Research Article

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TRANSDERMAL PERMEATION ENHANCEMENT OF IBUPROFEN AND ITS SOLID DISPERSIONS

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ABSTRACT
Terpenes are the most promising natural chemical enhancers used to amplify the transdermal permeation of drugs, among them monoterpenes and sesquiterpenes have been widely suggested. Permeation enhancement effect of various terpenes (nerolidol, farnesol, limonene, linalool, menthol, geraniol, carvone, fenchone etc.) in various combinations of preparations on ibuprofen (IBU) and its solid dispersions ($IBUSD_1$) from Carbopol 941 gel formulations (0.9 %) were studied. Skin permeation studies and release kinetics have shown farnesol (2.5 and 5 %) and geraniol (2.5 %) had the best permeation enhancement on the release rate of ibuprofen gel. Limonene (2.5 %), geraniol (2.5 and 5 %) had the best permeation enhancement on the release rate of ibuprofen solid dispersion gel. Ex-vivo studies of ibuprofen gel revealed that farnesol with highest lipophilicity (log P 5.31) significantly ($p < 0.0001$) increased the flux and permeability coefficient compared to control, with a flux rate of 605.6 $\mu g/cm^2/hr$ and permeability coefficient of 6.2 cm/h. Studies of ibuprofen solid dispersion gel revealed that limonene with highest lipophilicity (log P 4.58) significantly ($p < 0.0001$) increased the flux and permeability coefficient compared to control with a flux rate of 738.6 $\mu g/cm^2/h$ and permeability coefficient of 8.86 cm/h. Rank order of enhancement effect in terms of boiling point of terpenes for ibuprofen gel was farnesol (111°C) > geraniol (230°C) and that of ibuprofen solid dispersion gel was limonene (176 °C) > geraniol (230°C). All optimized formulations obeyed the Higuchi release kinetics and non fickian type of diffusion.
Keywords: Terpenes, Percutaneous permeation, Ibuprofen, Solid dispersion, Transdermal gel, Lipophilicity, Boiling point.

INTRODUCTION

Transdermal drug delivery system is most feasible alternative to oral delivery due to minor metabolic activity of skin and it is also potent route for drugs with short biological half life[1]. The crucial hindrance is the delivery of drug through stratum corneum, the upper most layer of skin. It consists of 10-15 layers of keratin rich corneocytes embedded in lipid matrix, considered to be the major barrier for dermal delivery[2]. Therefore, a profound knowledge about the penetration pathways and effect on the biochemical composition and structure of entire stratum corneum is prerequisite. Several propositions have been applied to bypass the natural barrier to avail the advantages of this route. Permeation enhancers are the most commonly employed method to lower the barrier property of skin by affecting the lipid and protein components of the skin. Though several classes of permeation enhancers, such as surfactants, fatty acids/esters, solvents, and azones have been considered they have shown irritancy potential at concentration required for effective permeation enhancement. The safest and the most effective class of permeation enhancers are Terpenes that are obtained naturally from biological sources, they are classified as generally regarded as safe (GRAS) by FDA that cause no skin toxicity or if any, only mild irritation. Though some may cause skin irritation but they did not cause lasting erythema[3]. Terpenes and terpenoids are usually the constituents of volatile oil or essential oils which are volatile in nature and are widely used therapeutically, as inhalations (e.g. eucalyptus oil), orally (e.g. peppermint oil), as mouthwashes and gargles (e.g. thymol). Also, many essential oils are used in aromatherapy nowadays. Besides these uses, terpenes exhibit excellent permeation-enhancing effects to facilitate transdermal drug delivery and can enhance the permeation of both lipophilic and hydrophilic drugs. Permeation enhancement activity of terpenes is relative to chemical structure as well as the physicochemical properties of the drug[4]. Terpenes enhance drug permeation by any of the following three mechanisms

- Disruption of the highly ordered lipid structure of stratum corneum
- Increased drug diffusivity in stratum corneum
- Increased drug partitioning into stratum corneum

Another mode of action that has been postulated is that the terpenoids open the polar pathways in the stratum corneum by increasing electrical conductivity of tissues. Ibuprofen is a propionic acid derivative and used as non-steroidal anti-inflammatory agent. It has been administered orally for the acute and long-term management of pain and inflammation. However, due to its short elimination half-life and other adverse effects, such as abdominal pain and ulceration of the gastrointestinal (GI) tract, restrict the oral use of this drug. By eliminating these side effects and improving the drug concentration at the target tissue, effective alternative is the delivery of ibuprofen by percutaneous application to treat a variety of conditions, including arthritis, ankle sprains and other soft-tissue injuries[5]. Among the NSAIDs frequently used ibuprofen (IBU) has relatively good permeability nevertheless; due to its intrinsically poor skin permeability ibuprofen (IBU) has shown difficulty to get an effective blood concentration by transdermal delivery. Therefore it is indispensable to employ permeation enhancers to increase the skin permeation rate of IBU in order to maintain an effective blood level[6] and also ibuprofen has been formulated into solid dispersion to increase its solubility.

