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RESEARCH ARTICLE

# Extrusion for pharma applications: An update

**Maël Gallas**[1,2] | **Pascal Boulet**[2] | **Victoire de Margerie**[1]

[1]Rondol Industrie, Nancy Cedex, France

[2]Institut Jean Lamour, UMR 7198 CNRS-Université de Lorraine, Nancy, France

**Correspondence**
Victoire de Margerie, Rondol Industrie, 2 Allée André Guinier, 54000 Nancy Cedex, France.
Email: victoire36@icloud.com

**Abstract**

This paper aims to give an overview of our current research and development on hot-melt extrusion (HME) for pharmaceutical formulation and drug delivery. Unfortunately, a large percentage of marketed drugs (40%) and those in the development pipeline (90%) are poorly water soluble. We use a few examples to show that solubility of APIs can be drastically improved by using HME to mix them with different biocompatible polymers and playing with the various process parameters (extrusion temperature, screw speed, screw configuration, etc.). The advantages of this technique are then presented as well as the further development needed to make this process fully industrial for pharmaceutical purposes.

**KEYWORDS**

drug delivery, drug formulation, hot melt extrusion, pharma polymers, vertical extrusion

## 1 | INTRODUCTION

Hot-melt extrusion (HME) technology is well-known by the food industry (pasta and chocolate) and also widely used for producing/shaping many materials (plastics, aluminium, and composites), but it has only been of interest for the pharmaceutical industry since the early 2000s.[1]

HME is a process which integrates several unit operations and in which the main material gets into the machine through a feeder and is then combined with various ingredients/additives to create the final product. Raw materials progress into a metal tube (the barrel) where they are very precisely heated up in a liquid state (the melt) and mixed thanks to the screws included in the barrel that create the 'mashing' effect. The melt is then pushed through a die (that gives the final shape) and cooled down (through air or water cooling), making the product available for further downstream processing.[2,3]

Over the last 20 years, hot melt extrusion (HME) has received a widespread interest as a continuous manufacturing technology in the pharmaceutical industry. Various drug delivery systems can be produced using this technology including pellets, tablets, films, implants, and nano-delivery systems.[4,5]

The main advantages of HME are that it is a cost-effective and solvent-free process that allows rapid production of drug formulations.[6–11] Active pharmaceutical ingredient(s) (API) sometimes are very expensive (above 1000 USD a gram) and therefore can benefit from micro-scale machines to minimize and control the batch size (50 g minimum lot size for a 10 mm extruder versus 1350 g for a 30 mm extruder) and hence, trial costs involving those APIs (if one 2 kg trial on a dosage form that includes 10% of a 5 k USD per g API costs 1 million USD, who would want to conduct a series of hundreds of trials to bring a new receipt for FDA approval and further industrialization? It becomes much more feasible with a trial of 100 g offering the same precision at a 50 k USD cost, etc.).

Also it is difficult to process API because they are usually sticky, temperature sensitive and shear sensitive

materials, therefore requiring optimization of all process parameters (barrel temperature, screw configuration, screw speed, melt pressure, etc.) or ingredients (plasticisers, $CO_2$, etc.) to lower the shear forces needed or the temperatures required to properly mix the final product, while avoiding thermal degradation.

Also controlling these process parameters with the smallest possible deviation is crucial to optimize the interference of the API with the functionality of the other components in the formulation (e.g., vitamin E TPGS has been reported to plasticise polyethylene oxide and enhance drug absorption by suppressing its melting point).

