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# Mathematical Modelling of transdermal vaccine delivery through solid silicon-coated microneedle for vaccine delivery applications

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## ABSTRACT

Mathematical modeling possesses a substantial perspective for estimating the proficiency of microneedles for effective vaccine delivery, which helps people working in the pharmaceutical industry to focus on MEMS (Microelectromechanical systems) based transdermal vaccine delivery applications. Microneedles are a substitute technique to convey vaccines into the dermis layer of skin structure. The mathematical model developed in this paper mimics the transfer of vaccines into the skin. This paper deals with the vaccine coated solid silicon triangular pyramidal-shaped microneedles to specify the vaccine release rate and drug administration profile. Based on these outcomes, for a microneedle coated with a drug, it is possible to predict the drug extricate rates before fabrication. Suitable mathematical modeling for vaccine delivery from coated microneedles systems into the dermis layer can sort out issues related to the design of microneedles, vaccine transport, and delivery behavior.

**Keywords:** Modelling, Microneedle, Silicon, Skin, Vaccine

## INTRODUCTION

Microneedles were substantially examined in the present day for vaccine and drug delivery in addition to reducing pain and extremely quick diagnosis of patients (Eneko et al., 2016). Microneedle fabrication and studies are ultimately at the present stage where profit-making is a practical possibility (Chavoshi et al., 2019). Microneedles were developed to penetrate by the stratum corneum to deliver vaccines to the viable epidermis where the vaccine particles disperse more comfortably into the dermis from where vaccine particles are (Olatunji et al., 2011) consumed into the blood. Vaccine delivery through microneedle is a superior option to some extent where faster dissolution is required, to shape the drug delivery process extra advantageous for the patients (Zoudani and Soltani, 2020).

Solid microneedles are coated with vaccine particles and administered to the skin layers (Amin and Ahmed, 2013). These solid microneedles do not disintegrate in the skin, which is progressively pulled out after the dissolution of the vaccine into the skin layers (Zhang et al., 2013). Solid microneedle performance depends on penetration, ease of vaccine particles that move into biological skin membrane layers, and biocompatibility of solid microneedle material (Al-Qallaf et al., 2007). Substantially, in biomedical applications such as vaccine delivery, electing size, shape, and materials is a crucial task where the mathematical model will assist in achieving this (Chen et al., 2016) characteristics.

Silicon furnishes outstanding versatility in microneedle fabrication processes such that silicon can be micro-structured in a variety of required sizes, designs, and shapes (Yadav et al., 2020). Silicon microneedles possess proficient biocompatibility, less toxicity, high strength, more toughness, and extremely low cost (Al-Qallaf B and Das, 2009). Previously, silicon was the single material selected for the fabrication process but nowadays many silicon dioxides (Pradeep and Raghavan, 2017) are used to get sharper tips and to enhance skin permittivity. An array of solid silicon microneedles was used for the timely and controlled delivery of vaccines into the skin (Malik et al., 2018).

In this paper, a mathematical model is obtained to simulate the delivery and solubility of vaccines into the blood by triangular pyramidal-shaped solid coated microneedle. The mathematical model will assist the appraisal and estimation of microneedle properties such as vaccine loading, the height of microneedle, and needle width to transfer vaccine into the skin. A model developed in the work is illustrating the solubility and release of coated vaccine from a single solid triangular pyramidal microneedle array into the skin structure. The model developed in this work is to represent the dissolving of the vaccine into the skin instantly when microneedle enters into the epidermis layer of skin structure.

## MATERIALS AND METHODS

The selection of material for microneedle (Fig.1a) fabrication is an overcritical factor to the production and execution of solid triangular pyramid microneedle. Mathematical models depend on various microneedle characteristics and numerous designs of microneedles. Silicon is recognized and used as the best microneedle fabrication material, which is suitable for vaccine delivery because of the arrival of MEMS/NEMS (Nano electro-mechanical systems) technology. Silicon provides outstanding biocompatibility, stability, strength, vaccine permeability, and flexibility in microneedle manufacture processes, which is utilized to give a variety of micro-structured sizes and shapes.

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Fig

.1. Schematic view of single microneedle (a). Single microneedle and skin structure with dimensions in mm (b). Vaccine transport in drug-coated microneedle

Authors had performed many numerical simulations (Fig.2) on a single microneedle to analyze the performance of microfabricated solid triangular pyramidal-shaped microneedle. The mathematical models developed in the work have been utilized substantially to validate the capability of the solid silicon triangular pyramidal microneedle array. During the simulation process authors evaluated different mechanical properties, diffusion of vaccine studies, permeation behavior and stresses, strains induced in the skin structure due to insertion of microneedle while delivering the vaccine (Fig.1b) which was already laminated on the surface of the needle.

