Effect of Lipophilicity on Microneedle-Mediated Iontophoretic Transdermal Delivery Across Human Skin *In Vitro*

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ABSTRACT: The effect of lipophilicity of drug on the microneedle (MN)-mediated iontophoretic delivery across dermatomed human skin was studied. Beta blockers with similar pK_a but varied log *P* values were selected as model drugs in this study. Iontophoresis (ITP) or MNs, when used independently, increased the transdermal flux of beta blockers as compared with passive delivery (PD). ITP across the MN-treated skin (MN + ITP) increased the permeation rate of all beta blockers as compared with PD ($p < 0.001$). The enhancement ratios (ER) for hydrophilic molecules (atenolol and sotalol) were 71- and 78-fold higher for ITP + MN as compared with PD. However, for lipophilic molecule such as propranolol, there was 10-fold increase in the ER as compared with PD. These observations were further substantiated by the skin retention data; an inverse relationship between the skin retention and the hydrophilicity of the drug was observed. The results in the present study point out that the lipophilicity of the molecule plays a significant role on the electrically assisted transdermal delivery of drugs across the microporated skin. Using the combination of ITP + MN, hydrophilic drugs (atenolol and sotalol) were delivered at a much higher rate as compared with lipophilic molecules (propranolol and acebutolol). © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:3784–3791, 2013

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INTRODUCTION

Transdermal delivery provides distinct benefits such as non-invasiveness, elimination of hepatic first-pass effect, reduction of systemic side effects, and high patient compliance.[1,2] However, the outermost skin layer, stratum corneum (SC), poses the main barrier for the permeation of drugs.[3] Various permeation enhancement techniques were used to increase the delivery of drugs across skin in therapeutic quantities.[4,5] Some of these include the use of chemical penetration enhancers,[6] iontophoresis (ITP),[7] and microneedles (MNs).[8] Among these, ITP and MN hold promising future as they have shown encouraging results for various drugs that are difficult-to-deliver across skin including biopharmaceutical agents. ITP delivers either charged or uncharged solutes across skin under the influence of an electric current.[9] Although the predominant pathway of iontophoretic transport is through skin appendages (hair follicles and sweat glands), the transcellular route across skin also contributes to enhanced drug permeation.[10] As drug delivery is proportionate to the amount of applied electrical potential, ITP offers an opportunity for programmable drug delivery. However, because ITP does not alter the skin barrier itself, it is limited to deliver drugs with molecular weight <10,000 Da.[11–13]

Microneedle technology utilizes needles that typically pierce across the epidermis creating channels for drug transport in the skin.[14] MNs can actively drive therapeutic moieties into the skin either as coated or encapsulated cargo via insertion.[15] MN technology has been explored for the delivery of various drugs, nanoparticles, and macromolecules across skin[16–19] without inducing any pain or discomfort.[20,21] The delivery of human growth hormone and desmopressin across hairless rat skin was facilitated by two layered dissolving MN.[22] Hollow microstructured transdermal system provided rapid delivery rates up to 300 μL/min for liquid formulations of naloxone HCl, human growth hormone, and equine tetanus antitoxin, in swine.[23] Maltose MN facilitated delivery of a large-molecular-weight model protein, immunoglobulin G, in solution across hairless rat skin.[24]

A combination strategy that involves the usage of more than one enhancement technique can result in additive or synergistic delivery of drugs across the skin.[25–28] ITP or MN acts independently of each other and each of them when used alone, are capable of enhancing skin permeation. ITP applied over MN pretreated skin has led to significant increase in the transdermal permeation of insulin and a fluorescein isothiocyanate-labeled bovine serum albumin across porcine skin as compared with either MN or ITP alone.[29] Although ITP alone was not effective to deliver daniplastim across hairless rat skin, microporation of skin resulted in a 30-fold increase in the permeation under the influence of ITP.[30] A combination of MN and ITP for delivery of insulin in a liposomal formulation across rat skin demonstrated a synergistic effect with 713-fold higher permeation than passive delivery (PD) across porcine skin.[31] Thus, the combination of ITP and MN showed synergism in enhancing the skin permeation. However, the effect of physicochemical properties of the drug molecule on the skin permeation under the influence of the combination strategy is not investigated.

