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Review Article

Scaling Injectable Pharmaceuticals: Roadblocks And Strategies

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ABSTRACT

overview focuses on various factors that affect the scalability of parenteral, it covers different factor right from environmental factors to pakaging and also covered some shipment and handling challenges after scale up as well, we had tried to give formulators an overview that will help them to understand the scale up challenge they must consider at the time of developing the strategy to develop parenteral formulation with the intent to raise the ratio of drug discovered and comercialized, as we see out many of drug molecule discovered very little have been scaled up, the article also gives solution to many of the problems encountered although it is in general term and may vary with different molecule. Formulators can get an overview of challenges they might face during scale up so they can handle during development stage that lead to ease in scelability.

INTRODUCTION

The scalability of parenteral formulations is crucial for bridging the gap between drug discovery and commercialization. This review explores the multifaceted challenges encountered during scale-up, encompassing environmental factors, equipment differences, process variability, sterility assurance, stability concerns, and packaging challenges. Environmental conditions such as temperature variations significantly influence process parameters like nucleation rates in lyophilization and understanding the criticality of maintaining sterile conditions throughout manufacturing. Equipment discrepancies between laboratory-scale and commercial-scale production introduce variability, impacting product quality and necessitating careful validation of new technologies like microfluidics. Process variability arises from critical steps such as solvent evaporation rates in microsphere manufacturing, affecting particle characteristics and formulation stability. Achieving sterility in parenteral products remains a formidable challenge, with implications for filtration efficiency and the choice of sterilization method. Stability issues, exacerbated by packaging material interactions and

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formulation handling, underscore the need for rigorous compatibility testing. Critical considerations include the impact of moisture and oxygen on drug integrity, particularly in lyophilized formulations and high-concentration biological products. This article provides an overview of these challenges and discusses potential solutions, emphasizing the importance of early-stage consideration of scalability factors to streamline formulation development and enhance product commercialization success rates.

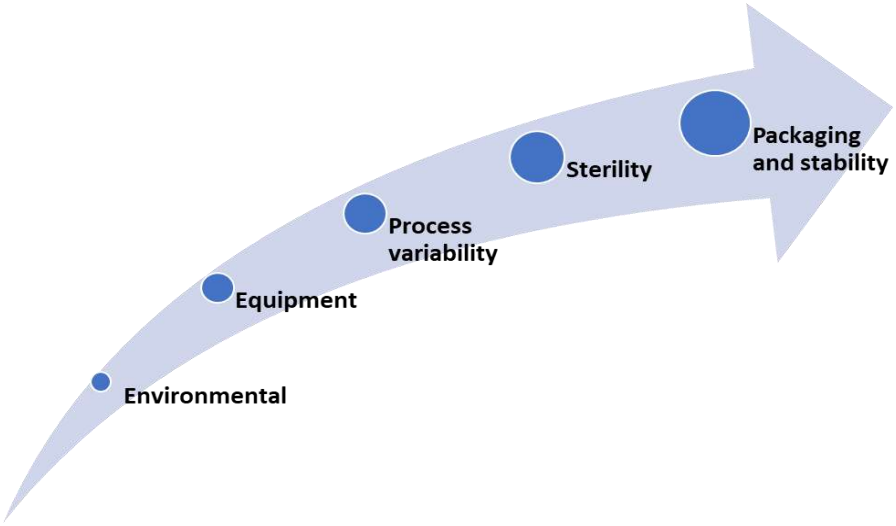

Figure 1 flow represinting challenges during scale up

Environmental Factor Affecting Scale Up

Change in environmental condition affect various process parameter in injectable scale up for example in lyophilization Nucleation rate change has been observed at production scale vs laboratory scale, as change in particulate matter that is quite low at aseptic production area. Temperature variation can also be one of the factors affecting process parameter variability. The nucleation temperature at the laboratory level (− 10 to − 15°C) is usually higher compared to that of the production level (below − 25°C). The difference in the nucleation temperature could affect the number and pore size of the ice crystals, which subsequently influence the primary drying time (1), the biggest chalenge in parenteral formulation scale up manufacturing is maintaining its sterility throughout the manufacturing process, such as in aseptic filling there is challenge bringing together different component like primary packaging materials (vials, stopper, seals, crimpers) and

