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The influence of process parameters on the physical characteristics of ceramic microneedles, evaluated using a factorial design

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Abstract

The paper presents the application of the factorial Design of Experiments (DoE) to evaluate the influence of process parameters on the physical characteristics of ceramic microneedles (CMN). In this study, an understanding of the fabrication process was achieved by performing a DoE based on varying two levels of five parameters. Statistical analyses were performed on the data to investigate whether the process parameters have a significant effect on the production of a patch of 25 microneedles (MN) with sharp tips. The study showed that four out of five main effects as well as an interaction between two parameters were significant.

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Keywords: Microneedles; design of experiments; self-setting ceramics; calcium sulphate; micromoulding

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1. Introduction

In recent years, MN devices have increasingly gained attention from the pharmaceutical research as an alternative drug delivery system [1]. MN overcome the issues associated with drug delivery systems that are administered via conventional routes such as oral and parenteral administration. In comparison to oral drug delivery systems, MN patches are advantageous in their avoidance of the drug first pass hepatic metabolism and gastrointestinal absorption. Contrary to the utilisation of current hypodermic needles, MN do not reach the nerves endings, they are painless. The skin is a tough external barrier which hinders the passage of large molecular-weight drugs across the skin [2]. Therefore, MN enhance the drug permeation into the skin as opposed to the conventional dermal patches which do not breach the stratum corneum.

MN are classified into four different groups: solid, coated, hollow and dissolvable MN. Solid MN are used to pierce the skin prior to the application of a drug-loaded formulation (two-step application). Coated MN are solid MN which can be used in one single step. The MN are coated with the drug prior to their application on the skin, and the drug is released following MN penetration. Hollow MN are solid MN in which a channel is used to inject a liquid drug formulation into the skin. Dissolvable MN are designed to be applied in one-step. They are inserted into the skin and the drug is released via a dissolution process [3]. The majority of research presented in the literature for the fabrication of dissolvable MN is focused on polymers and sugars. However, the use of these materials often involves high temperatures and organic solvents which can compromise the drug stability. Furthermore, the amount of drug added into the MN may decrease the mechanical strength of the dissolvable MN structure and hence, affect their penetration into the skin [4].

Self-setting ceramics are FDA-approved materials and their excellent moulding capabilities, biocompatibility and mechanical properties make them an exceptional alternative to overcome the limitations presented in using polymers and sugars. Moreover, the drug release pattern can be adapted by varying the porosity of the ceramic microstructure [2]. However, determining the variables and interactions that significantly influence the quality and reproducibility of the fabrication process is challenging. CMN are fabricated through a micromoulding compression process in which the mould filling step is especially difficult. An incomplete filling of the mould leads to imperfect MN structures being formed.

Design of Experiments (DoE) and statistically analysis have been widely used on formulation and process development. DOE is a systematic method to determine the relationship between the factors that affect a process (variables) and the output of that process (responses). Using DoE, one can evaluate the effect of each factor and possible interactions on each response in order to identify the critical factors on the basis of statistical analysis [5].

The main aim of this work was to evaluate the influence of process parameters on the physical characteristics of CMN using a factorial DoE. Initial work was performed on a fractional-factorial DoE in order to indicate major trends and to determine a promising direction for further experimentation using full-factorial DoE [6]. After the first screening, five potential significant factors were found. The initial treatment of the moulds (water prefilling process), the factors related to formulation (liquid-to-powder ratio and mixing time), the number of steps involved in the CMN fabrication process (one step (single-layer CMN) or two steps (bi-layer CMN)) and a post-treatment (use of a vacuum) were selected as the process parameters (factors) in the full-factorial DoE.

2. Experimental

2.1. Materials

Calcium sulphate hemihydrate >97% (Sigma Aldrich, Ireland) and deionised water were used to make the ceramic formulation. Polydimethylsiloxane (PDMS) moulds were manufactured and supplied by Tyndall National Institute, University College Cork. They were composed of 25 (5x5) pyramidal shape micro-cavities on the surface area of 1 cm2 having a depth of 500 μm for each cavity [7].

