

Scale down of fermentation Process

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Scale Down Studies

- In scale down studies the main objective is to carry out studies on smaller bioreactors in order to gain data and confidence and predict the behaviour how things actually will behave in large production fermentor.
- Scale down studies are also used while during the operation of large industrial scale fermentors in trouble shooting or trying to optimize the industrial scale fermentation.
- This method is called the fermentation monitoring experiment.
- The goal when scaling down is to create a small-scale or lab-scale system that mimics the performance of its large-scale (pilot or manufacturing) counterpart, when both the process parameters are varied within their operating ranges and also when a process parameter deviates outside its operating range.

The main type of studies in scale down

- **Medium design:** media relevant to the industrial situation should be used in development experiments.
- **Medium sterilization:** If batch sterilized in large scale its exposure time at a high temp will be greater than that experienced in the laboratory or pilot plant; thus sterilization in the smaller scale should be increased.
- Alternatively, medium sterilised in the production fermenter maybe used in the laboratory or pilot plant.
- **Inoculation procedures:** using inoculum of different ages as during production it is not possible to use inoculum in optimum condition.
- **Number of generations:** The industrial situation may be modelled in the laboratory by using serial subculture to ensure that the strain is sufficiently stable.
- **Mixing:** It is almost inevitable that the degree of mixing will decrease with an increase in scale.
- **Oxygen transfer rate:** Far higher oxygen transfer rates can be achieved in laboratory fermenters than in industrial-scale ones.

Rules of Scale Down

Similar model geometries and ratios of system

- The impeller and sparger designs, and placements within the vessel must be identical or similar.
- Wrong models used in scale down studies might invalidate the data obtained.
- Since a typical fermentation process might involved different fermentor capacities, scaling down will therefore be very challenging and proper strategies need to be developed during scale down studies.

Similar methods of analyses and monitoring be applied at scale down studies

- sample-dilution schemes and measurement times for calculating culture optical densities,
- wet and dry cell-weights,
- media metabolite levels.

... Rules of Scale Down

Sampling volume

- Due to the involvement of small scale fermentors which contained less working volume, the sampling volumes should be minimized to prevent depletion of culture broth beyond acceptable levels.
- If the sample size cannot be reduced, then adjust the frequency of sampling.

Oxygen transfers

- Mass transfer of oxygen between big and small fermentors is a critical issue in scale down studies.
- The efficiency of oxygen transfer on production scale fermentor is much lower compared to the lab scale fermentor.
- The strategy in doing scale down studies in oxygen transfer is to maintain similarity in sparger design, calibration and placement within the small fermentor and the large fermentor.
- If the sparger design is different between scales, then agitation, aeration and oxygen enrichment may need to be adjusted to provide equivalent oxygen transfer in the small fermentor.

... Rules of Scale Down

Inocula

- It is very important in doing inoculum development during scale down exercise to maintain the vessel geometries, incubation conditions, and working volumes whenever possible during the scale down exercise.
- If in the process it is not possible to obtain fermentors of similar geometries the operational control parameters may need to be adjusted to account for different vessel geometries.

Sterilizations

- During sterilization studies in scale down studies, the sterilization temperatures, procedures for probe calibration, and post-use cleaning protocols should be the similar as the large-scale fermentor.

... Rules of Scale Down

Fermentation Feed

- The raw materials used in scale down studies should be identical to those used for the full-scale process.

Fermentation Control Parameters

- Similar operating regimes and controls should be applied to the small scale fermentor such as:
 - process temperature
 - pH
 - inoculation percentages (v/v) for each step
 - schedule of feed-media additions.
- A linear adjustment method should be used for all the volume-dependent operational control-parameter set points except agitation.

... Fermentation Control Parameters

- The scale factor should be equivalent to the ratio of overall process volumes.
- Examples of linear adjustments in:
 - Pre-and post-sterilization volumes of growth media.
 - Feed media delivery rates.
 - Total airflow.
 - Oxygen flow rate.
- **Agitation rate**
- Set agitation in scale down studies to provide either representative :
 - oxygen transfer rate
 - tip speed (the distance that any selected point on the peripheral of the impeller travels in a set time),
 - Reynolds Number (Re , helps predict flow patterns in different fluid flow situations),
 - power-input per unit volume,
- Under conditions of similar fermentor geometry it is recommended that the oxygen transfer rate studies be carried out.

$$Re = \frac{\rho u L}{\mu}$$

Re = reynolds number

ρ = density of the fluid

u = flow speed

L = characteristic linear dimension

μ = dynamic viscosity of the fluid

... Fermentation Control Parameters

Culture growth

- Culture growth is a critical performance parameter for qualifying the scale-down studies.
- Oxygen utilization is a very important performance parameter for scale-down exercise.
- Similar patterns in dissolved oxygen profiles, and oxygen and airflow rates represent comparability in oxygen usage by the cultures at each scale.

Product yield

- A biochemical finger print should be established for both large scale and scale down fermentation for comparison for similarity in efficacy.

... Fermentation Control Parameters

Process sensitivity

- Process-control sensitivity for dissolved oxygen, pH, temperature, agitation and feed delivery must be verified at the small-scale.

Do scale down at few times

- In general, for greater confidence it is good to perform at least three small-scale runs to confirm reproducibility and to determine the inherent variability in the process.