Flexible Systems for Evolving Demands:

OSD Granulation in Modern Pharmaceutical Manufacturing

Expert Insights

Sponsored by

DIOSNA

WILEY

Contents

Introduction

In the realm of pharmaceutical manufacturing, the intricate process of converting drug compounds into oral solid dosage (OSD) forms is a cornerstone of the industry. At the heart of this transformation is granulation, a pivotal step that significantly influences the quality and characteristics of the final product. Granulation involves the agglomeration of fine drug particles into larger, more cohesive granules, enhancing flowability, compressibility, and ultimately, the effectiveness of the medication.

Currently, the industry grapples with the challenge of evolving production demands, requiring pharmaceutical plants to adapt rapidly to changing quantities and diverse product specifications. To meet these demands, granulation processes are undergoing a paradigm shift, necessitating flexible and efficient manufacturing systems. This involves a careful balance of parameters such as binder concentration, spray rate, and batch size in traditional granulation methods. As pharmaceutical manufacturers navigate this landscape, the quest for innovation in granulation processes becomes integral to achieving optimal product properties and ensuring the industry's capacity to meet evolving healthcare needs.

This whitepaper begins with a study on OSD manufacturing. Highlighting the importance of well-thought-out scale-up, the paper advocates a modular design for laboratory and pilot plants, enabling tool-free module exchange for efficient machine changeovers. Emphasizing Rapid Change (RC) capabilities between different bowl and batch sizes, the whitepaper underscores the significance of fast and safe changeovers in pharmaceutical plants. Using granulation as a practical example, it demonstrates how flexibility in production systems, particularly in wet granulation and fluidized bed drying, contributes to optimizing solid dosage form characteristics.

Next, a study on tangential-spray techniques in fluidized-bed granulation is provided. Tangential-spray offers benefits over top-spray, facilitating higher spraying rates, shorter processing times, and improved drying efficiency. Factors like nozzle position, pressure, and formulation composition significantly impact the granulation process, emphasizing the need for careful consideration in both apparatus technology and formulation for stable processes and optimal results. This study provides comprehensive insights into the advantages of tangential-spray granulation, highlighting the importance of considering both apparatus technology and formulation intricacies for achieving stable granulation processes in pharmaceutical production.

Overall, pharmaceutical manufacturing revolves around converting drug compounds into OSD forms through granulation. As the industry grapples with evolving demands, this whitepaper underscores the critical role of scale-up and modular design, showcasing their importance in optimizing granulation processes to enhance medication effectiveness and meet healthcare needs. This eBook also includes a further reading section highlighting relevant academic papers in fluidized-bed granulation, providing readers with additional resources for in-depth exploration of current research and advancements.

Through the methods and applications presented in this whitepaper, we hope to educate researchers on new technologies and techniques about the granulation process in OSD pharmaceuticals. To gain a deeper understanding of available options for improving your research, we encourage you to visit DIOSNA's Granulation Systems site.

Christene A. Smith, Ph.D.
Editor at Wiley

More flexibility for production of **solids**

Agile systems for the **granulation process**

DIOSNA

The world of OSD manufacturers has changed:

Smaller and changing quantities, more specialised and different products have to be produced more frequently in their plants in ever faster cycles. The granulation process therefore now places higher demands on flexibility of plant technology than it was just a few years ago.

- **Well-thought-out scale-up** clears the way for a **flexible concept**
- **Modular design** for laboratory and pilot plants
- **Tool-free exchange** of modules supports **fast machine changeover** to different processes
- **Adaption** of the machines **to different technologies**
- **Rapid Change (RC)** between different bowl and batch sizes are feasible

Fast and safe changeovers in pharmaceutical plants require, among other things, maximum efficiency in change-over time and short cleaning cycles. Production systems that can map different processes and whose modules can be changed without tools are advantageous here. Using granulation as an example, one can show how flexibility can be implemented in practice.

