Journal Of Harmonized Research (JOHR)

Journal Of Harmonized Research in Pharmacy
4(1), 2015, 60-63

ISSN 2321 – 0958

Original Research Article

TO STUDY THE *IN VITRO* EFFECT OF SOME ALCOHOL CONTAINING VOLATILE OILS AS THE SKIN PENETRATION ENHANCERS OF CURCUMIN

Ganju Kuldeep[1*] and Ganju Eisha[2]

[1]Principal, SIPTec, Gandhinagar, Bhopal, M.P.-462036
[2]Asst. Prof., School of Pharmacy & Research, People's University, Bhopal, M.P.-462037

Abstract: The effect of geraniol, linalool and nerol on the skin permeation of curcumin was investigated. The mechanism of skin permeation enhancement of curcumin by essential oils treatment was evaluated by Activation energy measurement. The effectiveness of the oils as the penetration enhancers was found to be in the following descending order: geraniol>linalool>nerol. The results of thermodynamic studies and of geraniol incorporated group suggested additional mechanisms for geraniol facilitated permeation. To conclude geraniol has been diagnosed to be thebest penetration enhancer of all others to allow curcumin pass through the skin epidermis.

Keywords: Geraniol, linalool, nerol, TDDS

1. Introduction

Curcumin, an extract from the Indian spice turmeric, has been investigated in a variety of human cancers including pancreatic, prostate, breast, head and neck cancer. The first published report demonstrating the topical use of curcumin in cancer reported a sustainable reduction in lesion size and pain.[1]Curcumin has antioxidant, anti-inflammatory, antiangiogenic and anticarcinogenic activity, although its clinical use is limited by low bioavailability.[2]More recently, several studies have examined curcumin's effect in inhibiting skin carcinogenesis. Additionally, numerous reports have identified signalling pathways related to epidermal growth factor receptors (EGFR) that are essential to formation and progression of cutaneous malignancy. The MTOR and MEK/ERK signalling cascades are two of the most well-studied pathways.[3] In a prior study by our group we subcutaneously injected immunodeficient mice with SRB12-p9 skin SCC and demonstrated that curcumin administered orally significantly inhibited tumor growth and down-regulated pS6, a well-established downstream biomarker of the MTOR and MEK/ERK pathways[4]. Curcumin's anti-carcinogenic effects have been linked to inhibition of the MEK/ERK signalling pathway

For Correspondence:
kuldeepganju@yahoo.com
Received on: February 2015
Accepted after revision: March 2015

in breast carcinogenesis, and researchers continue to explore these potential biomarkers in other cancers.[5] However, ERKs activity in cutaneous malignancy is not well defined in the literature. Hence, study was done to determine if topical curcumin was as efficacious as oral curcumin in a SCC skin xenograft model and elucidate the pathways downregulated by curcumin as potential biomarkers for future chemopreventive studies with the topical curcumin cream.[6] Transdermal delivery of drugs promises many advantages over oral or intravenous administration, though human skin provides an effective barrier to the permeation of most drugs in the form of stratum corneum (SC).[7&8] Success of the transdermal route depends on the ability of drugs to breach this barrier and permeate the skin at a rate sufficient to attain effective plasma concentration. There are many approaches employed to enhance the skin permeation rate of active moieties. However, the most convenient and widely implemented approach is the use of chemical penetration enhancers such as DMSO, DMF, azone, ionic surfactants, but their use are also associated with unpleasant and toxic side effects. In recent years there has been a search for natural compounds as permeation enhancers to improve drug permeation that also exhibit low toxicity while maintaining their enhancing activity.[9&10]The natural absorption promoters documented so far include essential oils, terpenes, terpenoids, fatty acid esters, fatty acid glycols, and herbal extracts. The essential oils are nontoxic, non-allergic, and compatible with drug and excipients, and have received much attention of researchers. Essential oils present a large range of chemically acceptable and relatively safe penetration enhancers to aid percutaneous drug delivery and are considered as GRAS (generally regarded as safe) compounds for medicinal use. They have been reported to use for permeation enhancement of both hydrophilic and lipophilic drugs. They cause no skin toxicity or if any, only mild irritation.[11]Antecedently, the feasibility of natural oils viz. corn (maize) oil, groundnut oil and jojoba oil as penetration enhancer was reported for enhanced transdermal olanzapine delivery.[12]In this quest, the present work was carried out to monitor the effect of commonly used essential oils namely geraniol, linalool and nerol on skin permeation of curcumin and to elucidate the mechanism of skin permeation enhancement.DSC studies help provide the information about their thermotropicbehaviour.[13] Antiproliferative effects of curcumin were demonstrated in an aggressive skin cancer cell line SRB12-p9 (compared to control). Topical formulation was as effective as oral curcumin at suppressing tumor growth in a mouse skin cancer model. Curcumin at 15 mg administered by oral, topical, or combined formulation significantly reduced tumor growth compared to control.[14]

2. Materials and methods

2.1. Materials

Curcumin, geraniol, linanool and nerol, NaOH, NaCl, ethanol, Sodium azide, Potassium dihydrogen orthophosphate, Sodium bromide, Potassium sulfate, HPLCgrade acetonitrile and methanol, trypsin were purchased from reliable sources.

