Symmetry and Structure in the Solid State

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Lecture – 55
Direct Method

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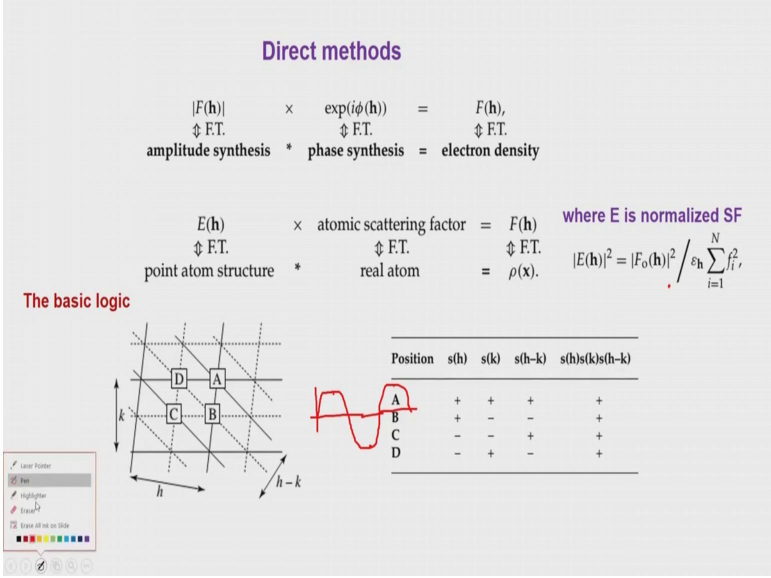

Direct methods

$$\begin{array}{ccccc} |F(\mathbf{h})| & \times & \exp(i\phi(\mathbf{h})) & = & F(\mathbf{h}), \\ \Updownarrow \text{F.T.} & & \Updownarrow \text{F.T.} & & \Updownarrow \text{F.T.} \\ \textbf{amplitude synthesis} & * & \textbf{phase synthesis} & = & \textbf{electron density} \end{array}$$

$$\begin{array}{ccccc} E(\mathbf{h}) & \times & \text{atomic scattering factor} & = & F(\mathbf{h}) \\ \Updownarrow \text{F.T.} & & \Updownarrow \text{F.T.} & & \Updownarrow \text{F.T.} \\ \text{point atom structure} & * & \text{real atom} & = & \rho(\mathbf{x}). \end{array}$$

where E is normalized SF

$$|E(\mathbf{h})|^2 = |F_o(\mathbf{h})|^2 \Big/ \varepsilon_{\mathbf{h}} \sum_{i=1}^{N} f_i^2,$$

The basic logic

Position	s(h)	s(k)	s(h−k)	s(h)s(k)s(h−k)
A	+	+	+	+
B	+	−	−	+
C	−	−	+	+
D	−	+	−	+

So, the requirement is to find get the E values from the observed structure factors the observed intensities we take the square root of the intensity, this epsilon h as I said is known as the extinction factor. There is nothing to do with extinction effect which we discussed earlier on its an extinction factor for example, if we have a p 2 1 upon c structure and we look at h o l reflections remember that l reflections are all absent by systematic absences. And therefore, the weight edge that gives is given to h o l is double the weight of a general h k l reflection.

Let me repeat, a general h k l reflection if we give a weightage of 1; that means, its it has whatever measurement we have is if the weight of one the h o l reflections because l odd is absent and only l even present it gets double the weight. And so when we are dealing with h o l reflections for this E calculation. By the way I should say that it is a h here is a vector which refers to h k l.

So, this E of h square now will be you will have to be divided by two times this quantity so; that means, the division the weight edge is now reduced by half. So, you give a weight value of epsilon h equals 2. So, depending upon the space group and the systematic absences you vary the value of epsilon h and therefore, you get a normalized structure, this structure factor is now effectively coming from point atoms. That means, atoms now are in a point and all the electron density is associated with that point and as a result you know you remember we define the delta function earlier on the diffraction is from a point atom we get a delta function. So, the contribution comes all of it will come from the point where the x y z is located with respect to the E value.

So, then what is the advantage, the advantage is now that it is not going to vary with respect to sin theta by lambda. So, the scattering angle it is independent of the scattering angle in principal. And so if it is independent of the scattering angle; that means, there is no change in the face that is associated with a point atom. So, we it becomes very easy now to put up a logic, the logic which we have is explained in this particular diagram this is a very crucial diagram see you look at three planes ok. This represents the one set of planes h k l let us say this is represented as h, it actually represents a h k l plane parallel planes you see.

So, the dark lines here of the parallel planes and the dotted lines between the parallel planes represent the halfway point; that means, if this is the distance at which the Bragg's law is validated if you now consider a cosine curve for example or a sin curve the crest is at these points and the trough at this point ok.

So, the crest and the trough are identified as plus and minus bias in this particular table, I will come to that table in a minute. So, now, we have a set of planes which are h k l and you see that in this h k l plane there are 4 regions of high electron density; that means, atoms are contained in these 4 regions A B C and D. So, these 4 regions contain atoms; that means, the value which you get for the structure factor and therefore, the E of h is be very large.

So, these we are now dealing with the highest possible values. So, after we get the E values we arrange them in the order of the value. So, the highest value is put on top the next highest next and so on. So, one once we order that we have to take the highest possible E values and take three planes, one plane is now this represented by h, the other plane is represented by k which is now this the origin. So, we have a k here and the k there and similarly the half points are denoted by dotted lines; that means, if they are now the troughs of the wave.