Lipophilicity plays an important role in the transdermal permeation by PD, MN, or ITP techniques. As each method has its own limitations when used alone, the use of their combination is becoming increasingly important as an enhancement strategy in the transdermal permeation. The factors influencing skin

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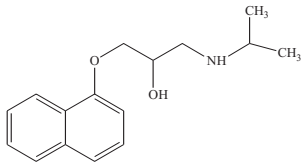
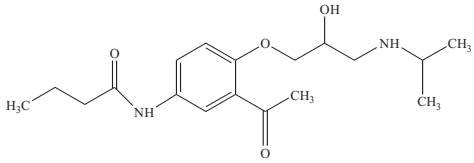
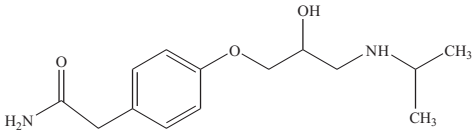
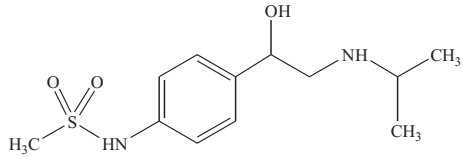
Table 1. Physical Properties and Structures of Beta Blockers

Beta Blocker	Molecular Weight (Free Base)	pK_a	Log *P*	Chemical Structure
Propranolol	259.35	9.26–9.50	2.58–3.65	
Acebutolol	336.43	9.20–9.40	1.43–1.87	
Atenolol	266.00	9.37–9.63	0.23–0.57	
Sotalol	272.36	9.80 (amine, 8.30 (sulfonamide)	−0.41–0.85	

permeation when MN and ITP are used in combination are not well understood. We believe that the lipophilicity plays an important role on MN-mediated transdermal ITP. Further, skin being negatively charged at the physiological pH, it possesses perm-selectivity toward positively charged molecules.[32–35] SC gets breached upon treatment with MN, and this affects its perm-selectivity, which in turn could affect the iontophoretic flux.[33] The outcome of this study addresses this key issue and provides an insight into the versatility of this combination approach for enhancing the transdermal delivery of molecules. Beta-blockers (propranolol, acebutalol, atenolol, and sotalol) were used as model drugs to investigate the effect of lipophilicity on the MN-mediated ITP. All physicochemical parameters such as pK_a and molecular weight are in the similar range, only log *P* of the drugs is varied (Table 1).

EXPERIMENTAL

Materials

Propranolol HCl was obtained from Letco Medical (Decatur, Alabama). Acebutolol HCl and sotalol HCl were obtained from MP Biomedicals (Solon, Ohio) and AvaChem Scientific (San Antonio, Texas), respectively. Atenolol HCl was synthesized in house from atenolol base procured from a commercial source (Letco Medical). The purity of Atenolol HCl was confirmed by nuclear magnetic resonance and infrared spectrometry analyses. Silver wire and silver chloride were purchased from Sigma–Aldrich (St. Louis, Missouri). Sodium chloride, potassium dihydrogen phosphate, and triethylamine were purchased from Fisher Scientific (Suwannee, Georgia).

Preparation of Drug Solution

Each drug in 100 mg quantity was dissolved in 10 mL of 25 mM Tris buffer (pH 7.0). In this solution, 43.83 mg of sodium chloride (75 mM) was dissolved to produce a clear solution. Tris buffer was used to minimize the fluctuations in pH and sodium chloride was included as a source of chloride ions to facilitate electrochemistry.

Skin Permeation Studies

Dermatomed human skin (thickness ~ 0.35 mm) was obtained from Allosource (Cincinnati, Ohio). To avoid inter-individual variations, the entire skin required for the study was collected from a single donor within 8 h of death and frozen at −70°C until use. An internal protocol of Auburn University was followed to ensure biosafety of personnel handling human tissue. *In vitro* studies were performed using vertical Franz diffusion cells (PermeGear, Hellertown, Pennsylvania). The frozen skin was thawed at ambient temperature for about 30 min. It was then cut, rinsed with water, and sandwiched between donor and receptor cells with the epidermis facing the donor cell. The receiver chamber was filled with 5 mL of 25 mM Tris buffer (pH 7.0) and maintained at 37°C with a water circulation jacket that surrounded the cells. The available diffusion area of the skin was 0.64 cm^2. The donor cell contained 500 μL of drug solution and covered with Parafilm to prevent evaporation. Stirring was maintained in the receptor cells with the help of the magnetic bars throughout the permeation study. At defined intervals, 500 μL aliquots from the receptor cells were collected and replaced with fresh buffer solution. The samples were stored in a refrigerator and analyzed within 24 h. All experiments were performed in four replicates.

Drug Extraction from Skin

At the end of the skin permeation study, the residual drug remaining on the surface of the skin was removed by cotton swabs. The surface was washed with Tris buffer (pH 7.0) and then gently wiped with a cotton swab (Q-tips®; Uniliver USA,