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Effect of essential oils as penetration enhancers for ibuprofen loaded transdermal gel formulations

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Abstract

The aim of the present study was to evaluate essential oils as penetration enhancers for transdermal gels using Ibuprofen as a model drug. Ibuprofen was formulated as a 5% carbopol gel. The amount of co-solvent (ethanol and propylene glycol) was optimized so as to obtain a homogenous gel. The prepared gels were evaluated for pH, spreading and homogeneity. Gel containing 5% drug, 0:15 proportion of ethanol: water and 1.5% carbopol was selected as base gel. The penetration of the gel was studied through cellulose membrane, egg shell membrane and rat skin. The gels containing different penetration enhancers were compared using various parameters like transdermal flux, permeability coefficient, and enhancement ratio and lag time. Anise oil was selected as the optimized essential oil for the gel formulations. The gel prepared using anise oil was studied for drug release kinetics and occlusivity. The gel was further studied for skin irritation in rat i.e. the formation of erythema and edema and compared with placebo gel and marketed formulation. The anise oil containing gel can be used to deliver therapeutically relevant doses of ibuprofen-like drugs.

Keywords: Essential oil, penetration enhancer, transdermal, gel, ibuprofen, ex vivo

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Introduction

Conventional systems of medication that require multi dose therapy are having many problems. The controlled drug delivery is a newer approach is to deliver drug in to systemic circulation at a1 predetermined rate. Our system should duplicate continuous intravenous infusion, which not only by passes hepatic 'first pass' elimination but also maintains a constant, prolonged and therapeutically effective drug level in the body. This is made possible by using intact skin as a port of drug administration to provide continuous delivery of drug in to systemic circulation. Following skin permeation, the drugs first reach the systemic circulation. The drug molecules are then transported to the target site, which could be relatively remote from the site of administration, to produce therapeutic action. Hence transdermal route is the most suitable route for drug administration that has shorter biological half-life (Gupta et al, 2021).The drug absorption across the skin layers varies for different drugs. Penetration enhancers are used for the drug permeation enhancement across skin mucosa. Penetration enhancer is also called as absorption promoter or absorption enhancers because it promotes the drug or penetrant absorption across the skin (Chandrashekhar and Shobha, 2008). Different classes of penetration enhancers including alcohols and polyols (ethanol, propylene glycol), surfactants (Tween, Span, SLS), fatty acids (Oleic acid), amines and amides (Azone, N-methyl pyrrolidone), terpenes (limonene) sulfoxides (dimethylsufoxide), esters (isopropyl myristate) have been used over decades. Essential oils like eucalyptus oil, anise oil, turpentine oil, peppermint oil, etc have been recently studied for their penetration enhancing effects in gels prepared for transdermal use for several drugs (Herman and Herman, 2015).

Inflammation of the skeletal muscles occurs in various conditions including arthritis and gout (Singh and Mishra, 2020). Nevertheless, these conditions are treated using systemic administration of the drug using oral route, much of these conditions require topical application of the drugs for immediate relief. Ibuprofen is a widely used drug in management of the inflammatory conditions. The aim of the present study was to evaluate essential oils as penetration enhancers for transdermal gels using Ibuprofen as a model drug.

Material and Methods

Ibuprofen was obtained as gift sample from Biocare remedies private limited (Gandhinagar, India), Carbopol 974P was obtained from Corel pharma chem (Ahmedabad India), HPMC, triethanolamine, ethanol and penetration enhancers were procured from CDH, New Delhi and used as obtained.

Determination of Ibuprofen in 6.8 pH Buffer

Stock solution was prepared by dissolving 10 mg of Ibuprofen in Buffer (pH6.8) and made make volume up to 100 ml by same solvent. This give the concentration of 100mcg/ml (stock solution). Solution was scanned for absorbance between 200-400nm using UV spectrophotometer (Shimadzu UV

-1800). Ibuprofen showed UV absorption maximum at 221nm.

Ibuprofen 100mg was weighed accurately and dissolved in 100 ml of phosphate buffer (pH 6.8), take 1ml from this solution and it was further diluted to 10 ml of pH 6.8 phosphate buffer to obtain solution of 100µg/ml, which was used as stock solution. From this stock solution take 0.5,1.0,1.5,2.0,2.5.3.03.5,4.0, and 4.5 ml solution were pipetted out in to 10 ml volumetric flask and the volume was made up to the mark with phosphate buffer pH 6.8 to get different concentrations (mcg/ml): 5, 10, 15, 20,25,30,35,40, and 4.5µg/ml absorbance's were taken at the wavelength of 221 nm. The standard curve was obtained by plotting absorbance vs. concentration in µg/ml.

