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Development and Scale Up Of a Chemical Process in Pharmaceutical Industry: A Case Study

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ABSTRACT
Every process has its own significance and one has to study factors which impact to the process and its procedure to be followed. This paper is more concerned of how a process is scaled up from lab scale to pilot plant scale, which is the major step in any industry because moving directly towards manufacturing level consumes time and money. The report introduces about pharmaceutical industry and how it is different from the other industries and provides firsthand experience for all the engineers to explore the equipment, process and unit operations included in it. First aspect of scale up is safety and then comes economy, purity and optimums. It includes the process and its unit operations such as reactors, distillation, filtration, crystallization, drying and the equipment involving these operations. Consequently, the scale up rules, factors influenced strategies and other considerations are observed. To learn and understand the unit process and operations with their importance, a case study taking one of the stages of production is discussed here.

Keywords: chemical processes, scaling up, reactors, unit operations, equipments, Safety.

I. INTRODUCTION

A chemical engineer is generally concerned with the industrial implementation of processes in which chemical[1] or microbiological conversion[2] of material takes place in conjunction with the transfer of mass, heat, and momentum[3-5]. These processes are scale dependent; that is, they behave differently on a small scale (in laboratories or pilot plants) and on a large scale (in production). There is no product that has been manufactured in a large scale, each and every raw material and the end product is been tested in a lab scale[6,7]. Then it followed by a tenfold manufacturing process. Due to this very reason this topic was zeroed in as research project. Lab chemists develop new products by testing it in a lab scale, the end result in proper format is sent to the process engineers. They also develop a chemical reaction process and pilot engineers try to interpret lab results. Chemists and Engineers should be very familiar with the scale up terminology also should have scale up skills and techniques to apply at the plant scale[8,9]. Chemical production is a result of several chemical reactions and purification steps[10,11]. Purification steps and processes yield are a direct function of the level of understanding of the reaction system. Reaction quality results have impact in separation technology. Production is usually performed on stirred vessels that are operated at batch or semi-batch configuration[12,13]. The choice process configuration is determined at the development stage of the project. Mixing should be understood well to get a desired product. Scale-up is generally defined as the process of increasing the batch size[14]. Scale-up of a process can also be viewed as a procedure for applying the same process[15] 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 pharmaceutical industry develops[16] produces and markets drugs or pharmaceuticals for use as medications. Pharmaceutical companies may deal in generic or in brand medications and medical devices. They are subject to a variety of laws and regulations that govern the patenting, testing, safety, efficacy and drugs. The reactions which indulge in pharmaceutical company are hazards, pyrophoric and sometimes flammable. These types of reactions should be handled carefully as it might costs lots of life and property[17-19] on over exposure. These reactions cannot be directly manufactured in a large scale, first these are tested in a lab by the resource and development department considering each factor such as reactivity, flammability and safety[20, 21].

II. METHOD

2.1 Major scale up factors:

Chemical Hygiene: Increased risks and chances for exposure to toxic substances, off-gases must be treated. Expanded Time Scale A reaction time differs a lot from the normal lab scale; it takes about 24 hrs or 2-3 days.

Heat Transfer: Laboratory flasks have a relatively high surface-to-volume ratio, not so in larger reactors, where heat transfer surface area/volume is greatly diminished, and where heating and cooling must be accomplished by means of a heat transfer medium pumped through a jacket or heating coil.
Reactor Mixing: Maintaining uniform mixing in proper proportions for the desired reaction

Operating Volume: This is usually not possible at scale because most reactors have maximum mixing levels of about 10-20% of their full capacity.

Reaction Control: Reaction rate can be regulated by controlled addition of a limiting reagent. Drying: Differences in particle size distribution, bulk density, flow ability, compressibility, etc., can all have a dramatic impact on the character of the product.
Raw material Charge: Charging reactants in the same proportions as in the lab is not possible in a large reactor, ranges of these proportions should be tested before.

Reactor Access: it is not very easy to add or remove any compound during the reaction because all the reactors are closed.

Work Up: concentrating the product by removing impurities by isolation, distillation and filtration.

2.2 Process engineering

Any process includes several unit operations form a product from a raw material first unit operation would be a reaction. Reaction is classified by different phases they are involved in. Homogenous: any single phase such as gas, liquid, solid. Heterogeneous: solid-liquid, liquid-gas, liquid- liquid. Then it is followed by workup which refers to series of manipulations required to isolate and purify products of a chemical reaction. Quenching a reaction is to deactivate any unreacted reagents. Quenching neutralizes the reactive species to stop the reaction to minimize the formation of impurities. Quench solutions are usually aqueous.

