Bioreactor Design and Analysis
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Lecture - 33
Scale-up of Bioreactors – Part 1

Welcome back students. So, today we are going to discuss about scale-up of reactors.

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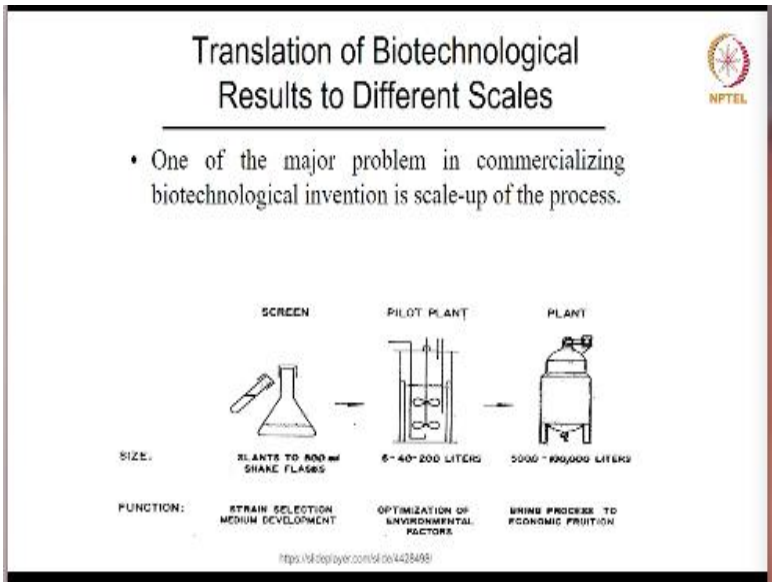

So, whenever there has to be a transitional knowledge from lab scale to industry level, there are different scales at which the technology has to be tested. So, one of the major problems in commercializing the biotechnological invention is scale-up of the process. So, generally what we observe in literature, we will come across people working at the shake flasks level and then at lab scale reactor levels.

But for at commercial scale, shape flasks level studies are generally done for screening purposes for selection of a high yielding fast growing cell line and which can go as high as 500 ml per litre shake flasks. So, generally medium optimization all these things add and other shake flask level. Then once you take it to the lab scale reactor level and then comes the pilot scale to check the reproducibility of the results obtained at the lab scale reactor, how is it getting reproduced at the pilot scale level?

Now, this pilot scale level the range the working volume ranges from 5 to 200 litres depending on the kind of production platform you are using and the kind of product, the

value of the product. Then the production scale plant, this can go as high as from 5000 to 100,000 litres. So, as I said before, the shake flask level studies or the slant level studies, they are generally used for strain selection and medium development.

Then at the pilot plant level, we check the reproducibility, where optimization is done to bring it closer to the lab scale reactor levels. So, at the lab scale reactor level, we carry out the optimization of environmental factors and so on. Then at the production scale, we bring the process to economic fruition.

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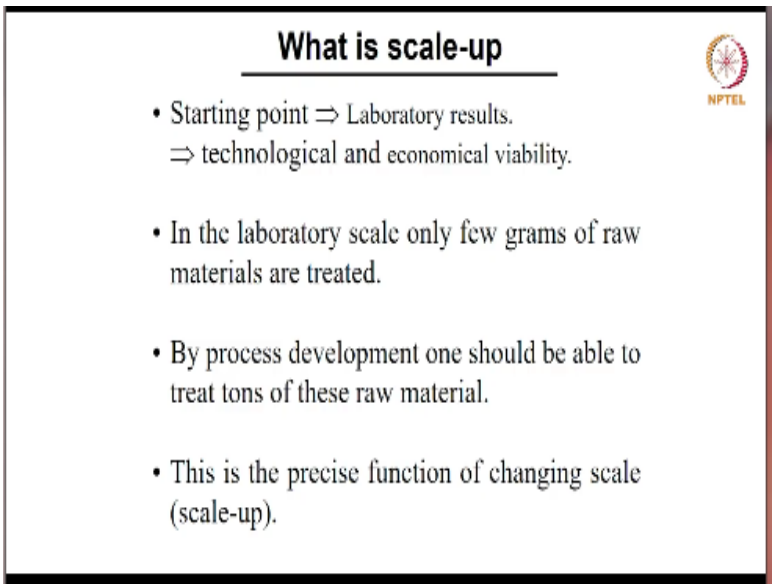

