Enhanced local delivery of topical anaesthetics

Anthony P Raphael¹, Elizabeth Payne¹, Marine Maestracci¹, H Peter Soyer¹ and Tarl W Prow¹

¹Dermatology Research Centre, The University of Queensland, School of Medicine, Translational Research Institute, Brisbane, Queensland, 4102, Australia.

a.raphael1@uq.edu.au

ABSTRACT SUMMARY

Elongated microparticles when mixed with a drug can be massaged into the skin resulting in disruption and increased permeability. However, an increase in vehicle viscosity decreases microparticle penetration. Our aim is to optimise and assess microparticle delivery in viscous formulations.

INTRODUCTION

Delivery of therapeutic and cosmetic agents into skin is hindered by the epidermal barriers [1]. We have recently developed a novel approach using elongated microparticles that can be mixed or coated with the drug of interest and massaged onto the skin. Data from pig and volunteer studies showed that the microparticles successfully penetrate and disrupt the skin resulting in enhanced drug delivery [2-3].

However, previous studies were done using low viscosity aqueous vehicles (saline or water), which differ from commercial gel / cream based products. Our aim is to investigate the influence vehicle property in particular viscosity has on the enhanced delivery of drugs to the skin using commercially available lignocaine gel/cream.

EXPERIMENTAL METHODS

The elongated microparticle populations were fabricated by either high energy ball milling or an in-house micro-chopping and filtering technique. A sample of the microparticles was assessed using stereomicroscopy to determine the size distribution prior to use.

Sodium fluorescein formulated in increasing concentrations of carboxymethylcellulose was delivered to pig skin and volunteers using elongated microparticles. Delivery was assessed using laser scanning and microscopy followed by optimisation of application technique (time and amount of microparticles). The optimised administration was used to deliver two commercially available topical anaesthetics (lignocaine gel and EMLA®) to volunteers, with functionality analysed using von frey filaments.

RESULTS AND DISCUSSION

The elongated microparticles used within this study were cylindrical shaped silica microparticles with a diameter of 9.3 ± 0.9 μm. Their mean length was 27.5 ± 9.8 μm with 50% of population between 20.9 μm and 32.6 μm (short), and long microparticles with a length 301.0 ± 209.5 μm, with 50% of population between 118.0 μm and 477.7 μm.

Fig 1: Microparticle application to volunteer skin. a) Clinical photograph of treatment sites. b) Water alone without microparticles. c-g) Dermoscopy images of treatment sites with microparticles applied with increasing concentration of CMC (0, 0.5, 1, 2 and 3%, respectively).
The microparticles were co-formulated with increasing concentrations of CMC and applied to the skin of volunteers. It was observed that the amount of erythema (redness) decreased with an increase in CMC concentration (Fig 1).

Transepidermal water loss (TEWL) of the treated areas was used to assess the integrity of the stratum corneum. Microparticles co-formulated in CMC (0.5-3%) resulted in a slight increase in TEWL however not significant. Microparticle co-formulated in water resulted in a significant 2-fold increase of TEWL compared to the other formulations.

In vivo reflectance microscopy of the treated areas was used to analyze the microparticle penetration characteristics. It was observed that there was no significant change in penetration depth, angle or length of microparticles in the skin. The only factor that changed was the amount of microparticles that successfully penetrated the skin.

Overall, these results show that an increase in viscosity significantly influences the ability of the microparticles to penetrate the skin. However, viscosity does not appear to have a role in influencing the penetration characteristics of the penetrated microparticles.

It was hypothesized that by increasing the amount of microparticles or time of administration the delivery could be enhanced when using viscous formulations. Therefore, 1% CMC was used as the test formulation and compared to the application of microparticles/water.

An increase in the amount of microparticles resulted in increased sodium fluorescein delivery (Fig 2). A similar response was observed with an increase in administration time. Overall, the results show that by maximizing the interaction between the microparticles, skin and applicator, the amount delivered can be increased. Therefore, by utilizing approaches that reduce the sedimentation time of the microparticles within the vehicle (ie. deposit microparticles on surface of skin instead of being in suspension), delivery can be optimized regardless of vehicle composition. The optimization process was translated to microparticle enhanced delivery of lignocaine gel and EMLA® resulting in increased delivery.

CONCLUSION

By increasing the time of application and amount of microparticles, successful drug delivery was achieved comparable to previous results using a water vehicle. The penetration characteristics (depth, microparticle length and angle) were not influenced by the viscosity of the vehicle. Finally, enhanced delivery of the anaesthetics resulted in positive biological responses. These results demonstrate that by optimising application conditions, elongated microparticles can be utilised within viscous vehicles for enhanced topical drug delivery.

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REFERENCES