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# Pharmaceutical Process Scale-Up

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## ABSTRACT

Pharmaceutical Process Scale-Up deals with a subject both fascinating and vitally important for the pharmaceutical industry-the procedures of transferring the results of R & D obtained on laboratory scale to the pilot plant and finally to production scale. The primary objective of the review is to provide insight into the practical aspects of process scale-up. As a source of information on batch enlargement techniques, it will be of practical interest to formulators, process engineers, validation specialists and quality assurance personnel, as well as production managers.

**Keywords:** Process Scale-Up, Laboratory scale, Pilot plant, Production scale, Validation

## I. INTRODUCTION

Any significant change in a process of making a pharmaceutical dosage form is a regulatory concern. Scale-Up and Post approval Changes (SUPAC) are of special interest to the FDA, as is evidenced by a growing number of regulatory documents released in the past several years by the Center for Drug Evaluation and Research (CDER), including Immediate Release Solid Oral Dosage Forms (SUPAC-IR), Modified Release Solid Oral Dosage Forms (SUPAC-MR), and Semisolid Dosage Forms (SUPAC-SS). Additional SUPAC guidance documents being developed include: Transdermal Delivery Systems (SUPAC-TDS), Bulk Actives (BACPAC), and Sterile Aqueous Solutions (PAC-SAS). Collaboration between the FDA, the pharmaceutical industry, and academia in this and other areas has recently been launched under the framework of the Product Quality Research Institute (PQRI). Scale-up problems may require post approval changes that affect formulation composition, site, and manufacturing process or equipment (from the regulatory standpoint, scale-up and scale-down are treated with the same degree of scrutiny)[1]. In a typical drug development cycle, once a set of clinical studies has been completed or an NDA/ANDA has been approved, it becomes very difficult to change the product or the process to accommodate specific production needs. Such needs may include changes in batch size and manufacturing equipment or process[2]. From one tablet press to another, one may aim to preserve

mechanical properties of a tablet (density and, by extension, energy used to obtain it) as well as its bioavailability (e.g., dissolution that may be affected by porosity). A scientifically sound approach would be to use the results of the dimensional analysis to model a particular production environment. Studies done on a class of equipment generally known as compaction simulators or tablet press replicators can be designed to facilitate the scale-up of tableting process by matching several major factors, such as compression force and rate of its application (punch velocity and displacement), in their dimensionless equivalent form[3-4].

## Scale-of-Agitation Approach for Suspensions

In order to reduce the problem of adequately dispersing the insoluble drug during the formulation of sterile aqueous suspensions, the micronized material, i.e., material with a particle size of 10–30_m, is used. Uniform distribution of the drug is required to ensure an adequate dose at the concentration per unit volume indicated on the label. Improper formulation or scale-up can result in caking of the insoluble material at the bottom of the container, making it difficult to disperse, to take up in a syringe, and thus to administer[5]. To avoid caking, various flocculating agents are added to the product. Proper scale-up, however, is essential for adequate mixing conditions, which affect the caking process. During scale-up of a suspension product, along with the parameters, already discussed, the settling rate should be considered. The presence of a two-phase, solid–liquid system classifies an agitation problem as a solid–suspension one. In such problems, the suspension of solid particles having a settling velocity greater than 0.5 ft/min (0.25 cm/sec) within a continuous liquid phase is the purpose of the proper agitation and scaleup. The estimated terminal settling velocity, ut, of spherical particles of a 10- to 30_ size in low-viscosity 1- to 300-cps suspensions is empirically determined as 1. For ease of analysis, the particle shape is assumed to be a sphere, since most of the studies for settling velocities are conducted on spherical beads. A different particle geometry (cylinders, disks, crushed solids, many crystalline forms) would not compromise the integrity of the analysis, due to the usage of micronized materials. First, one must determine the design settling velocity ud, which is a productof the terminal settling velocity ut and a correction factor $f$w[6-7].