MATERIAL AND METHODS

Ibuprofen was gifted by Sri Krishna Pharmaceuticals Ltd, Hyd., India. The terpenes namely nerolidol, farnesol, limonene, geraniol, limonene, linalool, carvone, fenchone and menthol were purchased from Alfa Aesar-A Johnson Matthey Company UK. Tween 80, potassium di hydrogen ortho phosphate and sodium hydroxide was obtained from SD Fine-Chem Pvt., Mumbai whereas Corel Pharma Chem, Ahmedabad supplied Carbopol 940.

Fourier Transform Infra-Red (FTIR) Spectroscopy

Drug and excipients compatibility was checked by FTIR study. Infrared spectrum of Ibuprofen and excipients was determined on Fourier Transform Infra-Red Spectroscopy (8400 S Shimadzu) using KBr dispersion method.

Preparation of Solid Dispersion

Accurately weighed quantities of IBU and the carrier Tween-80 in 0.25 (IBU SD_1), 0.5 (IBU SD_2) and 0.75 % (IBU SD_3) proportions were taken in petriplate and dissolved in methanol and mixed until drug and carrier are completely dissolved in the solvent and were evaporated at room temperature for 4 h. Resultant solid dispersion kept in refrigerator for 5 minutes to solidify and the solidified mass obtained in each case was scraped, crushed, pulverized and passed through an 80-mesh sieve and preserved in well-closed glass containers in desiccators at room temperature for future use.

Evaluation of Ibuprofen Solid Dispersion

Assay

Accurately weighed amounts of solid dispersions equivalent to 10 mg of drug was taken and dissolved in 20 ml methanol and the volume was made to 100 ml with buffer medium. Dispersions were filtered and diluted with buffer medium. Appropriate dilutions were made and the drug content was measured spectrophotometrically using placebo gel as blank at 222.4 nm. The percentage assay was calculated from the standard curve.

Partition coefficient

The partition coefficients between η-Octanol and water at 37ºC were determined by shake-flask method. η-Octanol and water solution was co-saturated with each other for 24 h at 37ºC before use. To the pre-equilibrated water (10 ml), known quantity of solid dispersion equivalent to 400 mg of drug was dissolved in aqueous solution. 10 ml of octanol was added to the 10 ml of aqueous solution of drug and kept for intermittent shaking for 3 h at 37ºC. Concentration of drug was determined spectrophotometrically by measuring absorbance at 222.6 nm in aqueous phase. The partition coefficient log P was calculated from the following equation[7].

$$\text{Log}\,P_{\frac{oct}{wat}} = \log\left(\frac{[solute]_{octanol}}{[solute]_{water}}\right)$$

Solubility Studies

Saturation solubility was determined by the shake-flask method. Solid dispersion in excess quantity was placed in separate glass stopper flasks containing 10 ml of distilled water. The samples were placed in an orbital shaker at 37°C and 100 rpm until equilibrium was achieved (48 h). The aliquots were filtered through Whatman No. 41 filter paper. Appropriate dilutions were made in distilled water and assayed spectrophotometrically at 222.6 nm[8].

Preparation of ibuprofen and its solid dispersion gels

An appropriate amount of carbopol 940 resin was soaked in water for 24 h. Under constant stirring to the carbopol solution appropriate amount of propylene glycol and triethanolamine were added until the gel was formed. Required quantity of ibuprofen or its optimised solid dispersion (IBU SD_1) was dissolved in methanol and added to the above mixture. The final weight of the gel was adjusted to 10 g with distilled water, to which various terpenes were incorporated in the concentration of 2.5 % and 5 %.

Evaluation of ibuprofen and its solid dispersion incorporated gel

Gels were evaluated for their clarity, pH, spreadability, viscosity, drug content, and *in-vitro, ex-vivo* diffusion studies, skin irritation and anti-inflammatory activity.

Clarity

It was determined by visual inspection under black and white background and it was graded as follows: turbid: +, clear: ++, very clear (glossy): +++.

