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Formulation and *In-vitro* Evaluation of Matrix Type Transdermal Patches Containing Telmisartan

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ABSTRACT
Matrix type transdermal patches of telmisartan were aimed to develop to overcome the drawbacks by oral application. Patches of telmisartan were prepared using polymers such as hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC) and Eudragit L 100 (EL 100) as film formers, dibutyl phthalate as a plasticizer and span 20 and sodium lauryl sulphate as permeation enhancers. The solvent evaporation method was employed to develop the patches using aluminum foil as the backing membrane. The prepared patches were evaluated for physicochemical properties, *in vitro* release and *in-vitro* permeation studies across shed snake skin Franz diffusion cell. On the basis of *in-vitro* release performance, HPMC:EL 100 in the ratio of 3:2 (TA3) was selected for incorporation of permeation enhancers. The permeation studies showed that formulation containing 5% span 20 (TD3) exhibited greatest cumulative amount of drug permeated (1771.86 mcg) in 24 h. The formulation TD3 was concluded as optimized formulation is likely to suffice the therapeutic requirement.

Keywords: transdermal patch, permeation enhancer, Eudragit, nonionic surfactant, *in-vitro*, telmisartan

INTRODUCTION
Telmisartan is a selective angiotensin II receptor blocker that reduces blood pressure by specifically inhibiting AT1 receptors, adrenal gland signaling, and the smooth muscle in the vascular system. This action decreases vasoconstriction and reduces the influence of aldosterone release triggered by angiotensin II [1,2]. Telmisartan show low water solubility, classifying it as a class II drug, which limits its ability to permeate human lipid bilayers. After oral administration, telmisartan show maximum plasma concentration (C_{max}) within the first hour. The bioavailability of orally administered telmisartan is nonlinear from dose ranging 20 to 160 mg [3,4].

Transdermal drug delivery systems (TDDS) deliver drugs through the skin to the systemic circulation at a controlled rate and maintain therapeutically effective concentrations for an extended period [5]. The TDDS avoids the risks and discomfort associated with parenteral therapy and enhances patient compliance. Transdermal patches are also easy to remove when need arises [6]. TDDS bypasses the first-pass metabolism of liver, thereby increasing the bioavailability of drug and also reduce gastrointestinal side effects associated with conventional dosage forms. Currently, transdermal systems provide therapy for 1 to 7 days with controlled plasma drug levels, reducing the frequency of dosing. This reduction in dose frequency gives an associated decrease in potential side effects [7,8]. This study aims to deliver telmisartan transdermally, through matrix type of patches to enhance the bioavailability of the drug.

MATERIALS
Telmisartan was received as a gift sample from Glenmark Pharmaceutical Limited, India. Ethyl cellulose (EC), hydroxypropyl methylcellulose (HPMC), sodium lauryl sulphate (SLS), span-20, dibutyl pthalate were purchased from SD Fine chemicals, Mumbai. Eudragit L-100, ethanol, chloroform, dichloromethane, were purchased from Himedia, All chemicals and reagents used in the present study were of analytical reagent grade (AR grade).

METHODS

Formulation of transdermal patches

Matrix-type transdermal patches of telmisartan were prepared by using the solvent evaporation method with varying ratio of hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC) and Eudragit L 100 (EL 100). Keeping the total polymers weight at 2 g and dissolved in sufficient quantity of isopropanol-dichloromethane (60:40) solvent system using magnetic stirrer. Dibutyl phthalate as a plasticizer and drug 20% w/w of the polymer weight was added gradually into the polymer solution with continuous stirring for 30 minutes. The eight formulations were prepared of each HPMC:EL-100 and HPMC:EC by using same drug and different polymers ratio without permeation enhancer in order to determine the optimum combination of polymers and drug. The optimized polymers ratio 6:4 (HPMC:EL-100) were mixed with the permeation enhancers like sodium laury sulphate (SLS) and span-20 in three different concentrations of total polymers weight. The resulting drug-polymers solution was poured in petridish and aluminum foil was used as backing membrane. The composition of transdermal formulations is given in Table 1 [9,10].

