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A multi-technique characterization of the stability of surfactant containing solid dispersion based buccal patches prepared by hot melt injection moulding

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ABSTRACT

This study investigates the stability of typically complex multi-component hydrophilic solid dispersions that could be used in a clinical application. Felodipine solid dispersions in two types of blends consisting of PEG, PEO and Tween 80 or Vit E TPGS were prepared by hot melt-injection moulding (HMIM) across a range of drug loadings and subjected to a range of storage conditions. Microscopy, thermal analysis, spectroscopy and powder X-ray diffraction were used to characterize the systems. The semi-solid surfactant TPGS showed a better solubilizing effect on the drug than the liquid surfactant Tween 80 in the fresh state and offered some degree of protection over the chemical degradation of PEG/PEO. Better storage stability was observed for the systems with low drug loading. Crystallization of a new metastable polymorphic form of felodipine in the patches with drug loadings at and above the saturation point was observed. Quantitative comparison of the data sets was achieved by a normalisation process and calculation of statistical variance. TPGS containing patches were more sensitive to the aging process than Tween containing patches. For both surfactants, such instability is more responsive to the storage temperature than humidity. This study established a methodology for probing the complex stabilities of multi-component dispersions.

1. Introduction

Surfactants, such as Tween 80 and TPGS, have been suggested for use as plasticizers in hot melt extruded solid dispersions to ease the extrusion process (Ghebremeskel et al., 2007; Goddeeris et al., 2008; Morris et al., 1992; Repka and McGinity, 2000, 2001). Recently it has also been reported that the addition of significant amount of surfactant can also improve the solubility of drugs in the matrix by creating phase separated surfactant rich drug compartments in which the drug is soluble (Alhijjaj et al., 2015, 2016). In some cases, the surfactants have been reported to be responsible for destabilizing the drug and cause crystallization of drug from the dispersions during storage (Galop, 2005; Ghebremeskel et al., 2006; Janssens et al., 2008; Wang et al., 2005). The mechanism of this destabilizing effect has been mainly attributed to the low T_g of such materials (Ghebremeskel et al., 2006; Janssens et al., 2008; Mosquera-Giraldo et al., 2014). However, the guidance for surfactant selection and control such destabilizing effects have been not fully developed. This study aims to contribute to a fuller understanding of the destabilization effect of the use of surfactants in hot melt extruded formulations by investigating the stability of two types surfactant-containing hot-melt injection moulded (HMIM) patches.

Whilst simple binary model systems can be of great value in understanding basic principles of stabilities of solid dispersions, practical formulations used in real clinical applications are often multi-component systems. It is clear that the likely behaviour of a clinically realistic formulation is going to be complicated. Therefore, this study systematically investigates such systems in order to be in a better position to predict how actual practical formulations will behave. The multi-component dispersion based patches described here are prepared using low temperature and single step processing without the use of organic solvents. They are mucoadhesive and could be applied clinically as buccal patches for improving the bioavailability of felodipine by bypassing hepatic metabolism which can remove up to 84% of the administered dose

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(Edgar et al., 1985). The formulations contained a mixture of polyethylene glycol (PEG), polyethylene oxide (PEO) and Tween 80 or D-α – tocopheryl polyethylene glycol 100 succinate (TPGS) in the ratio 4:3:3. This ratio was kept constant with felodipine loadings of 10, 20 and 30% w/w. The patches containing PEG/PEO and Tween 80 were abbreviated as CM1 while the ones containing PEG/PEO and TPGS were abbreviated as CM2. Previously the co-existences of multiple phases were identified in these multi-component patches (Alhijjaj et al., 2015, 2016). These phases are a surfactant rich phase containing drug and crystalline and amorphous polymer, amorphous and crystalline polymer phase which may also contain some surfactant and drug. The relationships between the phases are likely to change on storage as a result of the tendency to move to an equilibrium condition with time and the effects of temperature and humidity. If the drug is heterogeneously distributed at a microscopic level (Alhijjaj et al., 2015, 2016) there could be multiple drug crystallisation mechanisms which could result in polymorphic forms of the drug. In addition, the stability of each excipient may also impact on the overall stability of the formulations. For example, the crystalline PEG/PEO phase can exist in more than one crystalline form: a folded form and a linear form (Buckley and Kovacs, 1976; Craig, 1995). Changes of PEG/PEO from a less folded form to folded form on aging could be the secondary cause of drug instability as changes in crystallinity and crystal thickening on storage have been reported in literature (Bley et al., 2010; Damian et al., 2002; Dordunoo et al., 1997; Duong et al., 2015; Papageorgiou et al., 2006; Weuts et al., 2005). Taking into consideration of all the variables, this study first investigated the effects of the surfactants on the stability of the multi-component drug-free carrier systems. The impacts of drug incorporation on the stability of the carrier were then analyzed. Finally the effects of surfactants on the drug recrystallization were studied. The three streams of data with the use of data normalisation and variance analyses of the high quantity of thermal data allowed the analysis of the interconnected relationship between the stability of the excipients and the stability of the drug in a semi-crystalline multi-component dispersion.

