International Journal of Pharmaceutics 377 (2009) 70–75

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

The effect of drug concentration on solvent activity in silicone membranes

P. Santos [a], M. Machado [a], A.C. Watkinson [b], J. Hadgraft [a], M.E. Lane [a,*]

[a] Department of Pharmaceutics, The School of Pharmacy, University of London, 29-39 Brunswick Square, London, WC1N 1AX, United Kingdom
[b] Acrux Limited, 103-113 Stanley Street, West Melbourne VIC 3003, Australia

ARTICLE INFO

Article history:
Received 26 March 2009
Received in revised form 29 April 2009
Accepted 1 May 2009
Available online 9 May 2009

Keywords:
Supersaturation
Oxybutynin
Propylene glycol
Octyl salicylate
Silicone
Permeation

ABSTRACT

The effects of supersaturated formulations on drug permeation through artificial and biological membranes have been reported by a number of research groups. However, little information is known about solvent permeation from these supersaturated formulations, and in particular the effect of high drug concentrations and degree of saturation (DS) on solvent activity. The aim of this study was to determine the effect of the DS of a model drug, oxybutynin, on solvent and drug permeation. Supersaturated residues of oxybutynin in propylene glycol (PG) or (octyl salicylate) OSAL were prepared by the solvent evaporation method. In both formulations a high percentage (25%, v/v) of solvent was used in order to avoid solvent depletion. Permeation of PG and OSAL through silicone was monitored by GC and HPLC, respectively. All OSAL formulations permeated to a higher extent than PG formulations. A decrease in OSAL permeation with 5 DS formulations was observed in comparison with 1 DS or 2 DS formulations, indicating a decrease in solvent activity with drug concentration. In addition, the drug transport from the 5 DS formulation of OSAL was higher than the 1 and 2 DS formulations but lower than predicted. Based on both solvent and drug permeation, this suggests that the low drug permeation observed with 5 DS resulted from a decrease in solvent thermodynamic activity rather than a decrease in solute activity as a result of drug crystallisation. Using PG formulations, the PG permeation remained unaffected with the DS of the formulation, up to 5 DS.

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1. Introduction

Permeation of a compound through the stratum corneum (SC) depends on a number of physicochemical properties such as molecular weight, lipophilicity, polarity, capacity to form hydrogen bonds, solubility and ionisation. Passive permeation enhancement can be achieved by increasing the thermodynamic activity of the drug in the formulation or by co-administration of chemical permeation enhancers. The use of supersaturated formulations to increase drug thermodynamic activity, as a strategy in transdermal drug delivery, was first considered by Higuchi (1960). Supersaturation is a state where the drug is at a higher concentration than the solubility limit and as a consequence the drug flux should increase with increasing degree of saturation (DS). Techniques to produce supersaturated systems include the method of mixed cosolvents (Davis and Hadgraft, 1991), solvent evaporation (Coldman et al., 1969), and heating and cooling (Henmi et al., 1994).

While many workers have used supersaturated systems to enhance drug thermodynamic activity (Davis and Hadgraft, 1991; Pellett et al., 1994, 1997; Raghavan et al., 2000) few reports have shown that solvent/membrane interactions are also strongly dependent on the thermodynamic activity of the solvent. For example, Francoeur et al. (1990) measured the uptake of oleic acid into porcine skin and silastic from a series of ethanol:water vehicles. The uptake of oleic acid (OA) reached its maximum with the vehicle containing 40% ethanol, as the OA was completely solubilised at 40% or higher levels of ethanol. The authors suggested that the uptake of OA by silicone and porcine SC membranes was therefore controlled by OA thermodynamic activity in the applied ethanolic vehicle.

Twist and Zatz (1986) investigated the effects of interactive (vehicles which affect the membrane, e.g. ethanol/water) and non-interactive (vehicles which do not affect the membrane, e.g., water in contact with a silicone membrane) systems on the flux of parabens from saturated aqueous solutions across silicone membranes and observed a higher flux for propylparaben than methylparaben. However, when using mixtures of ethanol:water (interactive solvent), the flux of methylparaben was higher than that of propylparaben (Twist and Zatz, 1988). The authors suggested that the low flux of propylparaben from the ethanol/water mixture resulted from the high solubility of propylparaben in the system, which reduced the alcohol activity. As a result, the amount of alcohol taken up by the membrane decreased leading to a drop in propylparaben uptake and flux relative to that of methylparaben.

* Corresponding author. Tel.: +44 207 7535821; fax: +44 870 1659275.
E-mail address: majella.lane@btinternet.com (M.E. Lane).

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doi:10.1016/j.ijpharm.2009.05.002

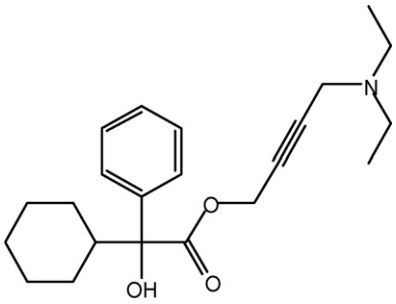


Fig. 1. Chemical structure of oxybutynin.

