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Review Article

Scale-Up Factors in the Development and Commercial Execution of Oral Solid Dosage Forms: A Current Industry Perspective

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Abstract

In the pharmaceutical industry, a major challenge is ensuring consistent quality of finished products as the batch scale shifts from laboratory to pilot to commercial levels. This review article aims to provide insights into the current industry practices and understanding of scale-up calculations and factors involved in the production of oral solid dosage forms. Pharmaceutical manufacturing encompasses various unit operations for oral solid dosage forms, including blending, wet granulation, dry granulation via roller compaction, milling, compression, and coating processes such as Wurster and film coating. Each unit operation's parameters significantly influence the final product's quality. As batch sizes increase, it becomes crucial to control various process parameters strategically to maintain product consistency. This article discusses the application of scale-up and scale-down calculations throughout different stages of unit operations, highlights the importance of scale-up factors in technology transfer from pilot to commercial scales, and reviews the current methodologies and industry perspectives on scale-up practices.

Keywords: *Scale-up, Pharmaceutical industry, Oral solid dosage forms, Granulation, Compression, Film coating*

Introduction

Oral solid dosage forms are final drug products designed to be ingested orally. Once swallowed, these forms dissolve in the gastrointestinal tract and the active ingredients are absorbed into the bloodstream. Examples of oral solid dosage forms include powders, granules, tablets, capsules, soft gels, gummies, dispersible films, and pills. These dosage forms are preferred for several reasons: they are relatively easy to administer, they can be clearly distinguished from one another, and their manufacturing processes are well-established and understood. Among oral solid dosage forms, tablets and capsules are the most common. Both consist of an active pharmaceutical ingredient (API), also known as the drug substance, along with various excipients. The manufacturing process for these dosage forms involves several unit operations, including blending, wet granulation (using a rapid mixer granulator or fluid bed processor), dry granulation (via roller compaction), milling, compression, Wurster coating, and film coating [1,2].During the early stages of drug product development, formulations and processes are created using active pharmaceutical ingredients (APIs) and excipients to ensure the quality, safety, and efficacy of the final drug products at the laboratory scale [3]. Once this formulation is established, the process is scaled up from the laboratory to pilot and eventually to commercial scales [4,5]. Throughout this technology transfer, the laboratory-scale formulation is generally finalized and remains unchanged, while process parameters are adjusted. For instance, as the scale of the granulation container increases, both the powder weight and the sizes of components like the impeller and chopper, as well as operational parameters, may need adjustment. These changes can impact the quality of the finished product [6]. Successful scale-up relies on a thorough understanding of the process parameters and the ability to adjust them appropriately to maintain the same quality observed at the laboratory scale.

Successful scale-up of a manufacturing process hinges on a deep understanding of the fundamental principles and insights into each unit operation, which are derived from mechanical insights into the process. The Food and Drug Administration (FDA) has introduced the Quality by Design (QbD) approach to facilitate the efficient and timely production of high-quality pharmaceutical products [7,8]. According to the International Conference on Harmonisation (ICH) guidelines specifically ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System) the scale-up process should be conducted to ensure product quality in alignment with the QbD principles. To meet these regulatory requirements, it is essential to establish methods for reducing variability during scale-up through a systematic understanding of the manufacturing process and the application of the QbD approach [9]. This review examines the application of mathematical considerations in scale-up calculations and explores various methodologies used in scaling up different unit operations for oral solid dosage forms. It aims to provide a systematic strategy to ensure the quality of finished dosage forms in the pharmaceutical industry.

Methods

Scale Up Process Basic Understanding

Using scientific approaches and mathematical calculations for process scale-up or scale-down can significantly reduce the risk of failure, ensure regulatory compliance, and lower costs associated with trial batches. These calculations help to establish robust and realistic parameters for scaling up or down pharmaceutical formulations [10]. When scaling unit process parameters, key considerations include equipment size, shape, working principle, and associated parameters. According to process modeling theory, processes are deemed similar if they exhibit geometric, kinematic, or dynamic similarity.

Scale-Up Strategy for Oral Solid Dosage Forms

The manufacturing of oral solid dosage forms tablets and capsules involves several key unit operations such as blending, granulation, milling, tableting, Wurster coating and film coating. Each of these operations requires a carefully planned scale-up strategy to ensure product quality and process efficiency. Detailed overview of the scale-up strategy for each unit operation are discussed.

A) Blending/Mixing in Pharmaceutical Manufacturing

Blending is a critical unit operation in the manufacture of oral solid dosage forms (e.g., tablets and capsules). It ensures uniformity of the final product by mixing active pharmaceutical ingredients (APIs) with excipients. Equipment used in pharmaceutical blending unit operations are Double-Cone Blenders, Bin Blenders, Octagonal Blenders, V-Blenders and Cubic Blenders [11,12]. The blend should have a degree of homogeneity during blending to ensure the quality of solid dosage forms, such as tablets and capsules [13,14]. The blend homogeneity is influenced by several factors, such as material attributes (for example particle size distribution, particle shape, density, surface properties, particle cohesive strength) and process parameters (for example blender design, rotational speed, occupancy level, and blending time) [15]. These factors affect the agglomeration and segregation of the blend during the blending process, which affect the blend homogeneity. However, experiments with appropriate scale up calculations are sufficient to confirm changes in the agglomeration and segregation of the blend caused by these factors [16]. Scale up considerations and current industry practices in scale up calculations for blending unit operations are presented in Table 1a. Different types of blenders (Figure 1) such as Mass Blenders, Ribbon Blenders, V Cone Blenders, Double Cone Blender, Octagonal Blender, Drum Blender, Bin Blenders and Vertical Blenders, working principles, key factors and advantages are presented in Table 1b.

B) Granulation in Pharmaceutical Manufacturing

Granulation is a crucial process in the pharmaceutical industry, particularly in the manufacture of solid dosage forms like tablets and capsules. It involves the formation of granules from a mixture of powders, which can improve the properties of the final product. Purpose of Granulation is to improve flow properties, enhance compressibility, reduce dust and improve uniformity [17,18]. Currently pharmaceutical industry adapted different types of granulation methods such as

i). Dry Granulation

Involves compressing powders into slugs or sheets and then milling them into granules. This method is used when the API is sensitive to moisture or heat. The process includes roller compaction and slugging. Typically roller compactors are used in dry granulation process.

ii). Wet Granulation

Involves adding a liquid binder to the powder mixture, which forms a wet mass that is then dried and sized into granules. This method typically includes preparation of binder solution, granulation, drying and sizing. Typically high shear rapid mixer granulators are used for wet granulation.

iii). Semi-Wet Granulation

A combination of wet and dry process involves in this granulation techniques, where a small amount of liquid binder is used, and the granules are only partially dried. Typically low shear fluid bed granulators are used in semi-wet granulation process.

