REVIEW PAPER

SOLID ORAL DOSAGE FORMS: TECHNOLOGY TRANSFER AND SCALE-UP PERSPECTIVE

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ABSTRACT

Scaling up any process requires an impeccable blend of artistry, scientific principles, and engineering expertise. Statistical methods are increasingly employed in experimental design and the establishment of empirical relationships among process parameters, material characteristics, and quality attributes in the present context. Scientists may design and scale-up processes with additional confidence and dependability by transforming measurement tools, quantitative analysis tools, or modelling tools from simple fact-finding process to advanced modelling tools. Technology transfer, a complicated process, involves a sequence of sharing experience, transfer of knowledge, communications, and large-scale inter-company and intra-company cooperation on a product and its established manufacturing methods from development stage to commercial production. Furthermore, it includes firm merger, facility change, movement to contract manufacturer, or acquisition. An effective scale-up and technology transfer requires knowledge about competencies, procedures, equipment, and regulatory requirements. This review tries to discuss various aspects of scale-up and technology transfer of solid oral dosage forms in shaping pharmaceutical industry.

Keywords: Scale-up, Scale down, Technology, Technology Transfer

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INTRODUCTION

The creation of new pharmaceutical goods and drug discovery depend on a suitable technology transfer. It is essential to enhance medication quality during research and production, ensuring that the set quality is effectively conveyed. According to WHO (WHO, 2011), transfer of technology is defined as "a logical procedure that controls the transfer of any process together with its documentation and professional expertise between development and manufacture or between manufacture sites". The route is systematically organized to transfer information and earned expertise during development and commercialization to the recipient. Technology transfer include both the transfer of paperwork and the recipient's demonstrated capability to effectively implement the essential components of the transferred technology, in accordance with the requirements of the involved parties and any pertinent regulatory authority. This encompasses the requisite knowledge, information, and skills necessary for the production of the drug substance and drug product at the receiving unit. Technology transfer is seen as equally important and essential to the development process. This practice is essential to reveal necessary information for transfer of technology from development to laboratory or manufacturing plant and from one manufacturing unit to other manufacturing unit. Fig. 1 shows technology transfer process flow for new product and site transfer product.

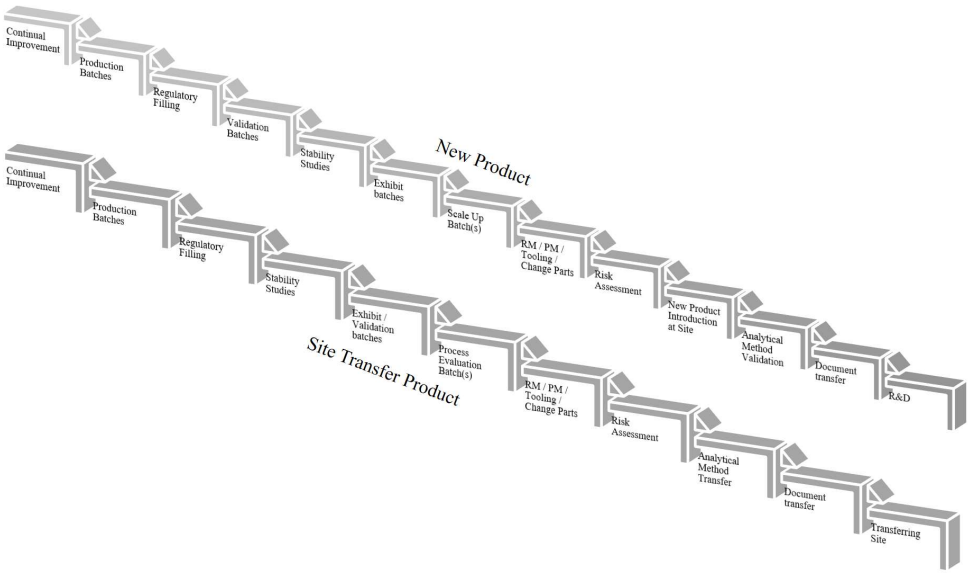

Figure Technology transfer process flow for new product and site transfer product

Scale-up of process relates to a subject that is both extremely interesting and important for the drug products. It is the process which transfer the laboratory scale outputs to pilot scale outputs and finally to the production scale outputs. One approach of scale up is to increase batch size. The scale-up of a process may also be seen as the application of the same process to different output quantities. It is essential to remember that scaling up a batch does not invariably result in an increase in processing volume.

Application of mathematical ideas of scale-up theory, discovery of scale-up invariants, establishment of in-process control methods are the keys to the ultimate development of robust products. Use of scientific approach to change any process not only saves the risk of failure but also reduces the cost of a trial batch that had to be executed to study the effects of different process parameters. Modeling theory posits that two processes are analogous if they exhibit geometric similarity, kinematic similarity, and dynamic similarity. Geometrically comparable systems are those that exhibit resemblance in shape and proportionality in all related linear dimensions. Kinematically similar systems are those systems, which have the motion similarity. It means the velocity ratio and acceleration ratio at the corresponding point between two systems are similar. Dynamically similar systems are those systems, which have force similarity. It means similar ratio of forces between their corresponding points. Dynamic similarity should satisfy the geometric similarity and dynamic similarity requirements. Fig. 2 shows scale dependent and independent critical process parameters for various stages of tablets.

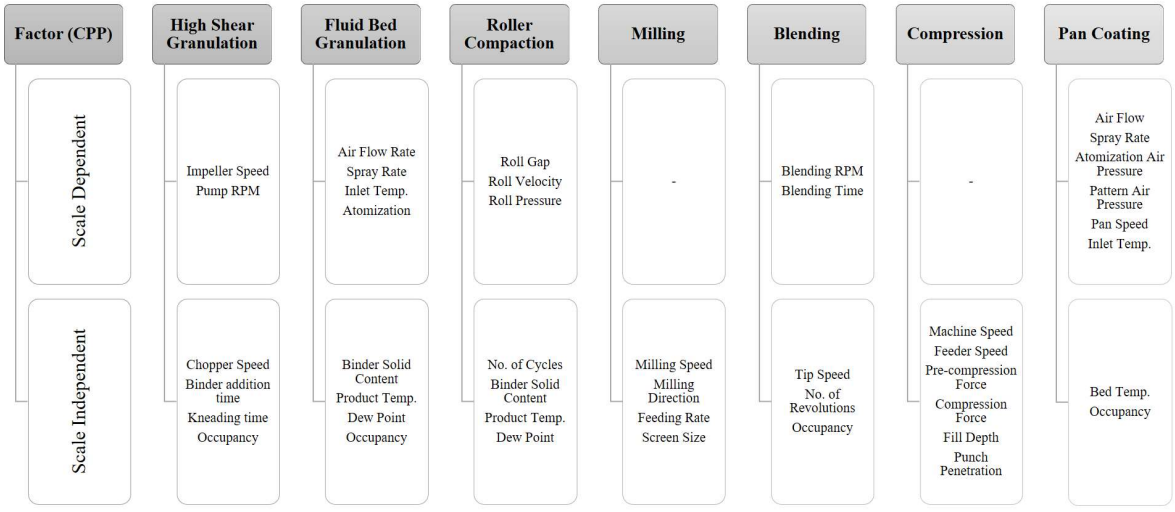

Figure Scale dependent and independent critical process parameters for various stages of tablets

This review covers basic concepts of technology transfer and scale-up in pharmaceutical industry with specific emphasis on solid oral dosage form.

