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MATRIX TYPE TRANSDERMAL THERAPEUTIC SYSTEM CONTAINING CAPTOPRIL: FORMULATION OPTIMIZATION, *IN VITRO* AND *EX VIVO* CHARACTERIZATION*

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Abstract: Transdermal therapeutic systems (TTS) containing captopril were developed by using synthetic and pH independent polymers, Eudragit RL 100 and RS 100. The formulations were characterized in terms of their appearance, thickness, captopril content, *in vitro* release rate and diffusion profiles. *In vitro* release studies demonstrated controlled release for each formulation developed. *In vitro* and *ex vivo* diffusion rate studies were performed through various synthetic membranes with different thickness, pore size and type (hydrophilic and hydrophobic) and through human skin by using Franz diffusion cells. Type of membrane and composition of the formulation affected the diffusion profiles of captopril from the transdermal therapeutic systems. Transdermal therapeutic systems containing captopril were successfully prepared and especially two of the formulations (F15 and F16) are considered to be suitable to administer captopril *via* skin.

Key words: captopril, transdermal delivery, patch, synthetic membranes, human skin

Captopril is the first orally effective angiotensin converting enzyme inhibitor developed and marketed. It is used in the chronical treatment of hypertension, congestive heart failure and left ventricular dysfunction post-myocardial infarction as first agent because of the absence of side effects in the majority of the patients. It has a relatively short elimination half life in plasma (2 h) and low oral bioavailability (60-75%) (1). For these reasons, by applying this drug as a transdermal therapeutic system, dosing intervals will expand so that patient compliance will increase and side effects will be minimized. Appropriate physicochemical properties for potential transdermal delivery are low molecular weight, [217.29 Da], low polarity, low melting point (105-108^{o}C) and low daily therapeutic dose (2). Captopril possesses all these properties except for low polarity.

Physicochemical properties of transdermal therapeutic systems

Transdermal patches are flexible pharmaceutical preparations of varying sizes, containing one or more active ingredients. They are designed to support the passage of drug substances from the surface of the skin, through its various layers and into the systemic circulation (3). They have been developed with the objective of overcoming the hepatogastrointestinal first pass metabolism, duplicating the benefits of intravenous drug infusion and achieving systemic rate controlled drug delivery (4). Drug levels can be maintained in the systemic circulation, within the therapeutic window for prolonged periods of time. Thus, duration of drug action following a single administration of the drug can be extended and the frequency of dosing is reduced. Patient compliance and acceptability of the drug therapy can be improved. Another advantage is that the drug therapy can be terminated by simply removing the patch from the skin. Also, in the cases where oral delivery is contraindicated or when the drug is poorly absorbed from the gastrointestinal tract, transdermal route of drug administration may be used (5).

The aim of our study was to develop a captopril transdermal therapeutic system (TTS) by using Eudragit RL 100 and RS 100, pH independent syn-

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thetic polymers and to evaluate their physical and chemical characteristics, the *in vitro* release rates as well as *in vitro* and *ex vivo* diffusion profiles of captopril from these formulations using various synthetic membranes and human skin.

MATERIALS

Captopril (MN Pharmaceuticals, Turkey), Eudragit RL 100 and Eudragit RS 100 (Röhm Pharma, Germany), polyethylene glycol 400, 1-hexanol, 1-octanol, 1-decanol, hexyl acetate, acetone and hexane (all from Merck, Germany), polyisobutylene (BASF), synthetic membranes (Millipore, USA).

METHODS

Solubility measurement of captopril

Excess amount of captopril was added into 30 mL of deaerated distilled water in a 50 mL stoppered bottle and shaked in a constant temperature water bath (Certomat WR, B. Braun Biotech International) at 32 ± 0.5°C until saturation. At appropriate time intervals, 1 mL samples were withdrawn, diluted and assayed spectrophotometrically at 200.5 nm (Shimadzu UV 1240 instrument). The measurements were performed in triplicate. A calibration curve was used for the determination of the amount dissolved.

