

Optimising drug formulation: The critical role of granulation

INTRODUCTION

In pharmaceutical development, the journey from active pharmaceutical ingredient (API) to a stable, effective oral solid dosage (OSD) form presents many challenges. Among the processes central to this transformation, granulation is a fundamental technique for overcoming common formulation hurdles and ensuring the quality and performance of oral solid medicines. It involves forming primary powder particles into larger, multi-particle units, or “granules,” which improves their physical and chemical attributes.

Developing successful solid dosage forms often presents difficulties such as poor powder flow, insufficient compressibility, uneven drug distribution and material separation. These issues can lead to significant manufacturing problems, reduced product quality and, ultimately, a less effective therapeutic outcome for patients. Granulation can effectively resolve these by improving flow properties, enhancing compaction characteristics, ensuring uniform content and reducing segregation. This streamlines manufacturing and enhances the developability of the final product.

However, implementing effective granulation is not an easy task. Choosing the correct granulation technology, optimising process parameters and successfully scaling up from laboratory to commercial production requires deep knowledge and a precise understanding of material science and engineering principles. Variations in raw materials, the need for precise control over granule characteristics and adherence to strict regulatory requirements all add layers of difficulty to this crucial process.



This whitepaper provides a detailed look at granulation, highlighting its vital role in modern drug formulation. In it, you will learn about:

- ▶ The range of granulation technologies, including wet granulation, dry granulation and specialised methods such as high-shear granulation and fluid bed granulation.
- ▶ The core reasons for choosing granulation over direct compression, outlining the specific advantages each method provides in addressing formulation issues.
- ▶ The inherent challenges associated with each granulation technique and the broader applicability of granulation processes.
- ▶ How Recipharm assists pharmaceutical developers in handling these complexities to deliver successful execution of granulation in drug formulation development.

OVERCOMING FORMULATION CHALLENGES WITH GRANULATION

The development of OSD forms often begins with direct compression, a seemingly straightforward method where powdered ingredients are directly compressed into tablets. While appealing due to its simplicity and reduced processing steps, direct compression is often limited by the physical properties of the APIs and excipients. Many drug substances possess poor flow characteristics, insufficient bulk density, or a tendency to segregate when mixed, making direct compression unsuitable for achieving a uniform, robust and consistently performing tablet. These limitations frequently necessitate the adoption of more advanced processing techniques, such as granulation.

Granulation serves as a critical pre-treatment step, transforming raw powder mixtures into a more desirable form for tableting or capsule filling. This process fundamentally alters the physical properties of the material, making it amenable to efficient and reproducible manufacturing. The primary goal is to improve powder flow, enhance compressibility and ensure uniformity of content within the final dosage unit.

Granulation is employed in formulation development for several reasons:

► Improved flow properties

Powders with poor flow characteristics, which often lead to issues such as inconsistent die filling, segregation and “bridging and arching” in hoppers, present significant manufacturing challenges. The particle shape and size are critical factors in determining the flow characteristics. When a powder consists of fine, irregularly shaped or angular particles, they tend to interlock, increase friction and resist free flow. Granulation addresses this by creating larger, more spherical and uniform particles. These larger particles flow more freely and consistently, allowing for precise and repeatable dosing during tablet compression or capsule filling.

► Increased density

Granulation increases density, for example, of spray-dried material or other APIs with very small particle sizes and low density. This is closely linked to improved flowability and downstream processability. The increased bulk density means that a greater mass of material can occupy a given volume, which is crucial for efficient handling, storage and transport, reducing packaging and shipping costs. Additionally, higher bulk density translates to more consistent die filling during tablet compression or capsule filling, ensuring accurate and uniform dosing in the final product.

► Enhanced compressibility

Achieving the desired tablet hardness and density is vital for achieving optimal product quality and stability. Many fine powders are inherently challenging to compress into strong tablets, often resulting in issues such as “lamination” (tablet splitting horizontally) and “capping” (the tablet top separating). Granulation transforms these fine particles into denser, more compressible granules, enabling the production of tablets with optimal mechanical strength and preventing common defects associated with tablet compression.

► Content uniformity

For low-dose drugs, ensuring that each tablet contains the precise amount of API is critical for therapeutic efficacy and patient safety. Fine powders, especially when the API constitutes a small percentage of the total formulation, are prone to segregation. By incorporating the API uniformly within larger granules, granulation locks the drug substance in place, thereby preventing segregation and ensuring consistent distribution of the drug throughout the dosage form.

