# Twin-Screw Granulation: Reviewing the Science, Advancing the Process

## Twin-Screw Granulation and Modern Formulation Challenges

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### From Lab to Production: The Value of TSG

Dr. Margarethe Richter's 2022 white paper outlined the advantages of continuous twin-screw granulation (TSG) for pharmaceutical manufacturing and highlighted the use of the **Thermo Scientific™ Pharma 24 Twin-screw Extruder:**

- Faster process development
- Reliable scale-up from R&D to production
- Enhanced reproducibility with integrated PAT
- Tailored granule properties for dissolution and strength

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### Introduction

Drug formulation continues to present challenges for pharmaceutical manufacturers, particularly as the industry faces increasing demand for flexible, efficient, and reproducible production methods. Formulating drugs for therapeutic consistency, rapid development, and cost-effective scale-up is more complex than ever in this era of personalized medicine, biologics, and other pharmaceutical compounds with poorly soluble small molecules. This complexity has spurred a shift toward advanced process technologies that offer improved control and modularity.

Among these technologies, hot-melt extrusion (HME) and twin-screw granulation (TSG) have emerged as leading methods for developing oral solid dosage forms. These techniques are especially important in continuous manufacturing environments where material efficiency, process control, and scalability are essential. Thermo Fisher Scientific's work in this area has emphasized how these tools address real-world pharmaceutical formulation demands.

This review revisits the foundational work on continuous twin-screw granulation written by Dr. Margarethe Richter and published by Thermo Fisher Scientific in 2022,[1] assessing those findings in light of subsequent technological advancements and literature. It examines the role of continuous manufacturing, highlights the advantages of TSG and HME, and concludes with an evaluation of Thermo Fisher's technologies and how they align with the latest trends in pharmaceutical development.

## TSG Enables Continuous, Scalable, and Efficient Drug Development

Dr. Richter's 2022 white paper explored the growing relevance of continuous twin-screw granulation (TSG) in pharmaceutical development.[1] It underscored TSG's role in accelerating drug development timelines and improving the reproducibility and scalability of manufacturing processes. The study centered on the use of Thermo Scientific™ Pharma series extruders—notably the Pharma 11, Pharma 16, and Pharma 24 models—which are geometrically comparable and designed for flexible scale-up from early research sizes to pilot and production levels. The original paper identified several key advantages of continuous TSG:

- **Process Efficiency and Flexibility:** Unlike batch granulation, TSG supports uninterrupted production, enabling rapid scale-up and minimizing downtime. This is crucial for flexible responses to demand and regulatory timelines.
- **Improved Reproducibility and Control:** TSG integrates with process analytical technology (PAT) systems, such as near-infrared spectroscopy, for real-time monitoring. These tools ensure consistent product quality and regulatory compliance.[2]
- **Modular Scalability:** The Pharma series extruders offer consistent geometry across scales, allowing lab-scale results to directly inform commercial production without redesigning the process.
- **Critical Process Parameter Optimization:** Variables such as screw configuration, liquid-to-solid ratio, feed rate, and barrel temperature were shown to affect granule properties like particle size distribution (PSD), density, and drug release profiles. Mastery of these parameters ensures product uniformity.
- **Granule Tailoring Capabilities:** The ability to fine-tune PSD in the granulation stage enables developers to engineer final dosage forms with specific dissolution profiles and mechanical strength.

By leveraging the Thermo Scientific Pharma series and TSG platform, developers can create more efficient, controllable, and transferable processes for oral dosage forms.

## Recent Innovations Driving the Adoption of TSG and HME

Since the publication of Thermo Fisher's paper, the pharmaceutical sector has made substantial progress in applying TSG and HME to new formulation strategies. Noteworthy advancements include the integration of additive manufacturing, improved process control techniques, and the development of specialized dosage forms. Here are just a few examples:

### Mucoadhesive Systems and Bilayer Tablets for Advanced Delivery

Twin-screw granulation (TSG) and hot-melt extrusion (HME) are enabling the development of advanced drug delivery systems such as mucoadhesive films and bilayer tablets, designed to improve bioavailability, control release, and support complex dosing strategies.

