International Journal of Pharmaceutics 513 (2016) 302–308

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Investigating the ability of nanoparticle-loaded hydroxypropyl methylcellulose and xanthan gum gels to enhance drug penetration into the skin

X.J. Cai[a], P. Mesquida[b], S.A. Jones[a,*]

[a] Institute of Pharmaceutical Science, School of Life Sciences & Medicine, Franklin-Wilkins Building, Kings College London, London, SE1 9NH, UK
[b] King's College London, Department of Physics, Strand, WC2R 2LS London, UK

ARTICLE INFO

Article history:
Received 6 July 2016
Received in revised form 18 August 2016
Accepted 26 August 2016
Available online 28 August 2016

Keywords:
Tetracaine
Nanoparticles
Skin
Aggregation
Gel
Skin
Permeation
HPMC
Xanthan gum

ABSTRACT

Nanoparticle-loaded topical formulations can disrupt drug aggregation through controlled drug-nanoparticle interactions to enhance topical drug delivery. However, the complex relationship between the drug, nanoparticle and formulation vehicle requires further understanding. The aim of this study was to use nanoparticle-loaded hydroxypropyl methylcellulose (HPMC) and xanthan gum gels to probe how the drug, nanoparticle and formulation vehicle interactions influenced the delivery of an aggregated drug into the skin. Tetracaine was chosen as a model drug. It was loaded into HPMC and xanthan gum gels, and it was presented to porcine skin using infinite and finite dosing protocols. Gel infinite doses showed no important differences in tetracaine skin permeation rate, but HPMC gel finite doses delivered the drug more efficiently ($46.99 \pm 7.96\ \mu g/cm^2/h$) compared to the xanthan gum ($1.16 \pm 0.14\ \mu g/cm^2/h$). Finite doses of the nanoparticle-loaded HPMC gel generated a 10-fold increase in drug flux ($109.95 \pm 28.63\ \mu g/cm^2/h$) compared to the equivalent xanthan gum system ($14.19 \pm 2.27\ \mu g/cm^2/h$). Rheology measurements suggested that the differences in the gels ability to administer the drug into the skin were not a consequence of gel-nanoparticle interactions rather, they were a consequence of the dehydration mediated diffusional restriction imparted on the drug by xanthan gum compared to the viscosity independent interactions of HPMC with the drug.

1. Introduction

When a drug aggregates it exhibits different physiochemical properties in solution compared to the non-aggregated form of the molecule (Potts and Guy, 1992; Wyn-Jones and Gormally, 1983; Shore et al., 1957; Potts and Guy, 1995). Therefore, at high drug concentrations, i.e., those above the critical aggregation concentration, it can be the properties of aggregates that determine a drug's behaviour rather than the individual molecules from which the aggregates are generated. The process of physical aggregation can hinder drug delivery into the skin after topical application, but it is not traditionally investigated during topical formulation development (Cai et al., 2016a; Inacio et al., 2016). Physical drug aggregation that occurs on the surface of the skin, is reversible at lower drug concentrations (Cai et al., 2016a). However, using low drug concentrations is not an effective solution to combat the problems associated with drug aggregation in topical formulations, as reducing the drug concentration applied to the skin can also reduce the clinical response to the preparation (Cai et al., 2016a).

Nanomaterials can break up drug aggregation even at high drug concentrations through surface interactions that make the drug more available for permeation (Luengo et al., 2006; Rouzes et al., 2003; Alvarez-Roman et al., 2004; Fangueiro et al., 2012). When nanoparticles act to break up aggregation, rather than acting as a drug carrier, they act on the skin surface, within the topical formulation, as a chemical penetration enhancer (Cai et al., 2016b). If the nanomaterials are 50 nm or larger they are unlikely to enter the body and therefore this approach raises very few additional toxicity concerns (Baroli et al., 2007; Ryman-Rasmussen et al., 2006; Wu et al., 2009 Ryman-Rasmussen et al., 2006; Wu et al., 2009). However, presenting a drug-nanoparticle combination to the surface of the skin presents a challenge because semi-solid formulation excipients can interact with both the drug and the nanoparticles (Moddaresi et al., 2010). If the drug-nanoparticle

* Corresponding author at: King's College London, Institute of Pharmaceutical Science, Franklin-Wilkins Building, 150 Stamford Street, London, SE1 9NH, UK.
E-mail address: stuart.jones@kcl.ac.uk (S.A. Jones).

http://dx.doi.org/10.1016/j.ijpharm.2016.08.055
0378-5173/

equilibrium is disrupted, this may have deleterious effects on the nanoparticle penetration enhancement effects when administered to the skin (Cai et al., 2016b). Therefore, more information is required with regards to the drug-nanoparticle-delivery vehicle interactions in topical formulations that attempt to administer an aggregated drug into the skin.