$$\mathbf{ud = ut}\ f\mathbf{w}$$

## Nonparenteral Liquids and Semisolids

A manufacturer's decision to scale up (or scale down) a process is ultimately rooted in the economics of the production process, i.e., in the cost of materiel, personnel, and equipment associated with the process and its control. While process scale-up often reduces the unit cost of production and is therefore economically advantageous, there are additional economic advantages conferred on the manufacturer by scaling up a process. Thus, process scale-up may allow for faster entry of a manufacturer into the marketplace or improved product distribution or response to market demands and correspondingly greater market-share retention.1 Given the potential advantages of process scale-up in the pharmaceutical industry, one would expect the scale-up task to be the focus of major efforts on the part of pharmaceutical manufacturers. However, the paucity of published studies or data on scale-up—particularly for nonparenteral liquids and semisolids—suggests otherwise[8-9]. On the other hand, one could argue that the paucity of published studies or data is nothing more than a reflection of the need to maintain a competitive advantage through secrecy. A clue to the resolution of the scale-up problem for liquids and semisolids resides in the recognition that their processing invariably involves the unit operation of mixing. Closer examination of this core unit operation reveals that flow conditions and viscosities during processing can vary by several orders of magnitude, depending upon the scale of scrutiny employed, i.e.,

whether on a microscopic (e.g., molecular) or a macroscopic (e.g., bulk) scale. Therefore, the key to effective processing scale-up is the appreciation and understanding of microscale and macroscale transport phenomena, i.e., diffusion and bulk flow, respectively. Transport by diffusion involves the flow of a property (e.g., mass, heat, momentum, electromagnetic energy) from a region of high concentration to a region[10].

## Material Transfer

Movement of liquids and semisolids through conduits or pipes from one location to another is accomplished by inducing flow with the aid of pumps. The induction of flow usually occurs as a result of one or more of the following energy transfer mechanisms: gravity, centrifugal force, displacement, electromagnetic force, mechanical impulse, or momentum transfer[11].

## Heat Transfer

On a laboratory scale, heat transfer occurs relatively rapidly, for the volume-to-surface- area ratio is relatively small; cooling or heating may or may not involve jacketed vessels[12]. However, on a pilot-plant or production scale, the volume-to-surfacearea ratio is relatively large. Consequently, heating or cooling of formulation components or product takes a finite time, during which system temperature, T°C,may vary considerably. Temperature-induced instability may be a substantial problem if a formulation is maintained at suboptimal temperatures for a prolonged period of time. Thus, jacketed vessels or immersion heaters or cooling units with rapid circulation times are an absolute necessity[13].

## How to Achieve Scale-Up

Full-scale tests using production equipment and involving no scale-up studies what so ever are sometimes resorted to when single-phase low-viscosity systems are involved and processing is considered to be predictable and directly scalable. By and large, these are unrealistic assumptions when viscous liquids, dispersions, or semisolids are involved. Furthermore, the expense associated with full-scale testing is substantial: Commercial-scale equipment is relatively inflexible and costly to operate[14]. Errors in full-scale processing involve large amounts of material. In so far as most liquids or semisolids are concerned then, full-scale tests are not an option. On the other hand, scale-up studies involving relatively low scale-up ratios and few changes in process variables are not necessarily a reasonable alternative to full-scale testing. For that matter, experimental designs employing minor, incremental, changes in processing equipment and conditions are unacceptable as well. These alternative test modes are inherently unacceptable because they consume time, an irreplaceable resource that must be utilized to its maximum advantage. Appropriate process development, by reducing costs and accelerating lead times, plays an important role in product development performance. In The Development Factory: Unlocking the Potential of Process Innovation, author Gary Pisano argues that while pharmaceuticals compete largely on the basis of product innovation, there is a hidden leverage in process development and manufacturing competence that provides more degrees of freedom, in developing products, to more adroit organizations than to their less adept competitors. Although Pisano focuses on drug synthesis and biotechnology process scale-up, his conclusions translate effectively to the manufacturing processes for drug dosage forms and delivery systems. In effect, scale-up issues need to be addressed jointly by pharmaceutical engineers and formulators as soon as a dosage form or delivery system appears to be commercially viable[15]. Scale-up studies should not be relegated to the final stages of product development, whether initiated at the behest of the FDA (to meet regulatory requirements) or marketing and sales divisions (to meet marketing directives or sales quotas). The worst scenario would entail the delay of scale-up studies until after commercial distribution (to accommodate unexpected