So, what is scale-up? So, scale-up as I said the starting point is the laboratory results. So, at the laboratory scale, we check the technological and the economical feasibility of the process. In the laboratory scale, only few grams of raw material can be processed. Now, by process development, one should be able to treat tons of the raw material or the substrate. Now, this is what is the function of changing scales or scale-up.

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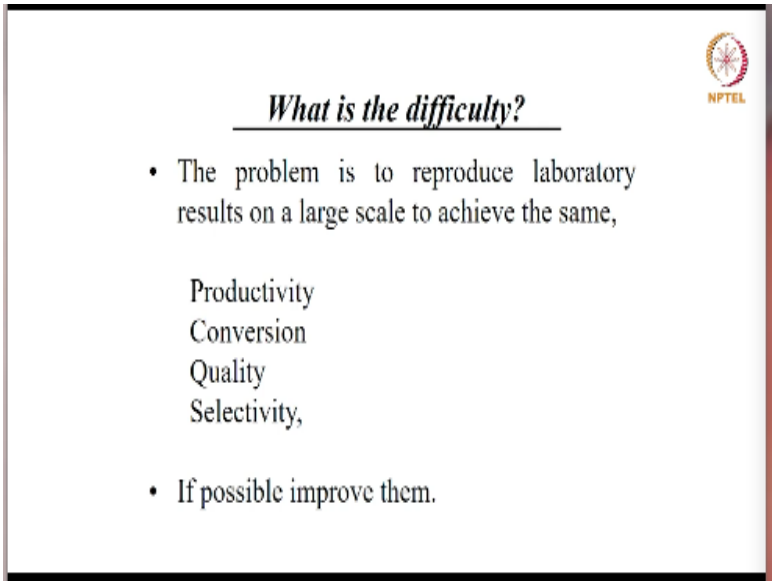

But, where lies the difficulty? The problem is to reproduce the laboratories result on a large scale to achieve the same productivity or same conversion of the substrate or same product quality or the selectivity and if possible. to improve it. But, generally the key is to reproduce the results.

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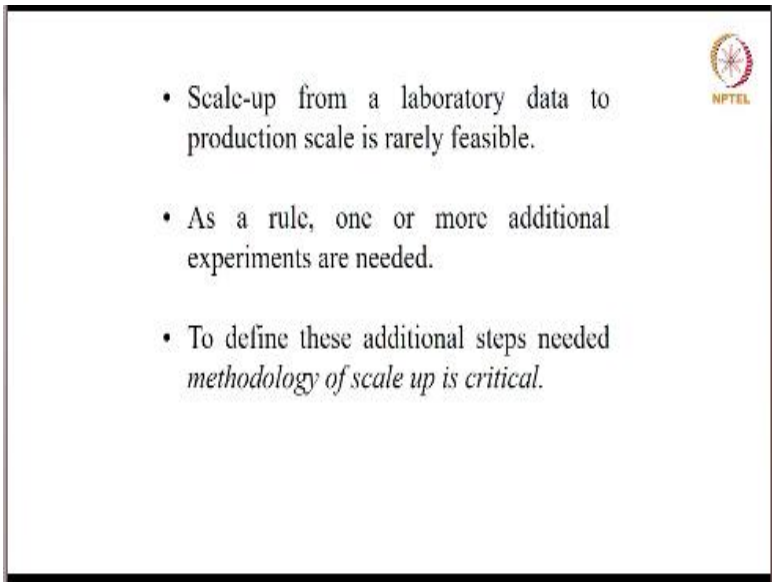

Now, scale-up from a laboratory data to production scale, it is rarely feasible and very challenging. As a rule, one or more additional experiments are anyways needed. So, to define these additional steps needed, methodology of scale-up is critical.

