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Diffusion properties of model compounds in artificial sebum

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Abstract

Sebaceous glands secrete an oily sebum into the hair follicle. Hence, it is necessary to understand the drug partition and diffusion properties in the sebum for the targeted delivery of therapeutic agents into the sebum-filled hair follicle. A new method was developed and used for determination of sebum flux of topical therapeutic agents and other model compounds. The drug transport through artificial sebum was conducted using sebum loaded filter (Transwell®) as a membrane, drug suspensions as donor phases and HP-β-CD buffer solution as a receiver phase. The experiment was performed at 37 °C for 2 h. The results of the drug transport studies indicate that the flux (J_{sebum}) through the artificial sebum is compound dependent and a bell-shaped curve was observed when $\log J_s$ versus alkyl side chain length of the compounds that proved to be different from the curves obtained upon plotting $\log J$ skin versus *c*log *P* for the same compounds, indicating the possibility to select appropriate compounds for sebum targeted delivery based on the differences in the skin flux and sebum transport profiles of the molecules.

Keywords: Artificial sebum; Flux; Permeability coefficient; Sebaceous gland; Hair follicle; Targeted delivery

1. Introduction

In the treatment of skin diseases and disorders, there are primarily two potential delivery mechanisms for topically applied drugs—transepidermal and transfollicular. In transepidermal delivery, transport of drugs occurs across the stratum corneum whereas in the transfollicular route, drug absorption/transport occurs through hair follicles and sebaceous glands. A number of studies have demonstrated that the hair follicles and the sebaceous glands contribute to the penetration of drugs across the skin (Bertolino et al., 1993; Lauer et al., 1995; Illel, 1997; Grams and Bouwstra, 2002; Vogt et al., 2005). Targeting drug delivery to the pilosebaceous unit (the hair follicle, sebaceous glands and the hair shaft) may allow increased deposition of active compounds into hair follicular ducts, while at the same time, retarding transepidermal transport. This could lead to better control of drug systemic exposure and improve the overall efficacy/safety margins. However, the main obstacles to access these sites are the structure of the hair follicle itself and the physicochemical environment present in the pilosebaceous unit. The keratinous layers of the inner and outer root sheaths and the glassy membrane surrounding the entire follicle may restrict passage of molecules deep within the follicle. To date, the transport details of drug molecules in hair follicle ducts and sebaceous glands are yet to be fully understood. The possible applications of such targeted follicular delivery include the treatment of hair growth abnormalities, as well as hair follicle-associated diseases, such as acne. Targeted drug delivery to the hair follicle can be managed by two quite different ways—the first being a *formulation approach* and the second being a *molecule modification approach* (Grams and Bouwstra, 2002). Several researchers using the formulation approach have established that improved localized delivery of drugs to the hair follicle can be achieved by varying the compositions of applied formulations (Meidan et al., 2005). In one case, the gains in localized delivery were achieved through the application of a system containing a particulate carrier (Toll et al., 2004) and in the second case by using sebum miscible excipients in the topical preparation (Motwani et al., 2004). In contrast, the molecule modification approach involves a tailoring of the physicochemical properties of a drug molecule, such as its size, polarity (lipophilicity), polar surface area, solubility parameter and/or charge, any of which has a potential to modulate delivery into the hair follicle (Lauer et al., 1995; Illel, 1997). Several recently published reviews concisely capture the experience and advances in this area (Hueber et al., 1994a,b; Lauer et al., 1997; Meidan et al., 2005; Vogt et al.,

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2005). In most of the studies performed, the role of sebum (an oily secretion produced by the sebaceous gland into the hair follicle) in follicular targeted delivery is poorly understood, except for a study on the use of differential scanning calorimetry to understand the nature of artificial sebum–excipient interactions (Motwani et al., 2001, 2002). Hence, an efficient drug delivery into the sebum-filled hair follicle and sebaceous gland would greatly depend on the partition/diffusion of the drug molecule in sebum. Until now, there were no reports available on the drug partition and diffusion in the sebum. In lieu of performing studies with human sebum samples, it is desirable to study drug partition and diffusion in a controlled environment by using artificial sebum which has similar chemical and physical properties as human sebum. Previously, we studied the partition of model compounds in artificial sebum/water in which we demonstrated that the partition coefficient of model drugs in artificial sebum is a primary function of chemical structure and lipophilicity of the molecule (Valiveti et al., 2007). Drug diffusion through the artificial sebum gives information about the mobility of the molecule in and out of the sebum from aqueous solution or suspensions. In this study, we have investigated the diffusion properties of model drugs in the artificial sebum and its relationship with the sebum partition coefficient, $c\log P$, and alkyl chain length.

