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Scale up of API

Ms. Bhoomi Trivedi,Prof. B.H.Shah
Chemical Engineering Department, L.D. College of Engineering,Ahmedabad-380015.
Email ID - bhoomitrivedi@yahoo.co.in

Abstract: The manufacturing Process of Active pharmaceutical ingredients (API) pharmaceutical process development process definition & objective is explained in detail. Different scale up perspectives will be explained for the pharmaceutical process development.
What parameters mainly changes during the scale up related to length, time and mixing are explained. Chemical process safety prevention is better to take care during the development stage and safe process development during the scale up. Effect of various process parameters like cooling capacities for different vessels and adiabatic temperature different for different vessels studies have been carried out. For most highly exothermic reaction which kind of risk assessment studies need to do that is mentioned. How calorimetry is being used for the calculation of heat of reaction mixture (Q) explained in detail. How calorimetry is directly or indirectly being used for mass transfer, heat transfer, mixing, concentration and dosing speed calculation. It also shows how this thing being connected to rate of reaction explained in detail. Case study relevant to this is explained in detail with graphs and related results. Batch reactor scale up designing from process side is explained with one of the case study for batch kind of stirr tank reactor with 4-balde pitch blade turbine. Drying scale up calculation is shown for one of the case. This thing is explained with the conclusion. Paper includes relevant references.
Key words: *Scale up introduction, highly exothermic reaction, Batch reactor scale up design, Drying scale up*

1.Introduction[1,2,6,7,10]:

- **Definition**

– Act of using results obtained from laboratory studies for designing a prototype and a pilot plant process; construction a pilot plant and using pilot plant data for designing and constructing a full scale plant or modifying an existing plant.

Pharmaceutical Process Scale-Up deals with a subject both fascinating and vitally important for the pharmaceutical industry—the procedures of transferring the results of R&D obtained on laboratory scale to the pilot plant and finally to production scale. The primary objective of this is to provide insight into the practical aspects of process scale-up. Scale-up is generally defined as the process of increasing the batch size. Scale-up of a process can also be viewed as a procedure for applying the same process to different output volumes. There is a subtle difference between these two definitions: batch size enlargement does not always translate into a size increase of the processing volume.

"The successful linkage of one unit operation to another defines the functionality of the overall manufacturing process. Each unit operation per se may be scalable, in accordance with a specific ratio, but the composite manufacturing process may not be, as the effective scale-up ratios may be different from one unit operation to another. Unexpected problems in scale-up are often a reflection of the dichotomy between unit operation scale-up and *process* scale-up. Furthermore, commercial production introduces problems that are not a major issue on a small scale: e.g. storage and materials handling may become problematic only when large quantities are involved; heat generated in the course of pilot plant or production scale processing may overwhelm the system's capacity for dissipation to an extent not anticipated based on prior laboratory-scale experience "

$$Scale-up\ ratio = \frac{large-scale\ \ production\ rate}{small-scale\ \ production\ rate}$$

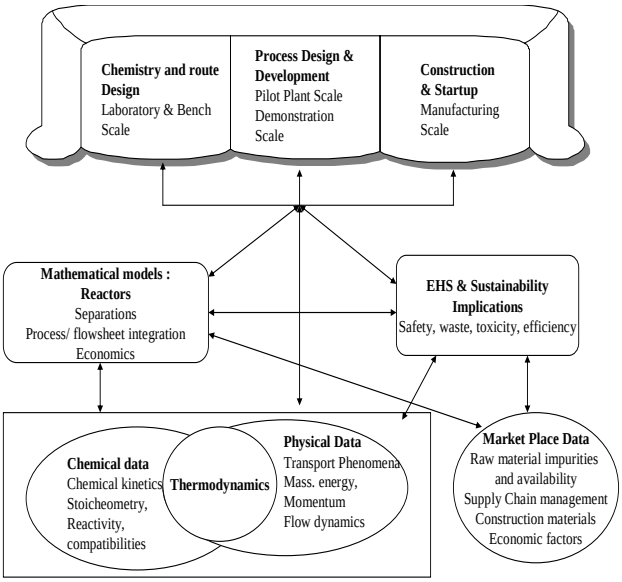
In moving from R&D to production scale, it is sometimes essential to have an intermediate batch scale. This is achieved at the so-called pilot scale, which is defined as the manufacturing of drug product by a procedure fully representative of and simulating that used for full manufacturing scale. However, inserting an intermediate step between R&D and production
scales does not in itself guarantee a smooth transition. A well-defined process may generate a perfect product in both the laboratory and the pilot plant and then fail quality assurance tests in production.

