Fundamentals and Applications of Supramolecular Chemistry
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Week 06
Lecture 30

W6L30_Properties of Pharmaceutical Cocrystals

So, hello, everybody. Now, let us continue our discussion further about co-crystals. Today, we will be discussing pharmaceutical co-crystals because the primary applications of co-crystals are in the field of pharmaceuticals, where it has been observed that drugs with a very poor solubility profile can now be chemically modified to improve the physicochemical properties of the drug.

And this has a lot of applications in the pharmaceutical industry because the manufacturing of large amounts of drugs, where different physical and chemical properties have been tuned, depends on this process of crystallization. So, in the process of pharmaceutical crystallization, the drug, which is also referred to as the API, that is, the active pharmaceutical ingredient, is an integral part of the pharmaceutical co-crystal.

And the co-crystal is a two-component crystal that is a unique phase of the substance, consisting of the drug and another substance called the co-former, which must be preferably soluble in water and also non-toxic.

So, these kinds of substances, which are non-toxic and chemically benign, are referred to as GRAS, which stands for generally regarded as safe. And as we have already looked at the classification of co-crystals, it can form either, co-crystals, salts, solvates, and polymorphs of co-crystals.

So there exists diversity in the co-crystals as well, and it is also important to keep in mind that crystalline drugs are important, but we also have the amorphous drugs, which are characterized by a high value of the Gibbs free energy, and therefore the dissolving property of these amorphous forms is extremely high; however, the problem with the amorphous drugs is their intrinsic stability. And these have a tendency to convert to the metastable form and finally to the thermodynamic form.

So, the industry would always like to work with amorphous forms that are more active and characterized by high values of the Gibbs free energy because they have higher solubility and dissolution profiles, but there are issues associated with their stability.

Also, it has to be kept in mind that solvates, particularly hydrates, are also useful because they have higher solubility properties. But if they tend to lose the water molecules, the solvent structure can collapse, and that can lead to the loss of crystallinity of the drug, keeping in mind that the crystalline form is the more active form.

Now, why this field is of extreme relevance in terms of application in the industry is that it finds application in the design of patents. This is where you have an invention, and you would like to protect that particular invention.

Now, when you say that research related to pharmaceutical ingredients can find a way into patents because you are increasing the innovativeness of the process, you are enhancing the property; in this regard, a patent becomes a viable option. However, before you think about making your research in pharmaceutical co-crystals into a patent, you have to consider the novelty aspect, the non-obviousness of the process, and the utility of the process.

So, novelty should not be something that is very obvious, and it should have applications or utility to serve society. So, in terms of novelty, you have a new composition of matter. Okay, so now you have a new solid-state formulation of the drug.

Non-obviousness is due to the fact that in this case, the identification of the co-former is important, and it is never a routine matter. So, the identification of the co-former that is going to bind with the drug to form the co-crystal is never routine.

Unlike the case of a salt, where an acid combines with a base to give you the salt and water, that is actually the reason why this process is non-obvious. The novelty lies in the fact that you have a new solid-state formulation of the drug, and it also lies in the non-obviousness of the process, which requires logical thinking, reasoning, and knowledge of intermolecular interactions. So based on these constructs, you should be able to design new co-crystals with new applications.

And the utility part is, as I told you, the enhancement in the physicochemical properties of drugs like dissolution and solubility, which have implications for the bioavailability of the drug. So now we see that co-crystals affect a large number of properties concerning the parent drug.

Just to reiterate once more, some of the most important properties that are relevant when considering pharmaceutical co-crystals and their impact on the design of new drugs and enhanced performance compared to the parent drug are solubility, stability, hydration properties, melting point, and mechanical properties like flowability and tabletability.

Finally, the PK, which I mentioned, refers to the pharmacokinetics profile, including bioavailability and permeability. And just to give you an example, there are some drugs that are actually liquid at room temperature or at temperatures between 0 and 20 degrees Celsius, and the idea is to improve the stability of this drug.

One such example is Propofol, which has a melting point of 18 degrees centigrade, and a co-crystal has been formed with isonicotinamide plus propofol, and the melting point is now 55 degrees centigrade; thus, this exhibits enhanced physicochemical properties.

