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A theoretical compartment model for antigen kinetics in the skin

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ABSTRACT

The skin is a promising location for vaccination with its abundant population of antigen capturing and presenting cells. The development of new techniques, such as the use of microneedles, can facilitate the delivery of vaccines into the skin. In recent years, many different types of microneedle arrays have been designed. However, their geometry and arrangement within an array may be optimized to trigger sufficient antigen presenting cells. A computational model can support the rational design of microneedle arrays. Therefore, the aim of the current study was to describe the distribution and kinetics of a delivered antigen within the skin using a theoretical compartment model, which included binding of antigens to receptors and their uptake by cells, and to determine which parameters should be measured to validate the model for a specific application. Multiple simulations were performed using a high and low antigen delivery dose and a range of values for the rate constants. The results indicated that the cells were highly saturated when a high dose was applied, while for a low dose saturation was only reached in 5% of the simulations. This was caused by the difference in the ratio between the administered dose and the available binding sites and suggests the dose should be adapted to the number of cells and receptors for a specific compound. The sensitivity analysis of the model parameters confirmed that the initial dose and receptor concentrations were indeed the two parameters that had the largest influence on the variance in antigen concentrations within the cells and circulation at equilibrium. Hence, these parameters are important to be measured in vivo. The presented pharmacokinetics model can be used in future computational models to predict the influence of microneedle array geometry to optimize their design.

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1. Introduction

Vaccines are traditionally delivered to subcutaneous or intramuscular tissues with a hypodermic needle and syringe. However, recent studies have reported that skin is a promising target for vaccine administration, since it is rich with antigen presenting cells (APCs), such as Langerhans cells and dermal dendritic cells (Al-Zahrani et al., 2012; van der Maaden et al., 2012). When an antigen is delivered in the epidermis and dermis, it will diffuse through the different skin layers (Raphael et al., 2013; Römgens et al., 2015). One of these layers, the viable epidermis, is mainly composed of keratinocytes, but also contains a large population of Langerhans cells (Koutsonanos et al., 2013). Beneath the epidermis lies the dermis, a relatively thick layer rich in collagen fibres. Among others, dermal dendritic cells reside in the dermis. After antigens are delivered into the skin, three options are possible:

1. They can be recognized, bind and be internalized by the cells residing in the skin (Giese, 2013; Koutsonanos et al., 2013). This uptake of antigens occurs by receptor-mediated endocytosis or by fluid phase pinocytosis (Abbas et al., 2012; Mizuno et al., 2004). Multiple receptors, such as Toll-like receptors and C-type receptors, play a role in the specific binding and internalization of antigens (Dzopalic et al., 2012; Flacher et al., 2006; Mizuno et al., 2004; Ueno et al., 2007). After internalization of antigens, the two populations of antigen presenting cells will mature and start to migrate towards the draining lymph nodes (Dzopalic et al., 2012). There, they present the processed antigens to T-cells, which initiates an adaptive immune response (Koutsonanos et al., 2013). The response mechanism of the APCs in the skin is influenced by the secretion of various signal molecules such as cytokines and chemokines (Koutsonanos et al., 2013), which are secreted by other skin cells, such as keratinocytes (Flacher et al., 2006), as a response to antigen encounter and other chemical and physical triggers.
2. Antigens can directly diffuse to the lymph nodes and activate the lymph node-resident dendritic cells (Abbas et al., 2012; Ueno et al., 2007).
3. Antigens can be transported away from the skin by uptake in the systemic circulation through the capillaries within the dermis.

To deliver antigens into the skin, microneedles are being developed. These microneedles are small projections that are often arranged in an

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array and are used to bypass the stratum corneum, which is impermeable to larger molecules (Bos and Meinardi, 2000). Microneedles can be hollow to inject a fluid, solid to make conduits in the skin, coated with an antigen or made of a dissolvable material containing the antigen (van der Maaden et al., 2012).

Although many microneedle types are now available, involving different types, geometries, and arrangements in an array (Indermun et al., 2014; Kim et al., 2012), little is known about their specific influences on the delivery and transport of the antigen and thus the effectiveness of the immune response. One of the few studies using coated microneedles reported that the immune response is mostly independent on the microneedle array geometry (Widera et al., 2006). By contrast, another study revealed an effect of microneedle array density on the immune response (Depelsenaire et al., 2014). In addition, the total volume of the microneedles on an array has been reported to influence the immune response when topically applying an antigen before treating the skin with microneedles (Carey et al., 2011; Pearson et al., 2015). These results suggest that the potency of the immune response may vary depending on the microneedle array geometry. To optimize microneedle array designs, it would be beneficial to develop a computational model which predicts the influence of various features of the microneedles on the resulting efficiency of the immune response.

