International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 591-599 www.ijprajournal.com ISSN: 2456-4494

Studies on effect of olive oil and clove oil as penetration enhancer for Hydroxy propyl methyl cellulose-Ethyl cellulose based transdermal patch

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Submitted: 10-07-2022 Accepted: 21-07-2022

ABSTRACT: The tough outermost lipid rich stratum corneum renders the skin impermeable to most of drugs that is considered as one of the challenges in development of transdermal patches.The aim of this work was to study effect of addition of natural penetration enhancers, clove oil and olive oil at two concentrations on permeation profile of model drug, paracetamol from hydroxy propyl methyl cellulose (HPMC) K4M- ethyl cellulose (EC) based transdermal patches.In this study, paracetamol (7.5% w/w) loaded transdermal patches were prepared using HPMC K4M and EC at varying ratios and concentrations of clove oil and olive oil as penetration enhancer (5% and 10% w/w)by solvent evaporation technique. Physico-mechanical and biopharmaceutical characterization tests such as weight variation, thickness, tensile strength, percentage moisture loss, percentage moisture absorption, folding endurance, flatness and in vitro skin permeation studies were carried out.From HPMC: EC (1:3) based patch, 46.23% paracetamol permeated in 10 h in absence of any penetration enhancer. Incorporation of 10% w/w of olive oil as penetration enhancer resulted in a significant increase in cumulative percentage permeation to 77.80% drug, as compared to clove oil. Clove oil or olive oil may act as penetration enhancer in concentration-dependent manner and F7 patch containing HPMC-EC at 1:3 ratio and olive oil at an optimized concentration (10% w/w) exhibited significant enhancement in drug permeation profile as compared to other patches which might be due to the esterification reaction between ethyl cellulose and free hydroxyl groups of oleic acid present in olive oil.

KEYWORDS: Clove oil, Ethylcellulose, Hydroxypropyl methyl cellulose, Olive oil, Penetration enhancer, Transdermal patch.

I.INTRODUCTION

Transdermal patches are rate-controlled drug delivery systems designed to deliver therapeutically optimum amount of drug into systemic circulation across the stratum corneum at a predetermined time and controlled rate. Transdermal patches offer several advantages which include avoidance of hepatic first pass metabolism, direct access to systemic circulation, maintenance of drug in blood at constant levels for prolonged duration which in turn can reduce the frequency and number of doses to be administered. Moreover, drug delivery across skin also lowers the incidences of gastro-intestinal side effects, increases patient compliance providing greater advantage in patients who are nauseated or unconscious. Relatively larger surface area of skin provides better absorption of drug into systemic circulation. [1-3]. A transdermal patch consists of backing layer, adhesive, drug, polymer, solvents, penetration enhancer and plasticizer. A wide range of polymers of natural, synthetic or semi-synthetic origin have been used for the fabrication of transdermal patches. Examples include xanthan gum, sodium alginate, chitosan, polyvinyl alcohol, polyvinylchloride, polyethylene, hydroxy propyl methyl cellulose (HPMC), ethyl cellulose (EC). [4-6]. Drug is entrapped/encapsulated inside a polymer/polymer blend, which controls the rate of release of drug from matrix type transdermal patches.

One of the major challenges of this route is difficulty in permeation of drug through the skin.

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Volume 7, Issue 4 July-Aug 2022, pp: 591-599 www.ijprajournal.com ISSN: 2456-4494

The skin, in particular, stratum corneum provides restricted entry to extraneous substances rendering drug penetration as the rate limiting step in percutaneous absorption. So, various Penetration Enhancers (PE) have been employed to promote the percutaneous absorption of a number of drugs. [7-10]. These materials should be non-toxic, non-irritating, pharmacologically inert, non-allergenic and compatible with drug and other excipients. Natural PE have advantages as compared to the synthetic PE in terms of lower irritating potential, sustainable mass production, easy availability and affordability. Examples of such natural penetration enhancers include clove oil, olive oil, peppermint oil etc. Clove oil is a volatile oil obtained from Eugenia caryophyllata, containing eugenol (82%) which is primarily responsible for enhancement of drug penetration across the skin. [11].Olive oil is fixed oil obtained from olives, the fruits of Olea europaea of family Oleaceae. Olive oil contains oleic acid and other unsaturated fatty acids. [12-19]. According to lipid-protein partition theory, these fatty acids containing C-18 carbon chains and one double bond in its structure are capable of forming links with stratum corneum thereby disrupting the intercellular lipid bilayer.