In another study, the influence of the parabens concentration on the flux through silicone membranes from application of an alcoholic solution was monitored (Twist and Zatz, 1990). This study demonstrated that the flux of paraben increased with paraben concentration, reached a maximum (which did not coincide with the saturated solubility) and then decreased with further increase in paraben concentration. Theoretical models confirmed that the flux of ethanol across the membrane also decreased with solvent activity.

The aim of the present study was to investigate the effect of drug concentration or DS on solvent thermodynamic activity and, consequently, on solvent uptake and drug permeation through silicone. Oxybutynin (Fig. 1) was selected as a model drug as it is a suitable candidate for transdermal drug delivery with a molecular weight of less than 500 Da, a log K_{oct} of 4.12, a melting point of 57 °C (Martindale, 2007; Miyamoto et al., 1995) and it is currently delivered via the transdermal route. Transdermal delivery of oxybutynin has shown comparable efficacy and improved significantly the anticholinergic safety profile compared to oral administration (Davila, 2003).

Propylene glycol (PG) and octyl salicylate (OSAL) were selected as the non-interactive and interactive solvents, respectively (Table 1). PG is widely used as a penetration enhancer in topical dermatological formulations (Bendras et al., 1995). PG readily permeates the skin and may carry the drug with it, as shown by correlations *in vitro* between the permeation of both PG and the drug (Mollgaard and Hoelgaard, 1983; Wotton et al., 1985; Squillante et al., 1998; Trottet et al., 2004). OSAL belongs to a class of skin permeation enhancers classified as GRAS, i.e., Generally Recognised As Safe (Reed et al., 1997; Finnin and Morgan, 1999). OSAL has traditionally been used as a chemical sunscreen and it is regarded as safe in concentrations up to 5% (v/v) (Funk et al., 1995). In transdermal drug delivery, OSAL has been used to enhance the permeation of testosterone, oestradiol and fentanyl through human skin using spray formulations (Morgan et al., 1998a,c; Traversa, 2005). Similar enhancement properties have been observed *in vitro* for testosterone when OSAL was used as a pure solvent or in combination with PG, under occlusive conditions using porcine skin (Nicolazzo et al., 2005).

As noted by other authors there are a number of advantages associated with model membranes, such as silicone, to study membrane transport processes (Ley and Bunge, 2007; Millerioux et al., 2009). Skin is a complex heterogeneous membrane and gaining an understanding of the mechanisms of action is often difficult. Knowledge of how drugs and formulation components permeate silicone membranes will also provide insight from the perspectives of release and controlled drug delivery from polymeric systems (Prokopowicz, 2009) and transport across polymers used for a number of applications, e.g. protective clothing, infusion bags, etc. The extent to which drugs and excipients may permeate such materials is also of importance for prediction of long term storage behaviour in such membranes and from an environmental perspective as silicones are used in protective clothing (Rivin et al., 2005).

2. Materials and methods

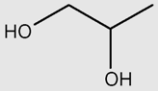
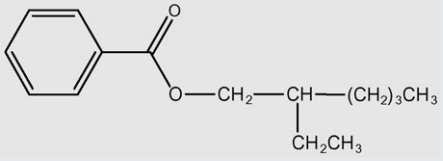
2.1. Materials

Oxybutynin free base was a gift from Acrux, Ltd. (Australia). PG and OSAL were purchased from Sigma (Australia). Phenylboronic acid and 1,2 butanediol, used for GC analysis as derivatisation and internal standard reagents, respectively, were produced by Fluka (Sigma, United Kingdom). Polyethylene glycol 20 oleyl ether (PEG-20-OE), ethanol (99%) and orthophosphoric acid (85%, v/v) were purchased from Sigma (United Kingdom). All HPLC grade solvents were purchased from Fisher (United Kingdom). Silicone membranes with a thickness of 125 μm were used for *in vitro* diffusion studies (Sil-Tec, Technical Products, USA).

2.2. Solubility studies

Saturated solubility values for oxybutynin in PG and OSAL were determined at 32 °C as reported previously (Dias et al., 2007). Using a calibrated micropipette, an aliquot of supernatant (100 μl) was

Table 1
Structure and physicochemical properties of PG and OSAL.

Propylene glycol (PG)	Octyl salicylate (OSAL)
	
MW[a] = 76.1 g/mol Log $K_{oct/wat}$[b] = −0.47 δ[c] = 28.64 MPa$^{1/2}$ Hygroscopic, viscous liquid. Miscible with water, acetone and chloroform. Soluble in ether[a]	MW[a] = 250.3 g/mol Log $K_{oct/wat}$[b] = 5.97 δ[c] = 21.74 MPa$^{1/2}$ Colourless to pale-yellow liquid. Miscible with cosmetic oils, silicone oils. Insoluble in water; freely soluble in absolute ethanol[a]

[a] Compound names, structure, molecular weight (MW), physical state and solubility taken from The Merck Index, 14th Edition, Merck Research Laboratories, 2006.

[b] Octanol:water partition coefficient calculated with Chemdraw® program (Cambridge Soft., UK).

[c] Solubility parameter (δ) estimated using Thermo Chemical Properties Estimation Software: Solubility Parameter Estimation from Fedor's Cohesive Energy (http://www.pirika.com/chem/TCPEE/TCPE.htm). The obtained values were multiplied by 2.0455 to convert from (cal/cm^3)$^{1/2}$ to MPa$^{1/2}$.

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