Homogeneity

It was determined by visual inspection for the appearance of gel and presence of any aggregates.

Determination of pH

pH of formulation determined by dispersing 0.5 g of gel in 100 ml of 7.4 phosphate buffer; it was checked using digital pH meter at constant temperature.

Spreadability

The spreadability of the gel formulations were determined by measuring the spreading diameter of 1 g of the gel between 20 X 20 cm glass plates after 1 minute. The mass of the upper plate was standardized at 150 g[9]. The spreadability was calculated by using the formula.

$$S = \frac{ml}{t}$$

Where, S = spreadability, m = weight tied to the upper glass slide, l = length of the glass slide, t = time taken in seconds

Determination of viscosity

Viscosity of prepared gels was determined by Brookfield programmable viscometer LVDV-II+PRO. The spindle number 64 was rotated at 50 rpm. Samples of the gels were allowed to settle over 30 minutes at the temperature (25 ± 1^0C) before measurements were taken.

Drug Content

100 mg of gel (equivalent to 5mg of drug) was taken and dissolved in 100 ml of pH 7.4 phosphate buffer. The placebo gel 100 mg was dissolved in the same buffer solution. The volumetric flasks were kept for shaking for 15 minutes. The solution was passed through the

Whatmann filter paper no. 42 and filtered. Appropriate dilutions were made and the drug content was measured spectrophotometrically against corresponding placebo gel at 222.4 nm.

Extrudability

The extrudability test was carried out by Pfizer hardness tester. A 15 g of gel was filled in aluminium tube. The plunger was adjusted to hold the tube properly. The pressure of 1 kg/cm^2 was applied for 30 sec. The quantity of gel extruded was weighed. The procedure was repeated at three equidistance places of tube. Test was carried in triplicate.

***In vitro* diffusion studies**

Diffusion study of the pure ibuprofen gel and its solid dispersion gel was performed using Franz diffusion cell. The cell was locally fabricated and volume of receptor compartment was 25 ml. In-between the donor and receptor compartments dialysis membrane was placed. Gel formulation (500 mg) equivalent to 25 mg of pure drug and its solid dispersion were taken on the dialysis membrane and the compartment clamped together. The receptor compartment was filled with phosphate buffer saline pH 7.4 and the hydrodynamics in the receptor compartment was maintained by stirring on a magnetic stirrer at 600 rpm. At pre-determined time intervals, 1 ml of samples were withdrawn and an equal volume of buffer was replaced. The samples were analyzed after appropriate dilution for drug content spectrophotometrically.

Evaluation of Optimized IBU and its IBUSD$_1$ transdermal Gel

***Ex-Vivo* skin permeation studies**

Preparation of rat abdominal skin

The experimental protocol was approved by the institutional animal ethical committee (IAEC) (ID number: PCE/ACE-6). Male wistar rats (150–180 g) were used for permeation study. Excess amount of ether anaesthesia was used to sacrifice the animal and an animal hair clipper was used remove abdominal hair. Excised abdominal skin section was observed for cuts and wounds. The dermal fat was removed using scalpel and washed under tap water. The skin was stored at −20°C and used within a week. *Ex-vivo* permeation rate studies such as % drug release, steady state transdermal flux (SSTF), permeability coefficient, lag time and enhancement ratio for percutaneous absorption of ibuprofen and its solid dispersion using terpenes across rat skin were estimated for optimized formulations with terpenes and compared with IBU (control) IBUSD$_1$ (control), IBU$_{gel}$, IBUSD$_{1gel}$. The ANOVA for these parameters were carried out using Graph pad prism software.

Steady state flux (µg/cm^2/h)

$$\text{Steady state flux (Jss)} = \frac{dm}{S\,dt}$$

Where dM - Amount of drug permeated, S - Unit cross-section area, t –time (t)

From the above equation, it is clear that the slope of the steady state portion of the permeation curve created by plotting the cumulative amount of drug permeated in micrograms versus time in hours is the flux.

Permeability coefficient (cm/h)

$$\text{The permeability coefficient (Kp)} = \frac{JSS}{CV}$$

CV is the total donor concentration of the formulation

Enhancement ratio

Used to evaluate the effect of permeation enhancer on diffusion and permeation of selected drug molecules is calculated by;

$$ER = \frac{\text{Permeability coefficient of drug with enhancer}}{\text{Permeation coefficient of drug alone}}$$

Lag Time (h)

Lag time is the time required for the drug to get released from the reservoir. It is calculated by plotting cumulative amount of drug permeated vs time. The x-intercept value gives the lag time.

