



COMPARATIVE EVALUATION OF MENTHOL AND EUGENOL AS SKIN PENETRATION ENHANCERS IN DICLOFENAC SODIUM TRANSDERMAL PATCHES

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ABSTRACT

Innovations in the area of drug delivery are taking place at a much faster pace as compared with the last two decades. Improved patient compliance and effectiveness are inextricable aspects of new drug delivery systems. Transdermal drug delivery system (TDDS) is one of the systems lying under the category of controlled drug delivery, in which deliver the drug through the skin in a predetermined and controlled rate. TDDS are adhesive drug-containing devices of defined surface area that delivers a predetermined amount of drug to the surface of intact skin at a pre-programmed rate to reach the systemic circulation. Transdermal delivery provides a leading edge over injectable and oral routes by increasing patient compliance and avoiding first-pass metabolism, respectively. In the present investigation formulation F1 to F4 were prepared by using EC, PEG, PVA Acetone, Eugenol and Menthol with solvent evaporation technique. The prepared patches F1 to F4 were evaluated for few physicochemical studies and all are within the limits. The in-vitro drug diffusion studies were done by using modified dissolution apparatuses Franz diffusion cell. Among all the formulations F4 was shown optimum drug release 99% for a period of 12h. This may be due to the presence of natural penetration enhancer Eugenol which promotes the penetration of drug. Hence it is concluded that the Eugenol is Good Penetration enhancer for the prepared transdermal patches which when compared to menthol.

Key words:

EC, PEG, PVA, Eugenol, and Menthol, Transdermal Drug Delivery.

INTRODUCTION

1.1. Controlled drug delivery

Treatments of acute and chronic diseases have been accomplished by delivery of drugs to patients using various pharmaceutical dosage forms. These dosage forms are known to provide a prompt release of drug. But recently several technical advancements have been done and resulted in new techniques for drug delivery. These

techniques are capable of controlling the rate of drug release. The term-controlled release has a meaning that goes beyond scope of sustained release. The release of drug ingredients from a controlled release drug delivery advances at a rate profile that is not only predictable kinetically, but also reproducible from one unit to other. The difference between sustained release and controlled release is shown by Fig.1.

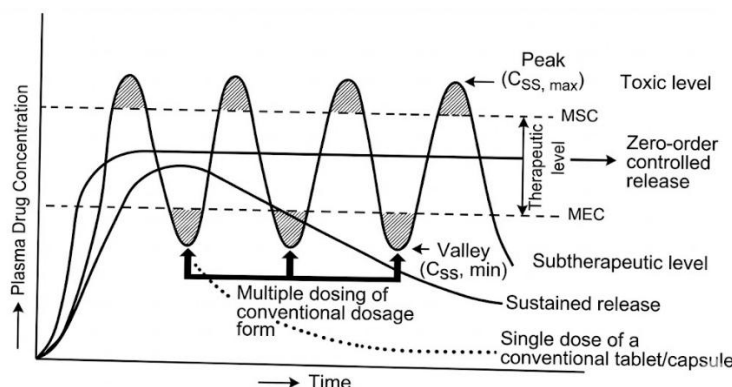


Figure 1: Comparative graphs of conventional, sustained and controlled release delivery systems.

1.2. Transdermal drug delivery: An Introduction

Innovations in the area of drug delivery are taking place at a much faster pace as compared with the last two decades. Improved patient compliance and effectiveness are inextricable aspects of new drug delivery systems.^{1, 2} A more radical approach has been to explore newer interfaces on the body for introducing therapeutics. One such approach, transdermal drug delivery, makes use of human skin as a port of entry for systemic delivery of drug molecules.³ Transdermal drug delivery system (TDDS) is one of the systems lying under the category of controlled drug delivery, in which the aim is to deliver the drug through the skin in a predetermined and controlled rate. TDDS are adhesive drug-containing devices of defined surface area that deliver a predetermined amount of drug to the surface of intact skin at a programmed rate to reach the systemic circulation.^{4,5} Transdermal delivery provides a leading edge over injectable and oral routes by increasing patient compliance and avoiding first-pass metabolism, respectively.

