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Dissolving Microneedle Patches as Vaccine Delivery Platforms

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SUMMARY

Microneedle (MN) patches overcome the drawbacks associated with parenteral route (risk of needle-prick injury, costly supervised administration, production of biohazardous waste) and deliver vaccines transcutaneously into general circulation. This study aimed to summarise three case studies relating to MN patch mediated vaccine delivery. Bacillus Calmette–Guérin (BCG), tetanus toxoid (TT) and rabies vaccine loaded patches were prepared using sodium alginate (SA), polyvinyl pyrollidone (PVP)/carboxymethyl cellulose (CMC) and PVP/hyaluronic acid (HA), respectively. MNs were evaluated for morphology, folding endurance, swelling and insertion ability. In-vivo immunogenic activity was assessed by recording several parameters e.g., immunoglobulin G (IgG), interferon gamma (IFN-γ), T-cell ($CD4^+$ and $CD8^+$) and rabies virus specific antibody count following MN patch application. MNs, displaying sharp tips and uniform surface, showed a folding endurance and swelling of ≥200 and ~70%, respectively indicating integrity and fluid uptake ability. MNs successfully penetrated into the skin simulant parafilm. MNs treated groups exhibited a significant increase in the IgG, IFN-γ, $CD4^+$, $CD8^+$, rabies virus specific antibody counts when compared to the control (untreated) groups and the results were comparable with standard intramuscular injection. Thus, MN patches can be used for transcutaneous vaccine delivery.

INTRODUCTION

Majority of the vaccines are delivered by parenteral route which involves several disadvantages e.g., invasive, poor patient compliance, risk of infection transmission in case of reusing needle, requirement of trained personnel and production of biohazardous waste. Transcutaneous route overcomes these limitations. Further, antigen-presenting and immune-accessory cells are abundantly present in the epidermis and dermis which makes skin an efficient immune-responsive site and a suitable target for vaccine delivery. However, conventional patch formulations are incapable of delivering vaccines (>500 Daltons) transcutaneously due to the barrier function of uppermost skin layer stratum corneum (Zafar *et al.,* 2020).

A MN patch, comprising of an array of micron-sized (25-2000 µm) sharp-tipped structures, penetrates in to the stratum corneum without inducing the pain receptors and delivers loaded vaccine to the systemic circulation (Arshad *et al.,* 2021).

MATERIALS AND METHODS

Materials: HA was purchased from REB technology, Zheijiang, China. PVP, SA, CMC, trehalose, sorbitol and polyethylene glycol 400 (PEG400) were obtained

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from Sigma Aldrich, Steinheim, Germany. Rabies vaccine B.P (INDIRAB®) was purchased from Bharat Biotech, Hyderabad, India. TT vaccine was bought from Amson Vaccine & Pharma Pvt Ltd, Islamabad, Pakistan. BCG vaccine was donated by a health facility, District Health Authority Multan, Pakistan.

Methods: Aqueous polymeric solutions comprising of SA/trehalose, PVP/CMC/sorbitol and PVP/HA/PEG400 were loaded with BCG, TT and rabies vaccine, respectively. The solutions were poured in polydimethylsiloxane (PDMS) molds and patches were prepared by vacuum micromolding technique. Physical evaluation of patches included measurement of thickness, width, determination of folding endurance, % swelling, morphology and insertion ability. Experiments involving animals were performed following approval from Ethical committee of Bahauddin Zakariya university Multan, Pakistan (BZU EC/827/2019, 190/PEC/2021, 210/PEC/2022). In-vivo immunogenic activity was assessed by recording several parameters including IgG, IFN-γ, $CD4^+$, $CD8^+$ and rabies virus specific antibody count following the application of prepared dissolving MN patches.

RESULTS AND DISCUSSION

MN patches showed a thickness and width of 0.85±0.05 mm and 7.8±0.1 mm, respectively. Patches exhibited a folding endurance and swelling of ≥200 and ~70%, respectively indicating structural integrity and fluid uptake ability of prepared formulations (which would allow mass transfer). MNs displayed pointed tips and uniform surface indicating thorough blending of formulation constituents (Fig. 1.). Conspicuously engraved marks of MNs on the skin simulant parafilm suggested that the microprojections would efficiently breach the stratum corneum and deliver loaded vaccines across skin layers.

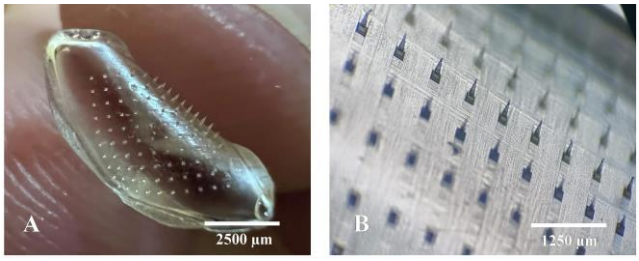

Fig. 1. *Digital (A) and optical microscopy (B) images of polymeric MN patch.*

During in-vivo immunogenicity study in Wistar albino rats, a significant increase in serum IgG titer was observed following vaccine loaded MN patch application when compared to the control (untreated) group and the results were comparable with the standard intramuscular injection (Fig. 2.). TT vaccine treatment led to an increase in IFN-γ, $CD4^+$ and $CD8^+$ counts while in case of rabies vaccine, an increase in rabies virus specific antibody titer was recorded. These results indicated induction of potent immune responses in all the cases.

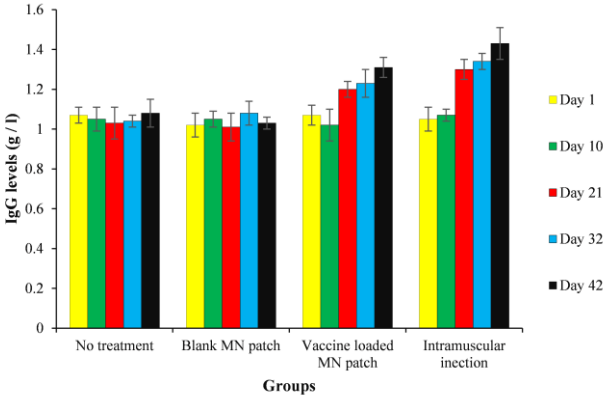

Fig. 2. *IgG levels measured over different time intervals for all groups*

CONCLUSIONS

Polymeric MN patches can be used for transcutaneous delivery of vaccines without inducing pain usually experienced with hypodermic needles.

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