Optimising microneedle arrays to increase skin permeability for transdermal delivery of drugs

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ABSTRACT
Improving drug permeability in skin is considered as one of the most important issues for designing new methods of transdermal drug delivery. Consequently, many techniques have been proposed to more effectively deliver drugs across the stratum corneum, including chemical enhancers or physical enhancer techniques, e.g., iontophoresis and ultrasound. Standard hypodermic injection is an effective method for drug delivery, but it causes difficulties in using it, either due to needle phobia or possibility of having skin infections. Patches are an alternative way for drug delivery across skin. However, this approach generally delivers drugs with low molecular weight and shows difficulties in permeability of high molecular solutes in skin. Microneedle is a new technology to enhance transdermal delivery of high molecular weight. This combines the concepts of transdermal drug delivery across the skin using patches and the hypodermic injections. The microneedles have been shown experimentally to increase the skin permeability by order of magnitude in vitro for a range of drugs varying in molecular size and weight. Different microneedle designs have been manufactured for transdermal drug delivery during the last 10 years. Recently, other questions appeared while using these microneedles, e.g., how to reduce needle diameters by which the hole produced to be as small as possible to exclude bacteria and other foreign particles. Another issue that has come up in this regard is how to correlate the skin thickness and microneedle length with the skin permeability. In this work, we have developed a framework which considers different classifications of skin thickness, arising from different races, sex groups, age and anatomical regions. This is done because of their implications in enhancing the process of transdermal drug delivery using microneedles. It is also obvious that in order to know the optimum design of these microneedles, the effect of the microneedle geometry on skin should be determined. However, this necessitates development of an optimization framework for skin permeability from these systems which includes many parameters (e.g., number of microneedles, microneedle radius, surface area of the patch, etc.). In the presented work an optimization algorithm for improving skin permeability to drugs using microneedle arrays is presented. The outcome of this work will be used to suggest optimum microneedle designs based on the parameters of interest.

NOMENCLATURE
A Surface area of the array (cm²)
A_h Patch surface area of hollow microneedles (cm²)
A_min Minimum patch surface area (cm²)
A_max Maximum patch surface area (cm²)
A_step Patch surface area increment for the search iteration of A loop(cm²)
A_s Patch surface area of solid microneedles (cm²)
A_opt Optimum patch surface area (cm)
D Diffusion coefficient (cm²/s)
f fractional skin area (-)
g optimization function (-)
g_opt Maximum value of g for the given input data (-)
K skin permeability (cm/s)
L Thickness of epidermis (cm)
L_h  Microneedle length (cm)
\(n\)  Number of microneedles per row (-)  
\(n^2\)  Total number of microneedles (-)  
\(n_{\min}\)  Minimum number of microneedles along one side (-)  
\(n_{\max}\)  Maximum number of microneedles along one side (-)  
\(n_{\text{step}}\)  Number of microneedles increment for the search iteration of \(n\) loop (-)  
\(n_{\text{opt}}\)  Optimum number of microneedles long one side that maximizes \(g\) (-)  
\(P_t\)  Pitch (cm)  
\(P_{t_{\text{opt}}}\)  Optimum pitch (cm)  
\(r\)  Radius of the residual hole (cm)  
The ratio of annular gap width to radius (-)  
\(R_{\text{h}}\)  Hollow microneedle radius (\(\mu m\))  
\(R_{\min}\)  Minimum microneedle radius (\(\mu m\))  
\(R_{\max}\)  Maximum microneedle radius (\(\mu m\))  
\(R_s\)  Solid microneedle radius (\(\mu m\))  
\(R_{\text{step}}\)  Microneedle radius increment for the search iteration of \(R\) loop (cm)  
\(R_{\text{opt}}\)  Optimum microneedle radius (cm)  
\(W\)  Annular gap width (cm)  
\(X\)  Total distance per row in the arrays (cm)  
\(\alpha\)  Aspect ratio of pitch over radius (-)  
\(\varepsilon\)  The ratio of annular gap width to radius (-)

