Multi-objective Optimization of Microneedle Design for Transdermal Drug Delivery

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Introduction

In recent decade, microneedle-based drug delivery has been recognized as an effective method of transdermal drug delivery and a potential alternative for hypodermis needles. Despite promises of this new technology, microneedle-based drug delivery to deeper layers of skin such as dermis and hypodermis, is still facing serious challenges. In such cases, large length of the needle would lead to increased chance of buckling as well as greater maximum bending stress in the structure. Changing the material properties is not always feasible due to limitations in the range of materials that could offer favorable biocompatibility and biodegradation characteristics. As a result, microneedle geometrical parameters such as diameter, and length should be carefully designed to address both efficient drug delivery and mechanical stability.

Despite significant advances in recent microfabrication technologies, less has been done to acquire a systematic understanding of the effect of each design parameters on mechanical performance of microneedles. Finding the best geometry of the microneedles over a wide range of design options could be challenging. For example, a large microneedle aspect ratio would lead to pronounced induced pain at the site of application, while a small aspect ratio will significantly increase chance of buckling.

A similar trade-off approach should be taken into consideration when thinking about design of flange-like base for improved stability. While it could decrease maximum bending stress created in the structure, they would add to the final cost and manufacturing complexity. Also, it would require revisiting the overall array design as they would change the interspacing pattern between each pair of adjacent microneedles resining on an array of microneedles.

Finite element method (FEM) is one of the major tools in design and optimization stages of engineering devices, particularly in detailed design steps. FEM-based simulations have been widely used in micro and macroscale analyses [1,2]. When coupled with state-of the art statistical tools, importance of FEM simulations become even more considerable. In fact, results from parametric FEM-based analyses could be used as a database for further extensive statistical studies such as sensitivity analysis or multi-objective optimization. Such an approach would add an extra level of reliability and robustness to the design process, as it is based on not only numerical techniques but also strong analytical tools.

Regarding this approach, parametric sweep feature in COMSOL Multiphysics ® provides an excellent tool for performing large-scale parametric studies to stablish a comprehensive database of simulation results. This unique feature allows one to perform extensive parametric study by considering various levels of design variables within the design space, gain a robust understanding of the effect of each design partaker, and multi-purposely optimize the system accordingly.

In conjunction with strong statistical tools such as analysis of variance (ANOVA) and multi-objective optimization techniques, one would further be able to study the dominance and effectiveness of design partakers. ANOVA has been recognized as a powerful tool in manufacturing systems [3,4]. It could further help design engineers decide which design parameters to compromise when facing dilemma over mechanical performance and physiological consideration of the skin tissue, such as interactions with skin [5].

The objective of this paper is to systematically analyze and study design of a microneedle for transdermal drug delivery. Unlike previous studies investigating mainly effect of different material properties, this paper deals primarily with the effect of geometrical design factors, as well as use of parametric sweep

feature in COMSOL®, for the first time, to establish a dataset for subsequent statistical analysis.

Numerical Model and Theoretical Framework

When pierced into the skin, microneedle structures undergo three major types of loading, namely, bending, axial, and buckling loading. To engineer a reliable microneedle structure, therefore, it is necessary to accommodate structural safety considerations in view of all these types of loadings. The criteria for bending and axial loadings are characterized by maximum deflection in the structure as well as maximum stress (usually von Misses stress) under bending and axial loading. To assess stability of the structure under buckling, a factor termed as critical load factor is calculated. This factor is in fact the ratio of the critical load, above which the microneedle will experience instability, to a given applied load. Critical buckling load factor is thus defined as:

$$\lambda = \frac{P_{critical}}{p_{applied}} \qquad (1)$$

As a result, it is desirable to design the microneedle geometry and material to maximize the critical load factor for a given applied load. Critical Euler's load for buckling ($P_{critical}$) is also defined as:

$$P_{critical} = \frac{\pi^2 EI}{(KL)^2} \quad (2)$$

In which *E* is the modulus of elasticity, *I* is the minimum area moment of inertia of cross section of the microneedle structure, *L* is unsupported length of the column, and *K* is the column effective length factor depending on the boundary conditions.

Furthermore, according to Euler–Bernoulli beam theory, bending stress of the microneedle structure, usually modeled as a beam, in each cross section could be described by:

$$\sigma_{bending} = \frac{Mz}{I} \qquad (3)$$

Where *M* is the bending moment, *z* is the distance from neutral axis, and *I* is the area moment of inertia of that cross section.

