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Conversion of sustained release omeprazole loaded buccal films into fast dissolving strips using supercritical carbon dioxide ($scCO_2$) processing, for potential paediatric drug delivery

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ABSTRACT

This study involves the development of thin oral solvent cast films for the potential delivery of the proton pump inhibitor, omeprazole (OME) *via* the buccal mucosa for paediatric patients. OME containing films were prepared from ethanolic gels (1% w/w) of metolose (MET) with polyethylene glycol (PEG 400) (0.5% w/w) as plasticiser, and L-arginine (L-arg) (0.2% w/w) as a stabilizer and dried in an oven at 40 °C. The blank and drug loaded films were divided into two groups, one group was subjected to supercritical carbon dioxide ($scCO_2$) treatment and the other group untreated. The untreated and $scCO_2$ treated films were then characterised using differential scanning calorimetry, thermogravimetric analysis, scanning electron microscopy, X-ray diffraction, Fourier transform infrared spectroscopy, hydration (swelling), mucoadhesion and *in vitro* drug dissolution studies. Treatment of the solvent cast films with $scCO_2$ caused significant changes to the functional and physical properties of the MET films. The original drug loaded MET films showed a sustained release of OME (1 h), whereas $scCO_2$ treatment of the formulations resulted in fast dissolving films with >90% drug release within 15 min.

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1. Introduction

There has been a growing interest in the design and development of novel formulations that are age appropriate particularly for paediatric and geriatric patients with swallowing difficulties (Lopez et al., 2015). Various formulations have been proposed to address this challenge including sublingual tablets, fast disintegrating tablets, buccal films and wafers. These have the advantage of being able to hydrate or dissolve in saliva to release the drug for absorption through the sublingual/buccal mucosa or more easily swallowed when compared to large volumes of liquids or whole tablets. Liu and co-workers in a review discussed the formulation factors affecting the acceptability of traditional oral medicines (*e.g.* tablets, capsules, liquids) in children including dysphagia (difficulty in swallowing) and flexibility of oral dosage forms. The review concluded that paediatric populations will benefit from novel formulations (including films) that overcome these challenge, such as getting the right formulation for the right age group, taste, smell and palatability. (Lui et al., 2014). In addition, these solid formulations are also suitable for drugs that are unstable in liquid or semi-solid dosage forms. Furthermore, buccal or sublingual absorption avoids gastric acid degradation and hepatic first pass metabolism, which allows administration of lower doses.

A good drug candidate for such application is the proton pump inhibitor omeprazole (5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole) which is an inhibitor of gastric acid secretion. Its stability in aqueous solution is entirely dependent on the initial pH and, it is rapidly degraded in acidic and neutral conditions but shows greater stability in alkaline medium. We have previously shown the potential of OME based buccal films for sustained delivery of *via* the buccal mucosa for paediatric administration (Khan et al., 2015) and demonstrated the release and permeation of the drug across

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pig buccal membrane (Khan et al., 2016). However, though OME is well absorbed from the gastrointestinal tract its oral bioavailability in humans is about 50% which suggests first pass metabolism for this drug. Therefore oral mucosa (buccal/sublingual) absorption combined with residual GIT absorption could constitute a potential approach for improving its oral bioavailability whilst also improving compliance in patients with difficulty in swallowing.

Choi and co-workers developed buccal adhesive tablets composed of sodium alginate, HPMC and croscarmellose sodium and loaded with OME and investigated the buccal permeation of the drug across hamster cheeks. They showed that plasma concentration of OME increased and reached a maximum of 370 ng/mL in 45 min after buccal administration with an absolute buccal bioavailability of omeprazole in hamsters of 13.76% (Choi et al., 2000). In another study, permeation of OME incorporated into different cyclodextrins with and without L-arg, through pig buccal mucosa was investigated (Figueiras et al., 2009). They showed that the amounts (μg) of drug permeating per cm^2/hour (flux) increased when L-arg was present, due to its stabilising effect on the inclusion complex formed. The flux values they reported were OME (2.382 μg/cm^2/h), OME_βCD (2.685 μg/cm^2/h), OME_MBCD (3.455 μg/cm^2/h), OME_βCD + Arg (4.161 μg/cm^2/h), and OME_MβCD + Arg (5.588 μg/cm^2/h).

Proton pump inhibitors (PPIs) such as OME block the hydrogen/potassium adenosine triphosphatase enzyme situated in the stomach wall thus inhibiting acid secretion, giving relief from ulcers of the oesophagus, stomach and duodenum and from gastro-oesophageal reflux disease (GERD). PPIs change their own chemical formula with the addition of H^+/K^+ adenosine triphosphatase enzyme in the parietal cells, resulting in the formation of an active chemical derivative by gaining a proton (H^+), which increases the pH of the stomach and reduces acid secretion from the wall of the stomach. The new protonated chemical compound also possesses the ability to bind with the parietal cells in the stomach wall, thus reducing further acid secretion (Chapman et al., 2011). Therefore systemic action following administration and absorption across alternative routes such as oral mucosa membranes is possible using appropriate formulations. For example, Widder and co-workers patented unidirectional films and tablets for the delivery of PPIs across the oral mucosa (Widder et al., 2004). Mansuri and co in their review, reported that buccal mucoadhesive formulations are potential means delivering PPIs to avoid degradation in the gastrointestinal tract when administered orally (Mansuri et al., 2016).