2.Potential Scale Up Issues and Strategy[10]

Scale- up Issues	Potential scale-up strategy
Mass Transfer	• Perform mixing and fluid dynamic studies and modeling (e.g., perform sensitivity to mixing studies) • Model fluid dynamics using computer modeling • Perform kinetic studies

	• Establish rate-limiting step mechanism • Consider effect of different phases (e.g., solid formation) • Determine critical design parameter for mixing system • When scaling up agitation consider type of agitator (e.g., pitch blade turbine, anchor type) • Consider other sources of turbulence and mixing
Heat Transfer	• Estimate heats of reaction using reaction calorimetry • Evaluate heating and cooling requirements • Perform dynamic heat balance to determine exothermic behavior and heat transfer rates • Perform reactive chemical testing such as differential scanning calorimetry and accelerated rate calorimetry • Use computer models to simulate plant conditions • Consider different methods of reactant incorporation (reverse addition, different feed place)

3. Scale –up process and how the various tools interact to provide the right information for the process at right development stage[10]:



4. Different parameters changes during the scale up

- **Length Scale parameter Changes on Scale-Up**

Length Scale Parameter	Change on Scale Up?
Linear vessel dimensions	Yes
Volume	Yes
Feed tube dimensions	Yes
Agitator impeller dimensions	Yes
Molecular size	No
Heat transfer area	Maybe
Surface area for vapor disengagement	Maybe
Solid particle size	Maybe

- **Time Scale Parameter Changes on Scale-UP**

Time Scale Parameter (Some or All of These Will Almost Certainly Change on Scale Up)
Vessel charge/discharge time
Feed time for reactants
Heating/cooling time
Time to pressurize or depressurize
Various mixing and blend times
Feed stream disintegration time
Time delays for maintenance, physically moving materials into and out of the Production area, waiting for availability of operating personnel, etc.

- **Mixing Parameter Variation for Various Scale Up Approaches with Geometric Similarity**

Mixing Scale Up Approach	Parameters Which Do Not Change	Parameters Which Will Change
Constant power per unit volume	Power per unit volume	• Plant impeller speed < pilot plant • Plant impeller tip speed > pilot plant • Plant maximum shear > pilot plant • Plant flow/unit volume < pilot plant • Plant blend time > pilot plant • Plant Reynolds Number > pilot plant

		(may change from laminar to turbulent flow)
Constant flow per unit volume	• Blend time • Impeller speed • Average shear	• Plant power/unit volume > pilot plant • Plant impeller tip speed > pilot plant • Plant maximum shear > pilot plant • Plant Reynolds Number > pilot plant (may change from laminar to turbulent flow)

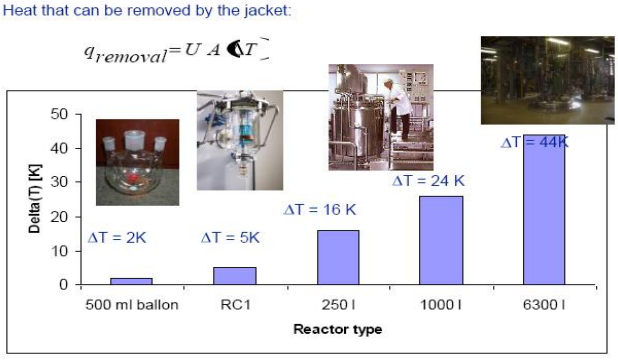
5. Cooling capacities of Different vessels:

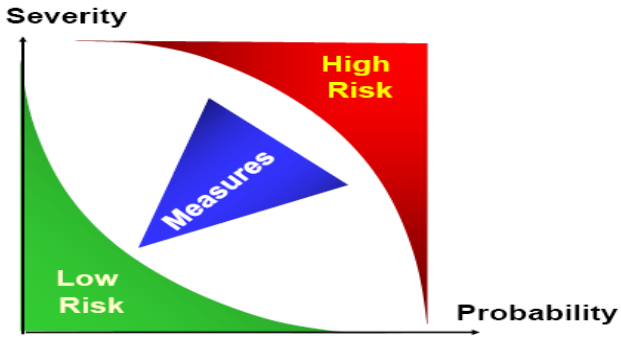
Reactor	heat transfer coëfficiënt	specific cooling area	specific heat transfer	ΔT needed on jacket to cool 30 W/L
	U (W/m²K)	(m²/m³)	U . A / V (W/lK)	
500 ml flask	200	86	17.2	**2**
RC1 1L vessel	150	40	6	**5**
250 L reactor	250	6,8	1,70	**16**
1000 L reactor	250	4,6	1,15	**26**
6300 L reactor	250	2,6	0,65	**44**

** ALWAYS OBSERVE AND REPORT TEMPERATURE CHANGES

Effect of temperature difference during scale-up:

6. Risk Assessment studies:





- **Process of Risk assessment:**
  - Look for the hazards & decide who might be harmed, and howevaluate the risks arising from the hazards and decide whether existing precautions are adequate or more should be done
  - Record the findings
  - Review the assessment from time to time and revise it if necessary

7. Reaction calorimetry for scale-up study[11]:

Calorimetry is the science of measuring the heat of chemical reactions or physical changes. The word calorimetry is derived from calorie, a unit of heat. Calorimeter is a device used for calorimetry.

- Reaction Calorimeter is an instrument capable of making absolute measurements of energy liberated or absorbed in a system wherein a chemical reaction / physical process is going on.
- Reaction calorimeter involves a reactor that simulates the industrial reactors wherein a chemical or a physical process is carried out.

Measurements

- Process variables: temperatures, stirrer speed, mass, pH, pressure, viscosity, ...
- Heat transfer coefficient (U)
- Specific heat (Cp)
- Heat production rate (ΔH)

Control

- Temperature, stirrer speed
- Dosing, pressure, pH, heat flow, liquid level

Reaction calorimetry study set up:

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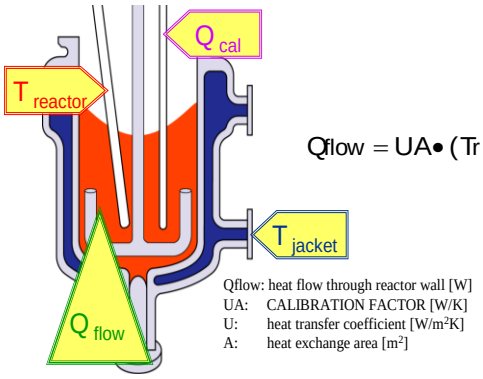
Calorimetry Measurement



$Qflow = UA \bullet (Tr - Tj)$

Qflow: heat flow through reactor wall [W]
UA: CALIBRATION FACTOR [W/K]
U: heat transfer coefficient [W/m²K]
A: heat exchange area [m²]

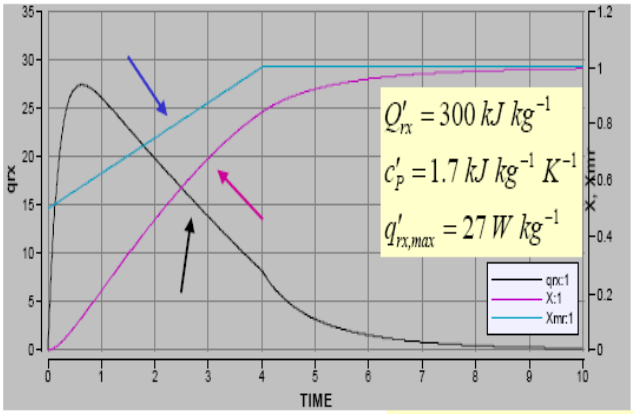
- **Heat flow terms:**

$Q_r = Q_{flow} + Q_{accu} + Q_{dos} - Q_c$
$Q_{flow} = UA * (T_r - T_j)$
$Q_{accu} = dT_r/dt * S (mc_p)$
$Q_{dos} = dm/dt * c_pdos (T_r - T_{dos})$