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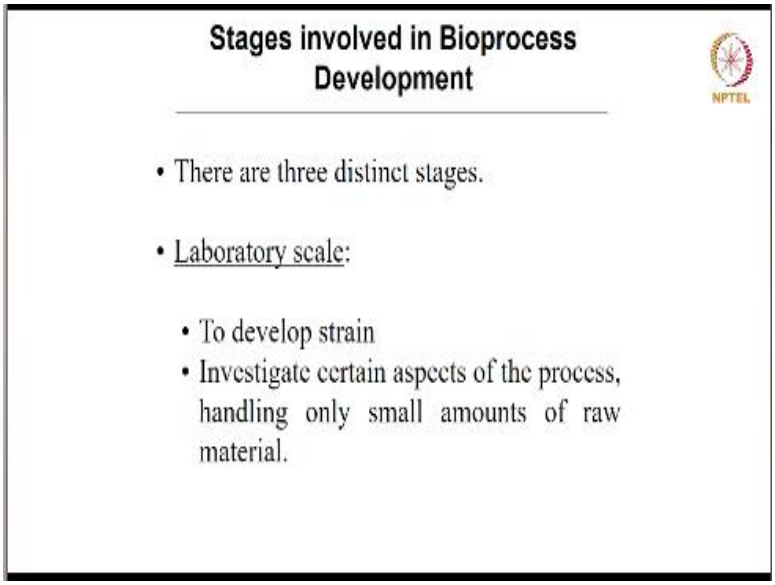

So, there are 3 distinct stages, as you could see from the schematic, laboratory scale, which is generally used to develop the strain to investigate certain aspects of the process, where we handle only small amounts of the raw material.

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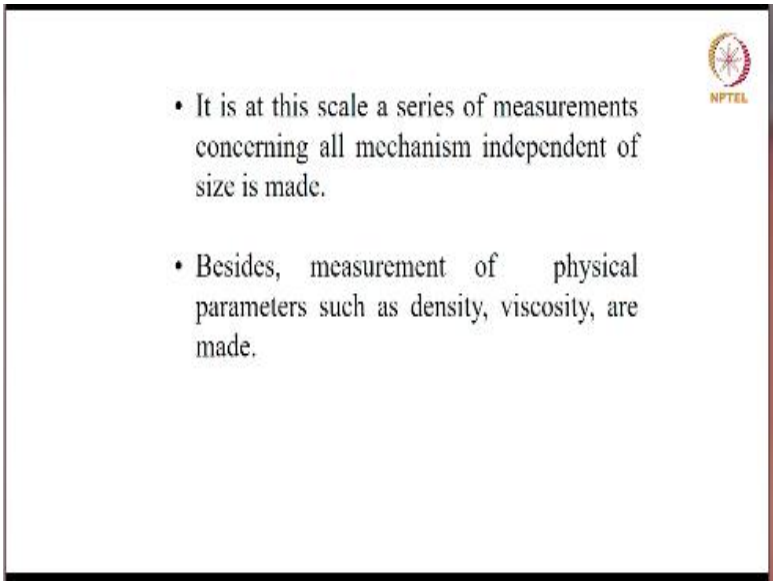

It is at this scale that a series of measurements concerning all the mechanisms which are independent of size can be made. Besides this, measurement of physical parameters such as density, viscosity, they can also be recorded.

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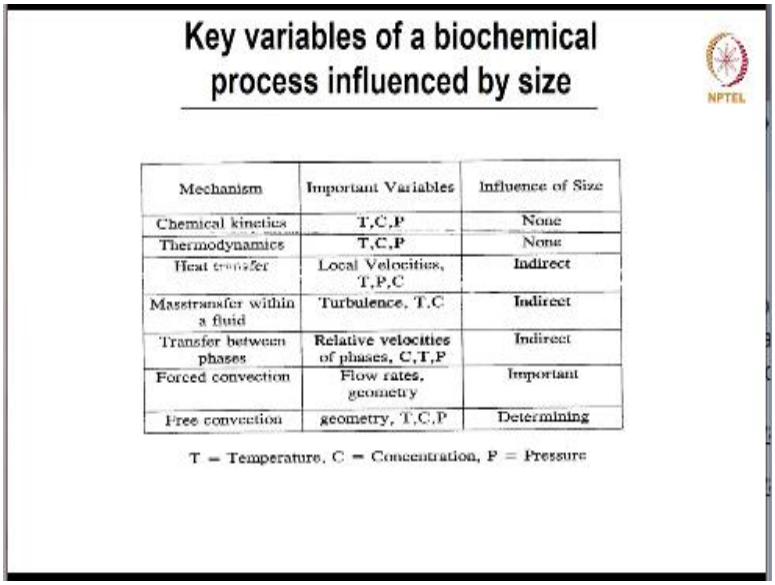

