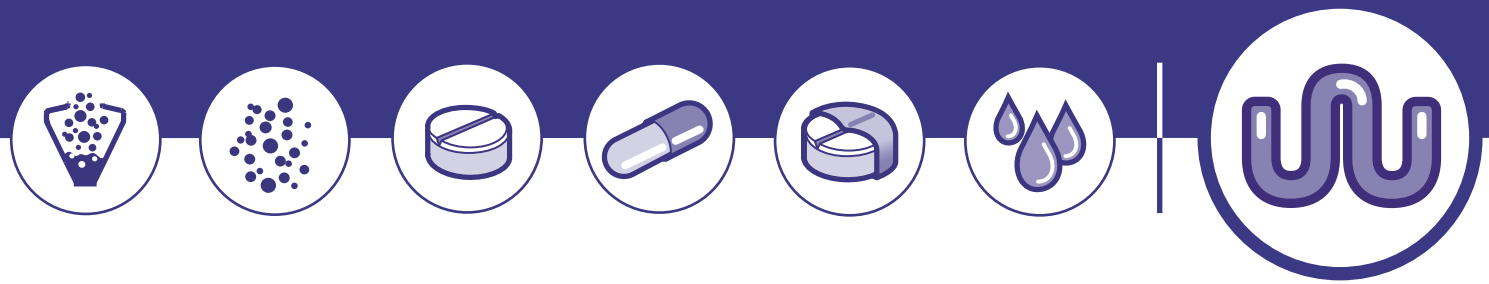
Extrusion-Molding-Coating process advantages for Continuous Manufacturing of oral solid dosage forms.

In exclusively for
International Pharmaceutical Industry, June 2021



In collaboration with CONTINUUS™ pharmaceuticals

IMA ACTIVE
Solid Dose Solutions

Case study

Extrusion-Molding-Coating process advantages for Continuous Manufacturing of oral solid dosage forms.

In collaboration with
CONTINUUS™ pharmaceuticals

Introduction

Traditionally, pharmaceutical industry has employed batch processes to manufacture solid oral dosage forms. In batch manufacturing, the typical lead time of a solid oral dosage form can be up to 1 year, [1] which can result in drug shortages in case of a significant change in the demand. In addition to major reductions in the production time and footprint, Continuous Manufacturing decreases the manufacturing costs significantly, [2] as well as the number of the unit operations involved. In batch processing, failing a quality control test may result in a large batch of material to be wasted. Continuous Manufacturing on the other hand can be coupled with in-line analytics to monitor the process material constantly and reject a much smaller quantity, in case of an anomaly. With the encouragement of regulatory bodies, [3,4] the pharmaceutical industry is shifting towards Continuous Manufacturing. Already approved drug products manufactured using continuous processes include Orkambi (US and EU) and Symdeko/Symkevi (US/EU) by Vertex, Prezista (US and EU) by Johnson & Johnson, Verzenio/Verzenios (US/EU) by Eli Lilly, and Daurismo (US) by Pfizer. [5]

This paper describes the principles and operation of the Extrusion Molding Coating (EMC) Unit operation at CONTINUUS Pharmaceuticals for Continuous Manufacturing of solid oral dosage forms starting from the active pharmaceutical ingredient (API) and excipients. The EMC unit has a mean residence time of a few minutes and is fully contained and automated. The capabilities and advantages of the EMC unit are discussed, in addition to its integration to upstream unit operations. The EMC unit has been extensively studied both as a stand-alone unit operation and as part of an integrated Continuous Manufacturing pilot plant [5,6] and proved its robustness and reproducibility during integrated runs over multiple days.