The objective of this study was to assess the extent of change in cumulative percentage of paracetamol permeated across skin from HPMC-EC patches with the increase in concentration of clove oil and olive oil as natural penetration enhancers, and to select the most suitable one and its optimized concentration.No previous work attempted to employ clove oil and olive oil as natural PE in facilitating drug permeation from hydroxy propyl methyl cellulose K4M- ethyl cellulosebased matrix type of transdermal patch.

II. EXPERIMENTATION

Materials and methods

Paracetamol was obtained from Balaji Drugs Private Ltd. New Delhi India. HPMC K4M was obtained from Samsung Fine Chemicals Ltd. South Korea. Ethyl cellulose (EC) was obtained from Loba Chemie Pvt. Ltd. Mumbai (India). Ethanol was obtained from Changshu Hongsheng Fine Chemical Co. Ltd. China. Buffer salts such as disodium hydrogen phosphate and potassium dihydrogen phosphate were procured from SDFineChemicalLtd,Bangalore. Double distilled water was used in all the experiments.

Preparationofdrug-loadedtransdermalfilms

[12-19]. Transdermal patches were prepared by solvent casting technique. At first, drug-free patches at HPMC: EC ratios of 1:1, 1:2, 1:3, 2:1 and 3:1, were prepared to check for the feasibility of the selected polymer combination to develop the films which could be cast easily, removed from the backing membrane with ease and possessed satisfactory physico-mechanical characteristics for transdermal application.Patches containing HPMC: EC at ratios of 1:2 and 1:3 were selected for drug loading. For drug-loaded patches, accurately weighed paracetamol(PCM) (7.5% w/w of total polymer weight) was dissolved in ethanol to form a clear solution. Then the required amounts of HPMC K4M and ethyl cellulose were added to drug solution. Dibutyl phthalate (30% w/w) was added to the dispersion as plasticizer and stirring continued on magnetic stirrer. [16-23].Finally, the viscous drug-polymeric dispersion was poured on to the mold, dried for 1.5 h at 55ºC. For patches containing clove oil and olive oil as natural penetration enhancer (5 and 10%w/w),the oils were added at the last step before casting on mold, and the resultant films were dried at lower temperature to prevent evaporation of the volatile clove oil. The cast films were then removed off from the mold and kept in a desiccator until further study. Composition of the patches is presented in Table 1.

Table 1 : Composition of transdermal patches

Formulation code	Paracetamol (% w/w)	HPMC K4M: EC	Clove oil (% w/w)	Olive oil (%w/w)
F1*	-	1:1	-	
F2*	-	1:2	-	
F2	7.5	1:2	-	
F3*	-	1:3	-	
F3	7.5	1:3	-	
F4	7.5	1:3	5	
F5	7.5	1:3	10	

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F6	7.5	1:3		5
F7	7.5	1:3		10
F8*	-	2:1	-	-
F9*	-	3:1	-	-

F1*, F2*, F3*, F8*, F9* indicate blank patches.

Pre-formulationstudies

Drug-excipient compatibility study

FT-IR spectroscopy was carried to assess the compatibility between paracetamol (PCM), HPMC K4M and EC. The pure drug, individual polymers and drug-polymer physical mixture were separately scanned in Bruker FT-IR spectrophotometer in the range of 4000-400 cm^{-1}. The pellets were prepared on potassium bromide press.

Solubility studies

The solubility of paracetamol in phosphate buffer (pH 5.5)was determined by equilibrium solubility method by adding excess amounts of paracetamol in the medium and keeping flask on a water bath shaker (REMI Equipment, Mumbai, India) for 24 h at 25°C. After 24 h, dispersions were filtered, suitably diluted and analyzed spectrophotometricallyin UV-Vis spectrophotometer**(**UV 1900I – SHIMADZU**)** at 257 nm and concentration of drug dissolved was obtained from the standard curve of the drug in the medium.

Physico-mechanical characterization of transdermal patches

Weight variation test

[24]. Weight variation test was carried out by weighing three different films of the individual batch and the average weight was calculated.

Thickness of film

The thickness of the films was measured at different points using Vernier caliper. The averages of three readings of each film at different points were considered.

Folding endurance

[25-26]. Folding endurance was measured manually for the prepared films. A strip of film was repeatedly folded along the same horizontal line till it broke. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance.

