International Journal of Pharmaceutics 479 (2015) 227–240

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

A review of pharmaceutical extrusion: Critical process parameters and scaling-up

J. Thiry *, F. Krier, B. Evrard

University of Liege (ULg), Department of Pharmacy, CIRM, Laboratory of Pharmaceutical Technology and Biopharmacy, CHU, Avenue de l'Hopital 1, B36, B-4000 Liege, Belgium

ARTICLE INFO

Article history:
Received 17 September 2014
Received in revised form 15 December 2014
Accepted 16 December 2014
Available online 22 December 2014

Keywords:
Pharmaceutical extrusion
Critical process parameters
Poorly water-soluble drugs
Cocrystallization
Scaling-up
Design space

ABSTRACT

Hot melt extrusion has been a widely used process in the pharmaceutical area for three decades. In this field, it is important to optimize the formulation in order to meet specific requirements. However, the process parameters of the extruder should be as much investigated as the formulation since they have a major impact on the final product characteristics. Moreover, a design space should be defined in order to obtain the expected product within the defined limits. This gives some freedom to operate as long as the processing parameters stay within the limits of the design space. Those limits can be investigated by varying randomly the process parameters but it is recommended to use design of experiments. An examination of the literature is reported in this review to summarize the impact of the variation of the process parameters on the final product properties. Indeed, the homogeneity of the mixing, the state of the drug (crystalline or amorphous), the dissolution rate, the residence time, can be influenced by variations in the process parameters. In particular, the impact of the following process parameters: temperature, screw design, screw speed and feeding, on the final product, has been reviewed.

Contents

Abbreviations: API, active pharmaceutical ingredient; AUDC, area under the dissolution curve; CaSt, calcium stearate; CBZ, carbamazepine; CAN, canrenone; CEL, celecoxib; CPM, chloropheniramine; DoE, design of experiment; DS, design space; DSC, differential scanning calorimetry; EC, ethylcellulos; EVA, ethylvinyl acetate; FDA, Food and Drug Administration; GRIS, griseofluvin; HME, hot melt extrusion; HPMC, hydroxypropylmethylcellulose; HPMCAS, hydroxypropylmethylcellulose acetate succinate; HPMCP, hydroxypropylmethylcellulose phthalate; IBU, ibuprofen; IND, indomethacin; ITZ, itraconazole; MPT, metoprolol tartrate; NIC, nicodamide; NMN, imodipine; NPN, ifedipine; PAR, paracetamol; PCL, poly(caprolactone); PEO, poly(ethylene glycol); PM, physical mixture; QbD, Quality by Design; SCH, sacharrin; SCP, solvent cocrystallization process; SCS, solid crystal suspension; SEM, scanning electron microscopy; SPI, spironolactone; SME, specific mechanical energy; ssEr, single screw extruder; ssHME, single screw hot-melt extrusion; TCA, *trans*-cinnamic acid; T_{deg}, degradation temperature; T_g, glass transition temperature; T_m, melting temperature; tsEr, twin screw extruder; tsHME, twin screw hot-melt extrusion; XRD, X-ray diffraction.

* Corresponding author. Tel.: +32 4 366 43 06; fax: +32 4 366 43 02.
E-mail address: jthiry@ulg.ac.be (J. Thiry).

http://dx.doi.org/10.1016/j.ijpharm.2014.12.036
0378-5173/

1. Introduction

Hot melt extrusion (HME) has become a well-established industrial manufacturing technology since its first introduction in the 19th century. Extrusion can be described as the process of converting a raw material into a product of uniform shape and density by forcing it through a die under defined conditions (Gerrens, 1994). An extruder is composed of two different parts: a conveying system and a die system. The conveying system transports the material through the barrel via the action of Archimedes' infinite screws and it can also impart a degree of distributive mixing if needed. The die system then forms the material into the desired shape.

Nowadays, more than half of all plastics are produced using this technique (Crowley et al., 2007). Moreover, extrusion has been used for a plethora of different technical applications, ranging from commercial wire formation (Dover, 1902) to the production of synthetic wine corks (Dinunzio et al., 2010). More anecdotally, extrusion is even known to be used in the manufacturing process of a McDonald's McRib sandwich (Hanna et al., 1996).

Over the last two decades, extrusion has been emerging in the pharmaceutical industry in the manufacture of various drug delivery systems such as granules, pellets, tablets, implants, transdermal systems and ophthalmic implants (Crowley et al., 2007).

