Effect of Natural Oils as Permeation Enhancer for Transdermal Delivery of Telmisartan

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ABSTRACT

Aim of the present study was to determine the feasibility of natural oils as permeation enhancers for the development of a transdermal delivery system of telmisartan. The penetration-enhancing potential of olive oil and clove oil on *in-vitro* permeation of telmisartan across shed snake skin was studied. The patches were evaluated for their physicochemical characteristics, *in-vitro* drug release, and *in-vitro* permeation studies. The system containing hydroxypropyl methylcellulose and Eudragit L-100 (6:4) as matrix forming agents and dibutyl phthalate (20%) as plasticizer was selected as the best formulation for incorporation of natural oils as penetration enhancers. All transdermal patches were found to be uniform with respect to physical characteristics. Formulation (T7) containing 10% olive oil was found to be a promising natural permeation enhancer for transdermal delivery of telmisartan with the greatest cumulative amount of drug permeated (1536 μg/cm^2) over 24 h. The studies indicated that the feasibility of transdermal delivery of telmisartan as a patch is likely to suffice the therapeutic requirement.

1. Introduction

Transdermal delivery represents an attractive alternative to oral administration of drugs and is poised to provide an alternative to hypodermic injection, too [1].For thousands of years, people have placed substances on the skin for therapeutic effects and, in the modern era, a variety of topical formulations have been developed to treat local medical conditions. Transdermal drug delivery system (TDDS) is a widely accepted means of drug delivery and transdermal patches are devised to treat various diseases [2].TDDS are extended release dosage forms that can offer a stable systemic drug concentration and avoid first pass metabolism. They can even avoid gastrointestinal problems associated with drugs and low absorption. These therapeutic advantages reflect the higher marketing potential of TDDS[3]. Most of the drug molecules penetrate through the skin through intercellular micro route and therefore the role of permeation or penetration enhancers in TDDS is vitalas they reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells[4].Chemical and natural penetration enhancers act as accelerators or sorption promoters and can enhance drug flux.

Angiotensin converting enzyme (ACE) inhibitors are becoming major choice of drugs for long term therapy. Regardless of their good tolerability, ACE inhibitors are known for their activity. A more steady action could be achievable if ACE inhibitors are given in the form of their pro-drugs or their active forms systemically through skin [5]. The telmisartan is very good choice to treat hypertension

but the oral bioavailability of telmisartan at 40 mg and 160 mg is 42% and 58%, respectively. Food decreases bioavailability of telmisartan. For instance, when the 40 mg dose is administered with food, a decrease of about 6% is seen, and with the 160 mg dose, there is a decrease of about 20% [6,7].

2. Materials

Telmisartan was received as a gift sample from Glenmark Pharmaceutical Limited, India. Hydroxypropyl methylcellulose, ethyl cellulose, olive oil, dibutylpthalate were purchased from SD Fine chemicals, Mumbai. Eudragit L-100, ethanol, chloroform, dichloromethane, were purchased from Himedia, Clove oil purchased from RV essential. All chemicals and reagents used in the present study were of analytical reagent grade (AR grade).

3. Methods

Formulation of transdermal patch

The polymers hydroxypropyl methylcellulose (HPMC) and Eudragit L 100 were weighed and mixed in different ratios by keeping the total polymers weight at 2 g and dissolved in sufficient quantity of isopropanol-dichloromethane (60:40) solvent system using magnetic stirrer. The dibutyl phthalate and drug 20% w/w of polymer weight was incorporated to the polymers solution and mixed thoroughly by continuous stirring for 30 minutes to obtain a homogenous solution. On the basis of preliminary studies, the optimized polymers ratio 6:4 (HPMC:EL100) were mixed with permeation enhancers such as olive oil and clove oil. The resulting drug-polymers solution was poured in petridish. The aluminum foil was used as backing membrane (Table 1) [8,9,10].

Evaluation of transdermal patches

All the prepared formulations were subjected for preliminary screening to check the effect of various polymer combinations.

Table 1. Composition of transdermal patches

F. Code	Permeation Enhancer (% w/w of polymer weight)	HPMC : EL 100 (Ratio)
T1	-	2:8
T2	-	4:6
T3	-	6:4
T4	-	8:2
T5	Olive oil 2%	6:4
T6	Olive oil 5 %	6:4
T7	Olive Oil 10 %	6:4
T8	Clove oil 2%	6:4
T9	Clove oil 5%	6:4
T10	Clove oil 10%	6:4

Thickness

The thickness of the formulated transdermal patches was measured by digital screw gauge with least count at three different points and the average thickness was calculated [11].