2.2. Methods

2.2.1. Ceramic microneedles fabrication

The ceramic formulation was prepared by manually mixing calcium sulphate hemihydrate with deionized water in a liquid-to-powder ratio (L/P) of either 0.3 or 0.4 mL/g. The mixing time varied from 30 to 90 seconds. The microneedles patches were manufactured using either one (Fig. 1a) or two layers (Fig. 1b) through a micromoulding process in which the ceramic formulation was compressed into the PDMS moulds. When manufactured in one layer, the cavities of the PDMS moulds and the backing layer were fabricated in the same step. When manufactured in two layers, cavities of PDMS moulds were first filled by compressing a thin ceramic layer followed by the addition of a second backing layer (fig 1b). The backing layer was composed of L/P ratio of 0.5 mL/g. In order to improve the mould filling step with the ceramic, a vacuum was used or not depending on the DoE run. The ceramic patches were allowed to cure for 24 hours at room temperature.

The result of the fabrication process was measured by using a CMN scoring system (response) to assess the quality of the MN patches. Each patch was imaged using a digital microscope with 400x magnification. Each MN on a patch was scored as per Table 1 and the values accumulated (CMN score). The scoring system ranged from 25 (no MN on the patches) to 100 (25 x MN with sharp tips) (Table 1). Ten patches were evaluated for each DoE run (n=10 patches).

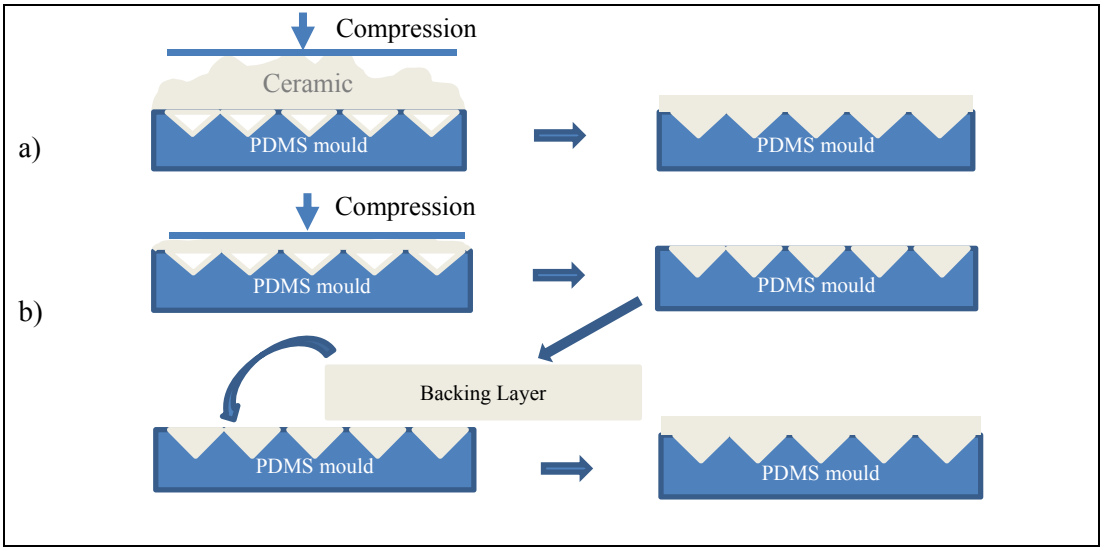

Fig. 1. Micromoulding steps to make the CMN. (a) Single layer CMN; (b) Bi-layer CMN.

Table 1. Scoring system.

Score	Description	MN Shape
1	No MN, backing layer only	
2	Stub MN	
3	MN with no sharp tip	
4	MN with sharp tip	

2.2.2. Design of experiments

Minitab 17 software was used to generate a set of experiment runs combining the factor levels presented in Table 2 as well as to analyse the results. A two-level five-factor factorial design was carried out (25 experiments). The response was the scoring of the CMN patches (Fig 2). The experiment matrix for the DOE study is presented in Table 3.

Table 2. 2-level CMN fabrication process parameters for the DoE.