Wet granulation and subsequent drying in fluidised bed systems have become indispensable in the production of solid dosage forms. After all, the mixture is optimally prepared for subsequent tabletting or coating. Granulation is also crucial because it is here that the product properties such as density, particle size distribution, flowability, compressibility, surface properties and release profile are set. In addition to the actual active ingredient, fillers such as lactose, mannitol or cellulose, binders such as starch, hypromellose or povidone, as well as disintegrants can be incorporated. For the patient, this is noticeable in a higher bioavailability or better homogeneity even with low-dose mixtures.

Mapping of **different process steps**

For the granulation of pharmaceuticals, high-shear mixing and fluid bed processes are used, among others, because they are very flexible. This is reasoned by a very wide range of designs and configurations in which several process steps are integrated such as drying, granulation or coating. These can also run in parallel. For this purpose, the systems are equipped with exchangeable bowls that are used for different process steps, such as mixing, drying, coating or filming. Tool-free changeover of the modules, options for containment or the connection of automatic feeding or discharging, air conditioning or solvent operation facilitate the changeover to different products and batches.

Basis is laid in **Scale-up**

With flexible systems, it is possible to switch between different technologies at a relatively early stage of development.

However, this can only be achieved if there is a straightforward scale-up concept. This is a basis for a smooth transfer of the processes to production scale. The most important aspect here is the geometric similarity of all bowl designs. For example, in mixing bowls, the ratio between diameter and height must be identical in all sizes in order to enable mathematical calculation of process parameters (e.g. via Froude number). Nevertheless, not all physical parameters can be scaled up or down at will. The step in a scale-up of a plant should therefore be a maximum of 1:10, whether it is mixed granulation, a single-pot process or fluid bed granulation. If larger steps are chosen, the uncertainties increase. Thus, inaccuracies creep in again and again during scale-up, the effects of which, however, only become apparent later in production or in quality control. Modular systems help to avoid these inaccuracies, especially in the early stages of development. Transferred to mixer-granulators, this means: For product development in the laboratory, mixers with a volume of 0.25 to 10 litres have proven their worth. So if a 6-litre bowl is chosen here, a 60-litre volume is selected for scale-up, for example for the production of clinical samples. Production can then start with 600 litres.

Identical bowl geometries are indispensable for reliable scale-up. The same design of mixing bowls allows reliable transferability from laboratory scale to production. DIOSNA mixers have the same design from the smallest bowl (0,25 l) to the bowl for production (1250 l).

Increased flexibility with a wide range of batch sizes: Rapid Change of bowls illustrated by DIOSNA's fluid bed processor **CAP 10-80 RC**

P1-6 Pharmaceutical mixer

Good start in the **lab and pilot phase**

For the later process the basis is laid already at an early stage. The leap into later production is all the easier if the laboratory or pilot plants also resemble the later process plant. Here, laboratory plants in a modular design offer the possibility of trying out different products and technologies and adapting the bowl sizes accordingly. Machines that cover a wide range of processes accelera-te the workflows in this phase.

The MiniLab RC laboratory system from DIOSNA was specially designed for the work in research and develop-ment. It covers a wide range of processes from drying to powder, pellet or tablet coating and spray granula-tion. This high efficiency is achieved by the two-in-one solution with the drum coater and the fluidised-bed dryer. The changeover takes place within minutes via an assembly and storage rack. Powerful air, measurement and control technology is also integrated in the housing of the laboratory unit and can be used by both units. The advantages of using this unit lie in its high flexibility, as a large batch range is covered.

A big plus in flexibility is added by the wide range of integration options of other systems. The P 1-6 phar-maceutical mixer is the perfect complement for mixing processes. With flexible systems, it is possible to switch between different technologies at a relatively early stage of development.

One size larger is the MidiLab RC, a mobile, highly flexible unit with a likewise extremely wide range of applica-tions. Both the fluid bed and tablet coating module can be used. While the coating module allows film and sugar coating in three different drum sizes, the fluid bed module offers drying, top– and tangential–spray as well as Wurster coating in four different material bowls. Here again, the modules can be changed without tools.