In recent years, the application of supercritical fluid technology in formulation development has shown tremendous success in the field of drug delivery (Brunner, 2010; Tabernero et al., 2012). A supercritical fluid (SCF) can be defined as a substance above its critical pressure (P_c) and temperature (T_c) where it exists as a single phase and possesses properties of both liquids and gases (Knez et al., 2015). The liquid-like density of SCF provides solvent power similar to a light hydrocarbon and its gas-like viscosity allows excellent mass transfer and higher diffusivity in a material (Shivonen et al., 1999). A number of different SCFs have been used in various applications such as organic synthesis, cleaning and materials processing (Tabernero et al., 2012; Duarte et al., 2015). However, carbon dioxide (CO_2) remains the most widely used SCF because of the advantages such as being environmentally benign, non-toxic, non-flammable, non-corrosive, readily available, affordable and easy to remove from the reaction systems in comparison to organic solvents. The low T_c (31.15 °C) and P_c (or 73.8 bar) of CO_2 makes it an ideal solvent for the processing of numerous pharmaceutical compounds (Ginty et al., 2005). Supercritical carbon dioxide ($scCO_2$) is known to be an excellent solvent for numerous low molecular weight non-polar compounds as well as some polar compounds (Mohamed and Eastoe, 2011). It also has good solubility of selected groups of polymers such as amorphous fluoropolymers and silicones (Kendall et al., 1999). Moreover, $scCO_2$ is also capable of acting as a swelling or plasticising agent by dissolving in a polymeric matrix (Cooper, 2000).

The applications of SCFs are widely reported for several pharmaceutical operations including crystallisation, micronisation, coating, product sterilisation and drug–cyclodextrin complexation (Rudrangi et al., 2015). Similarly, it has also been successfully applied in the development of thin films and scaffolds (Falk et al., 1997; Yañez et al., 2011; Cooper, 2000; Kiran, 2016). Processing with $scCO_2$ can impart interesting characteristics in thin films and scaffolds in terms of porosity, pore structures and crystallinity. Aydin et al. (2006) synthesised a copolymer of L-lactide and epsilon-caprolactone and used the resultant polymer to prepare composite films. Subsequently, the films were treated with $scCO_2$ to prepare highly porous sponges for potential use as scaffolds in tissue engineering. They reported that the scaffold pore sizes ranged between 40 and 80 μm and showed that the $scCO_2$ fabricated scaffolds possessed enhanced cell adhesion, proliferation and differentiation of L929 fibroblast cell line culture. Rinki and co-workers prepared porous chitosan scaffolds for cell culture, by reacting chitin with alkali in the presence of ($scCO_2$) (Rinki et al., 2009). Composite chitosan-nanohydroxyapatite based scaffolds have also been prepared by means of $scCO_2$ treatment (Karakeçili and Arıkan, 2012). In their study, nanohydroxyapatite particles were added to acetic acid based chitosan gels which were subsequently frozen, dried with acetone and treated with supercritical fluid which yielded porous scaffolds, with potential for use in bone tissue bio-engineering applications. The application of $scCO_2$ in the formulation of scaffolds and effect of associated parameters (*e.g.* pressure and temperature) on such systems are very well reported in the scientific literature but studies on the effect of $scCO_2$ processing on thin films for drug delivery purposes are scanty.

The aim of this study was to investigate the effect of $scCO_2$ processing on blank (BLK) and drug loaded (DL MET) films, and compare their properties with the non-treated films. The films (both $scCO_2$ treated and non-treated) have been functionally characterised for their surface morphology, water content, physico-chemical (crystalline/amorphous nature; physical interactions), hydration (swelling), adhesive and OME dissolution properties.

2. Materials and methods

2.1. Materials

Metolose (MET) was obtained as a gift from Shin Etsu (Stevenage, UK), polyethylene glycol (PEG 400), L-arginine (L-arg) and gelatine were all obtained from Sigma-Aldrich (Gillingham, UK). Ethanol, potassium dihydrogen phosphate and sodium hydroxide were purchased from Fisher Scientific (Leicester, UK) while Omeprazole (OME) was obtained from TCI (Tokyo, Japan).

2.2. Methods

2.2.1. Formulation (gel and film) development

Preliminary 1% w/w gels were prepared by adding the required weight of polymer (MET) to the relevant solvent (20% v/v ethanol) at room temperature. The polymeric gel was heated to 40 °C following complete hydration. Based on the total weight of polymer, the plasticiser (PEG) was added to obtain 0.5% w/w concentrations in the final gel. The resultant gel was cooled to room temperature and left stirring on a water bath for 30 min to achieve a homogeneous dispersion and then left overnight to remove all entrapped air bubbles.

Once a clear homogeneous gel was obtained, 20 g was gently poured into Petri dishes (86 mm diameter) and kept in a pre-heated oven at 60 °C for 24 h. The dried films were then carefully peeled off from the Petri dish and photographs taken using a digital camera. Films were then sealed in poly bags and placed in a desiccator over silica gel at room temperature until required.

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