Physical characterization of transdermal films

The prepared transdermal patches were evaluated for weight variation by individually weighing 10 randomly selected films. Thickness of patches was measured by micrometer at different points of every batch. [11] Drug content was determined by dissolving an accurately weighed portion of the patch in 100 ml of dichloromethane, which was then analyzed by UV spectrophotometer at 295 nm. Folding endurance was determined by repeatedly folding the film at the same place until it breaks and flatness was measured by determining percent constriction [12]. Tensile strength was determined by self constructed apparatus weight pulley method [10]. The moisture content and moisture uptake of prepared patches were determined by weighed individually and kept in desiccators containing activated calcium chloride and saturated solutions of potassium chloride respectively, at room temperature for 24 h and percentage of moisture content and uptake was calculated [13].

Table 1 Composition of telmisartan transdermal patches

Formulation Code	Permeation enhancer (% w/w of polymers weight)	HPMC:EL 100 (ratio)	HPMC: EC (ratio)
TA1	-	2:8	-
TA2	-	4:6	-
TA3	-	6:4	-
TA4	-	8:2	-
TB1	-	-	2:8
TB2	-	-	4:6
TB3	-	-	6:4
TB4	-	-	8:2
TC1	SLS 1%	6:4	-
TC2	SLS 2%	6:4	-
TC3	SLS 5%	6:4	-
TD1	Span-20 1%	6:4	-
TD2	Span-20 2%	6:4	-
TD3	Span-20 5%	6:4	-

In-vitro release studies

The *in vitro* drug release studies of prepared patches 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. The transdermal patches were covered with dialysis membrane. All dissolution studies were performed at 32±0.5°C at 50 rpm. Samples were withdrawn at different time intervals and analyzed UV spectroscopy (Shimadzu, Japan) [14,15].

***In-vitro* permeation studies**

In-vitro permeation studies were carried out in Franz diffusion cell apparatus with shed snake skin as a barrier. The shed snake skin 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 carefully sandwiched between the receptor and donor compartment. 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 was 40% ethanol in PBS 7.4 and agitated at 50 rpm by magnetic stirrer and temperature was maintained at 32±0.5°C. The samples were withdrawn at specific time intervals and replaced with equal amounts of diffusion medium [16,17].

Scanning electron microscopic study

The surface morphology of the optimized transdermal formulation TD3 was examined before and after permeation studies using scanning electron microscopy (Zeiss Evo 50). Samples patch was placed on an aluminum stub using a double-sided adhesive tape and making it electrically conductive by coating with a thin layer of gold palladium alloy in vacuum. The scanning electron microscope was operated at an acceleration voltage of 15 kV [18].

RESULTS AND DISCUSSION

Physical characterization of transdermal films

Smooth and transparent patches were obtained by polymer mixture of HPMC/EL 100 and HPMC/EC. The average weights of patches were varied from 231 to 243 mg, suggesting that the different batches were uniform in terms of weight and within acceptable limits. The thicknesses of films lying in range of 0.280 to 0.517 mm. The drug content was found in ranging from 92 to 97 %, which confirmed the uniformity of drug content across all batches. It is concluded that all patches had the same strip length before and after their cuts, indicating 100% flatness. No constrictions were observed indicating all patches had a smooth and flat surface. The tensile strength the of patches was found 0.355 to 0.515 kg/mm², which indicating that patches exhibit adequate flexibility and mechanical strength when applied to the skin over extended periods. The folding endurance was measured manually and found to range from 72 to 90. The moisture content and uptake were observed in the range from 2.14 to 6.19% and 2.37 to 8.85%, respectively. These findings suggest that the hydrophilicity of the polymers is directly related to the percentage of moisture content (figure 1) and moisture uptake (figure 2). The hydrophilicity order of the polymers was HPMC > EL 100 > EC. The observed pH was found in the range of 5.6 to 6.9, suggested that the patches will not induce skin irritation upon application.