So, if you have a wave let me make it clear because that is an important thing to happen to observe. So, if you now take wave which is like this ok. So, this to this is now the wavelength right, one single wavelength is the point here to that point or is it the point from here to that point. In fact, that is correct the point at this point to that point is the wavelength.

So, if this is the wavelength then you see that this is represented by solid lines and this is represented by dotted lines. So, the solid lines will now correspond to one single lambda. So, to d sin theta lambda is be satisfied and so, we will have these coming in the crests of the wave and this comes in the trough of the wave. So, the alternates so if you have a h k l plane which is shown here let me go back there, if you have a h k l plane which is now going here with respect to this origin. One unit away this is the next one which is going here, between them there is a set of dotted lines which essentially represent the trough of that particular wave which is associated with the plane h, which could be h 1 k 1 l 1, we call it as h let it be h 1 k 1 l 1.

Similarly, this is the value of k which is now represented perpendicular to that direction. So, let us say this, this and that and then the alternate dotted lines are indicated, and we take the third set of planes h minus k which is in the direction of the diagonals. So, we essentially represent all three directions here three so if the logic is the following. You consider three very strong E values h k l values which are intersecting with each other to represent this plane and they are intersecting in such a way that they passed through electron density positions A B C and D.

Now, what happens when it passes through A? When it passes through A the value of h as we see here is a full line; that means, it is positive the value of k is positive down here and the value of h minus k is also positive.

So, the three values now which intersect at a will give rise to plus plus plus so; that means, if you are looking at a central symmetric structure these three now represent a value equal to 0, the phase value equals 0. So, this is sin of h sin of k sin of s h minus k. Now the product of these three s h s k s h plus k will therefore, become positive this is what is important, when we have three very strongly diffracting planes which pass through either at the trough or at the crest through these points A B C and D where there is electron density. That means, atoms are located at these positions, then you will have the product of s h s k h k and s h minus k always positive and one can associate a probability with this and that is how direct methods are carried out.

So, we now, therefore, take three strong highest E values, these E values are defined in such a way that we have four points A B C D which are electron density rich and these three planes intersect such that they pass through these electron dense regions. So, whenever they pass through the crest we call them positive and whenever they passed through the dotted lines or the troughs we call it negative. So, the B position you see is except for the h which is now this way, this is the h value except for h which is positive at b these two are going to be negative, but the product is still positive.

Similarly, in the case of C you see that the value of l is positive the other h and k are negative. And so the product is still positive, the point D you have again one of them positive which is the k value which is positive here and these two are going to be negative.

So, essentially if you look at this diagram you have possible combinations where with individual signs associated with these planes, it hardly matters because there is rich electron density associated with these three planes and that electron density therefore, it gives for all four positions where there are atoms, the product of the signs is positive. So, that would mean that wherever there is an atom if you take intersecting planes those intersecting planes should be having a positive value. And this is the logic with which direct methods work because as you go to lower and lower E values the reliability with which you can assuredly say that these three products are positive becomes less and less.

So, you can calculate a certain probability that is associated with it, we do not go into the detail of this discussion because this is not in the purview of our current course. This needs an advanced crystallography course, but I will tell you how we normally do the direct methods.

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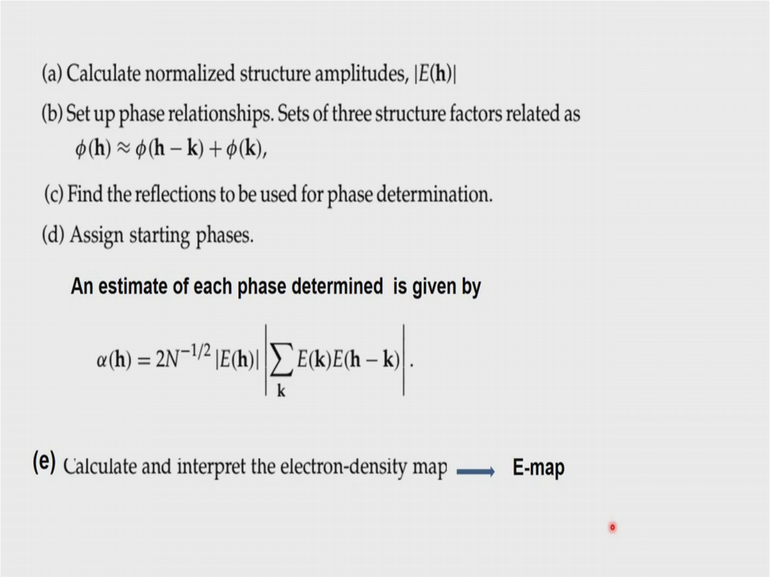

(a) Calculate normalized structure amplitudes, $|E(\mathbf{h})|$

(b) Set up phase relationships. Sets of three structure factors related as $\phi(\mathbf{h}) \approx \phi(\mathbf{h}-\mathbf{k}) + \phi(\mathbf{k})$,

(c) Find the reflections to be used for phase determination.

(d) Assign starting phases.

An estimate of each phase determined is given by

$$\alpha(\mathbf{h}) = 2N^{-1/2}|E(\mathbf{h})|\left|\sum_{\mathbf{k}} E(\mathbf{k})E(\mathbf{h}-\mathbf{k})\right|.$$

(e) Calculate and interpret the electron-density map → **E-map**

So, the direct methods now calculate normalized structure factor amplitudes, set up these phase relationships I showed it in terms of science, but they can have different values of phi depending on whether it is a central symmetric or a non-centrosymmetric structure.