In this paper, structural mechanics module from COMSOL Multiphysics ® version 5.3 is utilized to perform the above-mentioned analyses using an FEM approach. The current microneedle is considered solid, made from PMMA (Polymethyl methacrylate), with properties imported from Material Library module. Parametric Sweep study is used to evaluate effect of various design parameters indicated in Fig. 1.

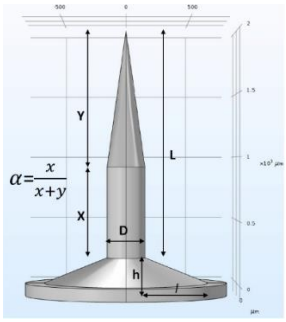


Figure 1. Illustration of the design parameters considered in this study.

These parameters include total length of the needle (*L*), diameter of the needle (*D*), diameter of the flange base (l), height of the base (h), and the ratio of cylindrical to conical section of the needle noted as *alpha*. Different levels are considered for each design parameter as tabulated in Table 1.

Table. 1 Considered levels for each design parameter.

Parameter name	Parameter value list	Parameter unit
alpha	range(0.1,0.1,0.9)	
D	150,300,450	um
l	10,100,200,300,400	um
h	10,200,400,600	um
L	1000,1500,2000,2500	um

Accordingly, total length of the microneedle changes between 1000 um to 2500 um to be long enough to reach the dermis layer. This is crucially imperative for transdermal delivery of macromolecules, such as vaccine delivery using microneedles.

To perform bending analysis, a total load of 20 mN is applied to the tip, in the lateral direction, while the base is fully constrained. To perform axial loading, a total pressure of 3.18 MPa, equal to the penetration pressure required to pierce the skin, is applied on the needle tip, while the base is completely constrained. Furthermore, to apply the buckling loading, a point load of 5 N is applied at the center of base, while the tip is held completely fixed, and the base can move only along the microneedle axis. A schematic of boundary conditions is illustrated in Fig. 2.

In this paper, we first perform a single-variable parametric study on the effect of different geometrical variables constituting the major parts of the microneedle structure shown in Fig. 1 varying between the values indicated in Table 1.

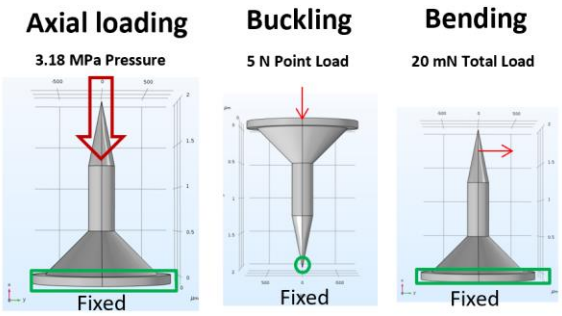


Figure 2. Specified boundary conditions for each type of analysis.

In the next step, parametric sweep feature in COMSOL Multiphysics ® is utilized to first build up an extensive database obtained from combinational simulations of all parametric levels shown in Table 1 (~2100 simulations). This database, which outputs the above mentioned five objective functions for each combination of design factors, is then used to perform a six-objective optimization study using Duckstein's method fully described in [6]. The sixth objective function is the maximum deliverable drug volume equal to total volume of the cylindrical and conical parts of the needle, excluding the base. Briefly, in this method a collective function incorporating all objective function is defined. This function represents distance of each design point from an ideal point having the best characteristics in terms of all objective functions. Design points therefore will be ranked depending how close they are to this ideal point. This collective function normalizes the corresponding values for each objective function and is defined by [6]:

$$L_p(x) = \sum_{i=1}^{k} [w_i^P \left[\frac{f_i(x) - f_i{}^0}{f_{i,max} - f_i{}^0}\right]^p]^{1/p} \quad (4)$$

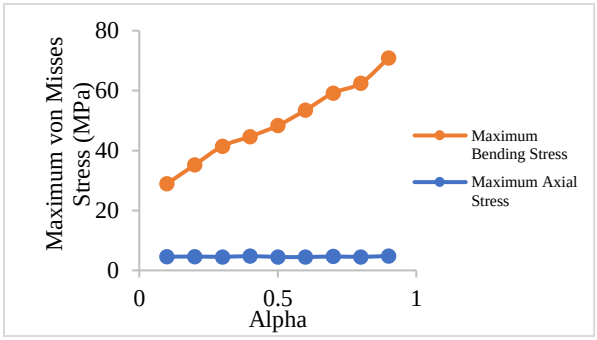
Where k is the total number of objective functions, w_i is the weight for the ith objective function, f_i is the value of objective function for a given design point, $f_{i,max}$ is the maximum value of objective function in the design space , and f_i^0 is the optimum (maximum or minimum) value for the ith objective function. The choice of p and w can vary. In this paper, these vales are 2, and 1, respectively.

