European Journal of Pharmaceutical Sciences 68 (2015) 137–143

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

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

Modelling of dissolving microneedles for transdermal drug delivery: Theoretical and experimental aspects

Kwang Seok Kim [a,1], Kevin Ita [b,2], Laurent Simon [a,*]

[a] Otto H. York Department of Chemical, Biological and Pharmaceutical Engineering, New Jersey Institute of Technology, University Heights, Newark, NJ 07102, USA
[b] College of Pharmacy, Touro University, Mare Island, Vallejo, CA 94592, USA

ARTICLE INFO

Article history:
Received 29 July 2014
Received in revised form 6 December 2014
Accepted 7 December 2014
Available online 13 December 2014

Keywords:
Dissolving microneedle array
Elimination
Pitch
Single needle model
Parameter estimation

ABSTRACT

A mathematical model was developed to predict the amount of drug delivered into the skin via the dissolution of a microneedle (MN). This approach differs markedly from previous research which focused on similar phenomena but failed to include a biological membrane. Dimensionless governing equations were derived to help predict the needle height and fate of the active ingredient in the skin layer after application of the device. Simulation studies with fentanyl revealed that the drug concentration was proportional to its mass fraction in the MN. The effect of the pitch on skin permeation was mildly nonlinear. A larger amount of fentanyl was delivered from microneedle arrays with smaller pitch size. The dissolution process was independent of changes in the elimination rate constant. An optimization algorithm was applied to show how to recover this parameter from needle height – time data.

1. Introduction

The stratum corneum (SC) is the outermost layer of the epidermis consisting mainly of dead cells. Its thickness, in the human skin, has been reported to be approximately 10 μm (Russell et al., 2008; Holbrook and Odland, 1974). It is the main barrier to transdermal drug delivery. Several investigations have been conducted to overcome this obstacle and thus promote molecular transport. Park and his coworkers attached a sample skin to a heat source to raise the temperature in a controlled manner. Calcein flux increased with the skin temperature (Park et al., 2008). Other researchers have used chemical penetration enhancers to increase the transdermal flux (Maurya and Murthy, 2014; Shang et al., 2014). A co-drug approach was also implemented to improve the transdermal delivery of naltrexol (Kiptoo et al., 2006). In diffusion cell studies with human skin, this strategy has resulted in a 4-fold increase in transdermal flux of naltrexol. In spite of progress made in the development of drug-delivery devices, the SC still hinders the permeation of many medications (Kimura et al., 2007; Frum et al., 2007; Simon, 2007; Simon et al., 2006; Dias et al., 2007). Microneedles (MNs) were introduced to remedy the situation (Ito et al., 2006; Verbaan et al., 2008; Prausnitz et al., 2004) and included different designs: solid, polymeric, coated or hollow. Hollow MNs have bores through which drugs are released to the skin by diffusion or Poiseuille flow (Hood et al., 2011). Although these needles are long enough to penetrate the SC, they are too short to reach the nociceptors which are located in the dermis (Kaur et al., 2014).

MN arrays can be fabricated by MEMS (Micro-Electro Mechanical Systems) technology, for details refer to (Pelesko and Vasquez, 2005; Nayak and Das, 2013). For the preparation soluble MNs, a biodegradable polymer (e.g., PLGA) containing the active pharmaceutical ingredient (API) is cast on the PDMS micro-mold (Nayak and Das, 2013; Lee et al., 2008). Microneedles, made of sucrose or a PVA/sucrose blend as a matrix material, can also be used as a drug vehicle for fast release (Miyano et al., 2005). Solid MNs are usually made of steels while soluble MNs are fragile and, thus, should be subjected to a force test, to achieve controlled release, where the maximum force exerted on the MN is measured before fracturing (Olatunji et al., 2014).

Significant research efforts are directed toward maximizing the applicability of MNs. These activities involve the optimization of MN patches, in terms of the skin permeability, by manipulating factors such as the number of MNs in an array, the shape, size and height of the MN, pitch (center-to-center distance between adjacent MNs) and the insertion force. Al-Qallaf and Das (2008) developed an algorithm for optimizing the skin permeability when an array of conical solid or hollow MNs is applied. For the patch

* Corresponding author. Tel.: +1 973 596 5263; fax: +1 973 596 8436.
E-mail addresses: ksbears@kgs.or.kr (K.S. Kim), kevin.ita@tu.edu (K. Ita), laurent.simon@njit.edu (L. Simon).
[1] Present address: Institute of Gas Safety R&D, Korea Gas Safety Corporation, 1390 Wongjung-ro, Eumseong-gun, Chungcheongbuk-do 369–811, South Korea. Tel.: +82 43 750 1644; fax: +82 43 750 1948.
[2] Tel.: +1 707 638 5994; fax: +1 707 638 5266.