So, this is just to give an example of how a co-crystal can actually stabilize our drug, which is quite active but exists in the liquid state almost at near room temperature. Above 20 degrees centigrade, it exists in the liquid state, but it can now be stabilized, and the formulation can be made into a solid by co-crystallization with iso nicotinamide.

So, keeping in mind the fact that drugs have to be developed, the pharmaceutical industry has classified the BCS system, which is the biopharmaceutical classification system. Where we now have effectively four domains, which are characterized by high permeability and high solubility, high permeability and low solubility, low permeability and low solubility, and then we have high solubility and low permeability.

So, this is called the BCS1 classification; this is the BCS2; this is the BCS3; and this is the BCS4 classification. So those drugs that are actually available in the market belong to biopharmaceutical classification 1, which is characterized by high permeability and a high magnitude of solubility.

In other words, this is the increasing solubility range, and this is the increasing permeability range. So in the second one, you will still be in the high permeability region, but there will be a drop in solubility. When you come into this particular region, it is the BCS class 4 drugs, and these are the BCS class 3 drugs.

So, the idea is to improve the classification; if you have a drug that has poor solubility, for example, BCS class 2, or you have a BCS class 4, then you would like to improve the solubility and go to BCS class 1.

Or if you have a low permeability, you would like to go from BCS class 3 to BCS class 1. And what has been observed is that many active drugs that enter the pipeline of clinical trials at the latest stage have been found to have issues related to solubility and permeability.

The idea is now to employ the method of co-crystallization to improve these physicochemical parameters. And it is also important to keep in mind what kinds of drugs are being made because drugs have a hydrophobic part and a hydrophilic part.

So those drugs that are mostly hydrophobic tend to pass through the lipid bilayers. They have to be transported across the lipid bilayer of the cells. Whereas those that have hydrophilic groups are the ones that stay in the blood serum, this determines the mode of transport of the drug.

It is also important to keep in mind that permeability is a crucial factor because the drug has to be absorbed across the gastrointestinal tract; thus, permeability is vital. Permeability can be modified by altering the structural features.

By modifying the structural features of the drug, you can actually improve the absorption and distribution of the drug across the gastrointestinal tract as well. So permeability is also another very important factor.

We need to actually design drugs using the technique of co-crystallization, which have enhanced solubility, so that we can work on the bioavailability of the API or the drug as well. Now the concept is that once the drug goes into solution or enters the blood serum, it should be available for a sufficient period of time. There are some drugs that perform the necessary action, and in a short period of time, the drug actually crystallizes or precipitates and is then metabolized and excreted from the system.

But there are some diseases where we need a sustained release of the drug into the blood serum that is available to the patient over a sufficient period of time. So in that process we need to maintain the required available concentration which can exhibit or exert the necessary pharmacokinetic effects.

So, in order to look at this process, which is the understanding of the pharmacokinetic profile, we can now examine this pharmacokinetic profile as follows. So, we have the concentration in plasma in micrograms per ml as a function of time, which is given in hours, and essentially this profile looks like this. Okay, here we can say this is 0, 5, 10, 15, 20, 25, and then we can have 2, 4, 6, 8, 10, 12, 14 micrograms per ml.

This is the y-axis, and the x-axis is the time. What we can now represent here is the Cmax concentration. This is referred to as Cmax, and this is the corresponding Tmax. This particular region, starting from 0 until the time the drug reaches the maximum concentration, is the process of absorption of the drug. What is essentially important is to probe this entire process for a period of one day, which is 24 hours.

So, it essentially tapers off to almost a value close to zero, and after the Tmax, it follows the process of elimination. So, the elimination process of the drug also starts, although we still have some features of absorption; mostly, it is the elimination that is important. So, this is the maximum concentration that we have, and this is the minimum effective concentration, and in between, this is the pharmacokinetic parameter, which is the therapeutic index of the pharmacokinetic profile.

So, this is the therapeutic index. So, we can see that Cmax represents the maximum concentration, Tmax represents the time necessary to achieve the maximum release of the drug, and the total area under the curve is represented as AUC, which actually signifies the dosage of the drug.