► Dust reduction

Fine powders can generate significant dust during manufacturing, posing risks to operator safety and resulting in material loss. Some airborne powders may also have a higher flammability and an increased risk of explosion. Granulation agglomerates these fine particles, substantially reducing airborne dust, improving workplace safety and minimising material waste.

While the general principles and benefits of granulation apply across various methods, it is important to understand the distinctions between the main technologies.



COMPARING WET AND DRY GRANULATION

There are two primary granulation methods: wet granulation and dry granulation. Each approach offers distinct advantages and presents unique considerations, making the choice dependent on the specific properties of the drug substance and excipients, as well as desired product characteristics.

The wet granulation process

Wet granulation is a widely used process that involves adding a liquid binder to a powder mixture to form granules. The liquid causes the powder particles to agglomerate through the formation of liquid bridges, which are then solidified by the binder. The process typically begins with blending the API and excipients. A liquid binder solution or suspension is then introduced to the powder bed while it is being agitated. This leads to the formation of moist agglomerates. Following this, the wet mass is usually sieved or milled to achieve a more uniform granule size before being dried.

The dry granulation process

Dry granulation, on the other hand, is an alternative method that forms granules without the use of a liquid binder, making it suitable for moisture- and heat-sensitive materials. It relies on the mechanical compaction of primary powder particles. In dry granulation, the powder mixture is first inserted into large, dense compacts (slugs) or ribbons. This compression can be achieved through a slugging process using a heavy-duty tablet press or, more commonly, with rollers. The compacted material is then milled or screened to produce granules of the desired size.

Standard equipment and methods

In wet granulation, high-shear mixers provide intense mixing and rapid granule formation, making them suitable for a wide range of materials. They are known for their efficiency and ability to produce dense granules. Meanwhile, fluid bed granulators combine

granulation and drying in one unit. Powder particles are suspended in an upward stream of air, and a binder solution is sprayed onto them. This method provides excellent control over granule growth and drying, often resulting in more porous granules, with an increased surface area for dissolution, improved wettability, faster disintegration and more controlled release potential.

For dry granulation, roller compaction is the most common method. Powder is fed between two counter-rotating rolls that compact it into a continuous ribbon or sheet. This ribbon is then milled into granules. Another dry granulation method, slugging, involves compressing large, flat tablets (slugs) from the powder mixture using a tablet press, which are then milled into granules.

Wet and dry granulation: Advantages and considerations

The choice between wet and dry granulation is far from arbitrary – it requires a careful, often complex, evaluation of their respective advantages and considerations. This decision is driven by a comprehensive assessment of various factors, including the unique physicochemical properties of the API (e.g., stability, density, particle size and shape), the excipients, the desired quality attributes of the final solid dosage form (such as tablet hardness, disintegration time and dissolution profile) and practical manufacturing considerations, such as process efficiency, cost and scalability. Each method presents a distinct set of benefits and considerations, and a thorough understanding of these is essential to select the optimal granulation technique that ensures drug stability, manufacturability, efficacy and patient safety.

Table 1: Advantages of wet and dry granulation

Wet granulation	Dry granulation
Wider range of materials Wet granulation is highly versatile and can effectively agglomerate materials that are not amenable to direct compression or dry granulation.	Fewer processing steps Compared to wet granulation, dry granulation eliminates the need for the addition of a liquid as well as a drying stage, simplifying the manufacturing process.
Better content uniformity The liquid binder helps distribute low-dose APIs more evenly throughout the formulation, ensuring consistent drug content in each granule and, subsequently, in the final dosage form.	No drying stage This is a key benefit for moisture-sensitive APIs, as it prevents hydrolysis or other moisture- and heat-induced degradation and reduces the time and energy required.
Higher tablet strength The strong bonds formed by the liquid binder often cause granules that compress into tablets with superior mechanical strength, reducing friability and breakage.	Suitable for moisture- and heat-sensitive drugs The absence of a liquid phase makes dry granulation ideal for compounds that degrade in the presence of water or solvents. Also, without a drying step, there is no exposure to elevated temperatures, protecting heat-labile APIs.

It is worth acknowledging that both wet and dry granulation methods have considerations that must be weighed against each other for each project. No single granulation technique is universally superior and what works optimally for one formulation may be unsuitable for another. Factors such as an API's sensitivity to moisture or heat, compressability, the required tablet strength, the complexity of the manufacturing process and sustainability objectives all play a significant role in choosing the correct granulation method

for the project. A blanket approach risks compromising product quality, increasing manufacturing costs or extending development timelines. Hence, a thorough evaluation of the specific properties of the drug product and the desired outcomes, coupled with a deep understanding of the limitations of each granulation method, is essential to make an informed decision and select the most appropriate and efficient process.

