

**PENETRATION AND ACCUMULATION PROFILE OF TOCOTRIENOLS AFTER TOPICAL APPLICATION OF A NANOEMULSION HYDROGEL IN VARIOUS DROPLET SIZES ONTO RAT SKIN**

**Tommy Julianto<sup>1</sup>, Rosa Pereira<sup>3,4</sup>, Yuen Kah Hay<sup>2</sup> and Abu Bakar Abdul Majeed<sup>1</sup>**

<sup>1</sup>Nanopharmacy Research Unit, Faculty of Pharmacy, Universiti Teknologi Mara, Puncak Alam, Selangor, Malaysia.

<sup>2</sup>School of Pharmaceutical Sciences, University Science of Malaysia, Penang, Malaysia.

<sup>3</sup>Centro de Química Medicinal, Universidade do Porto (CEQUIMED-UP), Portugal

<sup>4</sup>ISAVE, Amares, Portugal

**ABSTRACT**

The aim of this study was to correlate the mean droplet size of nanoemulsions containing  $\alpha$ -,  $\delta$ - and  $\gamma$ -tocotrienols with skin epidermis penetration and accumulation after topical application of the nanoemulsions in a hydrogel base. Vitamin E is a family name for naturally occurring tocopherols and tocotrienols in plants. The  $\alpha$ -,  $\beta$ -,  $\gamma$ - and  $\delta$ - homologues are determined by the amount and position of methyl substituents in the chromanol nucleus. Nano-emulsions are well known as very fine oil-in-water dispersions, having droplet covering the size range of 100–600 nm. Three nanoemulsion hydrogels (NH) formulations containing 2.75mg/g of palm tocotrienols extract, with droplet sizes of  $\pm 100$ nm,  $\pm 500$ nm and  $\pm 1000$ nm were prepared for this study. Forty five (45) male Sprague Dawley rats weighing between 238 g and 272 g were randomly divided into 3 groups of 15 rats which each group were divided into 5 different time of skin sampling post topical administration. After skin hair was shaven using a mechanical hair clipper, with the area of 2.54 cm<sup>2</sup>, 200 mg of nanoemulsion hydrogel formulation was applied on this region. After that, this region was closed by ventilated plastic cover for 1, 2, 3, 4 and 6 hours at difference rat before sacrifice. The excised rat skins were stored at  $-20^{\circ}\text{C}$  where they were received frozen and well preserved, and subsequently analyzed for tocotrienols. Tocotrienols penetration and accumulation into skin epidermis from nanoemulsion hydrogels (NH) at three different droplet sizes were in similar trend. The mean accumulation of tocotrienols in skin epidermis were in the range of 3 to 5 times for  $\pm 100$ nm NH compared to  $\pm 1000$ nm NH after 1, 2, 3, 4 and 6 hours of topical application, while tocotrienols accumulation of  $\pm 100$ nm NH compared to  $\pm 500$ nm NH and  $\pm 500$ nm NH compared to  $\pm 1000$ nm NH were found similar, approximately around 2 times. The statistical analysis shows significant difference between the accumulated  $\alpha$ -,  $\delta$ - and  $\gamma$ -tocotrienols in skin epidermis of  $\pm 100$ nm NH in comparison with  $\pm 500$ nm and  $\pm 1000$ nm NH, and  $\pm 500$ nm NH compared to  $\pm 1000$ nm NH. Effect of emulsion droplet size reduction on the  $\delta$ - tocotrienol penetration and accumulation in skin epidermis by topical application was greater compare to  $\alpha$ - and  $\gamma$ -tocotrienols. This is probably due to the polarity of  $\delta$ - tocotrienol is higher compare to  $\alpha$ -, and  $\gamma$ -tocotrienols by the presence of extra hydrogen at  $\delta$ - tocotrienol cromanol nucleus. The suitability of active polarity with stratum corneum is a driving force for better penetration into skin epidermis. On the basis of the results obtained, it is apparent that tocotrienols in  $\pm 100$ nm NH has been preferentially absorbed and accumulated into epidermis, follow by  $\pm 500$ nm NH and  $\pm 1000$ nm NH.

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