Table 1a: Process parameters, quality attributes, scale up considerations and industry practices for Blending unit operation.

Unit operation	Critical Process parameters	CQAs of Blend	Scale up considerations
Blending/Mixing	1. Type of blender 2. Blender fill level (% occupancy) 3. Blender speed	Blend flow Blend uniformity Blend Assay Content Uniformity Tablet Assay	**Geometric similarity:** consistent fill ratio **Dynamic similarity:** Froude Number $Fr = \frac{RPM2 \times D}{G} = \frac{rpm2 \times d}{g}$ $RPM = rpm \times \sqrt{\frac{d}{D}}$ Where, d and D lineal dimensions of both scales **Kinematic similarity:** consistent number of revolutions
Current industry practices			
Reproducibility	Ensuring that scale-up processes match lab-scale results.		
Process Parameters	Adjustments in speed, time, and loading based on scale.		
Equipment Design	Considerations for different dynamics in larger vs. smaller equipment.		
Validation	Experimental confirmation that scaling does not affect homogeneity.		
Computational Modelling	Use of simulations to predict and adjust scale-up processes.		
Quality Control	Regular monitoring to ensure blend uniformity and product quality.		

Figure 1: Different types of Pilot/commercial scale model blenders used in pharmaceutical blending unit operation; 1. Mass Blenders; 2. Ribbon Blender; 3. V Cone Blenders; 4. Double Cone Blender; 5. Octagonal Blender; 6. Drum Blender; 7. Bin Blender; 8. Vertical Blender.

i). Dry Granulation - Scale-Up Consideration and Industry Perspectives

Dry granulation is an alternative to both direct compression and wet granulation, particularly suited for active pharmaceutical ingredients (APIs) that are sensitive to moisture, have poor flow properties, or possess other physicochemical characteristics that are incompatible with direct compression or wet granulation. Unlike wet granulation, dry granulation does not involve the use of solvents or additional heating, which can introduce challenges related to physical or chemical stability, especially in formulations with amorphous solid dispersions or those prone to chemical degradation. Dry granulation offers several advantages over wet granulation, including a simpler process that is particularly beneficial for APIs that are sensitive to heat or water [19]. The two most commonly used methods for dry granulation are roller compaction and slugging.

Table 1b: Different types of blenders in pharmaceuticals and its working principles, key factors and advantages.

S No	Blender Name	Working principle	Key Factors	Advantages
1	**Mass Blender**	It is a horizontal mixing shaker housed in a steel casing. It features a simple rotational mechanism that operates at a very slow speed. The shaker is equipped with various blades designed for mixing, which are enclosed in a sealed container. This container is slightly tilted to facilitate the unloading of materials.	The instrument is constructed with a transparent carbon casing, allowing for visibility of the mixing materials from the outside. Additionally, it includes safety switches that stop the machine when the lid is opened, ensuring safe operation.	The equipment is primarily used in tablet granulation. It is employed for mixing both wet and dry lumps and is effective for blending highly viscous substances.
2	**Ribbon Blender**	A Ribbon Blender is a light-duty, low-shear blending device that falls under the category of connective blenders. It is primarily used for mixing dry and pre-processed powders.	The blender features a U-shaped shell and a rotating helical double ribbon-shaped stirrer.	It is designed to mix dry solid lumps efficiently and can also handle the processing of large batches of wet mass.
3	**V Cone Blenders**	V Cone Blenders, also known as twin shell blenders, are a type of tumbling blender. They are typically tilted at angles between 70 and 90 degrees, which facilitates the movement and blending of particles.	The distinctive 'V' shape of the blender promotes effective powder mixing, ensuring uniformity of granules, making it particularly well-suited for pharmaceutical applications.	**Ease of Use:** Simple operation and effective blending. **Space Efficiency:** Requires less installation space. **Cleanliness:** Easy to clean. **Manual Rotation:** Can be rotated manually for added convenience.
4	**Double Cone Blender**	A Double Cone Blender features two cone-shaped shells mounted on a cylindrical support. As a type of tumbling blender, it has its axis of rotation positioned at a 90° angle to the axis of the conical shells, which are arranged in a slanted orientation.	**Effective Mixing:** The design, combined with inner blades, ensures effective mixing and distribution of powders. **Loading Capacity:** Granules should fill up to two-thirds of the blender's capacity to achieve adequate mixing. **Ports and Valves:** Equipped with feeding and discharge ports, each with a butterfly valve, facilitating smooth operation. **Automatic Timer:** Includes a timer on the control panel for precise and automated operation.	Double Cone Blenders are ideal for the dry blending of less viscous substances.
5	**Octagonal Blender**	The Octagonal Blender is designed with shells that have octagonal ends and a rectangular-shaped middle section. The ends are securely connected with firm stands.	This type of blender falls into the category of tumbling blenders	Specifically used for the slow and gentle mixing of dry granules.
6	**Drum Blender**	The Drum Blender consists of a drum-shaped container, similar in shape to a gallon jug. As a type of tumbling blender, it achieves material blending through the rotation of the drum.	This rotational movement allows for the mixing of materials within the drum effectively.	**Easy to Operate:** The straightforward design makes drum blenders easy to use and maintain. **Minimal Setup:** Requires minimal setup and adjustments compared to more complex blending systems.
7	**Bin Blenders**	The Bin Blender, also known as a free-fall blender or V blender, is categorized as a tumbling blender. It features a shell that can be rectangular, square, or V-shaped and is typically portable, allowing it to be moved on a stand.	**Shape and Portability:** The shell can be in various shapes (rectangular, square, or V) and is designed to be portable. **Function:** The blending is achieved through the tumbling action, which ensures thorough mixing of the substances.	Ideal for mixing grainy substances and blending materials contained inside capsules.
8	**Vertical Blenders**	The Vertical Blender features a tapered auger shape, making it narrower at the top and wider at the bottom. It falls under the category of connective blenders. The blender is constructed with a stainless steel body, ensuring durability and ease of cleaning.	**Shape:** Tapered auger, narrow at the top and large diameter at the bottom. **Construction:** Made of stainless steel.	Primarily used for blending dry granules and pellets.