Extrusion and Injection Molding Technologies

A versatile method for Continuous Manufacturing of solid oral dosage forms from the API and excipients is integrated hot melt extrusion and injection molding. Hot melt extrusion (HME) has been used in many industries including plastics and food industries, and more recently the pharmaceutical industry as well, due to its efficiency in increasing bioavailability of poorly soluble drugs, [7] in addition to facilitating taste masking. [8] The process starts with feeding of powder API and excipient(s) into the extruder hopper in the desired ratio via gravimetric feeder(s). Depending on the formulation, the API can be pre-blended with the excipients or fed separately. While the mixture progresses through the extruder screw(s) and is being mixed, the temperature is elevated to melt the polymer(s) or the mixture, and obtain a homogeneous melt, facilitated by application of shear. The mixture is then passed through a die under high pressure and the extrudate is collected for further processing. There are extensive number of publications on HME, [9] facilitating the ease of selecting the suitable polymers for the desired solid oral dosage form properties. Different polymer properties can be utilized depending on the melting point of the API, whether it is crystalline or amorphous in the dosage form, and the desired drug release profile. The extruder barrel can be separated into different zones to customize the temperature gradient. Furthermore, the extruder can have a single screw or twin screws, and while the diameter of the screw can vary from 18 to 30 mm in the pilot scale, it can exceed 50-60 mm in the manufacturing scale. [10] The screw configuration can also be customized to modify the mixing and shear the mixture experiences. Vents can be implemented to the extruder to release trapped moisture inside the mixture.

Injection molding (IM), which has also been used in the plastics industry, consists of filling the melt into pre-designed mold cavities while applying a certain amount of pressure to produce the desired solid form. The molds can be customized to accommodate different tablet sizes and shapes, which affect the tablet properties. Combining the benefits of HME and IM processes was initially studied by the Novartis-MIT Center for Continuous Manufacturing [11] and further investigated by

other research groups. [12,13]
More recently, a fully integrated HME and IM process equipment has been developed by Continuus Pharmaceuticals and IMA. This unit, Extrusion-Molding-Coating (EMC), includes the extrusion, the molding and the coating processes and it is a fully customized and patented machine which allows the Continuous Manufacturing of solid oral doses directly from the powder API and excipient(s).
As visible from **Figure 1**, the powders are directly fed into the twin screw extruder which allows the melting and mixing of the formulation and the homogeneous material flows till the injection unit. Here, the material is injected into the mold simultaneously with the injection of the coating materials. The final shaping occurs thanks to cooling and hardening of the material in the mold cavities,

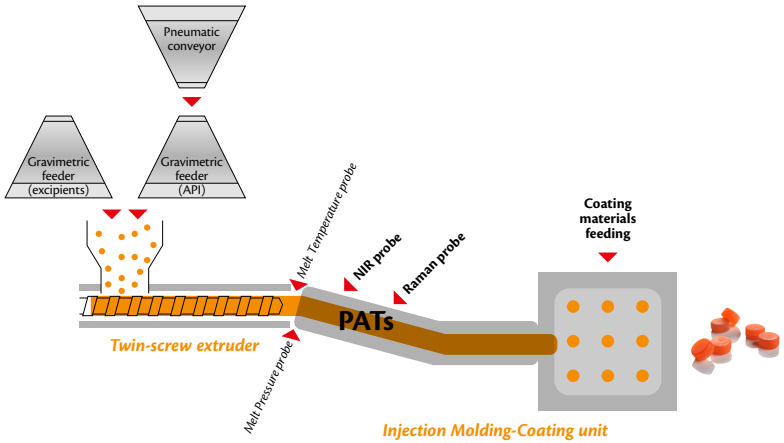


Figure 1. Extrusion-Molding-Coating (EMC) schematic view.

