



e-ISSN: 2319-8753 | p-ISSN: 2347-6710

IJRSET

International Journal of Innovative Research in
SCIENCE | ENGINEERING | TECHNOLOGY

A futuristic digital interface with a glowing globe in the center. The globe is surrounded by various data visualizations, including bar charts, line graphs, and network diagrams. The background is a dark blue with a grid pattern and some text elements like 'BUSINESS', 'NETWORK SEARCH', and 'WORLD'. The overall aesthetic is high-tech and data-driven.

INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH


IN SCIENCE | ENGINEERING | TECHNOLOGY

Volume 12, Issue 7, July 2023

ISSN INTERNATIONAL
STANDARD
SERIAL
NUMBER
INDIA

Impact Factor: 8.423

 9940 572 462

 6381 907 438

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 www.ijrset.com



Scale up Principles in Chemical Industries and Its Challenges

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ABSTRACT: A systematic approach to the early technical development of a new process can be achieved through fundamental and empirical approaches. This typically involves process-modeling and computer simulations that have been previously validated by laboratory and bench-scale testing. Subsequent pilot plants and cold-flow mock-ups provide additional process and engineering knowledge. But once all the pilot systems are successful, the desired cold-flow mock-ups completed and all the simulations validated, the true challenges of scale-up decisions begin. Further development to demonstration or commercial scale does not involve only technical decisions, but also requires compromises of both engineering and business considerations, since there are always restrictions on time and money. The linkage and consolidation of input and output data of all the involved process are then finally included as the final procedure in the scale-up process.

KEYWORDS: Scale-up, Pharmacy, Chemical Engineering, Stoichiometry.

I. INTRODUCTION

Why New Drugs are Important in Pharmacy?

There are so many reasons which say that there is a need for new and improvised strategies for better and safer treatment against complex diseases. When we look at the past years, there are only 20 new drugs which were approved annually. This could be the result of high attrition rates in clinical development in different areas of therapeutics. The main highlighted causes that were identified are the lack of efficacy and poor safety performance of the drug candidates [1].

Drug resistance through the loss of efficacy is another reason for the failure of therapeutic agents in today's era. It can be due to the down-regulation of the receptors for the specific action as repeated exposure of the same drug make the receptor saturated which results in less efficacy of the drug. It has been seen that there are many Pharmacoresistant patients which have severe medical syndromes and for the successful treatment of such patients we need a new drug which the patient can able to tolerate for their little side effects. Neurotoxicity, sedation, teratogenicity and psychiatric symptoms are some of the lacunas in many antiepileptic agents for which new agents are to be designed. Also, animal toxicity studies have been done where the toxicity issues in the developmental candidates in drug development are higher. Serious adverse drug reactions in the existing drugs are leading to an intended drug withdrawal from the clinics. Because of its presence with toxicity, polypharmacology viz. a novel approach of hitting the multiple targets for a specific disease has been proposed which has been shown to have more effect than complete inhibition of a single target. Thus it can be considered as a better strategy towards tackling such kind of awful situations. Similarly, in the case of antimicrobial therapy, many pathogens are not susceptible to any of the currently available drugs that could be due to possession of resistance development. Moreover, many patients are intolerant to the antibiotics which are effective against the infecting pathogens. For example, a patient treated with linezolid for Enterococcus faecium has shown to develop significant thrombocytopenia which resulted in a higher risk of bleeding. Also, we need new medicines to reduce the dosing schedules of available drugs as it has been seen over the past few decades that people are moving away for shorter hospital stays and to have such kind of treatment plan we don't have convenient single administered agents. For this, we can take the example of treatment against enterococcal endocarditis where four to six



weeks of therapy was needed with ampicillin and gentamicin. If there could be the availability of a single administered antimicrobial agent then, it can allow the patient to complete the course duration in a less period of time outside the hospital. So, new drugs are constantly required to have better therapeutic plans towards fighting with the existing diseases [2].

Scale up Process and its Significance in Pharmaceutical Manufacturing

Every process has its own relevance when it comes to process development and there are many factors which have to be taken care off before planning scale-up of any process (Fig.1) The scale-up process is nothing but the process of increasing the batch size in a way to achieve the results in a pre-requisite manner. The scale-up techniques are required to be thoroughly studied when any process has been planned to bescaled up because moving directly from the lab scale to industrial scale without any basis of process study can cost to a high risk of batch failure. So, by choosing and designing the synthetic route, and workup product isolation parameters, many of the difficulties in scale-up can be avoided. A chemical engineer is generally concerned with the process to be scaled up taking all the relevant parameters into considerations. The process before scaling up to the large, has to be studied for their lab scale and thereafter for its pilot scale as these processes are scale dependent and they behave differently in laboratories or pilot plant and on a large scale The pilot scale study allows the process for investigating the degree of physical and chemical stability, making process corrections and improvements for ensuring high success rate for manufacturing its large batch. It also helps to ensure the compatibility of the processing equipment and process control over the reaction time. In the product development process, Lab chemists develop the product in lab scale and then it is sent to the process engineers who also develop their reaction process taking all the parameters and terminology in a way so that it can be matched with the lab results [3].