Roller Compaction (RC) is a dry granulation technique that simultaneously densifies and agglomerates the powder blend to achieve increased packing density and granule size. In this process, the blend is compacted into ribbons using rollers, which are then milled into granules. Roller compaction reduces the risk of segregation, minimizes dust formation, and produces ribbons that can be processed into granules with improved flow properties. These granules are suitable for various subsequent processes, such as sachet filling, capsule filling, or tableting. Different scales and schematic representation of the roller compaction process is depicted in the Figure 2.

Scaling up of roller compaction involves utilizing traditional large-scale experimental designs to optimize the dry granulation process. This approach can be time-consuming and resource-intensive. To streamline scale-up and minimize the number of experiments, it is crucial to have a deep understanding of the process parameters and the attributes of both the ribbons and granules produced [20]. Key process parameters for roller compaction include roll gap, roll pressure, feed screw speed, roll speed, and roller shape. These parameters must be carefully adjusted to achieve the desired granulation outcomes [21]. The quality of the ribbon, which is the primary product of the roller compaction process, is assessed based on several attributes like Ribbon Density (an indicator of how compacted ribbon is), Ribbon Strength (reflects the mechanical strength of the ribbon), Ribbon Thickness (Affects the granule size and uniformity), Young's Modulus (Measures the ribbon's elasticity and rigidity), Ribbon Shape (Impacts the subsequent granule formation), and Moisture Content (Ensures the ribbon's stability and suitability for further processing). By focusing on these parameters and attributes, it is possible to optimize the roller compaction process effectively while reducing the need

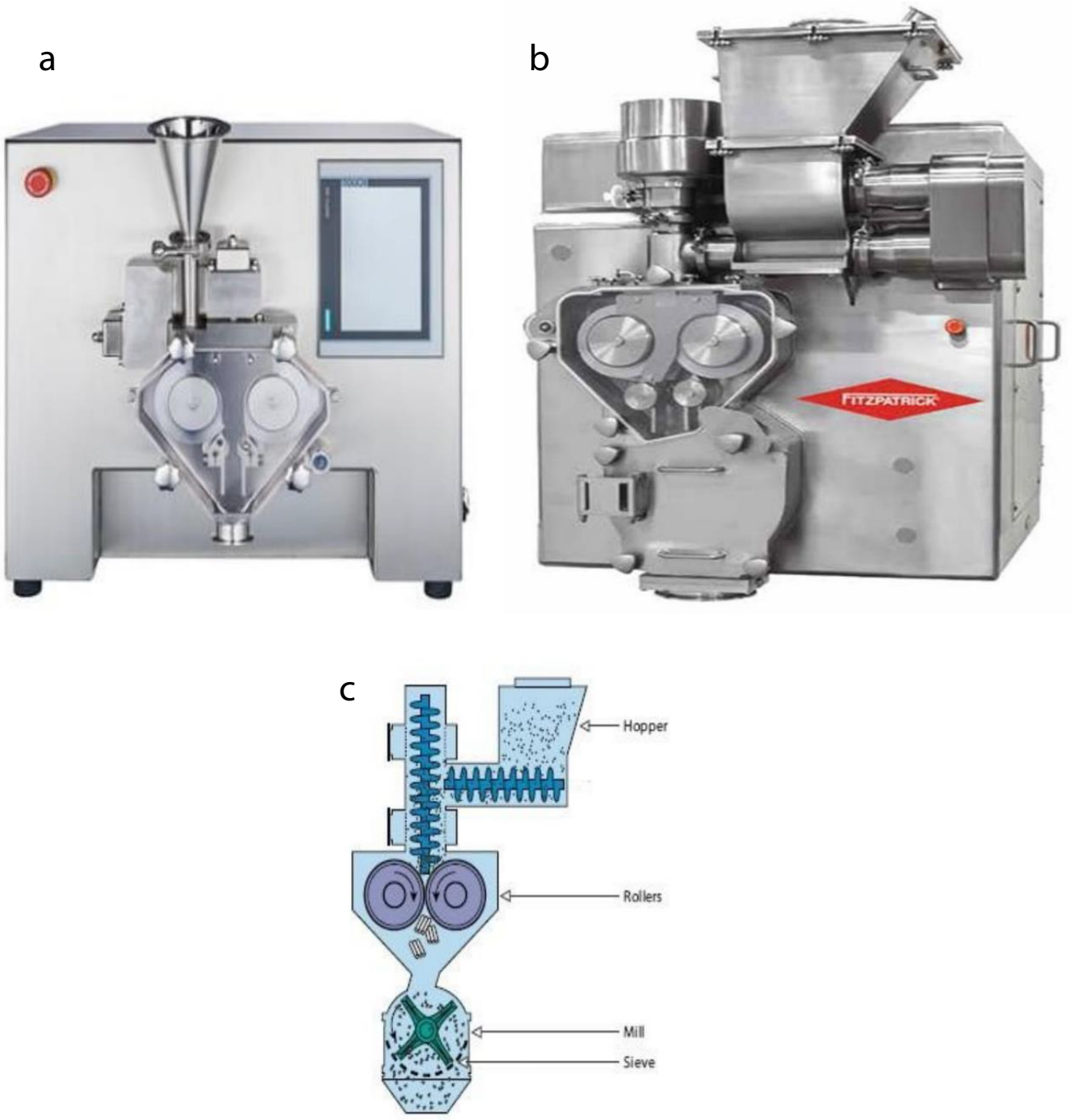

Figure 2: Different types of Roller compacters a) Lab scale model b) Pilot/Commercial Scale c) Schematic presentation of Roller Compactor.

for extensive experimentation. The rolling theory for granular solids developed by Johanson describes the pressure distribution along the rolls considering the physical characteristics of the powder and the equipment geometry. The dimensionless number frequently used in roller compaction is determined based on the Johanson theory [22]. Johanson proposed a model that predicts the density of ribbons made by roller compaction using the nip area and the volume between the roll gaps. Johanson proposed distinguishing two regions between the rolls, (i) a slip region where the roll speed is faster than the powder and there is only rearrangement of the particles and (ii) a nonslip region where the powder gets trapped between the rolls and becomes increasingly compacted until the gap. The transition from slip to nonslip region is defined by the so-called nip angle. In the nonslip region, it is assumed that the powder behaves as a solid body being deformed as the distance between the rolls narrows down to the gap. It is further assumed that the deformation has only one axial component such that it can be idealized as uniaxial compression. One source of discrepancy between the predictions of Johanson's

and Reynolds' model and the ribbon density measurements is the different compaction behaviour of the powder in the roller compactor compared to uniaxial compression tests [23,24] demonstrated that the roller compactor and a compaction simulator lead to different ribbon densities and built a model to account for that difference.