MidiLab RC with fluid bed module

Flexible in the **choice of technology**

In the laboratory or pilot plants, the respective process can also be evaluated, i.e. whether, for example, a top– or a tangential–spray process should rather be used. A decisive step: after all, any change to the existing spray technology in the pharmaceutical industry must later be recorded by a revalidation and requalification process, which can sometimes be very time-consuming depending on the content of the master batch manufacturing protocol. Therefore, it is even more important that certain procedures can be established before the actual manufacturing process in the laboratory or pilot phase.

In order to show the challenges and the influencing parameters when changing the process, it is worth taking a closer look at the granulation process, here the example of the top/tangential–spray process in fluidized bed drying. Here, the powder particles are fluidized. The liquid or binder solution is finely sprayed so that bridges are built between the powder particles. There are therefore enough parameters that influence the process. This includes, for example, the inlet air tempe-rature. The higher this is, the finer the granule. And vice versa, a larger granule results. Increased humidity also causes larger granules, but also longer drying times.

The position of the spray nozzle is also important. If the nozzle is too close to the fluidized bed, coarser granules are obtained. If the position is too high, the binder will be dried before it reaches the powder particles (spray drying effect) and finer agglomerates will be produced.

Minilab RC with fluid bed dryer filter and topspray nozzle

These few examples already show that many parameters determine the success of a granulation process. It is therefore all the more important to know these precisely and to master them with flexible plant concepts already in the laboratory and pilot phase.

Author: Andre Duwendag, Process Technologist Pharma, DIOSNA Dierks & Söhne GmbH

Fluidized-bed granulation

Top-spray versus tangential-spray

Support for decision making

General requirements for the apparatus technology

Ideally, fluidized-bed processing systems should have a modular design so that they can be individually adapted to the specific requirements of a given application. The key assemblies include the fluidized-bed processor and the air handling unit.

The process air is directed from underneath through the distributor plate in order to fluidize the product. The tangential airflow from this unit ensures uniform product movement and effective energy utilization. This delivers homogeneous product quality in spraying processes. Before the process air leaves the system, it is purified via an integrated filtration system. Single-chamber, dual-chamber, and cartridge filter systems are available for this purpose.

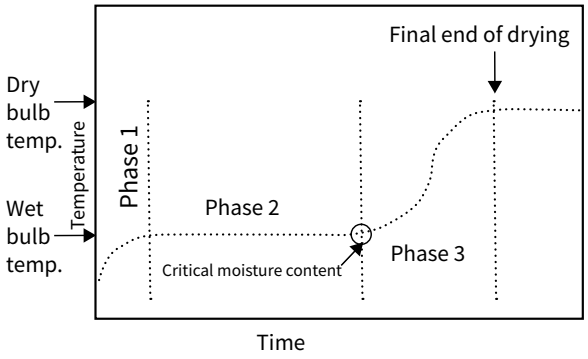
Depending on the application, suitable components and concepts are chosen for the downstream exhaust air treatment technology: static control filters, cleanable filtration systems, cycle operation with solvent recovery. The main focus is always on safeguarding the processes. Optimized airflow, efficient feeding and discharging concepts, as well as expertise in application engineering guarantee a high yield, fast processes, and reproducible quality of the end products.

In addition, there are also a number of other aspects that should also be considered or can play a significant role in the manufacturing process. For example, it is important that the apparatus is shock pressure resistant and that certified safety concepts are applied. Processes should take place in a way that is both reproducible and automated. Special containment rules apply in the case of highly active substances, in addition to which comprehensive cleaning concepts from WIP to CIP need to be incorporated. It goes without saying that an in-line quality control system, for example an integrated PAT system for humidity and particle size measurement, and compliance with pharmaceutical standards in accordance with GAMP 5, should be basic requirements.