For the development of successful drug delivery products that must meet specific quality requirements, the impact of process parameters has therefore been widely investigated in the literature.[10–12] Varying parameters can influence the uniformity of mixing, the physical state of incorporated drug and/or the drug release profile from the drug delivery system.[13,14]

Pharmaceutical class extruders must also meet regulatory requirements—the metallurgy of the contact parts must not be reactive, additive or absorptive with the product and the equipment must be configured for the cleaning and validation requirements associated with the Good Manufacturing Practices (GMP).[15]

Despite the potential of HME as an innovative technology and the advantages it offers, still few marketed drug-containing pharmaceutical products have been successfully manufactured while using HME,[16] mostly amorphous solid dispersions (ASD) that comprise blends of drug and polymer and that demonstrated improved bioavailability in vivo as compared to crystalline systems.[17–19] Table 1 describes the various types of biocompatible polymers with their main characteristics desired and undesired for extruded pharmaceutical products.

## 2 | NEW DEVELOPMENTS THANKS TO VERTICAL EXTRUSION

HME has already demonstrated in horizontal format its capability to offer specific advantages to address challenging pharmaceutical applications (more efficient for the patients, more easily compliant with FDA requirements and less capital intensive for the industry).

For example, the collaborative project between Rondol, BASF and Queen's University Belfast to develop and manufacture a robust child friendly fixed dose combination (FDC) of Artemether and Lumefantrine while reducing the dose strength of Lumefantrine and the frequency of administration of the FDC show promising results[20] as the potency of the high-cost API is improved.

We think that we can now further enhance extrusion process capability and reduce its cost thanks to the innovative vertical twin screw extruder from Rondol (Figure 1) that offers better mixing capability and temperature control along the zones of the barrel. It also allows for more efficient cooling and reduced contamination risks thanks to the removal of horizontal conveyors. In addition, it offers a low footprint of 0.5 $m^2$ comparing to 2.5 $m^2$ for horizontal extruders. And this while accommodating downstream auxiliary units with the same footprint.[21]

In more details,[22] the following steps were achieved in order to develop the 10 mm 40/1 vertical extruder starting from a 'classical' horizontal 10 mm 20/1 extruder:

- Lengthened the barrel in order to smoothen the mixing process for APIs that are fragile by nature.
- Positioned eight heating/cooling zones all along the barrel in order to better monitor the processing temperature of APIs that usually have a narrow range between melting and degradation.
- Changed metals used to manufacture parts (high-grade stainless-steel precision engineered).
- Redesigned many external parts (for easier feed or to avoid contamination between lots due to powder that would remain stuck in notches) and many internal parts (to make 'change over' easy in between lots).
- Made the extruder vertical to further reduce the contamination risk (thanks to gravitation) and to further decrease capital intensity of the process (thanks to the machine footprint divided by 5).
- Optimized the settings between screw configuration and speed, motor power and torque in order to start the mixing quicker/smoother and extract the filament with strong/stable pressure for easier downstream steps.

The joint work between Rondol, Queens University Belfast, Birmingham School of Pharma and Institut Jean Lamour to reformulate Hydroxychloroquine while using BASF Soluplus as a model polymeric carrier and both horizontal and vertical 10 mm twin screw extruders clearly demonstrated improved robustness with the vertical versus the horizontal extruder. The reduced variation of process parameters with the vertical extruder will enable high performance continuous manufacturing with minimum waste of (expensive) raw materials.[19]

Other recent examples include the common work between Rondol, Seqens and Institut Jean Lamour on acetylsalicylic acid (ASA) (Figure 2). It shows that ASA can be fully amorphous at loadings of up to 45% w/w