Weight variation

A digital weighing balance was used to weighing ten randomly selected patches and average weight was calculated[11].

Moisture content

The formulated transdermal films were weighed individually and kept for 24 hours at room temperature in a desiccator containing fused calcium chloride. After 24 h, the films were reweighed repeatedly weighed until remained constant, after that percentage moisture content was determined [12].

Moisture uptake

The weighed films were kept in desiccators at room temperature for 24 h containing saturated solution of potassium chloride. After 24 h, the films were reweighed again and again, until a constant weight was obtained [12].

Flatness

Longitudinal strips were cut from randomly selected transdermal films, one strip taken from the center and another from the other side of the patch. The length of each strip was measured and any variation in length was recorded to assess the flatness uniformity. A 0% constriction was considered as 100% flatness [13].

Tensile strength

The tensile strength of the films was determined by using a self designed apparatus. Apparatus consists of a pan suspended by using a strong thread and the other end of the thread was attached with the centre of the patch. The entire assembly was held like a beam balance and weights were kept on the pan. Weights required to break the patch was noted [14].

Folding endurance

The folding endurance of the prepared patches was assessed by repeatedly folding a strip of the film at the same point until it either broke or showed visible cracks [12].

Drug content uniformity

Portion (2 cm^2) of each patch from different formulations was dissolved in dichloromethane and continuously stirred for 24 hours using a magnetic stirrer to extract the drug from the patch. After filtration and dilution, the drug content (%) was measured spectrophotometrically at a wavelength of 295 nm [14].

In vitro drug release studies

The *in vitro* drug release studies of formulated films were evaluated by using a modified USP type II dissolution apparatus using 900 ml of 40% ethanol in phosphate buffer solution pH 7.4 as dissolution medium. Commercially available water impermeable adhesive backing membrane was applied over the transdermal film and fixed on glass plate by using cyanoacrylate adhesive. The transdermal patches were covered with dialysis membrane. All dissolution studies were performed at 32 ± 0.5°C and paddle was rotated at 50 rpm. Samples were withdrawn at different time intervals and analyzedspectrophotometrically at 295 nm[15,16].

Ex vivo skin permeation study

Ex vivo permeation studies were carried out in Franz diffusion cell apparatus having capacity of 11 ml and effective surface area of 2 cm^2The shed snake skin was used as a skin barrier and it was immersed in phosphate buffer solution pH 7.4 (PSB 7.4) for 1 h before the start of the studies. The shed snake skin was mounted between donor and recipient compartments of diffusion cell. The patch was placed on the skin with the drug matrix side toward the donor side and backing membrane on the

upper side. Receptor fluid wassame as dissolution medium. The temperature was maintained at 32 ± 0.5°C and agitated at 50 rpm by magnetic stirrer. The samples were withdrawn at specific time and replaced with fresh equal amounts of diffusion medium. The samples were analyzedspectrophotometrically at 295 nm [17,18].

4. Results and Discussions

Smooth and transparent patches were achieved using a mixture of HPMC and EL 100, which provided good elasticity and flexibility. It was observed that increasing the concentration of the permeation enhancer result in slight increase in the weight and thickness of the patches. Drug content uniformity ranged between 92 and 97%. All films maintained the same strip length before and after cutting, indicating 100% flatness, with no constrictions observed, confirming that all patches had a smooth and flat surface. The films retained their integrity even with general skin folding. The physicochemical characteristics of the transdermal films are summarized in Table 2.

Table 2. Physicochemical characteristics of prepared transdermal patches

F. Code	Thickness (mm)	Weight Variation (mg)	Drug Contents	Folding Endurance	Flatness	Tensile Strength (kg/mm^2)
T1	0.426 ± 0.08	232.53 ± 2.20	92.78 ± 0.21	72 ± 5.08	100	0.367 ± 0.06
T2	0.434 ± 0.03	231.49 ± 4.48	96.50± 0.57	76 ± 5.37	100	0.381 ± 0.07
T3	0.483 ± 0.01	231.57 ± 3.63	96.39 ± 0.45	79 ± 4.11	100	0.364 ± 0.03
T4	0.517 ± 0.06	234.48 ± 1.90	97.63 ± 0.36	79 ± 4.15	100	0.355 ± 0.05
T5	0.475 ± 0.07	234.30 ± 3.19	95.34 ± 0.28	78 ± 6.72	100	0.388 ± 0.06
T6	0.488 ± 0.05	236.62 ± 3.23	95.49 ± 0.30	80 ± 3.91	100	0.402 ± 0.04
T7	0.477 ± 0.09	243.99 ± 1.74	96.12 ± 0.42	83 ± 4.18	100	0.408 ± 0.05
T8	0.482 ± 0.06	235.29 ± 1.88	97.65 ± 0.21	78 ± 6.25	100	0.396 ± 0.10
T9	0.476 ± 0.04	239.35 ± 2.61	93.81 ± 0.32	73 ± 5.76	100	0.372 ± 0.09
T10	0.484 ± 0.08	242.11 ± 2.12	95.24 ± 0.17	70 ± 3.93	100	0.390 ± 0.08