Factors that influence the drying process

The basic physical principles of heat and mass transfer apply to the drying process. Heat is transmitted through convection onto the product in order to evaporate fluid, and mass is transmitted as vapor to the surrounding gas.

Phase 1	The material heats up from ambient temperature to the wet-bulb temperature of the air in the dryer.
Phase 2	The temperature is maintained until the moisture content of the granules is reduced to the critical value.
Phase 3	The material holds no free surface water, and the temperature starts to rise further at the end of drying (dry-bulb temperature).



Parikh, D. [2017] . How to optimize fluid bed processing tech nology. Elsevier Inc, London.

Key **comparison parameters**

In a case study in the DIOLab, DIOSNAs pharmaceutical technology center, the differentgranulationmethods were investigated in detail. The purpose of this study was to perform a comparative evaluation of the top-spray and tangential-spray granulation methods for the formulation of lactose-based granulates. The trials were carried out on the DIOSNA laboratory fluidized-bed processor Minilab RC with a 5-liter bowl. 960 g lactose (GranuLac 70, Meggle AG) and 20 g HPMC 606 (TYLOPUR, Shin-Etsu), dissolved in 480 g water, were used as the starting materials.

Trials using the tangential-spraying method

In the trials using the tangential-spraying method, the following parameters were investigated among others:

- Optimum nozzle adjustment and position
- Optimum spraying pressure
- Maximum spraying rate

Afterwards the following parameters were tested on the granulates produced:

- Particle size distribution (classic sieve analysis)
- Bulk density and tapped density
- Flow behavior (Hausner factor)
- Granulate form (microscope)

The first step was to look at the nozzle position. In the process, the optional second spray nozzle in the 5-liter bowl offered no advantages; one spray nozzle is sufficient for a successful process. However, an optional second nozzle can be used e.g. to spray in an active ingredient solution at the same time. In principle there were no differences in the particle size distribution regardless of the position chosen for the nozzle.

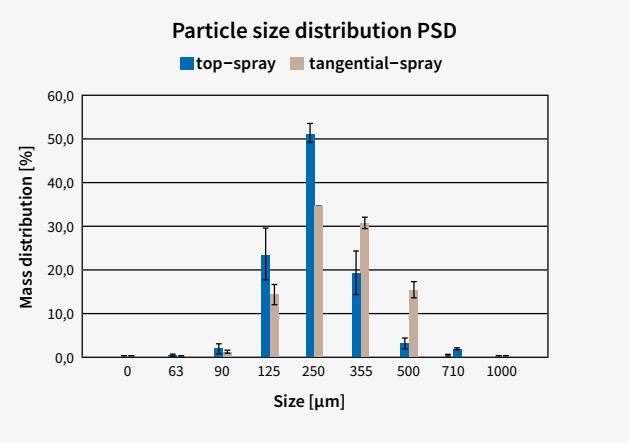
The spraying pressure was 0.25 bar, and different nozzle sizes were used. The result: With a smaller nozzle a lower pressure is sufficient, as the droplet size correlates with this. It should be mentioned here that a constant air inlet temperature of 65°C was chosen. Although higher inlet air temperatures enable higher spraying rates, many APIs in particular are thermolabile.

Advantages of the tangential-spray method

One of the advantages of the tangential-spray method is the reduced time required for the granulation process. The granulation fluid is added via a binary nozzle, which is arranged tangentially to the bottom part of the wall of the material bowl. As a result, higher spraying rates (30 percent) can be achieved. Spraying times are shorter and drying efficiency is dramatically improved.

In particular, less granulation fluid is required to achieve a certain particle size. The tangential-spray method can help to produce coarser granulates so that the final product has a broad particle size distribution. During the process it is possible to influence the desired properties via the pressure of the spray nozzle (droplet size). For example, lower pressure at the spray nozzle leads to a coarser granulate. However, with this method the granulate particles are more coarse-grained in general.

