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Title : SKIN DELIVERY OF 5-FLUOROURACIL VIA ETHOSOMES USING MICROWAVE AS SKIN PERMEATION ENHANCEMENT TECHNIQUE

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This project focused on formulation and investigation of interplay effects of ethosomes, ethanol and microwave for enhanced skin drug retention with minimal systemic absorption. The microwave was used to modify the skin barrier properties to enhance ethosomes and/or drug penetration/and drug retention which is detrimental to treat local malignant melanoma and to enhance patient compliance. Ethosomes are known to fuse with skin to enable local drug retention. Pre-treatment of skin with microwave and applying liquified medicine is deemed to "cement" the skin thereby raising skin drug deposition. 5-fluorouracil loaded ethosomes were prepared and subjected physicochemical characterization. The molecular characteristics of untreated, microwave and/or ethosomes and/or ethanol-treated skins were examined by ATR-FTIR and raman spectroscopy, DSC and SEM techniques. The skin drug retention was promoted using larger ethosomes with negative zeta potentials that repelled anionic lipids of skin and hindered vesicle and/or anionic drug penetration into deep layers. Due to low ethanol, they were less able to fluidize the lipid and defluidize the protein domains at epidermis to enlarge aqueous pores for drug permeation. Pre-treatment of skin by 2450 MHz microwave for 2.5 min further increased skin drug penetration and retention of E5 ethosomes and provided lower drug permeation than cases treated for 1.15 min and 5 min. Pre-treating skin with microwave fluidized lipid and defluidized protein domains of skin that promoted transdermal drug penetration. A 2.5 min treatment however might be accompanied by specific dermal protein fluidization via C=O moiety which translated to macromolecular swelling, narrowing of intercellular spaces at lower skin layers, increased drug retention and reduced drug permeation. Ethosomes in combination with microwave at 2450 MHz for 2.5 min promoted significant drug deposition in skin from ethosomes *in vivo* with reduced systemic absorption. Pre-treatment of human melanoma cells with microwave exerted cytotoxic effect and also facilitated the intracellular ethosomes accumulation by fluidizing the cell membrane phospholipids reflected by a significant increase in wavenumber corresponding to symmetric phosphate moiety. The endocytosis was primarily promoted by lipid rafts pathway where a significant reduction in fluorescence intensity was observed when melanoma cells were pre-incubated with nystatin. Combined microwave and ethanol pretreatment of skin increased skin drug retention and decreased permeation of aqueous 5-fluorouracil solution. The combination fluidized the skin lipidic domains, defluidized the hydrophilic regimens causing an increase in aqueous pores population and their sizes. The summative effect translated into an increased drug penetration, permeation and retention of drug solution in the skin. When microwave pre-treatment was combined with 100 µl ethanol, rapid movement of ethanol from epidermis to dermis under the gravity bringing extracted epidermal lipids downwards and accumulating them in dermis in addition to fluidization of the extracellular proteins at C-N moieties. The expanded proteins structure and epidermal lipids accumulation in dermis promoted skin drug retention by narrowing the permeation pathways and formation of an additional lipid barrier consisting of ceramide and palmitic acid in dermis.