So, key variables of a biochemical process which are influenced by size, like if, you see the mechanism, which is chemical kinetics of the process or thermodynamics of the process. They are independent of size; they are not influenced by the size. They are more influenced by other physical parameters like temperature, concentration of the components, pressure, then heat transfer. This may be indirectly related to the size.

Mass transfer within a fluid, where it is more influenced by the local velocities turbulence. It may be indirectly related to the size. Transfer between the phases, this again, it can be indirectly related to the size. Now, if we talk about the forced convection or the free convection, then size becomes very important, where other variables like flow rate, geometry, these parameters start playing a crucial role.

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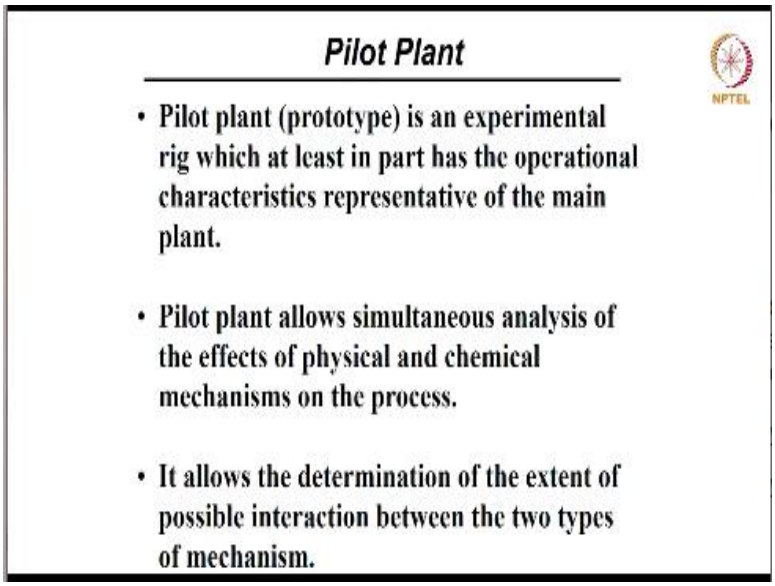

So, I was talking about pilot plant scale. So, what is a pilot plant which can call it as prototype? It is an experimental rig which at least in part has the operational characteristics, which are representative of the main production plant. Now, this pilot plant will allow us to do simultaneous analysis of the effects of various physical and chemical mechanisms on the process.

It allows the determination of the extent of possible interactions between the 2 types of mechanisms which means that physical and chemical mechanisms, the extent to which they are interacting,

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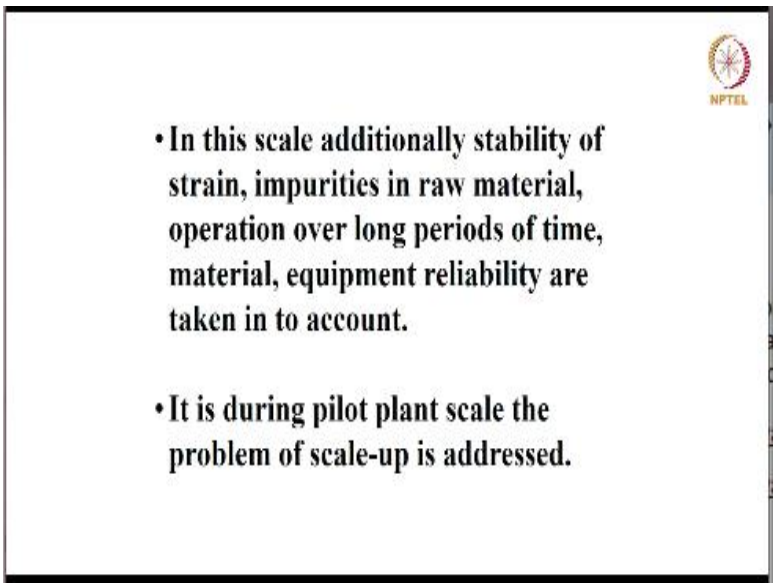