The next operation is extraction and it is a very common operation carried out to remove impurities from the product stream. A simple aqueous extraction that works well at the bench can turn into an emulsion at larger scale because of differences in agitation and the greater economic distances that materials have to migrate as the dispersion breaks. It is common to extract a mixture with acid to remove acidic by products with a wash in between. Distillation covers a number of unit operations involving boiling and vaporizing a liquid, and then separating and condensing vapors. One way is to remove the condensing vapor so that none return to the boiling point; another way is to reflux a portion of condensate is directed back. Then followed by filtration: the unit operation in which impurities, turbidity and major separation of liquids and solids takes place. The major driving force is pressure drop. A solvent is chosen which dissolves one component, while not dissolving another. Crystallization it is an operation which involves liquid solid separation, also mass transfer of a solute from the liquid solution to a pure solid crystallize phase occurs. The driving force is super saturation which is controlled by cooling. The last operation is drying: it is mass transfer process which involves removing of water or another solvent by evaporation. This process is often used as a final production step. Vacuum drying where heat is supplied by conduction or radiation mean while the vapor thus is removed by the vacuum system.

2.3 Scale up strategy

Scaling a process is not linear, design of the process has to control by one rate: kinetics, mass and heat transfer, blending, addition rate. The following factors[22,23] are the similarities in a scale up:

- Dynamic similarity: similar force ratios: Re, We, Fr
- Geometric similarities; similar reactor/agitator dimensions ratios.
- Kinematic: similar ratios of velocities profile.

Rate of heat is directly proportional to batch size (contact area). We have to maintain dynamic similarity during scale up. Rate of heat evolution is directly proportional to batch size.

2.3.1 Agitation characteristics:

The choice of impellers depends up on process goals, Process scale, and the presence of other sources of power. Agitator design for turbulent flow exhibit different mixing characteristics:

Table 1: Types of impellers

Axial impeller	**Radial impeller**
High Pumping and low shear rates	Low pumping and high shear rates
Pitched turbine. Propeller	Rushton turbine, flat blade turbine
Blending single phase liquids and solids	Multiphase fluids

Table 2: advantages and disadvantages of impellers

Agitators	**Uses**	**Adv/Dis Adv**	**Fluid/solid characteristics**
Anchors	High viscous flow Speed is proportional to dia	High power consumptions	Highly viscous
Propellers	-	Dead spot formations	1000cP, Low to medium viscous
FBT	Radial flow High required applications	Not recommended for gas dispersion applications	1000cP
PBT	Both radial al and axial flow High shear	Cost effective	1000-100000cP
Helical screw	Operates under laminar flow		1000-1000000

2.3.2 Material of construction

Table 3: Material of construction

Type of SS	**C**	**Mn**	**Ph**	**S**	**Si**	**Mo**	**Cr**	**Ni**	**Uses and application**
316	0.08	2	0.045	0.03	01	2.5	17	12	Greater resistance to pitting corrosion. Poor conductor of heat.
304	0.08	2	0.045	0.03	0.0 0.75		18	8	Austenite steel Poor conductor Ease into forming various shapes Mainly used for cryogenic compounds. has lower carbon content to minimize carbide precipitation and is used in high-temperature applications
Hastelloy	0.01	2	0.025	0.01	01	16	15	57	All the acidic reactions that contain halogens or metal halides
Glass lined.	Steel vessels coated with layer of high temperature glass enamel								Smooth, cleanable and chemical resistance. Cannot be used for extreme temperatures and large temperature difference

2.3.3 Impact by reactor dimensions

Table 4: Impact by reactor dimensions

Phenomena	**Reactor volume**	**L/D ratio**	**S/V ratio**
Chemical reaction	Significant	Weak and indirectly	Indirectly
Mass transfer	Only directly	Significant	Indirectly
Heat transfer	Weak and indirectly	Significant	Significant and indirect

2.3.4 Utility: Heating or cooling a reactor is provided by the mentioned utilities:

Table 5: Utilities

S.no	**Utility (large scale, plant)**	**Temperature range (degrees)**
1	Liquid nitrogen	-196 to -25
2	Chilled Brine (methanol, water)	-25 to 10
3	Chilled water	10 to 20
4	Common water	20 to 35
5	Hot water	35 to 75
6	Steam	To 150
7	Viscous Oil	Above 150

Compatibility of reactors: each reactor has been made up of different allow which makes it useful for particular solvents .each compound is given grade against each like ,Grade A corresponds to good compatibility and D is the worst grade and cannot be used in that particular reactor.

