UNIVERSITI TEKNOLOGI MARA

MICROWAVE MODULATED TRANSDERMAL DRUG DELIVERY USING CHITOSAN NANOCARRIER

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ABSTRACT

The chitosan has been used as the primary excipient in transdermal particulate dosage form design. This study investigated the transdermal drug delivery profiles and mechanisms of chitosan nanoparticles and their cellular uptake mechanisms by melanoma cells as a function of nanoparticles attributes and pre-treatment effects of skin by microwave. Low molecular weight chitosan of smaller size, higher zeta potential and degree of deacetylation were obtained via microwave ligation of polymer chains at solution state. Low molecular weight chitosan nanoparticles, loaded with free or conjugated 5-fluorouracil, were prepared by nanospray-drying technique with tween 20 and span 20 as additives. Folate was covalently attached to the chitosan-carboxymethyl 5- fluorouracil conjugate when necessary and subjected to nanoparticulation process. The transdermal drug delivery profiles of chitosan-carboxymethyl 5-fluorouracil nanoparticles across the untreated and microwave-treated skins (2450 MHz 5 min, 5 + 5 min; 3985 MHz 5 min) were examined, against microstructural changes of skin. Both constituent materials of nanoparticles and drug encapsulation were required to succeed the transdermal drug delivery. The drug transport was mediated via nanoparticles carrying the drug across the skin and/or diffusion of the earlier released drug molecules from skin surfaces. The drug/nanoparticles transport was facilitated through constituent nanoparticles, chitosan-drug conjugation and microwave fluidizing both protein/lipid domains of epidermis and dermis (O-H, N-H, C-H, C-N) and dermal trans-to-gauche lipid conformational changes. The microwave induced marked changes to the skin ceramide content homogeneity, whereas the nanoparticles largely affected the palmitic acid and keratin domains. Subjecting the skin to pre-treatment by microwave, the transdermal transport of chitosan-carboxymethyl 5-fluorouracil-folate conjugate nanoparticles and their drug exhibited a similar profile as folate-free nanoparticles. *In vitro* melanoma cell culture experiments with endocytotic inhibitors suggested that the internalization of these nanoparticles was largely associated with lipid-raft mediated route. The internalization of nanoparticles increased with prior treatment of melanoma cells with microwave (2450 MHz, 5 + 5 min). It was found that microwave fluidized the lipid regime of the cell membrane and this resulted in increased internalization of the nanoparticles. Overall, combination of microwave and nanotechnology synergized transdermal drug delivery and intracellular trafficking of nanoparticles through preferential skin/cell membrane fluidization at various protein/lipid domains.

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INTRODUCTION

1.1 OVERVIEW

Human civilizations have applied substances to the skin as cosmetics and medicinal agents, for thousands of years. However, it was not until the twentieth century that the skin came to be used as a drug delivery route. Oral route has been the most common and universal mode of drug administration for long time but nowadays, the drawbacks encountered with oral route such as poor bioavailability due to hepatic first pass metabolism and pronounced adverse effects are met with the requirement for an alternative administration technology. One of the delivery technologies is transdermal mechanism which means transport of materials through the skin for local and systemic effects. Transdermal drug delivery avoids gastrointestinal harsh enzymatic and acidic conditions which degrade drugs. In comparison to injection route, transdermal drug delivery is painless, easy to apply dosage form on skin and its quick removal is possible when adverse effects develop (Lavon & Kost, 2004; Gratieri & Kalia, 2013; Wong, 2014). However, the primary obstacle faced by scientists in transdermal drug delivery lies in the barrier function of stratum corneum, the outermost layer of epidermis.

In a normal adult human, skin is the largest of all organs covering approximately of 2 m^2 area of the body (Banga, 1998). Skin possesses three major layers, the upper most epidermis, the dermis and the innermost subcutaneous tissue (Leroy et al., 2014).The main skin structure that confers the barrier attribute is stratum corneum, the uppermost layer of the epidermis. The stratum corneum consists of keratin-rich corneocytes embedded in lipid lamellar matrix (Proksch, Brandner & Jensen, 2008; Garidel, Fölting, Schaller & Kerth, 2010). Both corneocytes and lipid lamellae represent the barrier to transdermal drug permeation across the skin. They limit the route to transport of drugs