We can also check the stability of the strain which means, if there are any impurities present in the raw material that batch to batch variation. We can check the sterility maintenance or sterile operations feasibility over a long period of time. We can check the equipment reliability. So, these are the additional things which can be looked into at pilot scale. It is the pilot scale level where the problem of scale-up is addressed.

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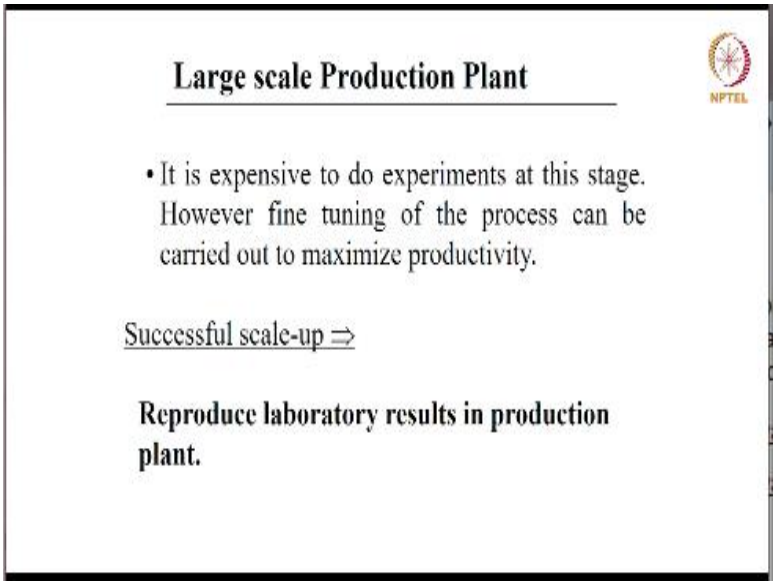

Now, sometimes depending on the production platforms or the product or the ease of experimentation, it can become very expensive to do experiments, all the experiments at pilot scale. However, some fine tuning of the process can be carried out to improve the productivities. But the major aim is at pilot scale is to check successful scale-up, which means the reproducibility of the lab scale results at the production scale.

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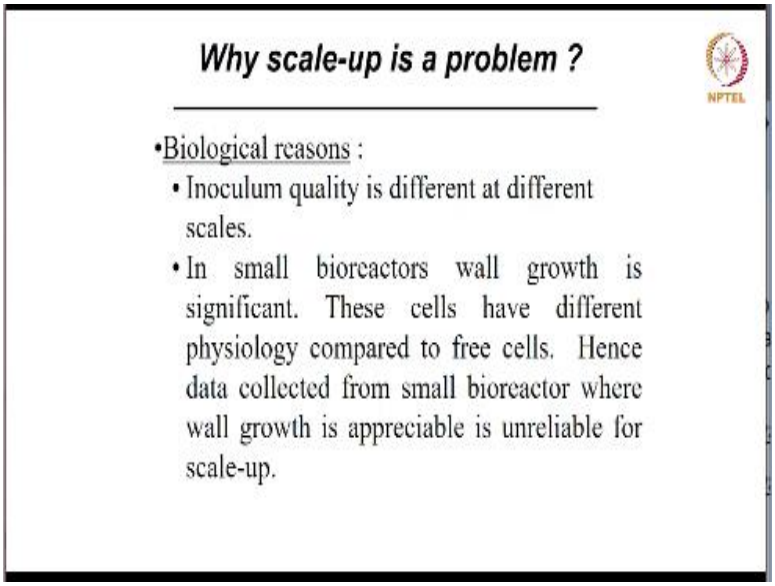

Now, why scale-up is so crucial and challenging? There are more biological reasons and bio technologically driven processes, which are responsible for it. Like for example, the inoculums quality, it can differ at different scales. Then in small bioreactors, why? Because, when to develop the inoculums the size of the reactor will change. So, in small bioreactors the wall growth may not be that significant.