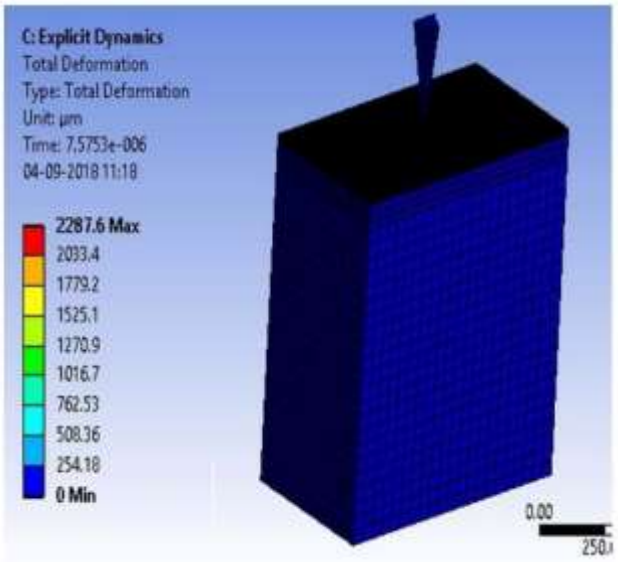


Fig.2. Simulation of the microneedle to pierce skin sample under loading

## MATHEMATICAL MODELLING OF MICRONEEDLE

Numerous combinations of forces developed through microneedle insertion into the skin are given in equation (1).

$$F_{penetration} = F_{buckling} + F_{friction} + F_{piercing} \quad (1)$$

$F_{buckling}$ was the force that deals with the total deformation of the skin, $F_{friction}$ was the force where friction-induced during microneedle insertion into the skin layers, and $F_{piercing}$ is the force that deals with the microneedle start piercing the stratum corneum layer of the skin. The above forces were evaluated for triangular pyramidal-shaped microneedle utilizing finite element analysis (FEA). The above forces are dependent on the geometry, mechanical characteristics of the microneedle. Simulation results from FEA are dependent on the size and shape of the microneedles.

The amount of vaccine entered into the skin, vaccine release, dampening of the internal skin structure was dependent on applied force and the connection among them is determined by effortless mathematical equations. Microneedle modeling is based on a single microneedle rather than considering the array of microneedles to obtain a precise estimation of the penetration force and to scrutinize the vaccine release into the skin structure.

Solid coated triangular pyramidal-shaped microneedle was utilized to generate holes on the skin structure where vaccines were applied when microneedles are removed after penetration. The pathways or holes generated by microneedles are considered as a reservoir or way to release the vaccine particles. The permeability (B) of the interiors of the reservoir is permitted to be illustrated by equation (2).

$$B = F\,\frac{J}{P} \quad (2)$$

Where P is the length of the hole developed by solid microneedle into the skin structure, F is the tiny area of the hole onto the skin and J is the dispersing coefficient of the triangular pyramidal-shaped solid microneedle.

To retrieve the improved microneedles diffusion in the skin structure, a function (a) established to designate the hole on a triangular-sh patch is given by

$$a = \frac{i^2 M^2}{K} \quad (3)$$

Pitch ($D_t$) is expressed as the origin to origin distance between two alongside microneedles. It indicates that the microneedles on an array do not adhere with each other to keep away from uneven pattern or failure of microneedles array.

$$D_t = \frac{\sqrt{K}}{i} \geq \beta M \qquad (4)$$

Where β is the aspect ratio that must be apedgreater than 2 to avoid adhesion between two microneedles.

To obtain various patterns such as a triangular, the pitch direction in horizontal ($D_{hn}$) and vertical directions ($Dv_m$) must be specified. The correlations between permeability (B) and dispersing coefficient of various vaccine molecules based on superlative variables must be calculated with equation (5).

Triangular (microneedle distribution in a array) B = 0.936 x J – 0.0007 (5)

To achieve a transdermal vaccine delivery approach a scaling analysis was developed, which indicates the interaction among various constant dimensionless variables of vaccine concentration and microneedle physical structure which is indicated in equation (6).

$$\frac{X_t}{X_s} = B^o \left[\!\left[\frac{S_a P^4 B_e}{V_b h J}\right]\!\right]^i \qquad (6)$$

$X_t$ and $X_s$ indica the vaccine compositions in blood and single microneedle. $B^o$ is the dimensionless constant, i is unknown power $S_a$ is the total surface area of microneedle array, $B_e$ is an elimination rate constant, h is the thickness of the skin structure, P is the length of the single microneedle, $V_b$ is the volume of the fluids, J is the dispersing coefficient of vaccine into skin structure.

