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Original Article

COMPARISON OF EFFECT OF PENETRATION ENHANCER ON DIFFERENT POLYMERS FOR DRUG DELIVERY

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ABSTRACT

Objective: Aliskiren hemifumarate is used for the treatment of hypertension. The aim of this research to study the effect on the delivery of drug using natural and synthetic permeation enhancers like limonene, cineol, β-cyclodextrin, and oleic acid by using different polymers. As different penetration acts differently with polymers.

Methods: Transdermal patches were prepared by the solvent evaporation technique. The controlled release polymers were used for the preparation of patches. The patches were prepared with different polymers and different plasticizer. The drug and polymer interaction study was performed by Fourier transform infrared spectra. *In vitro* permeation studies were conducted using pretreated cellophane membrane using franz diffusion cell.

Results: The prepared patches were evaluated for *in vitro* drug release, and the release profile was varied from 52.32% PGH (oleic acid) to 87.63% B (cineol). The permeability coefficient was found in the range of 5.82 to 8.32 cm/h, and corresponding flux was found between 281.61 to 729.08 µg/cm^2/h on the prepared patches and statistical analysis performed using t-test ($p<0.005$).

Conclusion: On the basis of the obtained results, it was concluded that patch prepared using methocel k 15 m as a polymer, glycerin as plasticizer and cineol as a permeation enhancer shows the maximum release. The increase in the release due to increase in the flux.

Keywords: Transdermal patch, Penetration enhancer, Permeability coefficient, Flux

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INTRODUCTION

Human skin is the most complex organ and provides an efficient barrier for transfer of the molecules. It prevents any loss of essential physiological substances from the body. The barrier offered by skin causes the difficulty for transdermal delivery of therapeutic agents [1, 2]. The absorption through the skin was increased by changing the barrier properties of the skin through rupturing the skin barrier properties. These are the agent which helps in the promotion of the absorption of drugs through the skin temporarily by transiently enhancing the skin permeability [3]. The permeation enhancers are inert and nontoxic substances having no therapeutic value but enhance the sorption of the drug through the skin by different approaches to permeation enhancement, such as chemical approaches which cause chemical changes by using chemicals such as terpenes, surface active agent and spans, etc. The other method involves like physical enhancement, biochemical enhancement, supersaturation enhancement, and bio-convertable prodrug. Ideally, reversible changes in the skin should be made of permeation enhancers without damaging viable cells [4, 5].

There are various mechanisms to promote the skin penetration. The penetration is mainly increased by the interaction of the enhancers with the polar head group of the lipids. The penetration of hydrophilic drugs occurred by lipid-lipid head group interaction and disruption, of the packing arrangement of the lipids. The main function of penetration enhancers by lipid disruption, protein modification, and partitioning promotion. In lipid disruption, the enhancer changes the structure of the stratum corneum of lipid organization and make it permeable to drugs e. g azone, terpene, dimethylsulfoxide. In protein modification the open up the dense protein structure and make it permeable e. g dimethyl sulfoxide and in partitioning promotion, they change the solution properties of horny layer and thus increase the partitioning of drugs, coenhancer [6-9].

Ideal characteristics of permeation enhancers: compatibility with the drug, have good solvent properties, doesn't show any adverse pharmacological activity inside the body, doesn't impart any color, odor, taste, chemically and physically stable.

The penetration enhancers are classified into three main types: drug vehicle based, chemical penetration enhancers and physical penetration enhancers.

In the present studies enhancer from different classes were selected for studies. The main function of the chemical enhancers to reversibly disrupt the various barriers of skin and known as absorption promoters which can enhance the flux. The selected enhancers were natural (limonene, cineol), surfactant (dimethyl oxide), complex forming (β-cyclodextrin) and span (oleic acid). Each enhancer was evaluated with different polymer and plasticizer [10-12].

The objective of the study was to compare the release effect of different permeation enhancer (natural and synthetic) from patches prepared using a different polymer with varying concentration and plasticizer. The best permeation enhancer was selected on the basis of the release of the drug from the patches.

MATERIALS AND METHODS

Materials

Aliskiren hemifumarate was a gift from the dr. morepen laboratories (India). The excipients like methocel (k 15m, k 100m), ethocel (k 15m, k 100m) was received as a gift sample from colorcon mumbai. The HPLC grade reagents and solvents procured commercially.