TECHNOLOGY TRANSFER

REQUIREMENT, IMPORTANCE AND OBJECTIVES

A set of process is prerequisite to introduce the product from development laboratory to large-scale production. The transfer of

technology and knowledge is essential to ensure product quality throughout production. Technology transfer is essential for the aforementioned research to achieve broader commercialization. Technology Transfer is a chance to diminish the expenses associated with medication discovery and development. A well-coordinated effort by the technology transfer team yields improved preliminary results and consistent operations, leading to the previous licensing, earlier launch, and enhanced market share.

Technology transfer is crucial for facilitating research that may be scaled for commercialization, particularly in the development of goods, to make the newly developed technology available for better manufacturing capability, marketing capability and commercial capability.

One of objectives of technology transfer is to clarify essential information of existing products among various manufacturing sites. In addition, to illustrate particular procedures and concern points for smooth technology transfer. The additional aims are to facilitate the transfer of information regarding processes and products between development and manufacturing, or among manufacturing locations, to get a comprehensive understanding of the product. This comprehension establishes the foundation for the control strategy, process, process validation, and continuous improvement initiatives.

PHASES IN THE TECHNOLOGY TRANSFER PROCESS

The transfer of technology is not a unilateral process. The development of new formulations undergoes many phases. In the formulation development stages, it is crucial to comprehend the procedures of employed operations, as well as the critical and non-critical parameters of each operation, the production environment, the availability of equipment, instruments, and excipients. These factors must be considered during the initial development stages to ensure successful subsequent scale-up. Necessary precaution during transfer of technology (Gorman, 2002) is required to enhance the product quality as developed in final formulation along with to assure quality for predetermined period. The progressions are categorized (John, 2017) into the following phases: research phase, development phase, production phase, and research phase incorporating technological development.

The quality design of medication items resembles that of drugs. It entails the design of qualities and functions. In addition, it covers data like physic-chemical properties, safety, efficacy and stability acquired from preclinical studies. For manufacturing drug products with designed qualities, it is essential to establish right quality control and manufacturing methods. For this, one can take the base of the results of small-scale researches followed by identification of proposed affecting factors in achieving consistency in scale-up batch and validation batches carried out to understand commercialization. When product specification is established, it is crucial to validate that the adequately of specification insist on the product quality. The relationship between the manufacturing formula's lower and higher limits and the product specification's control limits must be thoroughly comprehended, and the consistency between product quality and requirements should be maintained.

To this end, the development team responsible for site transfer must thoroughly comprehend the technical information required by the manufacturing division of the receiving party and establish a suitable evaluation method to ascertain whether the drug product to be manufactured meets the design quality standards. For consistent manufacturing, it is essential to consult the data of previous analogous items archived by the producer throughout factory production study.

Research and development provides technology transfer dossier or technical package, technology transfer document to production team or product development laboratory of receiving unit, which contains all information of drug product. It covers but not limited to master formula record, master packaging record, master formula, specifications, and standard testing procedures, etc.

Production commences following the confirmation from many validation batch studies that it can yield a stable product according to the transferred manufacturing recipe. The production plant accepting the technology is responsible for validation activities. The technology transfer within the research and development department is accountable for validations including performance qualification, cleaning validation, and process validation.

Scale-up encompasses the technical transfer of the product and processes from small-scale development. Studying production feasibility is essential during process development. Operators must underscore that the manufacturing process will function optimally if technology transfer is employed prudently. The efficient transfer of technology facilitates process optimization and preserves product quality.

Manufacturing of exhibit batches begins following the completion of successful scale-up batches. In exhibit batches, based on equipment capacity, batch size is extended. This is done for regulatory authorities for filling purpose. The purpose of three consecutive batches execution is to demonstrate process consistency and reproducibility. It also demonstrates that the manufacturing process is in the state of control throughout all stages.

FACTORS INFLUENCING TECHNOLOGY TRANSFER PROCESS

The success of any pharmaceutical sector is mostly due to the implementation of effective business and production practices. The industry must possess the capability for competitive pricing and the ability to equilibrate costs through elevated private sector prices and reduced public sector prices to maintain competitiveness. It should incorporate strategic planning. Create a conducive environment for direct integration, anticipating increased capacity utilization while reducing manufacturing costs. Although it might be challenging to pinpoint the size and/or nature of the market that would enable sustained economic production, it is typically the case that the larger the country or geographic region, the greater the market potential and investment attraction. To maintain the safety, efficacy, and quality of its products as well as the wellbeing of patients, industry, and particularly the pharmaceutical business, must continue to conform to regulatory norms. Nowadays, irrespective of markets viz. domestic, international, regulated, non-regulated, the skill to meet regulatory standards is a prerequisite for various technology transfer activities. Human capital, or skilled workforce, is an essential component of the technology transfer. The pace of technology transfer is directly and positively related to the level of intellectual property security. Information should be properly accessible to the firm or exchanged more often. When multinational pharmaceutical businesses foresee being unable to meet big clients' timetables and volume demands, they are more inclined to transfer technology to local manufacturers that stand to gain. Access to new machinery, training, expertise, and commercial partnerships should be available to the enterprise. This necessitates the potential of technology transfer to domestic producers, as the technology, equipment, and so on may be utilized financially beyond the initial purpose.

BARRIERS

In terms of distance and time, the technology transfer process is frequently lengthy. As a result, effective communication is a critical component of successful technology transfer. Efficient and effective two-way communication among key stakeholders will go a long way toward removing obstacles. The lack of predictability and the significant high-risk levels are acknowledged as important barriers to the successful establishment and operation of functional markets. Along with the transfer path due to restrictions on movement of information and materials impediments occur. To fulfill their duties and

obligations, all important participants and stakeholders must possess the essential knowledge and abilities. There may be a moral commitment (John, 2017) to overcoming the challenges, providing necessary technology, reducing risks, increase certainty, improved communication, building and strengthening the enabling environment and accordingly the capacity for technology transfer.

Various orientations exist between the technology supplier and the recipient. It encompasses many dimensions of time length, objectives (scientific and/or techno-economic), and risk assessment. Significant asymmetries exist between the supplier and the recipient regarding internal structure, size, skills, expertise, pricing, endowments, and other factors. The technology provider and recipient employ various approaches to achieve the expected outcomes. These strategies are typically diversified, including innovation-oriented, market-oriented, technology-oriented, and implementation-oriented approaches. Insufficient transfer of technical knowledge and inadequate collaboration between the source and recipient throughout the technology development phase are often apparent. Deficiencies in business management and negotiation abilities are evident on both sides, albeit they are typically more pronounced on the provider's side. The choice of suitable technology transfer mechanisms and the absence of precise evaluations of technology transfer can pose challenges. Moreover, there is frequently inadequate planning for the execution of research findings and the evaluation of implementation outcomes. The provider prioritizes innovation and knowledge sharing excessively, conflicting with industrial demands. Technology vendors sometimes possess insufficient knowledge regarding potential recipients. A lack of time for transitioning from old technologies hinders the practical use of emerging technologies.

The lack of developed infrastructure, market, and governmental incentives persists. The absence of a technical development strategy is evident. The absence of promotion and support for research and innovation is clearly evident. Protect against unexpected failures that are frequently intentional and can disrupt the deployment of innovations. The interest groups or lobbyists actively impede alterations and reforms within the legal framework, rendering technology transfer unfeasible or inefficient..

The substantial amount of tacit knowledge inherent in technologies complicates technology transfer, particularly with the latest solutions. Novel technologies must undergo rigorous testing and demonstration prior to established technologies. Technology is complex, rendering it difficult or unfeasible to adapt for production or market demands. The recipients are unable to adapt to the requisite technology's level and qualities.