Various concentration of ethanol and propylene glycol were used to formulate gels and based on preliminary studies concentration of ethanol and propylene glycol was fixed (Kushwaha et al, 2018); Abdul Rasool et al, 2010).

For preparation of gel, a specific amount of carbopol 974p (Table 1) was soaked in water overnight. Separately 5% drug was mixed in to the propylene glycol and stirred. 15 min for clear solution of drug. The drug solution was mixed with the polymer solution with continuous stirring at 250-300 rpm. 5% penetration enhancer was added to this solution and the solution was neutralized using triethanolamine to pH 6.8-7.2 in order to obtain the gel. The gel was then allowed to equilibrate for 24 h at room temperature.

Formulation of Gel

Table 1 Composition of the gel formulations

Formulation Code	PE	Ibuprofen	Carbopol 974P	Pluronic	HPMC	PG	Ethanol	TEA	Water
F1	-	5	0.75	-	-	10	1.0	1.5	qs
F2	Oleic acid	5	0.75	-	-	10	2.0	1.5	qs
F3	Capsaicin	5	0.75	-	-	10	3.0	1.0	qs
F4	Clove oil	5	0.75	-	-	10	4.0	1.5	qs
F5	Menthol	5	1.5	-	-	15	-	1.5	qs
F6	Anise oil	5	1.5	-	-	15	-	1.5	qs
F7	Cinnamon Oil	5	1.5	-	-	15	-	1.5	qs
F8	Eucalyptus Oil	5	1.5	-	-	15	-	1.5	qs
F9	Peppermint Oil	5	1.5	-	-	15	-	1.0	qs
F10	Turpentine Oil	5	1.5	-	-	15	-	1.4	qs
F11	Anise oil	5	-	20	-	15	-	1.0	qs
F12	Anise oil	5	-	-	2	15	-	1.0	qs
F13	DMSO	5	-	-	-	-	-	1.5	qs

Concentration of all PE in gel formulation is 5%

Evaluation of ibuprofentransdermal gel

All developed gel formulae were inspected for their homogeneity, consistency, spreadability test, color; presence of lumps by visual inspection after the gels have been set in the container (Kashyap et al, 2020).

pH determination

The pH of the gels was determined using digital pH meter. A specific quantity of developed gel was taken and dissolved in 100ml of phosphate buffer of pH 6.8. The beaker containing gel solution was mix on magnetic stirrer in order to get complete solubility of drug.). this dispersion was used to determine pH.

Determination of Spreadability

Spreading coefficient was measured by wooden block method. It consists of a wooden block, which is attached to a pulley at one end. Spreading coefficient was measured on the basis of slip and drag characteristics of gel. A lower glass slide was fixed on the wooden block.1 gm of gel was applied on the lower glass slide. The gel preparation was then sandwich between upper and lower slide. Another glass slide having the dimension of fixed ground slide and provided with the hook. A 1 Kg weight was placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the gel between the slides. Excess of the gel was scrapped off from the edges. The top plate was then subjected to pull of 80 gm. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted to calculate the spreading coefficient.

Viscosity

The viscosity of the different gel formulae was determined at 25°C using rotational Brookfield viscometer of cone and plate structure with spindle CPE-41 and CP-5221. The apparent viscosity was determined at shear rate 40 sec^{-1}.

Drug content and uniformity

A specific quantity of developed gel was taken and dissolved in 100ml of phosphate buffer of pH 6.8. The volumetric flask containing gel solution was shaken for 2hr on mechanical shaker in order to get complete solubility of drug. This solution was filtered using Millipore filter (0.45µm). After suitable dilution drug absorbance was recorded by using UV- visible spectrophotometer.

In-vitro Drug Diffusion Study

Release of Ibuprofen from various formulations was studies using a Franz diffusion cell (Syed et al, 2020). A standard cellulose membrane (soaked in pH 6.8 for two hours before use). One gram of gel was applied on the cellulose membrane and fix between receptor compartment and donor compartment. The receptor compartment was filled with 6.8 pH buffer. The cell was immersed to a depth of 1 cm below the surface of phosphate buffer in the receptor compartment and was agitated using a magnetic stirrer and a temperature of 37°C ± 0.5°C was maintained.