Skin irritation studies

A protocol for the study was prepared. After approval from Institutional Ethics Committee ID no. GPRCP /IAEC/11/13/3/PCE/AE-8, the study was conducted as per protocol. Skin irritation test was conducted to test the different formulations of patch upon the rabbit skin. The rabbits were divided into two groups having 6 animals each. The hair on the ventral surface was removed using a depilator. The test formulations were applied on the depilated area of the animal and kept under observation for 3 days. Symptoms of Flushing (Redness of skin), Papules, wheals and erythema, and marked oedema were observed[10].

Stability studies

The stability studies were carried out by keeping optimized formulations in glass containers with polypropylene closure for one month at room temperature. Known amount of gel was taken out at different time intervals like 0, 1st, 2nd, 4th week and was analyzed for appearance, pH, drug content and viscosity.

RESULTS AND DISCUSSION:

Characterization of ibuprofen: Ibuprofen was identified and characterized as per official compendia. The drug purity was determined by IR spectra. The drug water solubility was found to be 0.174 mg/ml. The partition coefficient of ibuprofen in n-octanol: pH 7.4 phosphate buffer was found to be 3.06. Figure 1 depicts release of IBU from IBU$_{gels}$ containing 2.5 % and 5 % of terpenes; it was observed that the drug release was increased with incorporation of terpenes as compared to control. Terpene concentration and the permeation rate have not shown any direct relationship[11]. The most outstanding penetration enhancer was geraniol (2.5 %) showing highest release rate of 3659.8 µg/cm^2/h$^{1/2}$ followed by farnesol (2.5 % and 5 %) with a release rate of 3382.6 and 3583.1 µg/cm^2/h$^{1/2}$