Table 2: Considerations for wet and dry granulation

Wet granulation	Dry granulation
More processing steps This method typically involves multiple stages: mixing, granulating, milling, drying and often a final sizing step. This can increase processing time and cost.	Better suited to materials with good compressibility Dry granulation relies on the powder mixture's inherent compactness. Materials with poor intrinsic compressibility may not form stable compacts.
Drying stage required The removal of the granulation liquid necessitates a drying step, which can be energy-intensive and time-consuming.	Potentially producing more dust The milling step after compaction can generate fine particles and dust, potentially leading to material loss and requiring careful dust control measures. However, this is often less severe than with the direct handling of the original fine powders.
Potential for drug degradation due to moisture and heat Drugs sensitive to hydrolysis or thermal degradation may be compromised during the wet granulation and drying processes.	Potential for lower tablet strength compared to wet granulation The bonds formed during dry granulation are typically mechanical rather than chemical, which can sometimes cause tablets with lower tensile strength compared to those made via wet granulation.
Drying energy consumption The energy consumption associated with drying and using solvents (if applicable) can affect the environmental footprint of the process.	Compaction and milling energy requirements Although it avoids drying energy, the energy consumption for compaction and milling should also be considered.



The effectiveness of dry granulation is significantly enhanced by access to advanced roller compaction technology and skilled personnel. Modern equipment provides precise control over force and speed, enabling optimal ribbon density and granule properties. Expertise in formulation development for dry granulation is crucial for selecting appropriate excipients and fine-tuning parameters to achieve the desired tablet characteristics.

Specific scenarios favouring wet or dry granulation

When APIs or formulations exhibit poor intrinsic compressibility, wet granulation provides a mechanism to create robust granules that can be compressed into strong tablets, as the liquid binder helps form stronger inter-particulate bonds. For low-dose drugs where precise content uniformity is crucial, wet granulation excels because the liquid phase ensures thorough mixing and distribution of the API within the granules, thereby preventing segregation. Additionally, for formulations requiring specific release profiles, the porosity and density of granules formed by wet granulation can be controlled by varying process parameters, which in turn influence the dissolution and release rate of the drug, allowing for tailoring specific immediate or modified release profiles.

Dry granulation is a valuable alternative. This approach enables APIs with low bulk density to be densified, improving their flowability and facilitating more efficient processing, as well as achieving higher tablet weights within a given die volume. Moisture-sensitive drugs are a primary driver for choosing dry granulation. By avoiding water, it protects APIs susceptible to hydrolysis or other moisture-induced degradation pathways. Similarly, eliminating the drying step eliminates exposure to elevated temperatures, making dry granulation an ideal process for thermally labile APIs. When the drug substance and excipients are suitable, dry granulation offers a more streamlined manufacturing process with fewer steps, potentially reducing processing time and costs compared to wet granulation.

THE IMPACT OF GRANULATION ON DRUG QUALITY AND PERFORMANCE

By modifying the physical properties of powder mixtures, granulation helps overcome inherent material limitations, resulting in superior dosage forms. The direct manipulation of particle properties through granulation has a profound effect on key quality and physical attributes of the final solid dosage form, including:

► Improved dissolution rate

For many drugs, especially those with low solubility, the rate at which the API dissolves from the dosage form is a critical determinant of its absorption and therapeutic effect. Granulation can be engineered to create porous granules with a larger effective surface area. This increased surface area, coupled with improved wettability, enables the dissolution medium to penetrate the granule more effectively, resulting in faster and more complete drug release.

► Enhanced wettability

Poorly wettable drug particles can float on the surface of dissolution media, hindering their release and absorption. By incorporating hydrophilic binders during granulation, particularly in wet granulation, the surface characteristics of the granules can be modified. This enhances their ability to absorb water and interact with biological fluids, resulting in more consistent and effective drug dissolution.

► Reduced sticking (adhesion to equipment)

Fine, cohesive powders often tend to stick to the surfaces of processing equipment, such as tablet punches and dies. This can lead to manufacturing downtime, reduced yield, and quality defects such as "picking" and "sticking" on tablets. Granulation produces larger, less cohesive particles with improved flow properties, significantly reducing their propensity to adhere to machinery surfaces during compression or capsule filling.

