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Controlled drug release from melt-extrudates through processing parameters: A chemometric approach

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ABSTRACT

The objective of this study was to tailor a drug release profile through the adjustment of some key processing parameters involved in melt-extrusion: die temperature, shear rate, die length and drug particle size. Two experimental designs were selected, namely a 2-level full factorial design to examine the effects and significance of the processing factors, and a central composite design of the surface responses to find the best set of factor levels to obtain given specifications of drug release. Extrudates of poly(ethylene-co-vinyl acetate) and phenylpropanolamine hydrochloride were prepared using a ram extruder. Drug release profiles from the matrix systems were fitted using a power law, for which a new mathematical expression of a burst release was provided. The burst release and exponent were selected as the responses. The processing factors had a drastic influence on the drug release. Within the domain that was investigated, the burst release and the exponent varied from 6 to 54% and 0.1 to 0.4, respectively, resulting in a time requires for 50% drug release extending from hours to weeks. These results demonstrated the possibilities of modulating the release profile by means of the processing parameters rather than through the classical approach of altering the formulation.

1. Introduction

Hot-melt extrusion (HME) is known to produce matrix systems that are able to release their active ingredients over an extended period of time, even in the cases of highly soluble drugs. However, a large burst release, i.e. the rapid release of an initial large amount of a drug before the release rate reaches a stable profile, is generally observed, especially for extrudates comprised of insoluble polymers, such as poly(ethylene-*co*-vinyl acetate) (EVAC), poly (vinyl acetate), ethyl cellulose and polymethacrylates, and water-soluble drugs. The burst effect can be seen either as detrimental to the creation of a long-term controlled-release system or, less often, as beneficial, e.g. when a rapid release of part of the dose is desired or when a variation in the release rates are required for different drugs (Huang and Brazel, 2001). Additionally, although the release of a drug can extend over a period of time that is beyond a month for some formulations, the presence of a percolation threshold may also lead to a considerable proportion of the drug remaining trapped within the matrix (Follonier et al., 1995; Zhang and McGinity, 2000; De Brabender et al., 2003; Özgüney et al., 2009; Almeida et al., 2012a).

A general approach to modulating drug release from matrix extrudates, mainly the burst release and the duration of the release, consists of varying the drug formulation either through the carrier, the additives, the drug/excipient ratio or the drug salt (see for instance Follonier et al., 1995; Zhang and McGinity, 2000; De Brabender et al., 2003; Verhoeven et al., 2006, 2008, 2009; Cheng et al., 2009; Quinten et al., 2009, 2011, 2012; Almeida et al., 2012a). The reader may also advantageously consult review articles or book chapters on the topic (McGinity and Zhang, 2003; McGinity et al., 2006; Crowley et al., 2007; Repka et al., 2012; Almeida et al., 2012b; Lang et al., 2014).

Although adjusting the formulation appears to be of the utmost importance in achieving the desired drug release patterns, the use of additives may present drawbacks for product development and may raise regulatory issues. A different and much less investigated approach is the optimization of the process parameters for the melt-extrusion, such as the temperature, shear rate, die shape and pressure at the die entrance. These processing parameters are generally set as the basis of the experimental conditions, allowing

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for, at least visually, the material to be correctly extruded. Subsequently, to achieve the desired drug release profile, most of the experiments are conducted through the modification and adjustment of the formulation. Additives are selected by comparing the drug release profiles from the various extrudate compositions, and are obtained under the same or other extrusion conditions. In this respect, because the processing parameters have not been fixed at their optimal values, any attempt to compare the performance of the final formulation may lead to erroneous conclusions. Few published papers have examined the consequences of varying the extrusion processing parameters for the production of sustained-release dosage forms on the drug release profile, Thus, guaifenesin release rates from ethylcellulose matrix tablets differed depending on the extrusion temperature (Crowley et al., 2004). The release of the model drug metoprolol tartrate from an ethylcellulose-based formulation prepared by HME was reported to be unaffected by the changes of the process parameters (Verhoeven et al., 2008). In contrast, temperature did affect the drug release of this drug from the same formulation but that was produced by injection moulding (Quinten et al., 2009), whereas it had no impact in case of Eudragit-based formulations (Quinten et al., 2012). For extrudates based upon EVAC and prepared by HME, metoprolol tartrate release was affected by low temperatures but not by the extrusion rate (Almeida et al., 2011). As for Özgüney et al. (2009), they observed a decreased release of theophylline from extrudates based upon poly(vinyl acetate) and povidone with increasing extrusion temperature, whereas a higher processing temperature resulted in a faster release of ibuprofen. This shows that the effect depends upon the relevant formulation and the production conditions that were used.