A first step in this process would be a model to describe the transport within the skin. Mathematical models have previously been used to predict the transport of topically applied drugs through the skin and into the circulation, as reviewed by Mitragotri et al. (2011), and Naegel et al. (2013). Models can be separated into those that consider the spatial distribution inside the skin (e.g. Dancik et al., 2012; Kretsos et al., 2008) and those considering the average concentration in various compartments of the skin (e.g. McCarley and Bunge, 2001). Both models have been developed on the macroscopic (tissue) and microscopic (cell) levels, where aspects such as metabolic activity, binding to skin components, diffusion and partitioning are considered. In addition, some models focused on the transport through the skin after drug administration with microneedles (Al-Qallaf et al., 2009; Kim et al., 2015; Lv et al., 2006; Zhang et al., 2009). Most of these models focus on transport to the systemic circulation, as opposed to kinetics within the skin. However, for vaccination purposes it is the latter which is critical, involving events such as the binding of antigens to receptors and their internalization by dendritic cells. For example, receptor mediated endocytosis can be included, which has been modelled at the microscopic level (Gex-Fabry and DeLisi, 1984).

The aim of the present study was to (1) develop a model that described the distribution of an antigen within different components of the skin and included the binding and internalization of the antigen by cells residing in the skin. (2) To determine which parameters should be accurately measured in an in vivo setup, because they demonstrate the largest influence on variation in equilibrium concentrations. This was achieved by developing a theoretical compartment (pharmacokinetic) model of the skin and its cells and by performing a sensitivity analysis on the model parameters, which were taken from those reported in the literature. This analysis was designed to determine which parameters should be measured accurately for a more precise output, providing a template to perform validation experiments which match specific applications.

2. Methods

2.1. Theoretical compartment model of skin kinetics

To describe the distribution of an antigen delivered to the skin, a theoretical compartment model was developed. In this type of model, the average concentration in a single compartment is considered as opposed to calculating the spatial concentration distribution. The present study extended a basic compartment (pharmacokinetic) model of the skin (McCarley and Bunge, 2001) with both a compartment representing antigens bound to receptors on the cell membrane and a compartment of the intracellular space. It was assumed that antigen uptake by cells only occurred via receptor-mediated endocytosis. The compartment model consisted of five compartments (Fig. 1), which are defined as follows:

- The microneedle (MN), or other delivery device
- The extracellular matrix of the skin (ECM)
- The receptors on the cell (rec)
- The intracellular space (cells)
- The blood and lymph circulation (circ).

The change in concentration of the antigen within or bound to these various compartments was described with a set of differential equations (Eqs. (1)–(5)):

$$\frac{dC_{MN}(t)}{dt} = -r(t), \tag{1}$$

$$\frac{dC_{ECM}(t)}{dt} = r(t) - k_a C_{ECM}(t)(R_{tot} - C_{rec}(t) - C_{cells}(t)) + k_d C_{rec}(t) - k_c C_{ECM}(t), \tag{2}$$

$$\frac{dC_{rec}(t)}{dt} = k_a C_{ECM}(t)(R_{tot} - C_{rec}(t) - C_{cells}(t)) - (k_d + k_{int}) C_{rec}(t), \tag{3}$$

$$\frac{dC_{circ}(t)}{dt} = k_c C_{ECM}(t), \tag{4}$$

$$\frac{dC_{cells}(t)}{dt} = k_{int} C_{rec}(t), \tag{5}$$

where C_α represents the antigen concentration in the different compartments with α = MN, ECM, circ, and cells; C_{rec} the concentration of antigens bound to the receptors; r the release rate from the microneedle; k_a and k_d indicate the association and dissociation rate constant of the antigens to bind to the receptors, respectively; k_{int} the rate of internalization of the antigen-receptor complex into the cell; k_c the rate of uptake into the circulation; R_{tot} the total initial concentration of receptors on the cell membranes; and t the time.

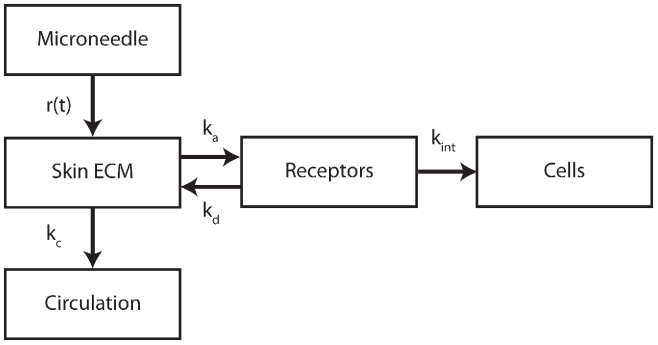

Fig. 1. Compartment model to describe the kinetics of antigens delivered into the skin. The concentration of an antigen in the extracellular matrix, bound to receptors on the cell membranes, inside the cells and in the circulation is determined by the release from the microneedle r and the exchange of antigens between the various compartments. This exchange is dependent on the rates k_β.

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