Table 6: compatibility of reactor

Solvents/type of reactor	**SS 304**	**SS 316**	**Hastelloy**
Organic halides(RX)	**A**	**D**	**A**
Potassium bromide/chloride	**A**	**D**	**A**
Barium chloride	**D**	**D**	**B**
Al-X	**D**	**D**	**A**

2.3.5 Filtration

Nutsche filter: Nutsche filter is of two types 1) open and 2) closed. These filters are commonly used for flammable substances. The driving force for filtration is pressure difference and is given by vacuum and nitrogen .For an open vessel, vacuum is placed or applied to the side of the Nutsche whereas in closed vessel the nitrogen is applied at the top and vacuum at the bottom which give rise to larger pressure difference .Vacuum filters are not used for hot solvents. pressure drop is less for vacuum filter. Moisture of filter cake is more for vacuum filter than pressure filter.

Fig.1: Nutsche filter

Fig.2: centrifuge filter

Centrifuge Filter: This type of filter uses the centrifugal force to separate the liquid and only if solid is product. The filter bags are placed inside the drum, the drum is rotated and mean while the solid is thrown out to the bags. Flammable substances are not filtered because heat is produced during rotation and it might damage the equipment.

2.3.6 Drying

Tray dryer is used for drying sticky materials, granular mass or crystalline materials, plastic substances, wet mass preparations, precipitates and pastes. It can be operated under the vacuum often with in direct heating; this is done in special vacuum tray dryers for the drying vitamins and the other heat sensitive products.

In tray dryer hot air is continuously circulated. Forced convection heating takes place to remove moister from the solids placed in trays. Simultaneously the moist air is removed partially .In the tray dryers the crude drugs, chemicals, powders and tablet granules are also dried and shows free flowing of the materials by picking up the water. Tray dryers require more labor to load and unload, process is time consuming, hence increases in the cost.

Vacuum Drier

Materials are dried by the principle or applications of vacuum. The water boils at a lower temperature when the pressure is lowered by creating the vacuum. The evaporation of water takes place faster. Heat sensitive materials, Dusty materials, and hygroscopic materials, toxic materials can be dried in this vacuum dyer. Feed materials containing the solvents are also dried by this vacuum dryer. The solvent material can be recovered by the condensation process. Handling of the materials is easy in this drying because of tray arrangement inside the dryer.It is easy for switching over to the next materials. Hollow shelves which are electrically heated can be used. It provides large surface area, so the heat can be easily transfer throughout the body of the dryer and fast drying action takes place. Hot water can be supplied throughout the dryer, helps in drying process at the desired temperature. Dryer is a batch type process. It has low efficiency, expensive; labor cost is too high for the running of the dryer. Maintaining the dryer is high. There is a danger of overheating due to steam produce. Heat transfer is low in vacuum dryer.