So, instead of sign you replace it by the phase. So, the phase of h is nearly equal to the phase associated with h minus k plus the phase associated with k. So, this is the relationship which we are going to use and find the reflections to be used for phase determination. Based on this you generate phases for let us say something like a 100 reflections you do not have to generate phases for all the reflections. The top E values are taken top 200 E values and within that 100 E values any combinations of this kind which we can develop, we can now associate this equation with them and find the reflections to be used for phase determination.

And then you assign starting phases to these, you can if you assign positive sign for everything in a central symmetric case you will get nothing you will get a very strong peak at the origin, because it is all phases cannot be all positive. Some of them must be positive some of them should be negative like the way we I indicated in this diagram, in the previous diagram.

So, based on this logic we calculate now what is the probability that this product is plus. So, in this example where I have shown the probability is 1.0, but we can calculate the probability as we go down in the E values the probability value keeps on going lower and lower. The confidence level with which we can assign these values become lower and lower; that means, the confidence with which we can assign phases for reflections become lower and lower, but then we can put a cutoff on the probability limit, let us say we cut it off at a value of 0.9.

Then we will get the solution for the phases for the first 10 top E values that may not be sufficient, what we want is reasonable number of reflections based on which we can calculate a Fourier map which is called the E map, and that Fourier map will give us the approximate positions of the atoms it will give us the trial structure. So, there is no involvement of whether it is the atom should be heavy or light it does not matter now because it is independent of the z value because we have taken this in the denominator we have normalized the structure factors. Since we have normalized the structure factors there is no dependence upon the nature of the atom, it is only dependent upon where the point atoms are situated and as a consequence this probability development of phases will depend upon how many starting phases we can have.

So, at this stage there are different ways in which one can do it, there is what is known as a symbolic addition method, there is what is known as a phase development method then phase criterium development method and so on. So, an estimate of each phase determined is given by this expression. So, this expression depends upon how strong these three reflections are and what is the total number of atoms in the structure.

So, we assign starting phases to a few reflections. For those reflections which we do not know the phases we can either give symbols which is known as the symbol symbolic addition method and try to solve the sign of the symbol if it is a central symmetric structure. Or you take about twenty such reflections, strong reflections give random phases to them.

So, use a random number generator and assign phases to them compute the E value, that will be wrong anyway you will not get any completely map it will be a junk. So, then what you do is you allow this to refine and you find the newer phases making use of the fact that we should always have this reliability on the strength of the E value, the stronger they we have E value the better is the phase determined.

So, keeping that in mind we can do an E map calculation based on the phases we generate we give random phases to about 20 of them, keep changing the phases using a random number generator every time calculate the E maps. So, 1000s of E maps can be calculated eventually, we will hit a combination which is closest to the final structure then the E map will give you the required I can positions.

So, this is why this method is called direct methods because it is, it can be directly calculated the phases and so we have therefore, the structure information. The ease with which programming can be done using random number generators and so on is mathematically very simple. And therefore, the computer programs which are available or extraordinarily fast, the computation is also fast because we use what is known as a fast Fourier algorithm FFT fast Fourier transform and that FFT will make sure that your E maps are computed at a very quick time.

So, one once you have that you calculate and interpret the electron density map which is referred to as the E map you will get the trial structure. I do not think beyond this we should worry about the phase determination protocols because that would make it an advanced crystallography course which we are not now really interested in. What we are interested in is the symmetry.

Now, where does the symmetry come into the picture here the symmetry came automatically into the picture, it came automatically into the picture because we are talking about the electron density and the associated phases with the planes which are strong a strongly reflecting plane. Therefore, in principle should have electron density in it or the contributions of various atoms to that particular plane should be very very positively significant.

If that has to be significant then the nature of the atoms that are arranged inside this particular space group should be related by a proper symmetry relationship. So, symmetry again now controls the way in which this propagation of the phases occur and therefore, again we have to see that our requirement of symmetry and the star in the structure is very very crucial. That is all I can tell about the methodologies in this particular course because it is otherwise becomes out of scope.

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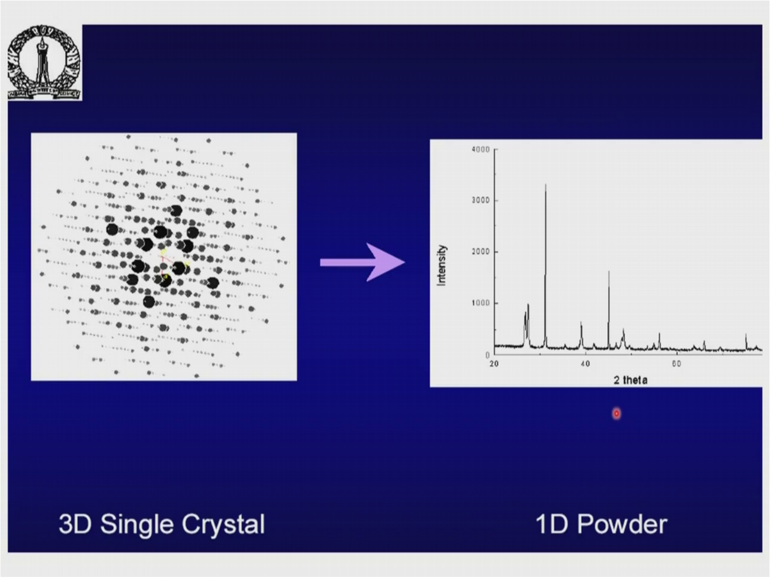

3D Single Crystal

1D Powder

We now change gears; we now change gears and go to a new area and this is an area where many of you are interested because it is not always possible to grows good quality single crystals. In many cases there are reasons why good quality single crystals will not grow at all; however, it is possible to get poly crystalline phases. So, poly crystalline growth is quite possible; that means, the size of the crystals or the crystallites as we call them are so small that each one is a single crystal, but then they come in the form of a powder. We cannot look under the microscope and separate if one single particle.