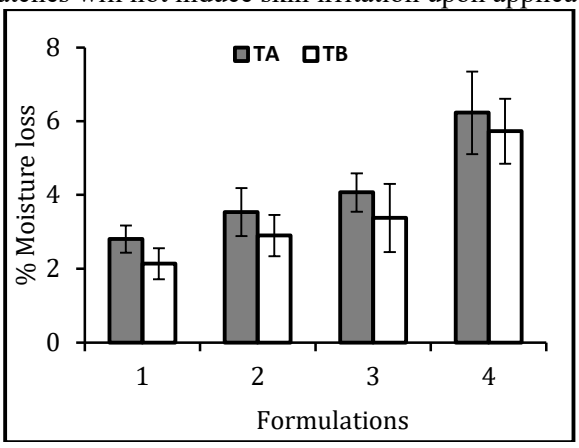

Figure 1. Percentage of moisture content

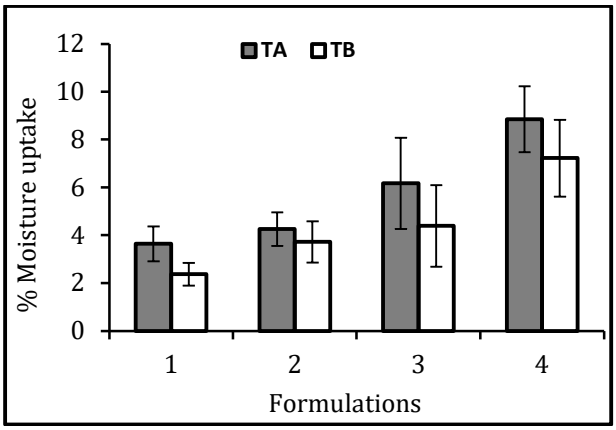

Figure 2. Percentage of moisture uptake

***In vitro* drug release studies**

Dissolution studies of transdermal patches are essential to verify the sustained release pattern. It is necessary to consistently maintain the drug concentration on the surface of the skin and ensure it remains higher than the drug concentration in the plasma to achieve a constant permeation and drug release rate. The cumulative drug release from the telmisrtan patches of without enhancer of HPMC:EL 100 was found 41-55% (figure 3) over a period of 24 hours. Similar results 37-46% (figure 4) were also found from the formulation containing HPMC:EC. The highest drug release 55% was found from the formulation TA3 containing HPMC/EL-100 (6:4), which was significantly greater than the lowest release of 37% from formulation TB1 (HPMC/EC, 2:8). The results showed that drug release from the patches increased as the increase in concentration of hydrophilic polymer. The increase in drug release was attributed to the higher concentration of the hydrophilic polymer in the polymer matrix [19]. This occurs because the dissolution of the water-soluble portion of the polymer matrix forms gel-like pores. These pores reduce the average diffusion path length of the drug molecules, facilitating a higher release rate into the diffusion medium [20].

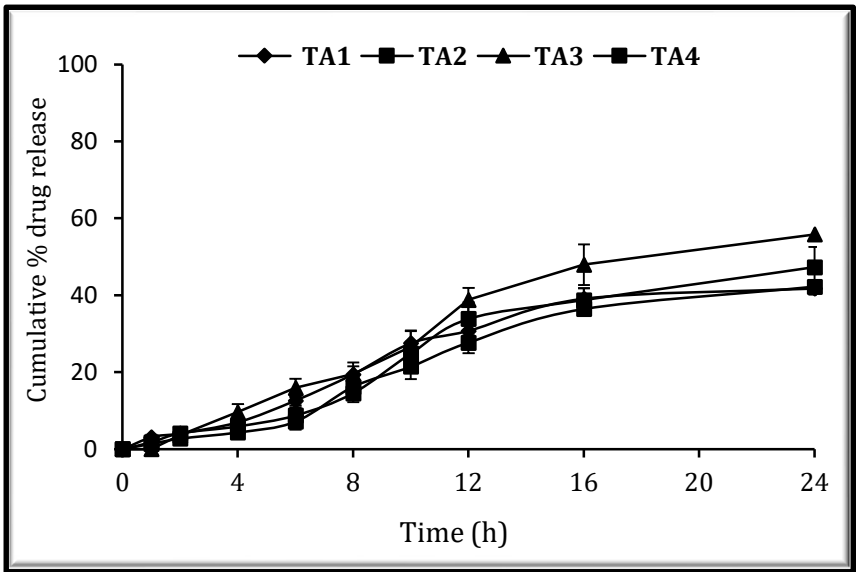

Figure 3. *In-vitro* release of telmisartan TDDS (HPMC/EL100) without permeation enhancer