Transdermal films containing aliskiren hemifumarate were prepared by evaporation of solvent technique using mercury substrate with a different polymer and different plasticizers.

Fourier transform infrared spectroscopy

To identify the interaction between the drug and the utilized polymers, infrared spectroscopy of pure drug and its physical

mixture with polymers was carried using infrared spectroscopy; the range selected was from 400 cm^{-1} to 4000 cm^{-1}.

Preparation of transdermal patches using different permeation enhancer

The patches were prepared by solvent evaporation method the detail on formulation provided in table 1. The plasticizers used in the formulation were glycerin and propylene glycol at a concentration of 150% w/w. About 5 ml of the solution was poured on the mercury substrate. The evaporation of the solvent was controlled by inverting the funnel over the poured solution in the mould. After 6-8 h, the dried patches were removed from the mould and packed in aluminum foil and placed over fused calcium chloride in desiccators at room temperature.

Table 1: Composition of transdermal patches along with details of polymers, plasticizer and permeation enhancers

S. No.	Formulation	Code	Composition (drug: polymer)	Plasticizer (% w/w)	Permeation enhancer	Casting solvent
1	Methocel K 15 M	B	1:1.5	150*	Limonene	Chloroform: Dichloromethane: Ethanol (2:2:1)
2	Methocel K 100 M	E	1:1.5		Cineol	---
3	Ethocel standard 10	J	1:1		β-Cyclodextrin	Chloroform
4	Methocel K 15 M	PGB	1:1.5	150#	Oleic acid	Chloroform: Dichloromethane: Ethanol(2:2:1)
5	Methocel K 100 M	PGD	1:1			Chloroform: Dichloromethane: Ethanol(2:2:1)
6	Ethocel standard 4	PGH	1:1.5			Chloroform

*Glycerin used as a plasticizer. # Propylene glycol used as a plasticizer.

Evaluation of transdermal patches

The prepared patches were subjected to physical and chemical evaluation.

Weight variation

It was determined by weighing three patches of each formulation.

Thickness

The thickness of patches can be measure from different locations.

Percentage moisture absorption

The weighed films were placed in a desiccator having 100 ml of saturated aluminum chloride solution, maintaining 79.50% RH percentage moisture absorption calculated after 3 d using the formula.

Percentage moisture absorption =

$$\frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage moisture loss

The accurately weighed films were kept in a desiccator containing anhydrous calcium chloride. The moisture loss after 3 d was calculated using the formula.

Percentage moisture loss =

$$\frac{\text{Final weight} - \text{Initial weight}}{\text{initial weight}} \times 100$$

Water vapour transmission rate

The amount of water vapour transmitted was calculated using the formula [13-18].

Water vapour transmission rate =

$$\frac{\text{Final weight} - \text{Initial weight}}{\text{Time} \times \text{Area}} \times 100$$

***In vitro* permeation studies of aliskiren hemifumarate using pretreated cellophane membrane**

The permeation of aliskiren hemifumarate was determined using franz diffusion cell. The membrane was mounted onto the diffusion cell with the one side facing the donor compartment and other end facing the receptor compartment. The receiving compartment was filled with dissolution media. For studies, the pretreated cellophane membrane was used and patches were cut into the pieces of 2.5 cm diameter and applied to the membrane. Finally, the receptor solution was withdrawn after different time interval like 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 24 h and the sample analyzed using ultraviolet spectrophotometer at 269 nm.

Data analysis

The cumulative amount of the drug penetrated through membrane was plotted against time from the slope, permeability coefficient and flux.

Permeability coefficient calculation

The data analysis was performed on data obtained from *in vitro* release and analysed by applying factor for volume correction.

Permeability coefficient is defined as the amount of the drug passage through the skin in a particular time (μg/cm^2/h). The permeability coefficient was calculated from the slope of the graph of percentage drug transported with time [19, 20].

$$PC = \text{Slope} \times Vd/S$$

*V*d is the volume of the donor solution in ml;

S is the surface area on which patch applied in cm.