2. Materials and methods

2.1. Materials

The model drug, felodipine, was purchased from Afine Chemicals Ltd (Hangzhou, China). Polysorbate (Tween® 80) with a molecular weight of 1310 g/mol and phosphorus pentoxide (P_2O_5) with a purity of 99% were purchased from Sigma-Aldrich (Dorset, UK). Polyethylene glycol (PEG) 4000 with an average molecular weight of 4060 g/mol was supplied from Sigma-Aldrich (Poole, UK). Polyethylene oxide (PEO) WSR 1105 with an average molecular weight of 900,000 g/mol was kindly donated by Colorcon Ltd (Dartford, UK). Vitamin E TPGS with a molecular weight of 1513 g/mol was kindly donated by BASF (Ludwigshafen, Germany). NaCl (≥99.0%) was purchased from Thermo Fisher Scientific (Geel, Belgium).

2.2. Preparation of placebo and felodipine loaded HMIM patches

A co-rotating twin screw bench-top hot melt extruder (HAAK MiniLab II Micro Compounder, Thermo Electron, Karlsruhe, Germany) with an injection moulding apparatus (HAAKE MiniJet System, Thermo Electron Corporation, Karlsruhe, Germany) was used in the fabrications of placebo and felodipine loaded solid dispersions. The injection mould allowed the production of patches with a final geometry of 25 mm × 25 mm × 0.5 mm. Two sets of formulations containing either Tween 80 (abbreviated as CM1) or TPGS (abbreviated as CM2) were prepared. Placebos and patches with 10, 20 and 30% w/w drug loadings were formulated with the PEG/PEO/surfactant weight ratios of 40/30/30, 36/27/27, 32/24/24 and 28/21/21, respectively. Before extrusion, physical mixtures of the formulations were prepared at different drug loadings by initially mixing of crystalline felodipine with either liquid Tween 80 or the molten TPGS (65 °C) followed by the addition of the other excipients and all the components of formulations were mixed thoroughly using a mortar and pestle for at least 2 min at room temperature. These mixtures were then fed into the extruder operating at a barrel temperature of 65 °C and a screw rotation of 100 rpm with 5 min of residence time. After extrusion, the extruded soft masses were loaded into the pre-heated cylinder of the injection moulding apparatus (65 °C). The materials were injected into the patch pre-heated mould (65 °C) under 300 bar pressure for 20 s. The patches were collected after being cooled inside the mould for 1 h at ambient temperature.

2.3. Storage conditions of the dispersion patches

After preparation, the placebo and drug loaded patches were immediately stored in four different conditions for 3-month stability testing. The four conditions are abbreviated as A, B, C and D conditions and they refer to room temperature with 0% relative humidity (RH), room temperature with 75% RH, 40 °C with 0% RH, and 40 °C with 75% RH, respectively. Storage containers containing phosphorus pentoxide (P_2O_5) were used to represent the 0% RH. Supersaturated NaCl solution was used to provide the 75% RH. A stability incubator (Genlab incubator, Genlab Ltd, Cheshire, UK) was used to provide the 40 °C condition. All samples were stored for 3 months and tested periodically.

2.4. Characterization of HMIM aged solid dispersions

2.4.1. Scanning electron microscopy (SEM)

For the purpose of comparison, fresh and aged samples at different conditions were scanned using JSM 5900LV Field Emission Scanning Electron Microscope (Jeol Ltd, Japan) equipped with a tungsten hairpin electron gun. Surfaces and cross sections (prepared by cutting the samples after dipping into liquid nitrogen) of all samples were investigated for the presence or absence of crystal growth and changes in the microstructure of the matrices. The scanned samples were coated with gold using a Polaron SC7640 sputter gold coater (Quorum Technologies, Newhaven, UK) prior to imaging.

2.4.2. Energy-dispersive X-ray spectroscopy (EDS)

In order to confirm the chemical identity of the detected crystal growth, the presence of the two chlorine atoms in the structure of felodipine were used as a chemical marker for the identification of drug crystals. EDS (INCA Energy manufactured by Oxford Instruments) combined with SEM was used. The analyses were conducted using single point X-ray acquisition mode with at least 3 points were analyzed for each morphological feature (crystals, matrix surface, matrix cross section) in the scanned area ≈ 0.5 × 0.5 cm^2 of the sample. The acquisition time was 30 s with electron acceleration voltage was 20 kV.

2.4.3. Powder X-ray diffraction (PXRD)

The diffraction patterns of the fresh and the aged samples were analyzed using Thermo ARL Xtra X-ray diffractometer (Thermo Scientific, Switzerland) equipped with a copper X-ray Tube