Percentage moisture loss

[27]. The films were weighed accurately and kept in a desiccator containing anhydrous calcium chloride as desiccant. Films were reweighed after exposing the films for 24 hrs. The percentage moisture loss was calculated using Equation 1

$$\text{Percentagemoistureloss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Intial weight}} \text{X100 (1)}$$

Percentage moisture absorption

The films were weighed accurately and placed in a vacuum desiccator containing saturated solution of potassium chloride.After 24 hours, the films were taken out and weighed. [28]. The percentage moisture absorption was calculated using Equation 2.

$$\text{Percentagemoistureabsorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Intial weight}} \text{X100(2)}$$

Tensile strength

Tensile strength of patches was determined by a modified pulley system on a patch of defined cross-sectional area. [29-30]. Weight was gradually increased so as to increase the pulling force till the breaking point could be reached. The force required to cause fine line of fracture in the patch was considered as tensile strength, determined by Equation 3 and expressed in kg/cm^2.The averages of three reading of each patch were recorded.

$$\text{Tensile strength} = \frac{\text{Tensile load at break}}{\text{Cross sectional area}} (3)$$

Percentage flatness test

Film was cut into strips. The length of these strips was measured to nearest centimeter without applying any additional pressure. The difference between the initial length of strips and the final length obtained after cutting of film was recorded. [22-25].The percentage constriction of patches was calculated by using the Equation 4.

$$\text{Percentage constriction} = \frac{\text{Initial length} - \text{Final length}}{\text{Final length}} \text{X100 (4)}$$

where 0% constriction indicates 100% flatness of patches.

In-vitro drug permeation study

Drug permeation studies were carried out in Franz diffusion cell.A specific dimension of films (1.76 cm^2) was fixed to the hydrated artificial dialysis membrane 60 (Himedia Laboratories Pvt. Ltd. Mumbai) and mounted onto the receptor compartment and wetted with minimum volume of

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 591-599 www.ijprajournal.com ISSN: 2456-4494

phosphate buffer (pH 5.5). The assembly was placed on a magnetic stirrer and stirred at 50 rpm, temperature being maintained at 32°C ± 1°C. An aliquot of 4ml was withdrawn at predetermined time points for a total period of 10 h and sink condition was maintained by replenishment with equal volume of fresh phosphate buffer. The aliquot withdrawn was filtered through Whatman filter paper (No 1), filtrate suitably diluted and measured spectrophotometrically at 257nm against blank. The cumulative percentage of drug permeated (CPP) at each time point was calculated from calibration curve of paracetamol in buffer. The drug permeation profile was constructed by plotting CPP vs time for the various formulations under investigation. [31-33].Then the drug release kinetics were studied by fitting the data to zero order kinetics, Higuchi kinetics and Korsmeyer-Peppas model.

III. RESULTS AND DISCUSSION

Drug-excipient compatibility study

The FTIR overlaid spectra of PCM, HPMC-EC and physical mixture of PCM-HPMC-EC is depicted in figure 1. All the characteristics absorption bands of PCM remained unchanged in the FTIR spectrum of the physical mixture of drug with polymers suggesting there is no chemical interaction between the drug and the polymers selected for the study.