Absence of a consistent framework for the thorough examination, analysis and assessment of the technological notion is observed. The lack of necessary mechanisms for acquiring technology transfer in poor nations is evident. Individuals' efficiency in their work environment has not been successfully integrated into technology transfer. The absence of rigorous examination of environmental, health, and safety implications of technology outcomes and their evaluation is also a contributing factor. Feasibility study of technology transfer is limiting funding valuation. Incorrect estimation of the concept of technology utility is also there. The presence of ethical issues in the technology transfer process. Lack of awareness, knowledge and efficiency, government focus is observed. Low market share, restricted access to online and scientific publishing, prequalification expense, national security considerations and limits on exports of certain technology is also observed. Inadequate financing in critical sectors, potential treaties, labor concerns, and so forth.

There are certain approaches to overcome aforementioned barriers. A seemingly simple approach exists for enabling organizations that receive public research funding to obtain and utilize patents on inventions developed during research activities. The rate of inward technology transfer will be contingent upon the relative political and economic stability of a nation, which may be seen as a requirement for any technology transfer. Even when the technology transfers from research-based pharmaceutical firms are altruistic, they must be sustainable to achieve their objectives. Addressing regional and global health challenges, and more importantly, enhancing the capacity of the health system necessitates political leadership. Patents can hinder researchers in conducting their investigations or in making the outcomes of their study accessible to the public. This has accelerated the inclination of specific publicly funded research institutions to eschew the utilization of protected technology, even in jurisdictions where no pertinent patent exists. For several governments aiming to enhance technical capacity, obtaining direct investment is crucial; nevertheless, optimizing the returns on that investment is also a significant consideration. This may indicate the necessity for sufficient capital markets. Governments can promote domestic investment through tax incentives and other measures aimed at facilitating technology transfer in compliance with international trade regulations. The few resources accessible to governments indicate that initiatives aimed at promoting technology transfer must be authentic and aligned with overarching policy objectives. A technology transfer plan focused on creating a whole new economic activity, as intricate and rigorously regulated as the pharmaceutical business, may provide a far bigger barrier than revitalizing an existing sector. Global endorsement of public sector research can be fostered through collaborative research agreements aimed at achieving certain objectives. It is prudent to concentrate efforts on technologies that yield substantial societal advantages. A proposed international treaty aims to facilitate negotiated access to information and technology, drawing on the reciprocity model typical of standard global trade talks. The notion of non-zero-sum implies that free commerce in products and scientific ideas can occur both bilaterally and multilaterally.

DOCUMENTATION

To offer the proper functioning of the whole transfer process itself and all of its allied contents, it’s desirable to review the SOPs for every process stage bearing in mind of the company requirements and its production areas good documentation system. The technology transfer package encompasses, but is not limited to, the scope and scheme of the batch, manufacturing process flowchart, critical material attributes, critical process parameters, critical quality attributes, details of raw materials, details of packaging materials, the manufacturer’s certificate of analysis, and specifications for raw materials, packaging materials, in-process materials, and finished products, bill of raw materials and packaging materials, trade dress proposal, test or manufacturing license, analytical requirements, method of analysis, analytical method validation and report, tooling drawings, change part drawings, cleaning procedures, cleaning validation report, process development report, scale-up report, dispensed material hold time plan, packaging plan, packaging configuration, stability plan, gap analysis, risk assessment etc.

WHO GUIDELINES

WHO published Technical Report Series, No.[961], Annex 7 (WHO, 2011) on Guidelines on Transfer of Technology in Pharmaceutical Manufacturing. This guideline covers various aspects of technology transfer in pharmaceutical manufacturing including organization and management, production related transfer, analytical method transfers, premises and equipment, documentation, qualification and verification, etc. The recommendations will apply to the production of active pharmaceutical ingredients, the manufacturing and packaging of bulk materials, the manufacturing and packaging of finished medicinal products, and/or the execution of analytical tests. The International Society issued recommendations (ISPE, 2003) regarding intra-company transfers in Pharmaceutical Engineering. The transfer of technology necessitates a systematic, documented strategy that encompasses comprehensive data on development, manufacturing, and quality

control, executed by qualified and proficient staff operating within a quality framework. The transmitting unit, receiving unit, and the unit overseeing the process are often included. This guideline discusses the fundamental concepts and prerequisites for effective technology transfer. Technology transfer is deemed effective if the recipient can consistently replicate the transferred process, technique, or product according to mutually agreed requirements, supported by recorded proof. The receiving unit should communicate back to the sending unit if it identifies problems with the transfer process. Technology transfer projects have legal and economic consequences If these concerns are likely to impede open communication about technical matters, they should be addressed prior to the planning and implementation of the transfer. A deficiency in transparency may result in an inadequate transmission of technology. The sending unit must provide a comprehensive description of the product, encompassing its qualitative and quantitative composition, physical characteristics, manufacturing process, in-process controls, control methods and specifications, packaging components and configuration, as well as any safety and handling considerations. The transmitting unit must include any pertinent information about the development history of the process necessary for subsequent development and/or process optimization after the successful transfer to the receiving unit. This material may encompass clinical development, scale-up initiatives, comprehensive development efforts, change history, issues examined, and outcomes. Clinical development Information includes rationales for selection of synthesis, route, form, and technology, product composition equipment, and clinical trials. Details on scale-up efforts encompass statistical optimization of essential process parameters, crucial quality features, process refinement, pilot scale development initiatives and documentation, as well as the quantity and status of produced batches. Comprehensive development reports encompass the quantity and status of generated batches, together with deviation and change control reports pertinent to the existing production process. The transmitting unit must furnish the receiving unit with information on any health, safety, and environmental concerns related to the manufacturing process.

The sending unit must furnish the receiving unit with pertinent information regarding current processing and testing, encompassing, but not limited to, (1) facility and equipment specifications (2) starting materials, relevant MSDS, and storage stipulations for raw materials and finished products (3) manufacturing procedures, including qualification of in-process hold durations and conditions, raw material sequencing, methods of addition, and bulk transfer between processing stages (4) analytical techniques (5) identification and rationale for control strategy (6) design space (7) validation (8) annual product quality assessments (9) stability (10) protocols and operational instructions for manufacturing and (11) environmental conditions (12) any specific requirements contingent upon the nature of the product to be transferred.

The receiving unit must detect any deficiencies in facilities, systems, and capabilities throughout the transfer, and convey them to the sending unit to assess the probability of achieving favorable product quality from the transfer process. Ensuring similar quality in products necessitates the comprehension and rectification of discrepancies. The receiving unit must assess its capacity to produce and package the product according to defined standards and prepare the necessary operating procedures and documentation before commencing production. Process development at the receiving unit should address (1) comparison and assessment of the suitability and qualification of the facility and equipment (2) the manufacturing process description and personnel flow and materials flow in receiving unit (3) determination of manufacturing critical steps, including hold times, endpoints, sampling points and sampling technique (WHO, 2005) (4) writing and approving SOPs for all production operations (such as dispensing, granulation or blending or solution preparation, tablet compression, tablet coating, encapsulation, liquid filling, primary and secondary packaging and in-process quality control), packaging cleaning, testing and storage (5) evaluation of the stability information with the creation of site-specific stability data (WHO, 2006) if necessary and (6) any changes made need to be in compliance with regulatory requirements.

SCALE-UP

Different scale-up factors (Dumpala et al., 2020) are useful for different unit operations during technology transfer of pharmaceutical products.