Fig 4: Vacuum drier

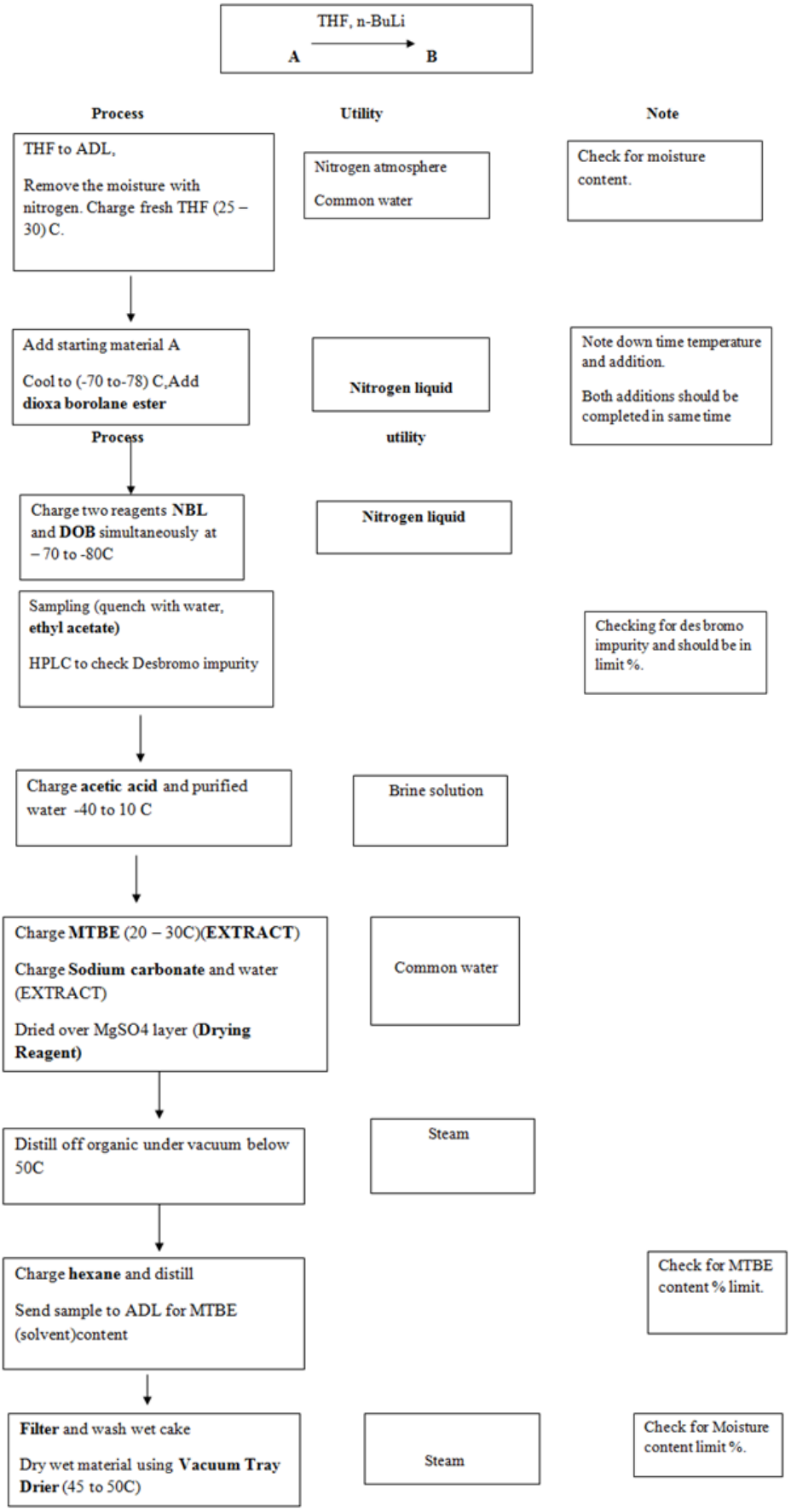
Fig.3: Tray Drier

III. RESULT AND DISCUSSIONS

This case study includes one of stage the manufacturing processes. This example shows each and every unit operations involved in a process and its work and necessary and also to understand reagents and raw materials addition in to a reactor. These case studies also explain scaling up from bench to pilot plant and also the important parameters to be noted like the batch time, temperature and pressure. Before actually handling any chemicals one must read MSDS (Material Safety Data Sheet).

In this Stage they are two important reagents which have to carefully charge in to the reactor those are di borolane ester and n-butyl lithium. The importance of addition of n-BuLi is that it removes or changes the structure of A to form desirable structure B. The change in structure results in an exothermic reaction. The addition temperature should be -70C, otherwise there are chances of impurities if the temperature increases. Temperature and time are critical parameters. We always have to keep dioxoborolane 0.1 to 0.2 equiv slightly higher than n-BuLi to avoid formation of des bromo impurity. If addition rate is fast and exothermic nature was observed to -45 to -40 C and Desbromo impurity is 30 to 40%.Temperature is a critical parameter and additions should be slow.

- **Process Flow Diagram**


THF, n-BuLi
A
B
Process
Utility
Note
THF to ADL,
Remove the moisture with nitrogen. Charge fresh THF (25 – 30) C.
Nitrogen atmosphere
Common water
Check for moisture content.
Add starting material A
Cool to (-70 to-78) C,Add dioxa borolane ester
Nitrogen liquid
Note down time temperature and addition.
Both additions should be completed in same time
Process
utility
Charge two reagents NBL and DOB simultaneously at – 70 to -80C
Nitrogen liquid
Sampling (quench with water, ethyl acetate)
HPLC to check Desbromo impurity
Checking for des bromo impurity and should be in limit %.
Charge acetic acid and purified water -40 to 10 C
Brine solution
Charge MTBE (20 – 30C)(EXTRACT)
Charge Sodium carbonate and water (EXTRACT)
Dried over MgSO4 layer (Drying Reagent)
Common water
Distill off organic under vacuum below 50C
Steam
Charge hexane and distill
Send sample to ADL for MTBE (solvent)content
Check for MTBE content % limit.
Filter and wash wet cake
Dry wet material using Vacuum Tray Drier (45 to 50C)
Steam
Check for Moisture content limit %.