Moisture content and moisture uptake were measured to assess the effects of the hydrophilic (HPMC) and lipophilic (EL 100) polymers in the patches. The moisture content and moisture uptake percentage ranged from 2.81 to 6.23 and 3.64 to 8.85, respectively. The study showed that an increase in the concentration of the hydrophilic polymer (HPMC) led to higher moisture content and moisture uptake in the films.

In-vitro drug release studies

Drug release studies are required for predicting the reproducibility of the rate and duration of drug release. The importance of drug release from matrices has been known for ensuring the sustained release performance. The cumulative % drug release from mixed polymers without permeation enhancer (T1-T4) was found tobe 41%-55% over 24 h.

The highest percentage of drug release were found from formulation T3 (HPMC:EL 100, 6:4). These results indicated that the release of drug from patches increases with increasing concentration of HPMC except the formulation T4. The results of in-vitro drug release are shownin figure 1. This is due to the fact that dissolution of an aqueous soluble fraction of the polymer matrix leads to the formation of gelataneous pores[19].

Therefore, the formulation T3 was selected for incorporation of permeation enhancers in concentration of 2%, 5%, and 10% for olive oil and clove oil. Results indicated that release rate of drug increased 67%-86% (figure 2) and 59%-68% (figure3) with increases in concentration of olive oil and clove oil respectively.This enhancement in drug release may be attributed to the solubilizer and emulsifying properties of oleic acid present in olive oil[21], whereas clove oil containsterpene components which increase in the saturation solubility of drug within the patch [22].

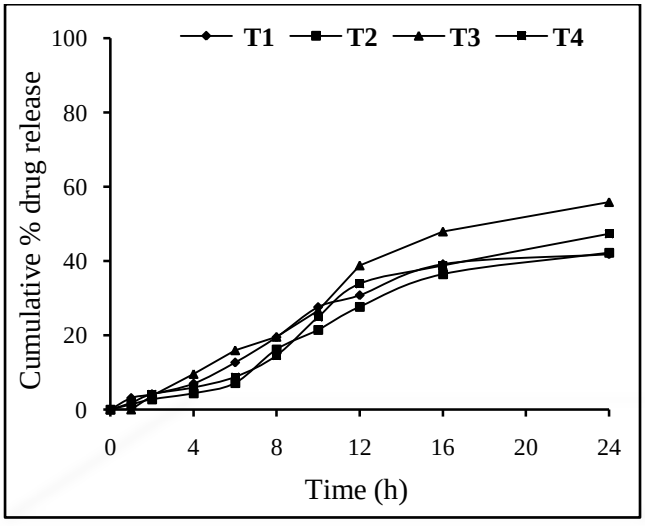

Figure 1.*In-vitro* drugrelease of telmisartan patches (HPMC/EL100) without permeation enhancer

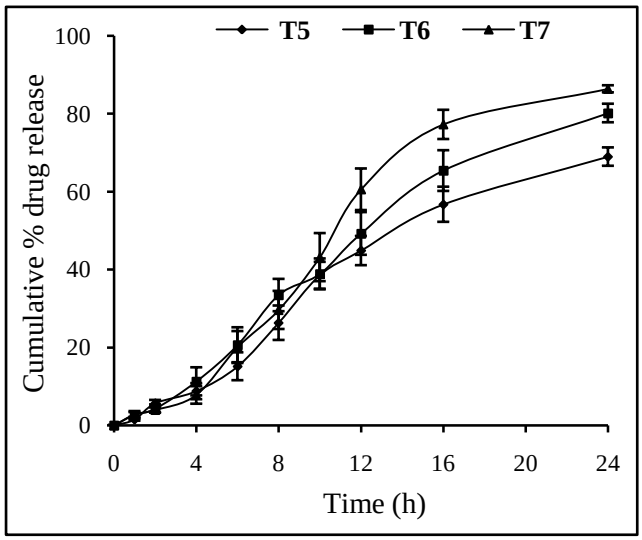

Figure 2. *In-vitro* drugrelease of telmisartan patches with olive oil as enhancer