GRANULATION SCALE-UP

The high shear mixers are used to provide high-quality mixing and uniform granules at minimal running costs and high production. Using an impeller and chopper, high-speed mechanical agitation is used to mix and wet massing. The impeller's shear and compaction forces cause mixing, densification, and agglomeration of the wet mass. Granulation is traditionally done in process steps (Yadav et al., 2010): (1) dry mixing (2) addition of binder (3) wet massing (4) wet milling/sieving of the granules, if necessary (5) drying and (6) milling/filtration.

Dimensionless groups must be established by dimensional analysis, as the dynamics of the wet granulation process cannot yet be precisely depicted by mathematical equations. Buckingham's Theorem classifies dimensionless groups as follows: (1) power number, $\pi1 = P/r^5\omega^3\rho$; (2) specific quantity of binder, $\pi2 = qt/V\rho$; (3) proportion of volume occupied by particles, $\pi3 = V/V^*$; (4) Froude number, $\pi4 = r\omega^2/g$; and (5) geometric number, $\pi5 = r/d$. In this context, P denotes power consumption, r represents the radius of the rotating blade, ω indicates angular velocity, ρ signifies the specific density of the particles, q refers to the mass (kg) of granulating liquid introduced per unit time, t is the duration of the process, V denotes the volume occupied by particles, V* represents the total volume of the vessel (mixer unit), g indicates gravitational acceleration, and d is the diameter of the vessel.

A high-shear granulation process may be scaled up using a few different theoretical methods. To get dimensionless numbers (Lord, 1915) that completely capture the process, use the Rayleigh approach (dimensional analysis). Dimensionless numbers like Newton, Froude, and Reynolds are frequently used to characterize the wet granulation process. The Newton number, a measure of power, shows the relationship between the resistance force acting on an impeller unit area and the inertia force. The Froude number (Horsthuis et al., 1993), a dynamic similarity criterion, shows the particles flow dynamics in a mixer. Reynolds number (Reynolds, 1883), a dynamic similarity criterion, used to understand similarity between viscous flows at various scales. Constant impeller tip speed (Zlokarnik, 1991) indicates uniform shear rate at different scale. The relative swept volume is the ratio of the total volume of granules to the volume of granules swept per unit time. Mixer torque rheometry (Rekhi et al., 1996) employs the rheological characteristics of the wet mass.

There are some conventional methods like power consumption, impeller torque, torque rheometer, reaction torque etc. are used for end point determination of granulation process. Because the measurement is inexpensive, does not need major mixer modifications, and corresponds well with granule growth, mixer motor power consumption (Emori et al., 1997; Leuenberger, 1983a, 1983b; Leuenberger et al., 1979; Ritala et al., 1988) is extensively utilized for end-point determination and scale-up. Additionally, there is some relationship between the intragranular porosity and power usage. The normalized granulation function, representing the integrated power profile across time, can effectively predict endpoints and is closely associated with granulate characteristics. A strain gauge should be affixed to the impeller shaft or at the junction between the motor and the impeller shaft for direct torque measurement (Corvari et al.,

1992a, 1992b; Ghanta, 1984; Levin, 2006; Terashita et al., 1990). A torque rheometer (Hariharan and Mehdizadeh, 2002; Travers et al., 1975; Parker et al., 1990; Rowe and Parker, 1994) is utilized to quantify the torque required to rotate the device's blades off-line and may assess the rheological properties of granulation. Reaction torque can be utilized to ascertain the endpoint, since the motor endeavors to rotate in the opposite direction as the impeller shaft spins, however is constrained from doing so due to its fixed position. The torque transducer can quantify the strain response in the fixed motor base. Other options exist in addition to the ways mentioned above. Both the power usage and the torque on the impeller may not be sensitive enough to accurately reveal the physical changes when agglomeration is occurring extremely quickly. Other suggestions have been made, such as using neural networks (Watano et al., 1997) or a quick image processing system (Watano, 2001) to regulate endpoints in order to define and anticipate the behavior of the wet granulation. Evaluation of granule tensile strength (Betz et al., 2003) in an addition method to power consumption to allow appropriate endpoint determination. Positron emission particle tracking (Laurent, 2005) may be used to study the powder flow patterns in wet granulation. There are emerging technologies such as acoustic (Belchamber, 2003; Rudd, 2004) and near-infrared (Miwa et al., 2000; Otsuka et al., 2003), focused beam reflectance (Alshihabi, 2013; Narang et al., 2017) measurements for end point determination of the granulation process.

Geometric similarity for wet granulation using raw materials is checked by fill ratio, the ratio of bed height and raw materials diameter. Kinematic similarity is checked by tip speed, the linear velocity at the tip of the impeller. Tip speed is related to the shear forces imparted by the impeller and is responsible for the movement within the bowl. Dynamic similarity is checked by Newton's power number, relative swept volume and Froude number. Newton's power number may be utilized to scale torque. Relative swept volume pertains to the effort or energy applied to the wet material during the granulation process. The Froude number pertains to the compaction forces acting on the wet material as a result of the centrifugal and centripetal forces produced by the plow..

FLUID BED PROCESS SCALE-UP

Fluid-bed processes are employed in the production of controlled-release products, and the process variables that require optimization during the scale-up of these processes are examined. Spray rate, atomization air pressure, input air temperature, fluidization air volume, batch size, and equipment type are some examples of these factors. Due to the potential impact of these characteristics on the ultimate performance of the controlled-release product, they must be meticulously evaluated during scale-up processes. If the fill ratio of the equipment is same across all sizes, then the air velocity should also be constant at any scale.

The equipment design, which may or may not be scalable with regard to its selected dimensional parameters or components, determines the scale from laboratory equipment to production-sized units. The equipment's design dictates its scalability from laboratory to production use based on its dimensional characteristics or components. The fluid bed method is fundamentally dependent on airflow. The air volume ratio of product is crucial to achieving a scale-up that is linear since airflow is one of the factors that determines how effectively a fluid bed system dries products. The product container cross-sectional area and how it is created in different sizes is another key design feature. If the cross-sectional area is intended to be linear, the scale-up of the binder spray rate can be linear.

The fluid bed agglomeration method consists of three steps: dry mixing, spray agglomeration, and drying to the necessary moisture content. All steps of the technique are equally essential. The quality of the granules is accurately evaluated during the spraying phase, which encompasses the continuous manufacture of granules and the evaporation of the binder solvent. Regulating humidity during scale-up is essential (Schaefer and Worts, 1978) as granule size is strongly correlated with the moisture content of the bed.

The process-air temperature, the spray nozzle's height above the bed, the binder addition rate, and the degree of binder atomization were the processing variables (Gore et al., 1985) that had the most effects on granule properties.

The two most significant aspects of fluid bed granulation are atomization air pressure and bed wetness. Fine droplets of binder solution are produced by using a high atomization air pressure. As a result, granule development will be influenced by atomization air pressure. Maintaining the same binder droplet size throughout scale-up of a fluid bed granulation process is a critical component to ensure effective scale-up. The impact of spray nozzle setup settings and air drying effectiveness was supported by Bonck (1993). The study found that more attention should be devoted to the often-overlooked nozzle atomizing air pressure and volume. When considering atomization air pressure, make sure that enough air is provided to the nozzle tip. The findings also reveal that the drying efficiency of the process air influences the final particle size of the granules.

When scaling up fluid bed processing, Jones (1985) has made suggestions for the process-related aspects that need to be taken into account. Because the large-scale unit has a higher degree of attrition than the smaller one, the granules bulk from the larger fluid bed is approximately 20% higher. In order to avoid the large agglomerates formation, he further emphasizes the significance of keeping the moisture content of the bed below a critical moisture level. The drying capacity in the large-scale unit must remain constant to ensure that the bed temperature matches that of the smaller unit, as the augmented airflow and temperature in a bigger unit facilitate a higher evaporation rate. This can be performed by increasing the spray rate, the airflow, the air temperature, or a blend of these factors to obtain the desired outcome. The fluidizing air velocity is maintained constant by increasing air volume as the equipment size results in an increase in the ratio of bed depth to air distributor.

