Symmetry and Structure in the Solid State
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Lecture – 58
Power Diffraction 3

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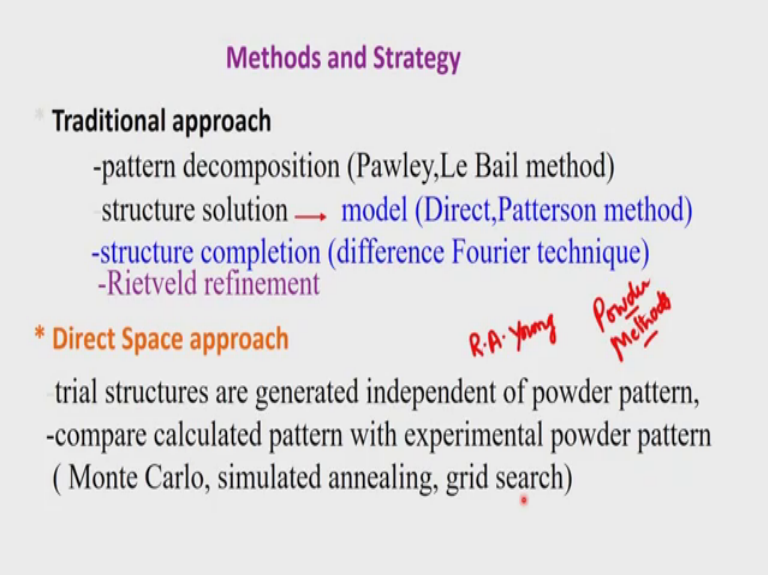

So, what is the method and strategy we use? We know now Rietveld refinement will help if we have a static model, but how do we get this static model? One is to do in any case we have to do the pattern decomposition and there are two mainly available methods one is due to Pawley and the other due to Le Bail and these two methods are there already in the program extra which we used.

The structure solution of course, we can develop a model either from direct methods or from Patterson methods and that can be now taken to structure completion by the difference Fourier technique and then we follow it put the structure in and do the Rietveld refinement where we refine the profile first take the profile to the final possible refined values of R p and R wp and then introduce the structural parameters put x y z etcetera and then do the structure refinement. It is not the straightforward procedure like in a single crystal where you just press a button and the least squares refinement gets done using all the parameters.

Here we have a certain specific wave in which we have to release the parameters because we are dealing with very subtle things. Remember the overlap in the powder pattern and the one d profile, so we have to be very cautious when we do the Rietveld refinement. So, initially we release the we first do the scale factor refinement and then we release the x y z, so there is an excellent book in fact, I should give the reference to the book here, this is the powder method where we describe the Rietveld refinement etcetera what is the edited by R. A. Young.

So R. A. Young edited this book called powder methods; methods and this particular book is IUCR text and available through oxford university press, so one can buy this book or read the book and this will now cover all these full approach because it is out of scope of this particular course. I just thought, I will mention the possibility of determining the structure other than these methods which is the traditional approach and that is referred to as the direct space approach. So, here we are directly trying to get a trial structure.

So, the trial structures are generated independent of the powder pattern, so we do not worry about the powder pattern. We can use techniques like Monte Carlo simulations, simulated annealing, grid search and of more recent origin is the genetic algorithms. So, these methods will allow you to give a starting model for the structure, these are again based on the knowledge which we have in the databases.

So, making use of the knowledge in the databases we can build a possible starting model for the structure run it through these theoretical approaches to get to a situation, where we are nearly correct in our structure. And then we can calculate compare the calculated pattern with experimental pattern and do the Rietveld refinement to solve the structure.