**TABLE 1** Various types of biocompatible polymers used in HME pharmaceuticals products

| Polymer | Medicines on the market | Grade | $T_g$ (°C) | $T_{degradation}$ (°C) | + | − |
|---|---|---|---|---|---|---|
| Povidone, polyvinyl pyrrolidonePVP | Resulin®<br>Cesamet® | Kollidon® 30 | 168 | 175 | Potential for H-bonding<br>Easily milled | Residual peroxides<br>Hygroscopic<br>API must be plasticized |
| | | Kollidon® 17 PF | 140 | 217 | Highly water soluble<br>Povidone suitable as solubilizer and crystallization inhibitor | |
| | | Kollidon® 12 PF | 72 | 196 | Highly water soluble<br>Povidone suitable as solubilizer and crystallization inhibitor | |
| Vinylpyrrolidone-vinylacetate copolymer (MW 45,000–70,000) | Kaletra®<br>Belsomra®<br>Viekirax®<br>Technivie®<br>Venclyxto®<br>Venclexta®<br>Maviret®<br>Mavyret® | Kollidon® VA 64 | 101 | 230 | More hydrophobic than vinylpyrrolidone<br>Recently obtained GRAS/SA status (Generally Recognized As Safe/ Self-Affirmed) by the U.S. Food & Drug Administration (FDA) for use in food and nutritional supplements e.g. vitamin and mineral tablets | |
| Polyethylene glycol, vinyl acetate, vinyl caprolactam graft copolymer (MW 90,000–140,000) | | Soluplus® | 70 | 250 | Very easily processed<br>amphiphilic properties<br>solubilizing high concentrations of poorly water-soluble APIs in amorphous solid dispersions (ASDs)<br>No chemical degradation even after extrusion at 220 °C<br>Low glass transition temperature for Soluplus® allows for lower temperatures during extrusion processes, resulting in less thermal stress to APIs<br>Solubility effects due to pH shifts can be avoided | |
| Hydroxypropyl cellulose (HPC) (MW 95,000) | Covera-HS®<br>Isoptin® SRE | Klucel® LF | 111 | 227 | Increased formulation stability<br>Nonionic polymer | |
| Hydroxypropylmethyl cellulose (HPMC) (MW 150,000) | Nurofen Meltlets lemon®<br>Opana ER® | Methocel™ K100M | 96 | 259 | Excellent nucleation inhibition<br>Non thermoplastic | Difficult to mill<br>API must be plasticized |

(Continues)

TABLE 1 (Continued)

| Polymer | Medicines on the market | Grade | $T_g$ (°C) | $T_{degradation}$ (°C) | + | − |
|---|---|---|---|---|---|---|
| Hydroxypropylmethyl cellulose (HPMC) (MW 25,000) | Nucynta®<br>Palladone®<br>Onmel®<br>Noxafil®<br>Eucreas®<br>Adalat SL®<br>Lacrisert® | Methocel™ K100LV | 147 | 259 | Excellent nucleation inhibition<br>Non thermoplastic | Difficult to mill<br>API must be plasticized |
| Hydroxypropyl methyl cellulose acetate succinate (HPMCAS) | | Affinisol™ | 115 | <250 | Excellent nucleation inhibition<br>Non thermoplastic | Difficult to mill<br>API must be plasticized |
| Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonio ethyl methacrylate chloride) 1:2:0.2 | | Eudragit RL® | 63 | 166 | Ionic polymer soluble above pH 5.5 | ionic polymer soluble above pH 5.5<br>API must be plasticized |
| Poly(methacrylic acid-co-methyl methacrylate) 1:1 | | Eudragit L® | 111 | 176 | Ionic polymer soluble above pH 5.5 | Ionic polymer soluble above pH 5.5<br>API must be plasticized |
| Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethylmethacrylate chloride) 1:2:0.1 | | Eudragit RS® | 64 | 170 | Ionic polymer soluble above pH 5.5 | Ionic polymer soluble above pH 5.5<br>API must be plasticized |
| Poly(butyl methacrylate-co-(2-demethylamino ethyl) methacrylate-co-methyl methacrylate) 1:2:1 | | Eudragit E PO® | 52 | 250 | Ionic polymer soluble above pH 5.5 | Ionic polymer soluble above pH 5.5 |

Sources: G. Gabriela et al. Polymer Selection for hot-melt extrusion Coupled to Fused Deposition Modeling in Pharmaceutics, Pharmaceutics, 2020, 12(9):795; J. C. Dinunzio et al. Melt extrusion In Formulating poorly water soluble drugs. Springer Science + Business Media, 2012; pp. 311–62; K. K. M. Kolter et al. Hot-melt extrusion with BASF pharma polymers—extrusion compendium. 2nd Revised and Enlarged Edition ed. Ludwigshafen, Germany: BASF SE, 2012.