These particles are of course, crystals. So, a large number of crystals now are assimilated in the form of a powder. So, they if we get a powder sample particularly an organic chemist synthesizes and gets a solid form of a in the form of a powder. The first check he will do is to put it with x r d, the reason why it is done is that if it gives a sharp set of reflections like this then it is a poly crystalline sample. It is possible that we do not get this kind of a sharp diffraction line when we do the X-ray measurement we may get a large hump like this.

Then the conclusion is that it is an amorphous material. So, it is possible to have amorphous materials also looking very shiny like for example, glass is not as crystalline material it is an amorphous solid. So, essentially what we therefore, do is in a three-dimensional single crystal which we discussed so far we have isolated h k l positions, but all these h k l information is contained in this one dimensional profile.

So, you have a three-dimensional reciprocal lattice which we have discussed so far.The three dimensional reciprocal lattice gets condensed into a one-dimensional profile like this. Whatever is the information here is also contained here, but there is a severe overlap of these reflections, because we are now plotting intensity versus 2 theta. This 2 theta is the scattering angle and as we go from 0 to let us say 90 degrees or 100 degrees the reflections which dominate are appearing here.

It may so happen that under each every peak there may be several reflections we do not know, but a typical x r d pattern with a good polycrystalline material will look like this. Now how do we use this information to get to the structure, this is something which is very crucial for pharma industries particularly because very often the growth of good quality single crystal is a issue, in many other cases also when materials are made and synthesized normally poly crystalline forms are available very quickly, but growing a single crystal of the material is a issue. This is a problem in organic inorganic or any other area of solid state chemistry.

So, we did discuss how we grow the crystals in the last couple of classes, but then even with we make all these attempts it may so happen that we may not get good quality single crystals. So, we have to deal with polycrystalline samples. So, if we have polycrystalline samples how do we get to the structure? That is the next issue which we will take up.

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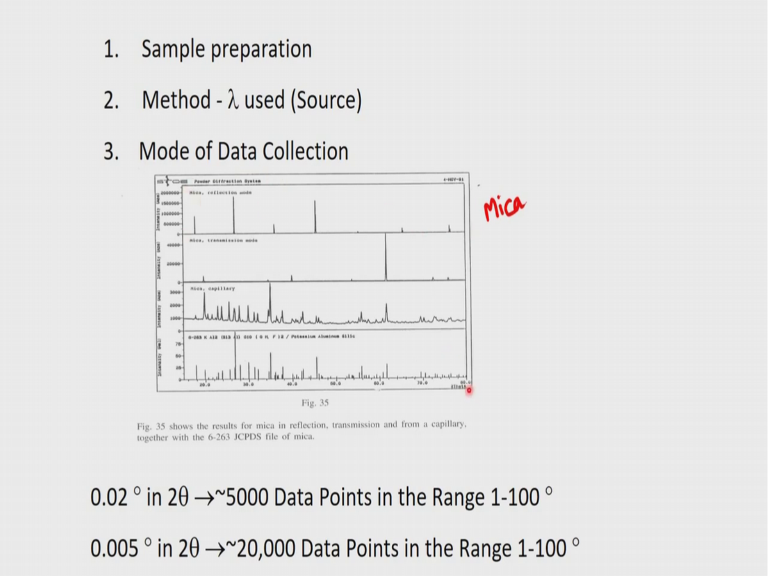

1. Sample preparation
2. Method - λ used (Source)
3. Mode of Data Collection

Fig. 35

Fig. 35 shows the results for mica in reflection, transmission and from a capillary, together with the 6-263 JCPDS file of mica.

0.02 ° in 2θ →~5000 Data Points in the Range 1-100 °

0.005 ° in 2θ →~20,000 Data Points in the Range 1-100 °

So, there are a certain set of cautionary points one has to take, which nobody takes when we do the powder diffraction. So, in case of a single crystal you do not have to take any cautionary steps this is another big advantage. If you get a good crystal single crystal you look at through the microscope and the microscope shows the extension effect, then you assume that the crystal is good put it on the diffractometer it will give you the diffraction spots. And if the spots are good and you have enough information on the reciprocal space, you will now know how to go to the structure determination and also final refinement and so on which we have briefly looked into.

So, we know the structure determination protocol for a single crystal. What happens in the case of a powder? We can just not take a powder and throw it on the diffractometer which most people do and you put it on the on the glass plate or whatever is the plate given by the company manufacturer and put the sample and then collect the data and then you will see a picture. And that picture if it is sharp enough peaks you say oh I have a polycrystalline sample.