The release rate for BCS Class II and IV drugs

Beyond direct manufacturing benefits, granulation plays a crucial role in optimising the bioavailability of specific drug classes, particularly those falling under the Biopharmaceutics Classification System (BCS) Class II and IV. The link between particle properties and drug bioavailability is direct and significant. For these classes, the rate and extent of absorption are often limited by the drug's solubility and/or permeability.

► BCS Class II drugs (low solubility, high permeability)

For these drugs, the dissolution rate is the rate-limiting step for absorption. Granulation can improve the dissolution rate by:

- **Creating porous granules:** The internal structure of the granules can be controlled to achieve a high degree of porosity, providing a larger surface area for solvent penetration and drug release.
- **Incorporating solubilisers/wetting agents:** During granulation, hydrophilic binders or other solubilising excipients can be incorporated uniformly, further enhancing the wettability and dissolution of the poorly soluble API. This makes the drug more readily available for absorption.

► BCS Class IV Drugs (low solubility, low permeability)

These drugs face challenges in both dissolution and permeability. While granulation primarily addresses dissolution, improving this aspect remains vital, as it ensures the drug is at least in solution and available to facilitate permeation. For BCS IV drugs, granulation strategies that maximise dissolution (such as highly porous granules and the use of excipients that enhance solubility) become even more critical to overcome the initial solubility barrier, even though permeability remains a subsequent challenge. By making the drug readily available in solution, granulation helps maximise the opportunity for absorption across biological membranes.

In essence, by controlling particle size, surface area and wettability, granulation directly influences the dissolution profile of the drug, which is a key factor in determining the bioavailability of BCS Class II and IV compounds. This makes granulation a strategic formulation choice for improving the therapeutic efficacy of these challenging drug substances.

CHALLENGES IN IMPLEMENTING EFFECTIVE GRANULATION

Granulation offers significant advantages in overcoming formulation and manufacturing challenges, but its successful implementation requires careful attention to a range of complexities. Moving from a concept to a scalable and compliant process involves navigating several critical hurdles.

Process parameter control and scaling up granulation processes

A primary challenge lies in identifying and controlling the process parameters that influence granule properties and, consequently, final product quality. This includes defining the ideal binder concentration, the precise liquid-to-solid ratio (for wet granulation) and other critical processing parameters such as mixing speed, mixing time, drying temperature and roller compaction force. These parameters are interconnected, and a slight deviation in one can significantly impact the others, leading to undesirable granule characteristics. Achieving a narrow and reproducible granule size distribution is also crucial for maintaining consistent flow, compressibility and dissolution. It is challenging, requiring precise control over the granulation process and subsequent milling steps. Deviations can lead to segregation, poor content uniformity and inconsistent tablet properties.

Scaling up a granulation process from laboratory or pilot scale to commercial manufacturing introduces its own set of challenges. Process dynamics and material behaviour can change significantly with increased batch size. What works efficiently and reproducibly on a small scale may not translate directly to larger equipment. Factors such as heat transfer, mixing efficiency and drying kinetics can behave differently, necessitating careful re-evaluation and adjustment of parameters. Maintaining consistent granule properties and final product quality (e.g., tablet hardness, dissolution) across varying batch sizes is a major objective, requiring a deep understanding of process and material interactions to predict and control changes during scale-up.

Raw material variability, equipment selection and maintenance

Variations in the raw materials themselves can pose significant challenges, even with a well-defined granulation process. APIs and excipients can exhibit batch-to-batch variations in particle size, morphology, surface energy, moisture content and purity. These differences, even subtle ones, can affect how materials interact during granulation, impacting binder absorption, granule growth and compressibility. To counteract material variability, robust process controls are essential, involving the real-time monitoring of critical process parameters (e.g., power consumption of mixers, ribbon density in roller compactors) and establishing appropriate in-process controls to ensure consistent granule quality despite fluctuations in raw materials.

Choosing the right equipment and ensuring it operates effectively and compliantly are also critical challenges. The choice of granulator (such as high-shear, fluid bed, or roller compactor) must align with the specific material properties and desired granule characteristics, as well as the manufacturing scale. Each type of equipment has distinct operational principles and limitations. Granulation equipment can be complex, making thorough cleaning a challenging task. Preventing cross-contamination between different products is crucial, requiring validated cleaning procedures, dedicated equipment, or careful scheduling.

