International Journal of Pharmaceutics 460 (2014) 240–247

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Dermal permeation of 2-hydroxypropyl acrylate, a model water-miscible compound: Effects of concentration, thermodynamic activity and skin hydration

H. Frederick Frasch[a,*], Ana M. Barbero[a], G. Scott Dotson[b], Annette L. Bunge[c]

[a] Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Morgantown, WV 26505, USA
[b] Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, OH 45226, USA
[c] Chemical and Biological Engineering Department, Colorado School of Mines, Golden, CO 80401, USA

ARTICLE INFO

Article history:
Received 15 August 2013
Received in revised form 31 October 2013
Accepted 4 November 2013
Available online 12 November 2013

Chemical compound studied in this article:
2-Hydroxypropyl acrylate (propylene glycol monoacrylate) (PubChem CID: 61249)

Keywords:
Skin absorption
Lag time
Stratum corneum
Skin hydration
Acrylic monomers
Thermodynamic activity

ABSTRACT

The goal of these studies was to measure and interpret the skin permeability characteristics of 2-hydroxypropyl acrylate (HPA) as a model compound that is completely miscible with water.
Methods: In vitro permeation from HPA-H_2O binary mixtures through human epidermis and silicone membranes was measured. Thermodynamic activities of HPA and H_2O in these mixtures were determined. Permeation was also measured through epidermis and silicone from donor solutions with constant HPA activity but different H_2O activities. Water uptake into desiccated human stratum corneum (SC) equilibrated with HPA-H_2O mixtures was determined.
Results: Steady-state flux of HPA through silicone was a linear function of HPA activity but not HPA concentration. For epidermis on the other hand, flux increased with HPA activity only for HPA activities $\leq$0.35. At constant HPA activity, flux decreased 4.5-fold as water activity decreased from 1 to 0.8. Incubation of SC with HPA-H_2O mixtures resulted in substantial changes in SC water content, dependent on the water activity of the mixture and consistent with measured SC water sorption data.
Conclusions: These experiments provide unequivocal evidence of a substantial increase in epidermal barrier function resulting from SC dehydration. Dehydration-related alterations in the SC appear responsible for the observed flux characteristics.

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1. Introduction

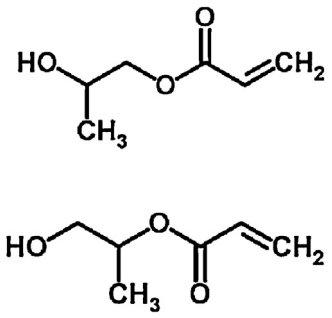
2-Hydroxypropyl acrylate (HPA, Table 1) is a monomer that is used primarily in thermosetting resins for surface coatings, adhesives, and textiles. HPA and water are miscible in all proportions at room temperature. Other chemicals with similarly high aqueous solubility display unusual skin permeation behavior. For example, the dermal permeation of 2-butoxyethanol (BE) in aqueous solutions has been a matter of debate based on the observation that steady-state dermal flux (J_{SS}) of BE is a strongly non-linear function of BE concentration (Johanson and Fernstrom, 1988; Traynor et al., 2007). Three distinct regions of behavior have been noted. At low concentrations, J_{SS} increases with increasing BE concentration. At intermediate concentrations, J_{SS} remains relatively constant, while at high concentrations, J_{SS} decreases with BE concentration to such an extent that flux from neat BE is about the same as from a 10 wt.% solution.

Bunge et al. (2012) have summarized these observations on BE and presented a reasonable explanation. They pointed out that the general driving force for permeation is thermodynamic activity, not concentration (Higuchi, 1960). Additionally, the thermodynamically appropriate metric for concentration is mole fraction and not volume fraction or weight fraction, which are typically used. For ideal solutions, thermodynamic activity is a linear function of mole fraction, but not, in general, of volume or weight fraction. Thus, for an ideal solution that does not alter the membrane barrier, J_{SS} is a linear function of the mole fraction of the chemical. BE-water forms a non-ideal solution. Therefore, the thermodynamic activity in aqueous BE solutions must be known in order to make informative observations on BE flux. Bunge et al. (2012) showed that activity-normalized BE fluxes are constant up to a weight fraction of about 0.8. For higher concentrations, a sharp drop in the activity-normalized flux corresponds to a sharp decrease in the thermodynamic activity of water in the solutions. Bunge et al. (2012) reasoned that BE steady-state fluxes can therefore be explained by the effects of BE-water solutions on skin hydration

* Corresponding author at: NIOSH, 1095 Willowdale Road, Morgantown, WV 26505, USA. Tel.: +1 304 285 5755; fax: +1 304 285 6041.
E-mail address: HFrasch@cdc.gov (H.F. Frasch).

0378-5173/$ – see front matter. Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.ijpharm.2013.11.007

Table 1
Some properties of HPA. CAS: Chemical Abstracts Service Registry Number. Structure of 2 isomers is shown—top: 2-hydroxypropyl acrylate; bottom: 2-hydroxy-1-methylethyl acrylate. $\log K_{ow}$: base 10 logarithm of octanol–water partition coefficient. CSID:55190, http://www.chemspider.com/Chemical-Structure.55190.html (accessed May 29, 2013).

CAS	Formula	Structure	*MW*	$\log K_{ow}$
25584-83-2	$C_6H_{10}O_3$		130.14	0.35

status. While the data support this hypothesis, no direct evidence was provided linking BE exposure and skin hydration.