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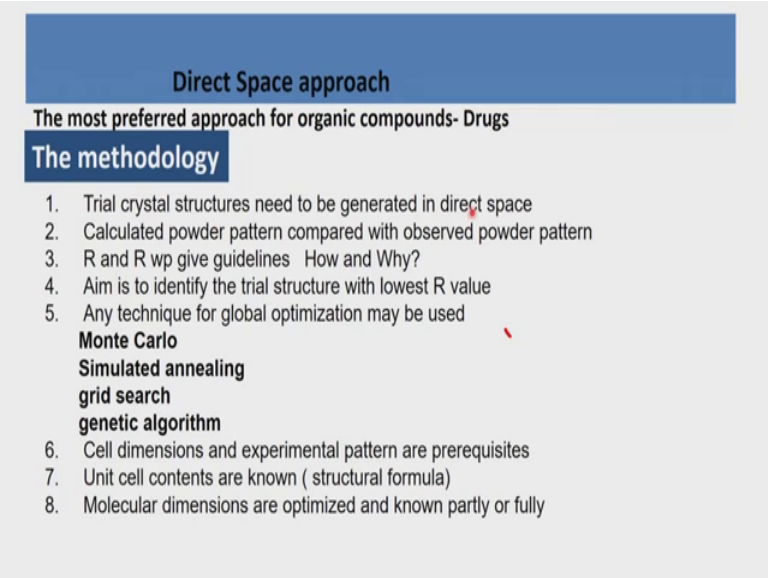

This direct space approach is undergoing a lot of new changes in fact, there are not many structures which have used this method and structures have been done, but it would be the most preferred approach if people are interested in pharmaceutical industry to determine the final structure, the complete structure of the compound with PXRD studies. So, the methodology the basic methodology is described here, first we get a trial story crystal structure need to be generated in direct space.

You can also use for example, other experimental techniques like NMR for example, you can get a starting model from NMR, a starting guess model from NMR put it into this procedure and then try to get to the structure the. So, once you have a trial structure you calculate the powder pattern compared with observed powder pattern. So, your R value and the R wp; R p and R wp will be the guidelines.

We already know how and why? Because R p and R wp are now the signatures of the nature of your material, these are the fingerprints of the nature of the material where the atoms are sitting. How the structure is developed decides the shape of your profile and also where the reflections appear.

And therefore, R and R wp give the guidelines and the aim is to identify the trial structure with rho a star value this is known as R factor search this is already practiced even in single crystal structure determination in earlier days before direct methods and Patterson methods took cover.

Particularly direct methods took over people were experimenting with this again the contribution of G. M. Ramachandran to this area has to be remembered. He did what is known as an R factor search using the vector search methodology, using the Patterson function he did what is known as an R factor search and identified the lowest R value which could give us the trial structure and then did the routine structure refinement this was with single crystal data.

Any technique for global optimization may be used Monte Carlo simulated grid search and genetic algorithm and cell dimensions and experimental of course, accurate cell dimensions and good experimental pattern are the prerequisites. So, the structural formulas as to be known and the molecular dimensions then are optimized if they are known partly or fully.

So, this is the approach which generally allows the structure determination directly without making any assumptions. These are undergoing a lot of changes there is lot of structures which are being solved now, but not to the extent of the number of structures which come every day from single crystal diffraction which is obvious because the methods are yet to be tested and checked out.

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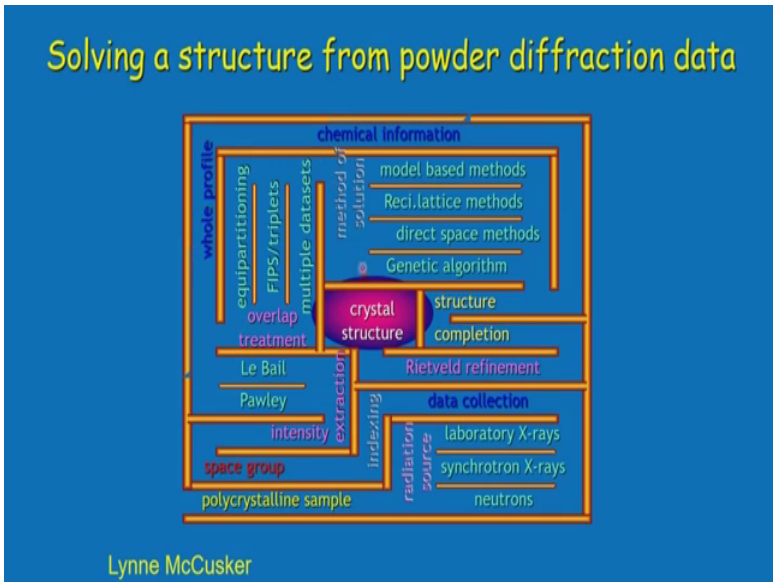

So much that my friend Lynne McCaskey who practices this art of structure, determination over the years made this maze. Now, this is in fact, maze the structure solution by powder diffraction is indeed a maze, so you start from the you start from.