Preparation of transdermal therapeutic systems

Plasticizer (PEG 400) and polymer (Eudragit RL 100 and/or Eudragit RS 100) were dissolved in acetone, then captopril solution in acetone was added and stirred by using a magnetic stirrer (RO 5 Power IKA Labortechnik, Germany). A glass mould of 5 cm diameter was coated with aluminium foil as impermeable backing layer. The solution prepared was poured into this mould and was allowed to dry at room temperature. Acetone was used in the minimal amount enough to solve the polymer and the drug. The preparation method of the formulations containing penetration enhancers, is the same, except that the enhancer was added just before pouring into the mould. The formulations containing polyisobutylene (PIB) adhesive layer were prepared by adding the solution of PIB in hexane onto the dry transdermal film prepared and was allowed to dry at room temperature. The composition of the formulations are listed in Table 1.

Table 1. Compositions of the TTS formulations containing captopril

Code	Eud.RL 100 (g)	Eud.RS 100 (g)	PEG 400 (%)	Captopril (%)	Enhancer (%)	PIB (g)
F1	2.0	-	20	5	-	-
F2	2.0	-	20	10	-	-
F3	2.0	-	20	20	-	-
*F4 a	1.0	-	20	20	-	-
b	1.0	-	20	10	-	-
F5	1.5	0.5	20	20	-	-
F6	2.0	-	20	20	5 (Hexanol)	-
F7	2.0	-	20	20	5 (Octanol)	-
F8	2.0	-	20	20	5 (Decanol)	-
F9	2.0	-	20	20	5 (Hexyl acetate)	-
F10	2.0	-	20	20	-	0.5
*F11 a	1.0	-	20	20	-	-
b	1.0	-	20	10	-	0.5
F12	1.5	0.5	20	20	-	0.5
*F13 a	1.0	-	20	20	-	-
b	0.65	0.35	20	10	-	0.5
F14	1.3	0.7	20	20	-	0.5
F15	1.3	0.7	20	20	-	0.2
*F16 a	1.0	-	20	20	-	-
b	1.0	-	20	10	-	0.2
F17	2.0	-	20	20	-	0.1
*F18 a	1.0	-	20	20	-	-
b	1.0	-	20	10	-	-

* Double layered systems a: lower layer b: upper layer

Table 2. Properties of the membranes used in the diffusion studies.

Membrane	Pore size (μm)	Thickness (μm)	Type	Chemical structure
GVHP	0.22	125	Hydrophobic	PVDF (polyvinylidenflouride)
FHLP	0.45	175	Hydrophobic	PTFE (polytetraflouroethylene)
HAWP	0.45	180	Hydrophilic	Mixed cellulose ester
VCWP	0.1	105	Hydrophilic	Mixed cellulose ester
Human skin	-	-	Lipophilic	-

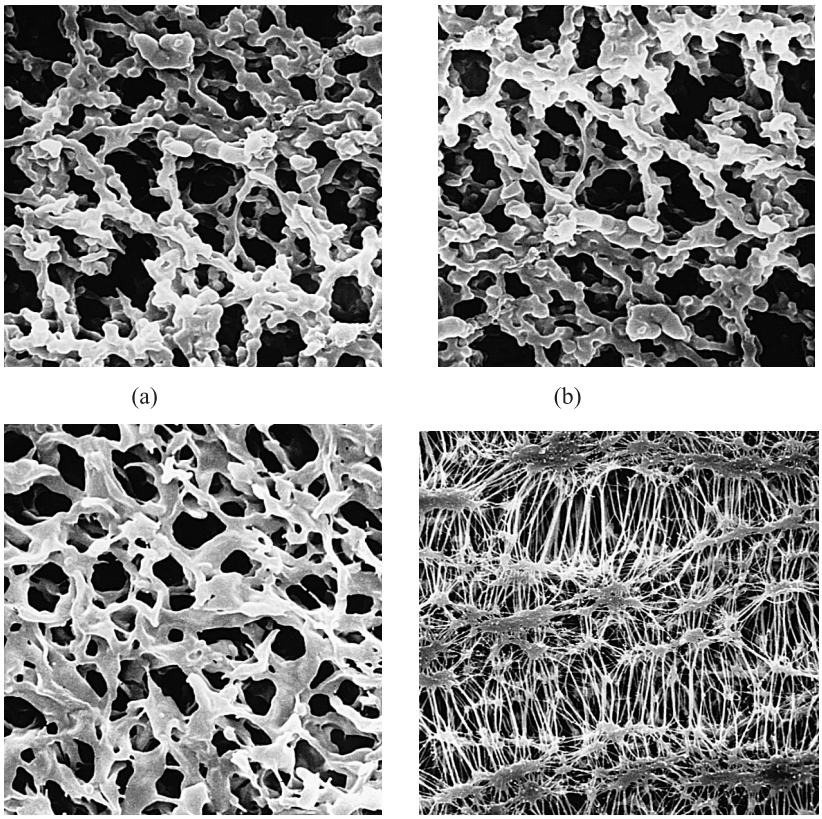

Figure 1. SEM photographs of (a) VCWP membrane, (b) HAWP membrane, (c) GVHP membrane and (d) FHLP membrane (15)