Flux is defined as the cumulative amount of the drug passes through the unit of the skin surface in specified time.

$$\text{Flux} = PC \times \text{concentration of donor solution } (\frac{\text{mg}}{\text{ml}})$$

RESULTS

The aim of the present study to evaluate the effect of natural and synthetic permeation enhancer on the release profile of the drug through transdermal patches. Patches prepared using various synthetic polymers with a different plasticizer.

Table 2: Result showing the effect of physicochemical properties of patches prepared using glycerin as a plasticizer

Formulation code	Weight variation (mg)		Percentage moisture absorption		Percentage moisture loss		Water vapor transmission rate(g/cm^2/h)		Thickness (mm)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
B	58.33	0.58	5.16	1.063	3.85	0.237	0.54	0.30	0.066	0.005
E	52.00	2.65	5.59	1.506	4.96	0.892	0.46	0.02	0.057	0.003
J	49.00	2.00	6.14	0.290	5.08	0.751	0.48	0.04	0.061	0.002
PGB	57.33	0.58	4.93	0.15	4.32	0.78	0.85	0.09	0.07	0.00
PGD	40.67	0.58	3.87	0.78	3.14	0.40	0.83	0.09	0.05	0.00
PGH	52.00	0.00	6.11	0.44	4.77	1.17	0.52	0.04	0.05	0.00

Results are expressed as mean±SD; n=3

Table 3: The *in vitro* permeation studies, permeability coefficient and flux from various formulations

Formulation	Cumulative % permeated	SD	Permeability coefficient (cm/h)	Flux (µg/cm²/h)
B (limonene)	72.45	0.01	6.72	486.70
B (cineol)	87.63	0.23	8.32	729.08
B (β-cyclodextrin)	67.38	1.56	6.67	449.48
B (oleic acid)	62.70	1.01	6.31	395.71
E (limonene)	61.66	0.03	6.20	382.59
E (cineol)	78.68	0.04	7.73	608.12
E (β-cyclodextrin)	65.64	0.50	6.72	440.97
E (oleic acid)	68.28	0.13	6.80	464.46
J (limonene)	75.79	0.04	7.60	575.67
J (cineol)	74.44	0.03	7.57	563.74
J (β-cyclodextrin)	64.20	1.79	6.49	416.59
J (oleic acid)	61.84	0.04	6.16	380.90
PGB (limonene)	73.32	0.10	7.22	529.04
PGB (cineol)	75.33	0.05	7.32	551.57
PGB (β-cyclodextrin)	75.89	0.02	7.79	590.93
PGB (oleic acid)	71.85	0.06	7.30	524.64
PGD (limonene)	72.66	0.06	7.38	535.94
PGD (cineol)	76.83	0.00	7.68	589.71
PGD (β-cyclodextrin)	61.84	0.04	6.45	398.66
PGD (oleic acid)	59.55	0.80	6.33	376.78
PGH (limonene)	74.23	0.02	7.34	544.54
PGH (cineol)	75.24	0.01	7.57	569.29
PGH (β-cyclodextrin)	59.24	0.27	5.92	350.43
PGH (oleic acid)	52.32	0.21	5.38	281.61

Results are expressed as mean±SD; n=3

DISCUSSION

Fourier transform infrared spectroscopy

The compatibility between drug and polymers was studied by fourier transform infrared spectra. The spectra were recorded to assess the interaction between polymers and the drug as shown in fig. 1 and 2. The infra-red spectrum shows no distinctive chemical and physical interaction with each other for scanning at a wavelength from 400 to 4000 cm^{-1}.

Weight variation

The average weight of the formulations was ranged from 40.67-58.33 mg. The difference in weight depends on varying polymer concentration and grade of the polymer.

Percentage moisture absorption

Moisture absorption studies indicated that the increase in the concentration of hydrophilic polymer was directly proportional to the increase in moisture content and moisture uptake of the patches. The moisture content of the prepared formulation was low, which could help the formulations remain stable and reduce brittleness during long-term storage. The moisture uptake of the formulation was also low, which could protect the formulations from microbial contamination and reduce bulkiness. The percentage moisture absorption varies from 3.87 to 6.14 for patches.

Percentage moisture loss

The percentage moisture loss from patches was ranging from 3.14 to 5.08.