And very often in industry what they do is to look at the diffraction pattern and then if the if they know roughly what the material is all about they get the diffraction pattern already they available in the databases and then put one on top of each other and compare the peaks and say oh we have made the same compound. These are all more or less criminal acts as far as diffraction is concerned, because X-ray diffraction needs a little more, it has a little more honor than what we people give.

So, it gives us more information than what is required, as I already said powder diffraction has all the information of the three-dimensional reciprocal lattice imaging and therefore, we should in principle be able to use powder diffraction even for structure determination. It is not just that we compare two samples and say oh they are one and the same one or if you get a slight differences in the peak positions we cannot say we have made a polymer or we have made a new compound and whatever. So, those conclusions which are done sometimes in industry have landed them in serious trouble and it should not be done.

So, what do we do, we first have to worry about how we prepare the sample for the diffraction experiment and of course, then we have to worry about what is the wavelength which we are going to use sample preparation. It is generally recommended that even though we get experiment to give us a powder, it is better that we make sure that the powder is nicely prepared, by prepared I mean we take the sample in a pestle and mortar and we grind the sample. We after grinding the sample in principle, in principle nobody seriously does it, but in principle we have to pass it through a sieve which has a certain dimension.

So, let us say we pass it through a sieve which has hundred microns and it is like you know getting the atta prepared for your chapatis. So, you just play with the sieve and then get the powder of 100 micron sizes only assimilated in one place. And take that as the sample and then you prepare the sample by the rule, by the method which you are going to use, the way there are three different ways in which you can collect powder data this is something which probably is not very well described everywhere.

The routine X-ray diffraction equipment which we get for powder diffraction is the reflection mode. You will have a sample on a horizontal glass plate you spread the sample on top of it then X-ray will come from here and then fall on the sample and the Bragg diffraction is satisfied. So, it will go at an angle satisfying the 2D sin theta and lambda and you will get the reflection and you may put a counter or a measuring device there the detector, and the detector will catch the intensity that is coming out and then you move the 2 theta circle so that the detector moves with it and collects with respect to two theta the data.

So, we get intensity versus 2 theta that is the usual geometry we have in many of the standard setups one can also collect the data with what is known as that if the transmission mode where the equipment is such that we now allow the X-rays to pass through the sample. The sample now can be rotated as well and as the sample rotates the X-rays pass through it and then they come out the diffraction is measured in 2 theta with respect to the detector.

So, this is a flat horizontal goniometer system where you have the goniometer put in a direction of the incoming radiation and that will now catch carry a container in which we have the sample. So, the sample is now exposed to the x rays in a perpendicular manner, it is no longer the reflection geometry it is called the transmission geometry.

The age old method of the powder diffraction which was discovered and used in the earlier days was to take the powder and fill it up in a capillary tube, these capillaries are very special and these capillaries have a property that they are not absorbing the X-ray radiation they indeed scatter the radiation very little other than the scattering that is coming from the sample. So, we have to now have the sample fully filled inside the capillary and now the capillary is rotated and this is known as the device shutter mode due to the two people who found this methodology.

So, we have a capillary, the capillary rotates in a direction perpendicular to the X-ray beam and we measure the diffraction coming out and that will be the 2 theta circle. So, in all these cases the data recorded is intensity versus 2 theta. So, suppose we have a compound this is the example of a compound you may not be able to see it so I will read it out, this is the sample which is, the sample is I will write it down what the sample is the sample is mica.

So, you have all seen mica sheets they are all layered and they are layered on top of each other. So, for the reflection geometry what you can do is take a sheet out, put it on your standard diffractometer setup and then do the reflection mode, when you do that you will get a pattern like the one shown on the top. This is the pattern you will get.

So, you are going to get effectively 1, 2, 3, 4, 5, 6, 7 peaks the externality is of course, 0 to 60 degrees which is shown here, but you will get this as the eighty degrees sorry 0 to 80 is shown here. So, you will get peaks corresponding to these h k l positions. So, you can find out h k l positions because 2 theta you get the d values from d you can find out what are those h k l values one once you know the A B C alpha beta gamma. You know that methodology, if you do the transmission mode you will get a different pattern altogether, it is not it is the same mica, but your x r d pattern is different.

Now, this is something which is to be explored very carefully the reason is that the atoms in mica are all in a given plane and so the scattering is dominated by that particular plane. So, you get very strong reflections of the planes here and in the case of a transmission mode that plane may be associated with this where you see no diffraction coming in the reflection mode you get a diffraction which is very strong here.

So, this tells us that these two methods are now indicating the mica to be two different compounds altogether, but it is not the case. This kind of a thing happens in many layered compounds, that a lot of people who work on layered in organic materials. Organic inorganic layers they are parallel pack them, they are hybrid structures. In all those situations these two methods are not the recommended methods for data collection, the recommended method is the device under approach the capillary method where you rotate the sample so it the crystallites inside the capillary they orient themselves in all possible directions.

So, X-rays now fall on those crystallites in different directions. So, you get diffraction in from all different orientations. So, you see a very complicated pattern for mica here, but what you see for these two modes is very different from each other and therefore, when we are dealing with two layered compounds one has to be extraordinarily careful. So, the method that is generally suggested to be used is the device shutter mode. In fact, device shutter mode is the best mode of data collection for any powder data, but this is not the case with all molecules and all structures. So, it is when we get a x r d to be taken we use the reflection geometry.