1.3 Skin structure

The skin is largest organ in the body. It protects against the influx of toxins and the efflux of water and it is largely impermeable to the penetration of foreign molecules. Skin serves as the point of administration for systemically active drugs. The topically applied drug will first be absorbed into the systemic circulation and then transported to target tissues. There are three layers that make up skin: epidermis, dermis and subcutaneous tissue. The epidermis, in particular the stratum corneum, is the major barrier to drug absorption. With respect to drug delivery, molecules must penetrate the stratum corneum, the viable epidermis, the papillary dermis and the capillary walls into the blood stream or lymph channels, whereupon they are removed from the skin by flow of blood or lymph.^{6, 7}

1.3.1 Epidermis

The epidermis is the outermost layer of the skin and varies in thickness with approximately 0.8 mm on the palms of

the hands and soles of the feet. It consists of multi-layered regions of epithelial cells and the viable epidermis is often referred to as the epidermal layers below the stratum corneum. The cellular content of the epidermis consists predominantly of keratinocytes (approximately 95% of cells), with other cells of the epidermal layers including melanocytes, Langerhans cells and Merkel cells. The stratum corneum is the most superficial layer of the epidermis. It is in direct contact with the external environment and its barrier properties may be partly related to its very high density (1.4 g/cm³ in the dry state) and its low hydration of 15%–20%. The cells of the stratum corneum are composed mainly of insoluble keratins (70%) and lipid (20%). Water in the stratum corneum is associated with keratin in the corneocytes.

1.2.2. Dermis

The dermis is approximately 2–3 mm thick and consists of collagenous (70%) and elastin fibres which give strength and elasticity to the skin. Blood vessels found in the dermis provide nutrients for both the dermis and epidermis.

1.3.3. Hypodermis

The hypodermis or subcutaneous layer is the deepest layer of the skin and consists of a network of fat cells. It is the contact layer between the skin and the underlying tissues of the body, such as muscles and bone. Therefore, the major functions of the hypodermis are protection against physical shock, heat insulation and support and conductance of the vascular and neural signals of the skin. Hypodermis-resident fat cells account for approximately 50% of the body's fat with the other predominant cells of the hypodermis consisting of fibroblasts and macrophages. The transdermal patch is developed in different ways but is basically classified into three types likely

- 1) Reservoir,
- 2) Polymer Matrix,
- 3) Micro reservoir

Reservoir system:

The reservoir system consists of three major components

- The drug reservoir
- The rate controlling membrane
- The adhesives

Basically, the drug reservoir contains drug and excipients situated in between impervious backing layer and rate controlling membrane. The drug reservoir contain drug in the form of gel, solution or suspension and the microporous or nonporous rate controlling membrane responsible for the release of the drug. One of the

important components of reservoir system is adhesive which were situated in between rate controlling membrane and release liner. The adhesive layer act as the immediate release layer as the adhesive is equilibrated with drug. The reservoir type of patch will distribute only after the equilibration of the adhesive layer. The hypoallergenic polymer was applied over the outer surface of the polymeric membrane. The drug is permeated through the membrane and adhesive to reach the skin.^{8, 9, 10}

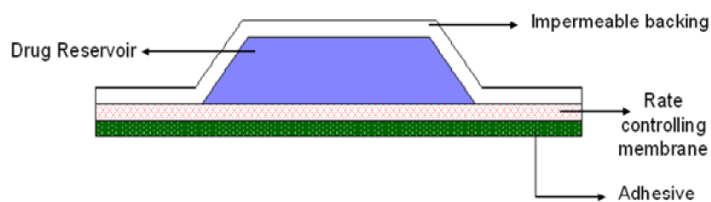


Figure 2: Reservoir system

2) Matrix system or monolithic system: The matrix system (Figure 2) also called the monolithic system consist of the drug in the form of solution or suspension which is

homogeneously dispersed into the hydrophilic or lipophilic polymer which is surrounded by the adhesive layer.¹¹

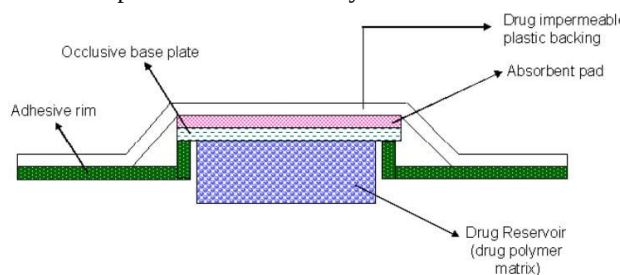


Figure 3: Matrix system

3) Micro-reservoir system: The reservoir and matrix system are combined to form the micro-reservoir system (Figure 5). In this the drug is first suspended in aqueous polymeric solution and then homogeneously this solution dispersed into lipophilic polymer. This process forms

thousands of un leachable and thermodynamically unstable microscopic spheres drug reservoirs. The in situ cross-linking thermodynamically stabilizes the dispersion.^{8, 11, 12.}

