AI in Drug Discovery and Development

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Welcome to the course "AI in Drug Discovery and Development." In today's session, we will take a look at the ADMET properties. So, by the end of this lecture, you will be able to understand the core principles of ADMET and their significance in drug development. As well as explaining how drugs are absorbed, distributed, metabolized in phase 1 and phase 2, and excreted from the body, identify key factors such as solubility, permeability, enzyme activity, and clearance that influence pharmacokinetics.

Interpret how ADMET properties affect drug efficacy, safety, and bioavailability. So, if you look at the routes of administration, the U.S. FDA has approved many distinct routes of administration for drug molecules. However, the oral cavity is the most common site because of its ease of access. So, you can see that whenever we take a drug, there are multiple ways to take that drug or administer it to the human body or an animal's body.

However, the oral route is the most commonly used method due to its ease of use. However, there are other routes as well. So, we will mainly talk about the oral route today. So, once a drug is administered, for example, through the oral route, what happens to the drug? Until it is excreted from the body. So, that is known as pharmacokinetics, which is the concept of what the body does to the drug: the absorption, distribution, metabolism, and excretion processes.

What the drug does to the body is known as pharmacodynamics. So, that is the difference between pharmacokinetics and pharmacodynamics. The drug is having an effect on the body similar to the therapeutic effect we are achieving, and that is due to the drug's actions. So, that is known as pharmacodynamics. So, there are, you know, once a drug goes into the body.

So, the first step is that it gets absorbed from the body into, you know, the blood, and that is known as systemic circulation. So, the process of absorption describes how the drugs enter the body and then, once they are absorbed, how they exert their effects. So, it is distributed because we have multiple organ systems in our bodies. So, the drug you know, once it gets into the bloodstream, So, after entering the bloodstream, it is distributed throughout the entire body. So, that process is known as the distribution and we will understand that as well.

And another important thing is metabolism because whatever goes into our body and does not belong to us is considered a xenobiotic. And then a genobiotic means something that does not belong to our body, and the body tries to neutralize or excrete it. Metabolism is the first process of excretion, in which the body tries to make substances either soluble in water so that they can be excreted through urine or excretable through feces. So, the metabolism processes describe what chemical modifications the drug molecule undergoes in the body and ultimately its elimination, which is the process by which the drug is eliminated from the body. Ultimately, toxicity is another factor that describes whether the drug causes harmful effects on the body.

So, how is the drug producing effects other than the desired therapeutic effects? So, if it is causing some side effects, those are not good. So, those are called toxic effects, and that is toxicity. So, starting with absorption, it refers to the translocation of a drug from its site of administration to the bloodstream. So, what we do is incorporate a drug into a specific formulation. So, these formulations can be, for example, a tablet, a capsule, a syrup, or a suspension.

Then these are administered to the patients, and the drug is released from that formulation and becomes available for absorption. Whenever we take a tablet, for example, that tablet goes into the stomach, and in the stomach fluid, the tablet gets disintegrated. After disintegration, the active constituent in that tablet, for example, if it is a Crocin tablet or a paracetamol tablet, that active constituent, paracetamol, is absorbed into the systemic circulation, which refers to the blood in this context. So, it is absorbed into the blood, and then it is distributed throughout the body. It finally travels to the site of action through systemic circulation.

For example, if you take a drug for, you know, a CNS disease, So, after being absorbed from the stomach, it enters systemic circulation and then, through the blood, goes to the brain, where it shows the desired therapeutic effect in treating CNS disease. So, there are multiple mechanisms of drug absorption, you know? So, basically, these can be divided into three categories: the first is transcellular transport. So, the drug moves across the cell by passing through the apical and basolateral membranes, as well as the cytoplasm. So, it includes passive diffusion, which is governed by the fixed laws of diffusion. It can also be carrier-mediated facilitated diffusion, where several carriers are involved that bind to the drug.

and form a complex that facilitates the transport of this drug across the membrane; then it can be active diffusion as well. There are energy-consuming diffusion processes that transport drug molecules against concentration gradients. So, you can see that these are represented in this figure. So, you have a high concentration of the drug, and then passive diffusion, without any active involvement, approaches the membrane. And then across the cell, actually, here, for example, we have blood, and it is being absorbed into the tissue.

And then the carrier-mediated transports, where a drug has a carrier that binds to it. And it will be transported to the basolateral layer, and then it will release the drug. And then we have the active diffusion where, you know, energy consumption is the major factor in transporting the drug. So, you can see here that the energy in the form of ATP is utilized to transport the drug from the blood to the tissues. And then you have the paracellular transport.