1. INTRODUCTION
One of main focuses in transdermal drug delivery research is to increase the permeability of drug penetrating the skin. Skin permeability is a key parameter that represents the path length of a molecule across a given skin thickness over unit time. Over the past few years, a number of different approaches have been proposed to enhance transdermal drug delivery, including chemical enhancers, iontophoresis, ultrasound, microneedle arrays, etc. The newest technology among them is the application of microneedle arrays proposed for the first time by Henry et al., as far as the authors know. These microneedles can be either hollow or solid made of silicon, polymer, stainless steel, etc. Microneedle arrays have been shown to markedly increase the skin permeability by up to three orders of magnitude. Teo et al. reviewed different microneedle designs that are currently being used for transdermal drug delivery. So far, microneedle systems with various dimensions have been fabricated (Table 1) with limited consideration of how to increase skin permeability. It is important to know the factors that affect skin permeability when applying microneedle arrays having significant impact on transdermal drug delivery. So far, different methods have been proposed to predict skin permeability across the stratum corneum for low molecular weight compounds. Wilschut et al. reviewed these models for predicting skin permeability of transdermal delivery of low molecular weight drugs. A theoretical in vitro approach appeared in the literature which describes the permeability of the skin when microneedles are inserted and removed as shown in equation (1). Wu et al. used macroneedles instead of microneedles and obtained a relationship between the number of bores and skin permeability. They also found a relationship between skin permeability and molecular weight of macromolecules across an animal skin.

It is apparent from the above literature that optimizing the dimensions of the microneedle arrays is important to enhance the solute diffusion across skin. Recently, there have been many investigations on optimizing different parameters for transdermal drug delivery. Wilke and Morrissey optimized mask shape of microneedles for three different shapes. They concluded that the square mask shape has is the optimum shape instead of diamond and circular shape. Khumpuang et al. determined the optimum location for various microneedle holes locations. The microneedle tip radius has also been optimized to improve the tip sharpness. In drug delivery methods, it is therefore logical to expect the optimum values of drug permeability depending on the dimensions of the microneedles. In general, the main aim of drug delivery optimization is to deliver a small quantity of a given drug in an effective manner (i.e., microneedles) to avoid any problems (e.g., the possibility of damaging the liver or low drug absorption). However, other questions have appeared recently while using these microneedles, e.g., how to reduce the sizes of holes produced by microneedles so that transport of bacteria and other foreign particles can be minimized.

Following the above discussions, the first objective of our research is to develop a framework to determine the optimum microneedles dimensions (e.g., number of microneedle, microneedle radius, surface area of the patch, etc). One of the key parameters included in this framework is the center-to-center spacing between two microneedles (pitch). To expand
our study to the potential of transdermal drug delivery both solid and hollow microneedles have been investigated. To provide quantitative analysis of in vitro skin permeation of drug from microneedle, we have theoretically studied the influence of microneedle geometry on skin permeability. This is done by using an in-house optimization model based on java program. To our knowledge, no previous study has attempted to optimize the effect of microneedle dimensions on skin permeability. The developed model also correlated the variation of skin thickness (anatomical region, sex, etc) to skin permeability. This is expected to lead to optimum microneedle design for each case study. The process of transdermal drug delivery has been improved by reaching the highest value of skin permeability. This is confirmed by comparing our optimized design with an existing design.

2. METHOD
For our study we adopted a simple theoretical in vitro model given by McAllister et al.: 

\[ K = \frac{D}{L} \]  

(1)

Where \( f \) represents the fractional area of the skin covered by the microneedles, \( D \) is the diffusivity of the skin to the drug molecule and \( L \) is the thickness of the epidermis, in case of using solid microneedles. The epidermis skin thickness in this case represents the thickness of abdomen human cadavers, while the value of the solute diffusivity in equation (1) was determined by using Stokes-Einstein equation.

In solid microneedles, the molecules do not move through the bore of the needle. Instead they traverse through the disruption in the epidermis to move from the surface of the microneedle to the receiver compartment. The path length of this skin disruption made by the microneedle represents the thickness of the layer. If equation (1) represents hollow microneedles with molecules diffusing through their bores, the microneedle bore length \( L_{bo} \) would be used instead. When the microneedles are inserted, and then removed, a circular shaped domain (hole) is obtained with a radius corresponding to the radius of the microneedle and an annular gap width \( W \). The fractional area with the insertion of the microneedles can be calculated based on the following equations:

\[ f = n\pi \left( \frac{R + W}{2} \right)^2 - R^2 \]  