respectively. Alcoholic terpenes geraniol (2.5 %) and farnesol (2.5 % and 5 %) was selected as an optimized formulation. They have shown significant increase in release rate of IBU compared with formulations, which showed minimal increase in the drug release rate. Figure 2 depicts the diffusion of $IBUSD_1$ from $IBUSD_{1gel}$ with terpenes which was well described by the Higuchi model, where the rate controlling step is the process of diffusion through the gel matrix. From Figure 2 of terpenes 5 % it can be stated that monoterpenes (alcohols > hydrocarbons > ketones) showed highest release rate than sesquiterpenes (alcohols). Geraniol (2.5 % and 5 %) and limonene (2.5 %) were selected as optimized formulation as geraniol (2.5 % and 5 %) showed highest release rate of 3659.8 and 3527.2 $\mu g/cm^2/h^{1/2}$ followed by limonene (2.5 %) with a release rate of 2262.4 $\mu g/cm^2/h^{1/2}$. Figure 3 depicts the relation between boiling point and permeation parameters of IBU and its $IBUSD_1$ from gel formulations. In particular previous report indicated that since they are volatile compound, boiling point of terpenes play an important role in enhancement of permeability of drugs. Farnesol (5 %) with boiling point of 111^0C boils at approximately 119^0C less than that of geraniol 230^0C showed increase in the IBU flux by 6.2 folds followed by geraniol (2.5 %) showing enhancement about 5.2 fold. Further low boiling point of farnesol 111^0C is an indication of weak cohesiveness or self-association of farnesol molecules, and therefore farnesol would interact with lipid components of the stratum corneum more easily, and thereby alter the barrier property. The same was observed with $IBUSD_1$ gel with limonene with boiling point 176 ^{o}C and geraniol with 230 ^{o}C. Limonene enhanced $IBUSD_1$ flux by 2.7 folds followed by geraniol (5 %) showing enhancement of 2.1 folds. Additional energy is required to free the respective functional group from geraniol resulting in strong self-association, as reflected by higher boiling point[12]. Figure 4 depicts relation between effect of lipophilicity of terpenes with percutaneous parameters of IBU and its $IBUSD_1$ from gel formulations. Farnesol with (log P 5.31) and geraniol with (log P 3.18) with decreasing order of lipophilicity, showed decrease in the permeated amount and flux of IBU. Similar results were observed with $IBUSD_1$ gel with limonene (log P 4.58) and geraniol (Log P 3.18) showing linear relationship between permeation and lipophilicity proving influence of lipophilicity on permeation[4]. *In vitro* diffusion studies of terpenes incorporated IBU_{gel} showed increased release rate with farnesol (2.5 and 5 %) and geraniol (2.5 %). Similarly limonene (2.5 %), geraniol (2.5 and 5 %) increased the release rate of $IBUSD_1$. *Ex vivo* studies revealed that flux of IBU and $IBUSD_1$ increased by 6.2 and 2.7 folds with farnesol (5 %) and Limonene (2.5 %) respectively. IBU_{gel} with farnesol having log P 5.31 and B.P 111^oC and geraniol having log P 3.18 and B.P 230^oC showed linear relationship of increase in permeation with increase in lipophilicity and decrease in permeation with increase in boiling point. The same was observed with $IBUSD_{gel}$ with limonene (log P 4.58 and176^oC) and geraniol (log P 3.18 and 230^oC). From the previous studies it was found that the release of lamotrigine was increased with increase in the boiling point of terpenes[13]. Terpenes possessing the properties of high lipophilicity, small size, low boiling point and low energy of vaporization are known as good sorption enhancers[4]. Farnesol possessing higher log P values with low boiling point compared to geraniol enhanced maximum permeation of IBU. Nerolidol and farnesol possessing higher log P values than the others have known to increase the permeation of alfasozin hydrochloride[14]. In general, absorption of hydrophilic drugs is known to be enhanced by terpenes with polar functional groups, whereas hydrocarbon terpenes are more active towards lipophilic drugs. Conversely, our results had shown that limonene a hydrocarbon terpene, was more effective in promoting the percutaneous permeation of $IBUSD_1$ (log P 2) from the gels, when compared with polar terpene such geraniol. It was reported that limonene was effective in enhancing the transport of hydrophilic molecule sumatriptan succinate[15] (log P 1.17) and oestradiol is not a very highly lipophilic drug (log P 2.29)[16]. The highest skin penetration of $IBUSD_1$ by limonene may be attributed to its lipophilic characteristics, low boiling point and ability to increase drug diffusivity by disrupting the normal packing of the skin. Farnesol share two important structural features i.e. presence of alcoholic group that is capable of hydrogen bonding and highly lipophilic with log P value 5.31 having a boiling point of 111^oC. These might be the reason behind the higher enhancement activity of farnesol compared to geraniol with log P of 3.18 and having high boiling point of 230^oC[17]. Farnesol showed concentration dependent action on IBU permeation across rat skin. Present results suggest that farnesol (5 %) a sesquiterpene is effective in skin penetration of IBU compared to geraniol a monoterpene. It was reported that sesquiterpenes (farnesol, nerolidol) were found to be more potent enhancers than monoterpenes (carvone, limonene oxide) for diclofenac sodium[11]. Therefore, we could find the clear structure-activity relationship of terpene and its effect on skin permeation. Limonene (2.5 %) a hydrocarbon terpene showed highest enhancement in the flux and permeability coefficient compared to polar terpene geraniol (2.5 % and 5 %). Enhancement activity of limonene is by increasing drug diffusivity by disrupting the normal packing of the skin[18]. Results were consistent with A.C. Williams and B. W. Barry where limonene was effective accelerants providing 4 fold increases in permeability coefficient of aqueous oestradiol (log P 2.29) compared to alcohols, ketones and epoxides[16]. Table 2 depicts one way ANOVA of IBU (control), IBU_{gel}, $IBU_{G2.5}$, $IBU_{F2.5}$ and IBU_{F5} formulations which suggesting that there was significant difference in flux ($P < 0.0001$), when compared with control and within the formulations. Permeability coefficient of IBU_{gel}, $IBU_{G2.5}$, $IBU_{F2.5}$ and $IBUF_5$ resulted in significantly higher than control ($P < 0.0001$). Significant difference ($P < 0.0001$) was observed when permeability coefficient was considered between IBU_{gel}, $IBU_{G2.5}$, IBU_{F5}, $IBU_{F2.5}$ formulations. Significant difference ($P < 0.001$) was observed when permeability coefficient was considered between IBU_{1gel}, $IBU_{F2.5}$ and $IBU_{G2.5}$ IBU_{F5}. The lag time of formulations with IBU_{gel}, $IBU_{G2.5}$, $IBU_{F2.5}$ and IBU_{F5} is significantly ($p < 0.0001$) greater than control and within the formulations, whereas lag time of $IBU_{F2.5}$ is

significantly ($p < 0.005$) greater than IBU_{F5}. Table 3 depicts one way ANOVA of formulations $IBUSD_1$ (control), $IBUSD_{1gel}$, $IBUSD_{1G2.5}$, $IBUSD_{1G5}$ and $IBUSD_{1L2.5}$ suggesting that there was significant difference ($P < 0.0001$) in flux, permeability coefficient and lag time of formulations when compared with control and within the formulations. No significant difference was observed for lag time within the formulations ($P > 0.05$).

