Downstream Processing
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Lecture No - 35
Crystallisation

This class we are going to see a new downstream process or a new unit operation that is, crystallization. So, in crystallization what we do? We try to recover the product in a solid form, in a very pure form. So, crystallization generally yields a very pure product. Generally, crystallization is done at the very end of the downstream processor. So, that means you have performed several steps like recovery, purification of the product and then you want to make the product in a solid form. So, this is generally in the end of your downstream.

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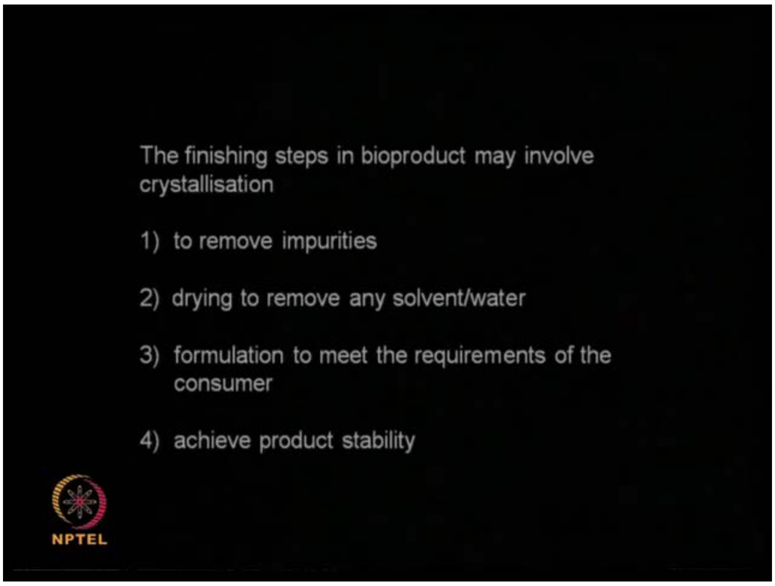

The finishing steps in bioproduct may involve crystallisation

1) to remove impurities
2) drying to remove any solvent/water
3) formulation to meet the requirements of the consumer
4) achieve product stability

Crystallization can also help you to remove impurities. That means only your product will crystallizes from the mother liquor where as the impurities are left behind. Impurities could be small molecules or even proteins and so on. You can also do crystallization to remove solvent or water because you are making solid from a solution. So, obviously you are removing the liquid, the water or the solvent.

Sometimes the consumer would like to formulate the product in a solid form. So, the consumer might be expecting the product to be handed over to him in a solid form or we can achieve product stability by converting your product into a solid form. Because, has you know if you have water present in your product it may lead to contamination microbial growth. Sometimes water might not be very good for a certain bio molecules. So, you want to completely dry your product, so there is no contamination. So, you can have a long term stability or shelf life of your product. So, because of all these reasons we resort to crystallization of your product.

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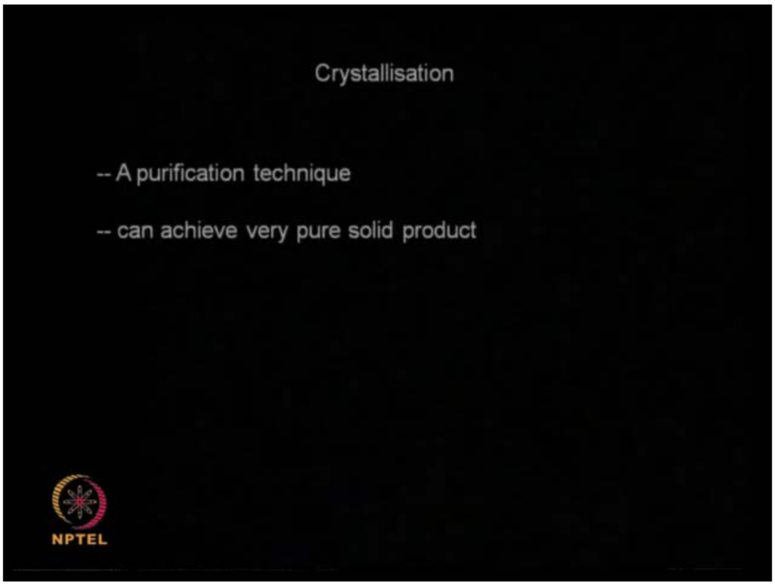

Crystallisation

-- A purification technique

-- can achieve very pure solid product

So, it is a purification technique and we can achieve very pure solid product, that is the advantage of crystallization. So, there is a difference between precipitation and crystallization. So, if a reaction takes place you are going to get a solid out of it, that is called precipitation. There, we are not bothered about the form in which the solid is. We are not bothered whether it is a crystal or whether it is a amour phase or a combination of everything but there you get a product. So, that is called precipitate where as in crystallization you resort to crystallization in order to get product solid in certain shape and size or in a form of a crystal.

A crystal has a define shape and size and the we are going to look at different types of crystals and as we go long in this particular course. So, crystal and has a shape and size. So, crystallization leads to the product in a particular shape and size where are has in a precipitation you are not bothered about the form of the solid. It could be amour phase, it could be like a gel, it could be crystallized, it could be a combination of all these things. So, that is the difference between a crystallization as well as these are the precipitation.

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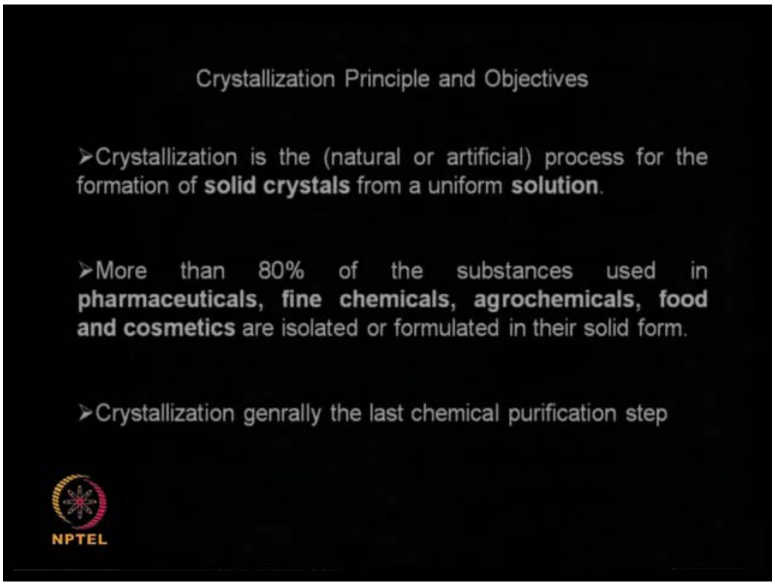

Crystallization Principle and Objectives

- Crystallization is the (natural or artificial) process for the formation of **solid crystals** from a uniform **solution**.
- More than 80% of the substances used in **pharmaceuticals, fine chemicals, agrochemicals, food and cosmetics** are isolated or formulated in their solid form.
- Crystallization genrally the last chemical purification step

So, what is the principle or objective of crystallization? So, it is a natural or artificial process that means, in a artificial process we induced crystallization by adding some chemical or heating and so on actually. The idea is to form solid crystals from a solution. A solution is generally called a super saturated solution. When normal solution will not get crystals but, we need to make a interior super saturated. So, we can make crystals out of pharmaceuticals so, many drugs have crystallized form, fine chemicals are form in the crystals agrochemicals. For a example, look at some of the pesticides, they are in the form of crystals.

Some of the food and cosmetic products, they are in the form of crystals. So, you get very pure product which can be than taken for further formulation. So, many pharmaceutical, fine chemicals, agrochemicals, food products, cosmetics, they are all in the form of crystals. So, generally crystallization is almost the last purification stage in your downstream processing actually.

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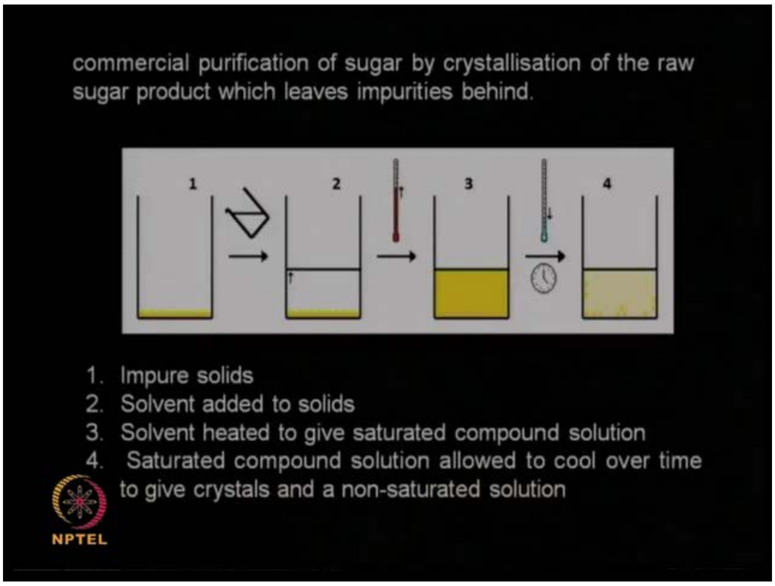

commercial purification of sugar by crystallisation of the raw sugar product which leaves impurities behind.

1. Impure solids
2. Solvent added to solids
3. Solvent heated to give saturated compound solution
4. Saturated compound solution allowed to cool over time to give crystals and a non-saturated solution

So, you may be might have all done this type of experiment long time back when we are kids. So, how do you get sugar crystals? We take impure sugar, put it in a water, keep on adding lot of sugar into a so that they solution becomes saturated. Now, when we start little bit heating, what happens? Whatever solid sugar that is not precipitate that is in the precipitated form that as not also dissolved will get dissolved. So, when we bring up the temperature, all the sugar will get completely dissolved, only impurity is may be left behind.

Ok now, we can filter and remove the impurities if you want or we can use decantation so that, the top saturated sugar solution is taken. And now, when we reduce the temperature what happens? Whatever sugar that is dissolved because as we keep reducing the temperature the solubility of the sugar in water goes down. So, the solution becomes super saturated and you start getting nice beautiful crystals of sugar.

Remember, you have we must have done this. So, this is one way of separating sugar from impurities. So, the impurities are not soluble, so sugar is soluble. So, you add all the sugar impures solid, rise the temperature so that the sugar completely dissolves. And, whatever solids that are left behind is precipitated which you filter it out then you bring down the temperature, sugar comes out as beautiful crystals. And, this sugar will be very pure because you have removed all the impurities. So, this is one good way of separating sugar from its impurities, so the solid impurities. Same thing I can, you can do for salt. In fact, sodium chloride, you get beautiful white crystals of sodium chloride and by doing this particular operation. So, fine chemicals are done the same way to get pure solid fine chemical.

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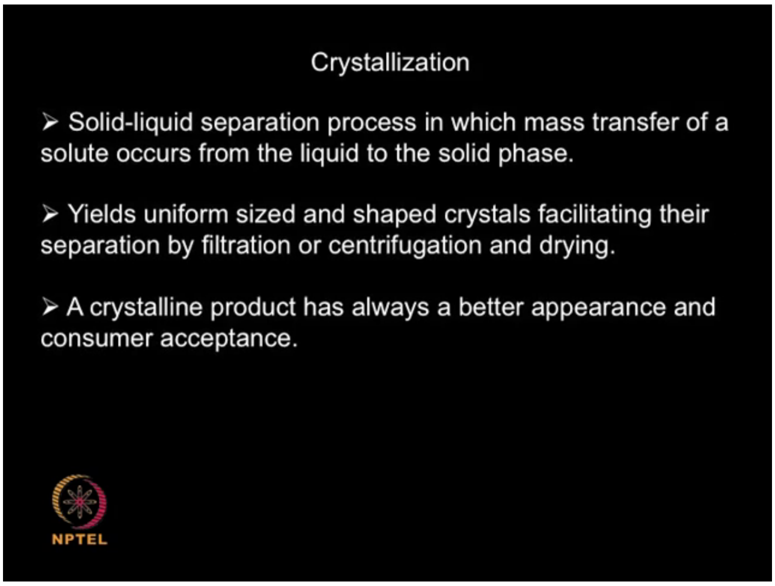

Crystallization

- Solid-liquid separation process in which mass transfer of a solute occurs from the liquid to the solid phase.
- Yields uniform sized and shaped crystals facilitating their separation by filtration or centrifugation and drying.
- A crystalline product has always a better appearance and consumer acceptance.

So, it is a solid liquid separation process. So, what you are doing? You are removing the solid from a solution containing the dissolved solid. So, there is a mass transfer of a solute occurs from the liquid to the solid phase. So, the solid that is present inside the solution starts coming out. It yields uniform sized and shaped crystals because crystals as you know as a certain size and shape so and as you do crystallization you are continuously getting the uniform sized solid out of the solution. And then, later on you can go resort to centrifugation or filtration to remove the solid from the liquid and then we can go to drying. So, a crystalline product will always have a better appearance then apprecipated product. So, the consumer is very happy and they accept your product that is the reason why you resort to crystallization.

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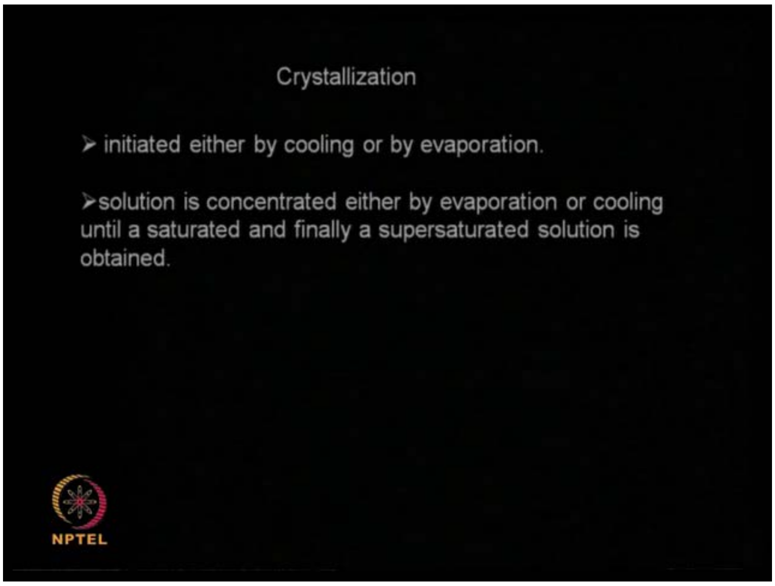

Crystallization

- initiated either by cooling or by evaporation.
- solution is concentrated either by evaporation or cooling until a saturated and finally a supersaturated solution is obtained.