Previously, scaling-up was accomplished by selecting the best-estimated process parameters. The use of factorial and modified factorial designs and search algorithms has recently become popular. Statistically built experimental designs can provide mathematical correlations between independent factors, such as process variables, and dependent variables, such as product attributes. This strategy still requires an effective laboratory or pilot-scale development effort, together with an understanding of the factors affecting product characteristics.

Comparable processing conditions must be maintained in pilot-scale research during the scaling-up process. The process conditions are: (1) the fluidization velocity of the process air; (2) the ratio of the granulation spray rate to the drying capacity of the fluidization air volume; and (3) the droplet size of the binder spray liquid. Based on the outcomes of operating pilot scale equipment, each of these numbers should be determined. To define the process's acceptable operating range, investigations using pilot scale equipment across a broad range should also be carried out.

ROLLER COMPACTION SCALE-UP

Using a parametric strategy is a typical technique for expanding a roller compaction process from a development stage to a commercial stage. The parametric approach focuses on calculating equivalency factors for commercial equipment parameter values. The equipment characteristics serve as the basis for the equivalency factors.

By taking into account roller diameter and width, the hydraulic pressure needed to provide the necessary force on the roll might be approximated when choosing commercial equipment roller pressure. The RPM can be adjusted to achieve a similar linear velocity of the roll used in production when selecting the roller speed of commercial equipment.

As an alternative, dwell time may be used as a measure to choose the right commercial equipment roller speed. In order to obtain the necessary throughput, roller speed and gap are frequently chosen to be synchronized. This approach ignores the ribbons and granules qualities, and potentially impacts downstream processes.

A different approach concentrates on the ribbon's characteristics and asks for modifying the ribbon's manufacturing settings to attain attribute values that are equivalent to those of commercially available devices created during development. Controlling ribbon production quality is meant to influence downstream granule characteristics (granule size distribution, compactability and solid fraction).

The manufacturing of ribbons and the milling of granules are the two sequential, independent, but linked sub-processes that make up the roller compaction unit operation. The solid proportion and thickness after recovery owing to relaxation are two quality characteristics of importance to ribbons. These two ribbon characteristics regulate the ribbon's breaking strength along with the general consolidation principle. Consequently, these qualities ought to affect the ribbon's behavior during milling. Given that prolonged recovery may affect ribbon strength, the indirect effects on ribbon recovery should be carefully examined.

In scaling up a roller compaction process, a crucial decision is whether to implement an automatic gap feedback control system or to maintain a fixed feed rate. This decision will determine which elements must be considered during the scale-up process. Without gap control, the impact on ribbon thickness from adjusting the gap in the roller compactor is negligible. Determining which process parameter to modify to get the desired intermediate feature requires a comprehensive understanding of the correlation between process parameters and ribbon/granule characteristics (Sprockel and Stamato, 2011).

DRYING SCALE-UP

The depth of the granulation bed must be precisely regulated during the scaling-up of the drying operation, and moisture and/or temperature probes must be used to track the drying progress. Airflow, granulation depth in trays, and air temperature are crucial variables to take into account while scaling up an oven drying process.

The drying process will be inefficient if the granular bed is excessively thick. When soluble dyes are used, dye migration to the granule surface is possible. During the drying phase, the drying process may also be monitored by doing regular multi-point granulation sampling to check moisture level. Drying periods at precise temperatures and airflow rates must be determined for each product and oven load.

Ideal load must be determined prior to scaling up fluidized bed drying processes. Additionally, because they all have an impact on drying time, the airflow rate, inlet air temperature, and entering air humidity must all be determined. The decrease in drying time is a fluidized bed dryer's key benefit.

Drying durations for fluidized beds often do not exceed one hour, in contrast to eight hours or longer for conventional ovens. However, scaling up a fluidized bed drying process is more challenging than scaling up a circulating hot air oven system. Significant seasonal variations in humidity and temperature may interfere with the drying process if the incoming air from the environment is unconditioned (Ramasubramaniyan et al., 2014).

SIZE REDUCTION SCALE-UP

The morphology and dimensions of particles are essential for the manufacturing of medicinal goods. These characteristics are influenced by the parent components, their physical and molecular interactions, and the processes they undergo.

Milling is the principal method employed for particle size reduction before the production of tablets and capsules. The substance is fragmented into smaller, uniform particles, which are subsequently blended, compacted, and coated into the final dosage form.

Before compression or encapsulation, the necessary particle size distribution is attained in the laboratory by manual screening or short manipulation using a small-scale milling device. As this process is escalated to support bigger, quicker presses with more intricate feed systems, it is essential that the equipment delivers the requisite output while controlling particle size and shape distribution, which are critical granulation attributes.

All material can be processed using an oscillating granulator, a hammer mill, a mechanical sieving apparatus, or a screening device to diminish the particle size of the dried granules from production-sized batches. Oscillating granulators operate efficiently when substantial portions of granules, including lumps or agglomerates, are not too hard. To prevent the production of an excessive quantity of fines, ensure that the device is not overfed.

Dry granulate is often milled to a certain particle size distribution in hammer mills. Particle size distribution may be regulated by adjusting the screen dimensions, milling velocity, type and quantity of hammers, blades utilized, and material input rate.

The appropriate milling tool for granule particle size reduction should be selected by initially assessing the characteristics of the unmilled granulation, followed by choosing the tool that will provide the requisite particle size distribution for enhanced performance in compression or encapsulation procedures.

Flowability, compressibility, tablet weight uniformity, content uniformity, and hardness are compressibility variables that may be impacted by particle size distribution. For instance, a granulator unable to fill the die cavity uniformly during compression can have too big of a particle size and not enough fine particles. As a result, there will be significant weight variations in the tablets.

Lubricants and glidants, formerly included into the final mix during the size operation at the laboratory scale, are now applied to the dried granule as an extension of the milling or sieving process (Ramasubramaniyan et al., 2014). This occurs because many of these additives, especially magnesium stearate, tend to aggregate when used in sufficient quantities to induce granulation in a blender.

BLENDING AND MIXING SCALE-UP

The homogeneity of the ingredients is directly affected by dry-particle blending in the manufacture of many pharmaceutical products. There are different sizes and geometries of mixers. A tumbling blender is a basic mixing apparatus comprising a hollow vessel connected to a spinning shaft. The blender is partially filled with contents and turned. Their primary features are substantial capacity, little shear stress, adaptability, containment, and ease of cleaning. A convection blender is a standard blender that generates flow using revolving impellers within a stationary housing. Blenders can deliver high shear, minimize component segregation, and facilitate moist granulation. The highest capacity is often the inverse of the maximum shear rate. No reliable method exists to forecast blending scale-up criteria for any blender type without previous analysis. The research must address rotation rate, filling level, mixing duration, and blender shape. Moreover, if the rotation rate is constant, meaning dynamic or kinematic variations, scaling up becomes more complex. The mixing need differs based on the material type, whether free-flowing or cohesive.

Free-flowing materials possess small interparticle cohesive forces enough to move the particles apart. The particles are larger than 100 μm and the interparticle forces of attraction are equal to or smaller than the particle weight. Not enough shears is required to mix the material, and tumbling blender is often preferred.

The main process risks are caused by segregation either during blending or at the discharge. It is important to understand that the majority of tumbling blenders are symmetrical, which might be

the largest barrier to achieving a uniform mixture before realizing scale-up needs.

