British Journal of Pharmacy

https://doi.org/10.5920/bjpharm.593

British Journal of Pharmacy

www.bjpharm.hud.ac.uk

Proceedings of the APS@FIP Conference 2018

Bilayer Dissolving Microneedles Incorporating Hypericin-Loaded Nanocapsules For Improved Localised Photodynamic Therapy

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ARTICLE INFO

Received: 25/05/2018
Accepted: 20/06/2018
Published: 03/04/2019

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KEYWORDS: Hypericin; microneedles; nanocapsules; PDT

SUMMARY

Hypericin (Hy) is a potent lipid soluble photosensitizer having broad pharmacological spectrum. Its poor water solubility leads to its aggregation in biological systems that diminishes its photodynamic activity (PDA) and its therapeutic applications. This study presents novel hydro-solving bilayer microneedle (MN) arrays incorporating Hy-loaded lipid nanocapsules (LNC) to prevent drug aggregation, enhance its delivery and local PDA. The Hy-LNC were prepared by a phase inversion technique and showed homogenous particle size distribution and high encapsulation efficiency (88.42 ± 0.11%). The bilayer MNs consist of a hydrogel cross-linked, drug free base plate and a Hy-loaded MN for one-step application. The dissolving MNs were fabricated from aqueous blends of 10% w/w poly vinyl alcohol and 30% w/w polyvinyl pyrrolidone by casting and pressure. The bilayer arrays showed good mechanical strength under a compression force of 32 N, with a height reduction of 10.14 ± 0.55% and sufficient insertion depth in both Parafilm M® and excised porcine skin. After 2h of application to excised pig skin, the MNs were completely dissolved ensuring the delivery of their payload and the base plate was removed intact, free from MN residuals.

INTRODUCTION

Hypericin, a phenanthroperylenequinone derivative, is a naturally-occurring photosensitizer extracted from Hypericum perforatum. Recently, it has gained great attention due to its versatile pharmacological effects. Unfortunately, the high hydrophobicity restricted the medical application of such a promising chromophore. Another major limitation for the topical PDT is insufficient skin penetration. Therefore, there is an emergent need for alternative delivery strategies rather than conventional ones.

Dissolving MNs are minimally-invasive micron-scale needles that can painlessly penetrate the stratum corneum barrier to dissolve and deliver their drug cargo. Lipid nanocapsules are synthetic nanocarriers. They have been applied for the delivery of many drugs by various routes. The present study aims at overcoming the aforementioned limitations by encapsulating the Hy inside LNCs, then further incorporation into bilayer dissolving MNs.

MATERIALS AND METHODS

Blank and Hy-loaded LNCs with Labrafac™ oily core and surfactant shell of Solutol HS 15 and Lipoid S 100 were prepared by the phase inversion method and

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characterized for particle size analysis (including polydispersity index (PDI)), drug content and encapsulation efficiency (EE%). For the preparation of Hy-loaded LNCs-MNs, equal weights of the polymer mixture and LNCs were mixed, cast into MN moulds and positive pressure was applied. After complete drying, a preformed dried crosslinked hydrogel base plate (PVA and citric acid) was adhered to the dried MNs. Mechanical strength and insertion depth were assessed.

RESULTS AND DISCUSSION

Blank (40.97 ± 0.22nm, PDI 0.022 ± 0.01) and loaded (60.95 ± 0.27nm, PDI 0.225 ± 0.01) LNCs were successfully prepared. The Hy-LNCs (100 µg/ml) showed EE% of 88.42 ± 0.11% and drug content of 101.99 ± 0.62%. The prepared Hy-loaded LNCs-MN (477 ± 6.53 µm) showed good mechanical strength with only 10.14 ± 0.55% in height reduction upon application of 32 N force, none of the needles was fractured, rather they became compressed.

In the Parafilm M® insertion test, the MNs penetrated to the third layer of Parafilm M®, nearly 79% of the needle height was inserted (Figure 1).

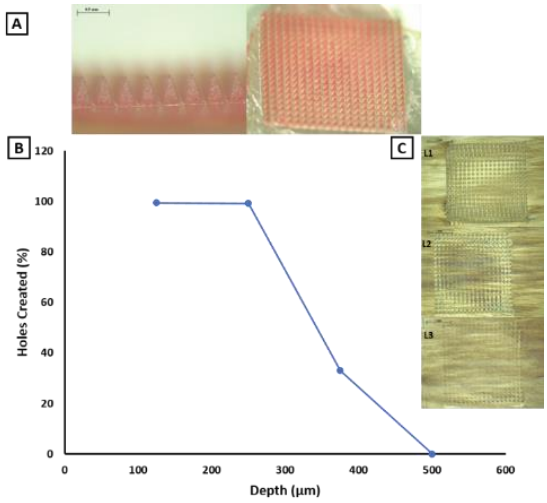

Fig. 1. *A) lateral and surface light microscope images for the Hy-LNCs-MNs. Parafilm M insertion test using 32 N; B) The percentage of holes created in each parafilm layer and C) The light microscope images of each layer.*

In agreement with the previous results, the optical coherence tomography images showed that MN arrays were strong enough to well penetrate the pig skin beyond the stratum corneum reaching insertion depth of approximately 248 µm (Figure 2).

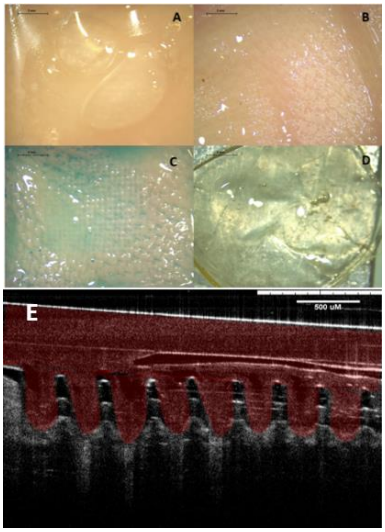

Fig. 2. *Insertion through excised full thickness pig skin for the bilayer MNs formula; A) MNs after 2h on skin, B) Impeded MNs after removal of the hydrogel base plate, C) MB stained skin with completely inserted MNs after removal of the base plate, and D) Intact base plate, without any MNs remaining, after removal from skin and E) Optical coherence tomography image after MNs insertion.*

CONCLUSIONS

The incorporation of Hy-LNC into the novel bilayer MNs overcame its aggregation and ensured the complete insertion of the drug-loaded MNs thus having the potential to deliver the Hy-LNCs to the viable skin layers after dissolution of the supporting polymer blends. Further drug deposition through excised pig skin and fluorescence bioimaging studies are to be done. This LNC-MN system is promising for improving Hy local availability and thus enhancing its photodynamic application

ACKNOWLEDGEMENTS

The authors thank the Newton Mosharafa Programme and the colleagues in the School of Pharmacy, QUB.

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