International Journal of Pharmaceutics 502 (2016) 10–17

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Investigating the influence of drug aggregation on the percutaneous penetration rate of tetracaine when applying low doses of the agent topically to the skin

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

[a] King's College London, Institute of Pharmaceutical Science, Franklin-Wilkins Building, 150 Stamford Street, SE1 9NH London, UK
[b] King's College London, Department of Physics, Strand, WC2R 2LS London, UK

ARTICLE INFO

Article history:
Received 23 December 2015
Received in revised form 2 February 2016
Accepted 3 February 2016
Available online 20 February 2016

Keywords:
Tetracaine
Transport
Aggregation
Skin
Penetration enhancer
Pain
Drug delivery

ABSTRACT

Understanding the molecular aggregation of therapeutic agents is particularly important when applying low doses of a drug to the surface of the skin. The aim of this study was to understand how the concentration of a drug influenced its molecular aggregation and its subsequent percutaneous penetration after topical application. A model drug tetracaine was shown to form a series of different aggregates across the μM (fluorescence spectroscopy) to mM (light scattering analysis) concentration range. The aggregate formation process was sensitive to the pH of the vehicle in which the drug was dissolved (pH 4, critical aggregation concentration (CAC) – 11 μM; pH 8, CAC – 7 μM) and it appeared to have an impact upon the drug's percutaneous penetration. At pH 4, increasing the concentration of the drug in the donor solution decreased the skin permeability coefficient (K_p) of tetracaine ($13.7 \pm 4.3 \times 10^{-3}$ cm/h to $0.06 \pm 0.02 \times 10^{-3}$ cm/h), whilst at pH 8, it increased the K_p ($29.9 \pm 9.9 \times 10^{-3}$ cm/h to $75.1 \pm 41.7 \times 10^{-3}$ cm/h). These data trends were reproduced in a silicone membrane and this supported the notion that the more polar aggregates formed at pH 4 acted to decrease the proportion of species available to pass through the skin, whilst the more hydrophobic aggregates formed in pH 8 increased the membrane diffusing species.

© 2016 Elsevier B.V. All rights reserved.

1. Introduction

Drug-vehicle interactions are known to have a significant influence on the ability of topically applied medicines to deliver actives into the skin (Benaouda et al., 2012a; Zhang et al., 2012). It has been previously shown that a certain degree of physical interaction between the active and the vehicle must occur to facilitate solubilisation of the drug, but if the physical interactions are too strong, then drug release from the product after application can be hindered (Benaouda et al., 2012b).

Drug-drug interactions are in equilibrium with drug-vehicle interactions in topical products and therefore, drug-drug interactions may also have the potential to modify the performance of a medicine applied topically to the skin. Several therapeutic agents that are formulated in skin products are known to exhibit strong drug-drug interactions, which can lead to aggregation in the solution state, but how this molecular aggregation influences the potential of a drug to penetrate into the skin has not previously received a lot of attention (Attwood, 1995; Schreier et al., 2000; Wyn-Jones and Gormally, 2016).

Molecular aggregation is known to modify the physiochemical properties of a drug. For example, a drug's lipophilicity, molecular size, degree of ionisation, hydrogen bonding can all change upon the formation of drug aggregates. These physiochemical property modifications brought about by concentration dependant molecular aggregation can influence drug permeation directly by modifying the drug-skin interactions (Bos and Meinardi, 2000; Potts and Guy, 1992, 1995; Shore et al., 1957). However, the skin is a highly restrictive barrier. Therefore, if drugs generate aggregate clusters with a size of larger than 10 nm, they would be unlikely to pass directly into the skin unless they could access the follicular transport route (Alvarez-Roman et al., 2004; Baroli et al., 2007; Lademann et al., 2007; Ryman-Rasmussen et al., 2006; Wu et al., 2009). Thus, in order to understand the influence of drug aggregation on percutaneous penetration, attempts must be made to characterise the drug aggregates formed when applied to the surface of the skin. In addition, to elucidate how these drug aggregates influence percutaneous penetration, due consideration must be given as to how they affect the availability of the membrane diffusing molecules.

Previous work has shown that when nano-sized drug aggregates are present in a solution added to the surface of the skin, they can slow down drug permeation (Inacio et al., 2016). This was

* Corresponding author.
E-mail address: stuart.jones@kcl.ac.uk (S.A. Jones).

http://dx.doi.org/10.1016/j.ijpharm.2016.02.007
0378-5173/© 2016 Elsevier B.V. All rights reserved.

assumed to be a consequence of the aggregation process reducing the quantity of free drug that was able to passively penetrate the membrane. In an ideal system, drug monomers would always be in equilibrium with the aggregated species and therefore, the interactions between the two systems may influence the quantity of molecules able to pass into the skin (Charman et al., 1991; James-Smith et al., 2011; Mikkelson et al., 1980). However, drug aggregation rarely follows the homogeneous process shown by simple surfactants due to the fact that their chemical structure is not designed specifically to confer amphiphilic properties like synthetic surfactant molecules. As a consequence, there is often not a single species of aggregate formed in solution. Rather, drugs can form different types of aggregates in a concentration dependant manner like polymers. This makes the interactions of these system hard to predict and it makes it feasible that the aggregation process could lead to either drug donor depletion during the transport of the drug (Higuchi, 1960; Mikkelson et al., 1980) or the availability of more favorable molecules for the the transport process (Moore et al., 2003a,b).