The polycrystalline sample and you have to end up in crystal structure. So, this is like the maze you have to find the way the shortest to the proper path through which we are to traverse to reach to the crystal structure.

So, what you do is first you collect the data using the radiation which could be laboratory X rays, synchrotron X rays, and neutrons all three can be used. And then we do the data collection and after the data collection we need to do the indexing, so we get the cell dimensions and then we find the space group we just the space group because in powder diffraction a unique determination of the space group is not possible.

So, if it is a monitoring system we tried and it is there is an indication of the space group identification, we can identify the all possible space group try the structure in all the space groups, so it is a little tedious, the approach is a bit too tedious. Then the intensity extraction so the intensity extraction Le Bail and Pawley is methods are available. One of the major problems here is from the Pawley crystalline to go to indexing and space group is a real ordeal and once you get over it you can intensity extract them with Le Bail and Pawley methods.

And then you have to treat the overlaps there are various ways in which mathematical ways which are available to treat the overlapping peaks and this can be done by collecting multiple data sets for example, at different wavelengths maybe and then see whether we can differentiate between the overlapping peaks. And then we use the method of structure determination, so model based methods, reciprocal lattice methods which we discussed the Patterson and the direct methods.

And then the direct space methods the use of Monte Carlo simulation and simulated annealing and so on and genetic algorithm. So, using any of these we now solve this structure, having solved the structure we have to now do a whole profile refinement, the whole profile has to be refined this is very very important. So, it is not just refined anything I hope this is visible the whole profile is it visible because the background is very similar to the color I have used here, so the whole profile is a must. So, whatever we do we have to consider the entire diffraction pattern.

So, as we said 3 degrees to 100 degrees into theta all that whole thing has to be considered. Snd then we of course, from there go to the chemical information which we have this is a must we should know what are the come what are the contents of the com

material in which it is made of number of phases etcetera; etcetera, then we go and complete the structure.

So, this is the first part of it, so we have the trial side, so you know in the same logic any structural determination is done in two steps, first we do all these things and get a trial structure. The trial structure now uses the data the extent of enormous amount of data the over determine data that is available and then refines the positions the thermal parameters etcetera is the same thing we do here, but we do it with Rietveld refinement; that means, we do both the profile as well as the structural data and then we go to the crystal structure.

So, this is the overall powder diffraction technique to start from the data up down here somewhere here and go to the structural determination there. So, what is required for this entire operation is a poly crystalline sample. So, if you see that if it is a single crystal data this maze is now FLT is very much reduced, so we do not have a maze, we can have a direct path to determine the crystal structure whereas, in powder diffraction you have to go through this maze of various steps before you come to the actual crystal structure.

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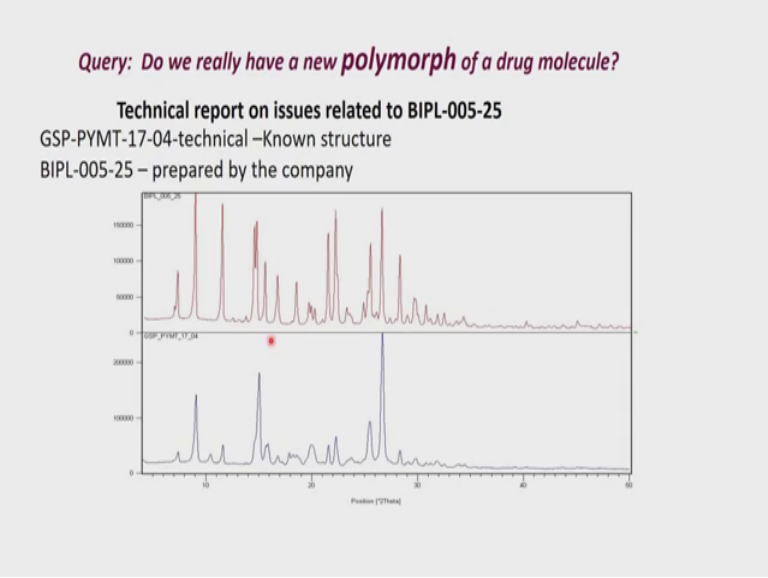