These cells may have different physiology as compared to free cells. But rather than developing in shake flask, if you are developing in reactors and then at larger reactors, the cells might adhere to the wall which you may not be able to see in the shake flask. So, your inoculums quality can change with the scale. Hence, data collected from a bioreactor level where the wall growth is appreciable can be unreliable for scale-up.

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If you see the picture here, it is a filamentous fungi and neurospora, which has grown on glucose. You can see how much volume growth. It is all growing adheres to the stainless steel parts of the reactors, you can see the film adhere to the baffles, nothing is visible.

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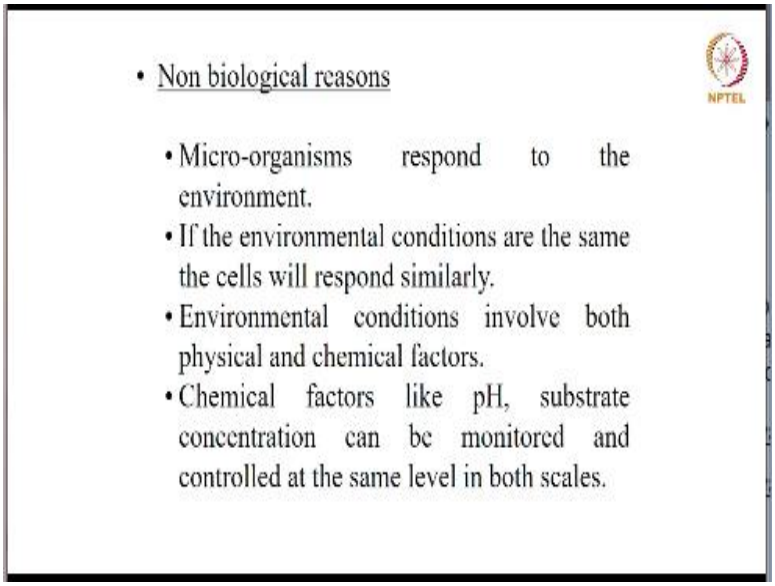

Then there are non-biological reasons like micro organisms can respond to the environment. If the environmental conditions are the same, the cells will respond similarly. Now, this

environment condition can both physical and chemical. Chemical factors like pH or substrate concentration which can be monitored and controlled at the same level in both the scales.

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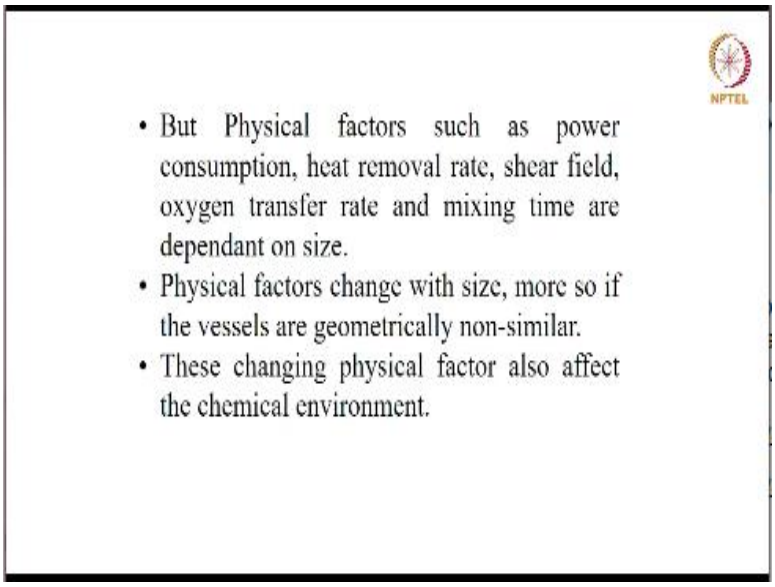

But the physical factors like for example, power consumption, heat removal rate, shear field, oxygen transfer rate, mixing time, they are dependent on size. Now, therefore, these factors can change with size and more, so, if the vessel are geometrically non-similar. So, therefore, these changing physical factors can in turn then affect the chemical environment.

