma proteins ;leading to elevation in the concentration of the free form of drug A in the plasma >>the concentration of the free form that is distributed to the site of action is beyond what was calculated previously in order to reach” the therapeutic level” >>leading to a possibility of toxicity (because of the elevation in the free form ) !

**SO WHAT SHOULD BE DONE WHEN WE KNOW THAT A PATIENT SHOULD TAKE TWO DRUGS SHOWING THIS Sort OF INTERACTION IN BETWEEN THEM ??**

-Simply each should be given separately at different times, **or** by choosing another drug that won’t affect the extent of binding to proteins !

**DRUG INTERACTION** IS a major and very common phenomenon among drugs and there is no way by which we can avoid it but we try our best and as much as possible to avoid it ,it’s something easy to handle in patients having a range less than 5-10 tablets per day ,but for a patient suffering from 4 major diseases (diabetes ,hypertension ,hyperglycemia…etc) for example and they could also be old and take multi vitamins and other drugs … here in this case the quantity of tablets administrated per day could be in a range of 10-15 per day ..and in this case it’s very rare and hard to avoid all drug interactions that may occur !

So drug-drug interaction isn’t something easy to control and considered as a problem for a patient taking a range of 5-10 tablets per a day ,but as we said previously we can use another drug listed under the same category (for example if we are taking a beta blocker drug ,we choose another beta blocker)or play with the time !!

**#A final very important point** regarding the protein binding is that when we say that 90% of a drug is bound to plasma proteins , that means that 90% of the amount that ***ENTERED THE BLOOD CIRCULATION*** is bound to plasma proteins ,***NOT 90% OF THE WHOLE DOSAGE OF THE DRUG THAT WAS ADMINESTRATED !!!!***

**Example :***100 mg dosage of a drug with 80% bioavailability was administrated orally ,90%of the drug was bound to plasma proteins (the extent of binding is 90%) ,calculate the amount of drug that is bound to plasma proteins in mgs?*

***The answer :***SINCE the bioavailability of the drug is 80% then 80 mg will enter the systemic circulation ,and 90% out of the 80 mg that entered the blood will bound to the plasma proteins :

***80 mg \* (90/100) = 72 mg >> this is the amount of drug that will bind to the plasma proteins and 8mg will be remaining in the free form !!***

**#*so the extent of binding and the amount of the drug that binds to plasma proteins is based on the amount of drug that enters the circulation ,not based on the whole dosage that was administrated !!!***

**THE SITES OF DRUG ABSORPTION:**

1. ***Oral mucosa /cavity is a site for drug absorption such as the sublingual tablets that are giving for patient with ischemic heart disease and should reach to the heart ,this type of tablets should be localized under the tongueAs well as the buccal tablets that are kept in the mouth ,and these two will be absorbed through oral mucosa***
2. ***Stomach for specific acidic drugs that requires acidic medium (part of the aspirin will be absorbed through the stomach )***
3. ***Intestinal mucosa is the major site of absorption of the majority of the drugs.***
4. ***Lungs***
5. ***Rectum***
6. ***Skin (when giving drugs topically administrated they will be absorbed through skin )>>an example of such drugs is the transdermal patches which are drugs that are given locally for heart disease problems and intended for systemic use (usually drugs that are giving topically are having a local effect not a systemic and these patches are exception)..***

#transdermal patch is a [medicated](http://en.wikipedia.org/wiki/Medicated) [adhesive](http://en.wikipedia.org/wiki/Adhesive) patch that is placed on the [skin](http://en.wikipedia.org/wiki/Skin) to deliver a specific [dose](http://en.wikipedia.org/wiki/Dose_(biochemistry)) of medication through the skin and into the [bloodstream](http://en.wikipedia.org/wiki/Bloodstream) *(this is an extra information using google so you can understand )!*

-when we administrate a capsule or tablet orally ,the tablet will disintegrate and get into smaller pieces where as the gelatinous cover of the capsule will be removed ,leaving the drug content to be dissolved in the solution ,then the drug should now get into the blood circulation by getting absorbed ,and in order to get into **the blood *vessel ,the drug should cross membranes*** ,and for drugs taken orally two membranes should be passed (the intestinal mucosal membrane and the endothelium layer of the blood vessel ‘blood vessel membrane’**)…. So the majooor factor affecting the absorption will be depending on the nature of the membranes ,which is the lipid solubility of the drug; the drug should be lipid soluble in order to pass the lipid bilayer membranes** !

***CONCLUSION*** : if the drug is lipid soluble it will smoothly and gently absorbed and get into the circulation by crossing the lipid bilayer membranes!!!!

So What do you think are the major factors that that affect the absorption of a drug ??