The *ex-vivo* drug release kinetics profile of optimized formulations was shown in Table 4; from r^2 values it was found that drug release followed first order. The drug release from the system was diffusion limited as it obeys Higuchi model equation, from the 'n' value of Korsemeyer Peppa's equation release mechanism was found to be Non Fickian diffusion.

Table 1: Evaluation of optimised Ibuprofen and its solid dispersion gels with various terpenes

Formula code	Drug content ± SD	pH ± SD	Spreadability (g.cm/sec) ± SD	Extru-dability	Homo-geneity	Viscosity (cps) ± SD	Flux J (µg/cm²/h²)	ER_{flux}	Permeability coefficient (cm/h)	Lag time
IBU_{gel}	97.8 ± 1.98	6.6 ± 0.15	8.2 ± 0.05	+ + +	++	49360 ± 0.05	382.0 ± 1.85	3.9	4.58 ± 1.22	0.4 ± 1.33
$IBUSD_{1\ gel}$	98.7 ± 2.21	6.2 ± 0.21	8.4 ± 0.12	+ + +	++	48410 ± 0.01	418.0 ± 2.22	1.5	5.01 ± 1.68	0.3 ± 1.25
$IBU_{F\ 2.5}$	97.1 ± 1.74	7.2 ± 0.11	8.7 ± 0.04	+ + +	++	47800 ± 0.03	452.6 ± 2.08	4.6	5.43 ± 2.02	0.21 ± 1.44
$IBU_{F\ 5}$	99.6 ± 2.11	7.4 ± 0.05	8.9 ± 0.15	+ + +	++	46550 ± 0.05	605.6 ± 1.22	6.2	7.27 ± 1.28	0.12 ± 1.45
$IBU_{G\ 2.5}$	98.1 ± 1.64	7.1 ± 0.17	9.1 ± 0.21	+ + +	++	47800 ± 0.02	505.8 ± 1.89	5.2	6.07 ± 1.76	0.16 ± 1.63
$IBUSD_{1\ G2.5}$	99.2 ± 2.09	7.2 ± 0.12	8.3 ± 0.11	+ + +	++	46250 ± 0.02	497.7 ± 2.56	1.8	5.97 ± 2.54	0.18 ± 2.09
$IBUSD_{1\ G5}$	98.1 ± 1.11	7.0 ± 0.15	9.3 ± 0.20	+ + +	++	47120 ± 0.05	585.9 ± 1.45	2.1	7.03 ± 1.89	0.15 ± 1.55
$IBUSD_{1\ Li2.5}$	99.2 ± 1.89	7 ± 0.12	8.5 ± 0.12	+ + +	++	43340 ± 0.03	738.6 ±1.68	2.7	8.86 ± 1.69	0.08 ± 1.22

Note: +++ very good, ++ good, + ok, IBU_{gel}-Plain ibuprofen gel without terpenes; IBUF2.5-gel containing 2.5 % of farnesol, IBU_{F5}-gel containing 5 % of farnesol. $IBU_{G2.5}$- gelcontaining 2.5 % of geraniol. $IBUSD_1$- Plain ibuprofen solid dispersion gel without terpenes; $IBUSD_{1Li2.5}$-gel containing 2.5 % of limonene, $IBUSD_{1G2.5}$-gelcontaining 2.5 % of geraniol, $IBUSD_{1G5}$-gel containing 5 % of geraniol. Values are expressed as Mean ± SD, n = 3

Table 2: Comparison of skin permeation parameters of IBU IBU_{gel}, $IBU_{G2.5}$, $IBU_{F2.5}$ and IBU_{F5} using one way ANOVA (Tukey's multiple comparison test)

Formulation code	SSTF	Permeability coefficient	Lag time
IBU vs IBU_{gel}	***	***	***
IBU vs $IBU_{G2.5}$	***	***	***
IBU vs $IBU_{F2.5}$	***	***	***
IBUvs IBU_{F5}	***	***	***
Comparison of permeation parameters within the formulations			
Formulation code	**SSTF**	**Permeability coefficient**	**Lag time**
IBU_{gel} vs $IBU_{G2.5}$	***	***	***
IBU_{gel} vs $IBU_{F2.5}$	***	**	***
IBU_{gel} vs IBU_{F5}	***	***	***
$IBU_{G2.5}$ vs $IBU_{F2.5}$	***	*	**
$IBU_{G2.5}$ vs IBU_{F5}	***	**	*
$IBU_{F2.5}$ vs IBU_{F5}	***	***	***
F value	32418	8157	3834

