Fundamentals and Applications of Supramolecular Chemistry
Deepak Chopra
Department of Chemistry
IISER Bhopal
Week 05
Lecture 29

W6L29_Case Studies on Polymorphism, Cocrystallization, Applications to Pharmaceutical Cocrystals

So, hello, everybody. So, now let us continue our discussion. So, in the previous lecture, we looked at the existence of polymorphism in different compounds, an anti-implantation agent, and the existence of dimorphs.

For example, we looked at the plate form and the block form, and we also looked at the differences in conformation, which also manifest themselves further in terms of different intermolecular interactions in the crystal packing. Now we will take another interesting case studies. We will be looking at concomitant polymorphism in fluorinated benzamide.

So, we have made these benzamides, where we have CF3 and fluoro-substituted moieties on the carbonyl side as well as the N-H side. And one such specific molecule, which has a CF3 here and a fluoro in the para position on the N-H side, exhibits this concomitant polymorphism.

Now, what is important to realize is that polymorphism is a very important phenomenon, a very subtle phenomenon, which is governed by the formation of different crystalline forms that are very sensitive to the crystallization conditions.

For example, when we have taken this particular compound, the code is given as A; when it is crystallized from DCM and hexane at low temperature, you can see it crystallizes in the form of blocks.

So, we call these blocks, and we refer to this form as the A2 form. When we actually do it with another combination of polar solvents like chloroform and non-polar solvents like hexane at low temperature, we again get these blocks.

So, you see that the blocks are obtained under low-temperature conditions in a combination of polar and nonpolar solvents. Now, when we change the solvent to benzene, which is completely nonpolar at low temperatures, we again see that we get the blocks that are the A2 form. But now, when we heat this solution in benzene to room temperature, we see concomitance observed on slight warming.

So, we get blocks and thin long plates. So, in this particular figure, you will be able to see that there are some blocks and some thin, long plates as well. So, you get these two distinct kinds of morphologies.

The plate form is referred to as A1, and the block form is referred to as A2. Then, in benzene, after heating for some time and then cooling and crystallizing at room temperature again, you get plates.

So now, initially, when you have slightly warmed up the solution in benzene from room temperature, you get both morphologies; but now, if you continue heating for some more time and then cool it, what crystallizes out is the plate form.

That means there is only the plate form now that is present. So, there is a conversion from the block form to the plate form. And then, when you crystallize it from toluene, it is crystallized at room temperature; again, you see concomitance on slight warming, and both forms are present, as you can see in this particular crystallization vial.

So, this is the phenomenon of concomitant polymorphism, where different polymorphs crystallize under identical crystallization conditions.

And so, what was observed is that the block form converts into the needle form upon warming, and to see whether this behavior is actually relevant in this particular system, we now perform a series of thermal characterizations using different techniques.

For example, we started with DSC, and then we also followed it up with HSM. So now we have the pure synthesized compound. So, we have recorded the bulk that is called A_bulk, on which we have recorded the DSC. As a function of temperature, you see that in the DSC traces of the compound, first there is a peak at 108 degrees centigrade, and then there is a tiny peak at 113 degrees centigrade.

So, it indicates that in the bulk phase, there are two polymorphs, one melting at 108 degrees and the other melting at 113 degrees, and the area under the peak indicates the relative abundance of these two forms, which means blocks are more present compared to plates.

Now, we conduct the crystallization experiments, and now we separate the plate morphology. So, in the plate morphology, when we do the DSC experiments, in the first heating cycle, you see that it melts at 112 degrees centigrade, and then you cool.

When you cool, you see that there is no recrystallization happening because of the thermal arrest; there is a hysteresis, and the supercooled liquid does not immediately crystallize. But after a certain period of time during the process of the second heating cycle, you see that when the second heating cycle begins, there is an exothermic peak

which indicates recrystallization of a form that melts at 95 degrees centigrade.

So, the recrystallization occurs during the process of the second heating cycle in the same DSC pan, and the form that is recrystallized is another metastable form that is not the plate form and melts at a much lower temperature, which is 95 degrees Celsius.

Along the same lines, we took the block form, and from the block form, we conducted the DSC experiment. Now this was done at 3 degrees centigrade per minute; we maintained the same scan rate, and we observed that there is a first endotherm at 108 degrees centigrade followed by another endotherm at 112 degrees centigrade.

So, this indicates that there is a possible phase transition at 108 degrees centigrade, which then converts into a new phase that melts at 112. Now, we know that the plate form melts at 112.

So, the chances are that the block form converts into the melt, converts into the plate form, and then melts at 112. And, once it has melted and you cool the pan, there is no recrystallization, and during the second heating cycle, you again see that the process of recrystallization takes place, followed by the melting of the metastable phase again at 95 degrees centigrade.