http://dx.doi.org/10.1016/j.ejps.2014.12.008
0928-0987/

Nomenclature

C	dimensionless concentration of drug in the skin layer
c	drug concentration in the skin layer (kg/m^3)
c_s	solubility of matrix material in water (kg/m^3)
d_s	depth of the skin layer (epidermis and dermis) (m)
H	dimensionless height of MN
h	height of MN (m)
K	ratio of the first-order drug elimination rate over drug-release rate
k_D	dissolution rate constant of matrix material (m/s)
k_L	elimination rate constant of drug at the bottom of skin layer (s^{-1})
MN	abbreviation of microneedle
N	the number of MNs in a row of a square array
p_w	pitch of MN (center-to-center distance) (m)
r	base radius of MN (m)
SC	abbreviation of stratum corneum
t	time (s)
V	dimensionless volume of skin layer
V_c	dimensionless volume of MN
v	volume of skin layer (also called *compartment*) (m^3)
v_c	volume of MN (m^3)

Greek letters

β	mass fraction of drug in MN
θ	half angle at the apex of MN (degree)
ρ	density of MN
Σ	dimensionless density of matrix material in MN
τ	dimensionless time
τ_0	characteristic time defined as $\rho h_0 \sin\theta / k_D c_s$ (s)
Ω	ratio of initial volumes of compartment to MN

Subscript

0	initial state

with solid MNs, the MN height was not considered under the assumption that the drug was mainly moving through the holes made by MNs and in a direction perpendicular to the skin (i.e., one-dimensional transport). As a result, it was found that the skin permeability increased with the radius and decreased as the patch area grew. The pitch size has a greater impact on skin permeability than its radius. In other research, a similar algorithm was applied to square (Al-Qallaf and Das, 2009a) and non-square (Al-Qallaf and Das, 2009b) distributions of MNs in an array. Davidson et al. (2008) showed that the isosceles right pentagon was the best shape for drug-coated microneedles to increase the effective skin permeability of insulin and reduce the effective skin thickness, i.e., the mean distance the dissolved drug has to travel before it is absorbed into the microcirculation. Cheun et al. (2014) recently helped visualize the cross section of stained porcine skin disrupted by MNs to show that an insufficient insertion force may reduce the performance of the system.

When designing soluble MNs, it is important to identify key feature differences between soluble and coated solid MNs. A notable contrast is that a single soluble MN can hold (or deliver) a much greater amount of API than the coated type. It should be noted that models for drug release from coated MNs, developed in previous studies, described an unlimited supply of API to the skin while the device itself can only hold very limited amount of API. The second observation is that the effect of the MN dissolution rate on the skin permeation cannot be neglected (Nayak and Das, 2013). Based on these differences, it is critical to include changes in drug concentration in the epidermis layer when estimating the skin permeation.

In the present study, a model of drug released from a single dissolving MN in a control volume is developed. The construct is such that the effect of a buffer space can be evaluate before the drug is ultimately absorbed into the microcirculation (e.g., the epidermis and dermis layer) can be evaluated. The behavior in the current single MN model is similar to that observed in the vicinity of most MNs in an array (Al-Qallaf et al., 2009). The main equations for drug concentration in the epidermis and dermis layers include the influences of the MN dissolution rate, its size and the drug clearance. These equations are written in dimensionless form to parameterize the model. Physically meaningful dimensionless groups are suggested and their effects on drug delivery are discussed. Skin metabolism is not considered because its effect on drug release by the MN was found to be negligible (Al-Qallaf et al., 2009). The discussions with the current model are applied to an array of sucrose MNs with encapsulated fentanyl. Derivations of the model equations are provided in Appendix A. The non-dimensionalization of the equations is based on the variables shown in the equations, not on the Buckingham Π theorem since it is difficult to assess the physical relevance of the parameters obtained by the latter approach.

2. Mathematical modelling

2.1. Dimensionless mathematical model and parameters

A model for dissolving microneedles is proposed. These conical needles are made from a water-soluble matrix, e.g., sucrose, premixed with an API. The needles are sufficiently long to be able to perforate both the epidermis and dermis but do not extend to nerves located deep inside the dermis. Once an MN patch is applied to the skin, the needles penetrate the epidermis and outer part of the dermis and begin to dissolve. The dissolution of the solid matrix results in the release and the accumulation of the drug in the dermis. Subsequently, the drug molecules enter the bloodstream by diffusion. Drug molecules disappear from the skin layer by an enzymatic metabolism. However, it is found that the rate of metabolic loss is low compared to other dynamics and its effect on the skin permeation can be ignored especially when the barriers (e.g., SC layer) are removed (Al-Qallaf et al., 2009).

Drug delivery from an array of MNs is estimated by assuming that MNs behave as though they are placed in an identical environment. In fact, in an N by N squarely distributed MN array, $4 \times (N-2)$ needles in the sides have 3 adjacent MNs and the 4 needles at the corners have only 2. All the others, $(N-2)^2$, have 4 adjacent MNs (see Fig. 1(a)). In an area of 4 cm^2, i.e., the size of a typical patch, the physiological environment slightly varies. For example, with $N = 100$, only 4 percent of MNs show different delivery pattern. This assumption, which has already been used in the optimization of an MN array (Al-Qallaf and Das, 2008; Al-Qallaf and Das, 2009a,b), can also be applied to a non-squarely distributed array.

With the above assumption, the single MN model in Fig. 1(b) consists of a conical MN submerged in a rectangular compartment. The top and the bottom of the compartment represent the SC and the bloodstream, respectively. Thus, the height is equivalent to the depth of the skin layer d_s. The width is equivalent to pitch p_w; there is no mass transport through the 4 sides. The volume of the com-