Effect of Propylene Glycol on Ibuprofen Absorption into Human Skin *In Vivo*

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ABSTRACT: The objective was to assess the impact of propylene glycol (PG), a common cosolvent in topical formulations, on the penetration of ibuprofen into human skin *in vivo*. Drug uptake into the stratum corneum (SC), following application of saturated formulations containing from 0 to 100% v/v PG, was assessed by tape-stripping. Dermatopharmacokinetic parameters, characterizing drug amount in and diffusivity through the SC, were derived. The solubility behavior of ibuprofen in PG–water mixtures was carefully evaluated, as were a number of other physical properties. Ibuprofen delivery depended on the level of PG in the vehicle, despite all formulations containing the drug at equal thermodynamic activity. PG appeared to alter the solubility of ibuprofen in the SC (presumably via its own uptake into the membrane), the effect becoming more important as the volume fraction of cosolvent in the formulation increased. In summary, tape-stripping experiments, with careful interpretation, can reveal details of a drug's bioavailability in the skin following topical application and may be used to probe the mechanism(s) by which certain excipients influence local drug delivery. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:185–197, 2008

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INTRODUCTION

Many drugs developed for the topical treatment of skin disease are poorly water-soluble and difficult to formulate. Furthermore, the elegant vehicles produced commercially often undergo rapid and extensive modification of their composition after application to the skin. For example, volatile components may evaporate and change the thermodynamic activity of the drug in the formulation;[1] in some instances, the drug may even precipitate on the skin surface. However, as the drug must dissolve into the stratum corneum (SC) to be absorbed, alterations in the properties of the vehicle may significantly impact upon the overall kinetics of drug uptake.

Ideally, to maximize delivery, the largest possible amount of drug should be dissolved in the formulation and become immediately bioavailable to the lipophilic SC.[2] In the case of water-insoluble drugs, the incorporation of a cosolvent into the formulation is a typical and, in general,

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profitable strategy.[3–6] Propylene glycol (PG) is a particularly useful example of an inexpensive, nontoxic, and well-tolerated cosolvent.[7] While considerable research into its efficacy and action has been reported in the literature,[8–13] a detailed examination of its direct mechanism at the formulation-SC interface *in vivo* has not been undertaken. In this study, the tape-stripping procedure in human volunteers is used to probe the manner in which PG as a cosolvent, administered at different levels in simple binary mixtures with water, determines the SC uptake and transport of the model drug, ibuprofen.

MATERIALS AND METHODS

Chemicals

S-(+)-Ibuprofen (Fluka, Buchs, Switzerland) was dissolved at saturation in various PG–water mixtures (Sigma-Aldrich, Steinheim, Germany). Solvents used for ibuprofen extraction and liquid chromatographic (HPLC) analysis were of analytical grade (Sigma-Aldrich). Citric acid monohydrate, sodium hydroxide (Sigma-Aldrich), and hydrochloric acid (Fluka) were used to prepare buffers.

Experimental Procedures

Ten volunteers (7 female, 3 male, 24–46 years) with no history of dermatological disease participated in this study, which was approved by the University of Geneva ethical committee. Informed consent was obtained from all subjects. The treated sites (4×5 cm) were nonhairy regions of the ventral forearm surface. Each treatment consisted of a 1.9 mL application of ibuprofen solution on a cellulose gauze (Tela, Basel, Switzerland) which was covered by an occlusive polyester layer (Scotchpak, 3M, St. Louis, MN) and affixed to the skin with an adhesive polyurethane film (Opsite, SmithNephew, Hull, UK). These applications are considered as infinite doses from which negligible drug depletion was anticipated during the experiment. After the chosen application time of 30 min, the patch was removed and excess formulation was gently removed using three dry cellulose swabs without any solvent.

Formulations

The vehicles studied were saturated solutions of ibuprofen in the following v/v mixtures of PG and water: 0:100, 25:75, 50:50, 75:25, and 100:0. The volume fraction (f) of the cosolvent was defined as $V_{PG}/(V_{PG} + V_{water})$. The saturated solutions were prepared by dissolving the amounts of ibuprofen necessary to fully saturate each PG/water mixture. These amounts were determined from the solubility experiments described below. The solutions were prepared and used immediately.

SC Sampling Protocol

The ibuprofen concentration profile across the SC following application in the different vehicles was determined by sequential removal of the outer skin layer by tape-stripping (Scotch Book Tape, 3M, St. Louis, MN). The SC sampling site was delimited by a template which exposed an area smaller than that treated with the formulation. The template was centered over the drug application site immediately before tape-stripping began. The size of the opening in the template (2×2.5 cm) was smaller than the individual tape-strips used. Differential weighing (Mettler AT 261 balance, Greifensee, Switzerland) of tape-strips allowed the amount of SC removed to be estimated. From this mass, and knowing the area of the tape, it was possible to calculate the SC thickness removed (using a SC density of 1 g/cm^3)[14] as a function of stripping and hence the corresponding position (or depth, x) within the barrier. The apparent SC thickness (L) was determined as described elsewhere[15] from measurements of transepidermal water loss (TEWL) as a function of SC removed. This permits the drug concentration profile to be expressed as a normalized function of relative position within the SC (x/L) and facilitates the comparison of data originating from different volunteers.[16–18] The TEWL measurements were made at a site adjacent to the treated skin to avoid residual vehicle effects on the TEWL readings, and to ensure that these measurements did not prolong the experiment to the point that the drug concentration profile could change significantly. Ten to twenty strips were taken from each treated site of each volunteer, the actual number depending most probably upon the efficiency of the tape-stripping process as well as the individual's SC thickness; however, the SC was never completely removed. All tapes were subsequently analyzed for ibuprofen; no strips were discarded, and it was assumed that any drug not removed by the surface cleaning process at the end of the