The quantity of material transferring across the symmetry plane influences the mixing rate. Certain blender models are designed asymmetrically, resulting in enhanced mixing efficiency. The mixing rate can be enhanced by tilting the vessel. Baffles can be strategically arranged to induce asymmetry; this technique has been validated in small-scale apparatus and has been implemented in the design of certain commercial-scale equipment. In the absence of these asymmetry-inducing approaches, meticulous attention to the loading process is essential, since it can significantly impact the mixing rate. If dispersion is the essential blending mechanism, non-systematic loading of various ingredients would significantly influence the mixing rate. In a V blender, it is preferable to load the blender either via the discharge valve or with equal quantities in each shell. This method ensures that about equal quantities of components will be present in each blender shell. Exercise caution while incorporating modest (□1%) components into the blender. Introducing a minimal quantity early in the loading procedure might direct the majority of the material into a single shell and considerably impede the mixing process. Exercise caution while incorporating tiny components into the blender. Introducing a little quantity early in the loading procedure may result in the majority of the material accumulating in a single shell, so considerably impeding the mixing process. Smaller blenders possess limited dispersion areas, rendering highly asymmetric loading less impactful on homogeneity. The extent of ultimate homogeneity may be influenced by the sequence of component addition (Fernando and Albert, 2005).

Given a geometrically identical blender and identical mixture composition, with scale changes, the fill level should be constant. The fraction of particles in the cascade layer relative to the bulk may drop considerably if the vessel size is increased while filling it to the same level. Even though at constant fill level, if the depth of the flowing layer is a crucial variable, it can be hard to match the mixing rate per revolution during scale adjustments. Tumbling blender scale-up is frequently advised (Fernando and Albert, 2005) using the Froude number. The generic equations of motion for a general "fluid" may be used to obtain the connection that balances the gravitational and inertial forces. Unfortunately, there is no experimental evidence to back up the viability of this strategy. If the powder flow–powder stress relationship can be determined, continuum mechanics may offer other dimensionless groups. The Froude number is derived from a continuum mechanics equation, but the continuum hypothesis may be overturned by the scale of the physical system for mixing granular materials.

An seldom employed scaling method involves aligning the tangential (wall) speed of the blender. This theory remains untested. Frequent infractions of this methodology that may result in instant issues encompass attempting to transition from one geometry to another, altering the fill level, and modifying the blender speed throughout the same blending duration.

A special situation occurs for cohesive powders when the adhesive force between the particles is at least an order of magnitude greater than the particle weight. In these systems, particles cease to travel freely; rather, they traverse in "chunks," with their characteristic size dictated by the magnitude of the cohesive tension. Cohesive blends frequently have two main effects: one ingredient (usually the active ingredient) is cohesive enough to show the formation of agglomerates, and the entire combination is cohesive enough to change how the ingredients flow in the blender.

Constant fill ratio i.e. keeping the ratio constant over all the lengths shows the geometrical similarity. The Froude number i.e. maintaining constant forces shows the dynamical similarity. Maintaining the same number of revolutions indicates kinematic similarity.

COMPRESSION SCALE-UP

Compression machine speed is calculated based on dwell time. While maintaining the depth of fill, we can obtain the desired tablet weight, thickness and hardness at any scale. Compaction involves applying pressure to densify the powder and generating physical bonds between powder particles to create this strength.

Compaction and compression work on the same principles. The material qualities of the particles being compacted and the equipment employed for the compaction operation are important considerations (Marshall, 1986). The essential mechanical unit of compression consists of three components: an upper punch, a lower punch, and a die. A powdered substance must be compressed between two punches within a die while an external force is applied to form a tablet.

It is evident that the majority of scale-impacts ups are seen in unit processes that take place before compression. There are a number of unique difficulties with scaling up compaction and which cannot be assessed at lesser scales. The list may consist of the following: (1) press speed; (2) force feeder overmixing of lubricant; (3) long-term heat buildup; (4) abrasive materials; and (5) tooling care.

Scale-up is primarily concerned with the formulation's strain rate sensitivity (or the impact on press speed). The goal of operations, in this instance increasing tablet production rate and, consequently, press speed, will be to boost efficiency whether product development activity is conducted on a single-stroke press or a small rotating press. There would be no worry for a material that deforms solely through brittle fracture. Plastic deformation causes strain rate sensitivity, and the influence of press speed is important. While some materials, like lactose, exhibit mostly brittle fracture behavior, nearly all materials possess a degree of plastic deformation, which is the principal property of certain substances, such as microcrystalline cellulose. According to standard parameter indications, the desired tablet hardness cannot be achieved at elevated press speeds. The sole solution to the problem may be to reduce the press speed.

The effects of lubrication, especially with magnesium stearate, depend not only on the quantity of components but also on the duration of mixing. Excessive mixing is acknowledged to induce particle dispersion and an increase in the hydrophobicity of this material. The repercussions of disintegration are well acknowledged. There is less knowledge on the impact of excessive lubrication or mixing on tablet hardness or tensile strength. Magnesium stearate, specifically, covers the surfaces of other components or granules to prevent particle interaction and adhesion, perhaps resulting in softer tablets. The formulation was compacted at the laboratory size without a forced feeder; scaling up at a single site using a gravity feeder and without a forced feeder may be optimal. Nevertheless, scaling up elsewhere using forced feeders may not get the desired tablet hardness. The conclusion was that the issue in this instance was not the press speed, but the excessive mixing of the lubricant in the force feeder of the tablet press, resulting in a softer tablet. If the medicine is very soluble, dissolving issues may not arise; conversely, delayed dissolution might provide a challenge for a drug with poor solubility.

It is impossible to duplicate the event in a full-sized batch and the corresponding duration of a compaction run, irrespective of the tablet press utilized at the laboratory or pilot scale. Given the duration of the compaction process, one must be vigilant regarding the possible accumulation of heat. Formulation scientists should examine the effects of a potential temperature rise on the stability or degradation of the active ingredient or heat-sensitive substance. Even in the absence of the tablet machine, the abrasive component in the mixture can produce this form of heat accumulation.

The tooling sets on the press must be precisely aligned to utilize an instrumented tablet press for regulating tablet weight. These devices function on the principle that a reduced fill weight generates a diminished force signal and conversely. Although the forces are unrecorded, the peak height remains constant, and

weight adjustments are implemented as required. Nonetheless, the force signals may also be influenced by alterations or fluctuations in the duration of the blows. Nonetheless, alterations or discrepancies in punch lengths may also influence the force signals. If a single punch is somewhat shorter than the others, diminished force is exerted on the powder mass, resulting in a decreased signal. These weight management systems will then conclude that the tablet is underweight. Consequently, the upkeep of tooling is very vital in scale-up operations.

Tablet hardness and disintegration are the most crucial variables or traits to watch out for while scaling up the compaction process.

The consistency of tablet weight will offer an indication of the efficiency of the powder flow, force feeder, or automated weight control system. The weight of a sample of five or ten tablets is typically what the operator is watching. It would be more instructive to look at the uniformity of each tablet, which is ultimately connected to dosage. Although force feeders may be used, the powder flow might not be satisfactory.

Similar factors will be monitored via tablet hardness uniformity, which may also reveal matched or mismatched punches on a tablet press. Keeping an eye on the tablet's behavior while the hardness is being tested may also be helpful. Occasionally, capping or lamination that is present during hardness testing but not after compaction may be a sign that a limiting force is present in the area. A plot of hardness verses force produces a parabolic form (Morris, 1996), which helps to visualize the situation. Poor hardness at high forces suggests a poor bonding resulting in a softer tablet during hardness testing. In this instance, a smaller compaction force can result in a tougher tablet.