- **Calculations:** Determination of the mass balance
  - Calculation of the calibration information & thermal conversion
  - Computation of the heat transfer coefficients & heat flow
  - Computation of the specific heat & reaction enthalpy

7.1 Case Study:

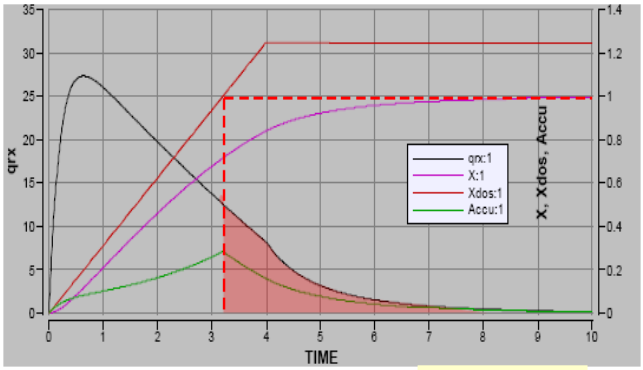
- Reaction A+B -> P
- A initially charged
- B fed at constant rate
- Mol ratio B / A = 1.25
- Process temperature: 80 °C
- Intended feed time 4 hrs
- Solvent xylene: MTT = 140 °C (boiling point)
- Limit for thermal stability: TD24= 115 °C



- Temperature: 80 °C,
- Feed time: 4 hrs
- Power in W/kg; time in hrs
- Thermal conversion

$$X = \frac{\int_0^t q'_{rx} \cdot d\tau}{\int_0^\infty q'_{rx} \cdot d\tau} = \frac{\int_0^t q'_{rx} \cdot d\tau}{Q'_{rx}}$$

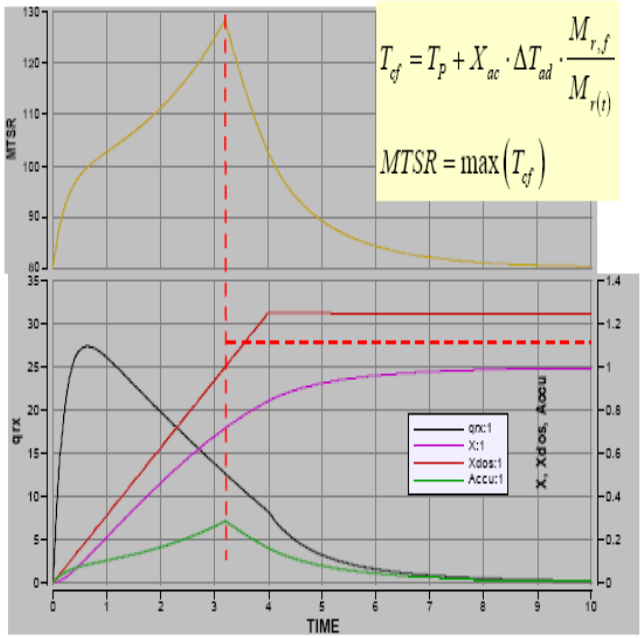
Semi Batch Reactor Experiment: Reaction calorimetry Accumulation Experiment



- Temperature: 80 °C,
- Feed 125% within 4 hrs
- Power in W/kg; time in hrs
- Accumulation

$$X = \frac{\int_0^t q'_{rx} \cdot d\tau}{Q'_{rx}}$$
$$X_{ac} = X_{dos} - X$$

TSR experiment: Thermal Risk assessment from calorimetry:



- Temperature 80 °C, Feed in 4 hrs
- Power in W/kg; time in hrs

Heat of Reaction: Q_{rx} = 300 kJ/kg
Specific heat capacity: C_p = 1.7 kJ/kgK
Adiabatic temperature rise $\Delta T_{ad} = \frac{Q_{rx}}{c_p} =$