Therefore, formulation TA3 show maximum drug release (55%) was selected for incorporation of permeation enhancers like SLS and span 20 in three different concentration *i.e.*1%, 2% and 5%. Moreover, the formulation TC1 containing ionic surfactant SLS 1% as permeation enhancer, exhibited the percentage of drug release 82%

in 24 h (figure 5). But further increase in concentration of SLS from 2% (TC2) to 5% (TC3), decreased in drug release was observed from 77% to 67% respectively, which may be due to formation of critical micelle concentration (CMC). Concentration of surfactants above CMC could probably make micelles of drug, which could be difficult to diffuse out from the patch [21]. Therefore, the formulations containing non ionic surfactant span-20 as a permeation enhancer, the release rate was increased from 70% to 90% with increases in concentration of span-20 1% to 5% respectively (figure 6). Among all formulations, the maximum percentage of drug release 90% was observed from the formulation TD3 containing 5% span-20. This increase in drug release in may be attributed to increased solubilization effect of non-ionic surfactant span-20 [22].

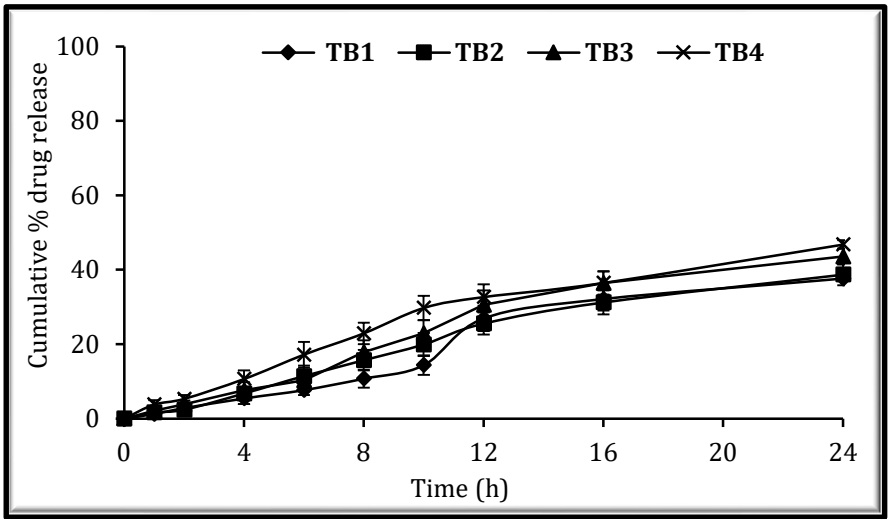

Figure 4. *In vitro* release of telmisartan TDDS (HPMC/EC) without permeation enhancer

