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Hot melt extruded transdermal films based on amorphous solid dispersions in Eudragit RS PO: The inclusion of hydrophilic additives to develop moisture-activated release systems

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ABSTRACT

A series of Eudragit RS PO-based hot melt extruded films were evaluated as potential transdermal systems, with particular emphasis on the inclusion of hydrophilic excipients to allow water sorption, which in turn would allow drug release on application to the skin. More specifically, sucrose, methyl cellulose, xanthan gum (Xantural®75), poloxamer (Pluronic®F127), Gelucire 44/14 were added to Eudragit RS PO and assessed in terms of physical structure (modulated temperature DSC (MTDSC), thermogravimetric analysis (TGA), powder XRD (PXRD), scanning electron microscopy(SEM)) and *in vitro* drug release and permeation properties. In addition, the effect of prior hydration on drug permeation was studied for selected systems. Phase separation was noted for sucrose, methylcellulose (high loading), xanthan gum (high loading), poloxamer and Gelucire 44/14 (high loading) using both visual observation and MTDSC. PXRD studies indicated drug crystallization within the phase separated systems. SEM studies broadly followed the same pattern. Dissolution studies indicated that the hydrophilic excipients considerably enhanced the release rate, while Franz diffusion cell studies showed a much greater variability in effectiveness, which we ascribe to the paucity of water of hydration present which would not allow swellable additives such as xanthan to release the drug. However, films containing Gelucire 44/14 emerged as the most satisfactory systems, despite the higher additive loaded systems showing drug phase separation. This may be related to emulsification rather than swelling on contact with water, as noted for the permeation studies involving pre-hydration. This strategy therefore presents a promising approach for triggered transdermal drug delivery, activated by hydration from the skin itself.

1. Introduction

Hot melt extrusion (HME) technology presents a range of opportunities to design innovative drug delivery systems, including patches within the field of transdermal delivery. HME possesses several advantages over traditional solvent casting methods for the preparation of patches, including continuous processing and avoidance of residual solvent (Breitenbach et al., 2009; Crowley et al., 2009; Munjal et al., 2006; Palem et al., 2013). Similarly, the transdermal route offers potential advantages of improved drug pharmacokinetics, elimination of gastrointestinal absorption problems and the hepatic first pass effect, reduction of dosing and improved patient compliance (Cevec and Vierl, 2010; Delgado-Charro and Guy, 2001).

In this study we investigate a new approach whereby we include hydrophilic agents in inert HME films which, on hydration, will potentially facilitate drug release. The model drug used was ibuprofen ([2-(4-isobutyl-phenyl) propionic acid], $C_{13}H_{18}O_2$, molecular weight 206.28). Despite having the most favourable safety profile of the non-steroidal anti-inflammatory agents (NSAIDs) (Potthast et al., 2005), ibuprofen may nevertheless cause gastrointestinal tract (GIT) problems if administered orally, hence there is continued interest in developing a transdermal delivery approach for ibuprofen that can circumvent such problems (Al-Saidan, 2004; Bazigha et al., 2010; Cilurzo et al., 2005; Ghosh et al., 2010; Iervolino et al., 2001; Stott et al., 1998). The selection of ibuprofen in this study for processing *via* HME is also of particular interest, particularly in relation to possible improvements in

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polymer extrudability due to the ability of this drug to act as a plasticizer during processing (Kidokoro et al., 2001; Siepmann et al., 2006).

In this work, Eudragit RS PO was used as the base polymer. This material is a glassy copolymer synthesized from acrylic acid and methacrylic acid esters with 5% of functional quaternary ammonium groups and has been used to prepare numerous dosages forms due to its biocompatibility and biological safety (Fujimori et al., 2005; Josephine et al., 2011). It is one of the recognized materials for hot melt extrusion (Andrews et al., 2009) as well as for transdermal applications (Cilurzo and Tosi, 2006; Gohel and Nagori, 2009; Kusum et al., 2003). Indeed, the relatively high viscosity of Eudragit RS PO on heating while dispersive mixing leading to molecular amorphous dispersion has been previously noted (Kim et al., 2002; Kolter et al., 2010). Therefore, the high concentration and thermodynamic activity of ibuprofen that can be achieved in this polymer may enhance its skin permeability. Here, hydrophilic excipients were investigated for formulation with Eudragit RS PO to enable creation of moisture-triggered delivery systems that may be hydrated by the skin itself. Sucrose, methyl cellulose and xanthan gum were selected due to their hydrophilicity and tolerable immunological profiles for skin applications. Pluronic® F127 or poloxamer 407 and Gelucire 44/14 were also used as amphiphilic excipients that can act as solubilising agents. Pluronic® F127 is a non-ionic tri-block copolymer of polyoxyethylene(PEO)-polyoxypropylene(PPO)-polyoxyethylene (PEO) (Cunha-Filho et al., 2012) with an HLB value of 22 (Chi et al., 1996); this material is considered to be non-irritant and non-sensitising in topical and transdermal applications (Escobar-Chávez et al., 2006; Rowe et al., 2009). Gelucire® 44/14, with HLB value of 14, is a mixture of monoesters, diesters and triesters of glycerol, and monoesters and diesters of polyethylene glycols (Antunes et al., 2013) that belongs to the lauryl polyoxylglycerides (macroglycerides) family. Because of its numerous pharmaceutical applications, such as self-emulsification (Barker et al., 2003), and biocompatibility (Rowe et al., 2009; Li et al., 2008), this material was investigated as an adjuvant to modulate the drug release properties from the transdermal patch systems.