Rowe et al. extended Johanson's model and proposed a modified Bingham number (Bm*) that represented the ratio of yield point to yield stress as follows:

$$Bm^* = \frac{C_S}{\gamma_0 \rho_{true} \pi D^2 W} \frac{(SA_{roll})^{0.5}}{S} \frac{N_S}{N_R}$$

Where Cs is the screw speed constant, 0 is pre consolidation factor, ρtrue is true density, π is circumference of the roll circle, D is the roll diameter, W is roll width, SA roll is roll surface area, S is roll gap, NS is feed screw speed and NR is roll speed. Bm* is easy to determine because the input parameters of Bm*consist of those that can be generally measured in the compaction process. The model-predicted values and the actual test results from WP 120 Pharma and WP 200 Pharma (Alexander werk, Remscheid, Germany) models are shown. By maintaining Bm*, it was possible to obtain a consistent ribbon density between the two operating scales. It was suggested that Bm* can be effectively used for the development of roller compaction scale-up [25]. Case studies suggest that dimensionless numbers for the prediction of ribbon density in dry granulation processes can be used successfully during the Scale-up process (Table 2).

ii). Wet Granulation - Scale-Up Consideration and Industry Perspectives

Wet granulation is a key process in pharmaceutical manufacturing used to produce granules from powders by incorporating a liquid binder (Figure 3).

This process is crucial for ensuring that the final granules exhibit desirable properties such as uniformity, good flowability, and compressibility [26]. The choice of equipment for wet granulation includes high-shear Rapid mixer granulators (RMG) and low shear fluid bed granulators (FBG). RMG involves mixing powders with the binder in a high-shear environment. The impeller and chopper facilitate the formation of granules by applying mechanical forces. FBG involves spraying the binder solution onto the powder bed in a fluidized state. The fluidized bed aids in the uniform distribution of the binder and granule formation. Granulation Process involves the dry powders, including the active pharmaceutical ingredient (API) and excipients (e.g., fillers,disintegrants, lubricants), are blended to ensure a uniform distribution. The blended powders are loaded into the high-shear granulator's mixing bowl. The liquid binder (e.g., water, ethanol, or polymer solution) is sprayed onto the powder bed. This binder helps in forming granules by adhering powder particles together. The impeller rotates on a horizontal plane, creating a high-shear environment that facilitates mixing and initial granule formation. The chopper, rotating either vertically or horizontally, breaks up large lumps and ensures the uniform size of granules by cutting and mixing [27]. Granulation end point determined by the granules continue to grow as the binder is added until they reach the desired size and consistency. The process is typically monitored to ensure that granules are not over granulated or under-granulated. The process is carefully controlled by adjusting parameters such as binder addition rate, impeller speed, and chopper speed. A predefined endpoint, based on granule size or moisture content, is set to determine when the granulation is complete. Scaling up a Rapid Mixer Granulator (RMG) involves translating process parameters from a smaller, laboratory-scale unit to a larger, production-scale unit while maintaining the desired granule quality and consistency (Table 3a and 3b). This process requires careful consideration of equipment design, power requirements, and process parameters. Below tabulated are the guide to some common scale-up calculations for RMG.

iii). Semi-Wet Granulation - Scale-Up Consideration and Industry Perspectives

Fluid Bed Processor (FBP) for granulation operates by passing hot air at high pressure through a distribution plate located at the bottom of the container, creating a fluidized bed of solid particles. This fluidized state, where particles are suspended in the air, facilitates drying. Granulating liquid or coating solutions are sprayed onto these fluidized particles through a spray nozzle, followed by drying with hot air. The fluidized bed processor operates on the principle of fluidization, where a gas (typically air) is passed through a bed of solid particles at a velocity sufficient to suspend the particles in the gas stream. Air is introduced through a perforated plate or distributor at the bottom of

Table 2: Critical process parameters, quality attributes, scale up considerations and industry practices for Roller compaction unit operation.

Equipment Manufacturer	Critical Process parameters	CQAs of Blend	Scale up considerations
Mini-Pactor (Gerteis Maschinen + Process Engineering AG, Jona, Switzerland)	Roll forces Roll gaps Roller speed Specific compaction force	Ribbon density Maximum roll surface pressure	Johanson's model Reynolds model Johanson's model was modified overestimation of maximum roll surface pressure
Chilsonator IR-220, IR-520 (The Fitzpatrick Co., IL, USA)	Roll pressure Roll gaps VFS: vertical screw speed; HFS: horizontal screw speed	Ribbon density Ribbon solid fraction	Joint-Y partial least squares (JYPLS) Relationships between ribbon porosity, roll speed, roll pressure, screw speed, true density and roll diameter
WP 120 Pharma, WP 200 Pharma (Alexanderwerk, Remscheid, Germany)	Roll speed Roll pressure Screw speed Roll width Roll diameter	Ribbon density Ribbon porosity Ribbon attributes: ribbon density and thickness Granules QAs: flow, bulk density and particle size distribution	Maintain the ratio between the roller gap and the roller diameter Johanson's model Constant ratio of screw speed to roller speed Modified Johanson's model Modified Bingham number