**MICRONEEDLE ARRAY FABRICATION BASED ON MATHEMATICAL MODEL**

The microneedle arrangement is a strong three-sided pyramid with a sharp tip portion, which gives sufficient quality and effortlessness of skin addition. The distance between one edge of the needle to the same edge on another needle in a 9 x 9 microneedles bunch is 600 µm. The stature of the microneedle is restricted to 350 µm to dispose of contact of microneedle with other adjoining needles. The base length of every single microneedle is restricted to 100 µm (Fig.3b).

At this moment we present a gadget reliant upon permeable silicon microneedles. Photolithography, wet etching, and anisotropic wet etching (TMAH) frameworks are solidified for the affirmation of microneedles (Fig.3a). CleWin an amazing cover configuration device is used to set up the optical veil for Positive Photoresist designing and to foster strong silicon microneedles. The oxide layer thickness was assessed by using Ellipsometer and surface morphology by SEM. Acquired needles are appropriate for Embeddings into skin securely and without any problem.

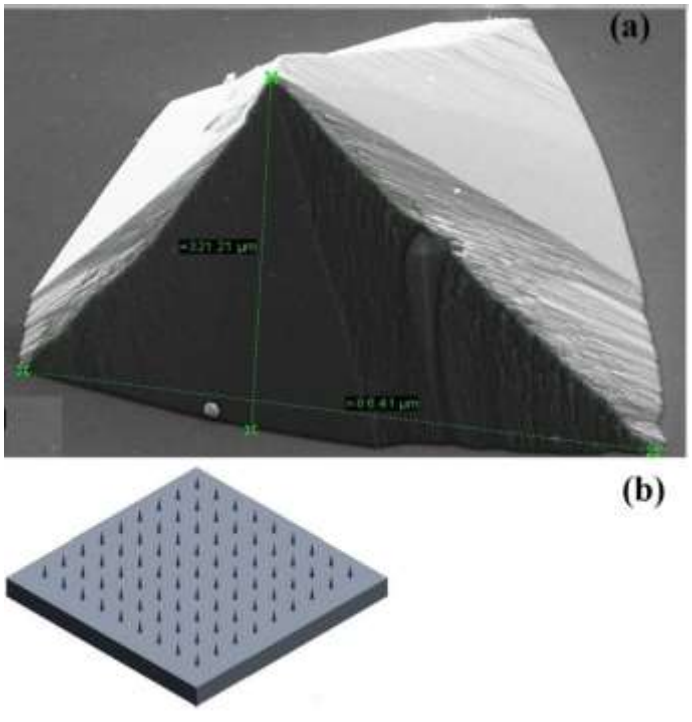


Fig.3. Fabrication of microneedle (a). Single microneedle fabricated and based on model (b). Final fabricated microneedle array with 81 needles.

## ADVANTAGES

This model is suitable to deliver several vaccine components integrated into a single array. A hypothetical model was proposed to assess the impact of infusion speed, blood perfusion rate, and tissue porosity on MN-based transdermal medication conveyance. Two investigations by Al-Qallaf et al. (2007, 2009) researched the impacts of an assortment of factors identified with microneedles and their effect on drug transport through the skin utilizing numerical models. A few elements considered in this examination were: microneedle length, a span of use, size of the fix, and application to distinctive anatomical districts. These models are only suitable for single microneedle but models developed in this work are suitable to develop microneedle array and validated experimentally. This generated optimum mathematical model of microneedles array is suitable to deliver vaccines without pain, improved brake force to insert the needle can deliver more amount of vaccine, it can be applied at any location on the body, more flexibility against the skin, less skin deformation with total needle insertion.

## CONCLUSIONS

The mathematical model developed was used to solve and study the effects of numerous microneedle parameters on the various activated cells in all three layers of skin structure. Microneedle simulations were evaluated the optimum values to apply the vaccine dosage quite properly and also deliver rate causing less effect on skin structure to reduce pain. Mathematical models of microneedle will authorize the systematic design and optimization of vaccine delivery systems. It is easy to solve an intricate range of vaccine delivery problems and also these models played crucial roles to develop microneedles for vaccine delivery for both manufacturers and researchers. Mathematical models generated in this paper helps in estimating future microneedles, vaccine delivery potentiality into the skin, fabrication of needle for the medical sector, challenges regarding vaccine diffusion into the skin structure is resolved.

## AUTHOR CONTRIBUTIONS

All the authors substantially contributed to the conception, compilation of data, checking, and approving the final version of the manuscript, and agreed to be accountable for its contents.


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## CONFLICT OF INTEREST

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## ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

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