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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].