1**.drug size** :the smaller the drug the better the absorption , and for large drugs this will cause no problems ,because if the drug is lipid soluble enough it’s going to be well absorbed even if its large !!

2**.lipid solubility** (the major factor affecting the absorption )

Regarding **to the lipid/water** **partition coefficient** here are some major information:

-it’s a ratio /factor/coefficient/constant by which we determine the solubility of a drug in lipid and compare it to its solubility in water .

- the higher this partition coefficient the better is the absorption .(when someone say that this partition is high that means that the solubility of this drug in lipids is higher than it’s solubility in water )!

-when this partition coefficient gets higher that means that the drug is more soluble in lipids than water.

-the higher the lipid soluibility of a drug the higher the partition coefficient and vice versa for water solubility when getting higher(the coefficient will get lower ) !

-among different drugs the drug that has the higher lipid/water partition coefficient …the higher it’s lipid solubility thus it will has the higher and better absorption .

Example : what will be the partition coefficient for a drug :

A: has a lipid solubility of 5 and water solubility of 1 ?

B:has a lipid solubility of 10 and water solubility of 1?

For drug A the coefficient is 5,wheras drug B has a coefficient of 10 …thus drug b will be better absorbed than drug A since it has higher lipid solubility (higher lipid/water partition coefficient )!!!

3- **Degree of ionization or environmental pH(**it’s also related to lipid solubility **):**

This is determined by an equation which correlates the PK of the acid or the base with the PH ,PK is constant to all chemicals (each chemical has its own constant PK),and what changes in different compartments of the body is the PH .

The equations:

**pH = pKa + log [A-]/[HA]>> this equation is for weak acids**

for an acid ionized form of the acid non ionized form of the acid

**pH = pKb + log [BOH]/[B+] >> this equation is for weak bases**

for a base non ionized form of the base ionized form of the base

* If the PH and PK of a drug is given <you can easily say and calculate in which form the drug will exist in that particular PH ,by using the previous equations .

For example for an acidic drug having a PH and PKa of 10 ,in what form the drug will exist ( the ionized or the unionized form)and calculate there concentrations ?(refer to the previous equations and solve it , but im not sure if these equations are required for the exam )

Assume that **log [A-]/[HA= 5/2 in this case the drug will be existing in its ionized form at a particular PH .**

**\*so** PH will determine in which form the drug exist in different compartments !

\*PH for example of the intestine is approximately 7

-blood PH is 7.4

-urine is approximately 5 since we consider it as an acidic environment.

-and at the site of action it’s important to determine and know at which form the drug will exist (ionized or non ionized form )based on the PH of that particular site of action .

\***important note** : what determines whether the drug is polar (water soluble) or non polar (lipid soluble ) are certain groups on the drug!

>>for example the drug will be considered as a water soluble drug(can’t cross membranes ) in the case of the presence of polar groups (such as the oxygen ,hydroxyl and carboxylic group )

And it will be considered as a lipid soluble drugs(able to cross the lipid bilayer membranes ) in the case of the presence of a non polar groups such as (benzene ,halogens …etc).

* when we produce the drug ,from it’s chemical structure we can determine whether it is water soluble or lipid soluble based on the polar and non polar groups it contains ,and whether it can cross membranes and reach its site of action or not , so what’s the point of producing a drug that can’t do so ,that’s why there shouldn’t be a drug that **is completely** **water soluble** **unless**  if we want it’s effect to be local ,and not to be absorbed to the systemic circulation .for example if we want a drug to do it’s action on intestines and produce a local effect on them ,we should give the patient a drug that is completely water soluble ,polar ionized orally given drug ,that wont be able to cross membranes and get into the circulation ,thus it will perform the action locally on intestines !!

**#non polar =lipid soluble=non ionized form :it’s the form that is able to cross membranes !**

**#polar=water soluble=ionized form of the drug :it’s the form of drug that is pharmacologically active and unable to cross membranes !!**

**Try to understand this example : a paracetamol is a drug giving to relieve headache (pain killer) and it targets the CNS ,suppose that we took 500 mg orally administrated tablet of that drug, ( pay attention to the sequence of the drug forms in each compartment ),when paracetamol reaches the intestine it should be in the “lipid soluble ,non polar”form in order to cross the intestinal membrane and gets into the blood circulation through the blood vessel membrane ,now the free form of the drug dissociated from the plasma protein should be also in the” unionized ,lipid soluble,non polar “form in order to distribute ,crossing several membranes reaching to the drug’s site of action(CNS)!!**

**\*remember that distribution of the drug from blood to the site of action ,involves also passage of several membranes ,so the drug should stay in its lipid soluble form ,in order to exit the blood stream,till reaching the site of action !**