So, how do you initiate crystallization? So, you can initiate crystallization by heating so that the water or solvent starts evaporating. So, that the solution becomes more concentrated and reaches a super saturation or we can reduce the temperature that is cooling. So, as you keep cooling again the solubility goes down in temperature, again the solution becomes super saturated. So, the key here is getting a super saturated solution. When you have a super saturated solution its high thermo dynamically unstable, the solid will automatically start coming out in a crystallized form.

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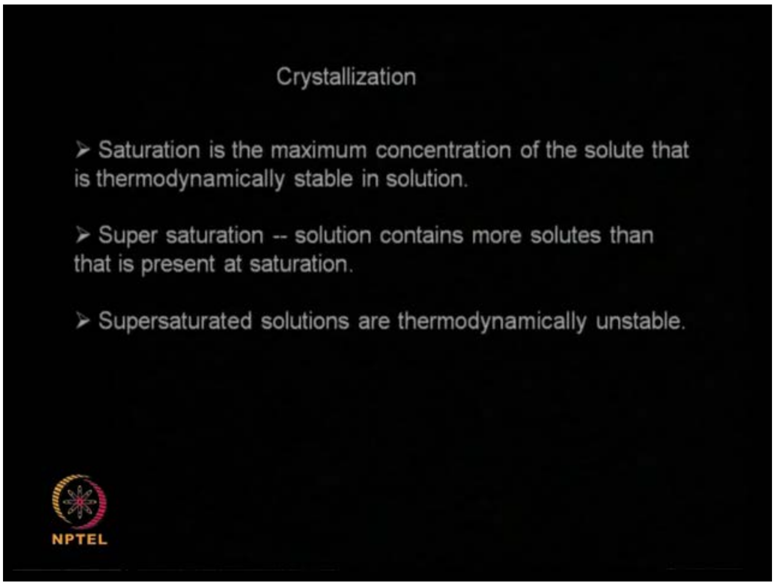

Crystallization

- Saturation is the maximum concentration of the solute that is thermodynamically stable in solution.
- Super saturation -- solution contains more solutes than that is present at saturation.
- Supersaturated solutions are thermodynamically unstable.

So, what is saturation? Saturation is a maximum concentration of the solute which is thermo dynamically stable in that solution. So, super saturation is a solution which contains more of solute than what should be present in saturated. So, super saturated solutions are thermo dynamically unstable and even small disturbance is even impurity is present can make the solids to come out as crystals. So, super saturated solution are a extremely unstable and sometimes you can add some sea crystals, so that the crystallization process is initiated. Sometimes the surface of the vessel if it is rough, sometimes the crystals are formed or if there are impurities present than again crystals are formed. So, it is highly unstable system.

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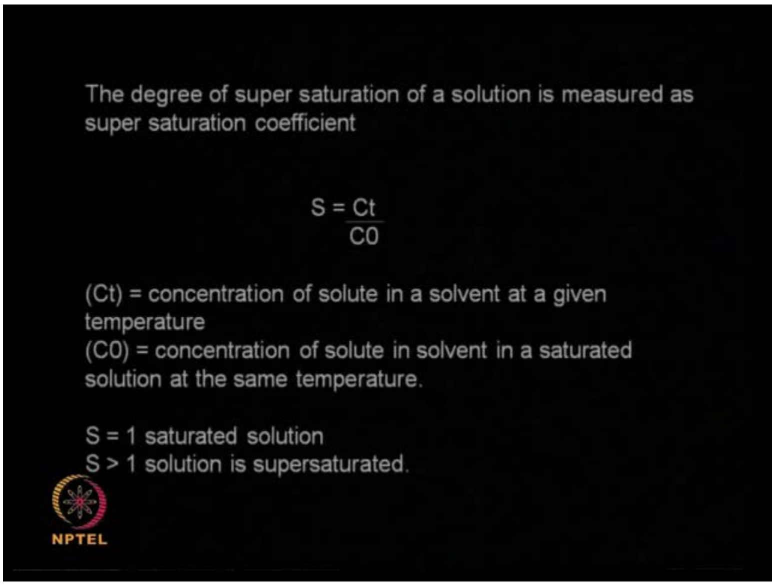

The degree of super saturation of a solution is measured as super saturation coefficient

$$S = \frac{Ct}{C0}$$

(Ct) = concentration of solute in a solvent at a given temperature
(C0) = concentration of solute in solvent in a saturated solution at the same temperature.

S = 1 saturated solution
S > 1 solution is supersaturated.

So, the degree of super saturation can be measured in terms of a number which is called a super saturation coefficient. So, S is equal to C t that is, the concentration of the solute in a solvent at a given temperature divided by concentration of solute in solvent in a saturated solution at the same temperature. So, C naught is the concentration at saturated and C t is the concentration currently that is present in the solution. So, if S is equal to 1 that means your solution is saturated, is S is greater than 1 then the solution is super saturated ok. Whereas, S is less than 1 than we can say it is under saturated that mean, we can still add some more solute and that solute will dissolve freely and nicely in the solvent.

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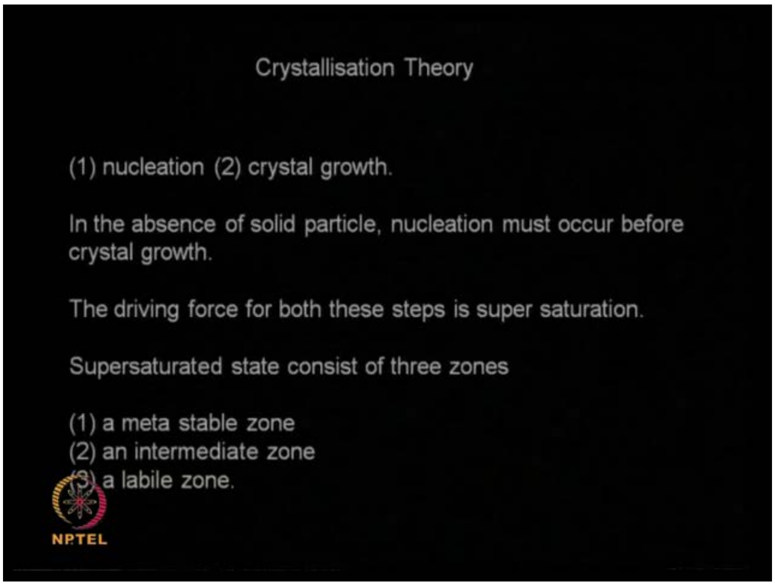

Crystallisation Theory

(1) nucleation (2) crystal growth.

In the absence of solid particle, nucleation must occur before crystal growth.

The driving force for both these steps is super saturation.

Supersaturated state consist of three zones

(1) a meta stable zone
(2) an intermediate zone
(3) a labile zone.

So, the crystallization theory states that there is going to be a nucleation and then a crystal growth. That means, 1st you should have a nucleation. So, if you have a solution containing your solute in a super saturated state you need nucleus initially and than that nucleus will start growing, that phase of those nuclei or the crystals will start growing and that is how the crystals grow. So, when we do not have any solid particles we need to have nucleation whereas we are having a seal particle than crystals will grow around that seed.

So, the driving force for both the steps is the super saturation. So, that is the driving force which pushes the solute which is and the solution phase in to the solid phase. So, the super saturated state contains three zones: One is called a meta stable zone, intermediate zone, a labile zone. So, three zones which determines the super saturated states and let us look at each one of them little bit in detail.

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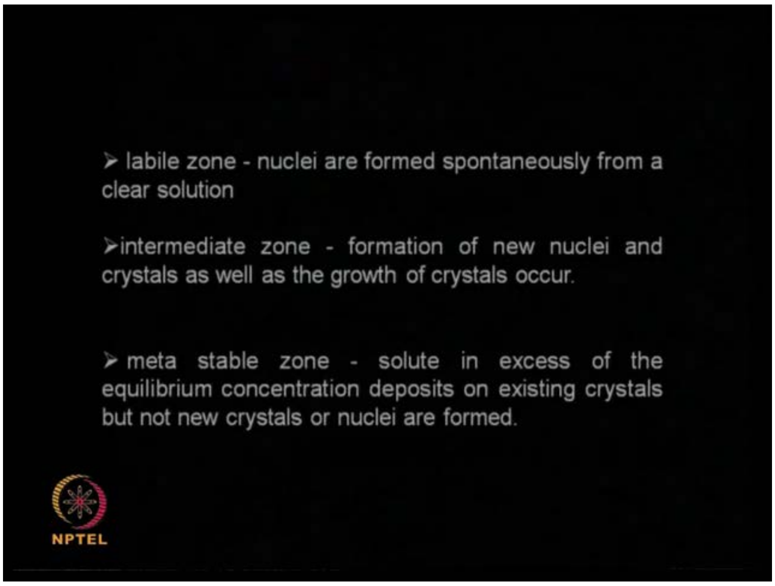

- labile zone - nuclei are formed spontaneously from a clear solution
- intermediate zone - formation of new nuclei and crystals as well as the growth of crystals occur.
- meta stable zone - solute in excess of the equilibrium concentration deposits on existing crystals but not new crystals or nuclei are formed.

A labile zone: so what is a labile zone? Labile zone, a nuclei are form spontaneously from a clear solution. So, if I have a solution immediately it forms nuclei. Intermediate zone is formation of new nuclei and a crystals as well. That means, the crystals also grow, nuclear also formed, so that is called the intermediate zone. Meta stable zone: the crystals, existing crystals start growing that means, no new crystals are formed or no new nuclei are formed. So, in the meta stable zone whatever crystals are present will start growing. In the labile zone new nuclei are formed where as in the intermediate zone not only new nuclei form but also the crystals also grow.

So, these are the three zones in which the super saturation crystallization process could be grouped into. So, if you have labile or intermediate zone you will be forming new crystals or new nuclei all the time where as in meta stable zone you are not forming new crystals but, the existing crystals start growing that they become bigger and bigger and bigger and so on actually.

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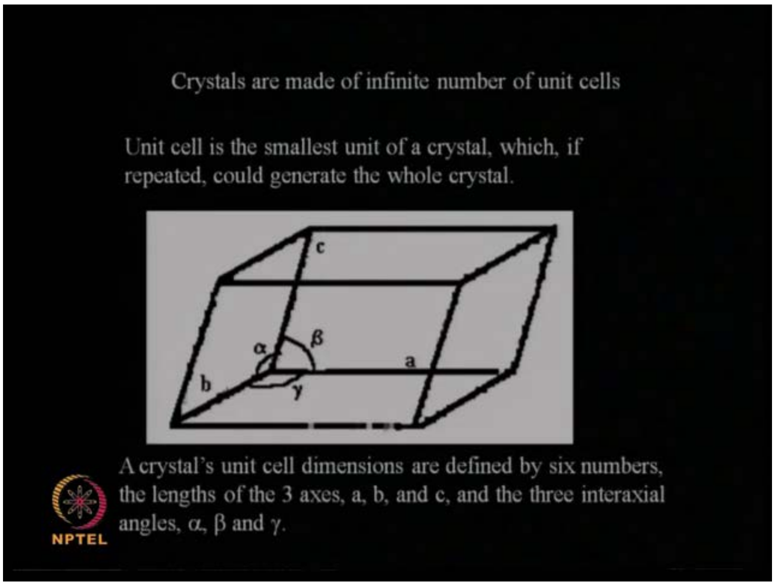

Crystals are made of infinite number of unit cells

Unit cell is the smallest unit of a crystal, which, if repeated, could generate the whole crystal.

A crystal's unit cell dimensions are defined by six numbers, the lengths of the 3 axes, a, b, and c, and the three interaxial angles, α, β and γ.

So, let us look at what is a crystal. A crystal contains infinite number of unit cells. So, there are something called unit cell, a three dimensional cell and crystal will have a repetition of this unit cell in all directions x y z direction. So, unit cell is the smallest unit of a crystal. So, if you take a crystal and keep breaking smaller, smaller, smaller, smaller, smaller, it will come to a single three dimensional structure which is a repetition of many times which makes the crystal.

So, the whole crystal is made up of this small unit cells. So, the crystal has totally six numbers: three lengths a b c and three angles, interaxial angles: alpha, beta, gamma. So, any crystal could be described with the six numbers: the three lengths a b c, alpha, beta, gamma. So, you can have different combinations of this, so you get different types of crystals. Sometimes you can have a equal to b equal to c, so you will get a something like a cube.

Sometimes you will have a and b may be equal c is not equal, sometimes none of them are equal. Same thing with the angles, sometimes angles are 90 degrees, sometimes the angles are not 90 degrees, the angles are much less than 90 degrees. So, you have a large number of permutation combinations. But still, they can grouped into beautiful structures or unit cells.

