Journal of Controlled Release 154 (2011) 148–155

Contents lists available at ScienceDirect

Journal of Controlled Release

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

Kinetics of skin resealing after insertion of microneedles in human subjects

Jyoti Gupta [a], Harvinder S. Gill [b,c], Samantha N. Andrews [b], Mark R. Prausnitz [a,b,*]

[a] School of Chemical & Biomolecular Engineering, Georgia Institute of Technology, Atlanta, Georgia 30332, USA
[b] Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology, Atlanta, Georgia 30332, USA
[c] Department of Chemical Engineering, Texas Tech University, Lubbock, Texas 79409, USA

ARTICLE INFO

Article history:
Received 22 January 2011
Accepted 17 May 2011
Available online 26 May 2011

Keywords:
Barrier resealing kinetics
Electrical impedance
Microneedles
Skin permeability
Transdermal drug delivery

ABSTRACT

Over the past decade, microneedles have been shown to dramatically increase skin permeability to a broad range of compounds by creating reversible microchannels in the skin. However, in order to achieve sustained transdermal drug delivery, the extent and duration of skin's increased permeability needs to be determined. In this study, we used electrical impedance spectroscopy to perform the first experiments in human subjects to analyze the resealing of skin's barrier properties after insertion of microneedles. Microneedles having a range of geometries were studied in conjunction with the effect of occlusion to test the hypothesis that increasing microneedle length, number, and cross-sectional area together with occlusion leads to an increase in skin resealing time that can exceed one day. Results indicated that in the absence of occlusion, all microneedle treated sites recovered barrier properties within 2 h, while occluded sites resealed more slowly, with resealing windows ranging from 3 to 40 h depending on microneedle geometry. Upon subsequent removal of occlusion, the skin barrier resealed rapidly. Longer microneedles, increased number of needles, and larger cross-sectional area demonstrated slower resealing kinetics indicating that microneedle geometry played a significant role in the barrier resealing process. Overall, this study showed that pre-treatment of skin with microneedles before applying an occlusive transdermal patch can increase skin permeability for more than one day, but nonetheless allow skin to reseal rapidly after patch removal.

© 2011 Elsevier B.V. All rights reserved.

1. Introduction

Transdermal drug delivery is an attractive alternative to traditional oral and hypodermic delivery, as it overcomes the limitations of first-pass metabolism encountered by oral administration and is safe, painless, and easy to use, in contrast to hypodermic needles [1]. Additionally, the large, accessible surface area of the skin makes it an appealing drug delivery route. Over the past few decades, transdermal patches have been developed to painlessly deliver drugs across the skin. However, the barrier properties offered by the skin's outermost 10–20 μm layer, viz. the stratum corneum, are responsible for poor skin permeability, allowing only a handful of drugs to transport across the skin at therapeutic rates.

Microneedles, which are micron-dimension needles, have been developed to increase skin permeability by creating microchannels in the skin that allow for increased transdermal transport of small and large drug molecules [2,3]. These microneedles are long enough to breach the skin's barrier to allow for drug transport, yet are short enough to avoid stimulating nerves, thereby avoiding pain [4,5].

Over the past decade, several studies have been conducted to show that microneedles are useful for transdermal drug delivery. Microneedles have been used to deliver drugs such as desmopressin [6], plasmid DNA [7], insulin [8], human growth hormone [9] and oligonucleotides [10], as well as vaccines against influenza [11], hepatitis B [7] and C [12], diphtheria [13], anthrax [14] and human papillomavirus [15] in animals [16]. More recently, microneedles have also advanced to human subjects to deliver influenza vaccine [17,18], naltrexone [19], methyl nicotinate [20], topical anesthetics [21] and insulin [22].

Microneedles can be fabricated as single- or multi-needle arrays having hollow channels or solid structures that can be coated with drug or made to encapsulate drug. Hollow microneedles actively deliver drug to the dermis through convective flow, similar to the mechanism of a hypodermic needle. Solid microneedles also deliver drug actively by either inserting drug-encapsulated needles or drug-coated needles into the skin. In each of these active delivery cases, from a safety standpoint it is desirable for the microchannels to close soon after needle removal to prevent permeation of undesired toxic substances or pathogenic microbes that may lead to infection at the treatment site.

Solid microneedles can also deliver drugs via passive diffusion by creating microchannels to increase skin permeability followed by the application of a drug-loaded patch on top of the channels [10,13,19,21,23]. To achieve sustained delivery, from an efficacy

* Corresponding author at: School of Chemical & Biomolecular Engineering, Georgia Institute of Technology, 315 Ferst Drive, Atlanta, GA 30332–0100, USA. Tel.: +1 404 894 5135; fax: +1 404 894 2291.
E-mail address: prausnitz@gatech.edu (M.R. Prausnitz).

0168-3659/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.jconrel.2011.05.021

standpoint, it is desirable for these microchannels to stay open as long as the drug patch is on the skin. However, it is also desirable for the holes to close quickly after patch removal to prevent site infection.

To achieve prolonged drug delivery using solid microneedles, it is important to determine the extent and duration of the skin's increased permeability because as with any skin wounds or abrasions, the holes created in the skin reseal over time due to the skin's natural repair mechanisms. Upon disruption of the stratum corneum barrier, lamellar body secretion is immediately initiated followed by synthesis of lipids, which are necessary to restore and maintain the stratum corneum barrier [24,25]. Because the kinetics of stratum corneum repair depend on the degree of barrier perturbation [26], it is also important to study stratum corneum repair following treatment with microneedles of various geometries. Further, because the presence of a drug-loaded patch on the treatment site covers (occludes) the skin, it is also necessary to study the effect of occlusion on skin resealing after microneedle treatment.