(2)

Where \( n \) is the total number of microneedles the patch, \( R \) is the radius of the microneedle, \( W \) is the annular gap width and \( A \) is the area of a given microneedle arrays. The fractional area after removing the microneedles from the skin is given by:

\[ f = n\pi \frac{r^2}{A} \]  

(3)

In this case \( r \) is the radius of the residual hole. This is the half of the radius while the microneedles were inserted because of the shrinkage of the skin. These equations are for calculating permeability. As equations (1) & (2) show, there are different variables that should be considered in designing microneedles arrays which include the radius of microneedles \( R \), surface area of microneedle arrays \( A \) and the total number of the microneedles \( n \). There is a fourth parameter, skin thickness, which is assumed to be constant. But in our case, it is a very important factor, e.g., how skin thickness varies in terms of different classifications.

We want to maximize skin permeability \( K \) in equation (1) for the case one where the microneedles are inserted by adopting equation (2) and assuming that it is a square patch so the total numbers of microneedles are \( n \) by \( n \) which is equal to \( n^2 \). Assuming that the diffusion coefficient \( D \) and skin thickness \( L \) are constant and the annular gap width \( W \) is a function of microneedle radius \( R \) as:

\[ W = \varepsilon R \]  

(4)

Where \( \varepsilon \) is the ratio of annular gap width to the radius of microneedle, such that:

\[ n_{\min} \leq n \leq n_{\max} \]  

(5)

\[ R_{\min} \leq R \leq R_{\max} \]  

(6)

\[ A_{\min} \leq A \leq A_{\max} \]  

(7)

2.1 FORMULATION OF OPTIMIZATION FUNCTION OF SKIN PERMEABILITY
Since \( L, D \) and \( \pi \) are constants, equation (1) can be reformulated as follows:

\[ g = c \frac{n^2 R^2}{A} \]  

(8)

Where \( c = \varepsilon(\varepsilon + 2) \)

Rewriting the problem statement,

\[ g = \frac{n^2 R^2}{A} \]  

(9)

From the first investigation of the above function, it is obvious that \( g \) has its maximum value at maximum \( n \) and \( R \) and minimum \( A \). Therefore, the desired solution would simply be:

\[ (n^2, R, A) \rightarrow (n_{\max}, R_{\max}, A_{\min}) \]

However, careful study of the microneedles patch geometry as shown in Fig. 1 reveals that there is another physical and manufacturing constrain which is the pitch \( (P_t) \), the center-to-center distance between two adjacent microneedles. This new constraint is given as follows:

\[ P_t \geq \alpha R \]  

(11)

Where \( \alpha > 2.0 \)

(i.e., \( \alpha \) is the aspect ratio of pitch over radius of microneedle)

Please note that, in order to determine the pitch we assume that in a given row of an array, the total distance for this row \( (X) \) is given by the following equation:

\[ X = n Pt \]  

(12)

Therefore, the area of a square array is:
\[ A = n^2 R^2 \]
\[ P_t = \frac{\sqrt{A}}{n} \quad \text{(13)} \]

The constraint equations (5-7) are reformulated to include the new following constrain:
\[ \frac{\sqrt{A}}{n} \geq \alpha R \quad \text{(14)} \]

2.2 OPTIMIZATION ALGORITHM

We have developed an in-house algorithm to search the whole space for \((n, R, A)\) by comparing each value of the \(g\) function at every point in the discrete space until it finds the optimum value which then mark corresponding \((n, R, A)\) as the optimum values. These optimum values of \(n, R, A\) are obtained for a given set of data by which the value of our optimized function \(g\) as defined in equation (10) reaches its maximum value. The main idea of our algorithm is to iterate through the whole space of \((n, R, A)\) using three nested loops to find the points represented as \((n_{\text{opt}}, R_{\text{opt}}, A_{\text{opt}})\) at which \(g\) is maximum provided that the geometrical condition is fulfilled. The input data are: \(n_{\text{min}}, n_{\text{max}}, n_{\text{step}}, R_{\text{min}}, R_{\text{max}}, R_{\text{step}}, A_{\text{min}}, A_{\text{max}}, A_{\text{step}}\) and \(\alpha\). The Output data are: \(g_{\text{opt}}, n_{\text{opt}}, R_{\text{opt}}, A_{\text{opt}}\) and \(P_{t_{\text{opt}}}\).