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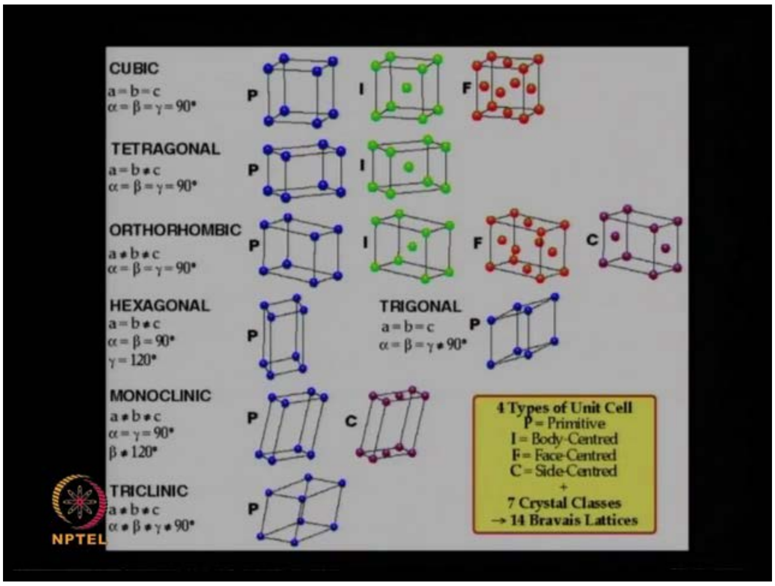

CUBIC
$a = b = c$
$\alpha = \beta = \gamma = 90^\circ$

TETRAGONAL
$a = b \neq c$
$\alpha = \beta = \gamma = 90^\circ$

ORTHORHOMBIC
$a \neq b \neq c$
$\alpha = \beta = \gamma = 90^\circ$

HEXAGONAL
$a = b \neq c$
$\alpha = \beta = 90^\circ$
$\gamma = 120^\circ$

TRIGONAL
$a = b = c$
$\alpha = \beta = \gamma \neq 90^\circ$

MONOCLINIC
$a \neq b \neq c$
$\alpha = \gamma = 90^\circ$
$\beta \neq 120^\circ$

TRICLINIC
$a \neq b \neq c$
$\alpha \neq \beta \neq \gamma \neq 90^\circ$

4 Types of Unit Cell
P = Primitive
I = Body-Centred
F = Face-Centred
C = Side-Centred
+
7 Crystal Classes
→ 14 Bravais Lattices

So, these are the seven crystal classes. There are seven crystal classes: one is called the cubic, next one is called the tetragonal, next one is called the orthorhombic, another one is called the hexagonal, another one is called the monoclinic, you have the trigonal and triclinic. So, you will see each one of them, the a b cs are different, alpha beta gamma are different. Cubic is the most simple very nice regular system where a b c are equal, alpha, beta, gamma are equal to 90 degrees. You all know this.

But then, you can have situations where a equal to b but they are not equal to c then, that is called tetragonal, again the angles are 90 degrees. Now, look at orthorhombic where a is not equal to b, b is not equal to c but alpha, beta, gamma are 90 degrees. Then comes the hexagonal where gamma is 120 but alpha and beta are 90 degrees, a equal to b, b is not equal to c. Then in trigonal a equal to b equal to c but gamma is not 90 degrees. Then we have monoclinic where a is not equal to b not equal to c, alpha and gamma are 90 but beta is 120. Then we have triclinic where nothing is equal, a is not equal to b, b is not equal to c, alpha is not equal to beta, beta is not equal to gamma and gamma is not equal to 90 degrees.

So, this is the most different system where as this is the most symmetric system. So, this is a most un symmetric, different. This is a most symmetric and similar system that is called the cubic. Now, these are the seven crystal classes. Now, there are some more variations in this crystal classes, right. We can have the body centered or the face centered. What is the body centered? You have an atom present inside the three dimensional structure that is called the body centered like that is the I. Face centered means you have an atom present on the face of the crystal ok.

So, in the cubic we can have a cube with atoms present only in the corner. We can have a situation where atoms present in the corners as well as in the center. That is called body centered I or we can have atoms present in the corners as well as atoms present on the face, that’s called the face centered. So, in a cubic we can have all three situations.

Whereas, in a tetragonal you can have the basic structure that is corner but, you can also have with the body centered as well. Look at orthorhombic we can have corners, we can have body centered, we can have face centered and we can also have side centered that means, only the side has, nothing else. In a hexagonal we cannot have anything in the body right because it is slightly and symmetric. Same thing with trigonal, same where as in monoclinic we can have not only the basic structure but also in the side centered.

In a triclinic we cannot have body or face centered we can have only the basic structure. So, if you add all this then we get 14 right, that is called 14 bravais lattices. So, a crystal there are 7 crystal classes and there are 14 bravais lattices. So, any solid when it crystallizes out will fall into one of this, so beautiful that we can easily put them into. The advantages, once you put them into that class, properties of many of this classes have been well documented.

So, we can tell may be some idea about its melting point, some idea about its dimensions, its purities and other properties can be sort of guest based on which class it falls into. So, all crystals will fall under 7 crystal classes and that is these: cubic, tetragonal, orthorhombic, hexagonal, trigonal, monoclinic, triclinic or it will fall under 14 bravais lattices ok. That’s do with the physics of it.

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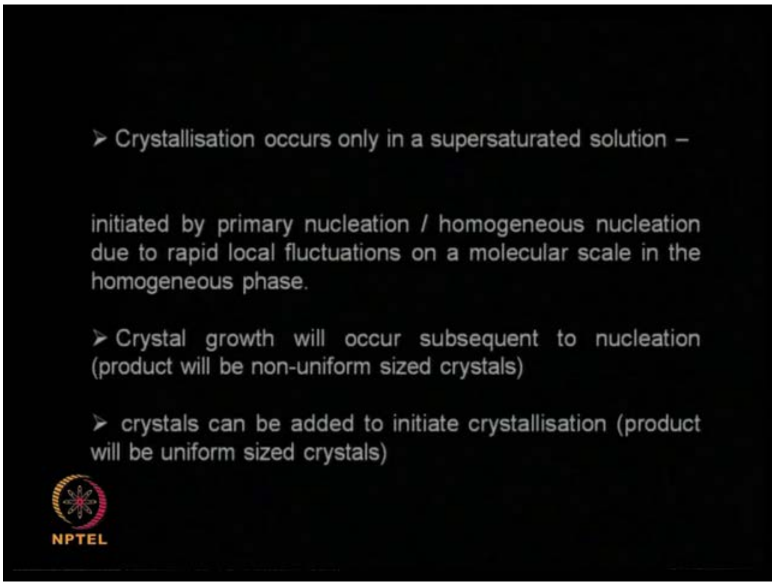

- Crystallisation occurs only in a supersaturated solution –

initiated by primary nucleation / homogeneous nucleation due to rapid local fluctuations on a molecular scale in the homogeneous phase.

- Crystal growth will occur subsequent to nucleation (product will be non-uniform sized crystals)
- crystals can be added to initiate crystallisation (product will be uniform sized crystals)

Now, let us go back again to the engineering side of it. So, crystallization occurs only in a super saturated solution. You need to have a primary nucleation that is homogeneous nucleation due to fluctuation on a molecular level or we can induce by adding very fine particles. That means, we can add to initiate crystallization but when it is happening because of nucleation then your product will be of non-uniform sized crystals.

Whereas, when you add certain crystals of known size of uniform size then the product will also be uniform size. So, generally we like to prefer this. So, what do you do? We make a super saturated solution and quickly add crystals of exact size. Then the product also will be of uniform size of one particular size now it is a mono disperse size where as if you allow it to nucleate and then crystallize you may have a poly disperse system other than a mono disperse system.

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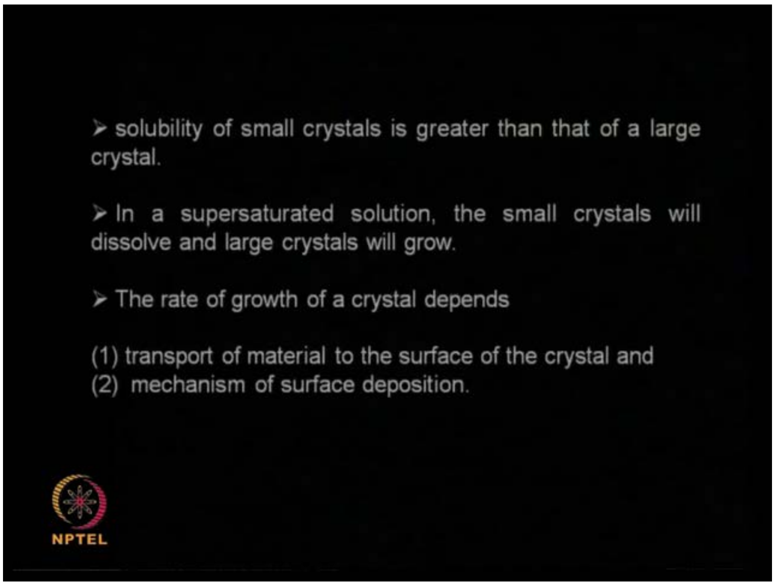

- solubility of small crystals is greater than that of a large crystal.
- In a supersaturated solution, the small crystals will dissolve and large crystals will grow.
- The rate of growth of a crystal depends

(1) transport of material to the surface of the crystal and
(2) mechanism of surface deposition.

And generally, solubility of small crystals is greater than that of the large crystals. So, when super saturation is happen crystallization is happening, the solid present or the solute present in the solutions starts coming out of crystals. So, what happens? Super saturated solution starts going becoming saturated and its be going to become less saturated. At that point of time some crystals can dissolve and again go into solution right. So, there can be a sort of dynamic equilibrium, in that situation small crystals can go into solution, large crystals will take much longer time to dissolve.

So, the in super saturated solution the small crystals will dissolve and large crystals will grow. The rate of growth of a crystal depends upon the transport of material to the surface of the crystal because the solute is present in the bulk solution. It has to get transported and come to the crystal surface and then surface deposition. How does this solid gets deposited on the surface of a the crystal? So, there could be repulsive forces, there could be attractive forces and so on. So, the mechanism of that deposition process, so these two things affect the rate of growth of crystal.

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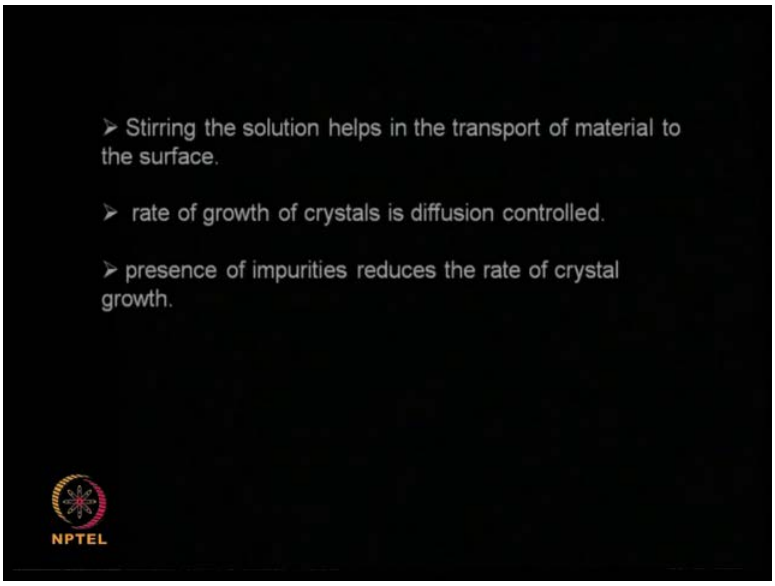

- Stirring the solution helps in the transport of material to the surface.
- rate of growth of crystals is diffusion controlled.
- presence of impurities reduces the rate of crystal growth.

So, I we can do stirring so that the material gets transported and come to this surface. The rate of growth of crystal is a diffusion controlled process actually. So, its diffusion controlled process and if there are impurities is present the rate of crystal growth also comes down. So, the crystallization process is become slow down because of presence of impurity. So, the whole process is diffusion controlled. Ideally I would like to do the crystallization very very fast and I get I would like to have uniform sized crystals.

This is an ideal situation but, what happens? The crystallization may be fast for some time and after sometime it will be very very slow, number 1. Number 2, although you would like to have a mono disperse system, how do you achieve mono disperse system? I said we can seed it with known and some known sized uniform particle but, sometimes nucleation also happens and then you may end up with the poly disperse system or poly disperse product.

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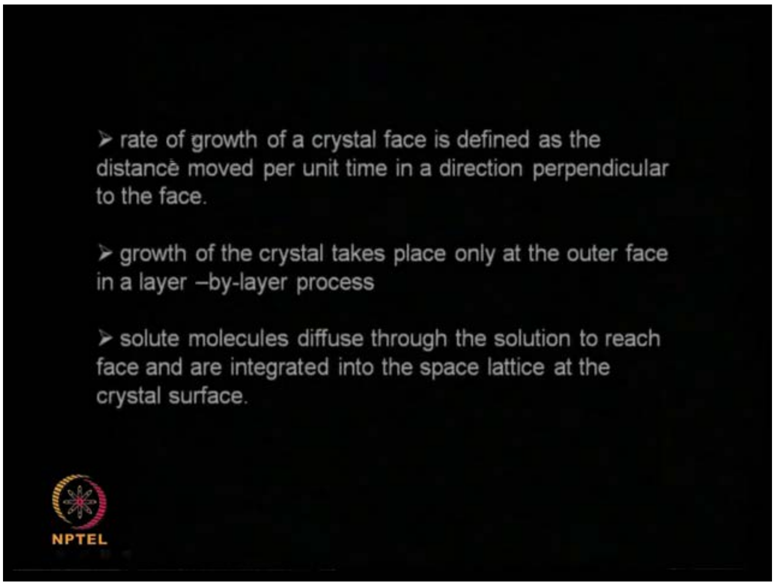

- rate of growth of a crystal face is defined as the distance moved per unit time in a direction perpendicular to the face.
- growth of the crystal takes place only at the outer face in a layer –by-layer process
- solute molecules diffuse through the solution to reach face and are integrated into the space lattice at the crystal surface.

So, the rate of growth of a crystal face is defined as the distance moved per unit time in a direction perpendicular to the face. As I said, we have crystals either monoclinic or orthorhombic or cubic so, it is slowly getting bigger and bigger. So, the face of the crystals starts moving with time that is what we call the growth of the crystal. So, growth of the crystal takes place only at the outer surface layer by layer. So, it does not happen inside so, outer surface keeps becoming bigger and bigger in a direction perpendicular to that. So, the solute molecules will diffuse through the solution and then reach the faces and then it gets integrated with the space face of the solid crystal surface.