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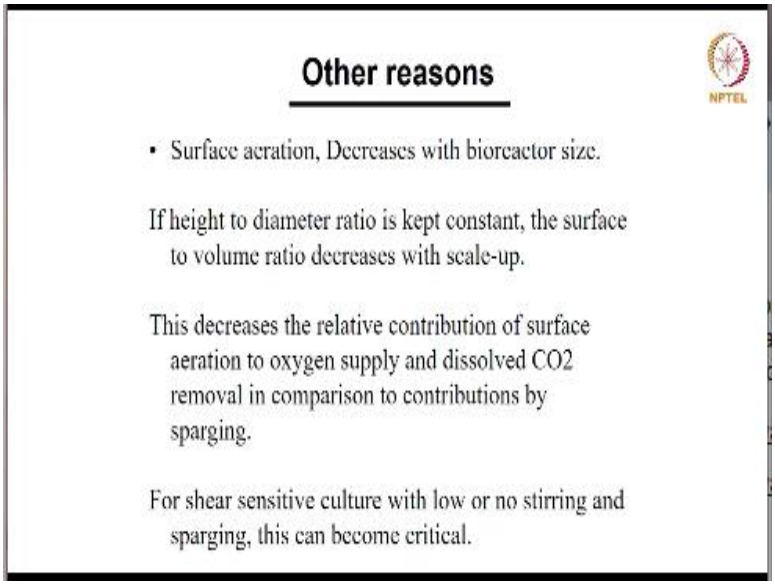

Other reasons can be your surface aeration, which decreases with the bioreactor size. If height to diameter ratio is kept constant, the surface to volume ratio will decrease with scale-up. So, your surface aeration can get impacted. Now, this would then decrease the relative

contribution of the surface aeration to oxygen supply and the dissolved CO 2 removal in comparison to contributions by sparging.

So, for shear sensitive cultures with low or no stirring and sparging, this scenario can become critical, because it can then impact the process.

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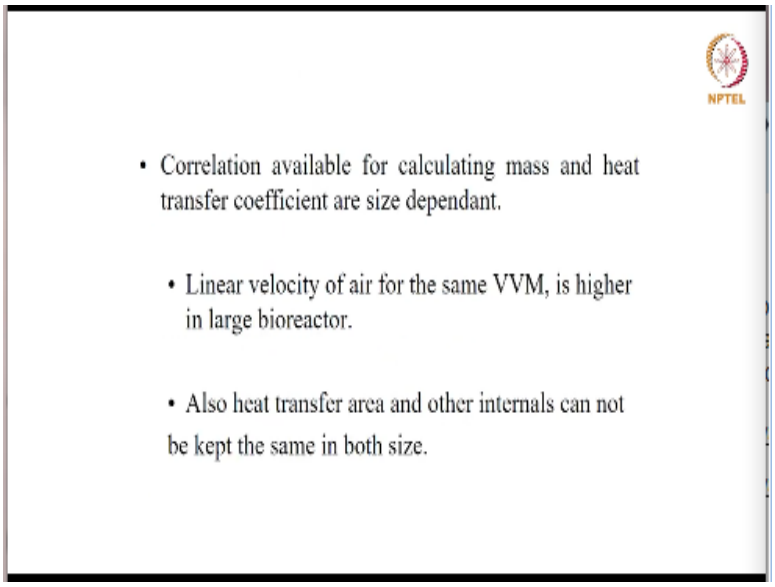

Now, there are empirical core relationships where the mass transfer and the heat transfer coefficients are found to be size dependent. The linear velocity of air for the same VVM is higher in large bioreactors. Similarly, the heat transfer area and other internals cannot be kept the same at different scales.

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