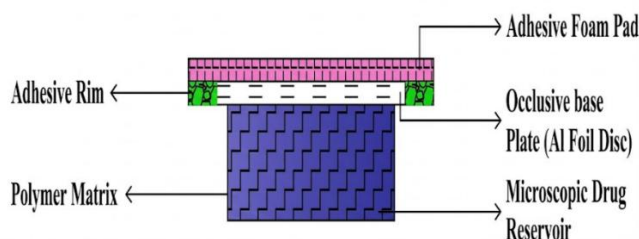


Figure 4: Micro-reservoir system

The aim of present study is to perform comparative study on menthol and eugenol as skin penetration enhancers for transdermal patches of diclofenac sodium. It is aim to prepare and evaluate their effectiveness to increasing drug absorption through the skin. The penetration enhancers is a one which leads to a higher drug flux and permeability coefficient, providing a basis for optimizing transdermal

delivery and potentially enhancing the efficacy of diclofenac sodium patches.

Objectives:

- To determine the effect of menthol and eugenol on diclofenac sodium permeation through the skin in vitro. This involves conducting in vitro permeation studies using Franz diffusion cells or similar systems.

- To evaluate the penetration enhancement effect of menthol and eugenol at various concentrations. This could involve testing different concentrations of each enhancer to determine the optimal concentration for maximizing drug permeation.
- To compare the permeation parameters (flux, permeability coefficient) of diclofenac sodium with and without the addition of menthol and eugenol. This will involve analyzing the rate and extent of drug penetration through the skin under different conditions.
- To assess the potential for local and systemic adverse effects associated with the use of menthol and eugenol as penetration enhancers. This may involve conducting safety assessments, including patch irritation tests and/or toxicity studies, to ensure the safety of the enhancers.

EXPERIMENTAL WORK

Calibration curve of Diclofenac Sodium

Preparation Methods:

Phosphate buffer preparation: Place 50ml of 0.2M Potassium hydrogen phthalate in a 200ml Volumetric flask, add the specified volume of 0.2M Sodium Hydroxide and then add distilled water to make up to the volume 200ml.

Preparation of 0.2M Potassium hydrogen phthalate solution: Dissolve 27.218 g of potassium hydrogen phthalate in sufficient distilled water containing in the 1000ml volumetric flask and to make up to the volume 1000ml.

Preparation of Solution for Calibration curve:

Stock solution 1: stock solution of drug 1mg/ml is prepared by dissolving 100mg of drug in 100ml of volumetric flask to get 1000µg/ml drug solution with vigorous shaking and further sonicated for about 10minutes.

Stock solution 2: 10ml of the stock solution 1 is diluted to 100ml with phosphate buffer PH 6.8 to get a stock solution was filtered through Whatman filter paper No.41

Dilution: Take the respective sample (0.2ml, 0.4ml, 0.6ml, 0.8ml, 1ml, 1.2ml, 1.4ml, 1.6ml, 1.8ml, 2ml, 2.2ml, 2.4ml) in each test tube, add phosphate buffer pH 6.8 to make total volume of 10ml to procedure (2, 4, 6, 10, 12, 14, 16, 18, 20, 22, and 24 µg/ml) respectively.

Determination of absorption maxima:

A UV absorption maximum was determined by scanning 10µg/ml solution of Diclofenac Sodium in phosphate buffer PH 6.8 in between 200-400nm by using UV-Visible spectrophotometer. Further a representative spectrum was drawn of Diclofenac Sodium in phosphate buffer PH 6.8

Preparation of Calibration Curve:

The Standard Solution for the drug having concentration 0.2, 0.4, 0.6, 0.8, and 1.0 µg/ml was prepared with phosphate buffer PH 6.8 from the stock solution. The absorbance of solution of pure diclofenac Sodium drug were measured at 276 λ max and a calibration curve was plotted between concentration of drug (µg/ml) on X-axis V/s absorbance on Y-axis to get the linearity and regression equation.