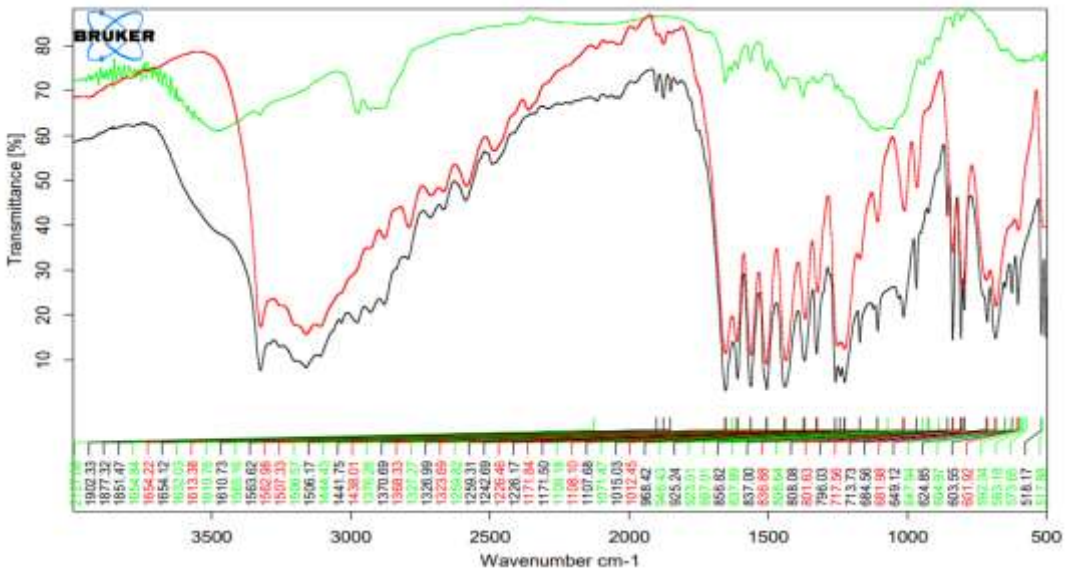

Fig 1: FTIR spectra of paracetamol, physical mixture of HPMCK4M-Ethyl cellulose and physical mixture of paracetamol-HPMCK4M-ethyl cellulose.

Paracetamol, HPMC-Ethyl cellulose , Paracetamol-HPMC-Ethyl cellulose.

Solubility studies

The solubility of paracetamol was experimentally found to be 1.69 mg/ml in phosphate buffer (pH 5.5).[27]. The reported values were found to lie in the range of 1.49-1.84 mg/ml.

Physico-mechanical characterization

The patches containing HPMC-EC at 1:1, 2:1, 3:1 i.e. formulation F1*, F8* and F9* were difficult to peel off from mold and were of inferior in terms of appearance, uniformity of thickness and flexibility. The results of weight variation, thickness and folding endurance, moisture loss and absorption studies of blank and drug loaded patches are presented in Table 2. There is minimum variation in weight or thickness of the films.For all the patches, percent moisture loss was negligible indicating the ability of patches to maintain their physical integrity in dry atmosphere. Low moisture absorption values for all patches indicatedless susceptibility of patches to microbial growth. Results of tensile strength studies revealed that the formulated patches possess sufficient mechanical strength (Table 2).An ideal patch should possess a smooth surface and it should not constrict with time. The results of the flatness study showed that none of the formulations had the differences between the initial length and final length of strips

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after their cuts. It indicates 100% flatness observed in the formulated patches (Table 2).

Table 2: Physico-mechanical properties of formulated patches

Formulation code	Weight variation (gm)	Thickness (mm)	Folding endurance	%Moisture absorption	%Moisture loss	Tensile strength (kg/cm^2)	% Flatness
F2*	0.430 ± 0.028865	0.203 ± 0.015275	>60	1.17	4.13	0.0023	100
F2	0.433± 0.028868	0.203 ± 0.015275	>60	1.17	4.13	0.0023	100
F3*	0.423± 0.028868	0.203± 0.015275	55	1.18	4.13	0.0028	100
F3	0.423± 0.028868	0.203± 0.015275	53	1.18	4.13	0.0027	100
F4	0.423± 0.028868	0.203± 0.015275	55	1.19	4.13	0.0028	100
F5	0.433 ± 0.028868	0.203± 0.015275	50	1.20	4.13	0.0024	100
F6	0.433 ± 0.028868	0.203± 0.015275	58	1.12	4.12	0.0028	100
F7	0.438 ± 0.028871	0.203± 0.015275	>60	1.15	4.11	0.0029	100

F2*, F3* indicate blank patches.

In-vitro drug permeation studies

In vitro permeation studies are predictive of in vivo performance of a drug. Drug permeation profiles of F2-F7 were more or less rectilinear and were indicative of the steady and slow permeation of drug in in vitro condition. From permeation profiles (Fig 2)it was evident that formulation F3 containing HPMC: EC at 1:3 was found to exhibit maximum sustaining effect on drug permeation, probably due to the presence of higher proportion of hydrophobic ethyl cellulose. which will be beneficial for controlled release of loaded drug at an optimum rate. [33]. A similar trend was observed in the drug permeation study of naproxen loaded patches where HPMC-EC patches (2:8) showed prolonged drug permeation (1800 mg/cm^2) as compared to HPMC-EC patches (8:2) releasing 2200 mg/cm^2 drug in 24 h. The reason may be attributed to the relatively hydrophobic nature of EC which has less affinity for water, resulting in decreased thermodynamic activity of the drug in the film and hence, lower drug flux. [34]. A similar effect was also observed in the drug permeation study of diltiazem loaded PVP-EC based transdermal patches. Similarly, formulation containing PVP:EC at 1:2 ratio resulted in more sustained permeation of diltiazem in 6 h as compared to that of patch containing PVP:EC at 2:1 ratio.