**Now when paracetamol reaches the CNS (IT’S SITE OF ACTION ,it’s form should be transferred into the pharmacological active one which is the “water soluble,polar,ionized”form , and imagine what could happen if the drug when reaching its site of action stayed on its lipid soluble form (it will keep moving from one compartment to another crossing different membranes and not getting the desired effect of the drug )!!**

**The drug in it’s ionized form now ,will do its action ,and after succeeding in doing its mission it has to be metabolized ,eliminated and excreted with feces out of the body , so the drug should get into the “non polar,unionized ,lipid soluble form “in order to be able to reach the major site of metabolism which is the LIVER !**

**Now at the liver the drug should be absorbed,….etc till eliminated outside the body through feces , and in order to get rid of the drug and excrete it as well as making sure that the drug isn’t moving between tissues and getting back to other compartments , THE DRUG SHOULD GET IN THE “POLAR,WATERSOLUBLE,IONZED FORM”and in this case the liver can perform its action on the drug till elimination !!!!**

**Finally >>>what makes these previous drug form changes(determination of the ionized and non ionized forms) :is the differences of PH between different compartments (intestine, plasma ,central nervous system ,liver …etc)!!**

**Example :-**

**Sulfanilamide Sulfathiazole Sulfacetamide**

**pKa 10 pKa 7 pKa 6**

**At pH 7**

These information of the concentration of the ionized and nonionized forms are calculated using this previous equation: **pH = pKa + log [A-]/[HA]**

**- -nilamide 0.1% I 99.9% NI**

**- -thiazole 50% I 50% NI**

**- -cetamide 99% I 1% NI**

**I:IONIZED FORM**

**NI:NON IONIZED FORM**

**These sulfa drugs mentioned above are chemotherapeutic antibacterial agents !!**

**Lets now move from one drug to another for further explanation:**

**-the 1st drug which is sulfanilamide at PH=7 exists in 0.1 % ionized form and 99.9% NI form ,so the majority of the drug exist in the NI form at ph =7 ,so this drug is considered as lipid soluble drug that is not pharmacologically active and exist in the non polar,non ionized form ,and it can crosses membranes well !!**

**- the 2nd drug which is Sulfathiazole at PH =7 exists in equal ionized and non ionized forms,thus 5o%of the drug will be pharmacologically active and the remaining 50% wont be active and will be able to cross membranes !!**

**-the 3rd drug which is Sulfacetamide at PH=7 exists in 99% I and 1% NI forms,this drug is almost completely water soluble ,pharmacologically active drug and can’t cross the membranes significantly …and this drug with these percentages is what they recommend at site of action ..so 99.9% of it is active and cant cross membranes !with these properties this drug can be used to effect the intestines locally since it can’t cross membranes nor getting into the circulation !!!]**

**Continuation of the factors affecting the drug absorption:**

**4.the concentration of the drug(the drug dose )>>>>the more the drug dose the more the amount of drug absorbed to the circulation … for example for a 100mg drug with 90%bioavailability ,90 mg will get absorbed to the circulation, if we took another 100 mg >>>>the amount of the drug exists in the intestine will be 200 mg thus 180 mg will get into the circulation(the absorption is now higher ) …this increasing in the dosage could lead to toxicity so be careful to that…**

**In hospitals many mistakes could happen while giving a patient a drug on 3 shifts for example .. some nurses could give a patient the 1st dosage of the drug and forget to record that ..so when the next nurse’s turn came and think the patient didn’t get his 1st dosage of the drug she gives him a doubled dosage ..and this is very dangerous and could lead to toxicity because the amount of drug absorbed to the circulation will be higher … and this could be more severe if the drug is given intravenously !!!**

**5- Surface area of absorption :the larger the surface area the better the absorption .**

**6-Blood circulation to absorbing area :the higher the blood surface of the blood circulation to that absorption surface area the better the absorption !!**

**-intestine>>large surface area >>rich blood supply >>thus leading to an excellent absorption !!**

**-lungs>>large surface area>>large blood flow (richly surrounded with blood vessels)>>excellent absorption as well !!**

**..NOT SURE ABOUT THIS INFORMATION: general anesthesia medications have to reach to the CNS to cause unconsciousness!!**

**7.route of administration will affect the absorption as well !**

**-IV is the fastest among oral ,and intramuscular and subcutaneous and other administered drugs ..because it’s directly injected to the blood circulation, you will bypass the absorption by taking an intravenously drug and 100% of the drug will be bioavailble in blood circulation .**