Regulatory compliance

Finally, adhering to global regulatory standards is a constant challenge throughout the drug development and manufacturing lifecycle, including granulation. All aspects of the granulation process, from raw material specifications to process validation and in-process controls, must meet stringent regulatory requirements. Detailed documentation and justification are required for regulatory submissions. Ensuring ongoing compliance with evolving guidelines adds another layer of complexity. Addressing these challenges effectively requires a combination of scientific understanding, advanced technological capabilities and extensive experience in pharmaceutical development and manufacturing.



ENABLING GRANULATION SUCCESS WITH RECIPHARM

Overcoming the complexities of granulation, as discussed in the previous section, requires more than just theoretical understanding; it demands practical expertise, advanced equipment and a strategic approach. Recipharm is a dedicated partner, helping drug developers harness the full benefits of granulation to create high-quality, effective and compliant solid dosage forms.

Recipharm possesses extensive experience in OSD formulation development, having successfully brought numerous products to market. This deep background informs our approach to granulation, allowing us to anticipate challenges and implement solutions that optimise drug performance and manufacturability. Our comprehensive granulation support covers the entire lifecycle of drug development, from early feasibility through commercial production.

Our granulation capabilities encompass a broad spectrum of services:

- ▶ **Compatibility studies** assess the stability of the API in the presence of selected excipients
- ▶ **Feasibility studies** assess the suitability of various granulation techniques for your specific API and excipient combination. This proactive approach helps identify the most promising pathways, minimising costly late-stage failures.
- ▶ **Process optimisation and scale-up** ensure that laboratory-scale success translates seamlessly to larger commercial batches. Our experts fine-tune parameters, mitigate scale-dependent issues, and establish robust processes to ensure consistent product quality.
- ▶ **Comprehensive analytical testing and characterisation**, which includes a detailed analysis of granule properties such as size distribution, density, flowability and compressibility, along with dissolution testing and content uniformity assessments. This data-driven approach ensures that the chosen granulation method yields granules that meet all predefined quality attributes.
- ▶ **GMP manufacturing facilities** provide flexible manufacturing options that can accommodate varying batch sizes and project complexities, ensuring continuity from development to market supply.
- ▶ **Dry granulation equipment**, including Gerteis roller compactors, which enhance our capacity and precision in handling moisture- and heat-sensitive compounds.



Gerteis roller compactors

Gerteis roller compactors are widely recognised in the pharmaceutical industry for their advanced dry granulation technology. They offer a range of features and benefits that make them a preferred choice for various applications, from lab-scale development to full-scale production. The key features of Gerteis compactors include:

- ▶ Floating Gap Technology that continually adjusts the distance between the rolls based on the amount of powder fed, ensuring constant force is applied to the powder, resulting in minimal fluctuations in granule properties.
- ▶ Precise process control (Process Analytical Technology integration) for online measurement and control of critical quality-relevant parameters like compaction force, roll gap and roll speed.
- ▶ Versatile feeding systems to ensure a consistent and controllable powder feed to the compaction area.

Navigating the global regulatory landscape can be discouraging. Recipharm offers dedicated regulatory support, helping clients navigate regulatory submissions and ensuring compliance with the highest international standards. Our experience helps streamline the approval process and mitigate potential regulatory hurdles. To illustrate our proficiency, we can provide case studies or examples of successful granulation projects where Recipharm