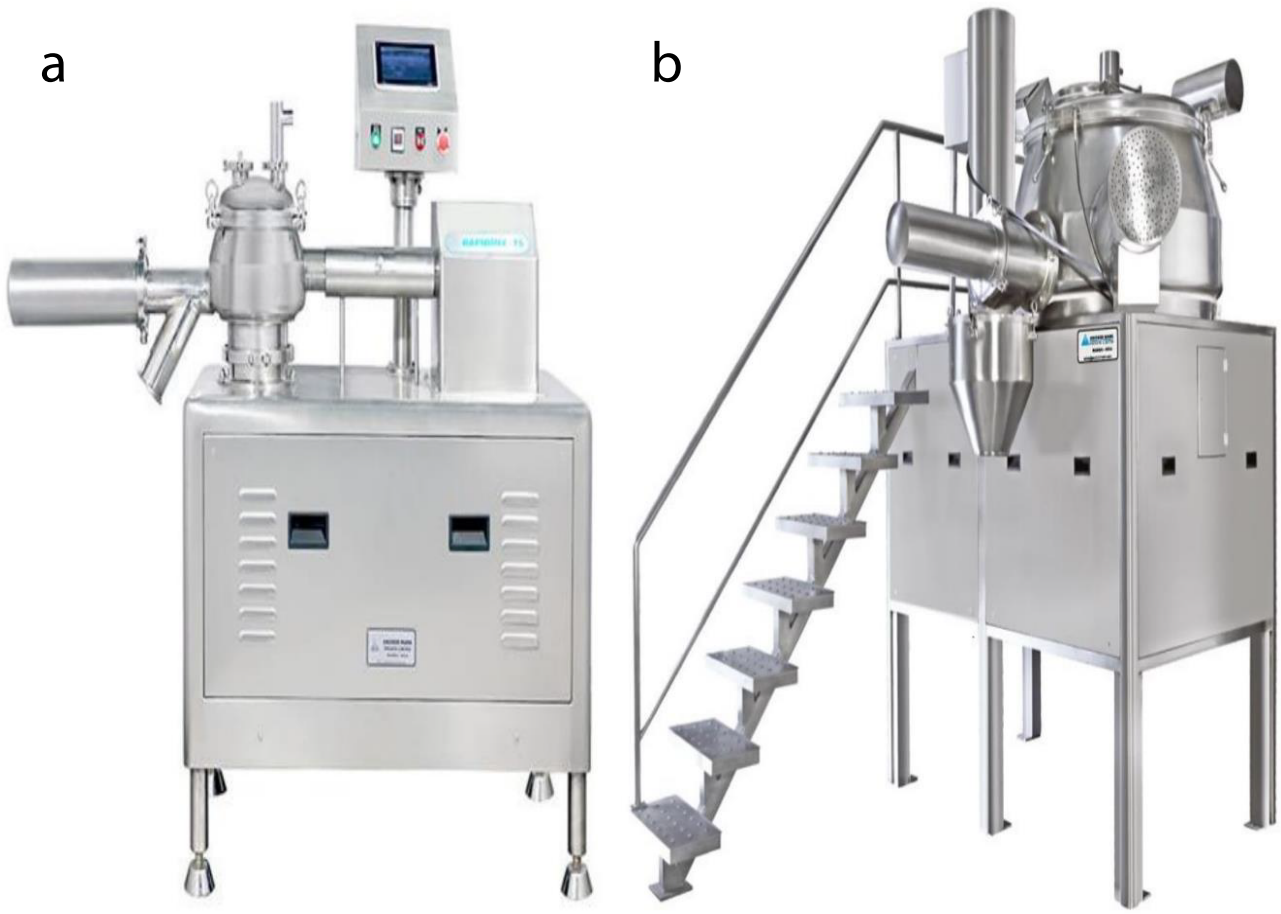

Figure 3: Different types of wet granulation process equipments used in pharmaceutical development a) Lab model rapid mixer granulator b) Pilot/Commercial scale rapid mixer granulator.

Table 3a: Critical process parameters, quality attributes, scale up considerations for RMG granulation unit operation.

Unit operation	Critical Process parameters	CQAs of Blend	Scale up considerations
Granulation	1. Binder spraying/addition rate 2. Chopper granulation rate (speed x time) 3. Impeller mixing rate (speed x time)	1. Granules flow 2. Blend Assay 3. Moisture content 4. Tablet Hardness and friability 5. Dissolution	Geometric similarity: Constant fill ratio (Height/diameter ratio) Dynamic similarity: Constant Newton's power number method and Impeller swept volume method Kinematic similarity: Constant impeller tip speed

Table 3b: Scale up considerations and industry practices for RMG granulation unit operation.

S No	Scale up Parameter	Description	Formulae
1	Volume Scale up ratio	The volume scaling ratio is calculated based on the ratio of the new batch size to the laboratory scale batch size. If VLab is the laboratory scale volume and Vnew is the new production scale volume Scale up ratio=Vnew/VLab	Scale up ratio=Vnew/VLab
2	Impeller and Chopper Power	The power required for mixing scales with the volume. The power requirement is often proportional to the cube of the scale-up ratio. Assuming Plab is the power required for the laboratory scale and Pnew is the power for the new scale $Pnew=Plab \times (Vnew/Vlab)^3$	$Pnew=Plab \times (Vnew/Vlab)^3$
3	Binder Ratio Volume of Binder	The binder to powder ratio should remain constant, but the total amount of binder will increase with batch size. If the binder ratio is known, calculate the volume of binder needed for the larger batch size Volume of Binder=Binder Ratio × Batch Size	Volume of Binder=Binder Ratio × Batch Size
4	Tip speed	The speed at which the edge of the impeller or chopper rotates relative to the center of the RMG. It is a function of the rotational speed of the impeller or chopper and the radius from the center of rotation to the tip. Tip Speed=Roller Speed × Radius or Tip Speed=π x diameter x RPM/t	Tip Speed=Roller Speed × Radius Or Tip Speed=π x diameter x RPM/t
5	Froude Number (Fr)	**Froude Number (Fr)** is a dimensionless number used in fluid dynamics and mixing processes to describe the relative importance of inertial forces compared to gravitational forces. $Fr=v^2/g.L$ v - tip speed of the impeller or chopper (m/s); g - acceleration due to gravity (approximately 9.81 m/s^2) L - characteristic length (e.g., diameter of the mixer) (m)	$Fr=v^2/g.L$

the bed, and as it flows upwards, it lifts the particles, making them behave like a fluid. During fluidization, various processes can be carried out: a binder solution or melt is sprayed onto the particles, causing them to agglomerate; hot air removes moisture from the particles; and a coating solution is applied, which is then dried. The air, now carrying moisture or coating material, exits through the top of the bed. Scaling up a FBP in the pharmaceutical industry involves several calculations and considerations to ensure that the process can be effectively transitioned from a laboratory or pilot scale to full-scale production [28,29]. The process must maintain product quality, efficiency, and compliance with regulatory standards. Here's a detailed guide on scale-up calculations and key factors for Fluidized Bed Processors. Scaling up a FBP involves maintaining similar fluidization conditions and process outcomes as in smaller scales. Key principles include maintaining the same fluidization regime, similar granulation or coating characteristics, and ensuring that drying or granulation efficiency scales proportionally (Table 4).

C) Compression in Pharmaceutical Manufacturing

Tablet compression is a critical process in pharmaceutical manufacturing that involves transforming powdered or granulated substances into solid tablets (Figure 4).