Note: (n = 3); One way ANOVA (Tukey's multiple comparison test); ***($P < 0.0001$);**($P < 0.001$); *($P < 0.005$); ns-Non-significant ($P > 0.05$)

Table 3: Comparison of skin permeation parameters of $IBUSD_1$, $IBUSD_{1gel}$, $IBUSD_{1Li2.5}$, $IBUSD_{1G2.5}$, $IBUSD_{1G5}$ using one way ANOVA (Tukey's multiple comparison test)

Formulation code	SSTF	Permeability coefficient	Lag time
$IBUSD_1$ vs $IBUSD_{1\ gel}$	***	***	***
$IBUSD_1$ vs IBU $SD_{1Li.5}$	***	***	***
$IBUSD_1$ vs $IBUSD_{1G2.5}$	***	***	***
$IBUSD_1$vs $IBUSD_{1G5}$	***	***	***
Comparison of permeation parameters within the formulations			
Formulation code	**SSTF**	**Permeability coefficient**	**Lag time**
$IBUSD_{1gel}$ vs $IBUSD_{1Li2.5}$	***	***	**Ns**
$IBUSD_{1gel}$ vs $IBUSD_{1G2.5}$	***	***	**Ns**
$IBUSD_{1gel}$ vs $IBUSD_{1G5}$	***	***	**Ns**
$IBUSD_{1Li2.5}$vs $IBUSD_{1G2.5}$	***	***	**Ns**
$IBUSD_{1Li2.5}$vs $IBUSD_{1G5}$	***	***	**Ns**
$IBUSD_{1G2.5}$vs $IBUSD_{1G5}$	***	***	**Ns**
F value	28464	8157	71.63

Note: (n = 3); One way ANOVA (Tukey's multiple comparison test); ***($P < 0.001$);**($P < 0.01$); *($P < 0.005$); ns-Non-significant ($P > 0.05$)

Table 4: *Ex-vivo* drug release kinetics of optimized formulation

Formulation code	Zero order	First order	Higuchi	Peppa's		Release mechanism
	r^2	r^2	r^2	r^2	n	
IBU_{gel}	0.778	0.928	0.993	0.945	0.985	Non-Fickian diffusion
$IBUSD_{1gel}$	0.896	0.916	0.982	0.954	0.688	Non-Fickian diffusion
$IBU_{F2.5}$	0.826	0.908	0.978	0.963	0.626	Non-Fickian diffusion
$IBUSD_{1Li2.5}$	0.830	0.912	0.982	0.922	0.830	Non-Fickian diffusion