Now, the next issue which we consider is issue which normally comes up in pharma industry. I will take two examples where which were sorted out in our laboratory using powder diffraction and profile refinements. So, a question came from a company, so I am going to use technical numbers now companies do not allow us to use the name of the

compound because these are all come under the, what we call as the CDA agreement the former people who are participating in this course they will realize what I am talking about.

So, this is the technical report on issues related to a compound which was made by a company and they called it BIPL 005 25. So, if we do not know what the compound is even today I do not know what the compound is, but it is I know now of course, because it is marketed now. So, the known structure which is reported in literature for which there was a patent which was taken by a company is called GSP PYMT-17-04 technically, now a by technical it means that they have the pure compound which they obtained from the company.

So, the idea is to see whether this is different from that to start with. So, what is normally done? You just record the powder pattern and put one powder pattern on top of the other this is what most of the pharma people we will do and when they did that we they found that there is something like extra peak here and some peaks here are looking different to them and then there is additional peak here which is probably is due to lack of crystallinity this is not really showing that.

So, when you record the two powder patterns, so you cannot immediately conclude that whether it is a polymorph of a drug molecule or not, you see that there is a lot of resemblance also between the two patterns, so the question came up whether it is a real polymorph. So, these are some of the problems which come which can only be solved by the knowledge which you have in symmetry, the knowledge which you have in diffraction and the knowledge which you have in structure determination otherwise these problems can never be sorted out ok. So, this is something which is very important that is why the course which we have studied in understanding symmetry and structure gains enormous importance in your future carrier.

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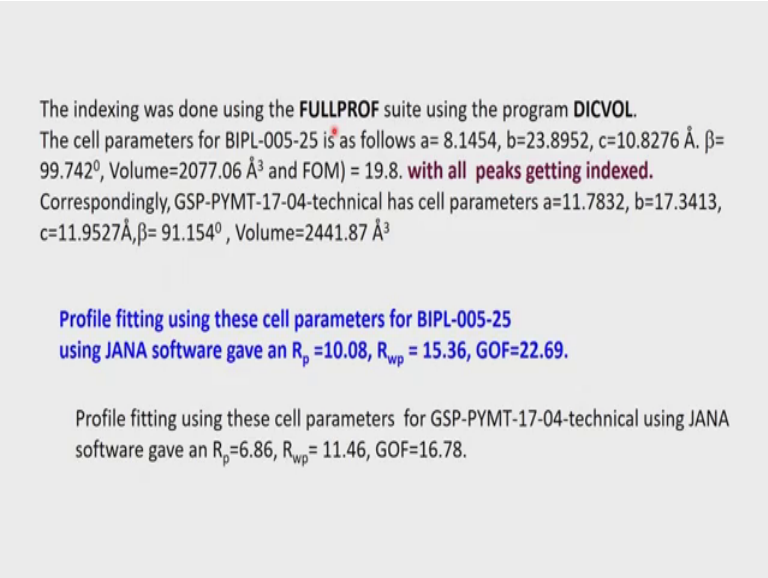

So, what was done? The indexing was done we used a package called fullprof I told you GS as in the previous case and fullprof and Yana. So, many I said, but we are using fullprof and yana in this protocol we can use whatever program we would like to use, but we use fullprof and use this program DIVCOL which I already mentioned to determine the unit cell dimensions. It so happens that the cell parameters of the company compound or 8.1, 23.8, c is 10.8, beta is 99.7 and the volume is 2077. And the figure of merit which tells you how well these cell parameters have been fitted using the profile refinement. So, what we did was to do a profile refinement.