attempting to fill thousands of vials under a clean air zone. Challenges around filteration such as validation of the product through the filter (where the filter needs to be challenged with 10,000,000 cells of a diminutive bacterium). Microbial growth potential is different at different biological center, hence extrapolating the data from biological lab to plant can give misleading results one must taste the same at manufacturing site. (19), Selection of excipients also has a crucial role that has an impact on designated class room area, which has direct impact on product quality, it must be tested and within limit for bacterial endotoxin, as well as microbial limit.

Equipment Differences Lead To Process Variability

Manufacturing vessels and equipment from small scale to large scale or pilot plant

The efficiency of emulsification in stirred tanks is directly related to the material flow within the vessel. For the large-scale production of highly viscous emulsions, sufficient material flow cannot be guaranteed, resulting in heterogeneous temperature zones and the uneven distribution of materials. The emulsifying shear zone in a rotor-stator stirrer is small, so the material is not processed uniformly. In slow, coalescence-controlled emulsification processes, such small emulsifying shear zones lead to a broad droplet distribution (7).

Novel technology such as microfluidics are now comonly used in lab scale but commercialization still remain challenge, as complex nature of the instrument, that ultimately needs complex and integrated manufacturing system, which lead to high cost of the equipment, and accuracy of same as lab scale is still questionable, high manufacturing accuracy is requied for manufacturing of microfluidic cartridges as they are integrated with multiple biosensor and microchannel, thus make it limitation to lab scale, although continious development and standerdisation in this field we can see the same comercialized in upcoming days. (18).

Design of equipment has an great impact on the sterilitry, equipment design should be such that it should maintain the sterility in the continious manufacturing process and protect the formulation from the external environment. Equipment used for traditional parentral manufacturing are not suitable for high concentrated biological drug product i.e 50 g/L or more as it may lead to heterogenous mixing in convenstional equipment, which can ultimately lead to analytical sampling error, there are many studies that depicts impact of cryo-protectant on homogenicity of sample. (20), its easier to get reproducible result in lab scale the same to achieve in manufacturing scale can be challenging, such as centrifugation, lyophilization, its also difficult to remove residual solvent completely in manufacturing scale as equipment are not that efficient at large scale compared with lab scale. Passage of long acting injectable through pump and values may lead to microcavitation and bubbles, after collapse of bubble create microscopic regions at high local temperature and pressure which may contribute to the generation of hydrogen and hydroxyl radicals and lead to the formation of protein aggregates and particles. (22)

Figure 2 Precigenome site: Nanogenerator

e.g.- Homogenizer

Homogenization technique have used from long back in production of nanomedicine, however has certain challenges due to high temperature that is generated during its application may have direct imact on Active Pharmaceutical Ingredient, also there are some challenges related to flow of liquid, i.e viscous liquid or sedimented particles generally require high pressure and also which may eventually lead to its blockage, its equipment design make it difficult to ensure proper cleaning and generation of cleaning validation report (17).

The most challenging factor that led to its scalability question is its batch to batch variation (13), however due to continious evolution in the fied of nanomedicine different technique have been came to picture to resolve this issue such as microfluidics, although this technique has its own sets of challenges such as lack of high throughput procedures. (12) Since each production technology has different operating parameters as well as each API and PLGA type have their own physicochemical peculiarities, it is therefore not possible to apply a single generic process to all nanoparticle preparations, and each nanosystem should be validated on a case-by-case basis we don't have flexibility to change line as per each product its not commercially feasible. (3) Incompletely characterized equipment, like homogenizers, results in improper mixing or nonuniform particle size reduction, respectively. During small-scale mixing laminar flow may not be predominant, however, during the scale-up it may show dominance Thus, if scaling of the process is solely done by turbulent flow without considering the effect of laminar flow, it will significantly affect the process at the production scale.