Formulation F7 containing 10% w/w of olive oil as penetration enhancer was found to exhibit maximum cumulative percentage permeation (77.80 %) of paracetamol in 10h. Fatty acids with C-18 carbon chain and a double bond present in the structure of olive oil are capable of disrupting the stratum corneum barrier in an efficient manner. On the other hand, F4 and F5 containing 5% and 10% w/w of clove oil as penetration enhancer exhibited lower cumulative percentage permeation (CPP) of only 52.44% and 59.96% paracetamol respectively in 10h. These data clearly reveal the superiority of olive oil as penetration enhancer as compared to clove oil. [35]. The effect of addition of olive oil as penetration enhancer was found to be evident from the drug permeation study of olanzapine loaded PVP-EC based transdermal patches. It was found that formulation containing PVP:EC (1:3) exhibited cumulative percentage permeation of 44.5% in 24 h without addition of olive oil. After the addition of olive oil (10% w/w) as penetration enhancer, cumulative percentage permeation was increased to 89.5% in 24 h.[36]. The effect of natural penetration enhancer was also evident in a study conducted by Soujanya et al. where a comparison between two natural penetration enhancers (cineole and eugenol) was made based on the result obtained from in-vitro skin permeation study of HPMC-EC lornoxicam loaded transdermal patches.

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It was observed that formulation containing HPMC-EC at 1:1 ratio and 0.25 ml eugenol which is the main active constituent found in clove oil acting as penetration enhancer exhibited maximum cumulative percentage permeation of 98.76 % in 24 h as compared to same patch containing 0.25 ml of cineole. However, in the present study, clove oil failed to produce satisfactory extent of permeation enhancement as opposed to olive oil and in both the cases, the effect was found to depend on concentration of natural PE.

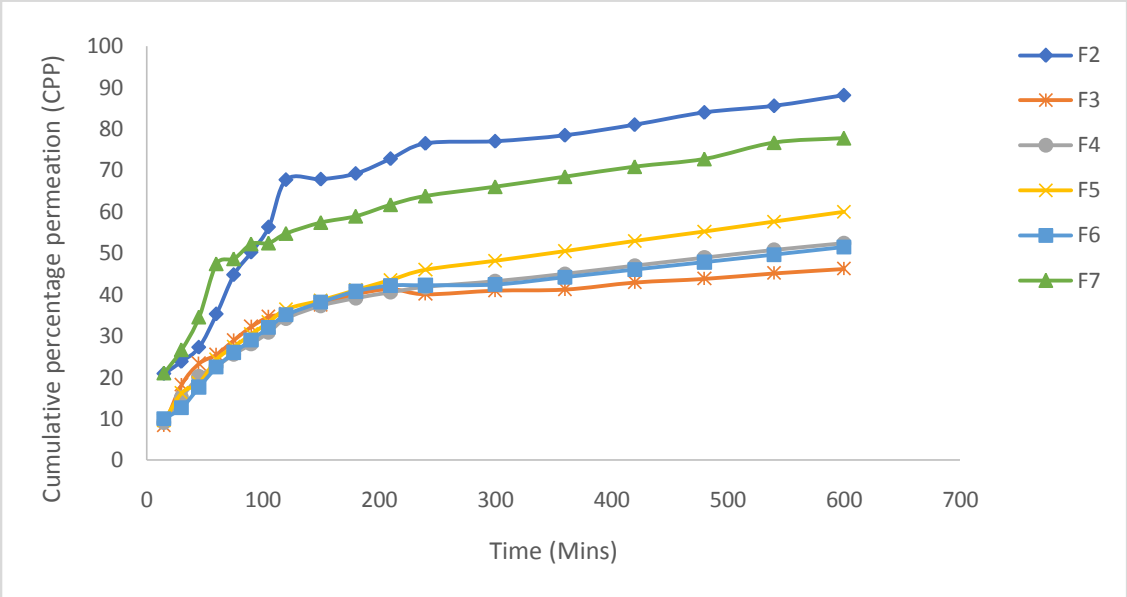

Fig 2: Effect of addition of varying concentrations (5% and 10%w/w) of clove oil and olive oil as PE on permeation profile of paracetamol from HPMC-EC basedpatches