The subsequent characteristics must be quantified if tablet presses are equipped with instrumentation that provides force measurements or, more critically, force versus time curves: (1) dwell time, (2) compression force, (3) ejection force, (4) displacement.

COATING SCALE-UP

The scale-up of a coating process involves far more than merely managing increased throughput and larger batch sizes, unlike many other unit operations. The application of coatings may significantly influence the aesthetic and functional attributes of a product over time. Furthermore, by the time it arrives to the coating phase, substantial resources (both temporal and financial) have already been allocated to that batch of product. Moreover, during the coating phase, considerable resources in terms of time and finances have already been expended..

Somewhat simplistically, a coating process is frequently scaled up by converting a laboratory-scale procedure to a pilot-scale, then a full-scale procedure, using the processing technology and further optimization of the large-scale process to account for factors whose influence could not have been easily predicted during previous process development operations. Potential process modifications that commonly occur during scale-up, regardless of the kind of coating process employed, include (1) increased batch size (2) increased attritional effect (3) increased spray rates (4) either more spray guns or a switch from single- to multi-head nozzles (5) increased drying air volume (6) increased processing time per batch.

When certain thermodynamic principles are used, many of these factors become relatively predictable. Increased processing time means larger exposure to stressful circumstances both mechanical and environmental conditions employed in the process, especially if the procedure is dependent on water, is less predictable and the fundamental reason is frequently of significant concern during the early commercial batch preparation.

In this regard, greater attention is often afforded when the applied coating serves a particular function, such as prolonging product shelf life or altering medication release characteristics. Inability to meet defined visual standards results in batch rejection, reprocessing, or sorting, even when the coating's purpose is solely aesthetic and for product identification, particularly when the quality of the inadequately coated product is unlikely to affect its efficacy.

The formulations (core and coating) exhibit adequate resistance to meet the operational requirements. In light of the escalating, if sometimes vaguely defined, stress associated with product scale-up, this necessity becomes increasingly vital. The critical characteristics of the coating process and their impact on the overall quality of the final product have been recognized and considered in the optimization of the process.

Several essential elements of the process ought to have been recognized following the establishment of a suitable laboratory-scale approach. Specific operating parameters (including input air temperature, coating formulation, and solids concentration) may be easily adapted to the large-scale process. Conversely, certain parameters necessitate modification, including (1) pan speed (2) drying air volume (3) pan load (4) number of spray guns (5) spray rate (6) distance from gun to bed (7) dynamics of the spray gun.

The amount of drying air, although potentially adjustable, is often determined by the recommendations of the equipment provider or the optimal conditions established for the installed air-handling system. The apparatus employed to achieve the typically recommended negative pressure pan settings must be utilized to compute the intake and exit air fan velocities. Upon determining the appropriate drying-air volume, this parameter becomes a critical determinant for other significant processing variables, such as spray rate.

Choosing the optimum pan speed really becomes more difficult than required. Tablet motion, which is highly impacted by pan speed, may obviously be a huge concern in terms of potential tablet fracture, surface erosion, and edge wear. On the other hand, the results collected by Porter et al. (1997) show that the pan speed has a significant impact on the uniformity of the distribution of the applied coating, with increased pan speeds being preferable in this case. Consequently, there exists a compelling need to develop tablet cores capable of withstanding elevated pan speeds to fully optimize coating uniformity. During scale-up, pan speeds are frequently chosen to be suboptimal, recognizing that attrition effects intensify with larger process sizes. Nonetheless, a reliable guideline is to determine the pan speed for bigger sizes by calculating the linear movement rate of the tablets in the coating pan, ensuring it achieves an equivalent linear velocity based on the pan speed utilized at the laboratory scale and the dimensions of the laboratory-scale apparatus. Consequently, the tablet's residence time in the spray zone at the larger size will match the duration achieved at the smaller scale, allowing optimization strategies utilized at the smaller scale to be effectively applied to enhance the uniformity of the coating distribution.

Determining the proper pan loading should not pose a difficult challenge in general. A certain charge of tablets is intended to fit in a coating pan with the specified dimensions. Unfortunately, filling by volume rather than by weight is the typical definition of pan loading. Consequently, the suitable pan loading by weight will vary among products according to their apparent density. Determining the optimal pan loading should not provide significant challenges, notwithstanding the permitted product variability. Challenges may occur at both the laboratory and manufacturing scales. Ensuring a pan is adequately filled is quite straightforward on a laboratory scale. This issue can be resolved by augmenting the active pill with placebos to provide full dosage, even if only a little quantity of the chemical is present. In large-scale production, pan loading often has little relation to the optimal loading for the pan and is mostly dictated by the overall batch weight of compressed tablets, which may be evenly distributed throughout all pan loads. There is a possibility that the quantity of tablets in a side-vented coating pan may be insufficient to fully cover the exhaust-air plenum. This potential problem may be mitigated in certain coating pan designs by including a sliding damper in the exhaust-air plenum to shield the

exposed region. The tablet is likely to adhere to the exposed metal surfaces due to the accumulation of coating liquid on the sidewalls of the coating pan or the increased exposure of the baffles to the spray. With some foresight, this issue may be resolved by modifying the gun's distance from the bed, its spacing, or the quantity of guns utilized. If the pan loading is uniform for a certain product, these methods are likely used. Remedial procedures are less likely to be employed when compression batch weights vary often. When the pan is properly filled, the baffles traverse the tablet bed as the pan rotates, modifying the tablet bed surface adequately to adjust the gun-to-bed distance. This condition can modify the characteristics of spray droplets that settle on tablet surfaces. The likelihood of tablet damage increases as the baffles become more exposed and as the pan speed requires constant adjustment to keep the tablet in motion, since less loaded pans are more challenging to manage. Consequently, although the compression batch weight is often articulated in relation to the functionalities of blenders, granulators, dryers, etc., it is essential to consider the capacities of the coating pans employed in product and process development.

It is imperative to ensure the spray zone is calibrated for many critical criteria in each film coating procedure. To guarantee that few, if any, tablets on the surface traverse the spray zone without acquiring a coating, ensure that the whole width of the tablet bed is coated. Calibrate the atomization and air pattern of each gun to provide optimal coverage while maintaining the integrity of the coating liquid. Refrain from excessive application on the pan's sides. Consequently, a critical decision that must be taken is the number of spray guns to employ. The answer may depend on the type of spray gun available. Certain spray guns outperform others in delivering extensive coverage while preserving spray quality.

The spray guns of production-scale equipment may differ from those utilized in the laboratory. The laboratory-size spray guns cannot reach the necessary spray rate or sustain efficient atomization at elevated spray rates on a bigger scale. The aim may be to decrease the quantity of guns necessary to optimize bed coverage per gun, or to increase the number of guns needed to limit coverage, hence enhancing the quality regarding smoothness and gloss of coated tablets.

The determination of the gun's location was sometimes reliant on rudimentary locating equipment, such as a ruler, assessed visually. To obtain ideal bed covering, allow extensive coverage, and maximize surface drying time, the location of the cannon must be modified.

Due to the limitations of laboratory scale, the distance of the gun to the bed is often set by individual preference. Upon transitioning to production size, there exists an increased possibility to reevaluate the placement of the gun, however rationality does not always govern this process. At production size, a sub-optimal quantity of guns may be accessible, necessitating their relocation to provide adequate bed coverage. The necessity might be significantly influenced by the utilization of various spray guns, which also necessitate repositioning to provide enough bed covering.