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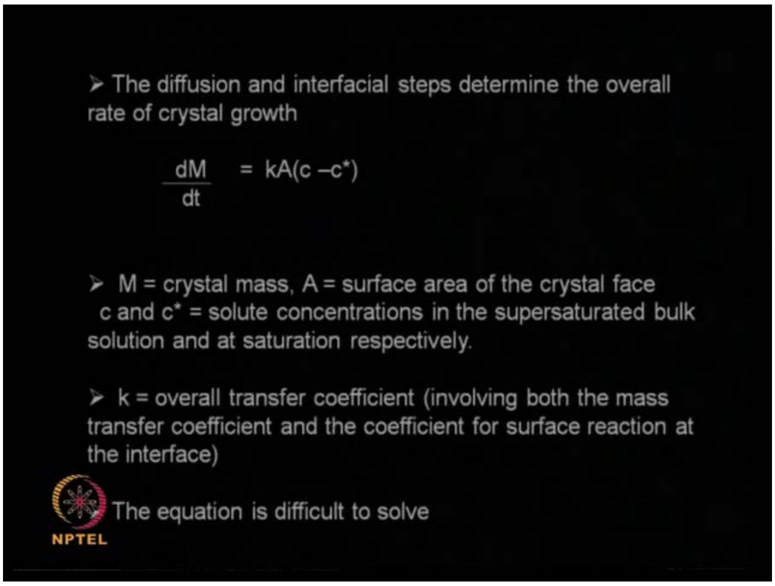

- The diffusion and interfacial steps determine the overall rate of crystal growth

$$\frac{dM}{dt} = kA(c - c^*)$$

- M = crystal mass, A = surface area of the crystal face c and c^* = solute concentrations in the supersaturated bulk solution and at saturation respectively.
- k = overall transfer coefficient (involving both the mass transfer coefficient and the coefficient for surface reaction at the interface)
- The equation is difficult to solve

So, this diffusion process can be defined like this: d M by d t is equal to k A c minus c star. M is the crystal mass so, d m by d t is the rate at which is a crystal mass is growing. This is equal to k, k is some transfer coefficient, some mass transfer coefficient or a crystal growth coefficient. A is the surface area of the crystal growth, c minus c star is the driving force, c is the concentration of the super saturated solution and c star is the concentration of the saturated solution. Once the solution becomes saturated you are not going to have solute spontaneously coming out as a solid right.

So, this is the driving force c minus c star. A is the surface area of the crystal, M is the crystal mass. So, this k is both mass transfer coefficient that mean mass transfer of the solute from the bulk coming down to near the crystal surface as well as the surface reaction when this new solid gets attach or get embedded with the crystal surface ok. So, we cannot solve this equation because crystal mass is also going up with time, area is also growing up with time. So, it is not so easy.

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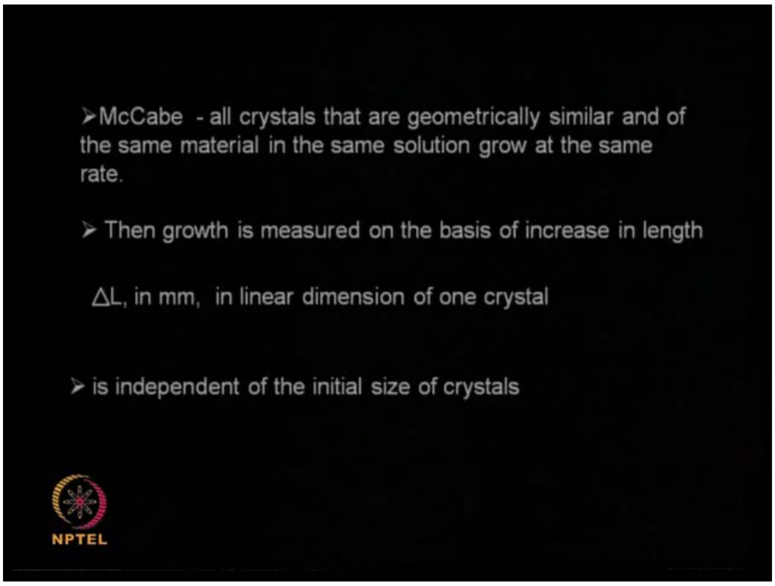

- McCabe - all crystals that are geometrically similar and of the same material in the same solution grow at the same rate.
- Then growth is measured on the basis of increase in length

  ΔL, in mm, in linear dimension of one crystal

- is independent of the initial size of crystals

So, the crystallization process has been slightly simplified is called the McCabe process where we say all crystals that are geometrically similar and of the same material in the sum same solution grow at the same rate ok. Then a growth is the function of the increase in length, delta L. So, we can just look at the linear dimension which it is growing and that we call it as a rate of growth of the crystal. If you are doing at the same material, same solution at the same operating condition so, it is independent of the initial size of the crystal. So, if when the crystal is in micron size or whether it has grown bigger so, the delta L talks about the that is delta L is increase in the length talks about the growth.

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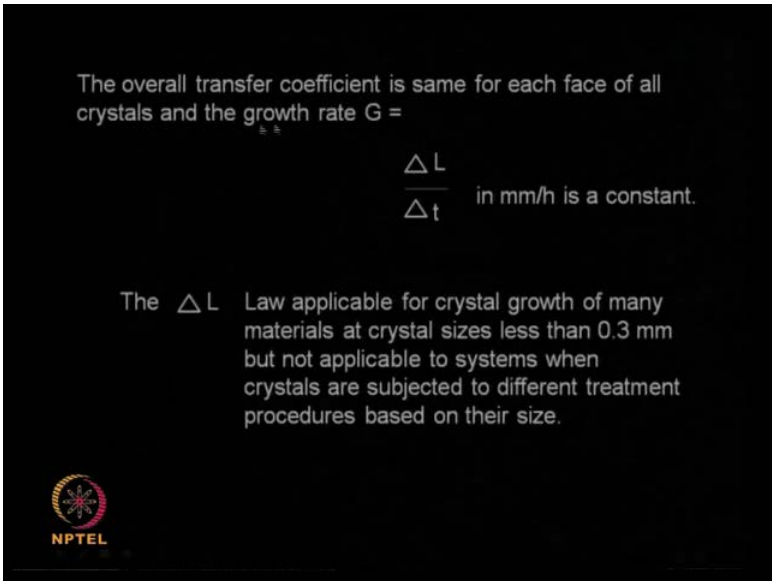

The overall transfer coefficient is same for each face of all crystals and the growth rate G =

$$\frac{\triangle L}{\triangle t}$$ in mm/h is a constant.

The $\triangle L$ Law applicable for crystal growth of many materials at crystal sizes less than 0.3 mm but not applicable to systems when crystals are subjected to different treatment procedures based on their size.

So, we can say though over all crystal growth is delta L by d t, delta L is the increase in length, delta t is the time. And, we say delta L by delta t is constant. So, irrespective of the size of the crystal whether the crystal is very very small or after about few hours it has become bigger delta L by delta t that is the growth rate which is constant. This is one of the rules ok. So, this is applicable for crystal growth of many materials but, it has to be smaller around up to 0.3mm.

But, it is not applicable when we have very large crystals or when we resort to different treatment strategies during the crystallization. As you know in crystallization process, what do we do? Sometimes we heat, sometimes we cool, sometimes we sterile, we do so many different processes so that the crystallization happen, so then it is not valid. But, until then we can say the rate of transfer and the way the crystals grow that is, the growth rate is equal to delta L by delta t that is mm by hour and it is constant.

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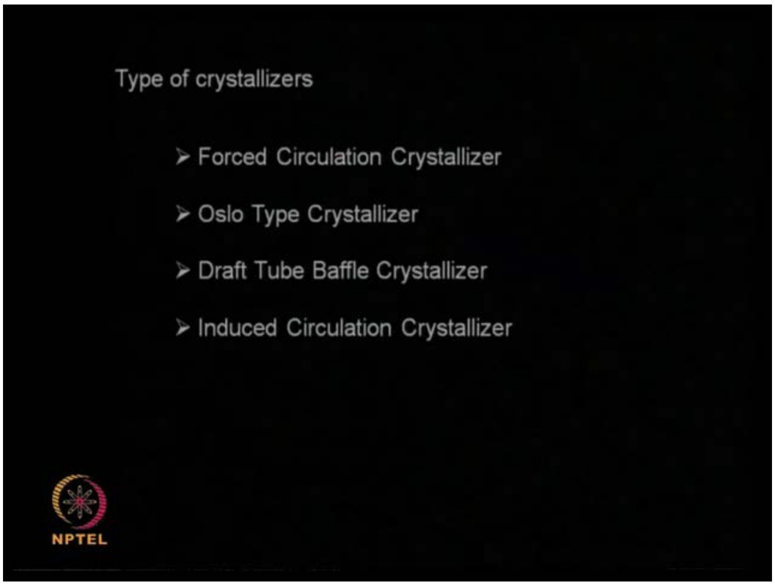

Type of crystallizers

- Forced Circulation Crystallizer
- Oslo Type Crystallizer
- Draft Tube Baffle Crystallizer
- Induced Circulation Crystallizer

There are many types of crystallizers available in the market. Some are called: forced circulation crystallizer, oslo type crystallizer, draft tube baffle crystallizer, induced circulation crystallizer and so on. So, each one has different types of designs and each one are used for certain applications and each one works on different principles as so has different advantages and disadvantages. We will briefly look at each one of this type of crystallizer.

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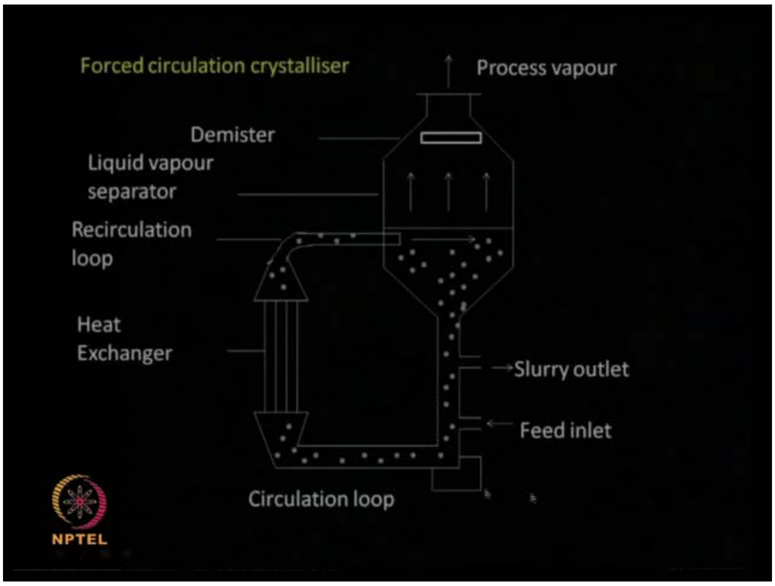

Forced circulation crystalliser

This called a forced circulazim crystallizer. So, what happens? You have a crystallizer. There is a heat exchanger so, it heats up, so the vapors are formed, vapors are go up so, the solution becomes super saturated. So, when the solution becomes super a saturated, crystallization takes place. So, we are feeding in here, we are taking out the slurry. So, the feed that comes in gets heated up so, vapors are formed, vapors are removed. When the vapors are removed the solution becomes super saturated so, the crystals are formed or existing crystals start growing, slurry is out here.

So, there is a recirculation loop. This happens automatically, why? As the vapors are formed the density goes up a liquid as a higher density so, there is an automatic circulation that is taking place. So, the circulation is happening externally, there is heat exchanger located here. So, here the liquid and the vapor are separated. So, the vapor comes out, if its water it will be water vapor, if it is a solvent it will be a solvent which we can collected. This is called a forced circulation crystallizer. There are no agitators in this type of design.

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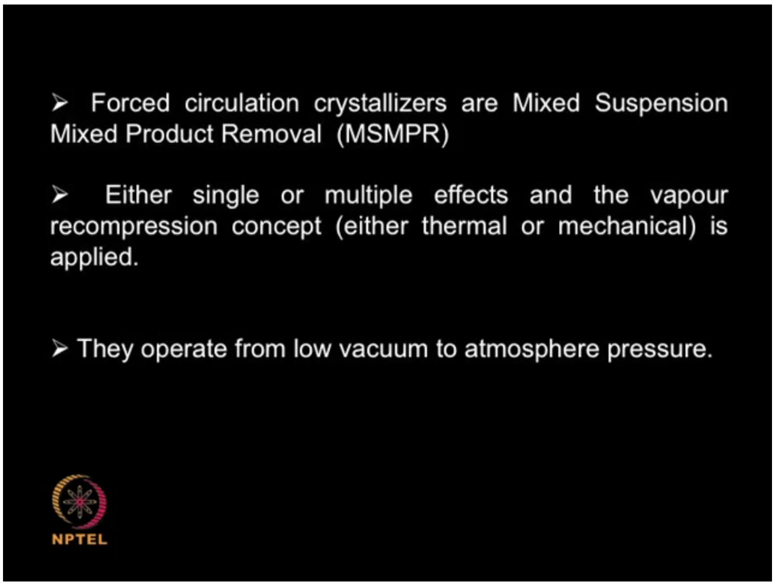

- Forced circulation crystallizers are Mixed Suspension Mixed Product Removal (MSMPR)
- Either single or multiple effects and the vapour recompression concept (either thermal or mechanical) is applied.
- They operate from low vacuum to atmosphere pressure.

So, they are also called mixed suspension mixed product removal. As we can see its suspended, you are removing product combination. We can have single or multiple effect. I will talk about what is a single effect and in multiple effect later. It can have a different types of recompression that means vapor can be recompressed using thermal or mechanical approach.

So, they operated at low vacuum to atmospheric pressure. If you want to remove the vapor, if it is a solvent we utilize vacuum so that the solvent gets operated very fast which water when you to heated up considerably and then we need to apply vacuum as well, so that the water vapor gets removed. Sometimes crystals you do not want to heat up too much because the crystal the color texture of the crystal gets disturbed if you are resorting to very high temperature.