***In-vitro* permeation studies**

After carrying out the in vitro dissolution studies, optimized formulations (T3, T7 and T10) of each batch were subjected to the *in-vitro*permeation studies. The results of drug permeation studies from optimized formulations with and without permeation

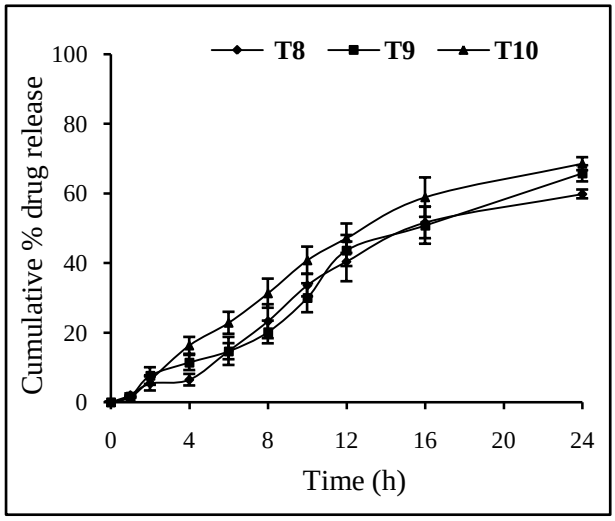

Figure 3. *In-vitro* drugrelease of telmisartan patches with clove oil as enhancer

enhancers using shed snake skin are depicted in figure 4. The formulation T3 (without enhancer) show cumulative amount of drugpermeated was 329 µg/cm^2 in 24 h with flux of 5.35 µg/cm^2/h. However, the transdermal patch containing 10% olive oil (T7) as a permeation enhancer, exhibited highest cumulative amount of drug permitted1536 µg/cm² over 24 hours,with a flux of 20.57 µg/cm²/h and 3.83 fold enhancement. Olive oil is thought to enhance permeation by increasing the membrane-vehicle partitioning tendency of the drug. Additionally, it has been suggested that vegetable oils penetrate the intracellular lipid phase of the membrane, increasing its fluidity and thereby reducing resistance to permeation, which can lead to an increase in flux [23].

Whereas the transdermal patches containing clove oil (T10) as permeation enhancer showed cumulative amount of drug permeated 1087µg/cm^2 in 24 h with flux 13.93 µg/cm^2/h and enhancement of 2.60 times. Several studies have shown that essential oils, such as clove oil

significantly enhance the permeability of both lipophilic and hydrophilic drugs. This effect is likely due to the binding to the stratum corneum, increasing the partition coefficient for lipophilic drugs and the diffusion coefficient for hydrophilic drugs [24].

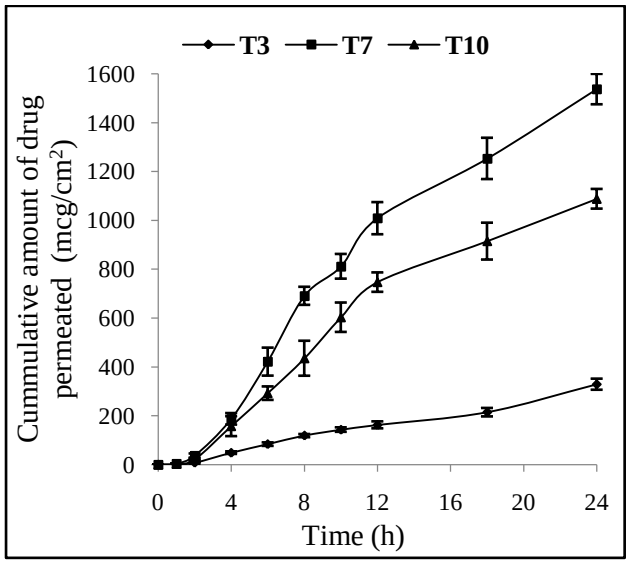

Figure 4. *In-vitro* permeation of telmisartanpatches

5. Conclusions

All the formulations showed good physicochemical properties such as thickness, weight variation, drug content, and folding endurance. The in vitro release data showed that drug release from the patch has been affected by concentration of the polymer. From this data, optimized formulations were screened. Effect of penetration enhancers such as olive oil and clove oil have been evaluated for optimized formulations using ex vivo permeation studies. These studies indicated that formulation T7 containing HPMC and EL 100 (6:4) with 10% olive oil as permeation enhancer found to be optimized formulation. Which gave maximum percent of drug release (86%) and amount of drug permeated (1536 µg/cm²) at 24 h.

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