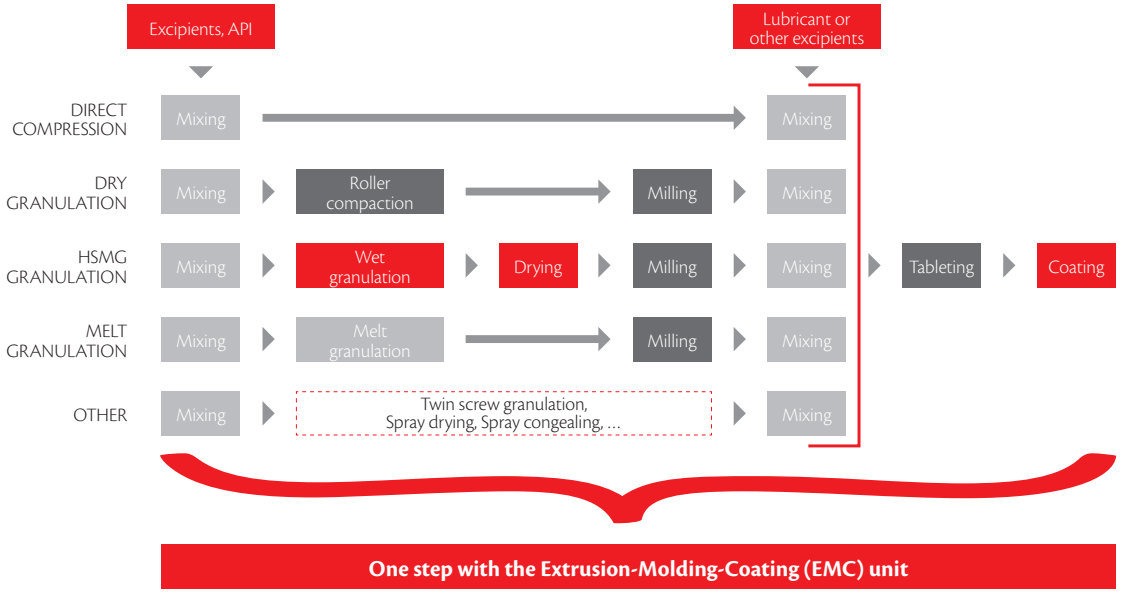


Figure 2. General schematic tableting process used to produce most solid dosage forms vs. integrated continuous Extrusion-Molding-Coating unit (EMC).

and lastly the drug product is automatically ejected and collected for packaging.

Batch vs. Continuous Manufacturing of Solid Oral Dosage Forms via the Extrusion-Molding-Coating (EMC) Unit

Currently, the majority of solid dosage forms are produced by a series of batch processes consisting of blending, wet granulation, drying, sizing, secondary blending, and tableting (**Figure 2**).
All these steps and processes have an associated cost, occupy space and require energy and personnel. In addition, they add time for process and scale up development, as well as for the quality control testing of the outputted intermediate material. Granulation is employed to avoid challenges associated with powder handling, such as: poor flowability, segregation and low bulk density, static electricity; and powder compaction properties. For instance, during wet granulation, a solvent is added to the powder blend to facilitate binding of powder particles into granules. Subsequently this product undergoes a drying step. As the typical granulation process might produce a broader particle size distribution than required, a corrective sizing step such as milling is included after the drying process. This milling step is highly energy consuming. The particles that did not pass the size criteria may be discarded or recycled and fed into the granulator,

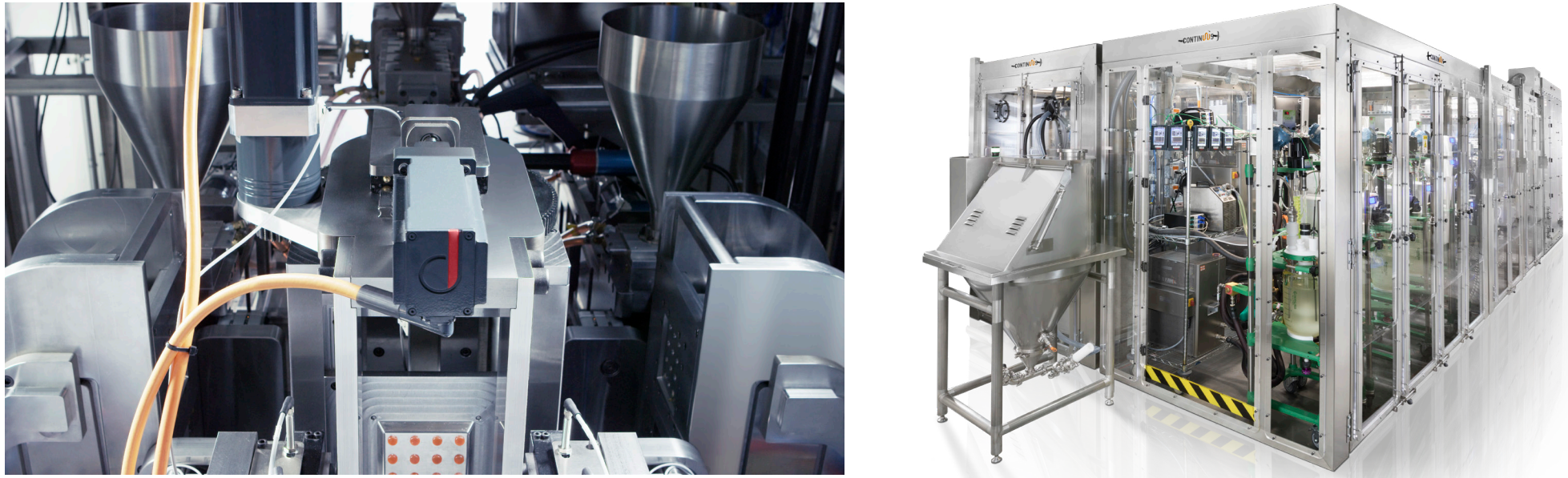


Figure 3. Extrusion-Molding-Coating unit (EMC) which is a fully integrated extrusion and injection molding/coating equipment (left) and Integrated Continuous Manufacturing (ICM) Pilot Plant where EMC allows the Drug Product manufacturing (right).