The aim of this project was to characterise the molecular aggregation of the model drug tetracaine at low drug concentrations and to understand the influence of the molecular aggregation process on transmembrane transport. Tetracaine was selected as a model drug in this study because it is known to aggregate in aqueous solutions (Attwood, 1995; Schreier et al., 2000). In addition, it was selected as its clinical use is hindered by its high penetration lag time (30 to 45 min). Reducing lag time could improve the drug's performance in patients as it is often used before venepuncture or venous cannulation (Joint Formulary Committee, 2012) . The focus of the study was to understand the aggregation process at low drug concentrations as it was suspected that the aggregates formed would be very different to the high concentrations previously assessed (Inacio et al., 2016). As a consequence, at low drug concentrations, tetracaine aggregation was characterised by three techniques: photon correlation spectroscopy, to correlate with the previous work, fluorescence spectroscopy, to assess aggregation at low drug concentrations and Fourier transform infrared spectroscopy (FTIR), to understand the intermolecular interactions. It was hoped that these three techniques would allow the drug aggregation process to be understood at drug concentrations ranging from the μM to the mM concentration range. The study compared tetracaine aggregation and percutaneous penetration in an aqueous vehicle set at pH 4 and pH 8 in order to assess if the ionisation of the drug would influence the aggregation and thus the percutaneous penetration. These two pHs were selected because tetracaine is a weak base with pKa's at the secondary and tertiary amine of 3.41 and 8.24 respectively at 32 °C. Using these pKa values at pH 4 it was predicted that 100% of the tertiary amine would be ionised and 23% of the secondary amine would be ionized, at pH 8 it was predicted that 72% of the tertiary amine would be ionised and 28% of tetracaine would be unionised. The drug transport was studied using a porcine epidermis and a silicone membrane to understand the manner in which aggregation influences transport through barriers with and without the potential for follicular transport.

2. Materials and methods

2.1. Materials

Tetracaine free base (≥98%) and hydrochloric acid were purchased from Sigma Aldrich, UK. Ultrapure water (18.2 MΩ) was used throughout this study.

2.2. Test sample preparation

Tetracaine solutions were prepared and adjusted to pH 4.0 or 8.0 using hydrochloric acid and equilibrated at 32 °C unless stated otherwise. Solutions were stirred for at least 24 h and the pH rechecked prior to analysis to ensure they were at equilibrium.

2.3. Photon correlation spectroscopy

The derived count rates were analysed by photon correlation spectroscopy (Malvern Nanoseries Zetasizer ZEN3600, Malvern Instruments Ltd, UK). Detection of the light scattering signal was achieved at a 173 degree backscattering angle with samples equilibrated at 32 °C using water as a dispersant (refractive index 1.33, viscosity 0.8872 cP). Each measurement comprised 10–14 runs. Triplicates of each sample were assessed.

2.4. Fluorescence spectroscopy

Fluorescence emission spectra were recorded using a fluorescence spectrometer fitted with a Xenon pulse lamp (Varian Cary Eclipse Fluorescence Spectrometer, Agilent Technologies, UK). Beer-Lambert's law can only be applied over a limited range of optical densities and at a high sample optical density, attenuation due to absorption of the incident light or the emitted light can lead to a decrease in intensity and a possible change in spectral distribution (Albani, 2008; Lakowicz, 2009). In light of the possibility of having a deviation in linearity due to the concentration of tetracaine and not its molecular aggregation, a Quartz fluorescence cell (Helima Fluorescence Cell, Helima UK Ltd., UK) with a 3 mm path length and an off-centre illumination was used to record the measurements. Excitation and emission slits were fixed at 5 nm. In all measurements, the excitation wavelength was set at 310 nm. The samples were scanned from 320 to 450 nm at a wavelength scan rate of 120 nm/min with a PMT detector gain of 600 V. The data were smoothed with a Savitzky Golay function filter size 25 using the Cary Eclipse software. The experiments were performed at a temperature of 32 °C. The system was chemically stable over 6 days and the effect of ion pairing with the ions dissolved in the aqueous solution was not significant (Data not shown).

2.5. Critical aggregation concentration (CAC) analysis

Two methods were used to identify the CACs and their values were compared (Khan and Shah, 2008). The first method employed a second derivative function that was applied to a Gaussian distribution function to determine the critical points, which could then be used to define the CAC with OriginPro (OriginPro version 8.6, Origin Lab Corporation, US). In the second method, the intersection of 2 linear models that were applied to the data was used to determine the CAC. The second of these two methods is traditionally used when determining the critical micelle concentration (CMC) of surfactants (Mukerjee and Karol, 1971).

2.6. FTIR analysis

Deuterated water (D_2O, Sigma Aldrich, UK) was employed to analyse the tetracaine solutions as it dampened the solvent signal in the 1700–1300 cm^{-1} and 3000–2850 cm^{-1} ranges. The samples were loaded into a demountable universal transmission cell system (Omni-Cell, Specac Ltd, UK) fitted with CaF_2 windows and a 25 μm Mylar spacer (Specac Ltd., UK). The pHs of the tetracaine solutions were maintained using DCl. All spectra were produced using 32 scans collected at a spectral resolution of 4 cm^{-1}. The data was recorded using a Spectrum One spectrometer (Perkin-Elmer

Download English Version:

https://daneshyari.com/en/article/2501046

Download Persian Version:

https://daneshyari.com/article/2501046

Daneshyari.com