Factors	Levels
A Prefilling moulds	Low: Yes
	High: No
B L/P (mL/g)	Low: 0.3
	High: 0.4
C Mixing time (s)	Low: 30
	High: 90
D Number of layers	Low: One
	High: Two
E Vacuum	Low: Yes
	High: No

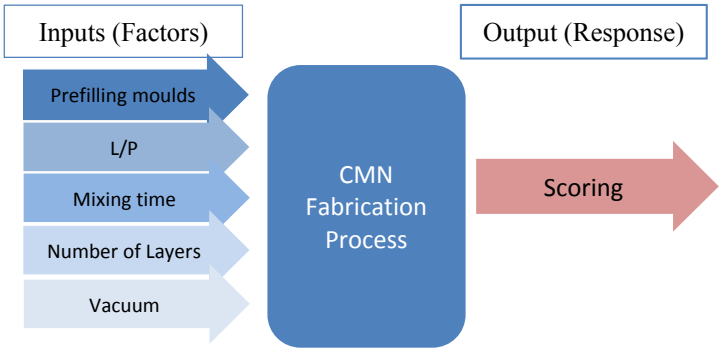

Fig. 2. Inputs and outputs involved in the DoE.

3. Results and discussion

The full-factorial DoE was used in order to identify the factors that were significant to the CMN fabrication process as well as to determine which of them causes the greatest variability to the output of the process (CMN score). The CMN score is the important physical characteristic of MN and this was used as an indication of the quality of the CMN patches. Prefilling versus non-prefilling the PDMS moulds with water as a pretreatment step (factor A) was examined to ascertain if a diffusion method aided by the presence of water in the mould cavities would improve the filling of the moulds with the formulation. The concentration of the ceramic in the formulation was also assessed by varying the L/P ratio (factor B). Another variable investigated was the mixing time of the ceramic formulation prior to application to the moulds (factor C). The application of one layer of the ceramic formulation followed by a subsequent second layer (two layers) was also examined (factor D). The use of the vacuum (factor E) was assessed in order to pull the formulation into the micro-sized cavities of the PDMS moulds. The response data are displayed as the average of the CMN scoring of the patches produced for each run (n=10), as shown in Table 3.

Table 3. Experiment matrix and results.

Run	Prefilling moulds	L/P (mL/g)	Mixing time	Number of layers	Vacuum	Scoring (mean ± STDEV) (response)
1	yes	0.3	low	one	yes	75 ± 5
2	no	0.3	low	one	yes	49± 11
3	yes	0.4	low	one	yes	66± 7
4	no	0.4	low	one	yes	60± 12
5	yes	0.3	high	one	yes	71± 12
6	no	0.3	high	one	yes	57± 7
7	yes	0.4	high	one	yes	54± 16
8	no	0.4	high	one	yes	40± 9
9	yes	0.3	low	two	yes	84± 9
10	no	0.3	low	two	yes	65± 12
11	yes	0.4	low	two	yes	76± 4
12	no	0.4	low	two	yes	69± 6
13	yes	0.3	high	two	yes	70± 17
14	no	0.3	high	two	yes	82± 4
15	yes	0.4	high	two	yes	62± 19
16	no	0.4	high	two	yes	54± 19
17	yes	0.3	low	one	no	72± 7
18	no	0.3	low	one	no	50± 13
19	yes	0.4	low	one	no	65± 8
20	no	0.4	low	one	no	45± 6
21	yes	0.3	high	one	no	59± 9
22	no	0.3	high	one	no	42± 14
23	yes	0.4	high	one	no	61± 7
24	no	0.4	high	one	no	38± 11
25	yes	0.3	low	two	no	81± 5
26	no	0.3	low	two	no	77± 8
27	yes	0.4	low	two	no	78± 7
28	no	0.4	low	two	no	66± 8
29	yes	0.3	high	two	no	75± 10
30	no	0.3	high	two	no	62± 9
31	yes	0.4	high	two	no	68± 12
32	no	0.4	high	two	no	52± 16

Main effects (A, B, C, D and E) as well as two-way interactions were included in the model when analysing the data. Our earlier work revealed that the three-factor and higher interaction terms were not significant and they were excluded from the model. The estimated positive and negative effects of each factor on the response are displayed in Table 4.