176 K Potential medium
Maximum temperature of synthesis reaction

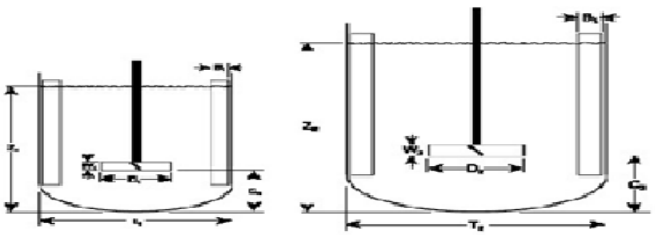
Maximum Accumulation $X_{ac,max}$ = 0.25
Reaction mass at max.
Accumulation $M_{r,st}$ =1.4 kg

MTSR = $T_p + X_{ac}.\ \Delta T_{ad}\frac{M_{rf}}{M_{r(t)}}$ =80+0.25×176 × $\frac{1.5}{1.4}$ =

128°C

8. Reactor Scale up:

Vessel geometry:	**Process Side:**
Tank Diameter T= 115 mm = 0.115 m	Impeller Type = 4-bladed pitched blade turbine
Liquid Volume V= 1 liter = 0.001 m^3	Impeller diameter D= 46 mm
Heat Transfer Area A= 0.043 m^2	Agitator speed N= 600 rpm = 10 rps
Liquid Height H= 104 mm = 0.104 m	Solvent Name = Water
Jacket Wall thermal conductivity for glass material = 1.05 W/m K	Temperature Tr= 1°C
	Fouling Factor h_{if} = 5000 W/m^2K



tip velocity v = π D_a n

= $\pi \times 0.046 \times 600$

= 86.70 rpm

= $\frac{86.70}{60}$

= 1.445 rps

Basis: 100 kg production per batch
Required volume to be filled with initial Stage-1 product of 100 kg is 25 volumes of all reactant solutions.
Hence working volume for the reactor at commercial scale = 100000 × 25

=

2500000 ml =2500 lit = 2.5 m^3
Consider the type of bottom head = torispherical
Take height of the liquid inside the reactor shell = h
Take inside diameter of reactor shell = D_i

Let, $\frac{h}{D_i}$ = 1

So, h = D_i

Inside volume of Torispherical head, $V_{working} = \frac{\pi}{4} D_i^2 h +$

$0.084672\ D_i^3 + \frac{\pi}{4} D_i^2 S_F$

Where, D_i = Inside diameter of reactor in mm
V = Working volume in m^3
S_F = Straight Flange, m = 1.5 in = 0.0381 m (Assume)

$2.5 = \frac{\pi}{4} D_i^3 + 0.084672\ D_i^3 + \frac{\pi}{4} D_i^2 \times 0.0381$

By solving above equation,
D_i = 1.399 m
So, Height of the liquid in the shell h = 1.399 m
Consider provision of 20% extra space for vapour- liquid disengagement, then actual height of shell of the reactor H= 1.2 m, Actual height of Shell H = 1.2× h= 1.2× 1.399 = 1.6788 m
Diameter of reactor at commercial scale = 1.399 m

Diameter of Agitator $D_a = \frac{\text{Diameter of reactor}}{3}$

$= \frac{1.399}{3}$

= 0.466 m

Tip velocity at Pilot plant and commercial scale both are same so, from this number of revolutions can be calculated,

v = π D_a n

$86.70 = \pi \times 0.466 \times n$

$n = \frac{86.70}{\pi \times 0.466}$

n = 59.222 rpm

n = 0.987 rps = 1 rps

9. Rotary batch vacuum Drier:

Vacuum rotary dryers are batch dryers, at least in currently available commercial form. Vacuum rotary dryer consist of horizontal cylindrical shell, suitably jacketed. Vacuum is applied to this unit through hollow trunnions with suitable packing glands. Rotary glands must be used also for admitting and removing the heating medium from the jacket. The inside of the shell may have lifting bars, welded longitudinally, to assist agitation of the solids.

The double cone rotating vacuum dryer is more common design. Although it is identical in operating design, the sloping walls of the cones permit more rapid emptying of solids when the dryer is in stationary position. The older cylindrical shape required continuous rotation during emptying to convey product to the discharge nozzles. As, a result, a circular dust hood was frequently necessary to enclose the discharge nozzle turning circle and prevent serious dust loses to the atmosphere during unloading. Several new designs of the double-cone type employ internal tubes or plate coils to provide additional heating surface.
In vacuum processing and drying the objective is to create a large temperature-driving force between the jacket and the

product. To accomplish this purpose at fairly low jacket temperatures, it is necessary to reduce the internal process pressure so that the liquid being removed will boil at a lower vapor pressure.