Finally, results of simulations are employed to study the order of significance of each design parameter on overall performance of the collective objective function L_p defined by Duckstein method.

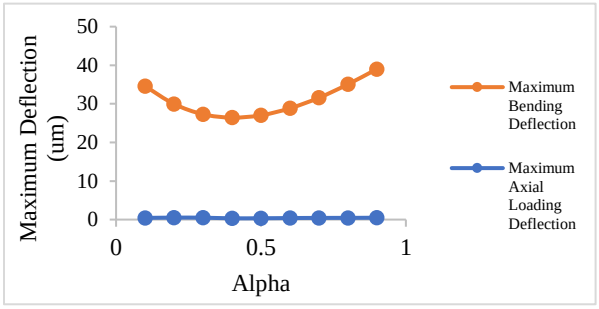
Statistical analyses via ANOVA was performed using software Minitab ®.

Results and Discussion

Results of single-variable parametric study for bending and axial loading analyses are provided in Figure 3, while Figure 4 represents the results of buckling analysis. For evaluation of effect of *alpha*, *D*, and *L*, the parameter of interest varied between the values indicated in Table 1 while the other non-changing parameters remained constant as D=150 um, L=1000 um, h=10 um, l=10 um, alpha=0.1. The same set of parameters was employed for evaluation of effect of *l* and *h* with the exception that, for *l*, *h* was 200 um, and for studying effect of varying h, *l* was considered 100 um. All the stress contours in Figure 5 represent von Misses stresses. As observed in Figure 3, bending stress and bending deflection becomes the major point of concern in these long (1000-2500 micron) microneedles, while generated maximum axial stress and axial deflection remains significantly smaller in most cases. Furthermore, the overall deflection and maximum stress, particularly in case of bending loading follows a non-linear trend.



A



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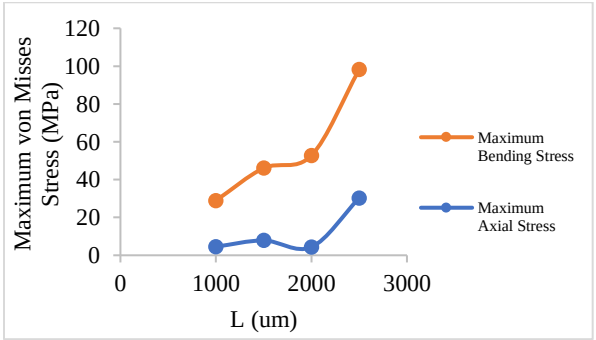

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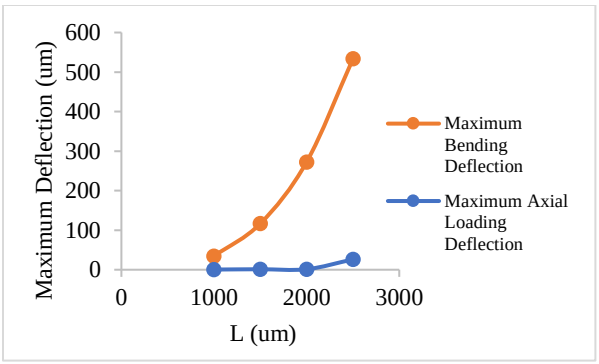
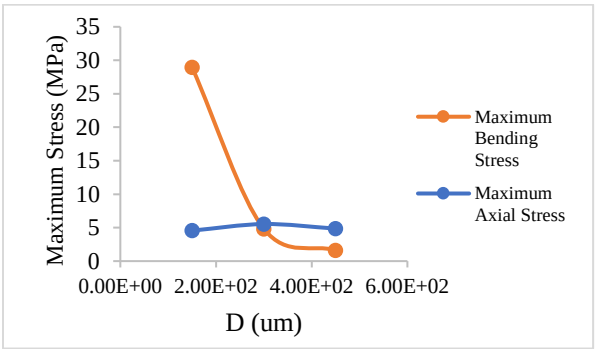
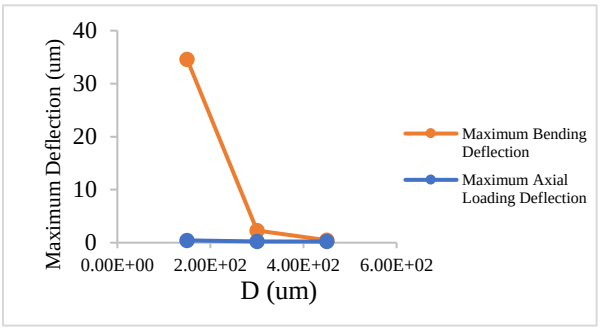