FORMULATION OF TRANSDERMAL PATCH

Preparation of transdermal patch:

Transdermal patches containing Diclofenac Sodium were prepared by the solvent evaporation technique. The drug Diclofenac sodium was dissolved in suitable solvent acetone. Polymers Ethyl cellulose and Polyvinyl Alcohol were taken. Polymeric solution kept under magnetic stirrer after 1hr get viscous solution. After the drug (Diclofenac) is add into the polymeric solution. Sufficient care was taken to prevent the formation of lumps. Glycerin was taken as a plasticizer and permeation enhancer like Eugenol, Menthol, added to the mixture separate preparation and mixed well. It was set aside for 2 h to exclude any entrapped air and was then transferred into a previously cleaned Petri plate, drying of patches was carried out in vacuum oven at oven room temperature (below 60°C). Dried patches were packed in Aluminum foil and stored in a desiccator for further evaluation.

INGREDIENTS	F1	F2	F3	F4	F5	F6
Drug (Diclofenac Sodium)	100	100	100	100	100	100
Acetone	10	10	10	10	10	10
PEG-4000(%)	40	40	40	40	40	40
PVA (%)	5	5	5	5	5	5
EC (%)	100	100	100	100	100	100
Menthol	0.5	1.0	-	-	-	-
Eugenol oil	-	-	0.5	1.0	-	-

EVALUATION PARAMETERS OF PATCHES:

The evaluation methods for transdermal dosage form can be classified into following types:

1. Physicochemical evaluation
2. *In vitro* evaluations

RESULTS AND DISCUSSION**Construction of calibration curve:**

Diclofenac sodium standard curve was carried out by using phosphate buffer 6.8ph and were observed at lambda max 276nm and the results was showed in the Table 1 and Figure 1.

Table 1: Standard graph of Diclofenac Sodium

Concentration($\mu\text{g/ml}$)	Absorbance at (276nm)
0	0
0.2	0.65
0.4	1.25
0.6	1.93
0.8	2.6
1	3.253

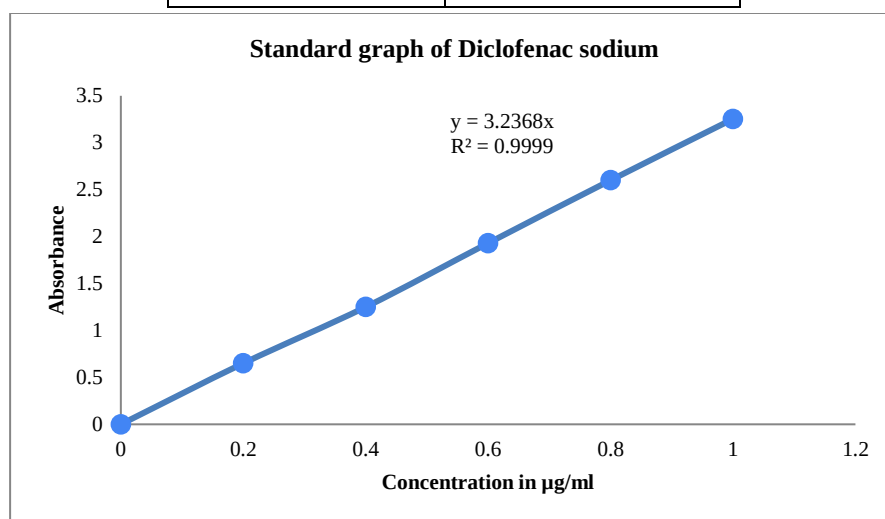


Figure 1 Standard calibration curve of diclofenac sodium

Compatibility studies:

IR SPECTROSCOPY:

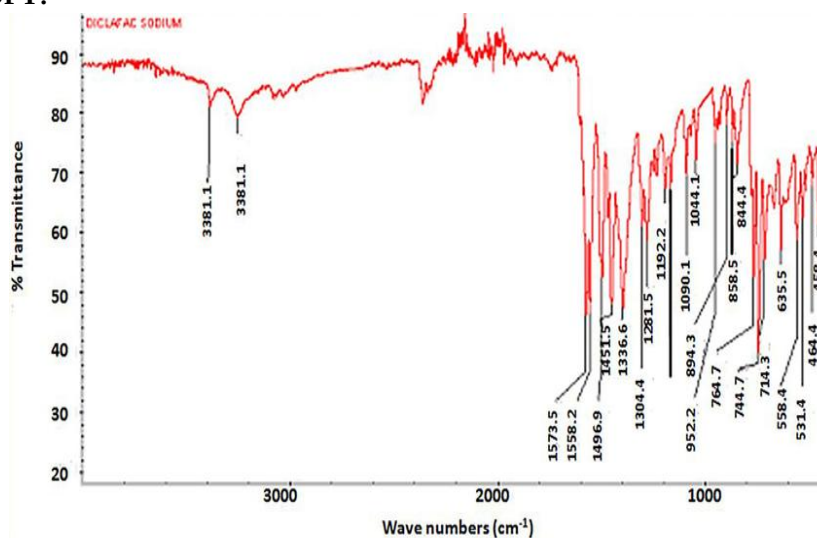


Figure 2: Diclofenac Sodium of FTIR

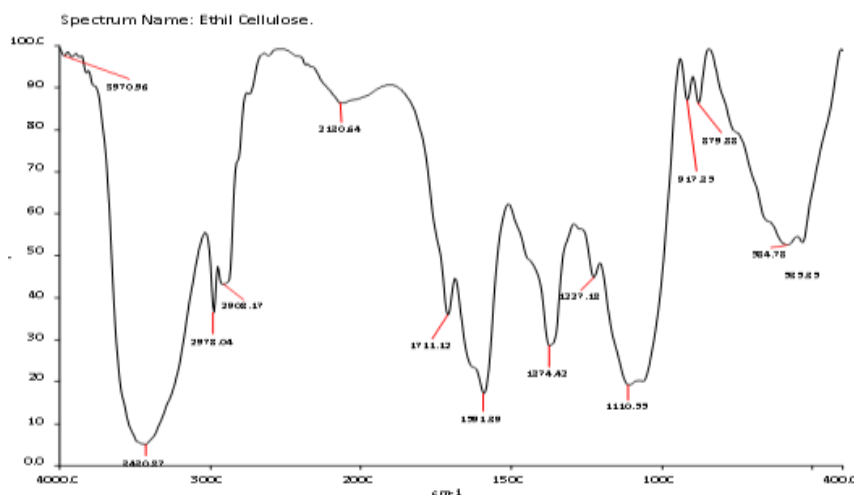


Figure 3: Polymer ethyl cellulose FTIR

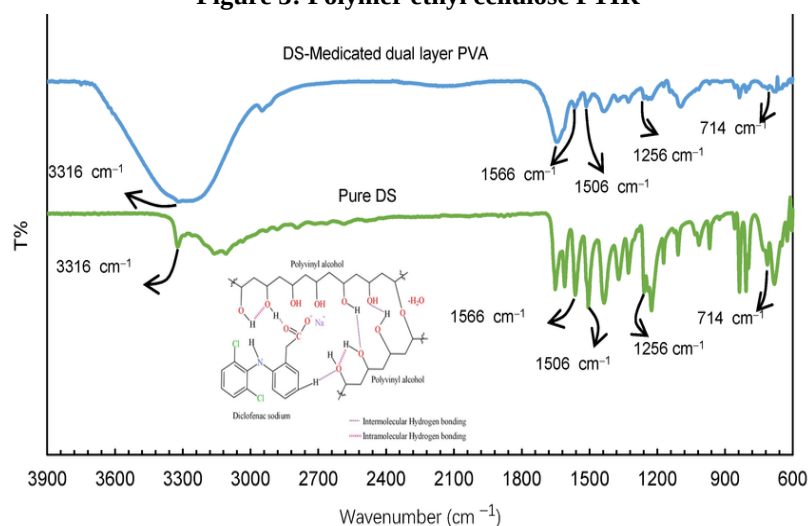


Figure 4: Transdermal patch of Diclofenac Sodium FTIR

The compatibility studies of the drug with excipients indicate no characteristic visual changes and no additional peaks were observed during FR-IR studies.

2. Evaluation of patches:

The prepared transdermal patches were evaluated and results was showed in the respected Tables 2 and 2.1.