Here we examine the effects of hydrophilic agent inclusion on the physical structure and *in vitro* drug release properties of ibuprofen dispersions in Eudragit RS PO. More specifically, we explore the concept of using a system which is inert on storage but which acts as an occlusive layer when placed on the stratum corneum, thereby resulting in water uptake into the film. This water would then alter the structure of the film so as to allow drug permeation; such alterations may include plasticization, swelling or emulsification. Furthermore, the use of an amorphous solid dispersion of the drug in the film may maximise the thermodynamic activity of the drug compared to the crystalline form, in turn aiding permeation. Here, we examine the relationship between composition, structure and release in order to evaluate the approach but also as a means of identifying the most promising systems for further study and development.

2. Materials and methods

2.1. Materials

Crystalline ibuprofen was kindly donated by BASF (25 US Quality) and Eudragit RS powder (PO) grade by Evonik Röhm Pharma polymers. Other excipients possessing hydrophilic character used include sucrose (Sigma-Aldrich), methylcellulose (Colorcon), Xantural®75 (CPkelco), Pluronic® F127 (BASF), Gelucire 44/14 (Gattefossé SA, Saint Priest, France).

2.2. Methods

2.2.1. Preparation of hot melt extruded ibuprofen based on Eudragit RS PO

Physical mixtures of the drug and the carrier blend of Eudragit and other hydrophilic excipients were prepared by simple mixing in a pestle and mortar. The mixes were fed into a co-rotating twin screw extruder (Haake Minilab II Micro Compounder, Thermo Scientific, Germany) equipped with a slit (sheet) die (orifice). Determination of the minimum ratio between these components was based on 30% w/w ibuprofen loading. Each batch size was formulated with total weight of 10 g. Temperatures of 90–100° C from the feed to the die end were used according to the formulation prepared and a screw speed was set at 100 rpm for four minutes, which was found to be suitable for the extrusion of these mixtures. The resultant extruded films were cooled along a customised conveyer belt to room temperature. These films were separated into unit doses (patches) of roughly equal size (approximately 24 mm^3). The films were stored between aluminium sheets, except for the ones containing Gelucire 44/14, which were stored between silicone sheets due to their high tack. The extrudable mixtures obtained as described above were characterised using techniques of MTDSC, PXRD and SEM and compared when appropriate with the equivalent physical mixes. The level of tackiness of the films was measured qualitatively for the current purposes by holding these films between thumb and index finger; for further developmental studies more quantitative methods such as texture analysis are available. The *in vitro* drug release experiment (dissolution test) and *in vitro* permeation studies were also carried out for the selected optimised formulations. These experiments are detailed in the following sections.

2.2.2. Analytical methods

Modulated temperature DSC (MTDSC) measurements were carried out using TA Instrument DSC Q1000, equipped with a refrigerated cooling system (RCS). Calibration was performed prior to each analysis; temperature calibration was performed using indium, benzoic acid and n-octadecane, while heat capacity calibration was performed using aluminium oxide. Data were analysed using TA Universal Analysis 2000 software and nitrogen was used as the purge gas through the DSC cell at a flow rate of 50 ml/min. TA instruments standard pans were used for all calorimetric studies, and the mass of each empty sample pan was matched to the mass of the empty reference pan within ±0.05 mg and all measurements were performed in triplicate. For the MTDSC experiments, an amplitude of ±0.265 °C, period of 100 s and underlying heating rate of 1 °C/min were used. The samples were subjected to two steps in this method. The first step was equilibration at −70° C, isothermal heating for 5 min followed by a second step of heating to 100° C. The glass transition temperatures (Tgs) were in all cases taken at the midpoint of the transitions from the reversing heat flow signals. All measurements were performed in triplicate. Thermal stability of the materials was studied using thermogravimetric analysis, which was performed using TGA Q5000 IR (TA Instruments, U.K). Samples (10.00–12.00 mg) were subjected to a single step of heating from 30 °C to 300° C at a heating rate of 10° C min^{-1}. All TGA runs were performed in open aluminium pans with a dry nitrogen gas purged at flow rates of 25 ml min^{-1} and 10 ml min^{-1} through the furnace and TGA head, respectively. Data were treated mathematically using TA Universal Analysis 2000 software to illustrate weight loss percentage and weight derivative loss signals. The extrusion temperatures were selected on the basis of their being below the decomposition temperature of the component with the lowest thermal stability (see Appendix A). The water content in the hydration study was