STEP IN SCALE UP

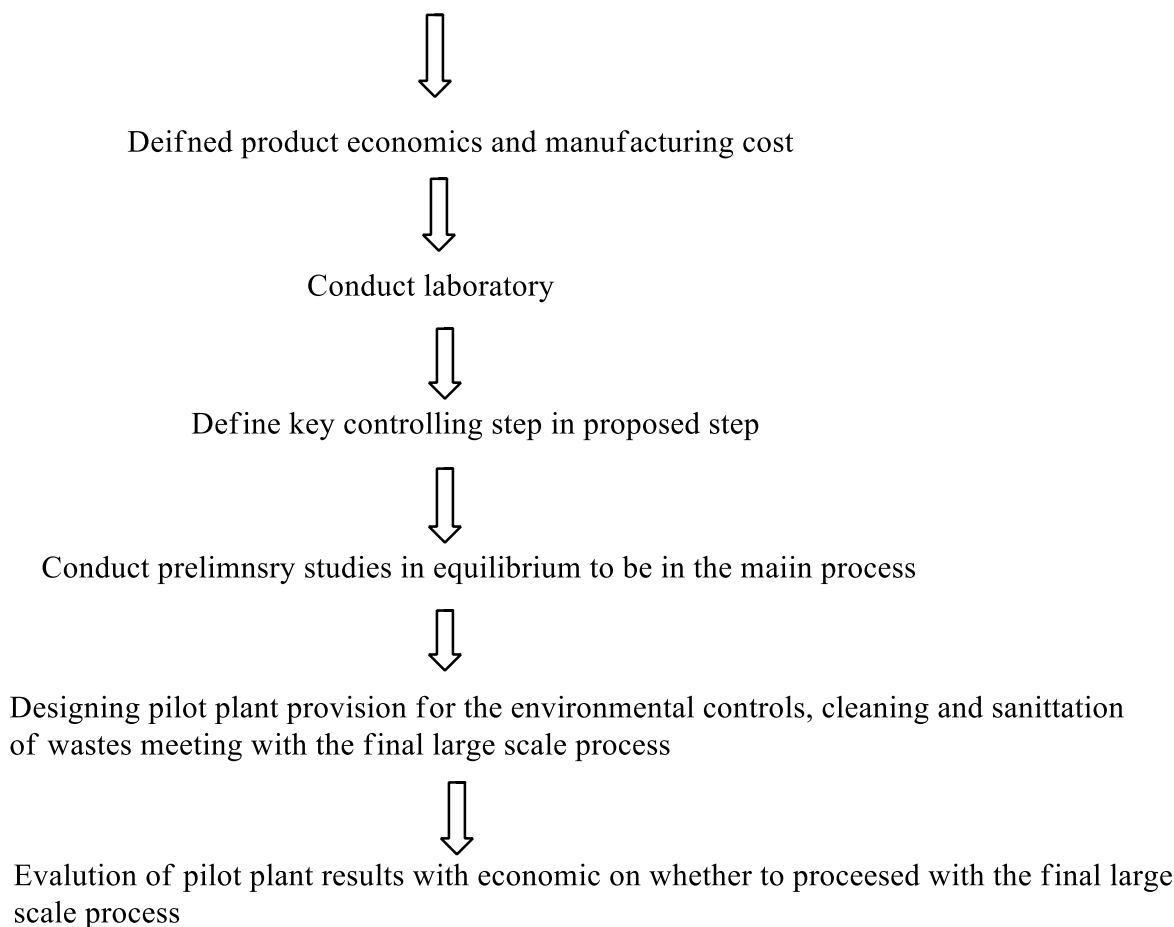


Figure:1 Steps to be taken during the scale-up process[4]

