Application of quality-by-design methodology for optimising a lidocaine-loaded dissolving microneedle formulation

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Background: Lidocaine topical creams are commonly used for local anaesthesia, particularly in skin surface surgical procedures and venipuncture. However, these generally show poor drug absorption levels and a slow onset of action. Dissolving microneedle arrays (dMNAs) are a promising alternative for this application, with a potentially quicker onset of action following lidocaine delivery into the epidermis and dermis. The properties of dMNAs are limited by the materials selected for their composition, so we aimed to apply Quality by Design (QbD) principles to optimise a lidocaine-loaded dMNA (Li-dMNA) formulation in this study.

Methods: QbD methodology was followed in this study. A sequential design of experiments (DoE) (screening, optimisation and verification) using custom mixture design was carried out to optimise a formulation composed of poly(vinyl alcohol) (PVA) 9-10 kDa, polyvinylpyrrolidone (PVP) 40 kDa, sucrose, and 5 mg lidocaine hydrochloride (Li-HCl) in an aqueous mixture. The dMNAs were prepared by micromoulding and five critical quality attributes (CQAs) were identified: physical attributes (brittleness and degree of deformation), mechanical strength (needle height reduction upon compression), skin penetration (in a model), dissolution time and Li-HCl content. The effects of the concentrations of the components as critical material attributes (CMAs) on the five CQAs were assessed using multivariate statistical analysis.

Results: Li-dMNAs were successfully fabricated from aqueous mixtures of the selected polymers and sucrose, as per the DoE. Statistical analysis of the characterisation results obtained showed the relative importance of the CMAs on the CQAs. High proportions of PVA and sucrose, and a low proportion of PVP, summing up to a total of 40% (w/w) in the fabrication mixture was found to produce Li-dMNA with good mechanical strength without compromising dissolution time. The resultant optimised design space, with settings ranging 14-17% (w/w) PVA, 21-24% (w/w) PVP and 1.95-2% (w/w) sucrose, is predicted to produce arrays with the best balance in quality attributes. A Level 2 control would to be achievable with this flexible optimised design space as opposed to the rigid traditional GMP approach to produce quality Li-dMNAs.

Conclusions: This work highlights the advantages of using the systematic and scientific QbD methodology to optimise a Li-dMNA formulation for lidocaine delivery. It also provides a prospective foundation for future developments of dMNAs and regulatory standards for microneedle arrays.