Table 2: Data Obtained from Physicochemical Evaluations:

Formulation code	Weight uniformity (mg)	Thickness uniformity(mm)	Drug content uniformity (%)	Moisture loss (%)	Folding endurance
F1	295	0.15	97.91	2.38	2
F2	299	0.14	97.86	1.98	3
F3	300	0.12	98.95	2.29	4
F4	298	0.13	97.21	2.63	3

Table 2.1: Evaluation of different properties.

Formulation code	Shear adhesive test (sec/mill sec)	Track properties	Thumb tack test	Flatness test	Percentage elongation break test	Rolling ball tack test	Quick stick (peel tack test) (sec/mill sec)
F1	06:89	Good	Good	±0.5	2.6	2.5	03:31
F2	11:22	Good	Good	±0.5	2.2	2.3	03:21
F3	8:15	Good	Good	±0.1	2.5	2.5	03:41
F4	12:24	Good	Good	±0.1	2.6	2.8	03:20

3. Modified *In vitro* dissolution study:

Prepared formulation F1 to F4 in vitro diffusion study was carried out by using modified dissolution apparatus Franz diffusion cell under specific condition such a temp maintained at $32 \pm 0.5^\circ\text{C}$. The diffusion was carried out for 12 h and the results showed in the Table 3 and graph was mentioned in the Figure 5.

Table 3: *In vitro* drug permeation Data of Diclofenac Sodium Transdermal patch

Time in hours	F1	F2	F3	F4
0	0	0	0	0
2	20	22	24	28
4	41	45	45	48
6	68	70	75	76
8	80	82	88	89
10	82	92	94	98
12	84	89	95	99

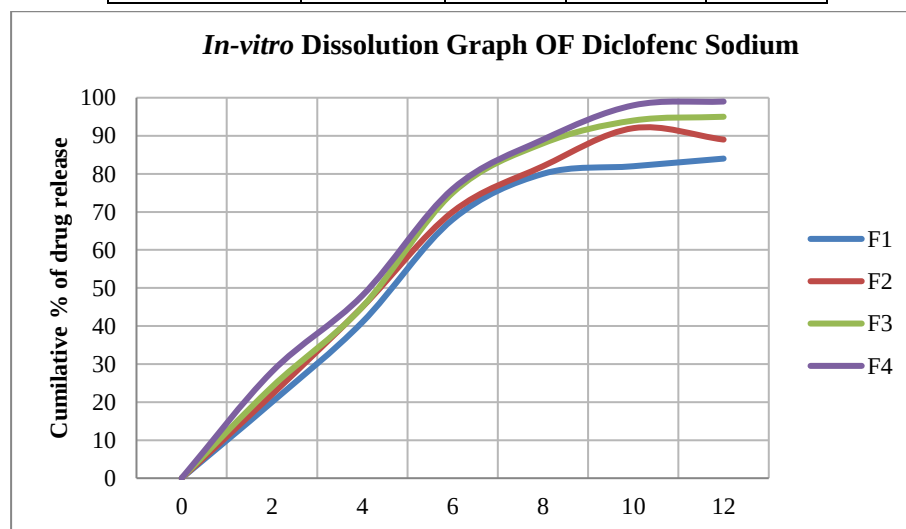


Figure 5: Cumulative % drug permeation of Diclofenac Sodium (F1, F2, F3, F4)

Drug interaction studies were carried out in order to determine the chemical interaction between drug and polymers. FTIR studies are revealed that there is no drug interactions between drug and polymer but only physical absorption. And the results were shown in the respective FTIR Spectrum.

CONCLUSION

In the present investigation an attempt was made to design and develop the formulation of Diclofenac sodium patches using different natural penetration enhances of menthol and Eugenol by solvent evaporation technique. Diclofenac Sodium patches was successfully formulated and evaluated as controlled release transdermal patches. The prepared patches F1 to F4 were evaluated for few physicochemical studies and all are within the limits. The

in-vitro drug diffusion studies were done by using modified dissolution apparatus Franz diffusion cell. Among all the formulations F4 was shown optimum drug release 99% for a period of 12h. This may be due to the presence of natural penetration enhancer Eugenol which promotes the penetration of drug.

Hence It is concluded that the Eugenol is Good Penetration Enhancer for the prepared transdermal patches which when compared to menthol.

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