Previous in-vivo studies performed in hairless guinea pigs have shown that microneedles increased skin permeability over a 48 h time period as characterized by transepidermal water loss [27]. Other studies have also been carried out in human subjects using transepidermal water loss to show that microneedle insertion leads to an increase in skin permeability, but the kinetics of repair were not examined [5,28]. Thus, no kinetic studies have been performed to determine the "window" of increased permeability following microneedle treatment and how it can be modulated.

In this study, we perform the first human experiments to analyze the resealing of skin's barrier properties after microneedle insertion and determine the duration of increased skin permeability as a function of microneedle geometry and skin occlusion. We also study the role of occlusion to influence the expected safety and efficacy of microneedle treatment as well as the relationship between pain and skin resealing time.

Several non-invasive biophysical tools such as transepidermal water loss (TEWL), infrared spectroscopy and electrical impedance spectroscopy have been evaluated to determine the in-vivo integrity of the stratum corneum barrier and permeability of skin [29,30]. Recent studies have also used confocal microscopy and optical coherence tomography to image holes made in the skin using microneedles [31–33]. While TEWL is the most commonly used evaluation tool, this method requires areas studied under occlusion to be un-occluded during the measurement procedure. Because this study specifically tested the effects of occlusion, we employed electrical impedance spectroscopy as our measurement tool so as to allow the occluded treatment sites to remain occluded throughout the experimental period.

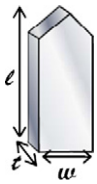
The skin's electrical resistance lies predominantly in the stratum corneum and any break in the integrity of the barrier leads to a decrease in skin impedance [34,35], thereby making impedance spectroscopy a useful tool to determine skin barrier integrity after microneedle insertion. Previous studies have demonstrated that there is a strong correlation between skin impedance and skin permeability with a decrease in skin impedance generally corresponding to an increase in skin permeability [36]. Additionally, impedance spectroscopy is a non-invasive and safe measurement tool that is often used in dermatology for the assessment of skin diseases and in the cosmetic industry to study the effect of cosmetics on skin [37].

2. Materials and methods

2.1. Microneedle fabrication

Five different microneedle geometries with varying microneedle length, number of needles, and base cross-sectional area (Table 1) were fabricated by laser cutting stainless steel sheets (Trinity Brand Industries, SS 304, 75 μm and 125 μm thick; McMaster-Carr, Atlanta, GA) using previously published methods [38]. The arrays were cleaned and electropolished as described previously [38] and then sterilized in a steam autoclave (Steris Amsco Renaissance 3033 Prevac Steam Sterilizer; Steris Corporation, Mentor, OH). The microneedle arrays had an overall footprint size of 12 mm by 12 mm.

Table 1
Parameters of the five different microneedle geometries and two experimental controls studied.

Treatment[1]	Length (*l*) μm	Thickness (*t*) μm	Width (*w*) μm	Number of Microneedles	
A	750	75	200	50	
B	750	75	200	10	
C	500	75	200	50	
D	1500	75	200	10	
E	750	125	500	50	
F	Hypodermic Needle (26 Gauge)				
G	No Treatment				

[1] All treatment conditions, with the exception of treatment F, were studied under occlusive and non-occlusive conditions. Treatment F was only studied in the absence of occlusion.

2.2. Electrodes and impedance measurement

Ag/AgCl dry electrodes (Thought Technology T-3404; 25 mm × 25 mm total area; 10 mm active electrode diameter; Stens Corporation, San Rafael, CA) were used as the measurement electrodes for the treatment sites. A large electrode with a highly conductive gel (Superior Silver Electrode with PermaGel, 70 mm total and active electrode diameter; Tyco Healthcare Uni-Patch, Wabasha, MN) was used as the reference electrode to keep the impedance contribution of the reference site at a negligibly low value. Impedance measurements were made by connecting the reference and measurement electrodes to an impedance meter (EIM-105 Prep-Check Electrode Impedance Meter; General Devices, Ridgefield, NJ) that applied a low frequency (30 Hz) alternating current and was modified with a 200 kΩ resistor (Ack Electronics, Atlanta, GA) in parallel to allow for measurement of skin impedance values greater than 200 kΩ.

2.3. Human subjects

Ten healthy adult human subjects (3 female, 7 male, age: 24–52) with no history of dermatological disease were recruited to participate in this study. Both the left and right volar forearms of all subjects were used in the study. Subjects were asked to refrain from application of any topical formulations or soaps on their arms, as well as to avoid any vigorous physical activity or extreme temperature showers one day prior to and throughout the duration of the experiment. In order to obtain hourly skin impedance data over a period of 48 h after treatment, subjects were divided into two groups of five individuals each. The first group provided data for time points 1–11 and 23–35 h post treatment and the second group generated data for time-points 12–22 and 36–48 h post treatment. Both groups also provided data for time-points −1, −0.5, and 0 (immediately after treatment) h.

Subjects remained in the study room throughout each data collection period. Prior to commencing skin impedance data collection on each study day, subjects were asked to rest in the controlled environment study room for 1 h in order to acclimate to the experimental conditions of 40% relative humidity and room temperature of 21 °C. The study was approved by the Georgia Tech Institutional Review Board and all subjects provided informed consent prior to participation.

2.4. Experimental design

A total of 11 sites (left arm: 6 and right arm: 5) were identified on the volar forearms of all ten subjects and were outlined with a pen.

Download English Version:

https://daneshyari.com/en/article/1424999

Download Persian Version:

https://daneshyari.com/article/1424999

Daneshyari.com