Got the cell dimensions the usual way, indexing solving for the cell dimensions and then we calculated this so called figure of merit which is essentially telling you how reliable this value is. It should be reasonably high value it is 19.8, the larger the value the better is the fit. So, let us not discuss this FOM because I have not talked to you about how this is coming about, but what is very important is this fact which is highlighted here all the peaks have to been in the indexed.

So, when you do a profile refinement it is also your job to make sure that all the peaks which appear are all indexed; that means, we have the HKL associated with every peak, there is no unindexed peak in the list with which you have determined the unit cell dimensions and this is a must when that is a must we know now that this is very uniquely determined unit cells for the system.

Then the other compound was also taken up using the same package, the same machine, the same characteristics associated with the machine, same conditions we find that the cell parameters are these and the volume is 2441. Now the two volumes are different and of course, the cell dimensions are different the beta is different, so do you conclude that it is a polymorph well we do not know. Because the indexing of course has been done uniquely, so that says that these two are single phase compounds anyway the marketed compound has to be single phase otherwise it will not be patented and patents will not be permitted.

So, the first excitement of this is to say that it is a new polymorph, but we cannot just say new polymorph and wind up the whole thing. So, what we have to do is to do the profile fitting, we do not need to do the structural determination we do only the profile refinement and the profile refinement gave the following values R p is 10.08 and R wp is 15.36 and there is a measurement of the accuracy with which it is fitted and that is 22.29.

These two values 10 and 15 are very reliable given the nature of the part the powder pattern we have. Normally in a very good powder diffraction pattern and particularly the one we discussed previously which was inorganic in nature we will not have that kind of quality powder diffraction coming in this case.

And therefore, what we see here is the two R factors which are reasonably reliable, so we say that this cell dimension has been reliably determined. So, also the next one we have to do the experiment on that as well and do the profile fitting using the same condition, same evaluation parameters.

We find there it is a slightly better fit it is more crystalline as you saw, here this material is more crystalline than this material which these people have made in the company, that depends upon the method of preparation the conditions in which they made and so on; obviously, they were claiming that the methods were different. And therefore, it has to be a new polymorph that is was their conclusion, but the conclusion cannot be unless it is absolutely verifiable it cannot be concluded that these two are the different compounds and therefore, polymorphs of the same material API.

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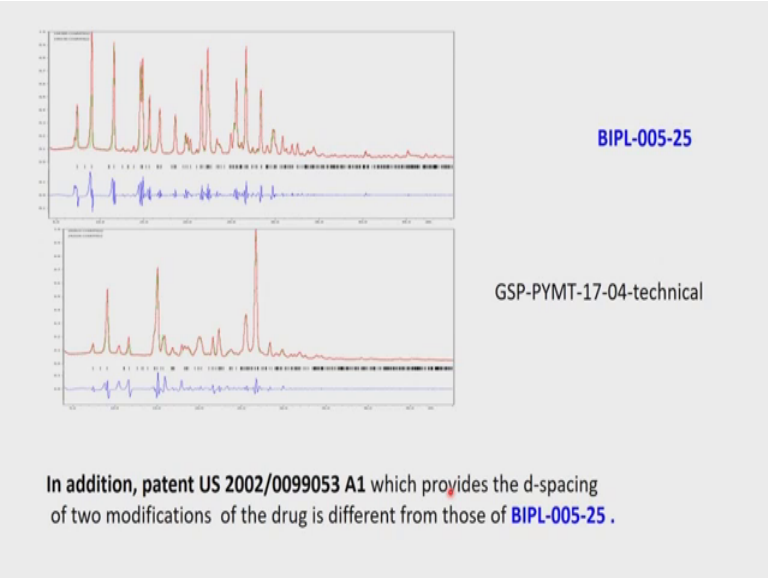

So, the profile fit results are shown here the this is the company compound and this is the profile fit for the available compound which is marketed. And these this is these two are of course, the APIs active pharmaceutical ingredients they are not the materials in tablet form. And, so the profile fit clearly shows that these two fits are very very accurate.

And in addition at that moment we came across a US patent which provided d spacing of two other modifications of the drug and we found that one of them is this the already patented material, the other one already marketed material. The other one the second form which is the drug is also different from that of behavior, so we also did the whole operation again on the second one. Even though the second one the pure API was not available, so we could not do a thorough analysis like what we did in this case.