The spray rate per gun at an industrial scale can be significantly elevated, requiring increased spacing between the guns to prevent localized overwetting (Porter, 2002). Unless the gun placement is optimized during process development, similar types of guns must be utilized, and the spray rate per gun should be kept within acceptable limits in both laboratory and production scales. It is futile to anticipate that it can traverse the distance from gun to bed.

Provided that no significant environmental variations occur during technology transfer, forecasting the spray rates to be utilized during scale-up is quite straightforward. Estimates for each scale of the process should generally be grounded in the relative airflow.

Better predictions can be made using thermodynamics principles if there is a significant change in environmental humidity or processing temperature. The disinterest towards spraying dynamics needs to be focused. The performance of spray guns can be correlated with the appearance and functionality related qualities of coated tablets. The incentive is high to learn more about the factors that impact gun performance and those dissimilarities that exist amongst guns supplied from diverse manufacturers.

Table 1. Different unit operations with their scale-up considerations and variables

Unit Operations	Scale-up Consideration	Process Variables	Product Variables	Machine Variables	Reference
Shear Granulation	Fill ratio (G)Tip Speed (K)Relative Swept Volume (D)Newton Number (D)Reynolds number (D)Froude Number (D)	Fill levelDry mixing time & Kneading timeGranulating fluid quantity, temp., addition method, addition time, addition rateImpeller & Chopper speed Power consumptionTip speedTorqueAddition Method of raw materialsBowl temp. (Jacket temp.)Product temp.	Blend particle size distributionParticle shapeFines Bulk and tapped densityAdhesive and cohesive propertiesViscoelasticity and PlasticityElasticityBrittlenessPolymorphic formElectrostatic propertiesMoisture level	Type of granulator Mixing vessel shape & sizeImpeller and Chopper size, shape, configuration, locationSpraying nozzle type and locationType of pumpGranulating fluid container working principle	Dumpala et al., 2020;Rahmanian et al., 2008;Yu et al., 2014
Fluid bed granulation	Liquid spray rate (D)Atomization air flow (D)Fluidization air flow (D)Froude Number (D)Reynolds number (D)Solid particle to gas density ratio (D)	Fill levelPreheating temp.Preheating timeGranulating fluid concentration, quantity, temp., viscosity, spraying time & rate, delivery method, holding timeAddition Method of raw materialsProduct temp.Atomization air pressureVolume, temp., dew point of Inlet airExhaust air temp., flowPressure differentialsFilter bag shaking interval and duration	Blend particle size distributionParticle shapeFines Bulk and tapped densityAdhesive and cohesive propertiesViscoelasticity and PlasticityElasticityBrittlenessPolymorphic formElectrostatic propertiesMoisture level	Fluid bed typeBottom screen size and typeAir distribution plateSpraying nozzle configuration, numbers, position)Filter typeOrifice size	Glicksman et al., 1994;Yu et al., 2014
Roller compaction	Ribbon porosity (G)Roll width (G)Roll force (K)	Auger speedDeaeration Speed, pressure and temp. of rollerFines reprocessed	Blend particle size distributionParticle shapeFines Bulk and tapped densityAdhesive and cohesive propertiesViscoelasticity and PlasticityElasticityBrittlenessPolymorphic formElectrostatic propertiesMoisture level	Type of compactorAuger type & designRoll shape, surface design, gap width	Allesø et al., 2016; Kazemi et al., 2017;Nathan et al., 2006;Yu et al., 2014
Size reduction	Tip speed (K)	Impact/cutting/screening millsMill Speed & Feeding rateFluid energy millNozzle pressureRate of feedingGranule/ribbon millingRate of feeding & Mill SpeedRibbon density, dimensions, porosity, and solid fraction	Blend particle size distributionParticle shapeFines Bulk and tapped densityAdhesive and cohesive propertiesViscoelasticity and PlasticityElasticityBrittlenessPolymorphic formElectrostatic propertiesMoisture levelGranule porosity	Impact/cutting/screening mills/ Granule/ribbon millingMill typeScreen size and typeBlade configuration, type, orientationFluid energy millGrinding nozzles quantityClassifier	Yu et al., 2014
Blending / Mixing	Fill ratio (G) Number of revolutions (K) Froude Number (D)	Occupancy Method and Order of addition of raw materialsBlending timeBlender speedMixing bar patternMethod of unloadingHolding timeEnvironment conditions	Particle size distributionParticle shapeFines Bulk and tapped densityAdhesive and cohesive propertiesElectrostatic propertiesMoisture level	Mixer or Blender Type Geometry of mixer	Yu et al., 2014
Drying	Base plate ratio (G) Occupancy (G)Gun nozzle size (G)Tip speed (K)	Fluidized bed dryerVolume, temp., dew point of inlet airOutlet air temp., flowProduct temp.Filter bag shaking interval and durationTime of dryingTrayThickness of bedDepth of TrayProduct depth and quantity per trayDrying time and temp.Air flowInlet air dew pointVacuum/microwaveMicrowave powerVacuum pressureTemp. of jacketCondenser temp.Impeller speedBleed air volumeElectric fieldSupplied energyTemp. of product, bowl and lidTime of drying	Particle size distributionParticle shapeFines Adhesive and cohesive propertiesViscoelasticity and PlasticityElasticityBrittlenessPolymorphic formElectrostatic propertiesMoisture level	Fluidized bedFilter type and orifice sizeTrayType of tray dryerType of tray liner Carts and trays per chamber	Yu et al., 2014
Compression	Dwell time (G)Blend resistance time in feeder (K)Fill Depth (G)	Fill depth of feederToolingMaximum punch loadMachine speedDwell length & timeFeeder speedPre & main compression force & Ejection forcePunch penetration depth	Particle size distributionParticle shapeFines Bulk and tapped densityAdhesive and cohesive propertiesViscoelasticity and PlasticityElasticityBrittlenessPolymorphic formElectrostatic propertiesMoisture level	Type of press and feed frame Hopper height, design and angleFeeder mechanism	Yu et al., 2014
Pan Coating	Brim volume (G)Occupancy (G)Spray rate (K)Pan diameter (G)Batch size (G)Spray rate/Air flow rate ratio (D)	Pan load levelPan rotation speedGun to bed and Gun to Gun distancePre-warming timeFlow rate, volume, temp., dew point of inlet airExhaust air temp., air flowBed temp.Spray rateAtomization and pattern air pressureDrying time	Tablet size, shape dimensionsHardnessPorosityDensityMoisture content	Type of pan coater Baffle Pan perforationsSpray nozzle & Nozzle orientation	Yu et al., 2014

CONCLUSION

Transferring technology properly is essential for improving product quality from design to provide a consistent, high-quality result. Technology transfer refers to a continual flow of information between the two parties in order to continue production, not only a one-time activity made by the transferring party to receiving one. A receiver unit can be judged to have

successfully transferred technology if it can consistently recreate the product or process using a set of agreed-upon parameters with the transferring unit and/or the developing unit. If the recipient of the technology is able to successfully employ it for business purposes and finally integrate it, the transfer is considered successful. Through improved communication and documentation, the technology transfer team can move technologies from development to commercialization with the appropriate efficiency. A collaborative effort leads to more successful first and consistent runs, which leads to faster licensing, earlier launches, and more market share. The plan, the people involved, and the process are the three main factors that need to be taken into account during an efficient technology transfer. Utilizing the technology transfer process to create new production systems and start-ups allows pharmaceutical companies to fully capitalize on recent advancements and better serve a market that is changing quickly. Scaling up and transitioning a process from laboratory size to pilot scale and many commercial manufacturing stages requires a thorough grasp of the integration of facility design, equipment design, scale factors, and process performance.

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