Compression is a critical and challenging step in tablet manufacturing. The way a powder blend is compressed directly impacts tablet hardness and friability, which are crucial for dosage form integrity and bioavailability. While the tablet press is essential for the compression process, the preparation of the powder blend is equally important to ensure it is suitable for compression. Understanding the physics and principles of the compression process is vital for managing these operations effectively. For high-dose or poorly compressible drugs, the study of compression becomes particularly important, especially when the relationship between compression force and tablet tensile strength is non-linear. A thorough grasp of compression dynamics also helps resolve many tableting issues, which often stem from various compression-related factors [30,31].

Compression Cycle

Understanding the different stages of the compression cycle is essential for comprehending how powder materials are compacted into tablets. It also provides valuable insights into the various formulation and compression variables that impact the quality of the finished tablet. Compression cycle is divided into following 4 phases: Pre-compression, Main-compression, Decompression and Ejection.

Pre-compression

As the name implies, pre-compression is the initial stage where a small force is applied to the powder bed to create partial compacts before the main compression. This is typically achieved using a pre-compression roller that is smaller than the main compression roller. However, the size of the pre-compression roller and the level of pre-compression force can vary based on the properties of the material being compressed. For instance, powders that are prone to brittle fracture may require a higher pre-compression force compared to the main compression force to achieve increased tablet hardness. In contrast, elastic powders need a gradual application of force to minimize elastic recovery and allow for stress relaxation. Optimal tablet formation is often achieved when the sizes of the main and pre-compression rollers and the forces applied are similar.

Table 4: Scale up considerations and industry practices for FBP granulation.

S No	Parameter	Description	Scale up consideration
1	Inlet Air Temperature and Dew Point	Inlet temperature and dew point should remain constant at each scale	Inlet temperature and dew point remain unchanged during scale up
2	Product Temperature	Product Temperature is a dependent variable that is influenced by inlet temperature, air volume, dew point and spray rate.	Product Temperature is a dependent variable that is influenced by: • Inlet temperature • Air volume • Dew point • Spray rate
3	Spray Rate	The spray rate needs to be scaled up to the same proportion as the air volume to maintain relative evaporation rates and moisture profiles.	Scale up factor for Spray Rate is as follows: $\mathbf{SR_2=SR_1AV_2/AV_1}$ Where: SR_2=Spray rate of Pilot Scale (g/min) AV_2=Air volume of Pilot Scale (CFM) SR_1=Spray rate of Lab Scale (g/min) AV_1=Air volume of Lab Scale (CFM)
4	Atomization Air Pressure	The atomization flow rate is the actual parameter that controls droplet size. Droplet size is inversely proportional to atomization air flow rate and directly proportional to spray rate.	Scale up factor for Atomization Air Volume (AAV) is as follows: $\mathbf{AAV_2=AAV_1SR_2/SR_1}$ Where: SR_2=Spray rate of Pilot Scale (g/min) AAV_2=Atomizing air volume of Pilot Scale (CFM) SR_1=Spray rate of Lab Scale (g/min) AAV_1=Atomizing air volume of Lab Scale (CFM)
5	Air volume	Air volume is scaled up using the cross sectional area of the bowl bottom screens. area of the bottom screens $A=\pi r^2$ Where: A=Bottom screen area (m^2) r=radius of bottom screen (m)	Scale up for Air volume is as follows: $AV_2=AV_1 A_1/A_2$ Where: A_1=Bottom screen area of Lab scale (m^2) A_2=Bottom screen area of Pilot Scale (m^2) AV_1=Air volume of Lab Scale (cfm) A_2=Air volume of Pilot Scale (cfm)

Figure 4: Different types of compression machines used in pharmaceutical development a) Lab model Single Punch Tablet Press and b) Pilot/commercial Scale Single Rotary Tablet Press.

Main Compression

During the main compression phase, inter particulate bonds are formed through particle rearrangement, which is followed by particle fragmentation and/or deformation. For powders with viscoelastic properties, special attention to compression conditions is necessary, as these conditions significantly influence the material's compression behavior and the overall tableting process.

Decompression

After the compression phase, the tablet experiences elastic recovery, which introduces various stresses. If these stresses exceed the tablet's ability to withstand them, structural failures can occur. For instance, high rates and degrees of elastic recovery may lead to issues such as tablet capping or lamination. Brittle fractures can also occur if the tablet undergoes brittle fracture during decompression. To alleviate stress, plastic deformation, which is time-dependent, can occur. The rate of decompression also influences the potential for structural failure. Therefore, incorporating plastically deforming agents, such as PVP or MCC, is recommended to enhance the tablet's ability to handle these stresses.

Ejection

Ejection is the final stage of the compression cycle, involving the separation of the tablet from the die wall. During this phase, friction and shear forces between the tablet and the die wall generate heat, which can lead to further bond formation. To minimize issues such as capping or laminating, lubrication is often used, as it reduces ejection forces. Powders with smaller particle sizes typically require higher ejection forces to effectively remove the tablets from the die. Industry perspective is to overall understanding the theoretical aspects of compression helps in selecting the optimal compression conditions for a given tablet product and at the same time can avoid the potential tableting problems thus saving significant time and resources.

D) Wurster Coating in Pharmaceutical Manufacturing

The Wurster fluid bed coating technique is renowned for its versatility and efficiency in coating applications [32]. This method is distinguished by its rapid heat and mass transfer capabilities and its ability to maintain temperature uniformity. Unlike traditional fluidized bed coating, which uses a more straightforward approach, the Wurster method employs a nozzle located at the bottom of a cylindrical draft tube to spray the coating solution. Particles are circulated through this tube, periodically passing through the spraying zone where they encounter fine droplets of the coating solution. This circulation not only ensures thorough mixing but also provides precise control over particle movement and coating quality. Wurster Coating Process is extensively utilized in the pharmaceutical industry for coating powders and pellets. Wurster systems can handle batch sizes ranging from 100 grams to 800 kilograms. This process is ideal for coating particles as small as 100 μm up to tablets. The Wurster coating chamber is typically slightly conical and features a cylindrical partition about half the diameter of the chamber's bottom. At the base of the chamber, an Air Distribution Plate (ADP), also known as an orifice plate, is installed. The ADP is divided into two areas: the open region beneath the Wurster column, which allows for greater air volume and velocity, and the more restricted areas. As air flows upward through the ADP, particles move past a spray nozzle positioned centrally within the up-bed region of the ADP. This nozzle, which is a binary type, has two

ports: one for the coating liquid and one for atomized air. The nozzle creates a solid cone spray pattern with a spray angle of approximately 30-50°, which defines the coating zone. The region outside the cylindrical partition is referred to as the down-bed area. The choice of ADP is based on the size and density of the material being coated. The height of the column regulates the horizontal flow rate of the substrate into the coating zone. As the coating process progresses and the mass of the material increases, the column height is adjusted to maintain the desired pellet flow rate.