Sample (1 ml) of the receptor compartment was taken at various interval of time (60, 120, 180, 240, 300, 360 minutes) over a period of 6 hours and assayed for Ibuprofen at 221 nm. The volume withdrawn at each time was replaced with drug free phosphate buffer. Withdrawn amount of sample was suitably diluted with fresh medium and Ibuprofen released at various intervals of time was calculated and plotted against time.

Drug release kinetic study

The data obtained from the in vitro release experiments were analyzed using linear regression method according to the following equations:

Zero – order equation: Q = kot

Where Q is the amount of drug released at time t, and ko is the zero- order release rate.

First – order equation: In (100 – Q) = in 100 – k1t

Where Q is the percent of drug release at time t, and k1 is the first – order release rate constant.

Higuchi's equation: $Q = k\, t^{1/2}$

Where Q is the percent of drug release at time t, and k is the diffusion rate constant.

Ex vivo permeation studies

Rat skin was used because it is more similar to human skin than other skin type. Wister male albino rat (average age 12-15 weeks old and weight 150-200gm) was excised from the abdominal region and was used. The hair of the abdominal region was shaved using an electric clip then rats were scarified by using cervical dislocation technique and by using ether. The abdominal skin was surgically removed and adhering subcutaneous fat was carefully cleaned and wash thoroughly with phosphate buffer pH 6.8. The procedure was carried out under approval of CPCSEA/institutional animal ethics committee (IAEC).

Ex vivo studies were performed by using Franz diffusion cell through excised hairless abdominal rat skin. The receptor compartment of the diffusion cells was filled with 23 ml of pH buffer. The epidermis was mounted onto Franz diffusion cell in such a way that the dermis side was in constant contact with receptor solution. The receptor compartment was filled with phosphate buffer (pH 6.8). The stratum corneum was facing the donor compartment which contained the gel formulation, and the hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead. 1 ml of sample was withdrawn at pre-determined time intervals (60, 120, 180, 240, 300, 360 minutes) from the receptor compartment and an equal volume of buffer was replaced. The samples were analyzed after appropriate dilution for drug content spectrophotometrically at 221 nm. The rate of skin permeation by the drug was measured as the flux, which was calculated from the slope of the linear part of each permeation profile.

Results and Discussion

The absorption maxima of ibuprofen in phosphate buffer pH 6.8 was found to be 221 nm and it was used for all the further studies. The drug was found to exhibit linearity in the concentration range of 0.5-4.5 µg/ml show and obeyed beer's law. The equation of the regression line of the calibration curve was found to be Absorbance = (0.156 X concentration) + 0.0257 with R^2 value of 0.9819.

Selection of polymer and cosolvents concentration

The optimization of the Carbopol as well as cosolvent concentration was performed by preparing gel with varying concentrations and the results in reported in table 2 and 3.

Table2Physical Evaluation of Carbopol 974P as Gelling Agent with Different Concentrations

Batch	Concentration of Carbopol	Physical Appearance of gel
A	0.25%	No gelling consistency
B	0.5%	Less thick
C	0.75%	Less thick
D	1.0%	Gelling consistency
E	1.5%	Gelling consistency

Drug is poorly soluble in water therefore ethanol was used as co-solvent for solubility, but ethanol has character to evaporate and when ethanol evaporated the drug from the formulation precipitated out. Propylene glycol was also used as co-solvent for solubilizing the drug. The use of propylene glycol without ethanol gives gelling consistency.

Table 3 Physical appearance of gel using varying proportions of ethanol: Propylene glycol

S.No	Ethanol: propylene glycol	Physical appearance
1	2:10	Drug precipitated out
2	3:10	Drug precipitated out
3	4:10	Drug precipitated out
4	0:15	Drug did not precipitate out

Evaluation of Transdermal Gel

The results of the physical evaluation of the gel formulations, pH and spreadability are presented in table 4.