reducing the overall efficiency of the operation. This entire series of batch processes can be replaced by the integrated hot melt extrusion and injection molding system (the EMC unit) at Continuus Pharmaceuticals (**Figure 3**). [5,6]

The EMC process is fully automated, the API and excipients are fed into the extruder by gravimetric feeders. The drug load of the final dosage form can be controlled by adjusting the feed rates of the API and excipient streams accordingly. The gravimetric feeders can be automatically fed by a pneumatic conveying system as integration with the upstream unit operations. This allows for a fully contained setup that prevents operators' exposure to potentially hazardous APIs. The twin screw extruder mixes and melts the formulation with the application of shear at high temperatures, and outputs a homogeneous melt into the transfer manifold, which connects the extruder to the injection unit. The mixture is then injected into the cavities of the tablet mold, where it cools down and solidifies. These tablets are then ejected from the mold and collected for further packaging. This entire process, from the extruder to the final molded drug product, has a mean residence time of approximately 5 minutes. Furthermore, the process does not require the usage of solvents, hence no further drying is necessary. This eliminates the need to test for residual solvent content as well. The process also reduces the number of personnel needed for operation significantly, as it is fully automated. In addition, since it has a high powder containment, it does not expose the operator(s) to hazards that come with having loose powder as part of the process. As it can be remotely controlled, safety concerns related to mechanical movements are also eliminated. Process analytical technologies (PATs) can be used in-line to continuously monitor the process performance, without the need of sampling, reducing off-line analytical work required. The process is highly versatile as it can be used for solid dosage forms with crystalline or amorphous APIs, low and high dosage strengths, as well as immediate-, modified- and controlled-release drug delivery systems, thanks to the availability of polymers with a wide variety of melting temperatures and solubility profiles.

The EMC Unit applications

The EMC unit operation has been studied extensively both as a standalone unit operation and integrated with upstream unit operations as part of an end-to-end integrated Continuous Manufacturing (ICM) pilot plant (**Figure 3**). [5,6] The end-to-end ICM pilot plant case study aimed at producing a commercially available generic drug, which is currently manufactured by batch processing, from its commercially available raw materials. The ICM plant continuously ran for 5 days and produced API which was constantly conveyed to the EMC over 3 days. In this study, a specific ratio of API and polymer blend was used and it was shown that the EMC produced in-specification tablets. [14] Prior to the final continuous run, the first part of the work has been a thorough preformulation and formulation study carried out simultaneously with evaluation of process feasibility and development. After some testing for process cycle development and automation of the process steps, Continuous Manufacturing runs were performed. The process cycle included selection and optimization of all process parameters like the twin screw speed, material's back pressure on the system, shot size for the injections, injection pressure profile, process individual zone temperatures, etc.

The aim of this work was to prove that the EMC is able to continuously produce in-spec tablets over multiple days and the drug product quality attributes were reproducible throughout the run.

The critical quality attributes (CQA) for these tablets included tablets physical attributes, API crystal form, API assay and uniformity of dosage units, individual and total impurities, and dissolution time. Content uniformity is essential to provide the same dosage strength in each dosage form. API crystal form is another key factor affecting performance of the dosage form since different crystal forms may have significantly different attributes such as solubility, dissolution rate and stability. During these experiments, in-line PATs were implemented: a nIR probe was used to monitor the assay/content uniformity of the API in the melt and a Raman probe was used to monitor the API's solid state. A combination of mass balance and HPLC was used as the corresponding off-line analyses to nIR and a combination of XRPD and DSC for Raman spectroscopy. A correlation between off-line primary analytical techniques and in-line PATs was assessed. The nIR API content predictions were shown to match the analysis results given by HPLC, and the API solid state predictions were compliant with the XRPD and DSC results. The critical process parameters were monitored, studied and controlled. Moreover, an additional work aimed at developing a model-based predictive in vitro dissolution testing was performed to demonstrate the equivalence of the predictive model to the routine off-line in vitro dissolution testing according to USP. This study proves unit robustness and process performance reproducibility and shows that the EMC unit can continuously manufacture tablets that are within specification over multiple days of run time.