We find that the pattern is different and the profile fit which we could do with whatever was available was not a not agreeing with the company sample. So, we concluded that the company sample therefore, is a new polymorph. I am told that the company has got this happened last year, so am told that the company has gone ahead and filed a patent I do not know what the results are, but this is something which we did for the that particular company.

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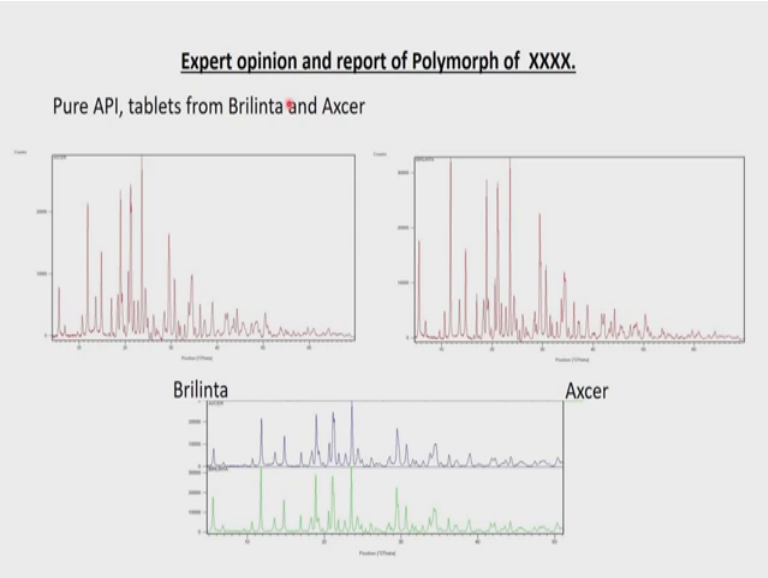

Then there is another case, there was the pure API which was made by a company, there were tablets made by the company and there were also tablets from two other companies, who were actually manufacturing and selling that product so, the company which we have, which approach to us wanted to know whether they have a new polymorph.

So, this was a little more challenging task because two companies have made these compounds and those two companies the powder diffraction pattern is shown here, if you look closely of course, we will overlap it you may say that they are one and the same. So, what was shown here in fact, below is a more clear cut description of how these peaks are developing, maybe the crystalline quality of one is slightly better than that of the other but these two are one and the same.

And this in fact, is the polymorph among several other polymorphs already reported. So, for this particular compound there are five polymorphs four polymorphs. So, the company thought that they have made a polymorph which is different from, these two fellows, these two fellows have made a polymorph which is characterized as polymorph II.

So, the company which came with the data I wanted to know whether this particular polymorph is different their particular compound is different from these two. Obviously, from the comparison here and also if one does the profile fit we see that these two components are one and the same and they belong to the so called polymorph II.

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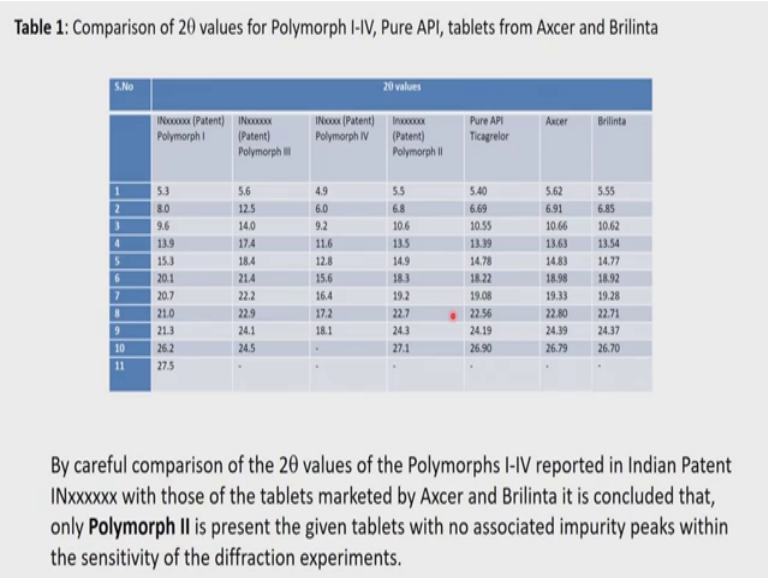