Safety: The most important scale up step where parameters such as pressure is maintained in order to control a runaway reaction. Safety relief valves and rupture disc are used either in combination or individually to maintain only a required pressure. Parameters like these are interpreted by both chemical and chemists before performing a reaction.

Type of Reaction

This reaction is highly exothermic reaction and temperature has be less than -70 C to ensure purity of the product.

Reactor: The reactor used in this stage is **Hastelloy stainless steel** reactor, it mainly consists of nickel and other metals which give a good chemical resistance and are cryo reactors i.e. can operate at lower temperatures up to 100°C.The maximum volume that can be operated is 1000L.
The minimum volume for stirring is 30L **(MSV),** the minimum volume to note the temperature is 30L (**TTV).**Valves used to maintain the pressure are Rupture disc and safety relief valve.
These two valves release the excess pressure in the reactor. **Scrubber and vent line** are used to remove gases which evolve during the reaction. Pressure in the reactor is maintained by nitrogen as it is inert.

Utilities: This stage requires less than -70 to – 80° C and which is not possible with dry ice as they do it in lab. The only alternate is **Liquid Nitrogen** as it has melting point about -196°C and it can easily maintain about -90°C in the reactor jacket to perform at our desirable temperature. The used volume of nitrogen liquid is measured in water column. When temperature about 25 – 30°C. When temperature about 25 to 30°C is required **CT water** is used as the utility and above temperature **Hot Water** is been used.

Addition of raw materials and reagents: Reagents MSDS have to be studied thoroughly to handle them, it includes its boiling point, auto ignition temperature, flame temperature water or moisture reactive agents. These reagents (n-BuLi) are kept in low pressure cylinders and a pipe which goes till the bottom of the cylinder to transport to a reactor. A three way valve is used to transport these reagents in to the reactor. Weight is determined by keeping it on the weigh balance while charging in to the reactor. Three valve is cleaned and dried by nitrogen, then a certain pressure is applied on the head of the pyrophoric agent(n-BuLi) by nitrogen and the liquid has no place to except through the pipe already inserted in the cylinder which is connected to a reactor. When shutting down it is flushed by the solvent in which it is present so that not even little amount of it is left in the reactor.

Observation

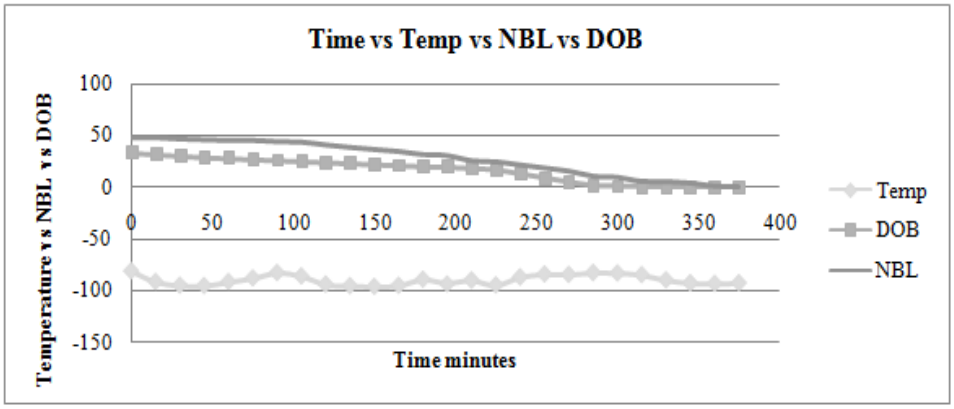


Figure: Time vs Temperature

IV. CONCLUSION

The industrial experience is interesting and with this one can understood that what skills a chemical engineer requires to fulfill industrial needs and also determination and kind of hard work one has to do to work in a chemical field. All the unit operations in the pharmaceutical industry which includes: how to choose a reactor based on the type of reaction, pH, and utilities required for that particular reaction, charging of pyrophoric reagents and also the pressure maintenances have been covered in this paper. The best way to minimize scale up problems is by data gathering and detailed process understanding. Having technical staffs – both chemists and engineers – that are well trained with up-to-date knowledge of current thinking can help with design of better processes with fewer scale up issues. Using outside help in the form of consultants with industry experience can be invaluable for companies wishing to design low-cost processes which can be easily scaled up[24] and in trouble-shooting persistent manufacturing problems.

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