So, whether you start from the plate form or the block form, it converts into the plate, the plate melts, and it converts into a metastable phase. Now, because there are two peaks here, we wanted to see the dependence of these peaks on the scan rate, as we observe that there is a phase transition followed by the melting of the new phase. So, we now conducted the experiment at different scan rates.

We did it at 1 degree centigrade, 3 degrees centigrade, which is already represented, and then we did it at 5 degrees centigrade and then 10 degrees centigrade. And we clearly see that when you do it at a faster scan rate, you only see the melting correspond to 107 degrees centigrade, which means it is only the melting of the block form that takes place.

However, when you do it at a slow scan rate, there is a phase transition followed by the melting of the plate form. So, the process of melting the plate form takes place when you have slow scan rates.

So, keeping all these things in mind, the fact that you have a phase transition followed by the melting of the new phase means you can actually overcome, or you actually need not have, that phase transition when you do it at a faster scan rate, which corresponds to the melting of the block form.

Now, you can see these things very clearly in the hot stage microscope. When you start

with the plate form and do it at a much lower scan rate, you will see that the plates melt at the characteristic 113.7 degrees centigrade, which corresponds to the melting point of the plate.

Now, when you start with the block form, this is the first heating cycle at around 108; you see that these crystals start getting opaque. They are transparent here; now they start getting opaque, and then you see there is slight formation; there is a growth of a new phase here at the expense of the block phase.

This is essentially the new plate phase that is being formed, and now you see that it has been completely converted into the plate phase, and then it melts at around 112. So, we continue with the temperature; it has completely melted at 113.

Now, when you cool it and then perform the second heating cycle, you see that it has solidified, and this new phase, which is the metastable phase, melts at 95 degrees centigrade.

And when you continue this process for a third heating-cooling cycle, it has again melted and converted into this metastable phase, which melts again at 194 degrees centigrade. So, the metastable state, once it is formed, stays for a considerable period of time, but it essentially originates from the phase transition of the block to the plate form, the melting of the plate form, followed by the conversion into the metastable state.

So, you can see that these kinds of interesting events can take place where you can determine the melting points of the different phases from DSC, supported by HSM studies as well.

So, this is to tell you that DSC, HSM, and morphological experiments give us very valuable information about the formation of polymorphs, their interconversion, stability, and so on and so forth.

So, with this background in mind, let us now go on to the next topic of discussion; we will now talk about another interesting phenomenon in the field of solid-state chemistry of organic molecules, and we call this co-crystallization.

So, in the case of co-crystallization, these are also referred to as multi-component crystals, where we have to start with at least two components in a certain stoichiometric ratio, say AmBn, which is formed from A and B in a certain stoichiometric ratio, and the properties of this new phase are different from those of A and B. And to start with, A is a solid, B is also a solid, and the new phase formed is also a solid, which we refer to as a co-crystal.

The formation of the co-crystal and the driving force for the formation of co-crystals originate from both the enthalpic and entropic terms.

From the enthalpy term, we understand that the intermolecular interactions between the A and B components are greater than the strength of the intermolecular interactions between A...A or B...B. So, A...A and B...B have a certain stability, but the nature of the interactions between A and B is more favorable and more stabilizing compared to that of the starting material, and that is what enthalpically drives the formation of co-crystals.

And there is also an entropic gain that comes from the entropy of mixing, which originates when we mix two reactants of similar size, shape, and chemical nature.

So, when we have two reactants that have similar size, shape, and chemical nature, and we mix them in a certain ratio, then the resulting phase formed is driven by the entropy of mixing as well. And co-crystals have a definite composition; they can exist in defined stoichiometric ratios, for example, 1:1, 1:2, 3:1, 2:1, etc.

And it is also important to note that we are now expanding the solid-state diversity of these compounds. So when we have A solid plus B solid, we are forming, say, AB solid. This is referred to as a co-crystal phase.

But when we are doing these experiments on the preparation of co-crystals, there is a possibility that you can also end up with polymorphs of A or B. You can also get co-crystal polymorphs of AB. Then there is also a possibility that once you have prepared the AB solid, you want to recrystallize it, and that is a time when you can have solvates of AB separately.

So, this expands the solid-state diversity domain of AB with respect to A or B. At the same time, if A is an acid component and B is a basic component, say, for example, A is a solid and B is a liquid, then it can form a new AB phase in a certain stoichiometric ratio where the acid has released the proton, becoming A minus, and the base has accepted the proton and becomes the conjugate acid of the base, and then there are strong electrostatic interactions that form the salt.