2. Materials and methods

2.1. Materials

Salicylic acid (purity 99%), cholesterol, octyl 4-hydroxybenzoate, methyl 4-hydroxybenzoate, ethyl 4-hydroxy benzoate, butyl-4-hydroxybenzoate and heptyl 4-hydroxybenzoate were obtained from Lancaster Synthesis, Inc. (Pelham, NH). 3,4-Dihydroxy benzoic acid (purity 98%), tretinoin, oxalic acid (purity >99%), *o*-phosphoric acid, paraffin wax (melting point, 58–62 °C), oleic acid, hexadecyl 4-hydroxybenzoate and 4-hydroxybenzoic acid were obtained from Aldrich Chemical Company, Inc. (Milwaukee, WI). Ketoconazole, minoxidil, cottonseed oil, palmitoleic acid, squalene and octanol were obtained from M.P. Biomedical, LLC (Aurora, OH). Lidocaine base (purity >98%), trifluroacetic acid, acetyl salicylic acid, methyl 5-acetyl salicylate, lidocaine HCl, prednisolone, hydrocortisone 21-caprylate, hydrocortisone 17-butyrate, hydrocortisone 17-valerate, hydrocortisone 17-acetate and propyl 4-hydroxybenzoate were obtained from Sigma Chemical Company, Inc. (St. Louis, MO). Coconut oil was obtained from Aldon Corporation (Avon, NY). Olive oil, hydrocortisone and palmitic acid were obtained from EMD Chemicals (Gibbstown, NJ). Spermaceti wax and cholesterol oleate were obtained from Sargent-Welch (Buffalo, IL) and Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan), respectively. Amyl 4-hydroxybenzoate, hexyl 4-hydroxybenzoate, phenyl 4-hydroxybenzoate, betamethasone, dexamethasone, nonyl 4-hydroxybenzoate and ethyhexyl 4-hydrxybenzoate were obtained from TCI America (Portland, OR). Acetonitrile, methanol, water for HPLC, tetrahydrofurone, acetic acid, potassium dihydrogen phosphate, sodium dihydrogen phosphate, disodium hydrogen phosphate and ammonium hydroxide were obtained from Mallinckrodt Baker, Inc. (Philipsburg, NJ). Adapalene and dodecyl 4-hydroxybenzoate were obtained from ChemPacific (Baltimore, MD) and Alfa Aesar (Ward Hill, MA), respectively.

2.2. Instruments

Equipment used consisted of a 1100 series high-pressure liquid chromatography (HPLC) instrument with an Agilent 1100 series autosampler and a Diode Array detector model 785A (Agilent Technologies, Inc., Palo Alto, CA) and an Innova® 4000 series incubator and shaker (New Brunswick Scientific Co., Inc., Edison, NJ).

2.3. Preparation of artificial sebum

The main components of the sebum are triglycerides, wax esters, squalene, cholesterol and cholesterol esters (Strauss et al., 1976). The chemical composition of the artificial sebum has been chosen based on the human sebum chemical composition reported in the literature (Walters and Roberts, 2002; Rosenthal, 1964; Greene et al., 1970; Nordstrom et al., 1986).

The chemical composition (%, w/w) of the artificial sebum is shown in Table 1. The ingredients were weighed out (%, w/w) in a glass beaker and heated at 60 °C with intermittent stirring until all the solids became a clear liquid (10 min). This was done to ensure uniform mixing of the model sebum lipids. The mixture was allowed to cool down at room temperature. All components of the artificial sebum were miscible at 60 °C and there were no visual indications of separation of sebum lipids. Moreover, the variation in the in vitro partition and diffusion data from different lots of the artificial sebum was less than 20% indicating a good reproducibility of preparation and uniformity of the artificial sebum prepared.

2.4. Drug transport through the artificial sebum

The drug transport through the artificial sebum is carried out in 24-well format (Transwell®, Corning Incorporated, NY). The supporting membrane (polycarbonate membrane, pore size of 0.4 μm) of each insert was loaded with 2.1 ± 0.2 mg of the artificial sebum (previously heated at 50–55 °C). A 150 μL aliquot of aqueous suspension of model drug (10 mg/mL in citrate–phosphate buffer (CPB, pH 5.5) equilibrated overnight on a shaker) was applied onto the insert and 1 mL of preheated (37 °C) 10% HP-β-cyclodextrin in the CPB was used as receiver solution. The entire study was carried out in an incubator at 37 °C and 125 rpm. The sampling interval was every 10 min for 2 h. At each sampling time, the entire receiver solution was replaced with fresh buffer. The withdrawn receiver solutions were analyzed for drug content using reported HPLC methods in the literature with or without modification. The cumulative quantity of drug in the receiver compartment was plotted as a function of time. The flux value for a given experiment was obtained from the linear slope (steady-state portion) of the cumulative amount of drug permeated versus time curve. The aqueous solubility of each compound was determined by centrifugation of the suspen-