e.g.- Lyophilizer

Lyophilizer design, lyophilization cycle development

Design and Size of the Equipment lead to change in process variability that was optimized at laboratory scale, that need to be reoptimized during pilot scale batches for example in Lyophilization. The design and size of lyophilizer directly impact on the lyophilization cycle, hence it may direct impact on Quality target product profile. Difference in shelf area, cooling rate and heating must be considered during scale up of lyophilized product and correlation must be made between the same. (1), it have also been seen in case of many parenteral formulation for example: - in nanosuspension by precipitation method it become more challenging on production scale to remove residual solvent due to its tedious process (2).

Process Variability:

Manufacturing of parentral formulation with optimized critical process parameter is upmost important as it affects the quality of finished product, for example in case of manufacturing of microsphere by solvent evaporation method, critical process step such as solvent evaporation rate, has great impact on particle size and shape and that makes it challenging to scale up, some times excipient might get absorbed, or degraded due to high temperature or shear during manufacturing, that need to be estimated before scale up. Process variability may also occur due to change in equipment design such as in case of lyophilization, vial heat transfer coefficient is used during scale up to optimise the same., as it has impact of vial diameter as well as chamber pressure. FDA encourages the use of various optimization software for optimization of critical process parameter such as Design of expert (DoE), which enable formulator to understand which are the most critical process parameter (CPP) that affect the quality of product and factors which have least impact on quality of product, and can be neglected so by using the software formulator can focus on CPP and optimise the same, for example

in homogenization critical process parameter like tip speed, flow rate, temperature, pressure, energy, density, no of cycle has direct impact on product quality attribute during scaleing up. While in case of lyophilization temperature, vaccum, time are critical process parameter that has major impact on same. The use of this software also has regulator feasibility, that help the formulator to justify the changes that are made in specific range (design space) (23)

Challenge To Achieve Sterility In Parenteral

Sterility in simple or Complex injectable are of major concerned during scaleup, for example, sterilization of liposomal preparations remains an issue, with each technique presenting its own limitations. Although filtration does not cause any degradation, it imposes size restrictions on the final products; saturated steam sterilization may be cheap and easy but it can cause product degradation, likewise for gama-irradiation. Though chemical 'cold' sterilization does not affect product integrity, residual solvent can cause toxicity issues. As for UV sterilization due to low penetration which lead to only surface sterilization, it is also not suitable for formulation such as liposome, which causes its degradation, (15) and dry heat sterilization due to stability at high temp, they are completely inappropriate in liposomal manufacturing (5) While aseptic manufacturing and filtration are the most commonly utilised methods of producing parenteral liposomes, the procedures involved are time-consuming and the equipment is extremely expensive and difficult to maintain. (5)

Filtration

Highly viscous flows need to be processed, the concept of linear scaling can be challenging. An increase in the viscosity of the permeate may cause the reduction of transmembrane pressure (the pressure difference between the two sides of the membrane) and diminish the filtration efficiency, which can be time consuming for large scale processes PLGA needs to be dissolved in organic solvents such as dichloromethane, ethyl acetate, dimethyl sulfoxide, etc., solvent compatibility with membrane filters must be evaluated carefully (8), extrapolation result of filter validation from lab scale to plant scale can be challenging, as different parameter are involved there is no linear relationship as we go from lab to manufacturing scale, scaling up filteration in long acting injectable should be observed for its shear stress, as high stress during cross flow filteration often leads to protein denaturation. (22) Also the selection of filters and maintaining their integrity is the crucial factors during scaleup.