So, reflection geometry is the preferred mode of data collection because it is cheap, the most of the commercially available instruments are using the reflection mode geometry. The entry in the database for mica is given below and you see that for every point here there is a corresponding h k l. So, this is the calculated pattern for mica. So, you can solve the structure of mica by growing a single crystal of mica and then determine the possible h k l positions and those h k l positions are shown as lines here and this is the therefore, the simulated x r d pattern and this is available in the database.

So, you see there is a one to one correspondence between this and that showing that all the peaks that are coming in the case of capillary are not impurity peaks they are all coming due to the presence of peaks which are in the structure of mica. But those now do not appear because of the fact that mica has the orientation effect this particular thing is known as the orientation effect this phenomena which we described in case of the refine the reflection mode as well as the transmission mode.

The highest peaks of these are coming due to the exposure of that particular plane from which the diffraction is coming and only that dominates because we are not either in this particular case of reflection mode we are not rotating the sample either. And so it is coming from one particular position. So, all these therefore, tell us that the mode of data collection is something which is very important it should be remembered, particularly when we are dealing with layered compounds.

Now, what is the quality and quantity of data one would like to have. If you want to determine a structure you should get as many data points as possible the same logic as in case of single crystal analysis where we had to use as many data points as possible; that means, the maximum extent of data which we can acquire in the two theta range. So, suppose let us say we go in the range of 1 to 100 if we go in the range of 0.02 degrees in 2 theta we get nearly 5000 data points.

So, we should never measure every data point in a powder pattern. So, we call it oh this is in the background this is in the peak and all that it is our decision, but basically we are measuring the intensity which is along the x axis y axis here at every point along 0.02 degrees in 2 theta.

If we go to synchrotron radiation we can measure it at 0.005 degrees in 2 theta. So, you get something like 20000 data points. So, one would say why we do this routine x r d let us go to synchrotron radiation. So, if you are determining the structure of sodium chloride why go to synchrotron radiation. So, you know you do not need a need a missile to kill a sparrow right, in Kannada we say [FL].

So, we do not have to go to find the structure of smaller molecules, smaller compounds to actually go to a synchrotron radiation; synchrotron radiation becomes a requirement when there are some special issues concerned with small molecules. What about protein structures? So, in case of protein structures we need large number of data points.

So, suppose we want to determine the structure of a protein somehow by the powder diffraction method which is nowadays a possibility even those are not many structures which have been determined people have done the powder diffraction pattern of structures which are known and try to fit the parameters associated with the structure to the observed diffraction pattern. There we can definitely use synchrotron radiation because we need lot more data points.

So, the requirement of the data points is one issue the second issue is of course, lies with the accuracy with which we measure. So, since we now have a sample properly prepared, we have a proper lambda used. So, we can change the lambda we don t have to use copper k alpha as is believed everywhere to be the mode of data collection we can use molybdenum we can use silver radiation. So, the more lower is the lambda value we know already about resolution we get better resolution.

So, use of silver radiation for example, will give us much better resolution than use of copper k alpha radiation you remember that formula where we calculated the number of possible reflections from may single crystal diffraction. We saw that in case of copper k alpha we had 14700 in case of molybdenum we had 142000 reflections. Silver radiation will probably give us more than 2 lakhs of reflections.

So, we can always use the right source for the right analysis. So, it is not always necessary to go to synchrotron radiation for powder work, if we are doing some other special observations with respect to let us say non-ambient work high temperature low temperature powder diffraction or for that matter we are looking at a in-situ reaction process which is occurring in a powder photochemical reaction and so on, then going to synchrotron radiation would be of enormous use. So, synchrotron radiation of course, can be used for powder data as well that is that is the in a nutshell the gist of the whole story.

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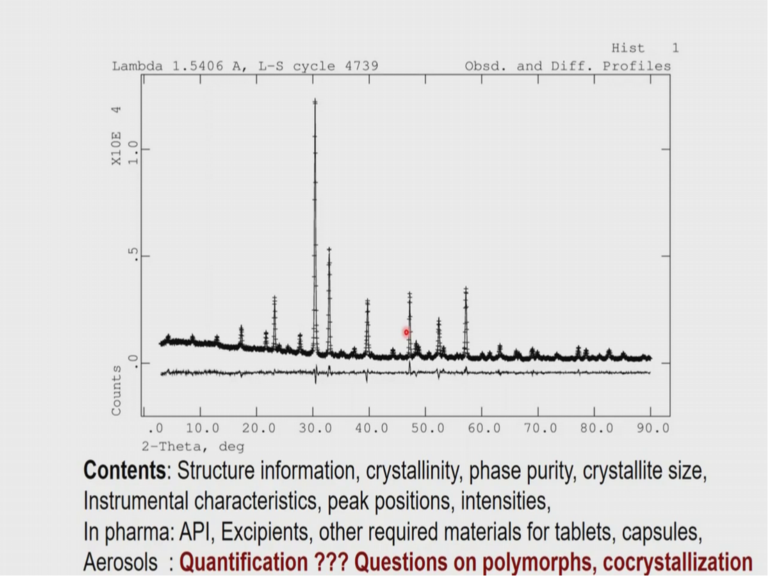

Contents: Structure information, crystallinity, phase purity, crystallite size, Instrumental characteristics, peak positions, intensities,
In pharma: API, Excipients, other required materials for tablets, capsules, Aerosols : **Quantification ??? Questions on polymorphs, cocrystallization**

So, what do we do first further with the powder data? See most of us do the powder data collection like this and if you go to pharmaceutical industry or for that matter any materials scientist they want the following information, they want the structure information if possible, they want to know the crystallinity the extent of crystal into this particularly. So, in case of pharmaceuticals they want the phase purity which is very important, they want the crystallite size and of course, the instrumentation characteristics become very crucial for aligning all these things, the positions of the peaks and intensities are very crucial.