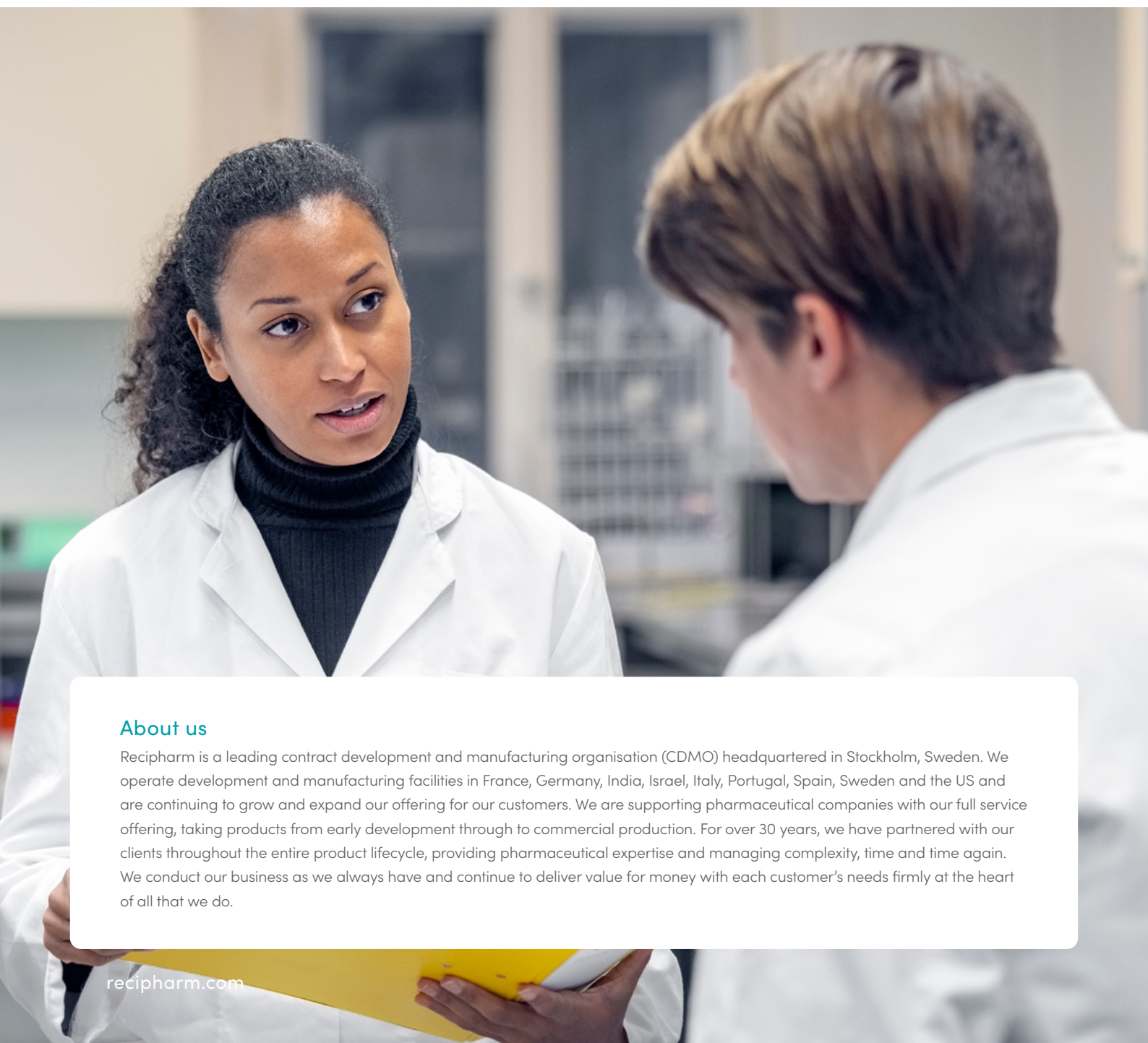
has helped clients overcome significant formulation challenges, leading to improved product performance and successful market entry. Partnering with Recipharm provides access to a wealth of experience and state-of-the-art facilities, empowering drug developers to achieve optimal drug formulation through expertly executed granulation.

THE VALUE OF EXPERT COLLABORATION

The journey of optimising drug formulation through granulation is complex, demanding precision, adaptability and deep scientific understanding. From overcoming inherent material challenges, such as poor flow and compressibility, to ensuring consistent quality and drug bioavailability, granulation proves to be an indispensable process in the development of robust OSD forms. However, navigating the intricacies of process parameter optimisation, scale-up, material variability and regulatory compliance presents significant hurdles for any drug developer.

Recipharm's comprehensive expertise in OSD formulation development, coupled with state-of-the-art granulation capabilities and robust analytical and manufacturing support, positions us to guide clients through every stage of their projects. By leveraging our understanding of both wet and dry granulation techniques, our investment in cutting-edge equipment and our proven track record in regulatory support, we empower drug developers to unlock the full potential of granulation for their unique products.

Talk to Recipharm's experts today to discuss how we can help you achieve optimal drug formulation and bring your products to market with confidence.



About us

Recipharm is a leading contract development and manufacturing organisation (CDMO) headquartered in Stockholm, Sweden. We operate development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden and the US and are continuing to grow and expand our offering for our customers. We are supporting pharmaceutical companies with our full service offering, taking products from early development through to commercial production. For over 30 years, we have partnered with our clients throughout the entire product lifecycle, providing pharmaceutical expertise and managing complexity, time and time again. We conduct our business as we always have and continue to deliver value for money with each customer's needs firmly at the heart of all that we do.