Mucoadhesive systems adhere to mucosal tissues, extending residence time and enhancing drug absorption. Ideal for transmucosal delivery, they support self-administration and non-invasive access, with easy termination. TSG and HME make it possible to embed bioadhesive polymers and active ingredients into stable, scalable formulations using continuous, solvent-free processes.

Bilayer tablets, meanwhile, offer formulation flexibility—supporting the co-delivery of multiple APIs or sequential release of a single drug. TSG and HME enable precise control over layer composition and performance, helping to optimize pharmacokinetics and patient adherence.

Singh et al. (2025) demonstrated how these technologies can be used to produce extended-release, 3D-printed dosage forms such as buccal films and multilayer tablets with APIs like diclofenac, paracetamol, and budesonide.[3] This reflects the broader shift toward customizable, multifunctional therapies made possible by continuous manufacturing —a trend underscored by the fact that oral and transmucosal delivery systems now represent over half of the global drug delivery market, signaling sustained investment and innovation in these patient-centric formats.[4]

### 3D Printing and FDM Coupled with HME

The integration of hot-melt extrusion (HME) with fused deposition modeling (FDM) 3D printing has emerged as a transformative approach in the additive manufacturing of pharmaceutical dosage forms. In this process, HME is leveraged to produce drug-loaded filaments that are subsequently used as feedstock for FDM printers. This combination enables precise, layer-by-layer fabrication of solid oral forms, offering unprecedented control over drug release profiles and geometries for personalization.

A key determinant of success in this approach is the miscibility between the active pharmaceutical ingredient (API) and the polymer matrix. Inadequate miscibility can lead to heterogeneous extrusion, resulting in filaments with poor mechanical properties, surface roughness, and inconsistent drug distribution.[5] Optimizing polymer-API compatibility is therefore crucial for ensuring both printability and therapeutic performance.

Notably, Zhang et al. (2022) demonstrated the practical viability of this technique through the fabrication of bilayer tablets using a dual-nozzle FDM system, underscoring the adaptability of HME-based filaments for complex multi-material printing.[6] Their work illustrates how combining HME and FDM can support the production of personalized, multi-release dosage forms—an increasingly important goal in modern pharmaceutical development. As a result, this hybrid approach is gaining

traction as a flexible and scalable method for on-demand drug delivery systems tailored to individual patient needs.

### Advanced Process Control through Model Predictive Control (MPC)

Building on foundational work in process analytical technology (PAT), the integration of model predictive control (MPC) represents a major advance in continuous manufacturing. While Dr. Richter emphasized the critical role of PAT in enabling real-time process understanding, we've since gained even greater insight—and capability—through closed-loop systems that automatically adjust key parameters mid-process.

MPC allows real-time monitoring and control of variables such as moisture content, API concentration, and throughput to ensure product quality and consistency.[7] Jelsch et al. (2023) demonstrated this with the Thermo Scientific™ Pharma 16 Twin-screw Extruder, showing how screw speed, feed rate, and barrel temperature can be dynamically optimized during the TSG process.[8] Granule properties like size, density, and composition were precisely modulated using feedback loops informed by NIR spectroscopy.

This level of process control underscores the value of precise, modular equipment in continuous manufacturing. Variability in blending or granulation can compromise API content uniformity or downstream performance. As such, MPC—alongside PAT—has become a vital tool for enhancing product robustness, accelerating development, and meeting regulatory expectations with confidence.

### Versatility and Modularity as Pillars of Innovation

The compatibility of TSG and HME with a wide range of excipients, APIs, and downstream processing steps underscores their versatility. These technologies have been successfully applied to produce multiple different types of entities:

- Controlled-release tablets
- Solubility-enhanced amorphous solid dispersions
- Abuse-deterrent formulations
- Immediate-release orally disintegrating tablets (ODTs)

Moreover, the transition to continuous manufacturing means that materials once considered too expensive or sensitive for large-scale production can now be processed efficiently. Thermo Fisher's modular extruder designs support this shift by enabling rapid changeover and low-volume development runs.