So, we have the x axis giving us the geometry the y axis giving us the structured information. So, the x axis is the one which is most crucial for most of the industries because they want to get to the cell dimensions and the possible crystal structure information that can be derived from this. Other than that in pharmaceutical industry they want to distinguish with the they find out the API the structure of the as prepared ingredient and pharmaceutical ingredient excipients if any other required materials for tablets capsules and so on.

And they also want to qualify in case of aerosols and then of course, the major thing lies in terms of polymorphs and co-crystallization. Co crystallization can give rise to solid solutions it can give rise to co-crystals it can give rise to eutectic phases and so on. So, all these issues come up and the answer comes from powder X-ray diffraction believe it or not and.

So, powder x r d therefore, is a very very powerful tool as I already mentioned earlier in some context that the cell dimension you determine from powder diffraction this is much more accurate than the cell dimensions you get from the single crystal measurements that is because the powder sample has a large number of crystallites, many many thousands of crystals whereas, a single crystal has only one crystal. So, that therefore, allows for averaging effect and therefore, you get very accurate cell dimensions and therefore, the determination of space groups and other things become fairly straightforward in that context.

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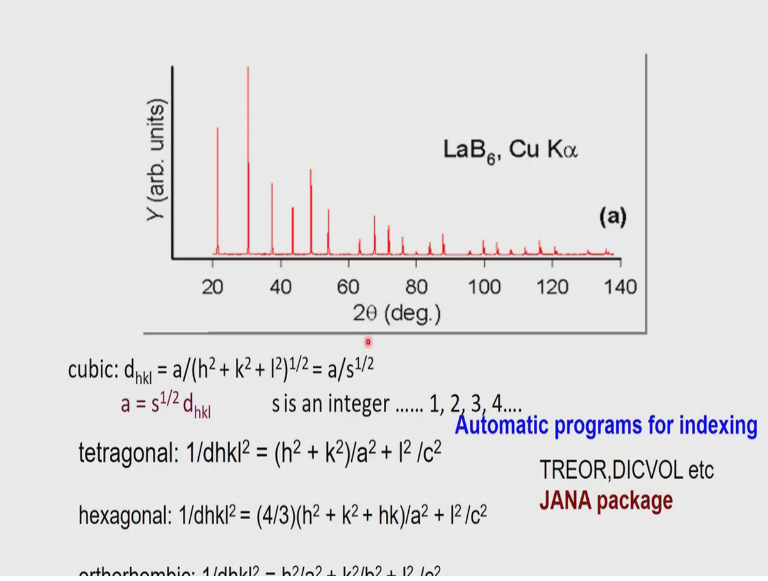

cubic: $d_{hkl} = a/(h^2 + k^2 + l^2)^{1/2} = a/s^{1/2}$

$a = s^{1/2} d_{hkl}$ s is an integer ...... 1, 2, 3, 4....

Automatic programs for indexing

tetragonal: $1/dhkl^2 = (h^2 + k^2)/a^2 + l^2/c^2$

TREOR,DICVOL etc

JANA package

hexagonal: $1/dhkl^2 = (4/3)(h^2 + k^2 + hk)/a^2 + l^2/c^2$

orthorhombic: $1/dhkl^2 = h^2/a^2 + k^2/b^2 + l^2/c^2$

Let us take the case of a standard sample you know most of the materials, most of the manufacturers give us this particular compound LaB 6 and if you record with copper K alpha you get a pattern like this a very beautiful pattern and you go from 20 degrees in this case to 100 and 40 degrees nearly and you get a beautiful pattern by beautiful I mean you see the background the background is steady throughout. So, there is no deviation in the background and you get peaks which are fairly sharp, if you look closely they have a certain width associated with them I do not have time to discuss with all; within this course what is the reason for the width and so on. That is again a very advanced course in powder diffractometer.

However, we see that these are the peaks. So, if the compound now belongs to a cubic see we discussed this already in case of single crystals, we found out how the d square h k l values can be determined in case we have the information on the h k l as well as the cell dimension. The cell dimensions can be determined one once we have h k l and d of h k l available to us and it varies from various systems cubics tetragonal hexagonal an orthorhombic and so on.

Most of these indexing is done through automatic programs which are available in free domain space, the program called TREOR, there is a program called DICVOL there is a package called free chris fire, but I am told by some of my students that chris fire is no longer active. Obviously because of the fact that chris fire probably was on a previous generation computing system and.

Now, the computers have changed their architecture. So, I did not nobody did make an attempt to write that program fresh possibly, but there is this JANA package which is again a free downloadable package which does everything it does single crystal refinements, it does standard powder diffraction analysis, it also done the does the so, called rietveld method which we will briefly touch upon as we go along further.