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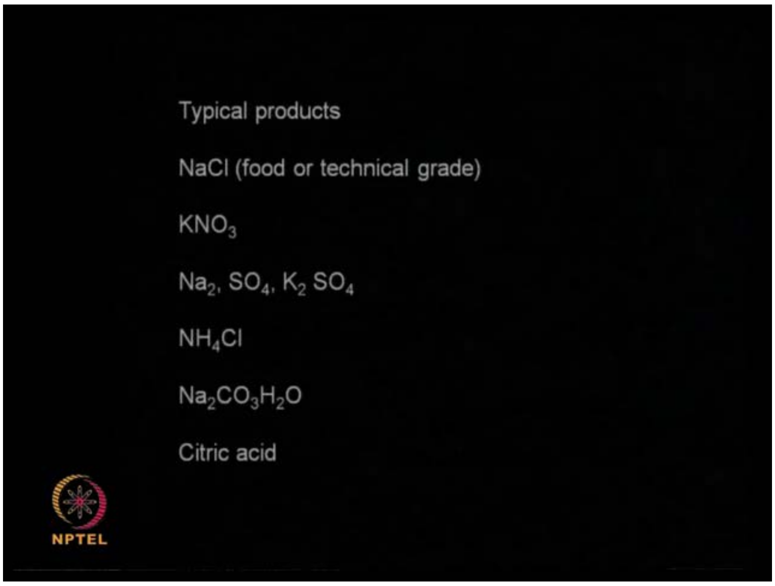

Typical products

NaCl (food or technical grade)

KNO_3

$Na_2, SO_4, K_2 SO_4$

NH_4Cl

$Na_2CO_3H_2O$

Citric acid

So, we can use this for: sodium chloride, food grade or technical grade, potassium nitrated, sodium sulfate, potassium sulfate, ammonium chloride, citric acids. So, it is the lot of products could be crystallized by this, it is a very simple system. And, we can scale it up to very large scales and is typical industrial by crystallizer.

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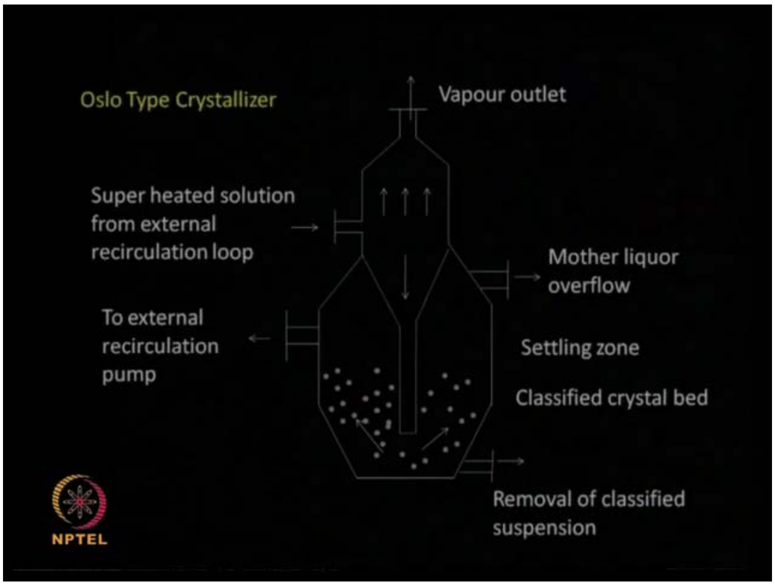

Let us look at the another one is called oslo type crystallizer. So, what is happening here? So here, we are introducing a super heated solution and the vapor goes up because it may be you are applying a vacuum. So, when you do that the solution gets super saturated so, which starts coming down. So, there is a crystal bed here and the solution flows through. When the solution flows through the crystal bed, the crystals become bigger and bigger ok.

So, bigger and bigger crystals are settling here and then the solution again raises which goes to a external pump as well as a heating system. So, you are heating up pure solution which enters here, vapor is removed or flashed because we may be applying a vacuum here. So, the super saturated solution comes down and there is a bed of solids. As the super saturated solution comes in contact with the bed the size of the crystals grow.

So, the super saturation goes down and now again it send to recirculation reheating and so on actually, ok. So, this is how this system works. So, in this system you are building up the size of the crystals because there is a bed of crystals and your super saturated solution flows through the bed of crystals. So, this is again industrial type of operation, so huge setup.

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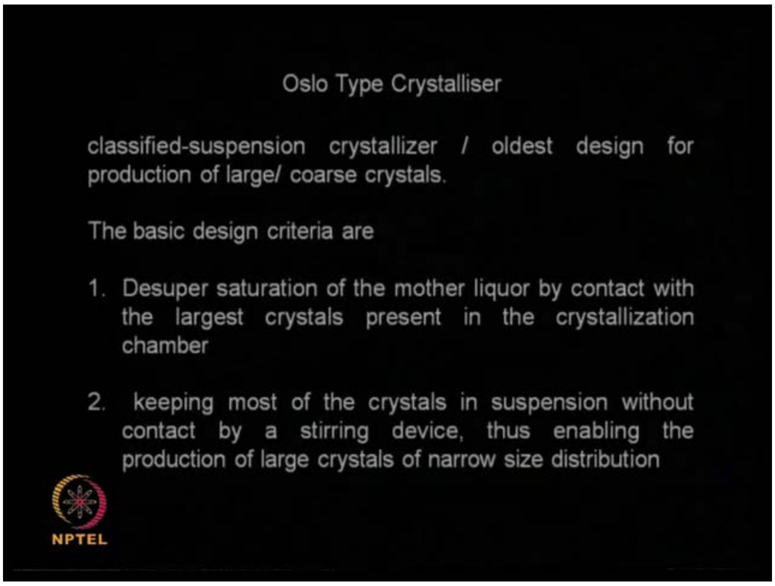

Oslo Type Crystalliser

classified-suspension crystallizer / oldest design for production of large/ coarse crystals.

The basic design criteria are

1. Desuper saturation of the mother liquor by contact with the largest crystals present in the crystallization chamber
2. keeping most of the crystals in suspension without contact by a stirring device, thus enabling the production of large crystals of narrow size distribution

So, it is called a classified suspension crystallizer, it is very old design. So, your d super saturation of the mother liquor happens because d super saturated solution comes in contact with the crystals. And, you are keeping most of the crystals suspension without contact by a stirring device thus, enabling production of large size crystals. So, the crystals that are at the bottom of the bed are going to become larger and larger because they come in contact with the super saturated solution.

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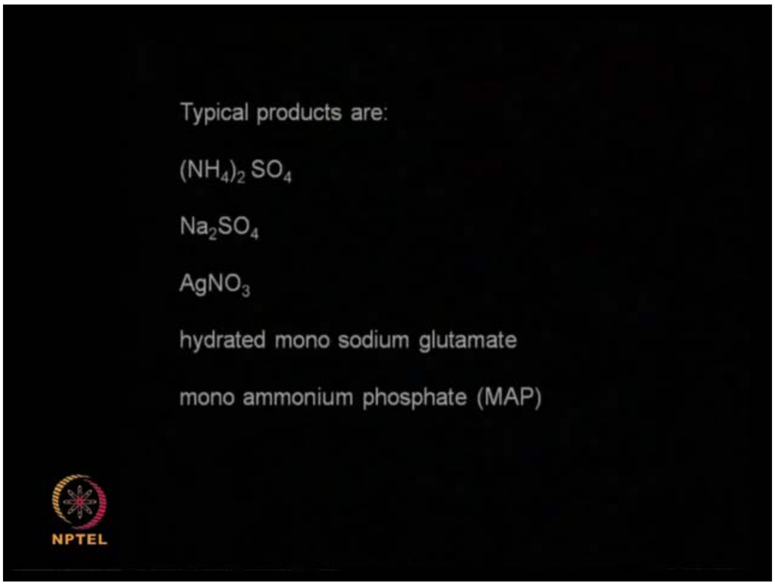

Typical products are:

$(NH_4)_2SO_4$

Na_2SO_4

$AgNO_3$

hydrated mono sodium glutamate

mono ammonium phosphate (MAP)

So, again this is used for: ammonium sulfate, sodium sulfite, silver nitrate, mono sodium glutamate, mono ammonium phosphate, large number of products can be done with this. We can get very large crystals with this type of arrangement.

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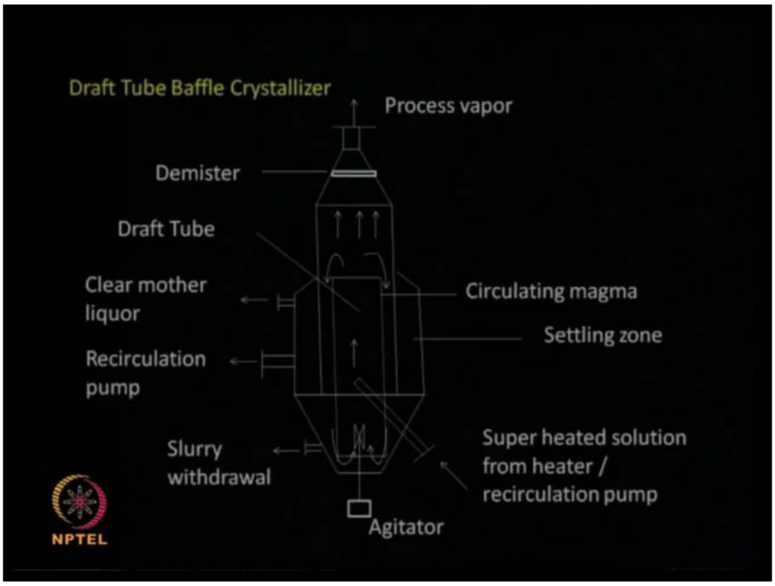
Draft Tube Baffle Crystallizer

Then we have the draft tube baffle crystallizer. So, you may have the draft tube here, there is a circulation. So, what happens in a draft tube? The solution rises because of the presents of vapor. As soon as a vapor gets disengaged and starts moving up the liquid is heavy so, this it is starts coming down. So, the solution raises because of bouncy force and as soon as vapor gets disengaged the liquid is heavier so, they start coming down. So, there is an automatic circulation created here ok. You also agitating so that you are not allowing the solids to settle down and you are introducing a super heated solution here so, as the vapor gets disengage they become super saturated ok.

At the same time you also have the recirculation pump here. So, this particular portion contains solid and liquid going round and round because of the circulation created by the draft tube. So, this can be operated and vacuumed here, you may be applying vacuum here. You are having recirculation pump here so that the liquid is moved round and round into the vessel.

Now, the slurry can be withdrawn from the bottom here where because you are going to keep accumulating your crystals here. And, the later on the you can resort whether centrifugal operation or you can resort to filtration so that the solid is separated from the liquid. This is called a draft tube baffle crystallizer because it has got a draft tube and the draft tube gives you the natural recirculation that is possible. The center, there is bouncy so the liquid and the solid and the vapor rises and on the sides the liquid and the solid comes down because of the weight.

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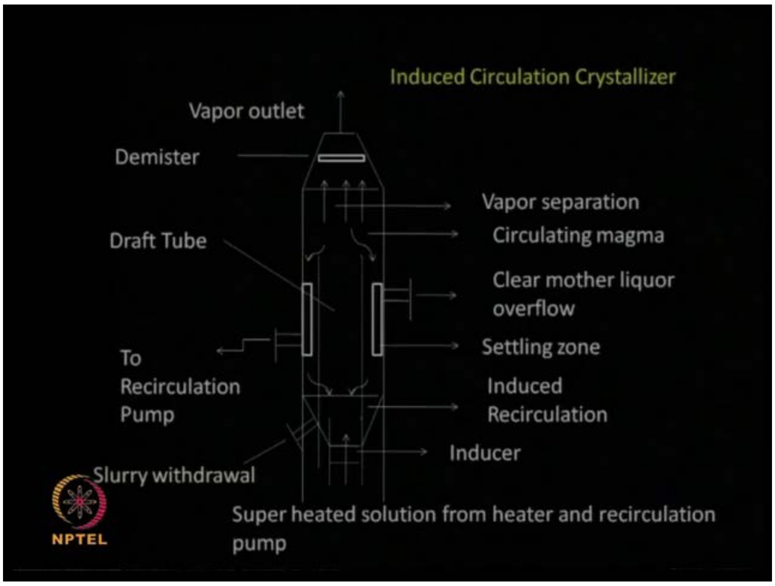

Induced Circulation Crystallizer

Vapor outlet

Demister

Draft Tube

To Recirculation Pump

Slurry withdrawal

Vapor separation

Circulating magma

Clear mother liquor overflow

Settling zone

Induced Recirculation

Inducer

Super heated solution from heater and recirculation pump

Another one is called the induced circulation crystallizer. So, we are trying to induce the circulation in this particular crystallizer. Again the slurry is withdrawn from there and you are inducing this type of circulation at the bottom so, are introducing a super heated solution from heater and a recirculation pump from the bottom actually ok. So, here on the top you are going to get a clear mother liquor over flow and then at the side you are going to also have a induced circulation taking place here and the vapor is removed from the top.

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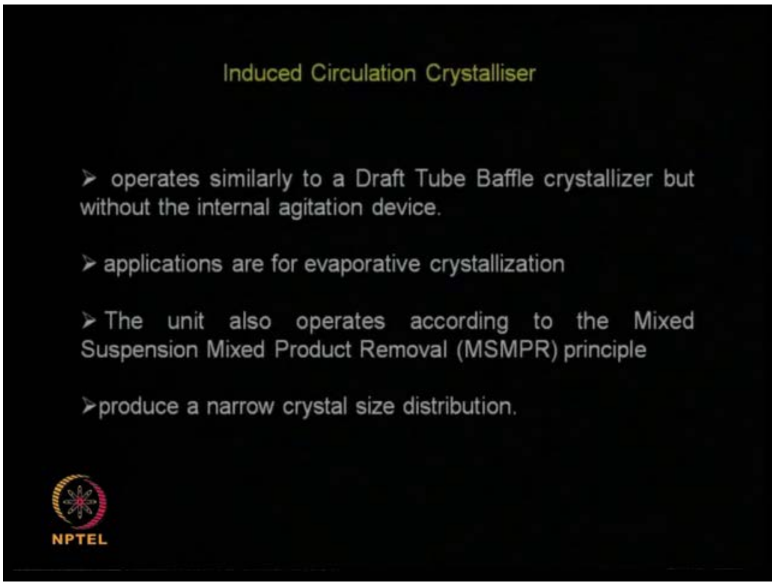

Induced Circulation Crystalliser

- operates similarly to a Draft Tube Baffle crystallizer but without the internal agitation device.
- applications are for evaporative crystallization
- The unit also operates according to the Mixed Suspension Mixed Product Removal (MSMPR) principle
- produce a narrow crystal size distribution.