So, this is a salt co-crystal. Essentially, the stabilizing entities here are the salt. You have A-, a compound, and this acid compound can also be a drug molecule that has ionizable protons. The protons are lost to the base; the base takes up the protons, and there is a complete proton transfer from the acid part to the basic part.

Now, these constituent species are ions or molecular ions, and then they interact with each other electrostatically to form the co-crystal salt. Along the same lines, we can also have polymorphs of these salts via rearrangement of different synthons, which can give

you the packing polymorphism in the case of these salts.

We can also have the solvates of these cocrystals; we can have hydrates, or we can have other solvents included with these cocrystals, and we can also have salts of B, assuming that B is basic and that we add a polar solvent from which it can take up a proton.

For example, if you add it to HCl, then the base B will take up the proton from HCl, forming the conjugate acid B plus H, and the chloride will be the counterion that will form the hydrochloride salt of the basic compound.

So, you can also have basic drugs; you need not always have acidic drugs. You can also have basic drugs, for example, which can be a part of the co-crystal formulation, and we can now have the corresponding salt, a hydrochloride salt of that basic component, which can also form solvates. So, this can form salts of B, and then the salts of B can also form solvates of B salt.

On one side, you have got the salt, different salt components, the different forms of salt, compared to the starting materials, and here you have got the co-crystals. So, this very interesting diversity exists when you want to make co-crystals.

Now, how do you make co-crystals? Co-crystals are prepared by the technique of mechanochemical grinding using a mortar and pestle. So, a mortar and pestle is used where you take the starting materials A and B, then mechanochemically grind these components A and B. The resulting solid is obtained, and the powder XRD diffraction pattern is recorded for the obtained phase.

If it is a new co-crystal phase, it will be very different from the powder XRD diffraction pattern of the starting components. Now, when you do this mixing in the absence of any solvent, it is called dry grinding, but sometimes, to assist the process of diffusion and achieve more homogeneous mixing of the reactants, we also add a few drops of a polar solvent.

For example, we can add methanol, and then we do something called liquid-assisted grinding. And then this liquid-assisted grinding, once we do it for a period of, say, 1 to 1.5 hours on average, allows you to again record the powder X-ray diffraction pattern of your co-crystallized solid, and you can do the phase analysis in a similar way to how you do for the polymorphs, which we discussed in the previous lecture.

And once you have confirmed the formation of the pure phase, there will initially be some impurities corresponding to the starting materials as well.

Now you can take this mechanochemically branded solid and put it for crystallization, and you will then be able to get crystals of different morphologies. You can also utilize this crystal to perform single crystal X-ray diffraction experiments, from which you will be able to determine the atomic connectivity of your co-crystal.

So, again here, similar to that of polymorphs, single crystal X-ray diffraction plays a very important role in determining the atomic connectivity and the composition of the obtained co-crystal phase. Now, it is very important to realize that the co-crystal contains neutral components.

It contains neutral components A and B, forming the solid, whereas the salt contains ionic species. So, you have A minus B H plus, and there is a very strong hydrogen bond between B and A minus, and depending upon how strongly the base abstracts the proton, there can be a transfer of this proton from A to B.

And this, to start with, hydrogen can be associated with the acid part; this is called a co-crystal, and then it starts getting dissociated. So, there is an intermediate position where there is a substantial lengthening.

So, this is, say, l1; this is l2. l1 is much less than l2, but here l1 is nearly equal to l2. And finally, when the proton is transferred to the base, then l1 is greater than l2.

So, this is a very interesting phenomenon which is observed in the solid state because depending upon the position of the proton, we can say whether it is a co-crystal or whether it is a salt. And there is an intermediate phase as well where the hydrogen atom is positioned symmetrically between or almost near symmetrically between the two acceptors and this phenomenon is referred to as the salt co-crystal continuum.

Okay, and it is only by a very careful structural characterization of these co-crystals and the treatment of the hydrogens that we will be able to unambiguously establish whether it exists as a co-crystal or as a salt.

In most cases, if you have good diffraction data, you will be able to locate the hydrogen atoms very cleanly, and you will be able to confidently say whether it exists as a salt, in the intermediate phase, or in the pure co-crystal phase. And therefore, the salts are characterized by high lattice energies in comparison to those of the neutral compounds.

Now, just as synthons play an important role in solid state, in co-crystals it is also the synthon arrangement, the synthon strength, and the arrangement of the different synthons in the crystal packing that originate from the interactions, the heteromeric interactions between the A and B entities, which contain the functional groups that engage in synthon formation and give rise to the co-crystal.

So, for example, if you have hydrogen-bonded cocrystals, we can have the well-known dimer; this is the acid dimer that we have all studied. So, this is the homodimer, this is the homosynthon; along the same lines, we can have another.