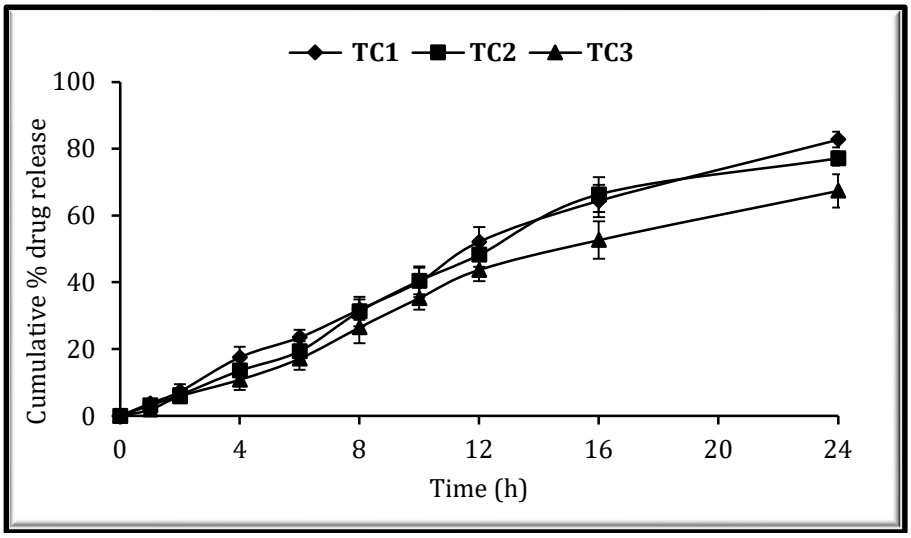

Figure 5: *In-vitro* release of telmisartan TDDS with SLS as enhancer

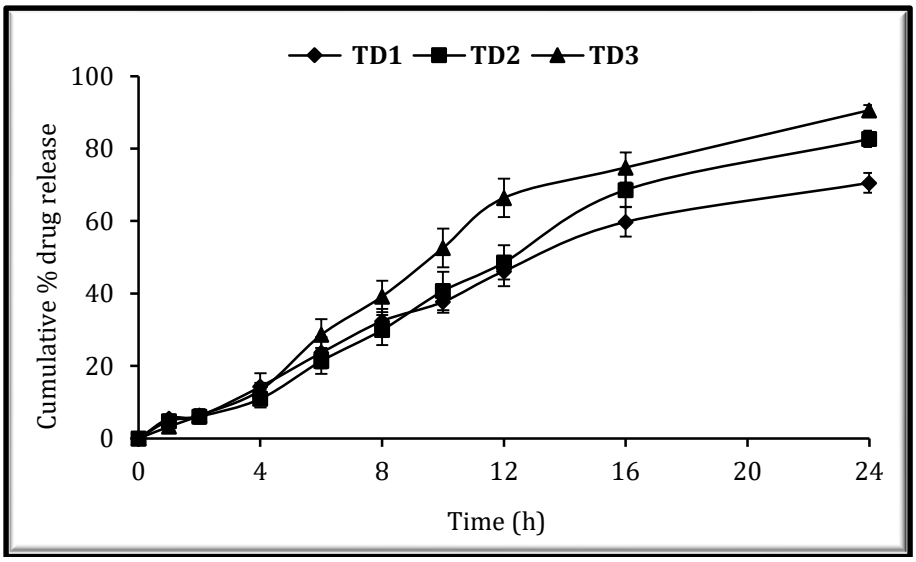

Figure 6: *In-vitro* release of telmisartan TDDS with span-20 as enhancer

***In-vitro* permeation studies**

In vitro skin permeation studies revealed that flux was significantly enhanced with the addition of permeation enhancers as compare to formulation (TA3) without permeation enhancer (Figure 7). The film (area of 2 cm^2) TD3 (span-20, 5%) exhibited the maximum cumulative amount of drug permeated (1771.86 µg/cm^2) in 24 h, which also showed that the addition of span-20 in transdermal films could satisfy permeation requirement of drug from transdermal drug delivery system to the systemic circulation. It has already been observed that nonionic surfactant like span-20 acts on the skin to produce enhancement in permeation of drugs by changing its permeability. These nonionic surfactants are lipophilic in nature and could be expected to penetrate skin easily and interact with the lipid matrix of stratum corneum of skin [23,24]. In contrast to SLS is ionic surfactant and expected to slowly penetrate the stratum corneum.