So, what is the advantage of this? It is almost like a draft tube baffle crystallizer. So, in a draft tube you have a draft tube crystallizer which creates recirculation. And, there is no internal agitation in a draft tube where as in a induced you also add an agitation so that, it will not allow the solids process to settle down. So, we can use it for a large number of application, it also works like this mixed suspension mixed product removal that is the original one. And, we can get very narrow crystal size distribution with this because you are not allowing the crystals to settle down ok. So, that is the advantage of this type of induced draft circulation system.

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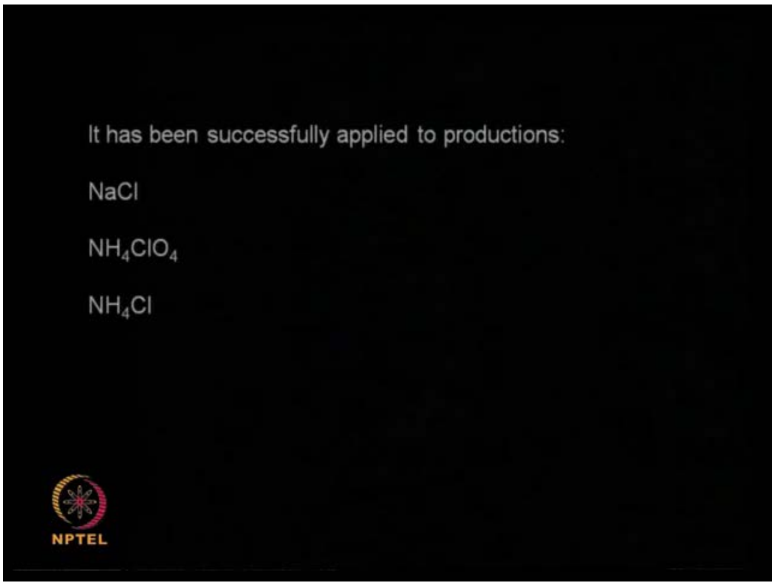

It has been successfully applied to productions:

$NaCl$

NH_4ClO_4

NH_4Cl

So, it has been successfully again used for large number of products starting from: ammonium chloride, sodium chloride and ammonium chlorate and so on actually.

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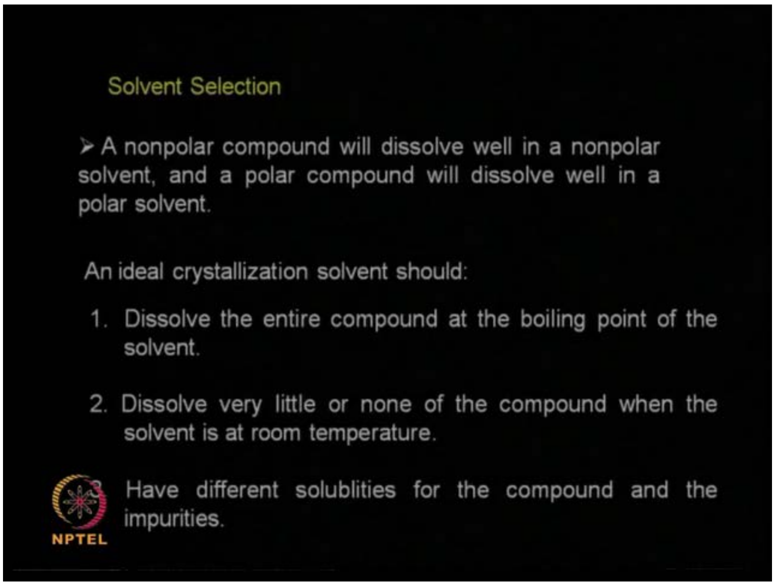

Solvent Selection

- A nonpolar compound will dissolve well in a nonpolar solvent, and a polar compound will dissolve well in a polar solvent.

An ideal crystallization solvent should:

1. Dissolve the entire compound at the boiling point of the solvent.
2. Dissolve very little or none of the compound when the solvent is at room temperature.
3. Have different solublities for the compound and the impurities.

So, how do you select the solvent? As I said, solvent could be water or it could be a organic liquid so, selection of the solvent is very very important. If you have a non-polar solid it will dissolve nicely in a non-polar solvent and polar compound will dissolve nicely in a polar solvent. So, need to think about what type of crystals you want to find prepare. It should dissolve the entire compound at the boiling point of the solvent ok. That is very very important. So, it should not be partially dissolving a solid, it should be able to dissolve to the entire compound. At room temperature you should not dissolve any of the compound that means, the solid at high boiling point should be completely solve in solution.

But, when we bring it down to room temperature the solid should completely come out has a crystal or a precipitate and the solubility of the solid at room temperature should be practically 0. Otherwise, at room temperature if some solid is present then that is going to go as a waste, you will not be able to recover that particular amount. And, the solubility of the solid or solute should be very different from the solubility of the impurities. If the impurity solubility is high then we are in trouble. You will not be able to remove the impurity from the solid. So, the solubility of the impurity should be low.

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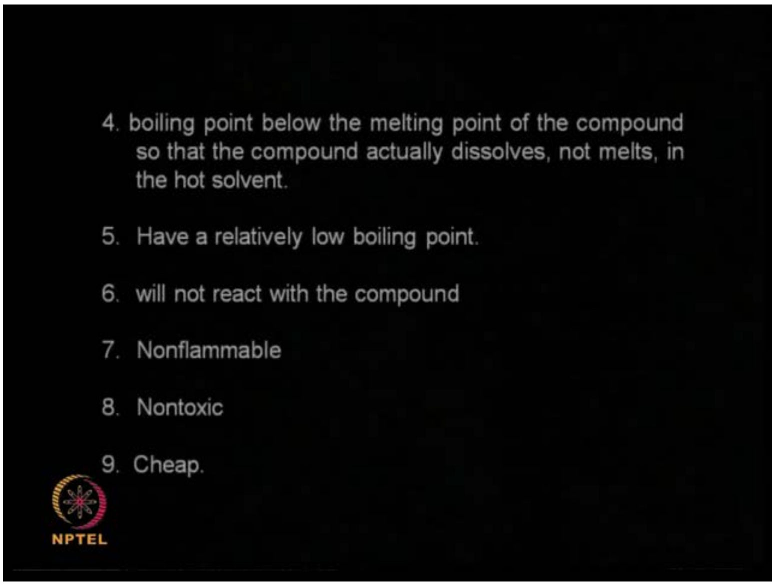

4. boiling point below the melting point of the compound so that the compound actually dissolves, not melts, in the hot solvent.
5. Have a relatively low boiling point.
6. will not react with the compound
7. Nonflammable
8. Nontoxic
9. Cheap.

And, the boiling point of the solvent should be much below the melting point of your compound otherwise what happens? If the boiling point is very high then your crystal will start melting. If it starts melting then it will be very difficult for you to separate out and if the solids melt it will form tarry product, it will not be accepted by the customer. So, it should also have a low boiling point. We do not want the boiling point to be very high then what happens? You may have to resort to high energy expenditure.

It should not react with the compound that is also very important there if it starts reacting then you will not be able to do the crystallization process. It should be non-flammable. That is very important, that is from the safety point of you. It should be not toxic because when it is in a industrial scale it should not affect the operators and it should be cheap. We do not want an exotic very expensive solvent and every solvent litter we lose we are losing money.

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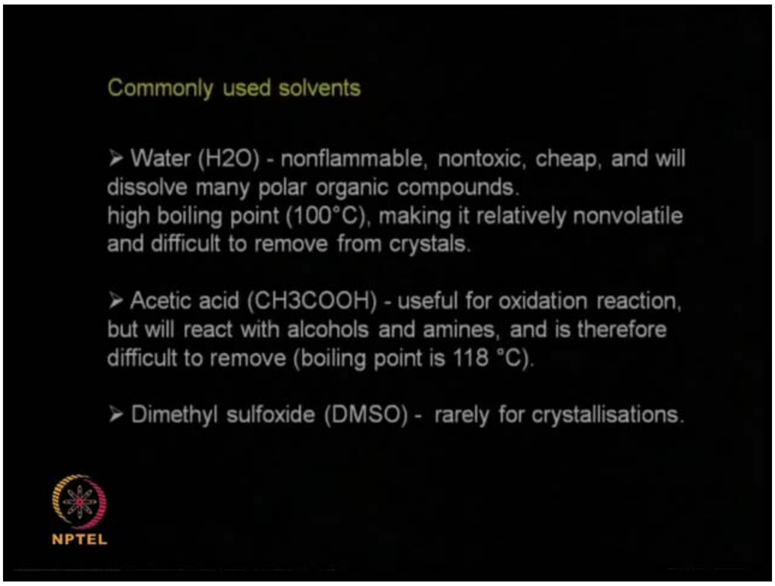

Commonly used solvents

- Water (H_2O) - nonflammable, nontoxic, cheap, and will dissolve many polar organic compounds.
high boiling point (100°C), making it relatively nonvolatile and difficult to remove from crystals.
- Acetic acid (CH_3COOH) - useful for oxidation reaction, but will react with alcohols and amines, and is therefore difficult to remove (boiling point is 118 °C).
- Dimethyl sulfoxide (DMSO) - rarely for crystallisations.

So, what are the commonly used solvent, water, because it is the most non-flammable, non-toxic, cheap and so on. But, only problem is it is got a very highly boiling point. So, we have to raise the temperature, we have to resort to vacuum and so on so the removal cost is very high. Acetic acid which useful it will but, it will react with the alcohols and amines and it is got a very high boiling point. Dimethyl sulfoxide D M S O, its not used in crystallization, it is used in reactions.

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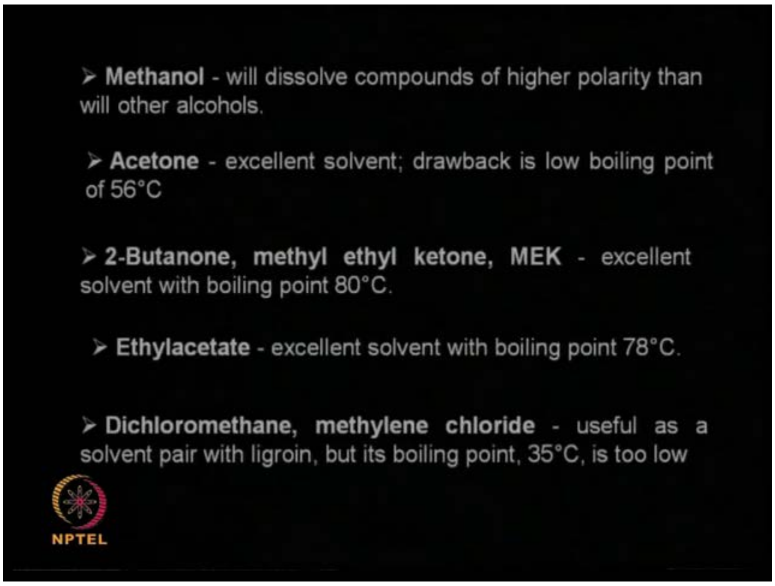

- **Methanol** - will dissolve compounds of higher polarity than will other alcohols.
- **Acetone** - excellent solvent; drawback is low boiling point of 56°C
- **2-Butanone, methyl ethyl ketone, MEK** - excellent solvent with boiling point 80°C.
- **Ethylacetate** - excellent solvent with boiling point 78°C.
- **Dichloromethane, methylene chloride** - useful as a solvent pair with ligroin, but its boiling point, 35°C, is too low

Methanol will dissolve compounds of high polarity. Acetone that is very good but, problem is it is got a very low boiling point. So, if you are operating this type of crystallizer in a hot country or in tropical place some acetone is lost. 2 butanone or M E K methyl ethyl ketone that is very good. It is a very good solvent, boiling point is very much low 80 degrees and it is have not as bad as acetone. Ethyl acetate again it is very good, dichloromethane it is good as a solvent pair but, it is got a very low boiling point so, it is absolutely no as a single solvent.

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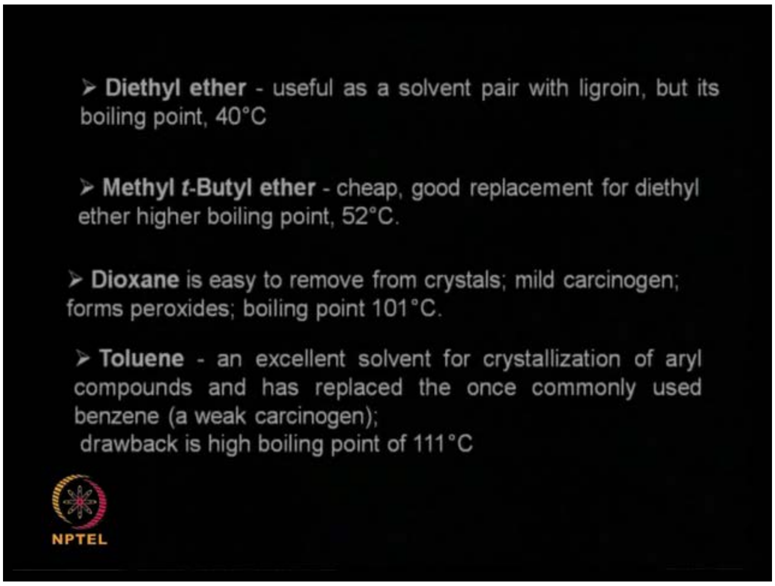

➢ **Diethyl ether** - useful as a solvent pair with ligroin, but its boiling point, 40°C

➢ **Methyl *t*-Butyl ether** - cheap, good replacement for diethyl ether higher boiling point, 52°C.

➢ **Dioxane** is easy to remove from crystals; mild carcinogen; forms peroxides; boiling point 101°C.

