ABSTRACT

The present investigation was aimed at studying the per se effect of herbal extracts containing alkaloids and coumarins (piper nigrum, Zingiber officinale, Angelica archangelica, Melilotus officinalis) and as well as their combination with chitosan (CTN) for possible use as percutaneous permeation enhancer. Overall, the results of the present investigation suggest a promising role of alkaloids and coumarins containing extracts in enhancing the percutaneous permeation of repaglinide (RGE). CTN was found to potentiate the permeation enhancing activity of these extracts. Further, the permeation enhancing activity of alkaloids and coumarins containing extracts and CTN was found to be mediated through their effect on microconstituents of epidermis which was manifested in the ultrastructure as evident in SEM and TEM photographs. The ultrastructural alterations and biochemical changes in rat skin after treatment with these extracts were correlated with the biophysical (transepidermal water loss) and thermotropic attributes (differential scanning calorimetric parameters). Hence, biochemical constitution and modification of epidermal ultrastructure seem to be inextricable aspects while understanding the percutaneous permeation activity of alkaloids and coumarins. Further, the normalization of contents of epidermal microconstituents after 48 h of application to viable rat skin rules out the possibility of irreversible damage by any of these agents. The application of patches containing mixture of alkaloids and coumarins containing extract and CTN resulted in sustained release of RGE which was able to control the blood glucose level in Streptozotocin-induced hyperglycemic rats through 24-36 h. Transdermal formulation containing Angelica archangelica extract-CTN mixture was observed to enhance the in vitro permeation of repaglinide by 8-fold as compared to control. Application of transdermal patch containing this formulation was able to control the increased blood glucose level in Steptozotocin-induced hypglycemic rats for 36 hours as judged by pharmacokinetic and pharmacodynamic investigations. Further, treatment on HaCaT cell line by these extracts were observed to influence the TJ plaque protein zonula occludens (ZO-
1) as evidenced by reduced immunofluorescence of anti-TJP1 (ZO-1) antibody in confocal laser scanning microscopic studies. The results of the investigation revealed a promising role of coumarins (Angelica archangelica extract being the most effective) in formulating transdermal patches of repaglinide for once-a-day application.