So, this was, you know, transcellular, which means the drug was actually going through the cell. And then we have paracellular transport, where the transport happens between the cells; in fact, the space between the cells is used to transport the drug. So, it is a concentration-dependent mechanism that facilitates the movement of substances across an epithelium by traversing the intracellular spaces between the epithelial cells. And then you have endocytosis, which is the process by which drugs are engulfed through the formation of membrane-bound vesicles within the cell. So, you have these truck molecules that get enclosed in vesicles, and then these vesicles are transported and release the truck on the other side of the cell.

So, there are multiple factors that can affect drug absorption. So, these can be, you know, the physicochemical factors such as solubility and dissociation rate. So, the higher the dissociation rate, the greater the solubility of the drug, which facilitates the absorption process. It can also be the lipophilicity and permeability, where the lipophilic character of the molecule is significant. So, it can easily permeate the biological membrane.

However, an increase in lipophilicity can also decrease solubility. And then, the lower the particle size, the greater the effective surface area, which results in a high dissolution rate and hence more absorption. Polymorphism occurs when the amorphous foams generally dissolve faster than the crystalline foam because no energy is needed to break the crystal lattice. And it is preferred, you know, to make those polymorphic formulations as well as to increase the solubility of low-solubility drugs. And then the biological properties can also affect absorption, so the GIT, pH, and pKa are important factors.

The pKa is the pH at which half of the drug is in its ionized form. So, the stomach pH is in the range of 1.4 to 2.1, while the small intestine pH is in the range of 6.1 to 7.5. So, those acidic drugs are absorbed better in the stomach because they are un-ionized there. However, the basic drugs are absorbed better in the intestine through passive diffusion. And then we have first-pass metabolism, which also affects absorption and describes the metabolism of a drug prior to its reaching systemic circulation. For drugs with high first-pass metabolism, there is a significantly reduced absorption. And then there are some other factors that can also affect the absorption of drugs, such as age, gastric emptying time, intestinal transit time, and disease status.

So, once the drug is absorbed, the next step is distribution. So, distribution can be defined as the movement of a drug to and from the blood and various tissues in the body. For example, fat, muscle, brain tissue, and the relative proportions of drugs in these tissues are important. So, the distribution of drugs is a passive diffusion process where one of the major parameters we use is called the volume of distribution (Vd). So, it is the volume in which the amount of drug needs to be uniformly dissolved to produce the observed blood concentration.

$$Vd = \text{Dose of the drug} / \text{Plasma Concentration}$$

So, what you can see here is an example in which you have a human, and this red line represents systemic circulation. So, if a person takes a drug orally, it goes into the systemic circulation. Now, this drug is diffusing into the body; it is diffusing to the liver, stomach, muscles, fat, and brain. So, if we determine the dose of the drug, for example, how much we have given, the person has taken 500 milligrams of paracetamol, and then we will determine the plasma concentration. So, how much is the concentration of the drug in the plasma? That will give us the Vd, or volume of distribution.

For example, let us see that the drug paracetamol has a Vd of 0.9 liters per kilogram for a 100 kg person. So, that will be, you know, 90 liters. So, 90 liters is the volume of distribution for paracetamol. Now, that 90 liters indicates the concentration that is found in the plasma, which you need.

To dissolve 500 milligrams of the drug into a volume of 90 liters. It means that the amount of drug in the tissue is higher than that in the plasma or blood. So, if it is even very large in the case of chloroquine, where the volume of distribution (Vd) of chloroquine is around 200 to 800 liters per kilogram, So, for a 100 kg person, that will be around 20,000 to 80,000 liters. So, it means that a very small amount of the drug is available in the plasma. So, the rest of that drug is like partitioning into or getting concentrated in either the fat or the other tissues surrounding the plasma.

If a drug has, you know, a Vd of less than 0.3 liters, it is considered to have a very small volume of distribution. However, if a drug has a Vd greater than 0.7 liters per kilogram, it is considered to have a relatively large volume of distribution. Because this free drug concentration, or the concentration in the plasma that is actually reaching the site of action, provides the desired therapeutic effect, it is important to monitor levels closely.

That can also be used to calculate the dose of the drug, such as when we know the drug's therapeutic range. And if we know the VD, we can calculate the dose: how much of a dose will be required to achieve that therapeutic effect? So, there are several factors that can affect drug distribution. One of them is protein binding, specifically plasma protein binding. So, plasma-bound drugs have no pharmacological effects; it is the free drug that exerts the therapeutic effect. Albumin is a major carrier of acidic drugs, whereas alpha-1 acid glycoprotein is the major carrier of basic drugs, and increased protein binding results in a larger volume of distribution (Vd).

So, if you have a lot of protein binding, the free drug in the plasma will be lower, and it will then increase the volume of distribution. And then you have the tissue protein binding as well; the binding of a drug to tissue may serve as a reservoir that prolongs the drug's action. The binding of a drug either to the plasma or to the tissue is generally reversible; more tissue binding of drugs decreases the volume of distribution. And then you have the other physiological factors, such as cardiac output, tissue volume, regional blood flow, and capillary permeability. So, all these factors they can also affect the distribution of the drug.