	Tangential-spray	Top-spray
Max. spraying pressure [bar]	0,25	0,75
Max. air inlet flow [m³/h]	75	63
Max. air inlet temperature [°C]	65	65
Max. pump speed [rpm]	28	18
Max. spraying rate [g/min]	23	16,3
Spraying time [min]	25:25	38:28
Binder solution [g]	500	500



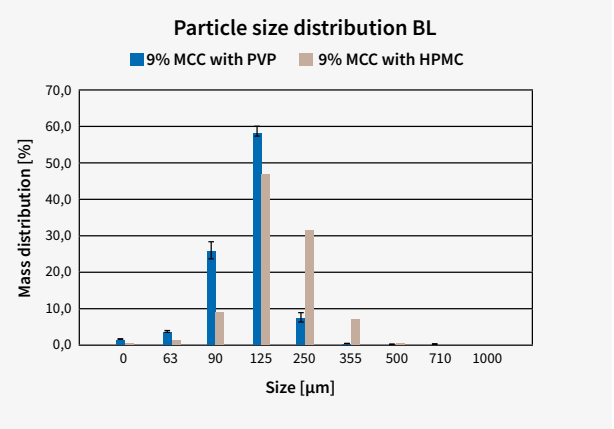
	Tangential-spray	Top-spray
Bulk density [g/mL]	0,54 ± 0,01	0,46 ± 0,01
Tamped density [g/mL]	0,64 ± 0,02	0,57 ± 0,01
Hausner factor	1,17 ± 0,02	1,23 ± 0,04

Factors that influence formulation

Microcrystalline cellulose (MCC) is added to the recipe in order to improve formulation of the tablets. MCC is highly compactable and is a widely used filling material in solid drug formulations. The proportion of MCC in tableting is typically between 10% and 30%. If this level is too high, disintegration after compaction is reduced for oral dosage forms. For this reason, formulations with three different levels of MCC were investigated:

Use of a higher share of HPMC 606 in the binder solution (BS) or formulation increases the size of the granulate. Afterwards HPMC was substituted with polyvinylpyrrolidone (PVP), which resulted in smaller granulation sizes. The particle size distribution was more focused in the trials with PVP. When PVP was used there was less variation in the granulation processes (smaller error bars).

	9% MCC + HPMC in BL	9% MCC + PVP in BL
Bulk density [g/mL]	0,49	0,56 ± 0,02
Tamped density [g/mL]	0,64	0,71 ± 0,02
Hausner factor	1,30	1,27 ± 0,02



Conclusion II: These results show that it is worth paying careful attention not only to the apparatus technology, but also to the formulation itself. This is the only way to achieve stable granulation processes.

Author: Michael Benjamin, Head of Technology, DIOSNA Dierks & Söhne

About us

DIOSNA - Quality Made in Germany

Everything under one roof: DIOSNA's machine engineering and technology offers everything from compact systems for small-scale operations to fully automated solutions for large-scale operations. The product portfolio offers mixers, granulators, dryers and coating systems for a variety of industries: from pharmaceuticals and cosmetics to feed and fine chemicals, as well as solutions for the food sector. It also provides a wide range of solutions for the most important dough production processes from dosing, pre-dough preparation and kneading to transfer logistics - for research, pilot and industrial production.

Joint product development with the customer, process planning as well as optimisation, efficient project management and comprehensive after-sales and value-added services are continuously optimised and customer-centred yesterday, today and tomorrow.

This is why DIOSNA customers have appreciated our quality, performance, competence and philosophy for over 135 years.