Macroscopic evaluation

General appearance, transparency, color, softness, homogeneity and flexibility of the TTSs were evaluated.

Thickness

Thickness of TTSs was measured at six different points using a micrometer, (LLG, Digital Caliper) with an accuracy of ±1 μm. Mean values are calculated and reported.

Captopril content

A sample of 3 cm diameter was cut from the TTS and divided into small pieces; these were put into 30 mL deaerated distilled water in a 50 mL stoppered bottle and shaken in a constant temperature water bath at 32 ± 0.5°C for 24 h. Then, the sample pieces were separated by filtering and extracted several times in the same way until no captopril was found in the filtrate. The filtrates were collected, diluted and assayed spectrophotometrically at 200.5 nm. The measurements were performed in triplicate.

In vitro release studies

In vitro release studies were performed using USP 26 paddle method. A sample of 3 cm diameter was cut from the formulation and sandwiched

between a 6 cm diameter watch glass and 18 mesh stainless steel, then put at the bottom of the dissolution vessel containing deaerated distilled water as dissolution medium, with screen facing upwards. A distance of 2.5 cm between the paddle and the surface of the screen was maintained during the test. The paddle speed was set at 50 rpm, temperature of dissolution medium was 32 ± 0.5°C. The vessel was covered with a plastic cover to minimize evaporation. Sink conditions were maintained throughout the experiment. One milliliter aliquots were withdrawn hourly for 7 h, diluted and assayed spectrophotometrically at 200.5 nm. Sample volume was replaced by deaerated distilled water. The release rate data were analyzed statistically. Captopril release kinetics data obtained from release rates were evaluated.

Diffusion studies

Diffusion experiments were conducted using Franz diffusion cells that have a receptor volume of 31 mL and a diffusional area of about 3.14 cm^2. The receptor chambers have side arms through which sample could be taken. Deaerated distilled water was used as the receptor phase. Various synthetic membranes with different properties (Tab. 2, Fig. 1) and excised human skin sample were used as the diffusion surface. The receptor compartment of the cells was maintained at 32 ± 0.5°C. Teflon coated magnets were used to agitate the receptor compartments to provide uniform mixing. Sink conditions were maintained throughout the experiment. At predetermined intervals, samples were taken from the receptor part and replaced with an equal volume of receptor phase. All samples were assayed using UV spectrophotometer.

Skin sample preparation

Excised human skin from a female volunteer (40 years old), who had undergone abdominal plastic surgery, was used. Immediately after excision, the skin was wrapped in aluminium foil and stored in polyethylene bags at -20°C until use. One night before the experiments, they were placed in a refrigerator at +4°C. Subcutaneous fat was removed by