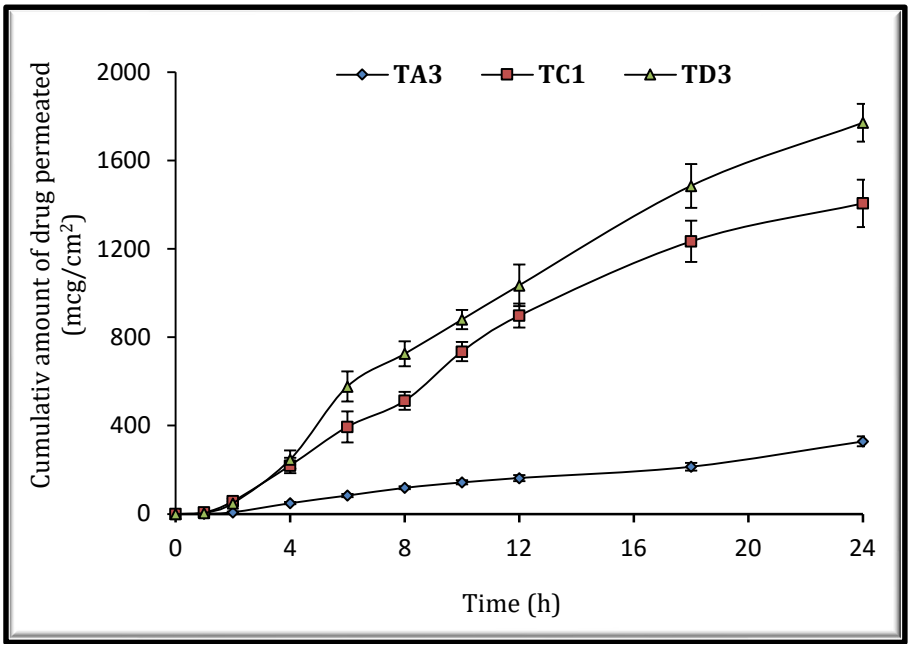

Figure 7. *In-vitro* permeation of telmisartan patches

The mechanism of penetration enhancement of ionic surfactant (SLS) may interact with keratin and lipid of stratum corneum cells, it alter the skin permeability by uncoiling the keratin filament, by increasing the fluidity of epidermal cells and also by increasing the hydration of skin due to hydrophobic interaction of alkyl chain with skin structure [25]. *In vitro* skin permeation results shows that, when the addition of permeation enhancers, flux gets increased significantly ($p < 0.05$) higher than control formulation (TA3) without permeation enhancer. The extent of flux enhancement factor with span-20 (TD3) was 4.37, higher than with SLS (TC1) 3.33 and control group (TA3). Lag time decreased significantly with the addition of span-20 and SLS. It has already been observed by other researcher [24], that the lag time is directly proportional to the diffusional path length of a molecule, which is, in turn, influenced by the tortuosity of the intercellular pathway in the stratum corneum [23].

Scanning electron microscopic study

The surface morphology of the transdermal patches, both before and after the in vitro permeation study, was examined using a scanning electron microscope (SEM) (Zeiss Evo, Germany). The results, shown in Figure 7, indicated that the drug was uniformly distributed within the prepared transdermal patch. After the permeation study, it was observed that the drug had been released from the patch onto the skin, allowing it to permeate through the skin into the systemic circulation.

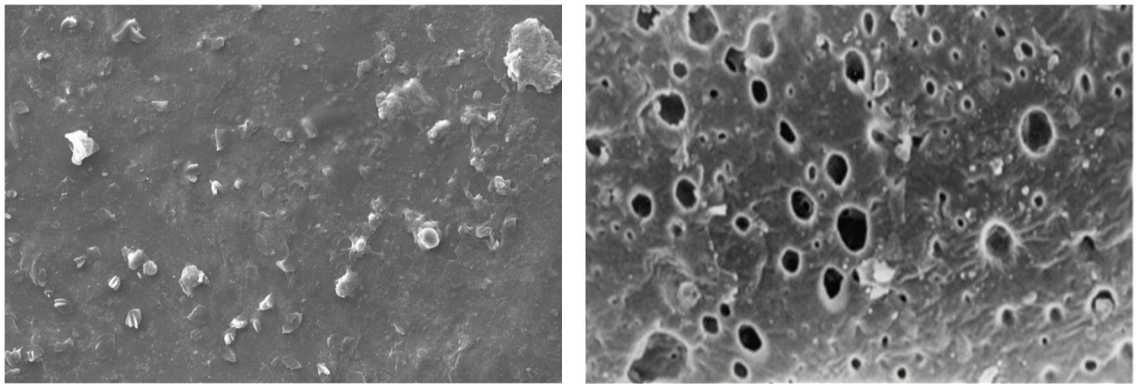

Figure 8. Scan photographs of telmisartan patch (TA3), a. Before permeation study, b. After permeation study

CONCLUSION

The prepared and optimized transdermal patches of telmisartan, using polymers like HPMC and EL 100 with span-20 as a permeation enhancer, demonstrated promising results. The studies suggest that the feasibility of delivering telmisartan through HPMC-EL 100 based matrix type transdermal patches containing nonionic surfactants as permeation enhancers. The developed transdermal drug delivery system of telmisartan could alternative to conventional oral dosage forms. These findings may offer researcher for further studies to optimize care of hypertensive patients.

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