D



E



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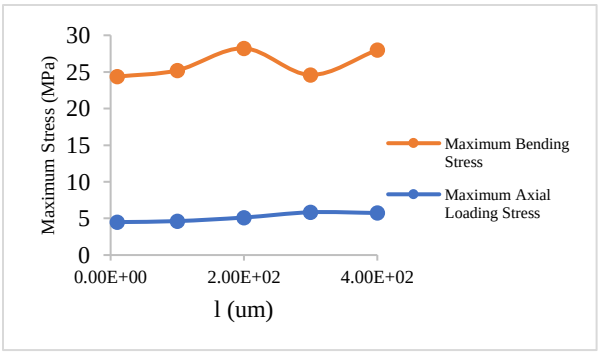

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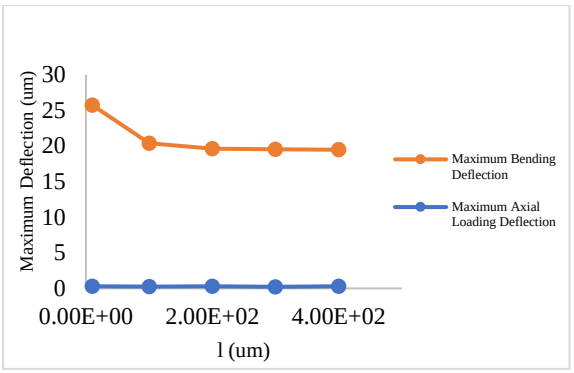

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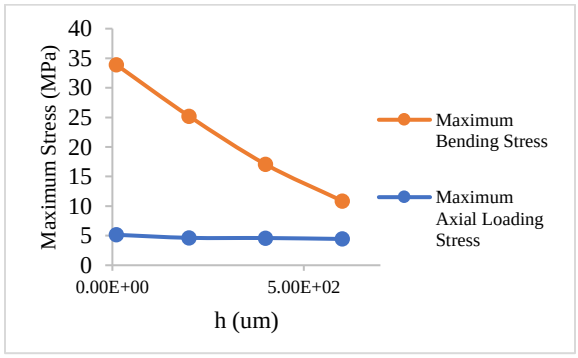
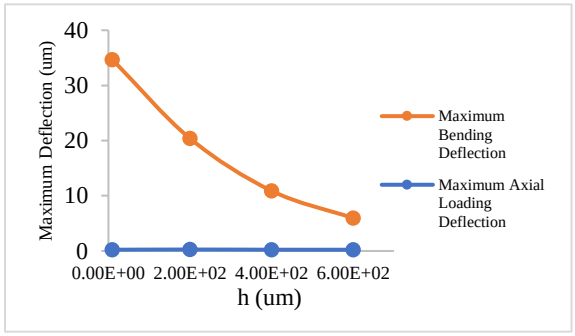


I



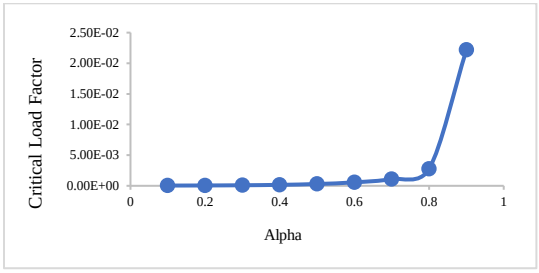
J

Figure 3. Effect of the considered design parameters on maximum von Misses stress (A,C,E,H,J) and maximum deflection (B,D,F,H,J) in the microneedle structure.