For the purpose of our work, a java swing program, ‘Microneedle System Optimization’ has been constructed to implement the above mentioned procedures. Fig. 2 shows the

![Graphical user interface of microneedles system optimization](image-url)
interface of the program with the input data at the top panel and output data at the right bottom panel. This optimization algorithm solves problem that appeared when using other available software. For example, the commercial software excel solver uses an optimization method called generalized reduced gradient (GRG). The GRG optimization method depends on the calculation of gradient second order partial differentiation. This requires the function under optimization to be continuous differentiable function within the optimization space. Since the problem under study is not continuous, it has an integer variable n, so it is not expected to get feasible results for this problem using Excel solver.

3. RESULTS AND DISCUSSIONS

3.1 OPTIMIZATION OF SURFACE AREA OF PATCH

Since the first fabrication of the microneedles for drug delivery, there have been many different sizes of the solid and hollow microneedles with different patch surface areas as shown in Table 1. Some researchers relate the surface area with the number of microneedles and call it ‘microneedles density’. However, the microneedle density may vary for given surface area of the arrays. As a result, the implications of the surface area and the microneedle density of the drug transport behaviour are not very clear. For example, Cormier et al. choose a needle density of 321 per cm² with a surface area of 2 cm². The microneedle density was different in another design proposed by Widera et al. with values of 140, 657 and 725 microneedles per cm² with an area of either 2 or 4 cm². As evident, these should be taken into consideration while designing the array system of the microneedles in the future.

The transdermal drug delivery for a given amount of drug is constrained by the surface area of microneedle arrays. In this work, we have carried out simulations to determine the optimum surface area of patch for given number of microneedles per row (n) of solid and hollow microneedles as shown in Fig. 3. The result of our optimization function shows that the optimum design for the range given in Table 1 for both solid and hollow microneedles are when the number of microneedle per row (n) equal 17 and 5, respectively. Based on our optimizing function, reaching the optimum surface area of microneedles improves the transdermal drug delivery process by increasing skin permeability. As shown in Fig. 3, the highest value of our optimization function (g) is obtained for a surface area of 0.4 cm² and radius of 0.0045 cm in case of solid microneedles. On the other hand, in case of hollow microneedles the highest value of g is obtained for a surface area of 0.19 cm² and radius of 0.0145 cm. We also argue that the distance of center-to-center between two adjacent microneedles (Pt) is a critical parameter and strongly depends on the microneedle radius which is discussed in section 3.4.

3.2 OPTIMIZATION OF MICRONEEDLE RADIUS

The radius of the microneedle has been considered as an important parameter when measuring the permeability of the skin using equation (1). Teo et al. show that by changing the radii of the microneedles, one can increases the skin permeability. In their study, the researchers use microneedles
array with a radius of 50 µm and then increase the radius to 150 µm. The result was very promising as it enhances transdermal penetration by a factor of 10 times. As shown in equation (2), there is a proportional relationship between the radius and the permeability of the skin. This is shown in Fig. 4 which indicates how the permeability of the skin based on our optimization function can be increased by changing the radius of the microneedle for a given number of microneedles per row (n). This means that the radius of the microneedle can affect the skin permeability which decreases or increases the drug delivery depending on the radii. The optimization function reaches its highest value for both solid and hollow microneedles when the radius of microneedle is 70 µm and 145 µm corresponding to a surface area of 0.44 cm² and 0.19 cm², respectively as shown in Fig. 4.

3.3 OPTIMIZATION OF THE NUMBERS OF MICRONEEDLES

The number of the microneedles is an important parameter in designing any microneedles array. Park et al. found that skin permeability increases by increasing the number of microneedles. Increasing the number of microneedle improve the efficiency of transdermal drug delivery. As expected, the numbers of microneedles may vary from one design to another. Some researchers have used a small number of these needles, e.g., 16 microneedles. McAllister et al. used a large number of microneedles up to 400. Sometimes, this number is related to surface area of the microneedles array which then defines as ‘microneedle density’ as explained previously. In order to increase the penetration efficiency, a high needle density is needed.