2.3 Preparation of TDDS

5% Transdermal patch of curcumin using 0.5% each of geraniol, nerol and linalool as penetration enhancers, and without any penetration enhancers, in PEG were prepared.

2.4 Preparation of rat skin and *in vitro* skin permeation studies

Goat skin was taken, and it was cleaned and washed with phosphate buffer of pH 7.4 and prepared for the study. Diffusion studies were performed using Diffusion cell[15] The effective diffusion area between two half cells was 5.26 cm^2 and the capacity of each half cell was 10 ml. The receiver fluid was equilibrated at 37 ± 0.5 °C and stirred with magnetic stirrer at a speed of 600 rpm.[16]

The *in vitro* permeation study was when Donor solution contains penetration enhancer in the vehicle.[17]

To both the donor and receptor solutions, sodium azide(0.0025%, w/v) was added to prevent any microbial growth. The samples (2 ml) were periodically withdrawn from the receptor compartment up to 24 h with replacement of fresh PBS to the receiver phase. The samples were filtered and analyzed for the drug content by UV method.[18]

Standard calibration curve of standard curcumin was made at 421 nm. The stock solution of curcumin of 10µg/ml was made in methanol and dilutions from 1-7µg/ml were made.[19]

2.5 Permeation enhancement mechanistic studies

Data analysis

Flux is the rate of change of the cumulative amount of drug passes per unit area and time through the skin. The flux was determined as the slope of steady state portion of the curve between the cumulative amounts of drug permeated (µg/cm^2) and time in (h). The permeability coefficient (*kp*) was calculated by dividing the flux by the initial drug concentration per unit area of the skin (µg/cm^2). The enhancement ratio (ER) was calculated by dividing *kp* in presence of enhancer by *kp* without enhancer (control).

Therapeutic transdermal daily dose (*Td*) of curcumin was calculated by the following equation.

$$Td = Do \times F/100$$

Where, F is the bioavailability in percentage after oral administration (33% for curcumin) and *Do* is the oral dose (25 mg for curcumin).

The permeated daily dose (*Dss*) was calculated from the following equation.

$$Dss = J \times Ta \times t$$

Where, *J* is the curcumin flux in µg/cm^2/h, *Ta* is the area of diffusion and *t* is the duration of treatment.

3. Results and discussion

3.1. Skin permeation studies

The increase in Flux is found to be significantly higher when geraniol is used as penetration enhancer. This increase in Flux suggests that a much higher percentage of curcumin can be absorbed with geraniol as enhancer in comparison with the control group, per day.

Table No. 1 : Skin Permeation Parameters of *In vitro* Skin Permeation Studies

Group	Flux	Enhancement Ratio	% increase in flux	Lag time (h)
Control	143±1.5	1	-	3.6±0.001
Test 1	260±1.4	1.6	42	0.04±0.002
Test 2	222±1.3	1.4	35	0.5±0.002
Test 3	180±1.2	1.5	37	0.4±0.001

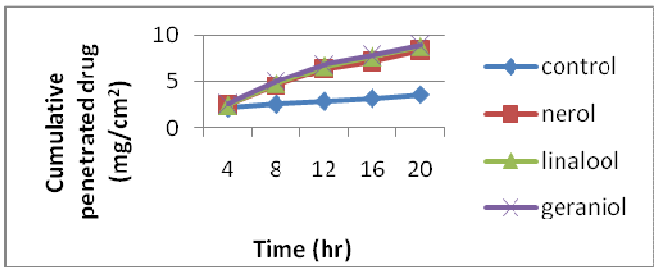

Fig. 1: Skin permeation profile of curcumin on concurrent treatment of test penetration enhancers with saturated solution of curcumin in the vehicle i.e. ethanol: PBS (1:9)

The results of the above two studies suggested the effectiveness of investigated essential oils as penetration enhancer in the following order: geraniol > linalool > nerol.