Now, to start with, you can know the solubility profile of your drug or your co-crystal, and the co-crystal is supposed to enhance the solubility profile, but that solubility profile might still not reflect the dissolution profiles, which are necessary to achieve the necessary therapeutic values.

So, in that regard, we have to make sure that the available concentration can exert the necessary therapeutic value, and that has to be achieved keeping in mind that the equilibrium solubility of the drug or the co-crystalline solution might not have sufficiently high values for it to exhibit the necessary therapeutic index.

So, in order to be able to do that, and as we said, we have now made salt co-crystals, we can have a salt where the solubility can be enhanced, and how this apparent solubility is achieved, enhancement in the apparent solubility is achieved for these poorly soluble drugs can be explained by the concept of the spring and parachute model. And what happens in a spring and parachute model is as follows: We can now look at the spring and parachute model, which is necessary to understand the solubility profiles of a drug in a co-crystal as a function of time. So, we can now look at this spring and parachute model.

We have the time axis here. We have the drug concentration, which can be done both in vitro, that is, in glass, as well as in live cells, that is, in vivo, as well. So, to start with, we have this increase in dissolution, and then there is the thermodynamic equilibrium which is achieved, where the solubility essentially becomes a constant. Compared to that, we have the spring effect. So, this, we can say, is like the parachute dropping, and here we can see this like a spring.

So, when you release the spring, there is a sudden spring motion; when you have compressed the spring, it stores potential energy, and now, when you release it, there is a displacement, and that release of energy is now converted into kinetic energy.

So, the spring motion essentially symbolizes the fact that you have a capsule where you have kept the drug compact, and now that drug is dissolved and released into the solution, and you can see that there are two or three processes happening here.

The first one that we mentioned is the simple achievement of the equilibrium solubility. The second one is only the spring effect, and the third one is a spring and parachute model. So, to start with, if you have one in the process, you have a crystalline form of the drug.

You have the crystalline form of the drug, which has actually been co-crystallized with your particular coformer. But to start with, we have the crystalline form, which has a low solubility. And then, in the case of two, we have a short-lived metastable species that achieves the Cmax value within a period of half to one hour.

It achieves the Cmax value and then converts within a short span of time into the low solubility crystalline form. So, the crystalline form, which is the thermodynamically more stable form and less soluble, converts from the short-lived metastable species into the low solubility crystalline form.

That means the one that is being released into the solution is essentially an amorphous form, and because the amorphous form is not very stable, it tends to convert immediately over a short period of time, let us say between half an hour to one hour, into the corresponding crystalline form.

In the third case, this is the spring effect, and then you have the parachute effect, where you now have a highly soluble drug form that has been co-crystallized with a suitable co-former, which is a metastable form and is stabilized by the co-former. Due to hydrogen bonding interactions, this particular association between the drug and the co-former maintains the necessary solubility profile, and it is only very slowly that the drug is released; this particular metastable species now converts into the low solubility form after a much longer time. So, to start with, we have a highly soluble drug now; because it is a co-crystal, it dissolves into the biological medium and maintains a necessary concentration of the drug in the blood plasma over an extended period of time. Say the time is now extended from 1 or 2 hours to at least 4 to 5 hours, which is the parachute effect, and then finally it goes down to the value of the equilibrium solubility where it has converted into the more crystalline form.

And we can look at this entire process physically as follows: we have, for example, a particular form of the drug. Okay, and we have co-crystallized it with, say, a co-former. So, we have the co-former here, and this is the crystalline form, and then the co-crystal dissolves.

So, once the co-crystal dissolves, we have these random aggregates now. So, we have these random aggregates, so they constitute the amorphous phase because the crystallinity is lost, and this is the spring effect where you have an active amount of these drug molecules floating around along with the co-former molecules.

So, before you form this particular co-crystal, you also have the parent drug. So, it can actually convert from the amorphous phase into the low-solubility crystalline form, or it can also convert into a metastable phase where the arrangements are now different.

So, you can have a different arrangement now of the drug molecules, and the co-former molecules can be sitting here, or sometimes it is not necessary for the co-crystal to form; it is simply the metastable form that forms. So, we now have a metastable form that exhibits the parachute effect. So, we start with a drug of a particular crystalline form, make the co-crystals that have enhanced solubility, dissolve it, and it forms an amorphous phase.