And then there are some physiological barriers, such as the tissue permeability of a drug, governed by certain physiological factors, including simple endothelial barriers. Simple cell membrane barriers: blood-brain barrier, blood-CSF barrier, blood-placental barrier, and blood-testis barrier. So, coming to the next thing, which is the metabolism: now, once the drug has reached systemic circulation. And now, as we know that the body is considering it a xenobiotic, the body will start treating it and trying to get rid of it. Metabolism is the first step; it is a process by which drugs undergo chemical alterations by various bodily systems to create compounds that are more easily excreted from the body.

So, these chemical alterations occur primarily in the liver and are known as biotransformations. For chiral drugs, one enantiomer might be metabolized to a greater extent than the other due to the stereoselectivity of the chiral metabolizing enzymes. So, there are key metabolic enzymes, such as the phase I and phase II reactions. So, the Phase 1 reactions include oxidation, reduction, hydrolysis, and carboxylation. So, usually the body introduces functional group modifications to a drug, and some of the enzymes that are involved in phase I metabolism are CYP450s, flavin monooxygenases, and epoxide hydrolases.

And then you have the Phase II reactions, which include most of the conjugation reactions. They generally produce these compounds, which are often very water-soluble. And the major enzymes involved are glutathione S-transferase, UDP-glucuronosyltransferases, UGT, sulfotransferases, acetyltransferases, and methyltransferases. So, this is an example of the metabolism of phenytoin. So, if phenytoin is insoluble in water, the metabolism by CYP in the introduction of a hydroxyl group leads to it being more soluble in water.

So, this is, you know, Phase 1 metabolism, and then Phase 2 metabolism. A 4-hydroxyphenytoin beta-D-glucuronide is formed when a sugar moiety is attached to phenytoin, which makes it highly soluble in water. So, then the body can easily get rid of it. Okay, after metabolism, the next thing is excretion. Once the body has metabolized the drug, it will start to excrete it.

Excretion is the collective term used for the irreversible removal of drugs from the body. Okay, so the major sites of excretion are the kidneys, which are involved in renal excretion through urine. Then we have the liver, which is also known for biliary excretion through the bile into the feces, and we have the lungs' respiratory system, which excretes the drug through breath, although it is a minor excretion pathway. So, mainly, excretion occurs through the kidneys and the liver in the form of urine or feces, and there are others, such as sweat, saliva, and tears. So, these can also be used to eliminate drugs from the body.

So, if you look at renal excretion, we have glomerular filtration, which is where free, unbound drug molecules are filtered from the blood into the kidney tubules. It is non-selective and unidirectional in nature, and there is active tubular secretion, in which the carrier-mediated, energy-dependent process is involved in excreting metabolites into the urine. And then these transporters in the kidney actively pump organic anions and cationic drugs from the blood into the urine. And then you have tubular reabsorption, where some drugs, especially lipid-soluble ones, are passively reabsorbed back into the bloodstream. So, some of the factors that affect excretion are drug polarity and solubility.

So the polar drugs or their metabolites are filtered in the kidneys and typically do not undergo reabsorption. So, they are subsequently excreted in the urine, and another factor is molecular size and protein binding. So very large molecules, for example, those greater than 20,000 Daltons, and drugs that are extensively bound to plasma proteins are unable to undergo passive glomerular filtration and are not easily excretable. And then, urinary pH is also a factor that can affect excretion. So, it has a significant impact on excretion as drug ionization changes depending on the alkaline or acidic environments.

Increased excretion occurs with weekly acidic drugs in basic urine and weekly basic drugs in acidic urine. So, that was, you know, up to excretion. Now let us have a look at the, you know, concept of half-life. So, the half-life is the period of time required for the concentration of the drug or the amount of the drug in the body to reduce to one-half. So, in general, the effect of the drug is considered to have a negligible therapeutic effect after four half-lives; that is, when only 6.25 percent of the original dose remains in the body.

So, if we have a half-life of 10 to 12 hours that enables once-a-day dosing, it means you only have to take one drug a day to achieve the therapeutic effect. But if we have, you know, a very short half-life, for example, of 2 to 3 hours, to maintain the steady-state concentration, you have to take multiple doses in a single day and consider extremely long half-lives, for example. Fifty to one hundred hours is generally not suitable because it can lead to these undesired side effects. Another term is clearance. So, it is a theoretical volume of body fluid containing a drug from which the drug is completely removed within a given time frame.

So, clearance is given by the rate of elimination divided by the plasma drug concentration.

Clearance = Rate of elimination/Plasma Drug Concentration

So, you can have, you know, for example, organ clearance at the individual organ level or total body clearance—that is, you know, renal clearance plus hepatic clearance plus the other clearances. So, renal clearance is defined as the volume of blood or plasma that is completely cleared of unchanged drug by the kidney per unit time, which is the rate of elimination divided by the plasma drug concentration.