market demands). Modular scale-up involves the scale-up of individual components or unit operations of a manufacturing process. The interactions among these individual operations comprise the potential scale-up problem, i.e., the inability to achieve sameness when the process is conducted on a different scale. When the physical or physicochemical properties of system components are known, the scalability of some unit operations may be predictable. Known scale-up correlations thus may allow scale-up when laboratory or pilot plant experience is minimal. The fundamental approach to process scaling involves mathematical modeling of the manufacturing process and experimental validation of the model at different scale-up ratios. In a paper on fluid dynamics in bubble column reactors, Lubbert and coworkers noted: "Until very recently fluid dynamical models of multiphase reactors were considered intractable. This situation is rapidly changing with the development of high-performance computers. Today's workstations allow new approaches to modeling. Insofar as the scale-up of pharmaceutical liquids (especially disperse systems) and semisolids is concerned, virtually no guidelines or models for scale-up have generally been available that have stood the test of time. Uhl and Von Essen, referring to the variety of rules of thumb, calculation methods, and extrapolation procedures in the literature, state, "Unfortunately, the prodigious literature and attributions to the subject [of scale-up] seemed to have served more to confound. Some allusions are specious, most rules are extremely limited in application, examples give too little data and limited analysis." Not surprisingly, then, the trial-and-error method is the one most often employed by formulators. As a result, serendipity and practical experience continue to play large roles in the successful pursuit of the scalable process[16].

## Principles of Similarity

Irrespective of the approach taken to scale-up, the scaling of unit operations and manufacturing processes requires a thorough appreciation of the principles of similarity. "Process similarity is achieved between two processes when they accomplish the same process objectives by the same mechanisms and produce the same product to the required specifications." Johnstone and Thring stress the importance of four types of similarity in effective process translation: (a) geometric similarity, (b) mechanical (static, kinematic, and dynamic) similarity, (c) thermal similarity, and (d) chemical similarity. Each of these similarities presupposes the attainment of the other similarities. In actuality, approximations of similarity are often necessary due to departures from ideality (e.g., differences in surface roughness, variations in temperature gradients, changes in mechanism)[17]. When such departures from ideality are not negligible, a correction of some kind has to be applied when scaling up or down: These scale effects must be determined before scaling of a unit operation or a manufacturing process can be pursued. It should be recognized that scale-up of multiphase systems, based on similarity, is often unsuccessful, since only one variable can be controlled at a time, i.e., at each scaleup level. Nonetheless, valuable mechanistic insights into unit operations can be achieved through similarity analyses[18].

## Mechanical Similarity

The application of force to a stationary or moving system can be described instatic, kinematic, or dynamic terms that define the mechanical similarity of processing equipment and the solids or liquids within their confines. Static similarity relates the deformation under constant stress of one body or structure to that of another; it exists when geometric similarity is maintained even as elastic or plastic deformation of stressed structural components occurs[19]. In contrast, kinematic similarity encompasses the additional dimension of time, while dynamic similarity involves the forces (e.g., pressure, gravitational, centrifugal) that accelerate or retard moving masses in dynamic systems. The inclusion of time as another dimension necessitates the

consideration of corresponding times, t_ and t, for which the time scale ratio **t,** defined as **t** _ t_/t, is a constant. Corresponding particles in disperse systems are geometrically similar particles that are centered on corresponding points at corresponding times. If two geometrically similar fluid systems are kinematically similar, their corresponding particles will trace out geometrically similar paths in corresponding intervals of time. Thus, their flow patterns will be geometrically similar and heat- or mass transfer rates in the two systems will be related to one another. Pharmaceutical engineers may prefer to characterize disperse system[20-25].