The kinetics of drug permeation was studied by fitting the data obtained from in vitro drug permeation studies to Higuchi kinetics, zero order and Korsmeyer Peppas model. The correlation coefficients obtained from Higuchi plot were found to be better and in the range of 0.9546 to 0. 9893. This indicates diffusional drug release of PCM from matrix type of HPMC-EC patches (with or without natural PE) as indicated in Table 3. There are some model-independent parameters such as steady-state flux, K_p, which need to be analyzed to compare drug permeation parameters. The measurement of flux across human skin provides a valuable insight into the formulation development of any dermatological product.[10]. According to Fick's second law of diffusion, the steady state diffusion flux (SS_{flux} : mg/cm^2 .min) of paracetamol was calculated from the slope of the linear portion of the plot of the cumulative percentage of paracetamol permeated per cm^2 of diffusion membrane at steady state against the time using linear regression analysis with the help of Equation 5

$$SS_{flux} = \frac{dQ}{dt} \times \frac{1}{A} \quad \text{---------- (Equation 5)}$$

Where dQ/dt is the slope of the linear portion of the curve i.e. cumulative percentage permeated per unit time (mg/min) and A is the diffusional area (sq cm).

For the quantification of permeability coefficient, Kp, the following equation (Equation 6) was employed

$$SS_{flux} = K_p \times C \quad \text{---------- (Equation 6)}$$

Where, C is the amount of paracetamol present in the area of patch used for the permeation study. Comparison of model-independent parameters such as steady state flux, K_p, values of HPMC-EC based patches are also presented in Table 3.

Table 3: Analysis of kinetic model and model independent parameters for paracetamol permeation from HPMC-EC based transdermal patches

Formulation code	Zero order kinetics (r^2 value)	Higuchi kinetics (r^2 value)	Korsmeyer Peppas Model (r^2 value)	Steady state flux (SS_{flux}) (mg/cm^2.min)	K_p
F2	0.8326	0.974	0.423	0.5680	0.02272

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F3	0.7844	0.9546	0.736	0.0512	0.00204
F4	0.849	0.9829	0.700	0.0530	0.00212
F5	0.8688	0.9893	0.656	0.0604	0.00241
F6	0.8383	0.9773	0.697	0.5660	0.02264
F7	0.8254	0.9715	0.583	0.5681	0.022724

Based on values of SS_{flux} and K_p presented in Table 3, the patches can be ranked as follows:
F7=F2>F6>F5>F4>F3.

But formulation F7 was capable to exhibit more sustaining effect on drug permeation profile as compared to F2 owing to the presence of higher proportion of hydrophobic polymer EC.
So, it is evident from table 3 and the corresponding ranking order of the patches that F7 patch containing 10% w/w of olive oil as penetration enhancer exhibited the highest value of steady state flux and permeability co efficient values as compared to F5 containing 10% w/w of clove oil. So, olive oil can act as better penetration enhancer than clove oil for HPMC-EC based patches. This might be attributed to the fact that EC can undergo probable esterification with the free hydroxyl groups of olive oil. Moreover, it was also observed that there was an increase in cumulative percentage permeation and as well as extent of drug permeation as indicated by steady state flux values, with the increase in the concentration of clove oil or olive oil as penetration enhancer. So, it clearly reveals the concentration dependent effect of natural penetration enhancers such as clove oil or olive oil on permeation profile of paracetamol from HPMC-EC based matrix patches.

IV. CONCLUSION AND FUTURE PROSPECT

Flexible, smooth and transparent films were obtained with optimum ratios of HPMC-EC. It was found that the transdermal patch with HPMC:EC (1:3) and10% olive oil showed the best permeation. Hence, it was concluded that olive oil mightbe a better option as compared to clove oil and other synthetic skin permeation enhancers so as to reduce skin irritating potential for permeating the drugsteadily through the skin from HPMC-EC based patches. Skin irritation study and in vivo studies on animal model should be conducted in future to ensure that the optimized patch with the selected polymer ratio and natural penetration enhancer is safe to use clinically. Accelerated stability testing can be conducted by exposing the prepared formulations to an accelerated condition of 40°C and 75% RH. for 6 months to detect any change in physical attributes or sign of degradation.

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