Conclusions

The amount of time, energy, footprint, cost, and number of equipment and personnel involved in pharmaceutical manufacturing can be reduced drastically by switching from batch to continuous processing. The Extrusion-Molding-Coating (EMC) unit can continuously produce solid oral dosage forms from the API and excipient powders within minutes, replacing multiple unit operations including granulation, drying, and milling, and without the use of solvents. It is a robust process that consistently produces dosage forms with specification; it is a fully contained and automated system, improving operator safety and product quality. Critical quality attributes such as API crystallinity and content uniformity are monitored in-line to ensure product quality. While extrusion improves bioavailability of poorly soluble drugs, as well as their taste masking, injection molding provides the flexibility to form tablets of different size and shapes, making the EMC unit an attractive alternative to batch manufacturing of solid oral dosage forms ■

References

1. Adamo A. et al., *On-demand continuous-flow production of pharmaceuticals in a compact, reconfigurable system*, "Science", 352, 61–67, 2016.
2. Schaber S. D. et al., *Economic Analysis of Integrated Continuous and Batch Pharmaceutical Manufacturing: A Case Study*, "Ind. Eng. Chem. Res.", 50, 10083–10092, 2011.
3. Allison G. et al., *Regulatory and Quality Considerations for Continuous Manufacturing*, "Continuous Manufacturing Symposium, May 20-24, 2014", "J. Pharm. Sci.", 104, 803–812, 2015.
4. Nasr M. M. et al., *Regulatory Perspectives on Continuous Pharmaceutical Manufacturing: Moving from Theory to Practice*, "International Symposium on the Continuous Manufacturing of Pharmaceuticals, September 26-27, 2016", "J. Pharm. Sci.", 106, 3199–3206, 2017.
5. Hu C. et al., *An automated modular assembly line for drugs in a miniaturized plant*, "Chem. Commun.", 56(7), 1026–1029, 2020.
6. Testa C. J. et al., *Design and Commercialization of an End-to-End Continuous Pharmaceutical Production Process: A Pilot Plant Case Study*, "Org. Process Res. Dev.", 24, 2874–2889, 2020.
7. Repka M. A. et al., *Applications of hot-melt extrusion for drug delivery*, "Expert Opin. Drug Deliv.", 5, 1357–1376, 2008.
8. Maniruzzaman M. et al., *Taste masking of paracetamol by hot-melt extrusion: an in vitro and in vivo evaluation*, "Eur. J. Pharm. Biopharm.", 80, 433–442, 2012.
9. Crowley M. M. et al., *Pharmaceutical Applications of Hot-Melt Extrusion: Part I*, "Drug Dev. Ind. Pharm.", 33, 909–926, 2007.
10. Patil H., Tiwari R. V., Repka M. A., *Hot-Melt Extrusion: from Theory to Application in Pharmaceutical Formulation*, "AAPS PharmSciTech", 17, 20–42, 2016.
11. Mascia S. et al., *End-to-End Continuous Manufacturing of Pharmaceuticals: Integrated Synthesis, Purification, and Final Dosage Formation*, "Angew. Chem. Int.", 52, 12359–12363, 2013.
12. Melocchi A. et al., *Evaluation of Hot-Melt Extrusion and Injection Molding for Continuous Manufacturing of Immediate-Release Tablets*, "J. Pharm. Sci.", 104, 1971–1980, 2015.
13. Puri V. et al., *Development of Maltodextrin-Based Immediate-Release Tablets Using an Integrated Twin-Screw Hot-Melt Extrusion and Injection-Molding Continuous Manufacturing Process*, "J. Pharm. Sci.", 106, 3328–3336, 2017.
14. *Feasibility studies of Continuous Manufacturing of Injection Molding Tablets via Extrusion-Molding-Coating (EMC)*, https://ima.it/pharma/feasibility-studies-of-continuous-manufacturing-of-injection-molding-tablets/, https://www.pharmtech.com/view/continuous-manufacturing-of-injection-molding-tablets