Table 4. Estimated effects for DoE data.

Term	Effect	p-value
A	0.0977	0.000
B	0.0353	0.002
C	0.3825	0.001
D	-0.0318	0.000
E	-2.6100	0.227
AD	4.6800	0.035

The effect quantifies the relative strength of the factors. The significance is based on the p-value and the test was carried out with a significance level of 0.05. The factors A, B, C, D and the interaction AD were determined to be significant factors in producing CMN patches (p value<0.05). These effects were determined to have a large impact on the quality of the patches fabrication (CMN scoring (n=10 patches)). However, the use of the vacuum (factor E) was not a significant factor in this study (p value >0.05).

In order to compare the relative magnitude and the statistical significance of the factors, a normal effect plot was analysed. As shown in Fig. 3, the straight line indicates the points where the factors exhibit no effects. The factors located further from the line are recognised as significant. The normal effect plot presented on Fig. 3 displays that factors A, B, C and D are significant factors while E is not found to be significant. This is in agreement with the above findings. The factors A, B and C had a negative effect which means that the average response decreased from a low to a high level for these factors. The number of layers (factor D) had a positive effect, therefore, the response increased with increasing the number of layers in the CMN fabrication process. The results also revealed that there was an interaction between the prefilling of the moulds (factor A) and the number of layers (factor D), as shown on Fig. 3. No other two-way interactions were deemed to be significant.

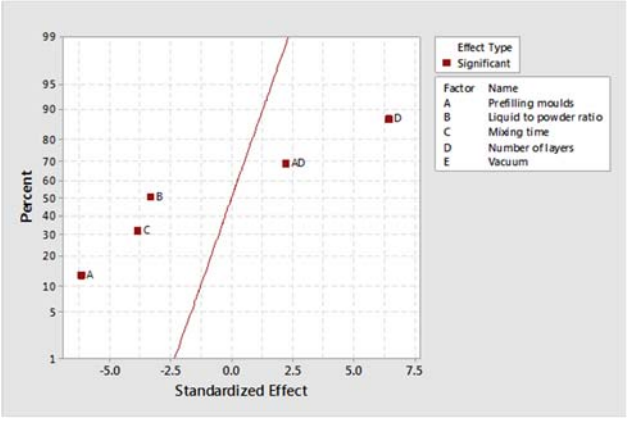

Fig. 3. Normal effects plot.

Fig. 4 indicates that there was an interaction between the prefilling of the moulds and the number of layers applied. Irrespective of the number of layers added, prefilling the moulds with water enhanced the quality of the patches fabricated. This may be due to a pre-wetting effect of the hydrophobic PDMS moulds by water. However,

the highest CMN scoring of the patches were obtained when two layers were applied. This suggests that the application of the backing layer caused more material to be compressed into the cavities.

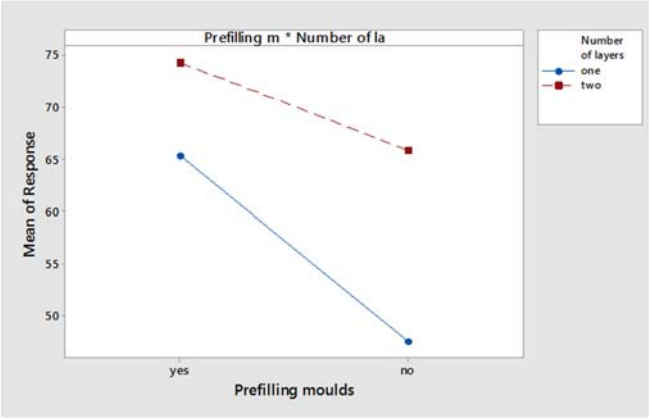

Fig. 4. Factor interaction plot.