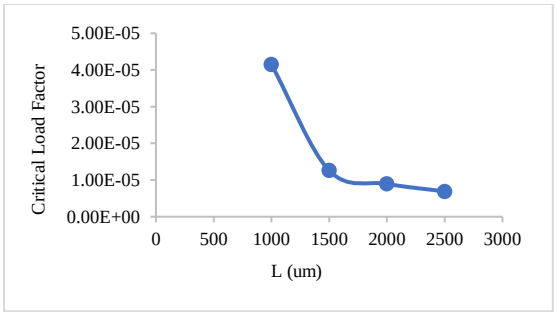
It was also evident that a value of *alpha* equal to 0.4 provided the optimum bending deflection behavior. Addition of the flange base reflected by increasing parameters *l* and *h* also generally decreased both types of stresses as well as deflections, enhancing stblity of the structure. It was also observed that changing the microneedle diameter from 150 to 300 micron significantly improved bending behavior by decreasing both maximum bending stress and deflection, 6 times more pronounced compared to going from 300 to 450 micron. This could be of high importance for physiological aspects of drug delivery since larger needle diameter could induce more pain at injection site.

The same consideration should be made when designing the length of the needle. As deduced from Figure 3, length of the needle generally increased the maximum deflection and stress. A larger needle length might be favorable in terms of maximum deliverable drug, but it reduced mechanical stability particularly under bending, it also increased chance of touching sensory receptors beneath the dermis layer.

Results of the buckling analysis are also depicted in Figure 4 A-E. As observed, increasing length of the needle (*L*) increased chance of instability, conversely, increasing diameter significantly increased the loading factor thus stability under buckling.



A



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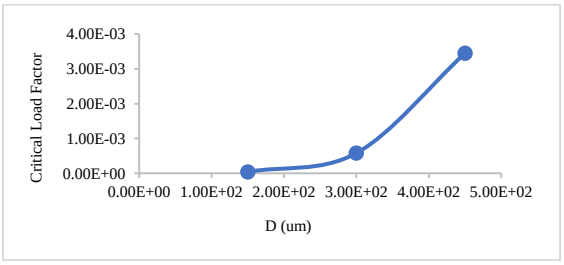

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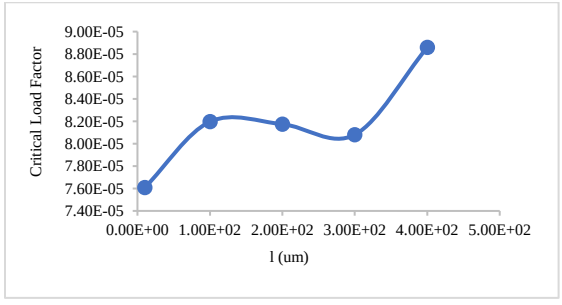

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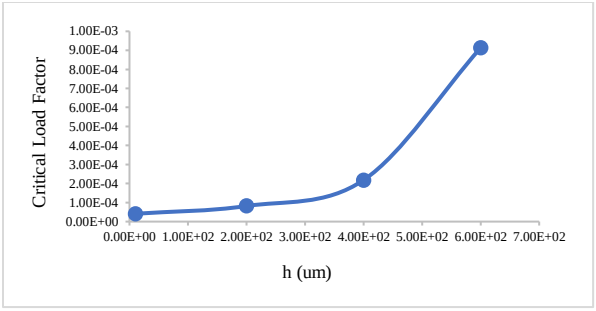
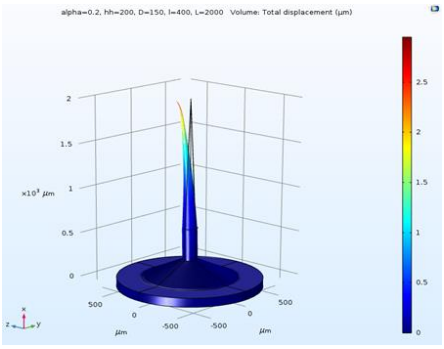
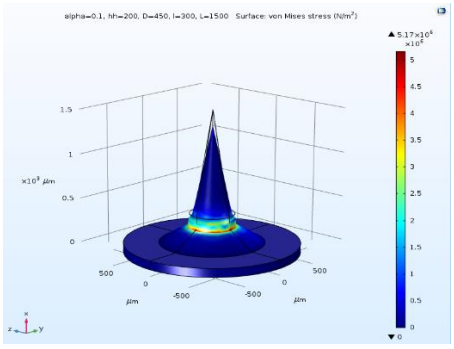


E

Figure 4. Effect of design paramters on cirtical buckling load, A-E corresponds to, effect of *alpha*,*L*,*D*,*l*, and h, respectively.



