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Title : MICROWAVE MODULATED TRANSDERMAL DRUG DELIVERY USING CHITOSAN NANOCARRIER

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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.