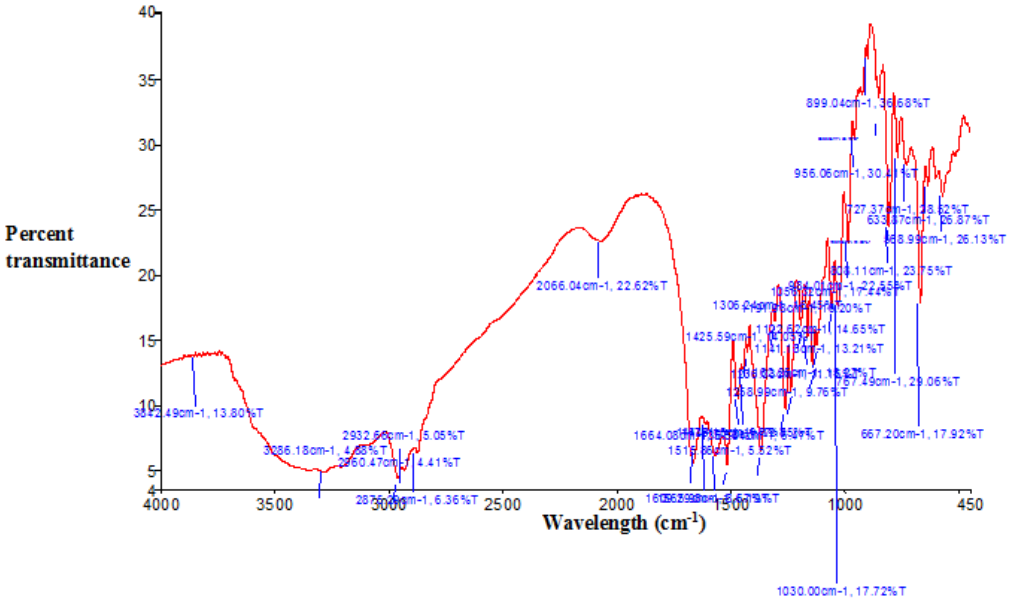

Fig. 1: FTIR spectra of aliskiren hemifumarate

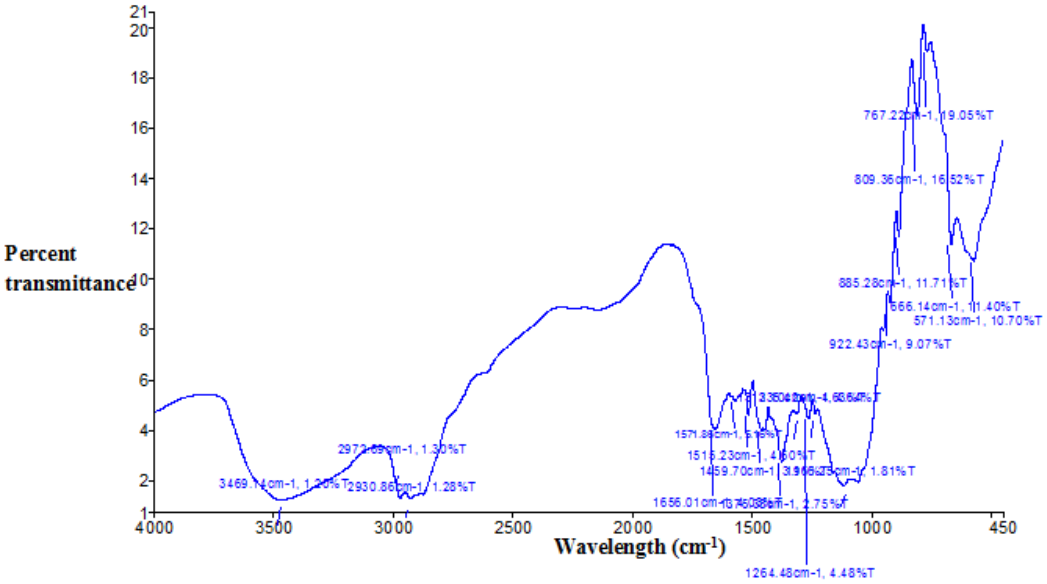

Fig. 2: FTIR spectra of aliskiren hemifumarate with polymer

Thickness

The thickness of the three patches varies from 0.05 to 0.066 mm.