Fig. 5 presents how the response varies depending on the level of significant factors. The largest main effects are showed by a line with the most pronounced slope. The method that Minitab software follows for calculating this is to subtract the average response in the high level from the average response in the low level of each factor. Factor A (prefilling of the moulds) was found to be affecting the fabrication process in a way that when they are prefilled, the pre-wetting of the hydrophobic moulds aids the filling of the cavities by the ceramic formulation. Regarding factor B (liquid-to powder ratio), when using a ratio of 0.3 mL/g, the formulation was drier and more viscous (wet powder) and therefore on application to the prefilled moulds, the ceramic precipitates into the cavities of the moulds through diffusion methods compared to the less viscous formulation (L/P ratio 0.4). However, more studies are required to verify this. The material used in this study was a self-setting ceramic material which means that it solidifies over time. Thus, a lower mixing time improves the quality of the patches (high CMN score) as this extends the working time of the formulation in the CMN fabrication process whereas the higher mixing time reduces the workability of the formulation (setting of the formulation prior to application). By fabricating the CMN in two steps the average CMN scoring had improved; more ceramic material being applied and compressed into the cavities. The summary of the estimated effects for the presented DoE study are presented in Table 5.

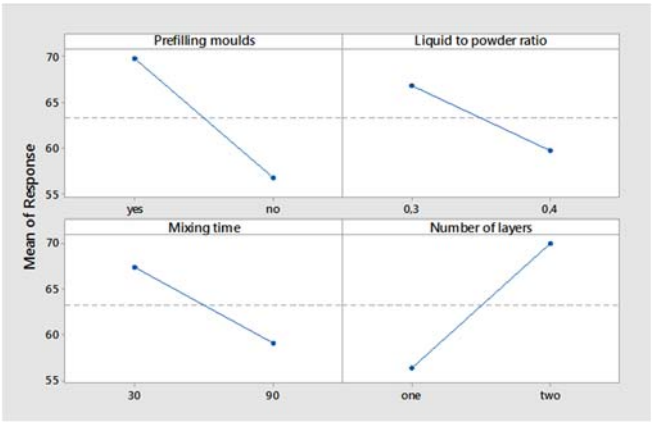

Fig. 5. Main effects plot for CMN scoring.

Table 5. Best combination of levels.

Prefilling moulds	L/P (mL/g)	Mixing time	Number of layers
Yes	0.3	low	two

In addition to the presented results, the standard deviation of the runs was analysed in order to identify which factor was affecting the variability of the fabrication process. Fig. 6 shows a normal plot of the effects on variability (STDEV). Factor C (mixing time) was found to be the only factor with a significant positive effect. This suggests that when the mixing increases, more of the formulation solidifies prior to its application causing more variability in the fabrication of the CMN. This result supports above findings related to the mixing time (Fig. 5).

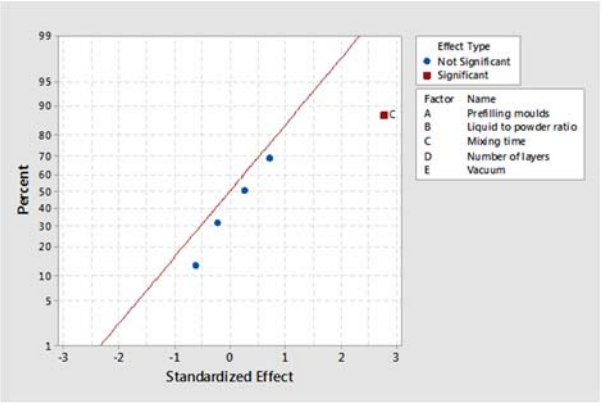

Fig. 6. Normal effects plot.

4. Conclusions

The factorial design of experiment was used to understand the micromoulding process developed for fabricating the CMN. The results revealed that four out of five single factors proposed in this study were significant variables. However, only factor C (mixing time) was found to affect the variability in the production of good quality patches (high CMN scoring due to 25 MN with sharp tips per patch). It was also found that a two-way interaction between factors A and D (prefilling and two layers) was present; indicting that a two-layer application of the formulation was facilitated by the prefilling of the moulds. The results of this DoE study are used for the fabrication of drug loaded CMN patches and further work will be focused on the influence of the drug addition on the CMN fabrication process.

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