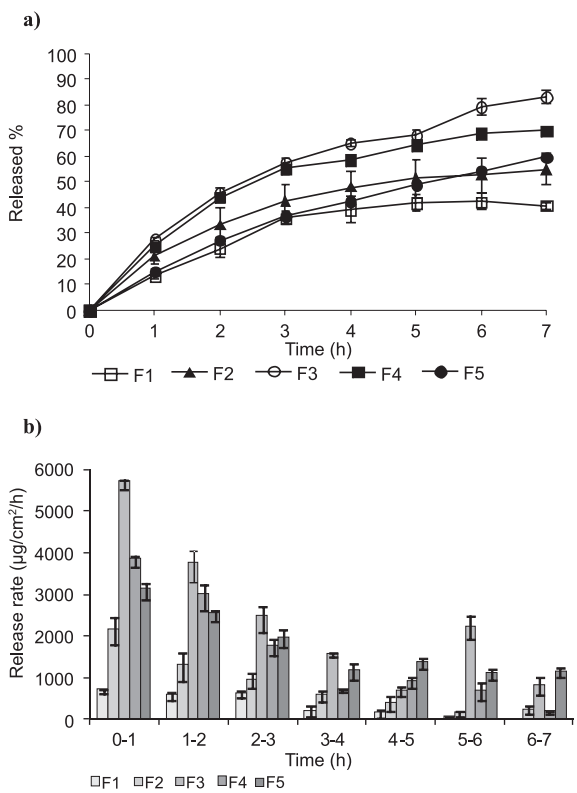

Figure 2. **a)** Effect of captopril concentration on the released percent of captopril from formulations (F1, F2, F3), addition of a second layer to F3 (F4) and addition of Eudragit RS 100 to F3 (F5). **b)** Effect of captopril concentration on the release rate of captopril from formulations (F1, F2, F3), addition of a second layer to F3 (F4) and addition of Eudragit RS 100 to F3 (F5) (the mean ± SD, n = 3)

Table 3. Thickness and captopril amount data of the transdermal therapeutic systems prepared.

Formulation code	Thickness (mm ± SD)	Captopril amount (% ± SD)
F1	1.000 ± 0.100	88.972 ± 3.028
F2	0.983 ± 0.029	97.471 ± 0.976
F3	0.983 ± 0.202	99.253 ± 0.310
F4	0.933 ± 0.058	98.325 ± 3.294
F5	1.050 ± 0.050	100.018 ± 1.011
F6	1.067 ± 0.115	98.711 ± 1.393
F7	1.033 ± 0.058	100.360 ± 1.011
F8	1.033 ± 0.029	99.829 ± 1.898
F9	1.017 ± 0.029	102.660 ± 1.119
F10	1.200 ± 0.100	96.359 ± 4.313
F11	1.217 ± 0.076	101.023 ± 3.319
F12	1.183 ± 0.076	101.426 ± 0.857
F13	1.167 ± 0.058	98.502 ± 1.613
F14	1.183 ± 0.029	99.621 ± 4.239
F15	1.160 ± 0.107	99.729 ± 0.847
F16	1.030 ± 0.049	100.108 ± 1.123
F17	1.060 ± 0.057	101.064 ± 1.078
F18	0.960 ± 0.062	101.275 ± 0.419

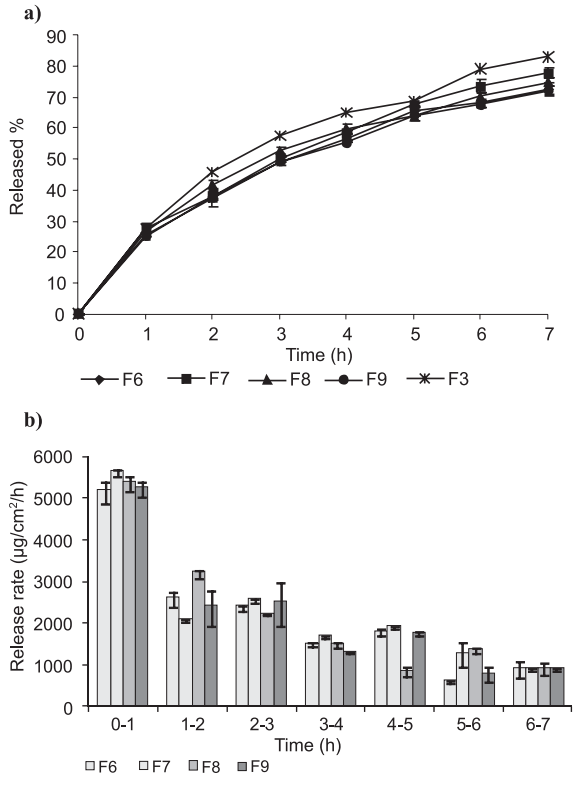

Figure 3. **a)** Effect of penetration enhancers on the released percent of captopril from formulations F6, F7, F8 and F9. **b)** Effect of penetration enhancers on the release rate of captopril from formulations F6, F7, F8 and F9 (mean ± SD, n = 3)