**FIGURE 1** Vertical all in one extruder twin screw 10 mm 40/1 D (left) and horizontal twin screw 10 mm 20/1 D (right) RONDOL Industrie

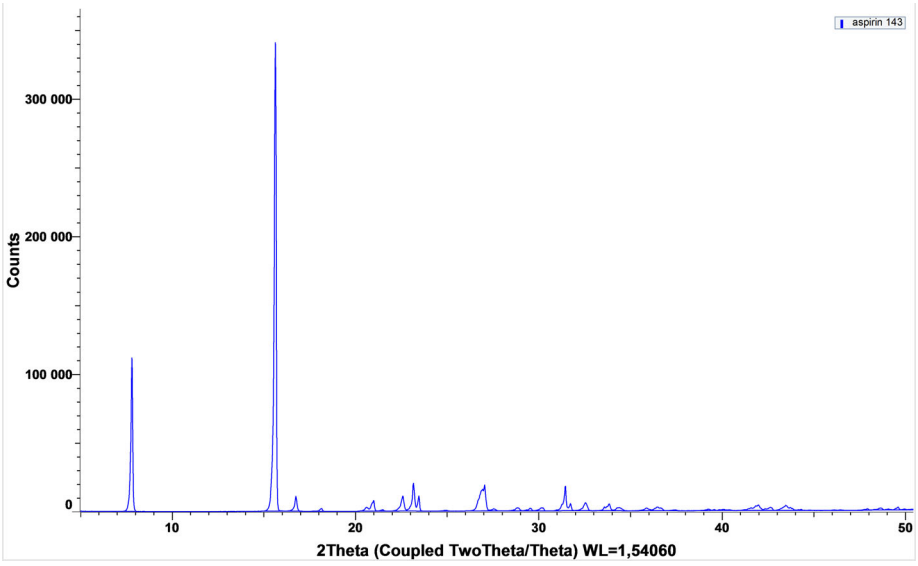


**FIGURE 2** XRD diffraction pattern for pure aspirin

(Figure 3) and remains so more than 6 weeks after the manufacture which is promising for their long-term stability. This opens up the door for a wider use of aspirin beyond pure painkilling applications and in the field of oncology.

Several parameters of the extruder, displayed in Figure 1, can play an important role in the dissolution of aspirin and more generally for pharmaceutical products. Depending on the mixture (drug + excipients polymer, plasticizer, etc.) these parameters should be precisely adjusted. First of all depending on the melting point of the API and on the glass transition temperature of the polymer, the temperature profile along the screw should be carefully determined. For example as explained below, we recently started to work on Camostat and found that it melts 10°C lower when it is previously mixed with 30% Soluplus. Taking account on our studies on HCQ,[19] ASA, and Camostat, the most important effect of the extruder is to increase the interaction of the API and excipient. First due to the precise mixing along the screw, the dispersion of the nanoparticles into the excipient progressively increases. But the dispersion is not the only key parameter as taking account on the decrease of the melting point of Camostat explained before, the interaction of the API with the excipient itself should also be an important parameter.