This is the homodimer or a homosynthon involving the acid, and this is involving the amide, the amide homodimer, and similarly, we can have an acid-amide heterodimer as well.

So, this is the N-H...O, and this is the O-H...O, and this is a heterodimer involving the acid and the amide. So, this kind of heterosynthons is also present in the case of the different co-crystals that are formed by the interaction between the acid and the basic functionality.

So, the carboxylic acid is the acidic component, the amide is a basic component, the N-H part is okay, and these can interact with each other. We can also have cases where the acid can interact with any nitrogen-containing species.

So, you can have, for example, pyridine, and pyridine can form O-H...N hydrogen bonds. So, the O-H...N synthon becomes extremely important, and there is a large number of co-crystals that contain this O-H...N hydrogen-bonded synthon, this coming from the acid part, and this is the basic part. Along the same lines, you can also have other nitrogen-containing species; for example, we can have this particular base which contains the lone pair.

We can have two nitrogen atoms, both basic in nature, and they can engage in hydrogen bond formation. And we can also have other cases as well, where we can have oxygen, as well as NH.

So, we can have different kinds of functionality that form these types of hetero synthons involving interaction between an acidic component and a basic component, and these are considered to be the primary synthons or the basic building blocks present in co-crystal systems. We can also consider even more extended structures now, where we can consider, for example, 3-amino phenols plus bipyridines.

So, here we can see, for example, N-H...N, and we have an O-H...N hydrogen bond. So, we have an O-H...N hydrogen bond here. We have an N-H...N hydrogen bond here, and this can now extend further. So, again we can have here the N-H...N and we will have here the N-H...O. So, we can have this kind of hexameric motifs 1, 2, 3, 4, 5, 6, and we can extend this further now; therefore, we have the ladder-like arrangement.

We have the ladder-like arrangement that is present. So, these are some of the fundamental building blocks in the case of co-crystals. What is more important in

co-crystals is why this field became very popular, exciting, and application-oriented: it gave birth to the discovery of pharmaceutical co-crystals, which are relevant in the drug industry. So, the drug industry is always interested in making drugs that have improved performance, particularly in terms of solubility and permeability.

Thus, solubility and permeability play an important role. And it is also important that when you formulate a drug, it conforms to the famous ADMET rule, where A stands for absorption, D stands for distribution, M stands for metabolism, E stands for elimination, and T stands for toxicity; this is what constitutes the pharmacokinetic profile of the drug, which we call PK.

So, this pharmacokinetic profile of the drug becomes extremely significant. Now there are two reasons why this concept of pharmaceutical co-crystals has become very important.

One is to enhance the chemical properties of the drug; that is, we can either obtain salts, which are going to be more soluble compared to the parent drug, which has poor solubility. We can also improve the physical properties of these drugs because when you make drugs, there are a lot of practical issues associated with drug formulation.

For example, the shelf life of the drug, the stability of the drug, the hygroscopicity of the drug, and the mechanical processing of the drug—that is, the tabletability of the drug and the powder characteristics of the drug.

Somehow, these properties play a very important role in drug processing as well. And it has been observed that co-crystal formation plays a very important role in overcoming some of these limitations regarding the properties of the drug.

For example, Norfloxacin, Norfloxacin with isonicotinamide, isonicotinamide, ofloxacin with diphenic acid, and itraconazole with succinic acid. These improve the solubility of drugs in the sense that they exhibit greater solubility compared to that of the parent drug.

And because there are also problems related to the uptake of water by the drug, which is not very favorable, particularly if atmospheric moisture is present, there is also a problem with the formulation of the drug, the packaging of the drug, and the storage of the drug. So, in this regard, caffeine is very sensitive to moisture.

There are problems associated with storage because it is susceptible to hydration with changes in atmospheric conditions or humidity levels outside, and this caffeine is now stabilized by forming a co-crystal with oxalic acid.

So, this co-crystal, which has been obtained, now has a better shelf life and is sufficiently stable for several weeks. Similarly, we have a very common drug called paracetamol,

which has poor compaction properties, referred to as tabletability.

We now make a co-crystal of paracetamol with oxalic acid, and this co-crystal has better tabletability. Therefore, you can make a nice tablet of this drug if you have the co-crystal form. When the pelleting of the drug takes place, compaction is better, and both the drug quality and the pill quality are also improved because of the nice flow characteristics.

So, paracetamol per se has poor compaction properties. The tablet that is formed is not very uniform and stable, whereas it has better tabletability with oxalic acid.

So, keeping in mind some of the most important applications of pharmaceutical co-crystals and that they enhance the solubility profiles, we will now look at pharmaceutical co-crystals in more detail in terms of different applications and the mechanism of their action in the case of drugs.

Thank you.