The effect of changing the number of the microneedle per row (n) on the permeability of the skin is shown in Fig. 5 in terms of the optimization function (g). The solid microneedles reach its highest value of our optimization function (g) at n=17 and n=20. These designs can be useful for either minimizing the cost (less number of microneedles) or for medical purposes (smaller microneedle radius), since both of these design has the same value of the optimization function. For hollow microneedles, the aspect ratio (α) is 6.

Figure 5. Effect of changing the number of microneedles per row (n) for solid (dark points) and hollow (light points) microneedle with their optimum radius on our optimization function (g), aspect ratio (α)=6.

Figure 6. Effect of changing the number of microneedles per row (n) for solid (dark points) and hollow (light points) microneedle for R_s=R_h=0.004 cm on our optimization function (g), aspect ratio (α)=6.

Figure 7. Effect of changing the aspect ratio (α) of solid (dark points) and hollow (light points) microneedles on pitch (pt) for various numbers of microneedles per row (n), (i.e., n=13,17,20 and n=5,10,15 for solid and hollow microneedles respectively).
microneedle, the optimized function \(g\) reaches its highest value at \(n=5\). In contrast, the effect of the number of microneedles of un-optimized design for a given microneedle radius (i.e. \(R=40 \mu m\)) on our optimization function are shown in Fig. 6. It is noticed that our optimization function depends on number of microneedles, surface area of patch and microneedle radius, which should be optimized in order to reach the highest value of our optimization function. This is obvious on the case of choosing un-optimized design of hollow microneedle, where the highest value has been obtained at \(n=15\) (i.e. \(R=40 \mu m\)). While the highest value has been reached in case of choosing the optimized design of hollow microneedles at \(n=5\) (i.e. \(R=145 \mu m\)). It indicates that the number of microneedles, surface area of microneedle arrays and microneedle radius are all connected to each other. The results illustrate that increasing the number of microneedle is not always the right way for increasing skin permeability.

3.4 OPTIMIZATION OF THE ASPECT RATIO

The aspect ratio relates to the center-to-center spacing (pitch) to the microneedle radius (\(R\)). As expected, this has a significant impact for any microneedle design. In general, the aspect ratio should be greater than 2, and if it is less than this an overlapping between the microneedles themselves will occurs. Therefore, if the pitch is too short, then the needles are placed too close to each other, which will prevent them from reaching the targeted depth. Since the first production of the microneedles for drug delivery, there have been many different values for this ratio. Some of these microneedles have a small aspect ratio of 2.7. Others have a larger aspect ratio of up to 13.3 as shown in Table 1, Fig. 7 and 8 depict the effect of changing the aspect ratio of both solid and hollow microneedles from 4 to 12. Fig. 7 gives the optimum pitch of various numbers of microneedles per row (\(n\)) for both solid and hollow microneedle arrays. It indicates that the aspect ratio has a major influence in case of designing hollow microneedles. The pitch reaches its highest value for either an aspect ratio of 10 or 12 (i.e. solid) and 8 or 12 (i.e. hollow). In contrast, the pitch reaches its lowest value for an aspect ratio of 4 and 6 for solid and hollow microneedles respectively. Fig. 8 reflects the influence of changing the aspect ratio of solid
and hollow microneedles on our optimization function. The highest value of our optimization function occurs at an aspect ratio of 4 for both cases. This figure also shows that for a given aspect ratio, changing the number of microneedles does not affect our optimization function. Obviously, for a given number of microneedles, a smaller aspect ratio would increase our optimization function.