These previously discussed investigations were conducted to evaluate the processability of the formulations and they did not focus on the approach of optimizing the release profile through the processing parameters. One work that investigates this objective is that by Henrist and Remon (1999), and this work is based upon a univariate experimental design. However, using corn starch as model swellable carrier, it was not possible to significantly modify the release profile of the slightly water-soluble drug theophylline monohydrate within a wide range by simply varying the processing parameters.

The aim of the present study was thus to examine whether a drug release profile could be tailored by this approach using a typical polymer that forms heterogeneous matrix extrudates. Statistical evaluation of the impacts of some of the main HME processing factors (die temperature, shear rate, die length as well as drug particle size) was conducted in two stages. Particle size has also been considered in this investigation because contradictory results have been reported regarding the effect of this factor. First, a 2-level full factorial design (FFD) with added centre points was performed to determine the significance of the factors and the interaction effects, as well as the curvature of the model. Secondly, a central composite design (CCD) was implemented by augmenting the FFD with a group of axial ("star") points that allows for the mapping of the process with the main factors in the area of the experimental domain. Here, the objective of the CCD with response surface methodology was not so much to optimize the process, but to find the best set of factor levels to hit a target by matching given specifications in terms of the drug release profile. Such a multivariate statistical approach has been described as a chemometric approach by some authors (Rudaz et al., 2001; Gabrielsson et al., 2002; Ferreira et al., 2007).

In the present study, the freely water-soluble phenylpropanolamine hydrochloride (PPA) and the hydrophobic poly(ethylene-*co*-vinyl acetate) (EVAC) were used as the model drug and carrier, respectively. Extrusion was conducted at temperatures far below the melting point of PPA (191–196 °C, USP), so that the crystalline state of the drug could be maintained. The hydrochloride salt of phenylpropanolamine is not thermodynamically compatible with the EVAC that was used, a semicrystalline copolymer (Almeida et al., 2011) characterised by a total solubility parameter δ_2 of approximately 17 $MPa^{0.5}$ (Machado et al., 2001; Camacho et al., 2013). In fact, the total solubility parameter of phenylpropanolamine hydrochloride δ_1 can be evaluated as follows. For amines, the difference in the solubility parameter between the free bases and their hydrochlorides has been shown to be ca. 8 $MPa^{0.5}$ (Kertes, 1964, 1965). Knowing that the total solubility parameter of phenylpropanolamine base is 31.9 $MPa^{0.5}$ (Hansen, 2007), this leads to a value of roughly 40 $MPa^{0.5}$ for the hydrochloride salt. Considering that the difference $(\delta_1 - \delta_2) \approx 23$ $MPa^{0.5}$, it is far above the limiting value of ≤ 5 $MPa^{0.5}$ necessary for thermodynamic compatibility. The persistence of the PPA crystalline state in the extrudates has been evidenced by the presence of an endothermic peak in the DSC thermogram that corresponds to the melting point of the drug (data not shown). Thus, the PPA-EVAC extrudates is typical of a prolonged release system comprised of a hydrophobic heterogeneous matrix and a hydrophilic drug.

2. Materials and methods

2.1. Materials

Poly(ethylene-*co*-vinyl acetate) (EVAC 14%, Fluka Chemie GmbH, Buchs, Switzerland) was cryo-milled (particle size <125 μm) and placed in an oven to eliminate any adsorbed water. Phenylpropanolamine hydrochloride (PPA), also purchased from Fluka, was separated into various size fractions (<20, 20–40 and 40–60 μm) by sieving. These size fractions are referred as 10, 30 and 50 μm, respectively. Blends comprised of 20% w/w PPA of the different size fractions and 80% w/w EVAC were prepared before the melt-extrusion was conducted.

2.2. Extrudate preparation

Melt-extrusion was conducted using a twin bore vertical ram extruder (RH-2200 Advanced Rheometer System, Rosand Precision Ltd., Stourbridge, GB), that was equipped with a piston compression load cell (0–20 kN). A Dynesco® pressure transducer that was located 10 mm above the die entrance measured the pressure in the range of 0–69 MPa. The barrel diameter was 12 mm, and the die entrance was tapered with a 45°- half-cone angle. Platinum resistances, housed inside the barrel wall at three different locations, controlled the barrel temperature.

The polymer/drug mixture was introduced in the preheated barrel and precompacted at 0.2 MPa for 5 min. The same cycle of preheating and precompaction was repeated before running the extrusion. This step was necessary to reach thermal equilibrium and to remove entrapped air from the mixture.

Extrusion was performed for different length-to-diameter (L/D) die ratios using a fixed 2-mm diameter die, and the extrudates were collected after the pressure at the die entrance reached a

Table 1
Experimental domain.

Factor Coded value		Low level −1	Centre level 0	High level 1
Temperature (°C)	X_1	95	117.5	140
Shear rate (s^{-1})	X_2	10	25	40
Die length (mm)	X_3	12	22	32
Size fraction (μm)	X_4	10	30	50