Scale up Principles in Chemical Industries

In the field of chemical engineering, the scale-up technique is considered an integral part. Many literature reviews have been published describing different aspects of scale-up techniques. Normally, prior to the large scale processing, any chemical process are first studied and optimized in a laboratory scale for studying the nature and behavioral study of the reaction parameters. The scaling up of the chemical process to a largescale consists of many units of steps. But, before going to a large scale, its mini-plant is set up (called a pilot plant) to confirm the measured data and parameters obtained in the laboratory scale process. Existence of a pilot plant scale means that the process development has been already shifted to the advanced scale where it tries to simulate the reaction conditions using similar apparatus and types of equipment thereof. Such kind of study starts from the laboratory and goes all around to the industrial scale providing all the vital information about the simulation of the reaction conditions as like laboratory scale reaction conditions. Hence, the practical scale-up of the process is not much easy as it requires long and case specified knowledge of chemical engineering. The scale-up framework of any chemical process follows four steps of primary procedures (Fig-2). The First procedure is lab protocol which can be obtained from the direct experiment, or from any patent document or publications. These lab protocols should provide all the necessary steps and quantities to be used on the laboratory scale. The second procedure is to design the simplest plant batch flow chart diagram. This flow diagram should include the entire step that is to be involved in the main process. This includes the volume of reactors, apparatus, and types of equipment to be used. The third procedure for scaling up any chemical process is to scale up each individual step in the flow diagram according to the desired framework. The linkage and consolidation of input and output data of all the involved process are then finally included as the final procedure in the scale-up process.

A small scale chemical production plant mostly run the multiple reaction process rather than a batch process as this makes the scale-up calculations more convenient. So, it means that the product of one process serves as a starting material for the subsequent reaction process. The main product after every reaction process brings many co/by-products, catalysts (if used) and unreacted reactants. Thus, each reaction step after completion passes with several processing, purification and isolation steps for obtaining the product of desired purity.[5]

Laboratory protocol



Plant flow chart with scale and reactors size



separate scale up each process



Linkage of process

Figure:3 The scale-up framework of a chemical process[5]

Challenges in Reaction Scale-up

Choosing Appropriate Conditions

For achieving a good scale up, it's always good to have some advice from chemical engineers. Many chemists think that certain reaction can only be controlled at a low temperature at -78°C but for achieving this much low temperature in a large scale batch, there is a chance of increase in the viscosity of the solvent which further can lead to low solubility of the reactants and also could be a possibility of formation of any by-products. This can result in non-homogeneity in that particular batch with a considerable amount of impurities. The encrustation of raw materials, intermediates, and products on the reaction vessel can also be a problem at this temperature. Some batches occasionally need such low temperatures; many processes can be operated at higher temperatures, provided the reagent is carefully dosed into the process at the same rate as the reaction is proceeding. This ensures that the stoichiometry is constant throughout the addition[8].

Reaction Stoichiometry

This signifies the process of calculating the number of moles of reactants which are involved in a reaction using the reaction coefficients. In case of batch processes, when reagent A is being added to the reagent B in any reactor, reaction stoichiometry tends to change with respect to time. Say, if product C is forming along with side-product D, the amount of C & D will depend on the ratio of A and B in the reactor which further depends on the rate of addition of A in B. Of course, in case of exothermic reactions, the dosing rate should be kept minimum to avoid any exothermicity in the reaction vessel. This concludes that it is important to understand the nature of the reaction which can help to signify the addition rate in any reaction procedure.

Mixing of Reagents

When the reagents are added in a laboratory, chemists usually add it in the surface of the agitated liquid and this works fine in the lab scale but in industrial scale, it could result in poor mixing of these liquids. At large scale, the reagents are added via recirculation loop in the area of high turbulence usually at the tip of the agitator. It must be ensured that during the addition of the reagent temperature and viscosity must be same as that of the components in the reaction vessels even if a critical reagent is added via a dip-pipe close to the tip of the agitator. Lack of selectivity may occur in fast reactions if the dip pipe diameter is too large, resulting in a slow flow rate from the dip pipe into the bulk solution.[6]

Solvent Extraction during Scale-up

During extraction in the laboratory, the chemist often does not record whether the aqueous phase was added to the organic, or vice-versa. Since in laboratories, it usually makes no difference to the outcome of the experiment. In the plant, if the reaction mixture is organic and the vessel is not full, it may be convenient to add water to it, whereas if the vessel is full and a larger vessel needs to be used for the extractions, the water could be added first depending on preferred operations. The order of addition can make a big difference in a large scale process as to whether emulsions will form or any disengagement of the layers, as well as their separation efficiency. Also, it can not only affect yield but also can impact the product quality, since a saturated solution of water in an organic solvent is an excellent hydrolysis medium for esters and other hydrolyzable groups (if any acid/base are present). At extended separation times, hydrolysis may then occur leading to higher amounts of by-products. For this reason the solvent ethyl acetate is a poor choice of extraction solvent for scale-up, particularly in acid/base work-ups, since the extended times the ethyl acetate is in contact with water when trace acids/bases are present will initiate hydrolysis of the solvent, leading to more acid (acetic acid) which further catalyzes hydrolysis.