For more information contact

DIOSNA Dierks & Söhne GmbH
Am Tie 23, 49086 Osnabrück, Germany
+49 541 33104-0
info@diosna.de
www.diosna.com

Further Readings

Control of Particle Size and Porosity in Continuous Fluidized-Bed Layering Granulation Processes

C. Neugebauer *et al*. 2020 Chem. Eng. Technol., 43: 813-818. DOI: 10.1002/ceat.201900435

Abstract:

Particle formulation processes such as continuous fluidized-bed layering granulation (FBLG) are widely applied in chemical, food, and pharmaceutical industries. Particle size and particle porosity are important product properties in FBLG. In this paper, a new concept is presented for the simultaneous control of both properties. The new concept allows stable process operation, automatic adjustment of the desired product properties, and rejection of unforseen disturbances.

Advanced 3D and 4D microstructure study of single granule formation for pharmaceutical powders using synchrotron x-ray imaging

S. Z. Danalou *et al*. 2023 AIChE J. 69(5) e18048. DOI: 10.1002/aic.18048

Abstract:

Monitoring the microstructure of the granule in the wet granulation process could play a decisive role in obtaining high-quality granules. Due to the complex, fast and opaque nature of wet granulation, it cannot be captured by conventional methods. In this study, synchrotron x-ray imaging was employed for the first time to investigate the internal real-time pore evolution during the granule formation process, based on the single droplet impact method. It was found that granules from coarser and more homogenous powders experienced a higher rate of pore evolution during nucleation with a more uniform pore distribution. Dynamic wetting studies showed the granule formation mechanisms, the crater mechanism was found for most binary mixtures with 50 wt. % excipients. According to the physical tests, the granules with lower porosity and finer pores exhibited higher hardness and a slower dissolution rate.

Experimental study of liquid vaporization in a fluidized bed

H. M. Silitonga *et al*. 2023 Can. J. Chem. Eng. 101(1), 172. DOI: 10.1002/cjce.24534

Abstract:

Liquid injection into a gas–solid fluidized bed has been applied in various industries, such as coating and granulation processes in pharmaceutical and food industries, reactor cooling in polyolefin production, fluid catalytic cracking, and fluid coking in the petroleum industry. A new experimental method has been successfully developed to monitor the vaporization rate of a liquid injected into a fluidized bed. In addition, it can be used to determine the mass of liquid accumulated in the bed at a steady state. With this new method, measurements have identified three phenomena that may increase the amount of liquid accumulated at steady state in a fluidized bed. (1) Gas mixing affects vaporization when the bed temperature is lower than the liquid boiling point. In liquid-rich regions of the bed, local vapour may build up, limiting the vaporization rate. Consequently, suitable emulsion to bubble gas transfer reduces the amount of accumulated liquid. (2) Solids mixing: hot particles from the rest of the bed must mix with the wetted particles to provide enough heat for vaporization. Good solids mixing reduces the amount of accumulated liquid. (3) Wet agglomerates formation: liquid trapped within wet agglomerates takes much longer to vaporize. The amount of accumulated liquid can be reduced by injecting the liquid in a well-agitated bed region, operating at a higher bed temperature, or increasing the flowrate of atomization gas

Mechanistic models for liquid binder evaporation in wet granulation

E. Heidari *et al*. 2023 Can. J. Chem. Eng. 101(1), 504. DOI: 10.1002/cjce.24371

Abstract:

In this study, binder evaporation as a significant microscale phenomenon in fluidized bed wet granulation has been investigated in three situations: a single droplet, a sessile droplet, and a liquid bridge. Single droplet evaporation has been analytically modelled by mass transfer analysis from a spherical droplet subjected to the relative velocity of the medium and considering evaporation rate variations versus droplet diameter. Then, the sessile droplet evaporation model has been used from the literature. Finally, the liquid bridge evaporation has been modelled, and the rupture time of the bridge has been computed. The local temperature dependence of air physicochemical properties has been considered in all models. The single and sessile droplet evaporation rates have been successfully validated by the experimental data of the air–water system. The effects of operational conditions and liquid/particle properties on each evaporation event have been evaluated and quantified. The results indicate that both the higher relative velocity between the air and a single droplet and the smaller equilibrium contact angle in a constant volume of sessile droplets increase the evaporation rate. Also, increasing the length of the binder bridge reduces the rupture time.