### Thermal Similarity

Heat flow, whether by radiation, conduction, convection, or the bulk transfer ofmatter, introduces temperature as another variable. Thus, for systems in motion, thermal similarity requires kinematic similarity[26-28].

### Chemical Similarity

This similarity state is concerned with the variation in chemical composition from point to point as a function of time. Chemical similarity, i.e., the existence of comparable concentration gradients, is dependent upon both thermal and kinematic similarity[29].

## Process Scale-up

### A. Regulatory

Scale-up is normally identified with an incremental increase in batch size until a desired level of production is obtained. In 1991, the American Association of Pharmaceutical Scientists (AAPS), along with the U.S. FDA held, a workshop on scale-up. Several speakers presented scale-up issues from the industrial and regulatory perspectives. For example, Shangraw divided scale-up problems in two general categories: those related to raw materials or formulation and those related to processing equipment[30]. He also indicated that it is essential to ascertain whether or not changes in raw materials have occurred before one looks at processing/equipment changes as a source of any problem[30-34].

### B. Scale-Up and Equipment Design

The scale-up from laboratory equipment to production-size units is dependent on equipment design, which may or may not have been scalable as far as its selected dimensional features or components is concerned. The importance of scalability is well understood and accepted by the manufacturers of fluid bed processors. Various sizes in their product line are logically designated and manufactured. Air flow in the fluid bed process is a critical parameter. The design and selection of the processor is very important for the laboratory and the production unit. Because air flow is one of the components of the drying capacity of a fluid bed system, the ratio of air volume per kg or liter of the product is very critical to achieve scale up that is linear. The other critical design feature is the cross-sectional area of the product container and how it has been designed throughout the various sizes that a manufacturer supplies. The relationship between various sizes of the process containers can be utilized to calculate the scale-up of binder spray rate; if the cross-sectional area is designed linearly, then the spray rate scale-up can be linear[35-36].

### C. Scale-Up and Process Factors

The fluid bed agglomeration process is a combination of three steps: dry mixing, spray agglomeration, and drying to a desired moisture level. These process steps are equally important. But the quality of the granules is really determined during the spraying stage, the process where constant building of granules and evaporation of binder solvent is taking place. Granule size is directly proportional to the bed humidity during granulation; hence, control of this humidity during scale-up is essential. Gore et al. studied the factors affecting the fluid bed process during scale-up.

The authors found that the processing factors that most affected granule characteristics were process-air temperature, height of the spray nozzle from the bed, rate of binder addition, and degree of atomization of the binder liquid. The atomizing air pressure and the wetness of the bed are two of the most important elements of fluid bed granulation. A higher atomizing air pressure yields a finer droplet of binder solution. Therefore granule growth, as described earlier in this section, will be affected by the atomizing air pressure. A major factor that must be considered during the scale-up of a fluid bed granulation process is maintaining the same droplet size of the binder for ensuring successful scale-up. A more recent study confirmed the influence of the spray nozzle setup parameters and the drying capacity of the air. The study concluded that more attention should be given[37-38].

## II. CONCLUSION

Scale-up is normally identified with an incremental increase in batch size until a desired level of production is obtained. Scale-up is generally process of increasing the batch size. Scale-up of a process can also be viewed as a procedure for applying the same process to different output volumes. There is a subtle difference between these two definitions: batch size enlargement does not always translate into a size increase of the processing volume. In mixing applications, scale-up is indeed concerned with increasing the linear dimensions from the laboratory to the plant size. On the other hand, processes exist (e.g., tableting) for which “scale-up” simply means enlarging the output by increasing the speed. To complete the picture, one should point out special procedures (especially in biotechnology) in which an increase of the scale is counterproductive and “scale-down” is required to improve the quality of the product.

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