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RESEARCH ARTICLE

The use of design of experiments to develop hot melt extrudates for extended release of diclofenac sodium

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ABSTRACT

The effect of formulation and processing parameters on processability and release from hot-melt extrusion (HME)-based matrices appears to be API and polym[illegible] was to design an extended-release formulation of diclofe[illegible] of experiment (DoE). The extrudates were prepared using a vertical lab-scale single screw extruder. A D-optimal design with 16 formulations was employed to evaluate and model the effect of diclofenac sodium, ethyl cellulose and Natrosol L levels on the release profile. The percentage of drug release at 2, 4, 8 and 16 h were the dependent variables. The formulation factors that affect drug release were identified and satisfactorily modeled. The goodness of fit (R^2) and goodness of prediction (Q^2) parameters obtained for release responses were 0.913 and 0.682 at 2 h, 0.946 and 0.67 at 4 h, 0.942 and 0.658 at 8 h, and 0.892 and 0.673 at 16 h, respectively. The design space of optimal fractions of ethyl cellulose and Natrosol L at various drug levels was successfully constructed by response surface methodology. In conclusion, the DoE approach helped to identify and quantify formulation variables that affect the release of diclofenac sodium from HME-based formulation.

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Hot-melt extrusion; design of experiments; diclofenac sodium; ethyl cellulose; hydroxyethyl cellulose; extended-release

Abbreviations: CSD: Colloidal silicon dioxide; DC: Direct compression; DoE: Design of experiments; EC: ethyl cellulose; HME: Hot-melt extrusion; PEG: Polyethylene glycol; PLS: partial least square; PM: Physical mixture; PSI: Pound-force per square inch; PXRD: Powder X-ray diffraction; Q^2: Goodness of prediction coefficient; R^2: Goodness of fit (coefficient of determination); RPM: Revolutions per minute; USP: United States Pharmacopeia

1. Introduction

There are various manufacturing techniques that have been effectively applied to prepare extended-release oral dosage forms. These techniques are mostly based on the use of polymeric systems to modulate the drug release in order to achieve the required therapeutic objectives (Liechty et al. 2010; Mansour et al. 2010). Among the different systems used to prepare oral extended release dosage forms, matrix systems whether they are hydrophilic or hydrophobic are perhaps the simplest and most cost-effective (Nokhodchi et al. 2012). In principle, they rely on homogeneous distribution of the drug into the rate controlling material(s) followed by conventional downstream processing using classical manufacturing equipment.

Hot-melt extrusion has been thoroughly investigated in the pharmaceutical field as a method to enhance the bioavailability of poorly soluble active pharmaceutical ingredient by formation of solid dispersions or solution (Sarode et al. 2013; Kate et al. 2016; Moradiya et al. 2016; Patil et al. 2016; Repka et al. 2018; Zhang et al. 2018; Alshafiee et al. 2019). Later on, however, it became far successful in preparing marketable extended release dosage form for various applications which would have been difficult to achieve using conventional manufacturing techniques (Tominaga et al. 2015; Tiwari et al. 2016). Since the pioneering work of Follonier et al. (1995), HME has established itself as a valid alternative for the manufacturing of matrix systems. In HME, the molten polymers resulted from the extrusion act as thermal binders and/or drug release retardants upon solidification and cooling. It offers advantages as being a continuous and solventless process where homogenous API distribution is achieved and compaction process can be bypassed. Nevertheless, thermal stability of the API is a prerequisite for the use of HME. Chemical and physical stability of the final dosage form may still present a challenge, especially for actives that undergo solid-state transformations upon storage (Hengsawas Surasarang et al. 2017; Censi et al. 2018).

Another underestimated drawback of HME technology for the manufacturing of extended-release drug delivery systems is that the process is complicated by miscibility of drug and carrier(s) and the effect of processing temperature(s) thereon. Thus, the effect of formulation and processing parameters on processability and release appears to be API and polymer dependent. In other words, whatever applicable for a certain formulation comprising specific levels of a model drug, polymeric carrier, plasticizer, and release modifier cannot be extrapolated to another formulation where the aforementioned formulation components have been varied. The sought release profile for another model drug might even change considerably upon switching one of the key excipients to another comparable excipient. Such lack of

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