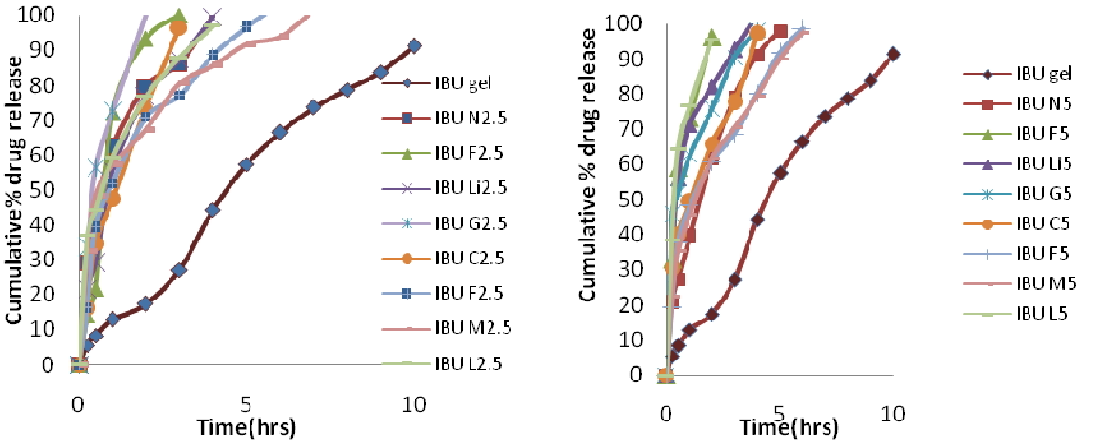

Figure 1: Release profiles of IBU_{gel} containing 2.5 % and 5 % terpenes

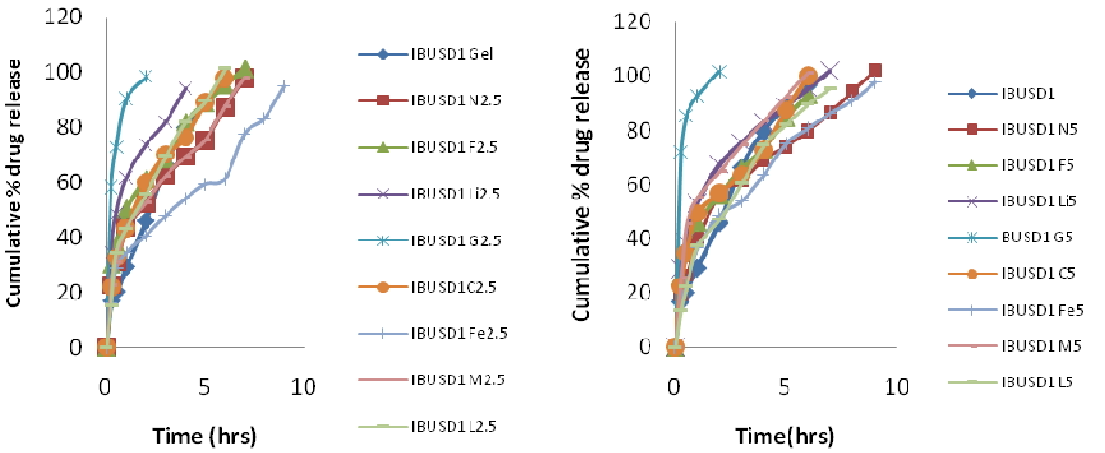

Figure 2: Release profiles of solid dispersion ibuprofen gel containing 2.5 % and 5 % terpenes

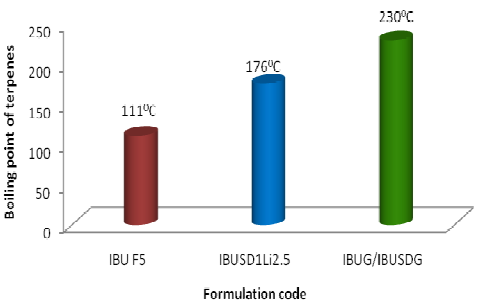

Figure 3: Boiling point of optimized formulations with terpenes

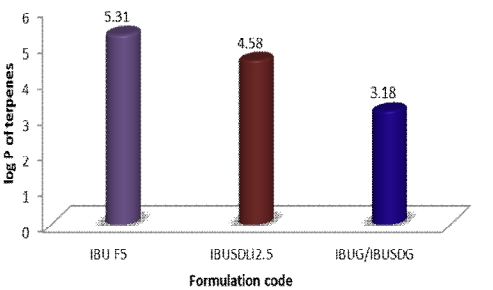

Figure 4: Relationship between log P of terpenes and skin permeation parameters

Skin irritation studies

Control placebo and formulations IBU_{F5}, $IBUSD_{1Li2.5}$ was devoid of any irritation potential and no edema was observed in any case. Irritation score for IBU_{F5}, $IBUSD_{1Li2.5}$ gels was zero, which indicated its safety and acceptability for topical administration.

Stability studies

The optimized formulations were stability tested by conducting stability studies for one month at room temperature on optimized formulations. The formulations were found to stable, with insignificant change in the appearance, drug content, viscosity and pH.

CONCLUSION

An attempt has been made to study effect of various terpenes (nerolidol, farnesol, limonene, linalool, menthol, geraniol, carvone, fenchone etc.) in various combinations of preparations on the percutaneous permeation of ibuprofen and its solid dispersions from carbopol 940 gel formulation. *Ex vivo* studies revealed that flux of IBU and $IBUSD_1$ increased by 6.2 and 2.7 folds with farnesol (5 %) and Limonene (2.5 %) respectively. IBU_{gel} with farnesol having log P 5.31 and B.P 111°C and geraniol having log P 3.18 and B.P 230°C showed linear relationship of increase in permeation with increase in lipophilicity and decrease in permeation with increase in boiling point. The same was observed with $IBUSD_{gel}$ with limonene (log P 4.58 and176^{o}C) and geraniol (log P 3.18 and 230°C). The results suggested that terpenes are effective natural percutaneous permeation enhancers for class II drugs like ibuprofen.

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