A



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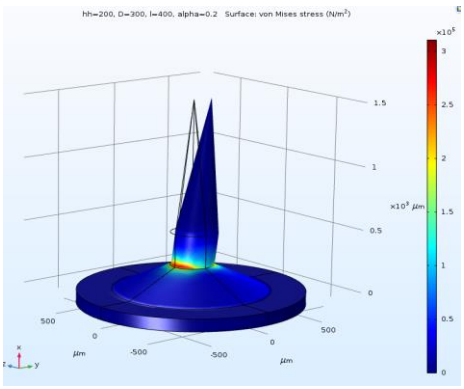

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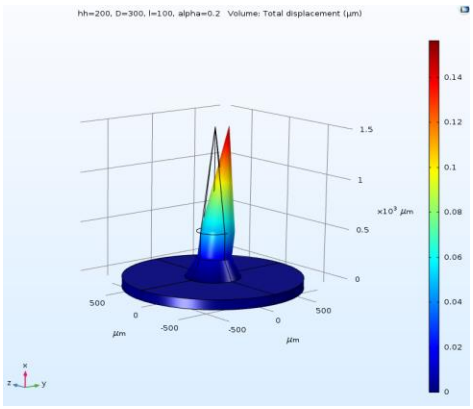

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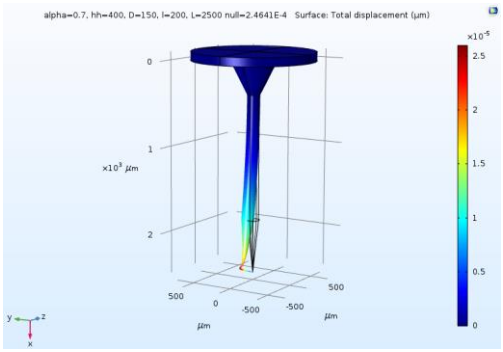

E

Figure 5. Contours of von Misses stress for different designs, under (A) axial, and (C) bending, and maximum deflection for different designs under (B) axial, (D) and bending loading (D), as well as (E) deflection mode under buckling.

As presented in Figure 5, illustrating contours for the deflection and von Misses stress in the three types of analyses, maximum deflection occurred at the tip of the microneedle, both under bending and axial loading. Evidently, maximum stress was seen at the base of the needle highlighting the necessity for employing additional structural improvement at the interface of microneedle axis and base.

As indicated in the results of single-variable parametric study, importance of each of these design parameters could vary and sometimes lead to conflicting trends in objective functions.

This would be particularly essential when taking the maximum deliverable drug into consideration. For instance, smaller *alpha* values in general provide more reliability in terms of maximum bending and axial stress, however, this would also decrease the cylindrical portion of the needle leading to smaller deliverable drug volumes. The same conflicting trend will be the case when increasing height and diameter of the base.

These conflicting behaviors thus necessitate employing a multi-objective optimization method to find the best trade-offs optimizing all objective functions simultaneously. Accordingly, result of Duckstein normalized multi-objective optimization approach is provided in Table 2. This table the top 10 best points, based on their ranking, for each of the considered needle diameters, which could be a toolbox for design engineers.

Table 2. Ranking of the top10 optimum points for each needle diameter (150 um, 300 um, and 450 um).