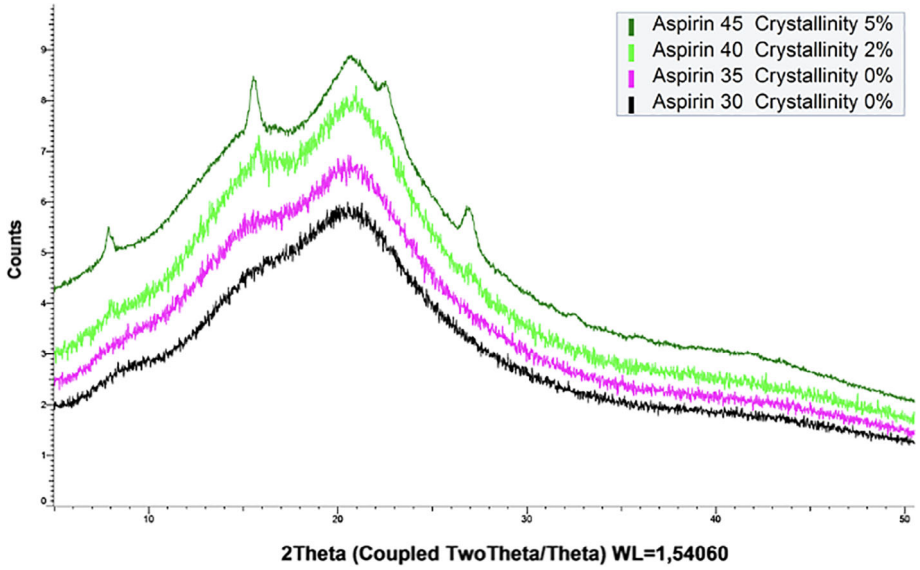


**FIGURE 3** XRD diffraction patterns for 30, 35, 40 and 45% w/w ASA-loaded pellets manufactured via hot melt extrusion at 130°C

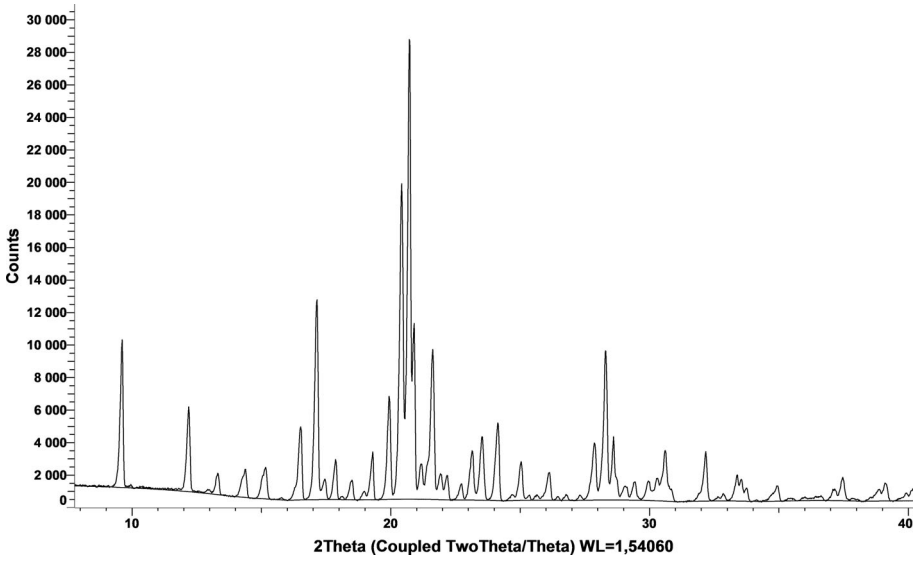


**FIGURE 4** XRD diffraction pattern of the pure Camostat

**TABLE 2** Determination of crystallinity of extruded Camostat sample by X-ray diffraction

| Sample number | Camostat (%) | Soluplus (%) | Kollidon 12PF (%) | Crystallinity after extrusion (%) | Crystallinity after 12 weeks in a closed atmosphere (%) |
|---|---|---|---|---|---|
| 1 | 60 | 40 | – | 6 | – |
| 2 | 50 | 40 | 10 | 3 | 4 |
| 3 | 40 | 60 | – | 10 | 14 |
| 4 | 30 | 70 | – | 6 | 10 |
| 5 | 40 | 50 | 10 | 1 | 2 |

