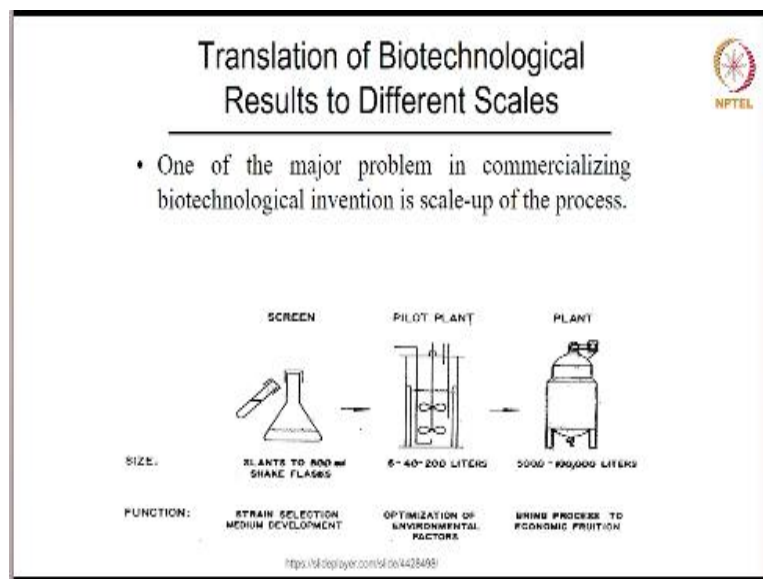


Bioreactor Design and Analysis
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Lecture - 33
Scale-up of Bioreactors – Part 1

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, shake 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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What is scale-up



- Starting point \Rightarrow Laboratory results.
 \Rightarrow technological and economical viability.
- In the laboratory scale only few grams of raw materials are treated.
- By process development one should be able to treat tons of these raw material.
- This is the precise function of changing scale (scale-up).

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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What is the difficulty?

- The problem is to reproduce laboratory results on a large scale to achieve the same,

Productivity
Conversion
Quality
Selectivity,
- If possible improve them.

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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- Scale-up from a laboratory data to production scale is rarely feasible.
- As a rule, one or more additional experiments are needed.
- To define these additional steps needed *methodology of scale up is critical.*

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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Stages involved in Bioprocess Development



- There are three distinct stages.
- Laboratory scale:
 - To develop strain
 - Investigate certain aspects of the process, handling only small amounts of raw material.

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 a series of measurements concerning all mechanism independent of size is made.
- Besides, measurement of physical parameters such as density, viscosity, are made.

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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Key variables of a biochemical process influenced by size



Mechanism	Important Variables	Influence of Size
Chemical kinetics	T, C, P	None
Thermodynamics	T, C, P	None
Heat transfer	Local Velocities, T, P, C	Indirect
Mass transfer within a fluid	Turbulence, T, C	Indirect
Transfer between phases	Relative velocities of phases, C, T, P	Indirect
Forced convection	Flow rates, geometry	Important
Free convection	geometry, T, C, P	Determining


T = Temperature, C = Concentration, P = Pressure

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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Pilot Plant

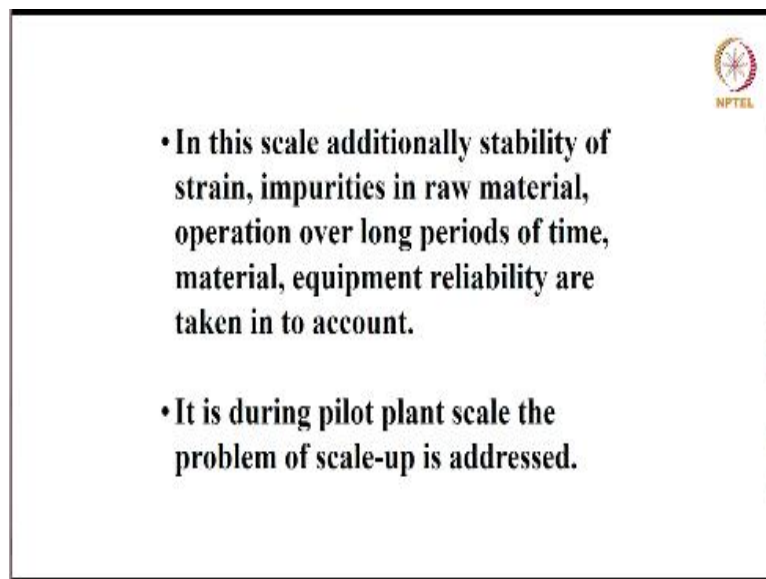


- **Pilot plant (prototype) is an experimental rig which at least in part has the operational characteristics representative of the main plant.**
- **Pilot plant allows simultaneous analysis of the effects of physical and chemical mechanisms on the process.**
- **It allows the determination of the extent of possible interaction between the two types of mechanism.**

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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Large scale Production Plant


- It is expensive to do experiments at this stage. However fine tuning of the process can be carried out to maximize productivity.

Successful scale-up ⇒

Reproduce laboratory results in production plant.

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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Why scale-up is a problem ?

- Biological reasons :
 - Inoculum quality is different at different scales.
 - In small bioreactors wall growth is significant. These cells have different physiology compared to free cells. Hence data collected from small bioreactor where wall growth is appreciable is unreliable for scale-up.

Now, why scale-up is so crucial and challenging? There are more biological reasons and biotechnologically driven processes, which are responsible for it. Like for example, the inoculum quality, it can differ at different scales. Then in small bioreactors, why? Because, when to develop the inoculum 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 inoculum 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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- Non biological reasons
 - Micro-organisms respond to the environment.
 - If the environmental conditions are the same the cells will respond similarly.
 - Environmental conditions involve both physical and chemical factors.
 - Chemical factors like pH, substrate concentration can be monitored and controlled at the same level in both scales.

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 Physical factors such as power consumption, heat removal rate, shear field, oxygen transfer rate and mixing time are dependant on size.
- Physical factors change with size, more so if the vessels are geometrically non-similar.
- These changing physical factor also affect the chemical environment.

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

- Surface aeration, Decreases with bioreactor size.

If height to diameter ratio is kept constant, the surface to volume ratio decreases with scale-up.

This decreases the relative contribution of surface aeration to oxygen supply and dissolved CO₂ removal in comparison to contributions by sparging.


For shear sensitive culture with low or no stirring and sparging, this can become critical.

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 CO₂ 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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- Correlation available for calculating mass and heat transfer coefficient are size dependant.
- Linear velocity of air for the same VVM, is higher in large bioreactor.
- Also heat transfer area and other internals can not be kept the same in both size.

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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Scale-up Principles



- Fundamental requirement is that small and large reactor should be similar.
- There are two types of similarity
 - Geometrical
 - Dynamic similarity of flow fields