4. Conclusion

Findings of the above study demonstrate that it is possible to achieve enhanced curcumin flux by test essential oils geraniol, linalool and nerol. However, only geraniolincorporation provided the target flux required to deliver therapeutic dose of curcuminpercutaneously. It is concluded that it is feasible to deliver therapeutically effective dose of curcumin via transdermal route using geraniol as penetration enhancer.

5. References

1. R. Kuttan, P. C. Sudheeran, and C. D. Josph, "Turmeric and curcumin as topical agents in cancer therapy," Tumori, vol. 73, no. 1, pp. 29–31, 1987.
2. C. H. Hsu and A. L. Cheng, "Clinical studies with curcumin," Advances in Experimental Medicine and Biology, vol. 595, pp. 471–480, 2007.
3. J. Dujic, S. Kippenberger, A. Ramirez-Bosca et al., "Curcumin in combination with visible light inhibits tumor growth in a xenografttumormodel," International Journal of Cancer, vol. 124, no. 6, pp. 1422–1428, 2009.
4. J. M. Phillips, C. Clark, L. Herman-Ferdinandez, et al., "Curcumin inhibits skin squamous cell carcinoma tumor growth in vivo," Otolaryngology—Head and Neck Surgery, vol. 145, pp. 58–63, 2011.
5. W. F. Hua, Y. S. Fu, Y. J. Liao et al., "Curcumin induces down-regulation of EZH2 expression through the MAPK pathway in MDA-MB-435 human breast cancer cells," European Journal of Pharmacology, vol. 637, no. 1–3, pp. 16–21, 2010.
6. J. S. Vourlekis and E. Szabo, "Predicting success in cancer prevention trials," Journal of the National Cancer Institute, vol. 95, no. 3, pp. 178–179, 2003.
7. A. Ahad, M. Aqil, K. Kohli, *et al.*Role of novel terpenes in transcutaneous permeation of valsartan: effectiveness and mechanism of actionDrug DevInd Pharm, 37 (2011), pp. 583–596
8. A. Ahad, M. Aqil, K. Kohli, *et al.*Interactions between novel terpenes and main components of rat and human skin: mechanistic view for transdermal delivery of propranolol hydrochloride, Curr Drug Deliv, 8 (2011), pp. 213–224
9. A. Ahad, M. Aqil, K. Kohli, *et al.*Chemical penetration enhancers: a patent reviewExpert OpinTher Pat, 19 (2009), pp. 969–988
10. N. Hassan, A. Ahad, M. Ali, *et al.*Chemical permeation enhancers for transbuccal drug deliveryExpert Opin Drug Deliv, 7 (2010), pp. 97–112
11. M. Aqil, A. Ahad, Y. Sultana, *et al.*Status of terpenes as skin penetration enhancers Drug Discov Today, 12 (2007), pp. 1061–1067
12. G. Aggarwal, S. Dhawan, S.L. Hari Kumar, Natural oils as skin permeation enhancers for transdermal delivery of olanzapine: in vitro and in vivo evaluation, Curr Drug Deliv, 9 (2012), pp. 172–181.
13. S.N. Tenjarla, R. Kasina, P. Puranajoti, *et al.*, Synthesis and evaluation of N-acetycurcuminrolinate esters - novel skin penetration enhancers, Int J Pharm, 192 (1999), pp. 147–158
14. KunalSonavane, Jeffrey Phillips, et al. Topical Curcumin-Based Cream Is Equivalent to Dietary Curcumin in a Skin Cancer Model, Journal of Skin Cancer Volume 2012 (2012), p.1
15. A. Ahad, M. Aqil, K. Kohli, *et al.*Formulation and optimization of nanotransfersomes using experimental design technique for accentuated transdermal delivery of valsartan, Nanomedicine, 8 (2012), pp. 237–249.
16. R. Jain, M. Aqil, A. Ahad, *et al.*Basil oil is a promising skin penetration enhancer for transdermal delivery of labetolol hydrochloride, Drug DevInd Pharm, 34 (2008), pp. 384–389.
17. K.S. Bhatia, J. Singh, Effect of linolenic acid/ethanol or limonene/ethanol and iontophoresis on the in vitro percutaneous absorption of LHRH and ultrastructure of human epidermis, Int J Pharm, 180 (1999), pp. 235–250
18. H. Jalalizadeh, E. Souri, H. Farsam, *et al.*,A high-performance liquid chromatographic assay for the determination of curcumin in plasma, Iran J PharmacolTher, 2 (2003), pp. 18–21.
19. Kiran Sharma, S. S. Agrawal, Monica Gupta, Development and Validation of UV spectrophotometric method for the estimation of Curcumin in Bulk Drug and Pharmaceutical Dosage Forms, nternational Journal of Drug Development & Research, April-June 2012 , Vol. 4, Issue 2, p.1-6.