Experimental investigation on drying performance of pharmaceutical granules in a pulsation-assisted fluidized bed dryer

C. Li *et al*. 2022 Can. J. Chem. Eng. 100(9), 2608. DOI: 10.1002/cjce.24485

Abstract:

Fluidized bed drying has been widely employed in pharmaceutical manufacturing processes. Due to the considerable cohesiveness of wet pharmaceutical granules, channelling phenomena pose significant challenges to fluidization and drying. In this work, the drying performance of pharmaceutical granules in a pulsation-assisted fluidized bed dryer was experimentally investigated. The drying rate and energy efficiency were investigated with representative pharmaceutical powders, including active pharmaceutical ingredients (APIs). It is found that the pulsed airflow is effective in enhancing the drying rate at higher superficial gas velocity. A lower pulsation frequency is more favourable to improve the drying rate. During the constant rate period, energy efficiency is between 60% and 45% for the drying process, while the energy efficiency decreases to 10% during the falling rate period. A pulsed fluidized bed dryer has shown a higher energy efficiency than a conventional one with a constant air flow. Among nine thin-layer drying models examined in this work, the Midilli and Kucuk model has shown the best agreement between the experimental data and the predicted results.

Estimation of the dominant size enlargement mechanism in spray fluidized bed processes

C. Rieck *et al*. 2020 AIChE J. 66 e16920. DOI: 10.1002/aic.16920

Abstract:

This work deals with estimating the dominant size enlargement mechanism in spray fluidized beds. A new process model is presented, which consists of population balances and a heat- and mass-transfer model. New methods to incorporate the wet surface fraction and the Stokes criterion are proposed, which allow for the probability of wet collisions and the probability of successful wet collisions to be calculated. The product of these parameters, the probability of successful collisions, is linked to the dominant size enlargement mechanism. Simulation studies were performed to investigate the influence of inlet gas temperature, viscosity, droplet size, and contact angle on the probability of successful collisions. Further simulation results based on experiments available in literature suggest that exceeding a probability of successful collisions of 0.001 is sufficient for agglomeration to become dominant. Otherwise, layering will be the dominant size enlargement mechanism. Finally, regime maps of layering and agglomeration are constructed.

Conclusion

As the pharmaceutical industry adapts to changing production demands, granulation processes are transforming, necessitating flexible and efficient manufacturing systems. Pharmaceutical manufacturers are seeking innovation in granulation processes to meet evolving healthcare needs and achieve optimal product properties.

The importance of well-thought-out scale-up is highlighted in the first study, which advocates a modular design for laboratory and pilot plants. This enables tool-free module exchange for efficient machine changeovers and emphasizes Rapid Change (RC) capabilities between different bowl and batch sizes. The study underscores the significance of fast and safe changeovers in pharmaceutical plants and demonstrates how flexibility in production systems contributes to optimizing solid dosage form characteristics, using granulation as a practical example.

The study on tangential-spray techniques in fluidized-bed granulation provides comprehensive insights into the advantages of tangential-spray granulation, highlighting the importance of considering both apparatus technology and formulation intricacies for achieving stable granulation processes in pharmaceutical production. Tangential-spray offers benefits over top-spray granulation, facilitating higher spraying rates, shorter processing times, and improved drying efficiency. Additionally, granulates obtained via tangential-spray have good flow characteristics, low fragility, and homogeneous distribution of active pharmaceutical ingredients (APIs). To achieve optimal results, both apparatus choice and the formulation should be carefully considered.

As the industry grapples with evolving demands, this eBook emphasizes the critical role of scale-up, modular design, and tangential-spray in optimizing granulation processes to enhance medication effectiveness and meet healthcare needs.

Christene A. Smith, Ph.D.
Editor at Wiley

WILEY

Imprint

Email: info@wiley-vch.de

Editor: Christene Smith

Sales contact: Hagen Reinhoff