Glycomics and Lipidopics

Extended Abstract

Synthesis of a New Tetrahydrogeraniol Derivative as Penetration Enhancer for Transdermal Drug Delivery

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Abstract:

Skin is one the most important sites for administration of drugs to obtain desired pharmacological effects either locally or through systemic bioavailability; and this has placed the transdermal route of drug delivery as an attractive and as one of the most innovative areas for conducting drug delivery research. However the *stratum corneum* in skin creates hurdles and acts as significant barrier for the permeation of drugs through skin. Penetration enhancers play a pivotal role to overcome such barriers and help enhance the permeation of drug through skin. However, penetration enhancement technology is challenging development and needs to be properly and skillfully addressed. The present investigation aimed to study the penetration enhancing effect of a newly synthesized alcohol derivative of an acyclic monoterpene (Tetrahydrogeraniol-THG). The new derivative, 5,9-Dimethyl-1-Decanol (DIMDOL), has been synthesized by a chemical reaction of the THG with Grignard reagent and ethylene oxide. Permeation enhancing effect of the synthesized derivative was explored for better transdermal penetration of the two model drugs viz. tramadol hydrochloride and 5-fluorouracil (5-FU) through the excised rat skin by conducting *in-vitro* permeation experiments employing Franz diffusion cells apparatus. The standard enhancers Azone and THG were used to compare penetration enhancing effect of the enhancers. It was revealed that DIMDOL could effectively enhance the permeability of both the drugs by 18.60 and 73.19 folds across the skin used with a lag time of 3.35 and 1.20 h, respectively. The newly synthesized derivative was found to significantly increase the partition coefficient and diffusion coefficient values. The results obtained suggest that DIMDOL can more effectively enhance the permeation of these model drugs, expectedly by affecting the stratum corneum and interacting with both lipid-rich layers and keratin-rich layers of the excised rat skin. Transdermal drug delivery is the delivery of drugs across epidermis to achieve systemic effects. It is a non-invasive method for drug administration with an improved approach and is capable of maintaining therapeutic plasma drug level for prolonged and extended period of times [1]. Properly designed and developed transdermal drug delivery systems (TDDS) may offer better solutions to the problems associated with other drug delivery systems currently in vogue. The systems have thus been developed as an alternative to oral and parenteral pharmaceutical forms. However, many drugs are unsuitable for use as transdermal therapeutic systems because of their low permeability through the human skin. The improvement of permeability using penetration enhancers may therefore be desirable [2]. During the last few years various penetration enhancers including aprotic solvents, several surfactants and Azone have been extensively studied by different investigators in order to explore their penetration enhancing effect. The exact mechanism of penetration enhancing effect of these enhancers over the skin is not very clear, however, the lipophilicity of such enhancers is considered to play an important role in this regard. It has been found that mostly the long-chain primary alcohols could be of greater value in this connection, apart from being cheaper and alos non-toxic in nature [3] and the number of carbon atoms in the chain may influence the enhancing effect. In our series of research work, previously we reported the synthesis of 5,9-Dimethyl-2-Decanol (DICNOL) and its evaluation as a potential percutaneous penetration enhancer[4]. The purpose of the present work is to synthesize 5,9-Dimethyl-1-Decanol (DIMDOL), another new derivative of Tetrahydrogeriniol (THG) and to investigate its enhancing effects on the penetration and transport of 5-Fluorouracil and Tramadol HCl through excised rat skin. IR spectra were obtained with Perkin Elmer-983 spectrometer. NMR spectra were recorded on PMX-60si instrument. Mass spectra were obtained with ZAB-HS-VG analytical organic mass spectrometry. Gas chromatography was performed with Shimadzu gas chromatographer GC-9A with C-R3A chromatopac. Permeation studies were performed employing Franz diffusion cells (PermeGear, Bethlehem, PA). Azone (Guangzhou Zhuji Factory, China), 5-Fluorouracil (Shanghai 12th Pharmaceutical Manufacturing Factory, China) and tramadol hydrochloride (Shi Jia Zhuang No. 1 Pharmaceutical Factory, China) were purchased locally. Tetrahydrogeraniol (Nanjing Perfume Factory, China) was also purchased from the local market and was purified up to contents of 99.9%. The remaining reagents used were purchased from the local

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market and all of them were analytical grade. The male white rats (Sprague Dawley) were obtained from the Animal House of the Zoology Department, University of Peshawar, KPK, Pakistan. Preparation of Tetrahydrogeranyl Chloride (C10 H21 CI) Tetrahydrogeranyl Chloride was prepared in the way as described in our previous reports [4, 5]. In brief, 56 ml (47.04g, 0.297 mol) tetrahydrogeranyl and 150 ml dry acetonitrile were mixed with 100 g (0.38 mol) triphenylphosphine. This mixture was shaken at 25 ^{0}C, followed by slow addition of 43 ml (68 g, 0.441 mol) dry carbon tetrachloride into it. The mixture was at 25 ^{0}C for 6 h and then left overnight. The supernatant solvent was removed under reduced pressure and the oily precipitate was filtered off with petroleum ether through a column containing dried silica gel. Petroleum ether was evaporated and the oil obtained was distilled to give tetrahydrogeranyl chloride; yield: 42 g (80 %) percentage purity (97.10 %) was fond by gas chromatography. In a three-necked flask, 50 ml of 2-ethylene chlorohydrins (95%) was taken, heated while stirring, followed by drop-wise addition of 45 ml of 40 % sodium hydroxide solution at 45 ^{0}C. A white precipitate was formed by the reaction of sodium hydroxide solution. The temperature of the reaction mixture began to fall and reached to 35 ^{0}C within 45 minutes. When the whole solution of sodium hydroxide was dropped into the flask, then the mixture was heated to about 90 ^{0}C and collected the ethylene oxide gas into a tube placed in ice-salt bath.

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