All the batches from ibuprofen gel were homogenous and all batches of ibuprofen is opaque except F11 because of difference in penetration enhancers and polymers. F1 and F2 exhibit transparent. All the batches show varying consistency due to difference in the concentration of polymers and different types of penetration enhancers. F6 and F5 exhibited excellent consistency, F1, F4 and F5 exhibit good consistency. F2, F3, F7, F8, F10, F12 showed moderate consistency. The pH values obtained were within limits of 6.8-7.2 complying the biological pH range of 4.5-7.5 according to USP. Spreading coefficient plays an important role in the patient's assessment of a topical product. The consistency for preparation

helps to ensure that a suitable dose is applied to the skin. Ibuprofen batch (F6 containing anise oil) provided good consistency and spreading coefficient as it required to minimum time to complete the distance of 7.5cm along with minimum weight placed in pan. Formulations F2, F3, F7 and F13 had poor consistency and spreading coefficient.

Table 4 Evaluation of gel formulations

Formulation Code	Physical Appearance	Homogeneity	Gel consistency	pH	Spreading coefficient
F1	Opaque	Homogenous	+++	6.9	14.75
F2	Transparent	Homogenous	++	7.0	14.32
F3	Opaque	Homogenous	++	7.12	13.9
F4	Opaque	Homogenous	+++	7.2	15.15
F5	Opaque	Homogenous	++++	7.0	15.08
F6	Opaque	Homogenous	++	7.1	15.64
F7	Opaque	Homogenous	++++	6.98	13.91
F8	Opaque	Homogenous	++	7.2	15.69
F9	Opaque	Homogenous	+++	6.8	15.25
F10	Opaque	Homogenous	++	7.0	14.56
F11	Transparent	Homogenous	++	6.9	13.51
F12	Opaque	Homogenous	++	6.99	14.94
F13	Opaque	Homogenous	+++	6.8	13.11

(++) moderate, (+++) good, (++++) excellent

Drug diffusion studies

The results of the in vitro permeation studies indicate that the formulation containing anise oil as the permeation enhancer (F6) exhibited the highest permeation efficiency of all the essential oils (Figure 1), releasing about 80% ibuprofen after 6h.

The ex vivo permeation study performed on excised rat skin affirmed the results of the in vitro studies by releasing 80% of ibuprofen across the rat skin after 6 h of the study. Thus anise oil was found to be the most effective permeation enhancer for formulating the transdermal gel.

The drug permeation of batch F7 was fitted to various kinetic models to identify the mechanism that best explains the permeation. It was fitted to zero order, first order, Higuchi and Korsmeyer and Pappas model (Table 5). The F-value for Korsmeyer and Peppas model is least and R square value is

closest to 1. Hence Korsmeyer and Peppas model was selected to explain the permeation kinetics. The value of diffusional exponent was 0.67 in Korsmeyer and Peppas model and therefore the release mechanism can be considered as anomalous diffusion.

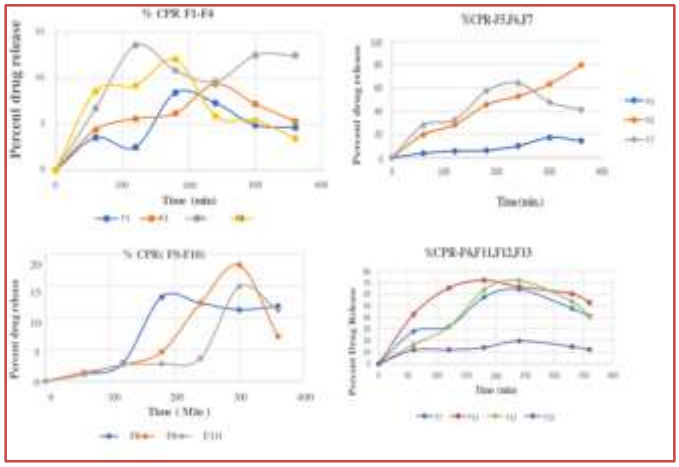

Figure 1 In vitro drug permeation across the dialysis membrane by different gel formulations

Table 5 Correlation coefficient (r) value for drug release kinetic of F6

	Zero order	First order	Higuchi	Korsmeyer and Peppas
F value	30.30	3.593248	16.08688	0.373942
R square	0.9712	0.994398	0.984687	0.999617

Conclusion

The present work was focused on developing a transdermal gel formulation of Ibuprofen containing different types of penetration enhancers to increase he permeability of drugs for symptomatic relief of rheumatoid arthritis. The results of the ex vivo studies confirm that the anise oil as permeation enhancer helped in the penetration of ibuprofen in to the rat skin quickly and thereby helped in release of the drug.

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