Table 4. Diffusion coefficients of captopril

Membrane	Formulation	Diffusion coefficient (D_{app})	± SD
FHLP	FM 10	$2.5264.\ 10^{-5}$	$15.0883.10^{-8}$
	FM 12	$8.4231.\ 10^{-6}$	$4.\ 8694.\ 10^{-8}$
	FM 13	$6.7638.\ 10^{-6}$	$8.5820.\ 10^{-9}$
	FM 15	$2.2390.\ 10^{-4}$	$1.6821.\ 10^{-8}$
	FM 16	$4.8147.\ 10^{-4}$	$4.6278.\ 10^{-8}$
	FM 17	$1.9685.\ 10^{-5}$	$7.1937.\ 10^{-7}$
GVHP	FM 11	$2.2576.\ 10^{-5}$	$1.3605.\ 10^{-11}$
	FM 13	$3.7474.\ 10^{-5}$	$4.0240.\ 10^{-7}$
	FM 14	$3.2082.\ 10^{-6}$	$2.2768.\ 10^{-9}$
	FM 17	$2.\ 5114.\ 10^{-6}$	$2.2527.\ 10^{-8}$
VCWP	FM 11	$1.6740.\ 10^{-7}$	$1.3123.\ 10^{-7}$
	FM 12	$8.1091.\ 10^{-6}$	$2.5483.\ 10^{-7}$
	FM 15	$4.1573.\ 10^{-8}$	$5.0136.\ 10^{-8}$
	FM 16	$1.2951.\ 10^{-4}$	$9.3690.\ 10^{-8}$
	FM 18	$7.4830.\ 10^{-3}$	$8.8621.\ 10^{-6}$
HAWP	FM 10	$7.8135.\ 10^{-6}$	$1.8759.\ 10^{-8}$
	FM 11	$3.9043.\ 10^{-6}$	$7.8238.\ 10^{-8}$
	FM 14	$3.2082.\ 10^{-6}$	$2.2768.\ 10^{-9}$
	FM 16	$9.9766.\ 10^{-9}$	$3.8418.\ 10^{-9}$
Human skin (Epidermis)	FM 15	$5.9920.\ 10^{-5}$	$1.7395.\ 10^{-7}$
	FM 16	$3.2502.\ 10^{-7}$	$5.3471.\ 10^{-7}$
	FM 18	2.9125	$3.2280.\ 10^{-7}$

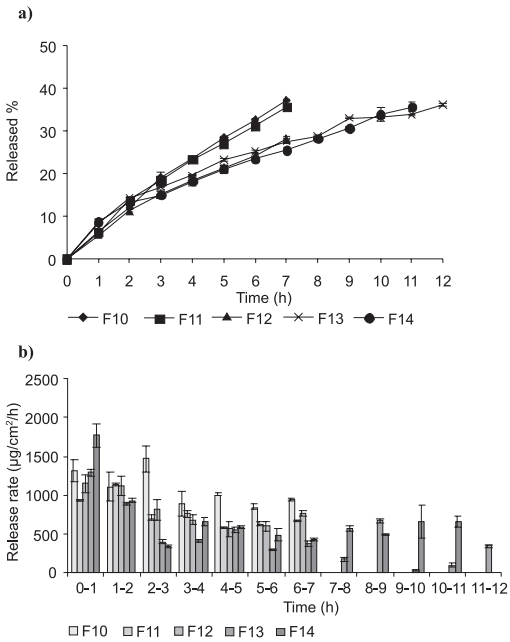

Figure 4. **a)** Effect of polyisobutylene adhesive layer on the release percent of captopril from formulations F10, F11, F12, F13 and F14. **b)** Effect of polyisobutylene adhesive layer on the release rate of captopril from formulations F10, F11, F12, F13 and F14 (the mean ± SD, n = 3)

means of a scalpel and the skin was immersed in Ringer solution at 60 ± 1°C for 90 s. Viable epidermis layer was peeled off and used for permeation experiments (6).

Data analysis

Apparent diffusion coefficients were calculated according to the following equation of Higuchi (7):

$$D_{app} = [(slope)^2 \times \pi] / 4C^2$$

where: D_{app} = apparent diffusion coefficient; slope - when the amount of drug released to the receptor per unit area is plotted *versus* square root of time, a straight line should be obtained, the slope of which is related to the release rate of captopril. Regression analysis was used to calculate the slope; C = the initial concentration of captopril.

Statistical analysis

The results were expressed as the means ± standard deviations. Unpaired, two-tailed *t*-tests were performed at each time point. The threshold for statistical significance was at $p < 0.05$.