Water vapour transmission rate

The water vapour transmission rate from patches was range from 0.46 to 0.85.

***In vitro* permeation studies**

The concentration of permeation enhancer was decided on the basis of published literature. Diffusion studies were performed using locally fabricated franz diffusion cell through pretreated cellophane membrane. Each permeation enhancer was formulated with a varying concentration of polymer, different polymers, and different plasticizer.

The *in vitro* release is helpful in predicting that how will it behave in the body. The cumulative percentage of *in vitro* release in 24 h by different enhancers was shown in table 2 and ranged from 52.32% PGH (oleic acid) to 87.63% B (cineol). The statistical analysis was performed, and results were analyzed using t-test ($p<0.005$). The difference was observed on *in vitro* release of drug between the formulations prepared using different plasticizer and a varying concentration of polymer. The highest release of the drug was observed in the formulation prepared using polymer methocel k 15 m and permeation enhancer cineol.

Permeability coefficient and flux

The permeability coefficient and flux were calculated. The values ranged from 5.82 to 8.32 cm/h for permeability and flux ranged from 281.61 to 729.08 µg/cm^2/h. The highest release was obtained from methocel k 15 m using cineol as penetration enhancer.

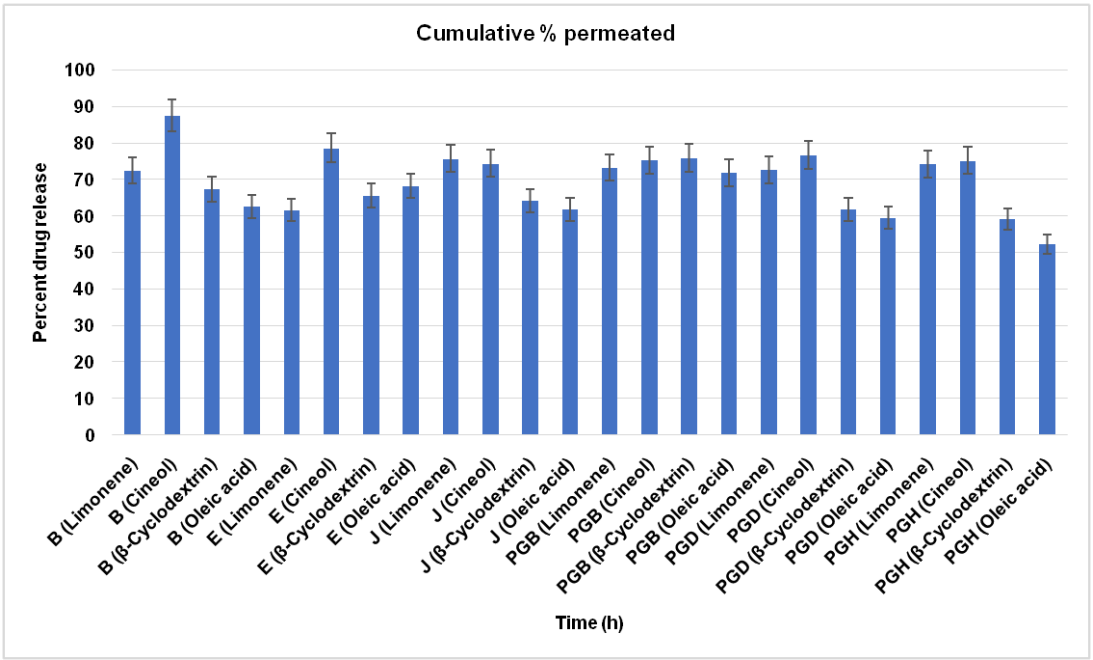

Fig. 3: Graph between time and percent drug release with different permeation enhancer (Results are expressed as mean±SD; n=3)

CONCLUSION

In the present study, various formulation of transdermal patches was prepared using different polymers and penetration enhancers. The effect of penetration enhancers was studied. All the formulation showed good uniformity with regard to drug content and other parameters. On performing *in vitro* drug release, it was observed that maximum release obtained using cineol (natural) as penetration enhancer along with methocel k 15m as a polymer. In conclusion, the delivery of the drug is promising and feasible with above-mentioned penetration enhancer with the specified polymer.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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