**-oral administration is slower than the intramuscular which is slower than the subcutaneous!**

**-there is a bioavailability to intramuscular and subcutaneous drugs (I think what the dr meant that they have a bioavailability of less than 100%),and the dosage wont get directly to the blood as in the case of IV ,for example in the case of the IM part of the drug will be absorbed and move slowly from the intramuscular side toward the systemic circulation !!and IV is the only route of administration that has no absorption (directly injected in blood ,no loss in the dosage administrated )!!**

**8. Dosage forms also affect the absorption ,the immediate release will be absorbed little faster than that of the timed /extended/ delayed/ controlled release dosage form !**

**\*The methods by which the drug is transferred across membranes, or the Mechanisms of drug transfer across membranes:**

**1.simple diffusion :it’s a method of diffusion by which the drug crosses from one side of the membrane to the other through very tiny pores exist in between cells ,what drive these particles of the drug to diffuse is the concentration gradient (and the particles will move from higher concentrations toward lower concentration and the drug will keep moving in that direction until all the amount of the drug had been absorbed)**

**Size is a basic determinant of this type of diffusion (in order to pass through these tiny pores the drug has to be very small )!**

**\*requirements of this type of diffusion :**

**-the drug has to be little bit lipid soluble , water soluble drugs could cross but to a limited degree (they have to be very small in order to be able to cross ,but unfortunately most of the drugs have large molecular weight exceeding 200 Dalton !**

**-thus it is not a popular way of transferring drugs among membranes!**

**so as a conclusion *small particles* will be able to diffuse and absorbed through simple diffusion ,and for water soluble drugs their size have to be much smaller than the size of the lipid soluble drugs in order to pass !!**

**-it exists for small molecules having a lipid solubility !**

**-energy nor carriers or anything is required in this method of diffusion ..all what we need is a concentration gradient forces the drug to move from higher to lower concentrated compartments or areas !**

**2.passive diffusion :**

**-*the most common and popular way by which the drug crosses membranes (*the most common method including both process diffusion and absorption)**

**-here the drug crosses the membrane itself rather than passing through pores between cells (such as that in simple diffusion ).**

**-the major driving force of this method is also the concentration gradient (from high to low ).**

**-here in passive diffusion there is no need for energy or carriers ,what is needed as we said previously is a concentration gradient .**

**-the most important thing regarding the passive diffusion is that the drug has to be lipid soluble !!**

**3.facilitated diffusion :as the name implies this method needs help >>it needs carriers !**

**-A carrier molecule in the membrane combines reversibly with the drug outside the cell membrane, and the carrier-drug complex diffuses rapidly across the membrane, releasing the drug at the interior surface. The process does *not require energy expenditure*, and transport against a concentration gradient cannot occur.(*transport from high to low concentration as well with the need for a carrier ).***

**-the carrier will take this drug from the side of intestines and release it to the blood vessel’s side .**

**- normally the carrier (a protein) which is present inside the cell(or embedded into the plasma membrane ,p.s I’m not sure about their exact location )should be preserved and present all the time and in all individuals ,other wise ;certain drugs wont be absorbed using this method !**

**-here also the drug has to be lipid soluble !!**

**4. active transport :**

**-Requires energy (ATP is needed for the absorption and movement of the drug ) with or without a carrier !!**

**-sometimes certain drugs require a carrier in addition to the ATP in the case of the active transport .**

**-lipid solubility is also something essential and required !**

**-The difference between the active transport among all other methods is that the movement of the drug and the absorption of it will be against the concentration gradient (from low to high) .**

**-always correlate energy to the active transport ,and since energy is required then something has to move against its concentration gradient (in active transport )**

-**Facilitated diffusion and active transport follow saturation kinetics because No. of carriers is *limited*)….so if we gave a patient a drug that fully saturated the carriers and other receptors already exist on the cell, then some time should be given until the carriers are ready and available again for further attachment with the drug particles !**

**5. Endocytosis this is applied to few number of drugs where the cell engulf the drug and releases it to the other side !**

**- Pinocytosis or**  "cell drinking means (engulfing of the extracellular fluid)..in the case of engulfing a liquid drug !

-**phagocytosis**  means (cell eating and engulfing solid particles ) in the case of a solid drug

#So endocytosis either to be by engulfing solid particles (phagocytosis ) or liquids (endocytosis )!!

**P.S:** SOME STUDENTS AT THE 1ST MINUTES OF THE LECTURE ASKED SOME QUESTIONSABOUT THE PREVIUOS LECTURE I DIDN’T MENTIONE THEM IN THE SHEET .

**>> DON’T FORGET IT TO STUDY THE SLIDES**

GOOD LUCK EVERYONE AND SORRY FOR BEING LATE !!

HOPE YOU UNDERSTAND IT !!:)

**Done by : Jumana Dalbah**