RESULTS AND DISCUSSION

Solubility measurement of captopril

The equilibrium solubility of captopril in deaerated distilled water was found to be 109 ± 0.967 mg/mL, indicating the sink condition limits for the *in vitro* release rate and diffusion studies.

Formulation development

Eudragit RL 100 and RS 100 were solved in acetone, poured into a glass mould and dried at room temperature. As the film obtained was very rigid, addition of a plasticizer was needed. PEG 400 as a plasticizer suitable for Eudragit was added in different ratios. Best flexibility for the application to the skin was achieved with 20% PEG 400. Aluminium foil was selected as backing layer. The amount of captopril, which has to penetrate through the skin per hour for providing effective plasma concentration is 1488 μg/h (8). It means that this amount must be released from the patch in order to achieve a controlled release system. Therefore, captopril amount was optimized according to release rate data obtained.

Physicochemical properties of transdermal therapeutic systems

All the formulations prepared were evaluated macroscopically and they were all transparent, colorless, soft, flexible and homogen films. Thickness and captopril content of TTSs are shown in Table 3; thickness values were approximately 1 mm and captopril amounts were found out to be within the range of 88.972 ± 3.028% and 102.660 ± 1.119% when all the formulations to be evaluated are considered.

***In vitro* release studies**

Formulation F1 contains 5% and formulation F2 10% captopril (Tab. 1) and their captopril release rates were not sufficient in order to achieve effective plasma concentration (Fig 2a and b), because the amount of captopril, which has to penetrate through the skin per hour for providing effective plasma concentration is 1488 μg/h (8), which means that this amount must be released from the patch. When captopril amount was increased to 20% (F3), the release was fast enough to reach the required rate, thus drug amount was fixed at 20%. A higher amount of captopril was not added, as it leads to crystallization of captopril (9). Park et al. found out that for transdermal captopril patches prepared by using polyacrylate adhesives, the optimum captopril concentration was 20%. Captopril crystals occurred when it was used in 30% and higher ratios. Formulations F4 and F5 were prepared in order to control the burst effect seen with F3 during the first three hours (Fig. 2a and b). F4 is a double layered Eudragit RL 100 formulation containing 20% captopril in the lower layer and 10% captopril in the upper layer. F5 is a formulation containing 20% captopril and a mixture of Eudragit RL 100 and RS 100. The problem of burst effect was almost overcome with F4 and F5, especially F5. When compared with F3, it can be seen that release rates from F4 and F5 are significantly lower than F3 ($p < 0.05$) (Fig. 2b).

Penetration enhancers are substances which facilitate the absorption of substances by temporarily diminishing the impermeability of the skin. They should be non-toxic, non-irritating and non-allergenic, they should have no pharmacological activity within the body. When the patch is removed from the skin, barrier properties should return rapidly and fully. They should be compatible both with formulation excipients and drugs. They also should be cosmetically acceptable with an appropriate skin "feel" (10). Penetration capacity of captopril from gel formulations (11) as well as from TTS (12, 13) were studied. Wu et al. investigated the effect of various penetration enhancers on the *in vitro* release profile of captopril; hexanol, octanol, decanol and hexyl acetate were found to be the most enhancing ones. For this reason F6, F7, F8 and F9 were prepared by addition of these enhancers to the formulation F3 (Tab. 1). The release percent from formula-