Ranking out of 2160 points	Alpha	h (um)	D (um)	l (um)	L (um)
1	0.9	4.00E+02	4.50E+02	1.00E+01	1.00E+03
2	0.9	4.00E+02	4.50E+02	1.00E+02	1.00E+03
3	0.9	4.00E+02	4.50E+02	2.00E+02	1.00E+03
4	0.9	4.00E+02	4.50E+02	3.00E+02	1.00E+03
5	0.8	6.00E+02	4.50E+02	2.00E+02	1.00E+03
6	0.9	1.00E+01	4.50E+02	1.00E+01	2.00E+03
7	0.9	4.00E+02	4.50E+02	1.00E+01	2.50E+03
8	0.8	6.00E+02	4.50E+02	3.00E+02	1.00E+03
9	0.9	4.00E+02	4.50E+02	1.00E+02	2.50E+03
10	0.8	6.00E+02	4.50E+02	1.00E+02	1.00E+03
437	0.9	6.00E+02	3.00E+02	1.00E+01	1.00E+03
440	0.9	6.00E+02	3.00E+02	3.00E+02	1.00E+03
445	0.9	6.00E+02	3.00E+02	4.00E+02	1.00E+03
504	0.9	6.00E+02	3.00E+02	1.00E+02	1.00E+03
639	0.1	2.00E+02	3.00E+02	1.00E+01	2.50E+03
641	0.1	4.00E+02	3.00E+02	1.00E+01	2.50E+03
644	0.1	6.00E+02	3.00E+02	1.00E+01	2.50E+03
646	0.9	4.00E+02	3.00E+02	1.00E+01	2.50E+03
649	0.1	1.00E+01	3.00E+02	1.00E+01	2.50E+03
1441	0.9	6.00E+02	1.50E+02	1.00E+02	1.00E+03
1442	0.9	6.00E+02	1.50E+02	2.00E+02	1.00E+03
1443	0.9	6.00E+02	1.50E+02	3.00E+02	1.00E+03
1444	0.9	6.00E+02	1.50E+02	4.00E+02	1.00E+03
1445	0.1	6.00E+02	1.50E+02	1.00E+02	1.50E+03
1446	0.2	6.00E+02	1.50E+02	1.00E+02	1.50E+03
1447	0.1	6.00E+02	1.50E+02	2.00E+02	1.50E+03
1448	0.1	6.00E+02	1.50E+02	1.00E+02	2.00E+03
1449	0.9	6.00E+02	1.50E+02	1.00E+01	1.00E+03
1450	0.1	4.00E+02	1.50E+02	1.00E+02	1.50E+03

Furthermore, results of one-way ANOVA with or without consideration of maximum deliverable drug volume as an objective function are provided in Tables 3 & 4, respectively. F-value and p-value are statistical tools that could provide insight into importance of each design parameter on the overall function representing the 6 or 5 objective functions. As observed, in the former case (Table 3), all design parameters had a significant influence on the objective functions ($p<1e-6$), in which needle diameter had the highest percentage of contribution equal to 81 %.

Table 3. Result of ANOVA considering maximum deliverable drug volume.

Source	DF	Adj SS	Adj MS	F-Value	P-Value	Percentage of contribution	Ranking
Alpha	8	0.3918	0.049	7.82	0.00000	0.466507989	3
h	3	0.929	0.3097	49.46	0.00000	1.106140688	2
D	2	68.8091	34.4046	5494.37	0.00000	81.92954277	1
l	4	0.292	0.073	11.66	0.00000	0.347678236	4
L	3	0.1697	0.0566	9.03	0.00001	0.202058208	5
Error	2139	13.394	0.0063				
Total	2159	83.9857					

Table 4. Result of ANOVA without consideration of maximum deliverable drug volume.

Source	DF	Adj SS	Adj MS	F-Value	P-Value	Percentage of contribution	Ranking
Alpha	8	1.6454	0.20568	24.03	0.00000	3.330250	3
h	3	1.6356	0.5452	63.69	0.00000	3.310415	4
D	2	18.0386	9.01929	1053.69	0.00000	36.50969383	1
l	4	0.0418	0.01045	1.22	0.30000	0.084602198	5
L	3	9.7372	3.24573	379.19	0.00000	19.7078593	2
Error	2139	18.3092	0.00856				
Total	2159	49.4077					

On the other hand, without considering the maximum deliverable volume, effect of parameter *l* became negligible, and needle dimeter, total needle length, alpha, and height of the base became the 1st to 4th important design factors, respectively. In both cases, needle diameter appears to be the most important design factor. These results could be used to gain insight into the parameters that could be compensated when considering other aspect of functionality of microneedles such as reduced pain induction, or manufacturing cost.

Conclusions

In this paper, for the first-time unique feature of parametric sweep study in COMSOL was coupled with statistical tools to gain a fundamental understanding of the mechanics of microneedles in transdermal drug delivery. Subsequently, a multi-objective approach was employed to find the optimum design points within more than 2000 simulation results. Obtained results were then utilized to study the significance of each design parameter on the overall performance of the microneedle mechanics. Results indicated needle diameter as the most important geometrical factor. Results of this study could find wide application in design and development procedures of microneedle for macromolecule delivery such as vaccination.

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