Terminal Sterilization:

In case of sterilization its easy to get effective sterilization when we deal with small volume, but to achieve the same effectiveness in large volume find to be challenging, for example, in case of UV/ gamma sterilization, the large volume size of container make it less efficient, also the time and cost might play a major role while dealing with ,large volume parentral sterilization (10), although there are different sets of challenges in thermolabile materials, For example, nanoparticles terminal sterilization, such as change in morphology or change in zeta potential as well as PDI and some time toxic phenomenon are also observed in biological testing hence make it difficult to scale up while maintaining the sterility without affecting the core nature of nanoparticles (10),After terminal sterilization by autoclaving there could be some lipopolysaccharide left which may lead to stimulation of immune response after administration, to avoid the same pyrogen testing is necessary after terminal sterilization. (11), in case of biological formulation such as protein and peptides extra precaution must be taken during gamma sterilization as they are highly suseptible to degradation, or alternative method should be prefered (21)

Stability Challenges In Parenterals

The majority of parenteral protein formulations consist of proteins and excipients in an aqueous based system. Processing conditions and external factors such as shifts in pH, changes in temperature, surface interactions and extraneous impurities can destabilise proteins, provoking their chemical and physical structural degradation . In some cases, aqueous formulations of therapeutic proteins do not provide adequate stability and therefore, a dried state formulation is a favoured, alternative approach which can aid the stability and prolong the shelf-life of protein products (6)

However , lyophilisation also has the potential to cause protein damage due to stresses during both the freezing and drying phases . Hence, an appropriate excipient composition like lyoprotectant and cryoprotectant are required to protect proteins from stresses experienced during the lyophilisation process. (6). Sterilization procedures such as gamma irradiation or autoclaving can be detrimental to thermosensitive APIs, for example in case of PLGA based nanoformulation, PLGA chain alteration, and affect the overall characteristics of the nanoformulation itself (8) Similarly in case of sterilization of RM (rasagiline mesylate) loaded microspheres by gamma-irradiation induced modifications of surface morphology, which were easily detected by SEM. (9)

Packaging

Packaging material must be choosen carefully as it has direct contact with drug and excipient, its compatibility with the product must be tested before the scale up, it can create problem such as absorption or leaching which ultimately has negative impact on the product. The closure of parentral dosage form must be adastested for its oxygen and moisture barrier properties as most of drugs are sensitive to moisture and oxygen that lead to its degradation, also type of glass used and pH of the formulation as an impact on formulation (13)(14). Increase in unkown impurities have been seen in lyophilized formulation due to residual moisture in elsastomeric stopper. Coated stopper, and optimization of drying temperature can help to resolve such issues., (16). There can be sterility assurance issue in case of lyophilized vials where dillution at the time of injection is done mannually, as well as apropriate volume delivery can be challenging.(17), auto injector can be great advantage to tackle with such issue There is also challenge of transfer of primary packaging material that are not sterilized at formulation manufacturer end, rather are sterilized by manufactures only, such as plastic vials, there is challenge to transfer the material in (ISO 5) aseptic compartment, which had made it less popular in pharmaceutical industry as compared to glass vials. (21), improper labelling on large volume parentral bag due to its flexible nature can be challenge, which have now been resolved using barcode system. Packaging material need to be tested for compatibility in storage condition for example biological concentrated solution are stored in frozen condition which can change integrity (20). Primary packaging affect biotherapeutic as its surface interaction with protein can cause its degradation due to interaction with leachable, or it can get destabilised mostly during its handling and shipment.

CONCLUSION

Scaling up injectable formulations presents multifaceted challenges rooted in environmental factors, equipment disparities, process variability, sterilization hurdles, stability concerns, and packaging intricacies. These complexities underscore the necessity for comprehensive validation and adaptation of processes and materials at each stage of scale-up, ensuring the safety, efficacy and quality of injectable pharmaceuticals. Addressing these challenges requires continuous innovation, rigorous validation, and collaborative efforts across

disciplines to advance the field of injectable formulation scale-up.

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