The amorphous phase is a short-lived species that can increase the drug concentration and then get converted into the more crystalline soluble form, or it can then convert into the metastable form, which essentially exhibits the parachute effect.

So, this kind of processes takes place, and this very nicely explains the enhanced solubility in poorly soluble drugs. So, keeping this in mind, let us look at one particular example where we can examine co-crystals in the drug Riluzole.

Now, Riluzole is, as you can see, the structure of Riluzole; it contains a CF3 group and an amino group here. And we have tried to co-crystallize this with different diacids like malonic acid, succinic acid, glutaric acid, adipic acid, sorbic acid, and also some bases like dimethylaminopyridine and nicotinic acid.

And this compound is actually used for the treatment of amyotrophic lateral sclerosis, and it is a highly water-insoluble drug at neutral pH. The idea was to make new co-crystals and improve the physicochemical properties of this particular riluzole drug. And we got many co-crystals, and then for adipic acid, we obtained two particular forms: Form 1 and Form 2. We obtained a co-crystal with malonic acid, then with succinic acid, followed by pimelic acid, then azelaic acid, di-methylaminopyridine, and we also obtained it with nicotinic acid.

And you can see that the melting point of the co-crystal is between the melting points, is basically close to the melting point of the drug, and that is very interesting because you do not essentially change the melting point to very high values; otherwise, the lattice energy is also higher, and that has to be overcome when the co-crystal dissolves in the biological medium.

So, the melting points of the coformer are given here, and in most cases, the melting point of the co-crystal is comparable, like 114, closer to that of riluzole itself. In the case of SORBA, the melting point is even lower, whereas in the case of SBRA, it is actually enhanced to 136 degrees centigrade. So keeping this in mind, I can now show you some of the interesting structures that have been obtained by co-crystallization. So here you can see that this is the adipic acid which contains CO2H, CH2, CH2, CH2, CH2, CO2H.

It is held by strong N-H...O and O-H...N hydrogen bonds. This is a very important hydrogen bond that connects the co-former with the drug molecule, and then these drug molecules are further connected by weak C-H...O and C-H...F hydrogen bonds between the riluzole molecules, which form a layered structure, as you can see.

So, this is the structure of the co-crystal phase. Then we can see malonic acid as well, and in the case of malonic acid, you can see that it has formed a salt. So, salt means that one of the carboxylate hydrogens in this particular carboxylate group has lost its hydrogen, and it has now protonated the corresponding nitrogen of the riluzole ring. So now the nitrogen gets protonated, and it forms N plus H.

So this particular nitrogen here now gets protonated. So, you have the salt formation, and again you can see the arrangement of the hydrogen bond; this is the N-H···O, and this is also the neutral N-H, and this is the protonated $N\text{-}H^{+}\cdots O^{-}$.

So, you get these subtle changes in the hydrogen bonds, with one having the charged species between the N-H and the O minus. And so you have this kind of co-crystal structure. In the case of nicotinic acid, it is interesting to keep in mind that nicotinic acid itself exists in the zwitterionic form.

So you have CO2 minus here and the N plus H; this is the zwitterion, and then this forms hydrogen bonds with your drug molecules. You can see here the hydrogen bond; this is the N-H...O hydrogen bond, this is the C-H...O hydrogen bond, and you have this network of hydrogen bonds that connect the drug molecule with your co-former, which is nicotinic acid. So, these are the physicochemical properties.

So, you can see that the dissolution rate has been enhanced for SORBA, which is your sorbic acid, and it is the highest in the case of SORBA. You can see here that it is enhanced seven times in comparison to that of riluzole. So, these are the intrinsic dissolution rates, this is the equilibrium solubility, and this is the absorption coefficient.

And here you can see that for malonic acid, the solubility is highest for the co-crystal with malonic acid. But for SORBA, for SBRA, and for one form of adipic acid, which was the more dominant form, the solubility is enhanced in comparison to that of the drug riluzole.

So, this tells us that co-crystals are very interesting entities and have intriguing applications in the drug industry. So, with this, we come to a close of this lecture, and now we will move on to the next set of topics starting next week.

Thank you.