Human skin permeability measurements for HPA are, to our knowledge, lacking in the peer reviewed literature. Dermal exposure to HPA may occur during its manufacture, transportation and industrial use. Dedicated systems designed to handle HPA during loading and unloading procedures limit the risk of exposure to spills or leaks during transportation (SIDS, 2004). Nevertheless, moderate systemic toxicity of this chemical, which is also known to be a severe skin irritant, warrants the study of its dermal absorption potential. Therefore one goal of the present study was to provide these data for dermal risk assessment purposes.

HPA is not used in aqueous solutions in the industrial setting, but the miscibility of this chemical in water presented an opportunity to investigate its skin permeation in a manner comparable with the well-studied water miscible chemical BE. Steady-state fluxes and lag times of HPA in both heat separated human epidermal membranes and silicone rubber membranes were undertaken over the full range of HPA-H_2O concentrations. Thermodynamic activities of HPA and H_2O in aqueous solutions of HPA were measured to gain knowledge of the driving force for permeation and to gain insight into the effect of H_2O activity on skin permeation. A further set of permeation experiments was designed such that HPA thermodynamic activity could be held constant, while H_2O activity was varied from about 0.8 to 1. Finally, water uptake into desiccated human stratum corneum was measured following incubation in aqueous HPA solutions. Results presented here offer incontrovertible evidence that stratum corneum becomes dehydrated with increasing HPA concentrations, and that this dehydration substantially increases the barrier property of the skin to this chemical.

2. Methods

2.1. Materials

Fresh full thickness human skin samples from Caucasian female (age range: 32–62 y) nonmalignant mammoplasties were obtained on the day of surgery from the West Virginia University Tissue Bank. Skin was submersed in 60 °C buffer for 60 s. Epidermis was teased from underlying tissue with cotton swabs, floated onto buffer + 10% glycerol, and stored frozen (−85 °C) until use. Medical grade silicone rubber sheeting (thickness: 0.020 in. and 0.040 in.) was purchased from Bioplexus.

Commercial grade HPA (CAS: 25584-83-2) was purchased from Monomer-Polymer & Dajac Laboratories, Inc. (Lot number 22-49-4: reported purity 97.5%; methyl ethyl hydroquinone added (reported 217 ppm) to inhibit spontaneous polymerization). Typical commercial formulations of HPA consist of two isomers containing approximately 75–80% 2-hydroxypropyl acrylate and 20–25% 1-methyl-2-hydroxyethyl acrylate (SIDS, 2005). In preliminary studies, there were no discernible differences in the permeability of the 2 isomers. Because of this observation, and because this product is marketed as "HPA", in all studies described here the sum of the isomers was taken as the HPA quantity.

Tritiated water (specific activity, 1 mCi/g (37 MBq/g)) was purchased from Moravek Biochemicals. Hanks balanced salt solution (HBSS) was purchased from Gibco-Invitrogen Corporation. Soluene 350 (tissue solubilizer) and Ultima Gold (liquid scintillation fluid) came from PerkinElmer. Other chemicals were purchased from Sigma–Aldrich or affiliates and were the highest purity available. Trypsin was type II-S from porcine pancreas. Poly(ethylene glycol) (PEG-1500) had a *MW* range of 1400–1600. Buffer (pH 7.40 @ 37 °C) consisted of 5.96 g HEPES buffer, 0.32 g $NaHCO_3$, and 0.05 g gentamicin sulfate added to 1000 mL HBSS.

2.2. HPA solutions

All solutions were mixed gravimetrically. HPA-H_2O solutions were mixed to achieve desired mole fractions (x_{HPA}) or volume fractions (ϕ_{HPA}) of HPA. These are defined as:

$$x_{HPA} = \frac{n_{HPA}}{n_{HPA} + n_{H_2O}} = \frac{m_{HPA}/MW_{HPA}}{(m_{HPA}/MW_{HPA}) + (m_{H_2O}/MW_{H_2O})}, \quad (1)$$

where n is the number of moles, m is mass and *MW* is molecular weight. The *MW* of HPA is 130.14; that of H_2O is 18.02.

$$\phi_{HPA} = \frac{V_{HPA}}{V_{HPA} + V_{H_2O}} = \frac{m_{HPA}/\rho_{HPA}}{(m_{HPA}/\rho_{HPA}) + (m_{H_2O}/\rho_{H_2O})}, \quad (2)$$

where V is volume and ρ is density. The ρ of HPA is 1.045 g/mL (SIDS, 2005) and that of water is 1.000 g/mL.

PEG-1500-H_2O solutions were mixed to achieve desired mass fractions (w_{PEG}), defined as:

$$w_{PEG} = \frac{m_{PEG}}{m_{PEG} + m_{H_2O}}. \quad (3)$$

HPA-PEG-1500-H_2O solutions were mixed to achieve desired volume fractions of HPA in solvent consisting of PEG-1500-H_2O solutions of given w_{PEG}:

$$\phi_{HPA} = \frac{V_{HPA}}{V_{HPA} + V_{H_2O} + V_{PEG}} = \frac{m_{HPA}/\rho_{HPA}}{(m_{HPA}/\rho_{HPA}) + (m_{PEG}/w_{PEG}\rho_{PEG})}, \quad (4)$$