Scaling up the Wurster coating process involves increasing the equipment size to handle larger batch capacities, ranging from small lab-scale units to industrial-scale machines (Figure 5).

Larger systems require careful design to maintain consistent coating quality and process efficiency. Equipment dimensions, including the height and diameter of the coating chamber and the size of the Air Distribution Plate (ADP), must be scaled proportionally to ensure effective particle fluidization and coating (Table 5).

As batch size increases, maintaining optimal airflow dynamics becomes crucial. The airflow rate, velocity, and distribution must be adjusted to ensure uniform coating. Larger systems may require modifications to the ADP to accommodate increased air volume and maintain desired particle circulation and spray pattern. The configuration of spray nozzles needs to be scaled to match the increased batch size. Ensuring consistent liquid atomization and spray pattern is essential to achieve uniform coating thickness. In larger systems, multiple nozzles may be used to cover the expanded coating zone. Process parameters such as temperature, airflow, and coating solution viscosity must be carefully calibrated. Industry perspectives as scale-up introduces more variables, precise control of these parameters is necessary to maintain coating uniformity and avoid issues such as over or under coating. Scaling up involves adjustments in material handling to accommodate the larger volume and ensure smooth transfer and processing of the particles. This includes considerations for feeding systems, particle flow control, and uniform distribution within the coating chamber.

E) Film Coating in Pharmaceutical Manufacturing

Film coating is a widely used technique in pharmaceutical manufacturing to apply a thin layer of coating material onto tablets, and other dosage forms (Figure 6).

This coating process enhances the appearance, improves the stability, and controls the release of active ingredients in pharmaceutical products. Different film coating formulations can be used to achieve controlled or modified-release properties. This allows for the gradual release of the drug over time, improving therapeutic outcomes and patient compliance. Film coatings can improve the appearance of dosage forms, making them more appealing to patients. Additionally, they can mask the taste of unpleasant drugs, making oral administration more acceptable [33]. Choosing the wrong film coating equipment or using subpar technology can lead to significant film coating defects. These defects can greatly affect the quality, efficacy, and appearance of pharmaceutical products. It's essential to identify and address these issues to maintain product integrity and ensure compliance. Below is an overview of common film coating defects and their potential causes, as detailed in Table 6a. Scaling up of film coating processes in pharmaceutical manufacturing involves several important considerations to ensure that the coating process remains effective and consistent as production volumes increase Table 6b.

Figure 5: Different types of Wurster coating equipments used in pharmaceutical development a) Lab model b) Pilot/Commercial scale model.

Table 5: Scale up considerations and industry practices for Wurster coating.

S No	Parameter	Description	Scale up consideration
1	Spray Rate	The spray rate needs to be scaled up to the same proportion as the air volume to maintain relative evaporation rates and moisture profiles.	Scale up factor for Spray Rate is as follows: $\mathbf{SR_2=SR_1AV_2/AV_1}$ Where: SR_2=Spray rate of Pilot Scale (g/min) AV_2=Air volume of Pilot Scale (CFM) SR_1=Spray rate of Lab Scale (g/min) AV_1=Air volume of Lab Scale (CFM)
2	Atomization Air Pressure	The atomization flow rate is the actual parameter that controls droplet size. Droplet size is inversely proportional to atomization air flow rate and directly proportional to spray rate.	Scale up factor for Atomization Air Volume (AAV) is as follows: $\mathbf{AAV_2=AAV_1SR_2/SR_1}$ Where: SR_2=Spray rate of Pilot Scale (g/min) AAV_2=Atomizing air volume of Pilot Scale (CFM) SR_1=Spray rate of Lab Scale (g/min) AAV_1=Atomizing air volume of Lab Scale (CFM)
3	Air volume	Air volume is scaled up using the cross sectional area of the bowl bottom screens. area of the bottom screens $A=\pi r^2$ Where: A=Bottom screen area (m^2) r=radius of bottom screen (m)	Scale up for Air volume is as follows: $AV_2=AV_1 A_1/A_2$ Where: A_1=Bottom screen area of Lab scale (m^2) A_2=Bottom screen area of Pilot Scale (m^2) AV_1=Air volume of Lab Scale (cfm) A_2=Air volume of Pilot Scale (cfm)
4	Inlet Air Temperature and Dew Point	Inlet temperature and dew point should remain constant at each scale	Inlet temperature and dew point remain unchanged during scale up
5	Product Temperature	Product Temperature is a dependent variable that is influenced by inlet temperature, air volume, dew point and spray rate.	Product Temperature is a dependent variable that is influenced by: • Inlet temperature • Air volume • Dew point • Spray rate

Figure 6: Different types of Film coating equipment used in pharmaceutical development a) Lab model and b) Pilot/commercial Scale film coating equipment.

Current Industry Persepctives

Current industry perspectives on scale-up calculations emphasize a comprehensive understanding of both the scientific and operational aspects of production. By leveraging the scale up calculations, advanced methodologies such as Design of Expert (DoE) and quality by design (QbD), along with a keen focus on cost, equipment selection, and regulatory compliance, pharmaceutical companies can navigate the complexities of scaling up oral solid dosage forms effectively. Adapting to technological advancements and maintaining a proactive approach to risk management will be crucial for success in an increasingly competitive landscape.

Table 6a: Pharmaceutical film coating defects, route cause and remedial action.