Renal Clearance = Rate of elimination/Plasma drug concentration

So, it measures the ability of the kidneys to eliminate drugs and is the net result of glomerular filtration, tubular secretion, and tubular reabsorption. So, the rate of elimination is equal to the rate of filtration plus the rate of secretion minus the rate of reabsorption.

Rate of elimination = Rate of filtration + Rate of secretion – Rate of reabsorption

So, the drugs that are removed from the blood by the kidneys through the filtration of unbound drugs in plasma at the glomerulus; the filtration rate of a drug is given by the rate of filtration,

$$\textit{Rate of filtration} = f_u * C_p * GFR$$

which is f_u multiplied by C_p. Multiplied by GFR, where f_u is the fraction unbound in plasma, C_p is the plasma drug concentration, and GFR is the glomerular filtration rate, another clearance term you should know is hepatic clearance, which is the volume of blood that is cleared of the drug by the liver per unit of time. So, there are three main factors: blood flow through the organ, the free fraction of the drug in blood (f_u), and intrinsic clearance (Cl int). So, hepatic clearance can be given by

$$\textit{Hepatic Clearance} = Q\ [f_u * Cl_{int}/Q + f_u * Cl_{int}]$$

q multiplied by f_u multiplied by cl intrinsic divided by q plus f_u multiplied by cl intrinsic. So, as we said, those molecules, if they are acting on other targets as well, can be proven to be effective.

They can provide information on the toxicity as well as the side effects that are toxic in nature. So, toxicity is the state of being noxious or is described as a drug's ability to poison the body. So, drug toxicity can occur if a drug's concentration exceeds the therapeutic range; this may occur secondary to an unintentional or intentional overdose. Or it could be due to drug accumulation; there might be multiple factors, such as the patient's age, drug doses, polypharmacy, or genetics, that can lead to toxicity.

So, there are several mechanisms of drug-induced toxicity. There can be mechanism-based toxicity, where we know that the molecule works on a target. So, this is due to the interaction of the drug with the same target that produces the desired therapeutic response. It can also be immune hypersensitivity, where the drugs or their metabolites react with proteins in the body as haptens to induce antibodies and immune responses. Or it can be off-target toxicity, where the drugs that are not specific in their interactions bind to an alternative target, causing harm. Or they can be bioactivation or, you know, covalent modifications, where many drugs are converted into reactive metabolites.

Another possibility is that the modified proteins induce immune responses linked to the second context of toxicity. So, we use a lot of methods for in vitro and in vivo toxicity testing. So, the in vivo toxicity testing is performed using general toxicity testing to assess, you know, after a single or repeated dose. The carcinogenicity testing, by evaluating a drug's potential to induce cancer, can be done using DART testing. where the assessment of the potential adverse effects of a drug on the developing fetus and reproductive system is conducted and then it can involve ocular toxicity testing, which evaluates the potential adverse effects of the drug on the eyes and the ocular tissues.

Or we can use in vitro assays like the bacterial reverse mutation assay, known as the Ames assay, or the in vitro chromosomal elaboration assay. The micronucleus assay and the HERJ assay evaluate the toxicity of a drug on the heart channels, which are known risk factors for arrhythmias. Now we have another important term, which is LD50, also known as lethal dose 50. The median lethal dose is a statistically derived dose at which 50 percent of the animals are expected to die. So, typically it is obtained from the acute toxicity studies, and if we have lower LD50 values, it indicates higher acute toxicity.

So, for example, the oral LD50 of 0 to 50 milligrams per kilogram is considered highly toxic, and an LD50 greater than 2000 milligrams per kilogram is considered low toxicity. So, we need to because it is said that everything is toxic; only the dose decides whether it will be toxic or not. Actually, even water is toxic if you use it in excess. So, the LD50 value is very high, which means that we have a very large safe window where, even if the drug concentration in the body becomes high, it will not lead to any toxic effects. So, summarizing all this, the adverse properties determine how a drug is absorbed, distributed, metabolized, and eliminated from the body.

Factors such as solubility, permeability, enzymatic activity, and clearance rates critically impact drug performance. And there are phase 1 and phase 2 metabolic processes that influence the chemical transformation and detoxification of drugs. Understanding all these ADMET properties is essential for optimizing drug efficacy, minimizing toxicity, and ensuring safety in patients. So, now we have seen what those ADMET properties are and why they are important. In the later sessions, we will see how we can use AI to predict or learn more about them, and we can use them as screening tools.

Okay, in the end, I have a small activity for you. So, what you have to do is collect the volume of distribution (VD) data for at least 10 approved drugs from a drug bank. Or you can use any other database as well and then just take a look at the comparison, compare it, and reflect as well. And with that, I would like to say thank you.