HME presents many advantages such as the possibility of working without solvents, thus avoiding the need for subsequent drying steps (Bruce et al., 2005); it is a low cost process that allows fast production with a small ecological footprint and the ability to work continuously. While HME has several advantages, its use is also limited because of its difficulty in processing thermally labile drugs.

Pharmaceutical extrudates are generally produced by heating and then softening a mixture of a drug and a thermoplastic polymer followed by extrusion of the molten mass through a die. This results in the production of cylinders or films depending on the shape of the die. In addition, other excipients such as surfactants, salts, superdisintegrants, plasticizers and antioxidants may be added during the extrusion process if required (Hughey et al., 2013; Repka et al., 2007). The most common additives are plasticizers, which facilitate the extrusion process by reducing the glass transition temperature of the polymers (Crowley et al., 2007). Supercritical carbon dioxide (CO_2) can also be used as a plasticizer (Lyons et al., 2007; Verreck et al., 2006), but in this particular case, the plasticizing effect is temporary, since it returns to its gas state at room pressure and temperature. As a result of this phenomenon, the resulting extrudate is a sort of brittle hard foam.

The release of the active pharmaceutical ingredient (API) and the quality of the final product can be fine-tuned by modifying the excipients. For example, some polymers have a different dissolution pH, which can allow the targeting of a specific part of the gastro-intestinal tract (Miller et al., 2008). Some polymers can also control the release of the API in order to observe an immediate (Janssens et al., 2007), a delayed (Bruce et al., 2005) or a sustained release (Verhoeven et al., 2006). Another very important aspect to bear in mind is the affinity between the API and the polymer matrix, especially when aiming for enhancement of the bioavailability of poorly soluble drugs (Shah et al., 2013). It is for this reason that a screening process of different polymers is generally needed in order to obtain the best solid dispersion (Sarode et al., 2012). The formulation step is therefore very important because it will have a critical impact on the final quality of the product.

Since extrusion is a complex process, which is very versatile and flexible, the process parameters need to be taken into account in order to obtain the best final product (Romanski et al., 2013). The limits of the process, within which the final product will meet the previously set expectations, must be determined; this is called the "Design Space" (DS). Nowadays, the Food and Drug Administration (FDA), other regulatory agencies and standard-setting organizations are willing to establish Quality by Design (QbD) guidance relevant to the requirements of the pharmaceutical industry (U.S. Department of Health and Human Services Food and Drug Administration, 2004). These regulatory bodies suggest the use of a design of experiments (DoE) approach, which provides a structured and organized method for determining the relationship between the factors affecting a process and the response of that process to the changing of these factors. Some DoE software has helped to simplify QbD studies by overlaying confidence and prediction intervals with configurable colors onto one-factor response plots. These limits then frame the DS, which makes it easier to ensure that those limits are not violated and that researchers are working within this defined DS (Anderson, 2011). Nevertheless, the use of DoE is not mandatory in the pharmaceutical field and process parameters can be investigated without using this approach.

It is known that the optimization of processing parameters, the characterization and performance evaluation of the product, and the assessment of its stability are crucial tasks in the successful application of HME within pharmaceutical formulations (Sarode et al., 2012).

Thus this review is dedicated to a discussion of the most common process parameters and the measurement of the impact that variations in these parameters has on the quality of the final product. This review contains a detailed description of studies focusing on the following process parameters: temperature of the barrel, screw design, size and configuration, screw speed and feeding. The impact of these variations on the properties of the final product, such as the state of the API, the release of the API *in-vitro* and/or *in-vivo* is also described.

These discussions focus on the most current applications of HME for both single screw extrusion (ssHME) and twin screw extrusion (tsHME).

2. Equipment

A typical extrusion set up consists of a motor, which acts as a drive unit, an extrusion barrel, a rotating screw and an extrusion die (Chokshi and Zia, 2004).

The extruder must be able to rotate the screw at a predetermined speed. At the same time, the torque and shear generated by the extruded material and the screws must be compensated. The extruder is connected to a central control unit in order to control the process parameters such as screw speed and temperature, and therefore pressure. This electronic control unit will also act as a monitoring system (Maniruzzaman et al., 2012).

A very important characteristic to consider, whether the extrusion equipment is a single screw (ssEr) or twin screw extruder