### How Thermo Fisher Scientific Supports Evolving Formulation Needs

While much of this review has focused on general trends and literature-supported findings, it is clear that Thermo Fisher's technology portfolio has supported many of these advancements.

For example, researchers in the Jelsch et al. study used a Thermo Scientific Pharma 16 extruder with TSG capabilities to develop and validate their MPC-based control strategy.[8] The equipment's configurability, precision, and PAT compatibility made it suitable for modeling both expected and stress-condition scenarios. Likewise, the Thermo Scientific Pharma 11 and Pharma 24 extruders are used widely across industry and academia for developing scalable continuous manufacturing protocols.

### Case Study: Unlocking Complex Drug Delivery with Twin-Screw Extrusion

**Pikralida,** a CRO and biotech company, demonstrates how Thermo Fisher's TSG and TSE technologies enable advanced formulation strategies—from solubility enhancement to dual-API delivery.

**Noteworthy Outcomes**

- **Improved Solubility:**
  "Hot-melt extrusion significantly improves the solubility of the active substance…"
- **Controlled & Dual Release:**
  "Extruding one API with a thermoplastic polymer protected APIs from each other and modified their release profile."
- **Versatile Applications:**
  "We use the same Thermo Fisher extruder for injection molding, continuous wet granulation, pelletization, and filament production for 3D printing."

Pikralida's experience shows how TSG enables flexible, scalable solutions for modern drug delivery challenges—from complex formulations to personalized dosage forms.

Watch the **full testimonial.**

Dr. Richter's original paper correctly anticipated the growth of modular, PAT-enabled continuous systems as a cornerstone of pharmaceutical innovation. Her insights remain relevant as industry emphasis shifts towards different priorities:

- Reducing development timelines
- De-risking scale-up
- Enhancing patient-specific formulation
- Minimizing material waste

Thermo Fisher Scientific's extruders, feeders, and analytical tools provide an integrated, scalable platform to meet these challenges. Whether for early-stage R&D or full commercial production, the company's continuous manufacturing solutions support faster, more efficient drug development.

## From Lab to Production: Complete Solutions for Drug Formulation

### Thermo Scientific™ Pharma 11 Extruder

- Ideal for lab-scale R&D
- Early-stage development and testing

**Learn more ›**

### Thermo Scientific™ Pharma 16 Extruder

- R&D and pilot-scale versatility
- Seamless scale-up to small batches

**Learn more ›**

### Thermo Scientific™ Pharma 24 Extruder

- Full-scale production
- High throughput, consistent quality

**Learn more ›**

### Thermo Scientific™ Powder Rheology Accessories

- Precise measurement; reduces waste.
- Customizable, reliable protocols.

**Learn more ›**

## Conclusion: Looking Ahead with Twin-screw Granulation and Thermo Fisher's Role

Continuous twin-screw granulation and hot-melt extrusion represent transformative approaches in modern pharmaceutical manufacturing. These technologies improve scalability, efficiency, and product quality while enabling new dosage forms tailored to patient needs. Supported by advances in additive manufacturing, real-time control, and continuous processing, TSG and HME are becoming indispensable for modern formulators.

As this review has demonstrated, Thermo Fisher Scientific's equipment and thought leadership continue to play a crucial role in this evolution. The Pharma series extruders have become platforms of choice for researchers and manufacturers looking to develop robust, transferable, and innovative formulation strategies.

For those interested in exploring continuous granulation or extrusion, Thermo Fisher provides not only the hardware but also application support and collaborative opportunities. We encourage you to review our published case studies or speak with our experts to learn how Thermo Fisher Scientific can support your next formulation challenge.

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