So we recently investigated the behavior of Camostat (CAM) known as a serine protease inhibitor (Figure 4). As shown in Table 2 by mixing with Soluplus we can dissolve more than 40%w/w Camostat in Soluplus by extrusion at 200°C with a screw speed of 100 rpm. Moreover, this dissolution is improved by adding 10%

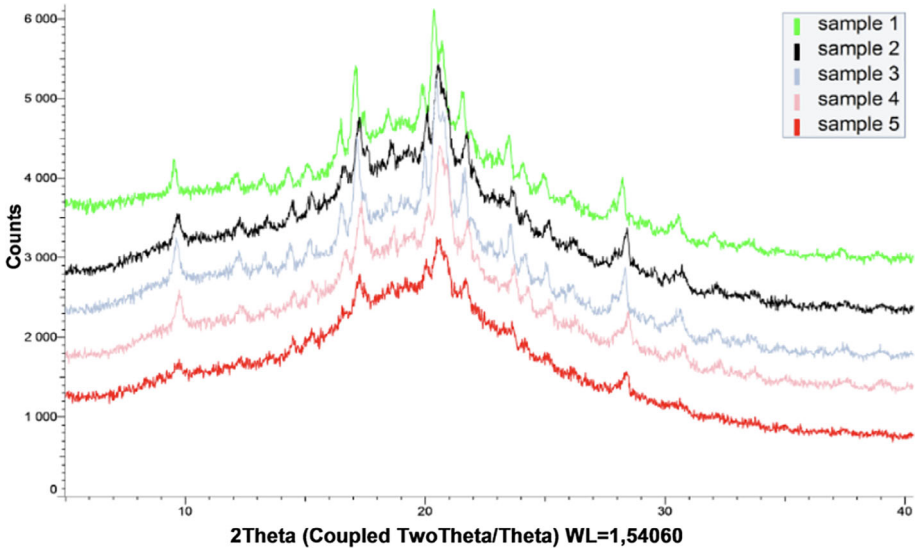


**FIGURE 5** XRD diffraction patterns for the 30, 40, 50 and 60% w/w (see Table 1) of Camostat-loaded pellets manufactured via hot melt extrusion at 200°C

of Kollidon 12PF to partly substitute for Soluplus (see sample n° 2 in Table 2). The mixture is stabilized if the sample is kept in a closed atmosphere even after 12 weeks, Figure 5 displays the x-ray diffractograms of the sample mentioned in Table 2. Moreover, keeping the sample in a closed plastic bags, XRD measurement have shown that the crystallinity does not evolves, even after 18 months, showing that the extruded mixture samples can be considered as a stable materials.

## 3 | CONCLUSION AND PERSPECTIVES

Vertical parallel twin-screw extrusion now seems to be the new frontier and the breakthrough that will make the pharma extrusion market size become bigger and HME become a standard pharmaceutical technology.

We have indeed investigated a few APIs using this new vertical extruder with specific parameters, showing a great improvement of the dissolution of the API in the excipient. This improved dissolution is due to the increase of the dispersion but also that of the interaction of the API with the excipient by applying specific parameters of the extruder. These parameters can be the temperature profile along the screw, the screw configuration, the screw speed, and so on, and obviously the correct couple API/excipient. For each mixture, all these variables need to be monitored to improve the dissolution.

The interaction of the excipient with the API should be the key parameter to study in the coming years to understand and to choose the better mixture for each API. Small angle X-ray scattering (SAXS) and more precisely Ultra SAXS (USAXS) should be carried out to investigate this interesting subject as it can provide how and where both ingredients (API/polymer) interact together.

The correlation of this interaction with the improved dissolution profile of the formulated drugs should be an avenue for lowering drugs' capital and operating costs while maintaining their therapeutic performance and reducing their secondary effects.[23] In that perspective we have created a joint project in order to develop an optimization/scale up software and predict/improve pharmaceutical products characteristics (amorphization and solubility) as a function of blend composition and extrusion process parameters.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ORCID

*Maël Gallas* https://orcid.org/0000-0002-0533-4101

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