➢ **Toluene** - an excellent solvent for crystallization of aryl compounds and has replaced the once commonly used benzene (a weak carcinogen);
drawback is high boiling point of 111°C

Diethyl ether again it is good as a solvent pair with some other solvent but, very bad boiling point. Methyl t-butyl ether: not bad 52 degrees so, it can be used in colder climates, cheap. Dioxane: easy to remove from crystals its slightly carcinogen but, the boiling point is high. Toluene: it is a very good solvent for crystallization but, boiling point is very high.

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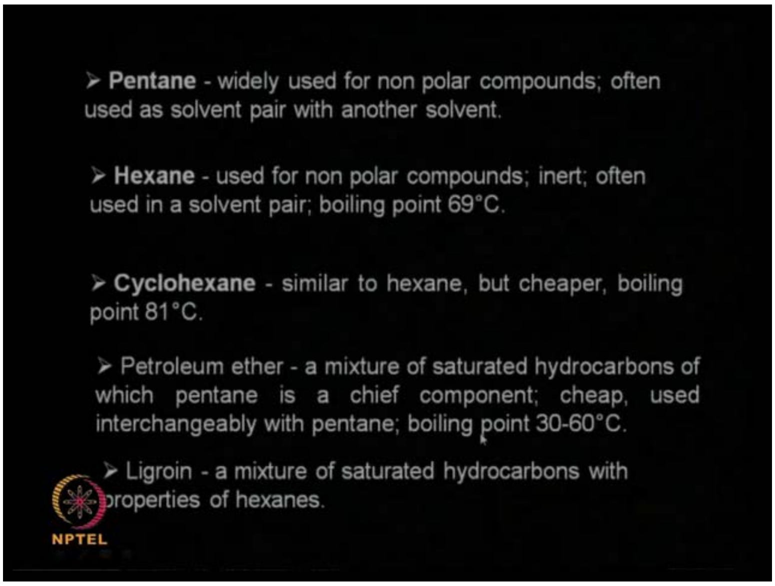

- **Pentane** - widely used for non polar compounds; often used as solvent pair with another solvent.
- **Hexane** - used for non polar compounds; inert; often used in a solvent pair; boiling point 69°C.
- **Cyclohexane** - similar to hexane, but cheaper, boiling point 81°C.
- Petroleum ether - a mixture of saturated hydrocarbons of which pentane is a chief component; cheap, used interchangeably with pentane; boiling point 30-60°C.
- Ligroin - a mixture of saturated hydrocarbons with properties of hexanes.

Pentane: it is good for non-polar compounds because it is in organic so it is very good so but, it can be used in combination with some other solvent not per say because it is low boiling. Hexane: it is very good, 69 degrees centigrade, it is good for hydrophobic chemicals phyto chemicals and so on. It can be used as a solvent pair that means it can be used in combination with another solvent. Cyclohexane: it is cheap similar to hexane, 81 degrees very good for hydrophobic compounds. Petroleum ether: cheap, it has a range of boiling point 30 to 60 and can be combine with pentane and so on. Ligroin: it is a mixture of saturated hydrocarbons with properties similar to hexane actually, you know. So, it is got a range of boiling point rather than single value.

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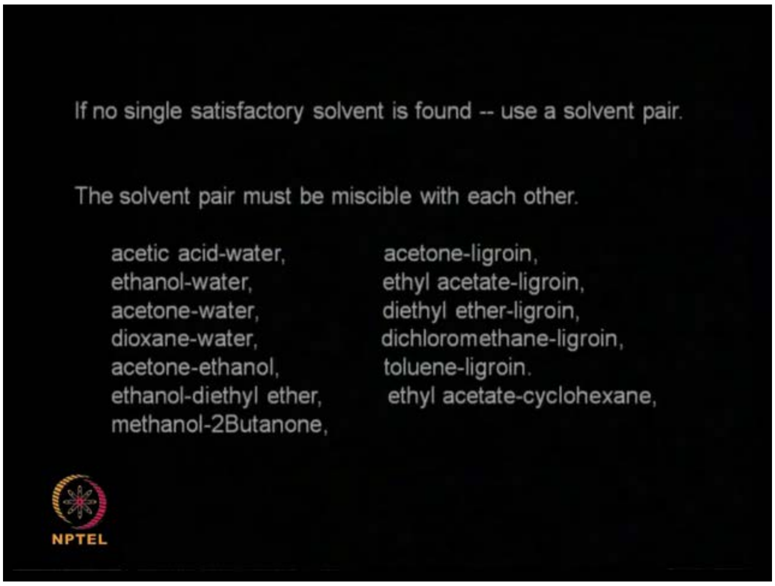

If no single satisfactory solvent is found -- use a solvent pair.

The solvent pair must be miscible with each other.

acetic acid-water,
ethanol-water,
acetone-water,
dioxane-water,
acetone-ethanol,
ethanol-diethyl ether,
methanol-2Butanone,

acetone-ligroin,
ethyl acetate-ligroin,
diethyl ether-ligroin,
dichloromethane-ligroin,
toluene-ligroin.
ethyl acetate-cyclohexane,

So, many solvents: low boilers, high boilers, hydrophobic, hydro phallic so, you need to select depending upon your am bean conditions, the type of solids you want to precipitate or crystallize out and so on actually. So, if no single solvent is satisfactory we can have combinations of two solvent that is called a solvent pair. But, there should be mixable with each other, they should not be separating out.

Then we are in big problem. So, we can have: acetic acid-water, ethanol-water, acetone-water, dioxane-water. So, nice polar solvent or we can also have ligroin which is almost like hexane type, dichloromethane ligroin, ethyl acetate cyclohexane. So, here large number of solvent pair is also available which can act as a a good solvent for precisation, if you think a single solvent is not very satisfactory.

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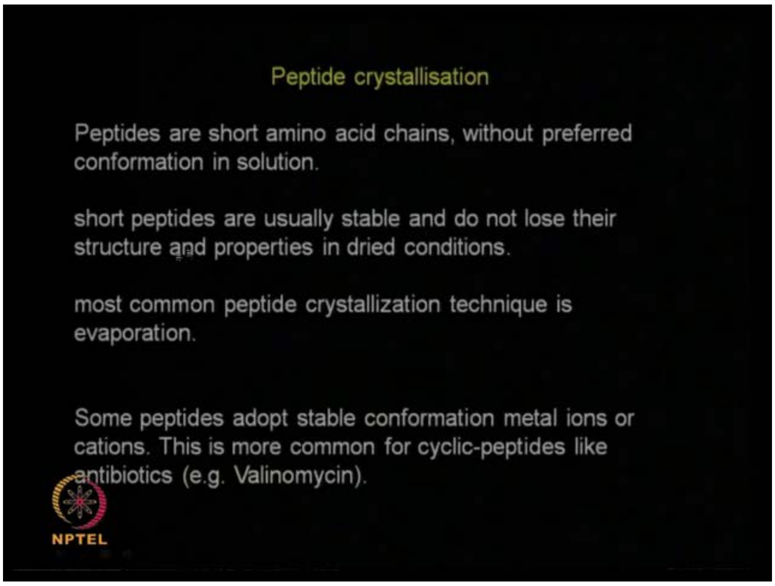

Peptide crystallisation

Peptides are short amino acid chains, without preferred conformation in solution.

short peptides are usually stable and do not lose their structure and properties in dried conditions.

most common peptide crystallization technique is evaporation.

Some peptides adopt stable conformation metal ions or cations. This is more common for cyclic-peptides like antibiotics (e.g. Valinomycin).

Peptides can be crystallized, as you know peptides are short amino acid chains and they had do not have any conformation like protein and so, they are quite stable. They do not lose their structure and properties in dried conditions. So, generally how do you crystalize this? By operations so, we rise the temperature so the solvent evaporates. The some peptides adopt stable conformation metal ions or cations. So, that is like a cyclic peptides like antibiotics and so on actually.

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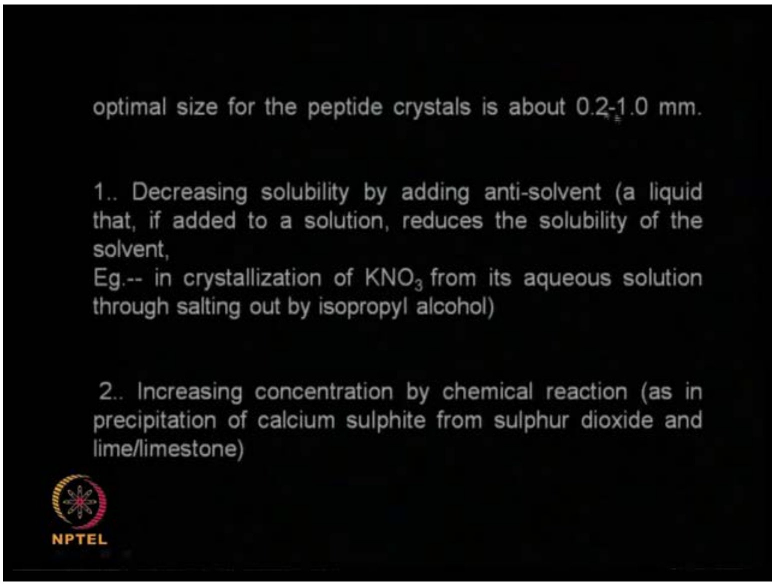

optimal size for the peptide crystals is about 0.2-1.0 mm.

1.. Decreasing solubility by adding anti-solvent (a liquid that, if added to a solution, reduces the solubility of the solvent,
Eg.-- in crystallization of KNO_3 from its aqueous solution through salting out by isopropyl alcohol)

2.. Increasing concentration by chemical reaction (as in precipitation of calcium sulphite from sulphur dioxide and lime/limestone)

So, optimal size for peptide crystals are 0.2 to 1 mm. So, how do you do peptide crystallization? We can decrease the solubility by adding an anti-solvent that means, a liquid that if added to a solution reduces solubility like crystallization of k when k potassium nitrate from its aqueous solution through salting out by isopropyl alcohol. So, when I add isopropyl alcohol the solubility of potassium nitrate decreases in aqueous solution or increasing concentration by chemical reaction. So, there is a chemical reaction so, the concentration increases. So, it comes out as a precipitate so, like in precipitation of calcium sulphite from sulphur dioxide and lime. So, these are the two ways by which we can precipitate or crystalize peptides.

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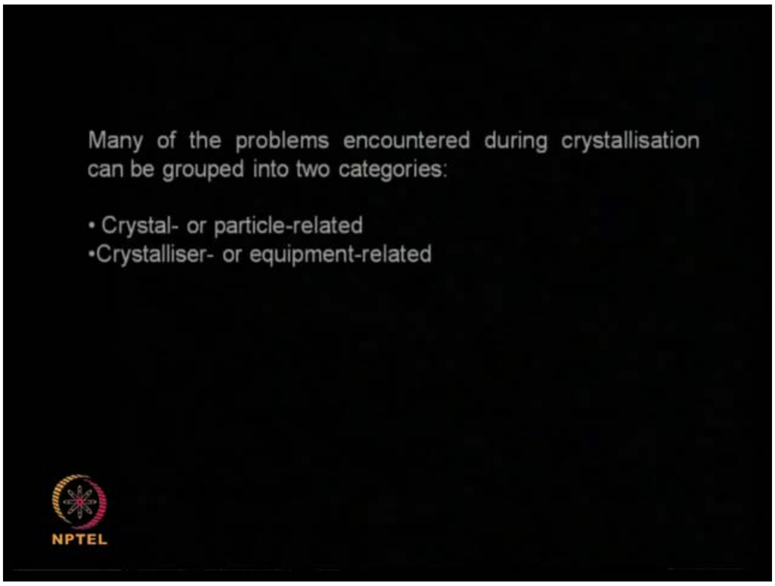

Many of the problems encountered during crystallisation can be grouped into two categories:

- Crystal- or particle-related
- Crystalliser- or equipment-related

There are many problems that are encountered during crystallization. So, they can be related as problems because of crystals or particle related or problems because of the equipment or the crystalliser related. So, particle related could be because of presence of impurities, solvents, reactions, boiling points, a miscibility’s, viscosity’s and so on. Crystallizers is more related to equipment, mixing, agitation, heating, flow rate, vapour removal and so on actually.

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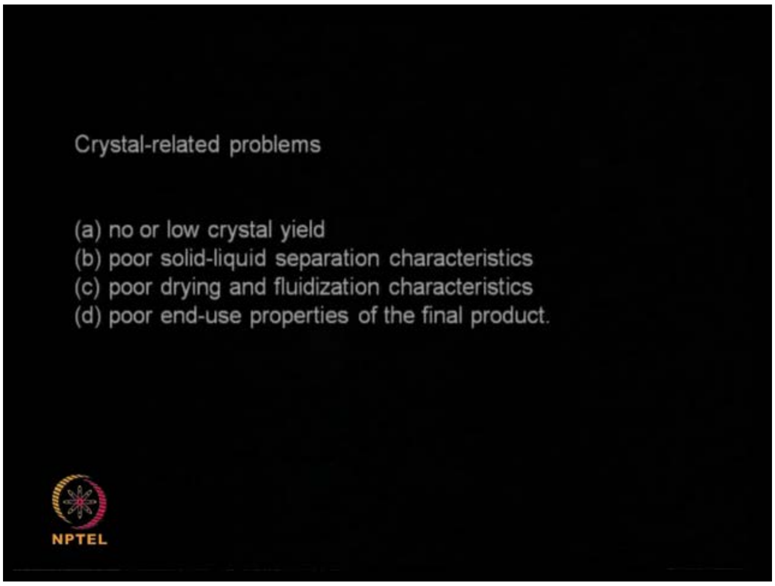

Crystal-related problems

(a) no or low crystal yield
(b) poor solid-liquid separation characteristics
(c) poor drying and fluidization characteristics
(d) poor end-use properties of the final product.

So, the crystal related problem leads to: low crystal yield, poor solid liquid separation, poor drying and fluidization. That means, after your crystallization you are not able to dry fully or poor end use properties. That means, the final product is not having all the properties of the real solid because of some impurities or because of removal of solvent or because of the type of crystal that is formed and so on.