So, what was done was the data of all the polymorphs are listed here. So, you can see that the in the patent it is a Indian patent, there are 1 2 3 4 polymorphs I listed them slightly differently just for comparison sake. You see the polymorph I here, polymorph II here, III here, polymorph IV there and polymorph II here this is the reported in the patent. And these are the so called the 2 theta values for the wave length which is common in all of them they are given the 2 theta values, you see for polymorph I it is 5.3, 8, 9 and so on.

Polymorph III is different it is 5.6, 12, 14 and so on; polymorph IV is 4.6, 6, 9, 11. So, they are different from the point of view of comparing the individual peaks and polymorph II is 5.5, 6.8, 10.8 etcetera. Now if you look at the pure form of the this name of the compound is this Ticagrelor, this particular compound was given to us by the company and this is the values of 2 theta. You see that the Axcer and Brilinta also have the same or nearly the same values of 2 theta; we did a profile fit, but we knew beforehand that they do not have a new polymorph.

They have a polymorph two all three companies have the same polymorph two this disappointed the company, but this is this shows the power of analyzing the structures by powder diffraction particularly in identification of the polymorph. So, the world of caution is that we should not take two samples overlap with each other and say we have that new compound have a new polymorph.

So, the conclusion should be done by doing a profile refinement, if structural data is available to the Rietveld refinement. And of course if we can go the single crystals, no doubt that you can get the structure to the accuracy with which you can argue that is a new polymorph.

So, what I will try to do in powder diffraction therefore, in the last maybe an hour or so is essentially to give you the basics of powder diffraction the indexing procedure and based on the indexing procedure. We have gone ahead and talked about the nature of the profile the way in which you can do the profile fitting and then the inert the this the decomposition of the pattern and followed by the profile refinement and also eventually the Rietveld refinement if structure is known.

We have also discussed where the sources for structures can come from the databases, from literature and also from the fact that there are similarities between earlier observed structures and the new newly made structure. If you are aware that, we have done only a doping or replacement or a substitution on a given compound and if the cell dimensions are nearly the same, we know now that there probably isomorphous in nature, so we can use the same structure information.

So, basically we need a starting model either we do single crystal structure or we do this we need a starting model. So, on once we have the starting model we can go and do the refinement. So, the refinement procedure that we use therefore, either in single crystals or in powder, in principle also tells whether we have this right starting model or the wrong starting model. Suppose we have the correct starting model then the refinement will proceed smoothly we can keep on improving the parameters, so you are accuracies in positions and thermal parameters will improve.

The structural details which you can get in terms of bond lengths angles etcetera will also improve, but that is not the situation which will exist if the starting model is wrong or for that matter if your assignments of atoms is wrong what you called as carbon is not carbon, but it is nitrogen and things like that this can happen in organic systems you can probably replace the position of nitrogen with a carbon in your structure and R factor is looking very good.

So, what you have to therefore, do is you always have to do after the final structure is finalized a difference Fourier map. There are two advantages of doing the difference

Fourier map, the first advantage is it will now check whether all the positions of the atoms we have determined with the thermal parameters are so accurate that you will not be left with any density which has not accounted for in the neighborhood of that atom. So, if there is a density which is left in the neighborhood of that atom, the assignment you have given to that atom is probably wrong.

So, if there is a mistake made between a carbon atom and a nitrogen atom it is very easily seen in the difference Fourier map. Difference Fourier map will also assist you in identifying the positions of the hydrogen atoms because hydrogen atoms now we will start so are showing up one once the structure is accurately determined. There are situations where hydrogen atoms probably are not determined accurately even by this approach; then there is stereo chemical way of fixing the hydrogen's which we discussed already along with the so called riding hydrogen refinement process procedure.

So, as they add the heavier atoms change positions the hydrogen's will ride with them. So, considering all this we atomic identification and the determination of positions and of the atoms and all that are now available and we always have the Fourier analysis to verify the accuracy that is associated with the structure.