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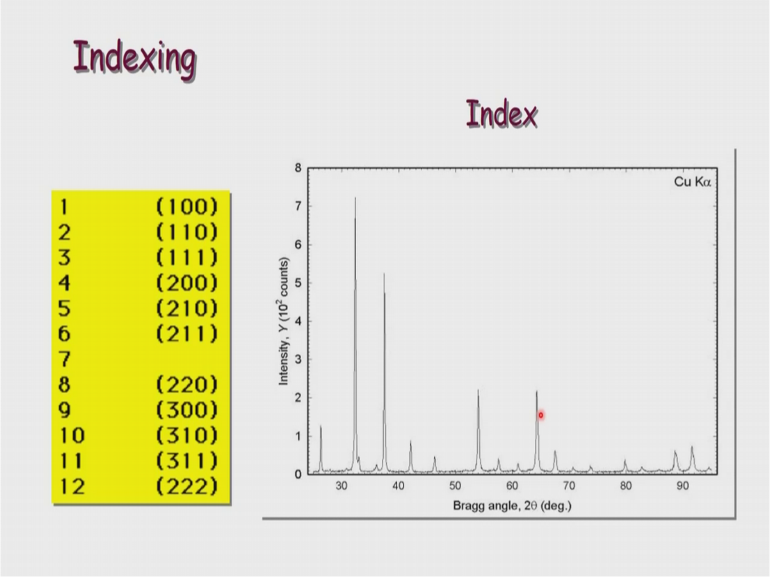

Indexing

Index

1	(100)
2	(110)
3	(111)
4	(200)
5	(210)
6	(211)
7	
8	(220)
9	(300)
10	(310)
11	(311)
12	(222)

So, how do we index the spots. So, now, you see here is a pattern ok, there you have 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 etcetera so many peaks ok. So, I will take the first 12 peaks associated with this and these first 12 peaks I will start giving the least possible h k l values; that means, I will start with 100, then the second one is 110, third one is 111 this is a cubic system. So, in a cubic system what you have is this expression h square plus k square plus l square is equal to half to the power half right.

So, what are the h k l values we can think of? We can think of the h k l values to be h equals 100 and in a cubic system 100 is same as 010 is same as 001. So, we do not need to consider those and that is why the next one we consider is h equals 1, k equals 1 so that is why it becomes 110 then of course, 111 we go to 200, 210 or 211 then 220, 300, 310, 311, 222 in a cubic system. So, all these now we will h square plus k square plus l square is equal to 1 in this case h square plus k square plus l square is equal to 2 in this case.

So, you give these numbers 1, 2, 3, 4, 5 when you come to number seven you cannot have a combination of h k l which is integer and it will generate the number 7. So, we will not have seven in other words h square plus k square plus l squared equals 7 is not possible check it out. So, give different values of h different values of k different values of l you will not get to 7. So, we have to leave it out and then the rest is 220, 300, th310 etcetera so, this is the process of indexing.

So, if you have a cubic system a simple cubic system and you have the formula h square plus k square plus l square and you are dividing this by a square to get to the value of d of h k l what you get from this is the I versus 2 theta from 2 theta you calculate sin theta and then 2 d sin theta and lambda will give you the d values those d values. Now you associate with these planes, the very highest index could be 100, the next one is 100, 110 and so on.

So, when you give these values these will now start to fit with each other. If this is a cubic system, if it is not a cubic system we will not get integral fits of this kind, then you have to think that this system does not belong to a cubic system. So, the process of indexing therefore, is all automatized so we are not in a position to go to the discussion of how we index it. So, we have to go to these program packages which will do these indexing whatever be the crystal system.

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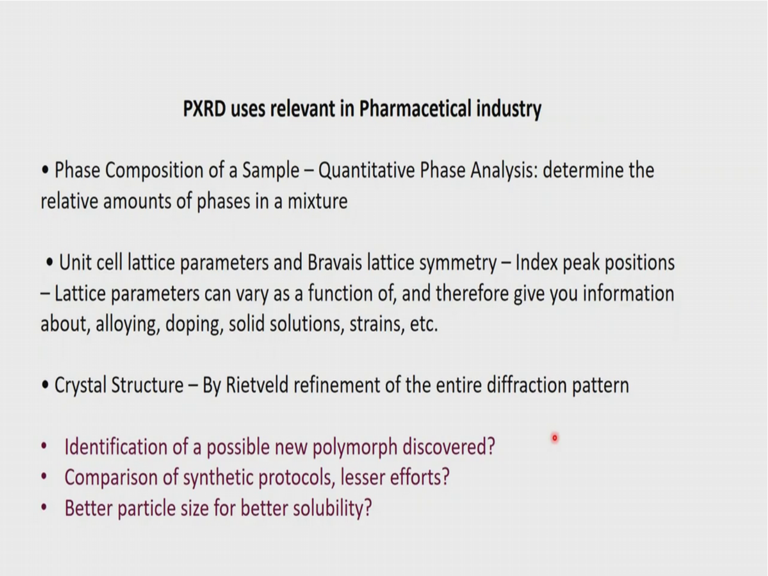

PXRD uses relevant in Pharmacetical industry

- Phase Composition of a Sample – Quantitative Phase Analysis: determine the relative amounts of phases in a mixture

- Unit cell lattice parameters and Bravais lattice symmetry – Index peak positions – Lattice parameters can vary as a function of, and therefore give you information about, alloying, doping, solid solutions, strains, etc.

- Crystal Structure – By Rietveld refinement of the entire diffraction pattern

- Identification of a possible new polymorph discovered?
- Comparison of synthetic protocols, lesser efforts?
- Better particle size for better solubility?

So, what I will do is instead of going into the detail of powder diffraction I will discuss the powder diffraction uses relevant in pharmaceutical industry. This is also we can generalize it in chemistry for example.