A topical gel is a one-phase system and it therefore represents the simplest vehicle in which a drug can be applied to the skin. However, the gelling agent and the solvent that are combined to generate a gel do interact with the drug in order to solubilise it. Through these interactions the topical vehicle controls the drug's thermodynamic activity (Watkinson et al., 2009), it influences the drug's diffusion coefficient towards its site of absorption (Welin-Berger et al., 2001; Radebaugh and Simonelli, 1983) and it interacts with the skin barrier upon which it is deposited during the delivery process (Cross et al., 2001a; Dal Pozzo and Pastori, 1996). Therefore, a complex relationship between the gel formulation factors and drug delivery usually exists. This complexity is increased when attempting to administer both an aggregated drug and a nanoparticle to the skin because the drug concentration will influence its aggregation state and its thermodynamic activity, the gelling agent concentration will influence the vehicle viscosity and aesthetic characteristics of the preparation and the gelling agent's chemical and structure features will dictate the vehicle's interactions with the drug, the nanoparticles and the skin. Previous work that has investigated nanoparticle behaviour in topical formulations has concentrated on nanoparticle-vehicle interactions as in these published studies the drug is typically incorporated within the nanocarrier and not adsorbed to its surface like in a system where nanoparticles are used to disrupt molecular aggregation (Moddaresi et al., 2010; Hasanovic et al., 2009; Batheja et al., 2011). Therefore, in order to generate an effective nanoparticle-loaded gel that facilitates de-aggregation of a drug to enhance its penetration into the skin using nanomaterials, further research is needed to determine the relationships between the drug, gel and nanoparticles such that drug permeation into the skin from this novel preparation can be controlled.

The aim of this study was to use nanoparticle-loaded hydroxyl methylcellulose (HPMC) and xanthan gum gels to probe how the drug, nanoparticle and formulation vehicle interactions influenced the delivery of an aggregated drug into the skin. Tetracaine was selected as a model drug as it has previously been shown to aggregate (Schreier et al., 2000; Attwood, 1995). It has a slow onset of action clinically (Covino, 1980) and nanoparticles with a negative surface charge have been shown to interact with the positively charged drug and modify its behaviour (Cai et al., 2016b). The experiments were conducted at pH 8 because Ametop, a commercially marketed gel, was formulated at pH 8 and the aggregation properties of tetracaine had been previously studied at this pH (Cai et al., 2016a). HPMC was chosen to produce the semi-solid formulation due its ability to form a gel with a large pore size, which minimises the potential for the gel structure to impart diffusional restriction on the drug (Mohamed et al., 2015). A spray formulation was used to apply the HPMC system as this allowed the mixing of the nanoparticles and the drug only upon drug application, which avoided any physical instability issues that could reduce the homogeneity of dosing. The sprays were optimised in terms of evaporation kinetics, spray characterization, spray recovery and viscosity to ensure accurate dosing in the skin permeation studies. The HPMC system was compared with xanthan gum as it presented a negatively charged, tight gel and it allowed the direct use of the commercial Ametop formulation in the studies. Two drug application protocols were used to dose the drug to the skin: infinite dose and finite dose studies because it was anticipated that the formulation viscosity, which may increase during finite dosing, could be influential in the delivery of the drug into the skin. Silica nanoparticles ($Nano_{SiO_2}$) were used to represent the nanoparticle surfaces with which the model drug tetracaine could interact. $Nano_{SiO_2}$ were co-administered to the skin and no drug was encapsulated into the particles or adsorbed onto their surface prior to administration. The semi-solid dosage form's macroviscosity were measured using traditional 'cone and plate' rheometry to have a better understanding of the interactions taking place in the system, i.e., between the drug, nanoparticle and formulation.

2. Materials and methods

2.1. Materials

HPMC powder (grade 65SH viscosity 400 cP and 50 cP, brand name Metolose) was provided by Shin-Etsu Chemical Ltd., Japan. Tetracaine free base (≥98%), hydrochloric acid, acetic acid and sodium acetate were purchased from Sigma Aldrich, UK. Commercially available Ametop gels were supplied by AAH Pharmaceuticals, UK. The Ametop gel contained tetracaine, sodium hydroxide, sodium methyl-*p*-hydroxybenzoate, sodium propyl-*p*-hydroxybenzoate, monobasic potassium phosphate, xanthan gum, sodium chloride and purified water. Silica nanoparticles ($Nano_{SiO_2}$), with a diameter of 200 nm (Psi-0.2), were obtained from Kisker Biotech GmbH and Co., Germany. Ultrapure water (18.2 MΩ) was used throughout this study unless stated otherwise. Phosphate-buffered saline tablets were supplied by Oxoid Limited, UK. Acetonitrile, methanol and water (high-performance liquid chromatography (HPLC grade) were obtained from Fisher Scientific International, UK.

2.2. Formulation preparation

The HPMC solutions were prepared by stirring HPMC powder slowly into pH 8 water at 70 °C and allowing the system to hydrate for 24 h at 5 °C. The formulations were then transferred into 50 mL plastic spray bottles (Boots, UK). Three HPMC formulations were produced with polymer concentrations of 1% and 2% of Grade 65 (viscosity 400 cP, 65SH400) and 3% of Grade 65 (viscosity 50 cP, 65SH50) because concentrations above these levels were unable to spray through the nozzle of the dosing system used to apply them to the skin in the permeation studies. The xanthan gum formulation used the commercial Ametop formulation as supplied and did not need further characterisation.

2.3. Evaporation kinetics

Thirty actuations from each spray formulation (i.e. 1% 65SH400, 2% 65SH400, 3% 65SH50) were applied to a tared weighing boat on an analytical balance and monitored for weight loss after application. Weight of the formulation (g) was plotted against time (min). The rate of solvent evaporation was calculated using a line of best fit. The study lasted for 48 h to ensure the applied formulations were completely dry and no further weight loss occurred. Triplicate experiments were performed.

2.4. Spray characterisation

The spray formulation placed at a distance of 5 cm vertically above a piece of filter paper and two shots was actuated from the spray canister holding the formulation onto the filter paper. The spray was allowed to dry and the film residue shape was outlined using a marker. The shortest diameter and the longest diameter of film residue shape were measured. The measurements were used