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SKIN DRUG PERMEATION CHARACTERISTICS OF OLIGOCHITOSAN- AND CARBOXYMETHYLOLIGOCHITOSAN-CARBOXYMETHYL-5-FLUOROURACIL CONJUGATE NANOPARTICLES

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Abstract

The skin drug permeation characteristics of nanoparticles made of oligochitosan- and carboxymethyl-oligochitosan (CM-oligochitosan) conjugate of polar prodrug, carboxymethyl-5-fluorouracil (CMFU), were investigated. The polymer-drug conjugates were prepared by carbodiimide chemistry and processed into solid nanoparticles using nanospray drying technique. The skin drug permeation of nanoparticles was profiled *in vitro* using the *Sprague dawley* rat's skin, against neat 5-fluorouracil. The changes in the microstructure of skin with reference to the application of nanoparticles were examined by ATR-Fourier Transform Infrared (ATR-FTIR) spectroscopy, Differential Scanning Calorimetry (DSC) and Scanning Electron Microscopy (SEM) techniques.

The oligochitosan-CMFU and CM-oligochitosan-CMFU conjugate nanoparticles were characterized by particle sizes of 117.72 ± 46.90 nm and 229.10 ± 57.05 nm, polydispersity indices of 0.43 ± 0.14 and 0.60 ± 0.15, zeta potentials of -23.04 ± 11.23 mV and -55.92 ± 24.48 mV, and drug contents of 4.55 ± 0.08 %w/w and 2.29 ± 0.27 %w/w, respectively. The levels of skin drug permeation were found to progress in the following order: CM-oligochitosan-CMFU nanoparticles > oligochitosan-CMFU nanoparticles > CMFU, following 24 h of diffusion study.

ATR-FTIR spectra of the untreated skin were characterized by C-H stretching vibrational peaks (asymmetric and symmetric CH_2) associated with the lipid alkyl chains of epidermis at 2918.63 ± 0.02 cm^{-1} and 2850.56 ± 0.15 cm^{-1}. Similar peaks were not observable in skin samples treated with CM-oligochitosan-CMFU nanoparticles. The CM-oligochitosan-CMFU nanoparticles could have interacted with skin and fluidized its lipid packing thus facilitating skin drug permeation. Skin treated with CM-oligochitosan-CMFU nanoparticles and oligochitosan-CMFU nanoparticles had FTIR amide I band being shifted to lower wavenumber from 1646.83 ± 1.08 cm^{-1} (untreated epidermis) to 1642.40 ± 3.72 cm^{-1} and 1643.27 ± 2.47 cm^{-1} respectively, unlike that of CMFU. This was attributed to keratin condensation which in turn led to shrinkage of corneocytes. The summative changes of lipid and protein regimes of skin brought about the formation of larger intercellular aqueous pores which then eased skin drug permeation.

The FTIR findings were supported by thermal and microscopy analysis of the same skin. The DSC melting temperature (65.92 ± 0.57°C) and endothermic enthalpy (2.82 ± 0.69 J/g) of untreated skin related to lamellar lipid structure decreased when the skin was treated with CM-oligochitosan-CMFU nanoparticles and oligochitosan-CMFU nanoparticles. Both strength and extent of lipidic matrix interaction of skin were reduced in response to nanoparticles application. CM-oligochitosan-CMFU nanoparticles, being the most contributive in skin drug permeation, were able to induce pore formation on skin surfaces possibly via strong charge-charge repulsion with anionic lipid-rich skin. Oligochitosan-CMFU nanoparticles with lower negative zeta potential on the other hand only resulted in uneven skin surfaces, whereas the surfaces of skin remained intact when it was treated with CMFU.