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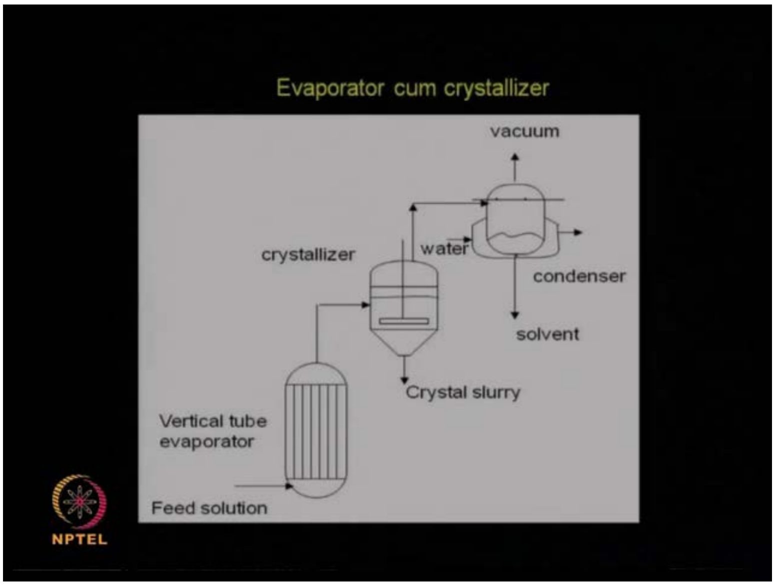

Evaporator cum crystallizer

So, there are different types of crystallizers. The mode of crystallization, we talked about types of crystallizers now, we look at mode of crystallization. So, we can have a feed solution we can have we have vertical tube evaporator. So, you form here a liquid and a vapour. So, when the entire the crystallizer the vapour evaporates and goes up so, you get super saturated solutions or the crystal slurry forms. Now, this vapour Gaussian and which is removed by vacuum that is called the evaporator vacuum crystallizer. So, you are evaporating the solution and then you are crystalizing because you have formed the super saturation here.

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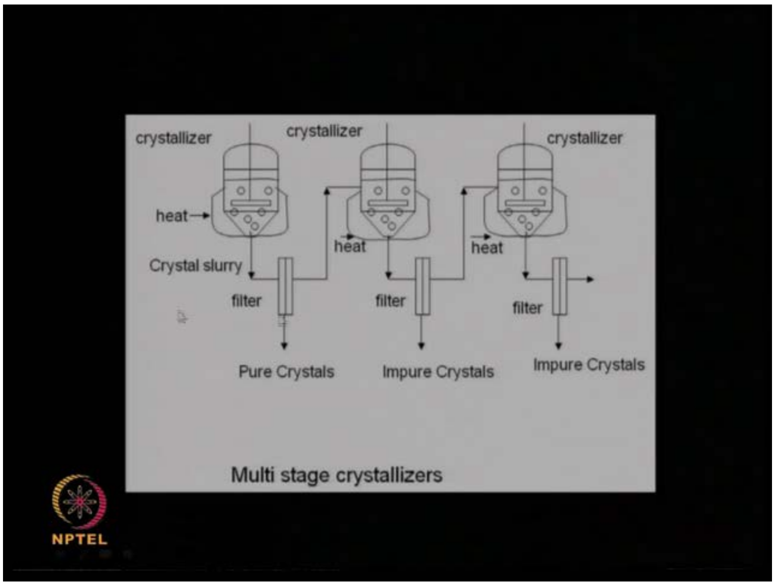

Multi stage crystallizers

In multi stage crystallizer is a very energy integrated system. So, what happens here is we have we are heating it up so, there are vapours that are formed. So, crystals are formed so, which is removed in a filter. And, this solution goes into the next crystallizer where again your heating it up and again some more crystals are formed and the remaining crystal remaining solution goes to the third crystallizer and so on.

So, we have very pure crystals formed in the first stage later on you may have having impure crystals. So, you are trying to remove as much of the solid that is possible by having several stages. So, the idea is that you do not leave any solid in the mother liquor that is called the multi stage crystallizer. But then, you need to have several vessels and several filters and each vessel is heated up so that super saturation is achieved.

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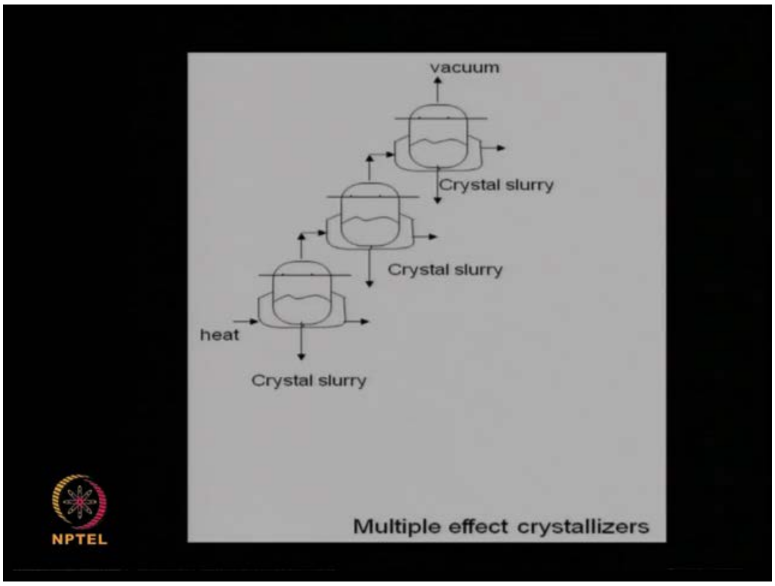

Multiple effect crystallizers

Another type of crystal that is called the multi effect crystallizer that means, the vapour that is generator which is very very hot in one stage is used to heat up the second stage. That means, you do not use any fresh steam in the second stage. So, you use steam in the first stage to heat the solution, vapour is formed. So, the solution become super saturated, crystals are formed as crystal study.

Now, this vapour which is very hot goes to the second stage as the heating fluid which heats the solution that present and super saturated leading to crystals. Now, this vapour which is formed in the second stage goes to the third stage to heat up the solution crystal. So, the vapour in the first stage goes to the heater in the second stage and the vapour in the second stage that is form goes to the heater in the third stage.

That way, you are using steam only in one stage that way you are economizing on the steam necessary to produce these crystal. This is called the multiple effect crystallizer. In fact, this type of designs are used in manufacture of sugar crystals. So, you may have 3 or 4 different stages or effects of crystallizers where you get crystals in each one of this stages and the amount of heat used is extremely low. So, by applying vacuum in the very final stage you are drawing the vapour from the stage 1 to stage 2 to stage 3 to stage 4. So, the amount of heat required or the amount of external heat you are supplying is minimal here only, you are not supplying heat in each one of these stages ok.

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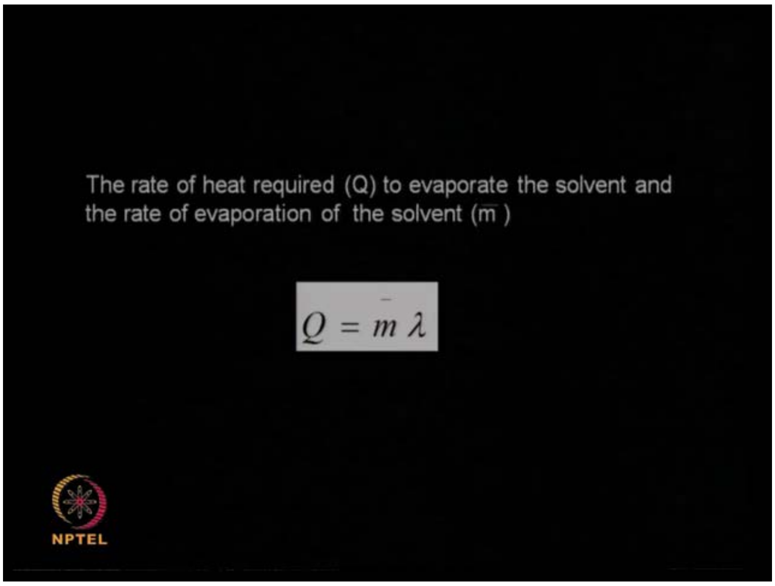

The rate of heat required (Q) to evaporate the solvent and the rate of evaporation of the solvent ($\bar{m}$)

$$Q = \bar{m}\,\lambda$$

So, what is the rate of heat required to evaporate a solvent? This is just the heat balance. If you assume that there are no loses the rate of heat required you are going to evaporate the solvent right. So, you are going to have the lambda that is the heat of vaporization of the solvent into m bar, m bar is the rate of evaporation of the solvent. So, the rate of heat required in the left hand side is equal to the rate of evaporation of the solvent into lambda which is the heat of vaporization of the solvent ok. So, if the heat of vaporization or the latent heat of vaporization of the solvent is high the amount of heat required is also very very high. That is why, in the previous slides when we talked about locating a solvent we said that we should have lower boiling point or lower heat of vaporization so that, the amount of heat required is also very very low.

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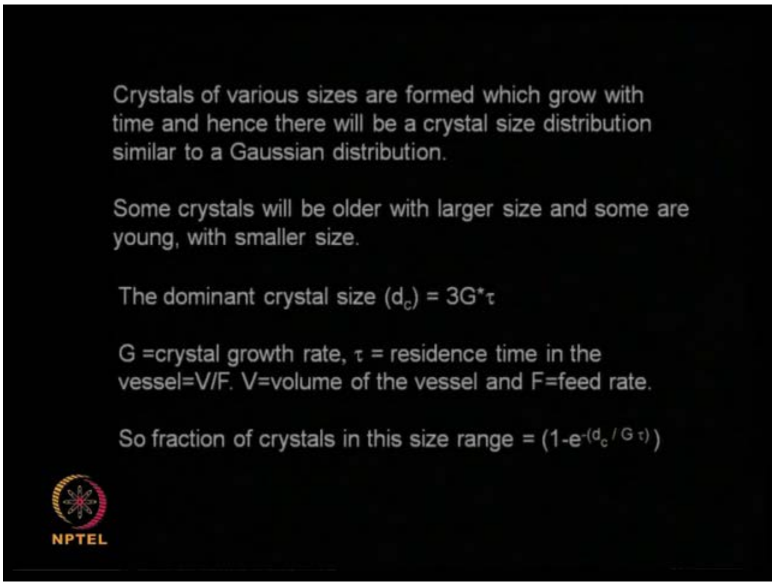

Crystals of various sizes are formed which grow with time and hence there will be a crystal size distribution similar to a Gaussian distribution.

Some crystals will be older with larger size and some are young, with smaller size.

The dominant crystal size (d_c) = $3G^*\tau$

G =crystal growth rate, τ = residence time in the vessel=V/F. V=volume of the vessel and F=feed rate.

So fraction of crystals in this size range = $(1-e^{-(d_c/G\tau)})$

So, the crystals of various sizes are formed which grow in time and generally you although you would like to have a mono dispose that means crystals of one single size. It is not going to be it will be following a Gaussian or a uniform distribution. So, that means some crystals will be older so, they will have larger size. Some crystals will be young so, they will have smaller size.

So, the dominant crystal size d c is given by 3 G into tau, tau is the residence time in the vessel that is, volume in the vessel divided by flow rate or feed rate and G is the crystal growth rate. So, fraction of crystals in this size range will be 1 minus e that is, exponent rise to the power minus d c by G tau that is the equation. So, the fraction of the crystals in this size range will be like this actually and the crystal growth rate I talked about based on the G is equal to delta l by delta t which is constant. That means change in the dimension, unit dimension of the crystal as a function per time is a constant.

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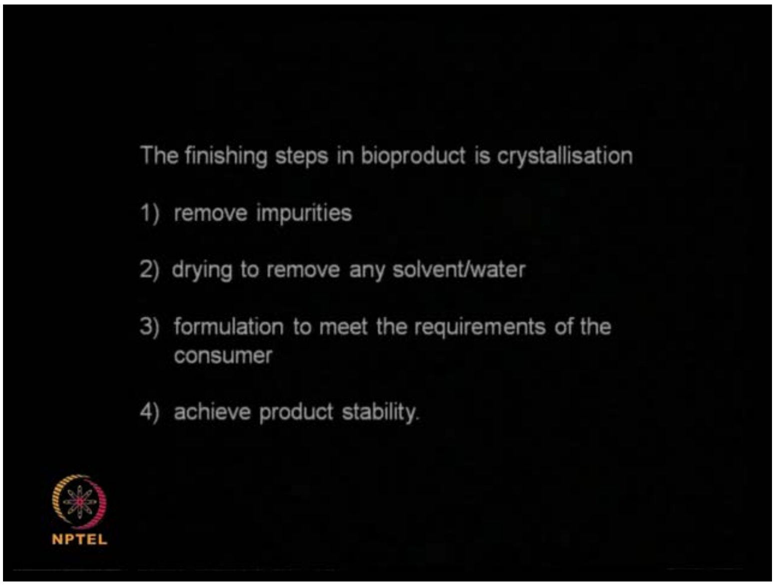

The finishing steps in bioproduct is crystallisation

1) remove impurities
2) drying to remove any solvent/water
3) formulation to meet the requirements of the consumer
4) achieve product stability.

So, to conclude we can say crystallization is the most important downstream process which is generally resorted to and the late very last stage where you are interested in a solid product after we have done a recovery, after you have done purification of your product. So, we can resort the crystallization of peptides, cyclic peptides and metabolites salts and so on and go main goal is to remove the impurities that is present, dried drawing to remove any solvent or water that is present.

Thereby, the product will have longer shelf life or stability. Sometimes your customer would like to have the product in a solid form because he would like to formulate your product in either in a biopharmaceutical product or in a cosmetic type of industry. So, again you need to have your product in a crystal form and I also say mentioned that there are 7 different classes of crystals moving from cubic to ortho clinic, orthorhombic and so on. And, all solids will, all solid crystals will fall into this group. So, by putting them into different groups we are able to generalize on the characteristic of each group.