### 3.5 EFFECT OF THE SKIN THICKNESS

It is important to consider various physiological functions of skin which affect the natural behaviour of skin barrier and hence influence the performance of the microneedles for transdermal drug delivery. There are also other factors that should be taken into consideration. These factors play important roles in the transportation of any solute released from the microneedles, and therefore influence the rate of drug delivery through the human skin. The skin thickness can vary according to different races, different sex different ages and different anatomical regions. The skin thickness in terms of anatomical region has been considered to be one of the most important factors that influence the percutaneous absorption. Artz et al. proved that the ratio of epidermis to dermis has a significant variation from one anatomical region to another. This is an important issue in determining the effect of the depth of skin and to relate this in designing the microneedle arrays. Other studies compared the skin thickness between males and females. Lee and Hwang found that Koreans women have thinner skin than Koreans men in almost 12 anatomical regions. As explained previously, in equation (1) L represents epidermis skin thickness in case of solid microneedle arrays. The implications of changing the epidermis thickness on skin permeability for calcein as a model drug are shown in Fig. 9 and 10. There has been a significant increase of skin permeability between optimized and un-optimized designs in both Figures. Fig. 9 illustrates the influence of skin permeability for three different anatomical sites (i.e., abdomen, back and back of leg) of male. The difference in skin permeability shows the necessity to consider the variation of skin thickness according to anatomical region, when applying solid microneedle arrays into human skin for any medical applications. Fig. 10 shows the different of skin permeability between male and female for the same anatomical site (i.e. sole). This also proves the essentiality of relating the classification of skin thickness when designing microneedle arrays.

### 3.6 EFFECT OF THE MICRONEEDLE LENGTH

Another parameter that can affect the permeability of drugs in skin is the length of microneedle arrays. This parameter replaces skin thickness in case of hollow microneedles as explained before. To address this issue, the influence of this parameter on skin permeability is shown in Fig. 11.

![Figure 11. Effect of changing microneedle length (Lh) of various numbers of microneedles per row (n) when using hollow microneedles on skin permeability (k).](image)

### Table 2. The values of parameters for both designs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>McAllister's Design</th>
<th>Our Optimized Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of microneedles per row, n</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Microneedle radius, R (cm)</td>
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<td>0.0019</td>
</tr>
<tr>
<td>Surface Area of the Patch, A (cm)</td>
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<td>0.04</td>
</tr>
<tr>
<td>Pitch, Pt (cm)</td>
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<td>0.01</td>
</tr>
<tr>
<td>Aspect ratio, α (-)</td>
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<td>3.75</td>
</tr>
</tbody>
</table>
parameter has been investigated to have a better understanding of its influence on skin permeability for hollow microneedle arrays. As shown in Fig. 11 different dimensions of microneedle lengths have been compared. Clearly the higher is the microneedle length, the lower is the skin permeability across epidermis. This illustrates that skin permeability is a function of microneedle length in hollow microneedle arrays. In contrast, skin permeability is a function of epidermis thickness in case of solid microneedle arrays.

3.7 EFFECT OF SKIN PERMEABILITY

To evaluate the usefulness of our optimization model on increasing skin permeability, the dimensions of our optimized model were compared with a previous model as shown in Table 2. The results of skin permeability for both designs have been given in Fig. 12. In our work, the microneedle arrays proposed by McAllister et al. have been optimized. The result shows an increase of 8 folds for skin permeability when using our optimized model, which improve the process of transdermal drug delivery. This is due to the effects of increasing microneedle radius and decreasing the surface area of the patch. This has been done with the consideration of keeping the same number of microneedles per row (i.e., n=20) and aspect ratio of pitch over microneedle radius (i.e., α=3.75).

4. CONCLUSIONS

An optimization algorithm for improving drug permeability in skin for different designs was developed in this work. This is a general approach and it does not rely on specification of any fabrication materials. This in-house algorithm has been used to improve the efficacy of drug delivery process by increasing skin permeability to a level of interest. This algorithm has been developed to achieve the optimum design for both solid and hollow microneedles by considering microneedle geometries. All the optimized microneedle designs had higher skin permeability when the aspect ratio of pitch over microneedle radius (α) is decreased. We concluded that the aspect ratio of pitch over microneedle radius is a key parameter while adjusting the dimensions of microneedles. The results of our optimization tool suggest that skin permeability can be increased by adjusting the optimum parameters (e.g. number of microneedles, microneedle radius, etc) of microneedle. The thickness of skin strongly depends on skin permeability for different skin classifications (e.g., race, sex, age, etc). This shows that the skin thickness should be considered while designing microneedle arrays. Our optimization technique showed that calcein (a model drug) was delivered and that the skin permeability was increased by 8 folds compared with the previous design. This optimization approach is expected to be suitable for designing drug delivery technique for any medical applications which overcomes low skin permeability for a given drug. Overall, this study demonstrates the feasibility of predicting skin permeability for transdermal drug delivery (TDD) across skin using microneedle arrays.

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REFERENCES