The high solubility of water in ethyl acetate and vice-versa means that aqueous layers, unless heavily salted, are rich in organics (and thus more difficult to dispose of) whereas the ethyl acetate layers have high water contents and may need drying before further processing. Isopropyl acetate and butyl acetate, though more expensive initially, may actually be more cost effective overall in scale up, particularly since solvent recovery is easier because the low water content in the solvent leads to higher recoveries.[7]

Input values in Scale-up

Reactants

During scale-up, the solvents must be chosen based on the stoichiometric ratios obtained during the laboratory synthesis of the compounds. Even in cases where the laboratory procedure uses one reactant in excess (more than the stoichiometric amount), a linear scale-up method has to be applied. The excess use of one reactant is normally used in order to assure that the conversion takes place fully. Therefore, it is important to use the same relative amount of reactants on a larger scale.

Solvents

A solvent is an important part of every chemical reactions. Unlike reagents, solvents being used as one of the reactants in certain cases are not used in stoichiometric quantity. Since, small quantities of solvents are normally used in the laboratory scale, on the industrial scale, they are used in relatively high quantities. So, such large quantities of solvents are often tried to be recovered by the industry if it could be possible.

Catalysts

Catalyst has an important role in the successful completion of the reaction process. However, they are usually used in small quantities Catalysts often contain transition metals, for example, platinum, with a significant environmental impact and high purchase prices. Recovery of catalyst in the laboratory scale would not look justified because of its very small amounts. Therefore, the laboratory procedures usually not bother about the problem of its recycling. But, the



scenario considerably changes when it comes to industrial scale where catalysts are used in Kgs. In these cases, recycling of catalysts becomes an important part to deal with. Therefore, in a scale-up, it has to be assessed whether a catalyst could be recycled or not.

Heating Energy

The heating energy implicates the energy required to raise the reaction mixture to a certain temperature and to keep it for the duration of the reaction. The total amount of energy needed depends on several factors. It can significantly vary depending on the reactor (type, size, surface, material, insulation), the heating element (type, size, surface, material, efficiency), or the reaction parameters (quantity, temperature, time, specific heat capacity of the reaction mixture, endothermic/ exothermic). Many of these factors (e.g. reactor, heating element) depend more on the actual plant design than on the reaction itself. Hence, an exact calculation of their values is only possible if a detailed plant design is available[8].

The reaction mixture describes the output of any chemical process which contains the active compound known to have certain biological effects. The reaction mixture many times used as a starting material for the subsequent step of any synthetic route.

Product Yield

The product is not always considered as the final product rather it can be an intermediate product serving as a starting material for another reaction process. However, this conclusion is not that trivial. An industrial production might aim for high purity of the end product, which could involve additional purification steps, resulting in an even lower yield compared to that of lab experiments. The degree by which the yield changes from a laboratory scale to an industrial production depends on various factors. Those factors could be comprised of the required purity, price/value of the material, type, and the number of involved steps or the type of reaction.

II. CONCLUSION

It is quite common in chemical reactions that apart the wanted product, one or several further products can result from the overall reaction. Such further products can potentially be used as inputs for other process systems. It should further need to be investigate and acknowledge time to time.

REFERENCES

1. Hornberg, Jorrit J. Simple drugs do not cure complex diseases: the need for multi-targeted drugs. RSC Publishing, Cambridge, UK, 2012.
2. Rice, Louis B. "Do we really need new anti-infective drugs?." *Current opinion in pharmacology* 3, no. 5 (2003): 459-463.
3. Savita Belwal et al. *Int. Journal of Engineering Research and Application* www.ijera.com ISSN: 2248-9622, Vol. 6, Issue 7, (Part -2) July 2016, 81-88
4. https://www.academia.edu/8939649/PILOT_PLANT_SCALE_UP_TECHNIQUES_CONTENTS_INTRODUCTION_ON_PILOT_PLANT_AND_SCALE_UP
5. Piccinno, Fabiano, Roland Hischer, Stefan Seeger, and Claudia Som. "From laboratory to industrial scale: a scale-up framework for chemical processes in life cycle assessment studies." *Journal of Cleaner Production* 135 (2016): 1085-1097.
6. https://www.academia.edu/14371734/Chemical_Industry_Digest_How_To_Minimise_chemical_industry_Digest_Magazine, July 2010.
7. Unger, Thomas. "Significance of angiotensin type 1 receptor blockade: why are angiotensin II receptor blockers different?." *The American journal of cardiology* 84, no. 10 (1999): 9-15.
8. Barreras, Amy, and Cheryle Gurk-Turner. "Angiotensin II receptor blockers." In *Baylo University Medical Center Proceedings*, vol. 16, no. 1, pp. 123-126. Taylor & Francis, 2003.



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