Calculation:

30% Methanol is present in final API So,

Total feed material (API) $= \frac{100}{0.7} = 142.86$ kg

Bulk Density of Final API = 0.4 gm/cc = 400 kg/m^3

For drying of 100 kg of material required volume $= \frac{100}{400} = 0.25$ m^3

fig: Rotary batch vacuum Drier

For designing of Vacuum rotary drier 50% of extra space required if it is filled fully then it will create a problem in rotation.

So, Required vacuum drier is of 500 lit = 0.5 m^3

Required Drying temperature From Lab & Pilot scale drying is 35°C.

So, At this temperature need to remove methanol content from API then required Vacuum pressure is 5 mmHg.

So, Volume of Drier $V = \frac{\pi}{4}D2h_1 + 2/3\ \pi\ r2h^2$

$$V = \pi/4\ D^2h_1 + 2/3\ \pi \left(\frac{D}{2}\right)^2 h^2$$

$$V = \frac{\pi}{4}D^2h_1 + \frac{1}{6}\pi D^2h_2$$

$$\text{Sin}60° = \frac{h_2}{L}$$

$$\tan 60° = \frac{h_2}{\frac{D}{2}} = h_2 = 0.866\ D$$

As, $h_1 = D$

Keeping this values in above shown equation,

$V = 1.466\ D^3$

$0.5 = 1.466\ (D)^3$

D = 0.699 m = Inside diameter

Take a wall thickness of 5 mm

So, Shell OD $D_o = 0.699 + 2(0.005) = 0.709$ m

Let width of jacket = 50 mm

Mean Diameter of Jacket $D_j = 0.709+0.05 = 0.714$ mm

For this kind of drier 50% of extra height required so,

H = 0.709 × 1.5 = 1.0635 m

So,

Area required A= π D H

$= \pi \times 0.709 \times 1.0635 = 2.36$ m^2

Service fluid is hot water which is being passed through jacket

Overall heat transfer coefficient of methanol when service fluid is hot water & Organics inside the shell is between 30 to 200 W/m^2°C. Mostly for rotary kind of dryer overall heat transfer coefficient is 35 W/m^2°C

U = 35 W/m^2°C

Temperature of jacket side flowing fluid = 45°C = t_1

Temperature of fluid coming out of jacket = 40°C = t_2

Temperature of Material inside the shell = 35°C = T_1

Temperature of material coming out after drying = 35°C = T_2

Area A =2.36 m^2

Mean Temperature Difference LMTD $= \frac{(t_2-T_1)-(t_1-T_2)}{\ln\left[\frac{(t_2-T_1)}{(t_1-T_2)}\right]}$

By keeping all this values in equation of LMTD

LMTD = 7.21°C

$Q = U\ A\ \Delta T_m$

Q = 35× 2.36× 7.21 = 585.73 W = 0.58573 kW

$Q = \dot{m} C_p\ \Delta T$

m = mass flow rate of hot water flowing inside the jacket = kg/s

C_p = Specific heat of water = 1 J/kg °C

Hot water flowing inside the jacket = 45°C

Water coming out from the jacket = 40°C

By keeping all this values in Above shown Formula for Q,

m = 0.117 kg/s

$Q = \dot{m}\ \lambda = 0.58573 = \dot{m} \times 628.821$

m = 0.000932 kg/s = 3.35 kg/h

As, calculated for removing 42.86 kg of methanol required time is = 42.86/3.35 = 12.35 hrs

So, Evaporation Rate $= \frac{42.86}{12\times2.32}$ = 1.539 kg/hr m^2

10. Conclusion:

Process scale-up of liquids and semisolids not only is an absolutely essential part of pharmaceutical manufacturing but also is a crucial part of the regulatory process. The dearth of research publications to date must reflect either the avoidance of scale-up issues by pharmaceutical formulators and technologists due to their inherent complexity or a concern that scale-up experimentation and data constitute trade secrets that must not be disclosed lest competitive advantages be lost. Right kind of designing of reactor is most important. And after drug development (API) drying is most important thing to take care.

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