Film coating defect	Definition	Possible root cause	Remedy
Orange Peel Effect	The surface of the coated tablet appears rough or dimpled, resembling the texture of an orange peel	High Viscosity: Coating solution too thick. Improper Atomization: Spray nozzles not functioning properly. Inadequate Drying: Insufficient drying or high humidity during the process.	Adjust Viscosity: Dilute the coating solution to achieve the right viscosity. Optimize Spray System: Ensure proper nozzle maintenance and spray pattern adjustment. Control Drying Conditions: Maintain appropriate humidity and temperature during drying.
Cracking	The film coating develops cracks or splits, which may affect the integrity of the tablet.	Overdrying: Excessive drying leading to film brittleness. Inappropriate Coating Thickness: Coating too thick or too thin. High Solvent Evaporation Rates: Fast evaporation leading to stress on the film.	Adjust Drying Time: Reduce drying time or temperature to prevent over-drying. Optimize Coating Thickness: Adjust application to ensure uniform coating. Control Solvent Rates: Modify solvent evaporation rates by adjusting the formulation or drying conditions
Peeling or Lifting	The coating film starts to peel off or lift away from the tablet surface.	Poor Adhesion: Inadequate bonding between the coating and tablet core. Excessive Moisture: Coating application in high humidity conditions. Incompatible Coating Formulation: Inappropriate formulation for the core material.	Improve Adhesion: Use bonding agents or adjust formulation to enhance adhesion. Control Humidity: Ensure proper environmental conditions during coating application. Verify Formulation Compatibility: Adjust coating formulation to better suit the tablet core material.
Color Variations	Uneven color distribution or streaks in the coating.	Inconsistent Mixing: Poorly mixed coating solution. Inconsistent Application: Variations in spray pattern or application rate. Quality of Colorants: Variability in colorant quality or concentration.	Ensure Thorough Mixing: Mix coating solution thoroughly before application. Optimize Application Technique: Adjust spray settings and ensure uniform application. Use Consistent Colorants: Verify colorant quality and consistency.
Shiner or Gloss Defects	Areas of excessive gloss or shininess on the coating.	Over-application of Gloss Agents: Excessive use of gloss-enhancing agents. Uneven Drying: Inconsistent drying leading to localized gloss variations.	Adjust Gloss Agents: Reduce the concentration of gloss-enhancing agents. Control Drying Conditions: Ensure uniform drying conditions to prevent gloss variation.
Bubbles or Blistering	Formation of bubbles or blisters on the coating surface.	Air Entrapment: Air bubbles trapped in the coating solution. Inadequate Drying: Insufficient drying causing gas bubbles to form. High Coating Solution Viscosity: Thick solution leading to poor film formation.	Remove Air Bubbles: Degas the coating solution before application. Optimize Drying: Adjust drying conditions to ensure complete solvent evaporation. Adjust Solution Viscosity: Modify the viscosity to improve coating application.
Chalking	The coating appears powdery or chalky.	Inadequate Film Formation: Poor film formation or incomplete drying. High Polymer Content: Excessive polymer concentration in the coating solution.	Ensure Proper Film Formation: Adjust formulation and drying conditions for optimal film formation. Reduce Polymer Concentration: Modify the polymer content to avoid excess chalking.
Surface Crystallization	Crystals form on the coating surface	Solvent Issues: High solvent evaporation rates or incompatible solvents. Improper Drying Conditions: Uneven drying leading to crystallization.	Adjust Solvent Usage: Modify solvent evaporation rates and ensure compatibility. Control Drying Conditions: Maintain consistent drying conditions to prevent crystallization.
Residue or Deposits	Residual coating material or deposits on the tablets.	Excessive Coating Solution: Over-application of coating. Inadequate Drying: Incomplete drying leading to residue.	Control Application Amount: Apply coating in appropriate quantities. Improve Drying: Ensure thorough and complete drying to prevent residue formation.
Streaking or Uneven Coating	Visible streaks or uneven application of the coating.	Inconsistent Spray Pattern: Issues with spray nozzle or application technique. Variable Pan Speed: Inconsistent rotation speed of the coating pan. Improper Formulation: Inadequate formulation leading to uneven coating.	Maintain Spray Equipment: Ensure spray nozzles are functioning correctly and evenly. Optimize Pan Speed: Adjust the rotation speed to achieve a uniform coating. Verify Formulation: Ensure formulation is well-suited for even coating application.

Table 6b: Scale up considerations and industry practices for Film coating.

S No	Parameter	Description	Scale up consideration
1	Pan load	Pan load at pilot scale shall be kept similar to lab scale and can be calculated based on the Brim volume of coating pan.	Scale up factor for Spray Rate is as follows: $M_2=M_1/V_1*V_2$ Where: M_2 - Pan Load of Pilot Scale (Kg) V_2 - Brim volume of Pilot Scale (Lit.) M_1 - Pan Load of Lab Scale (Kg) V_1 - Brim volume of Lab Scale (Lit.)
2	Pan speed	Pan speed at pilot scale shall be calculated based on the pan radius of coating pan. Preferably same coating pan design gives most appropriate scale up results.	Scale up factor for Spray Rate is as follows: $\omega_2=(\omega_1^{2}*R_1/R_2)^{\wedge 1/2}$ Where: ω_2 . Pan speed of Pilot Scale (rpm) R_2 - Pan radius of Pilot Scale (inch) ω_1 . Pan speed of Lab Scale (rpm) R_1 - Pan radius of Lab Scale (inch)
3	Spray Rate	The spray rate needs to be scaled up to the same proportion as the air volume to maintain relative evaporation rates and moisture profiles.	Scale up factor for Spray Rate is as follows: $SR_2=SR_1*a_1/a_2*M_2/M_1$ Where: SR_2=Spray rate of Pilot Scale (g/min) M_2 - Pan Load of Pilot Scale (Kg) a_2=spray area of of Pilot Scale (inch) SR_1=Spray rate of Lab Scale (g/min) M_1 - Pan Load of Lab Scale (Kg) a_1=spray area of Lab Scale (inch)

4	Inlet air flow	Ensure that the inlet airflow is distributed evenly throughout the coating pan. Proper air distribution helps in achieving consistent coating across all tablets.	Scale up factor for inlet air flow is as follows: $q_2=q_1/r_1*r_2$ where: q_2 – inlet air flow of Pilot Scale (CFM) r_2 – spray rate of pilot scale (g/min.) q_1 – inlet air flow of Lab Scale (CFM) r_1 – spray rate of Lab scale (g/min.)

Conclusion

The scale-up of oral solid dosage forms (OSDFs) is a critical phase in pharmaceutical development that directly influences product quality, regulatory compliance, and market success. The successful scale-up of OSDFs is a multifaceted challenge that requires strategic planning and execution. By focusing on these critical factors integrated processes, quality assurance, economic considerations, regulatory compliance, technological advancements, risk management, and continuous improvement pharmaceutical industries can enhance their chances of delivering high-quality products to the market. As the industry evolves, maintaining a forward-thinking approach will be essential for navigating complexities and ensuring sustainable success in a competitive landscape.

Conflicts of Interest

The authors declare no conflict of interest

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