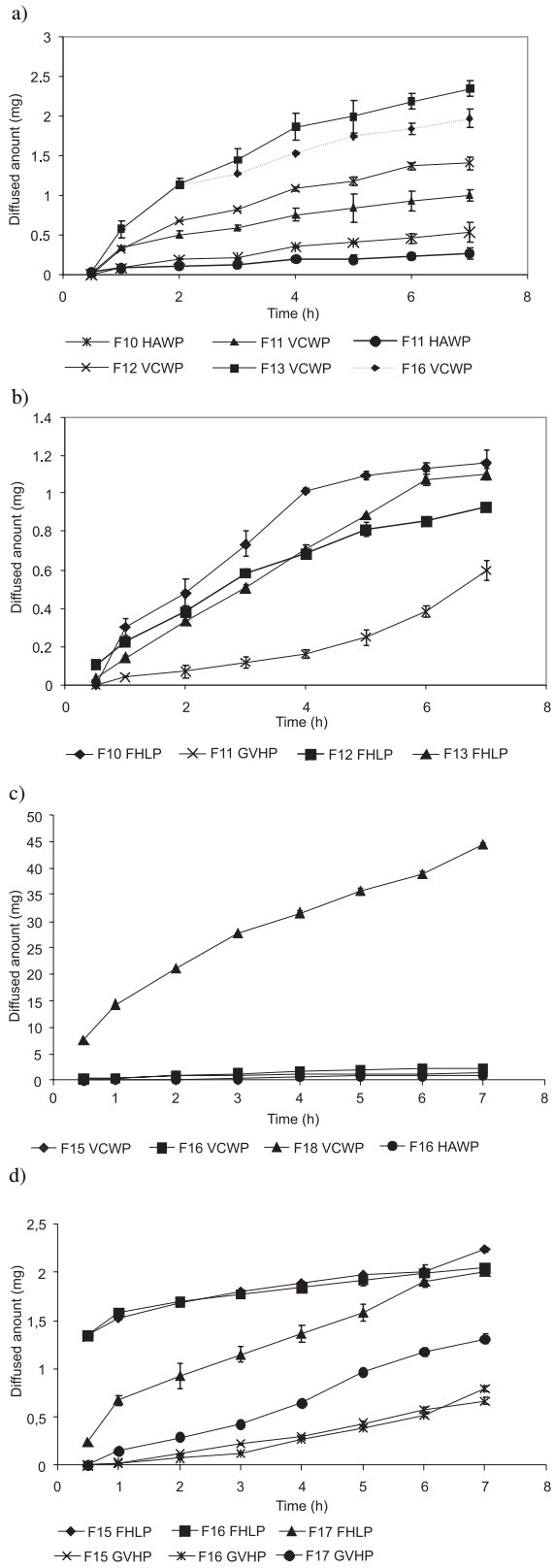

Figure 5. **a)** Effect of hydrophilic membranes on the diffusion of captopril. **b)** Effect of hydrophobic membranes on the diffusion of captopril. **c)** Effect of PIB amount on the diffusion of captopril through hydrophilic membranes. **d)** Effect of PIB amount on the diffusion of captopril through hydrophobic membranes (the mean ± SD, n = 3)

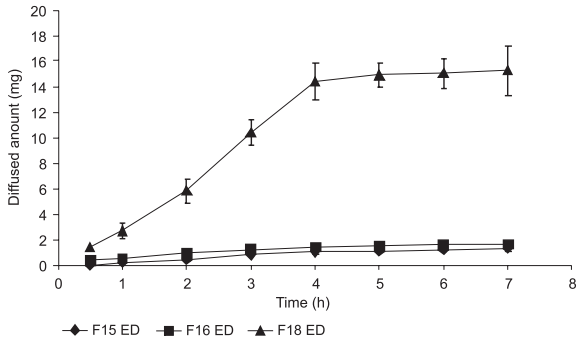

Figure 6. Diffusion of captopril through human epidermis (the mean ± SD, n = 3)

tions containing penetration enhancers (F6, F7, F8 and F9) were compared with F3 (Fig. 3a). No significant difference between the release profiles were seen ($p > 0.05$). Addition of these substances to the patch did not alter its *in vitro* dissolution characteristics, and they may be useful for the penetration of the drug. The release rates of captopril from formulations containing penetration enhancers (F6, F7, F8 and F9) are shown in Figure 3b.

In order to evaluate the effect of the addition of an adhesive layer, formulations F10, F11 and F12 were prepared by the addition of polyisobutylene layer on F3, F4 and F5, respectively (14). It was seen that in addition to its adhesive effect, PIB layer also decreased the burst effects and controlled the release of captopril (Fig. 4a and b). Release rates from F10, F11 and F12 were significantly lower than F3, F4 and F5, respectively ($p < 0.05$), due to the rate controlling effect of PIB. As a significant decrease was observed in the burst effect, F13 and F14 were prepared by changing the Eudragit RL 100 and RS 100 ratios of F11 and F12 (Tab. 1). F14 started to disperse in the dissolution medium after 11 h, so that further release could not be followed. It was seen that the release rate from F13 was significantly lower than F11 ($p < 0.05$) (Fig. 4a and b). As both formulations contain PIB layer, this difference may be attributed to the addition of Eudragit RS 100. No significant difference was found between the release rates from F12 and F14 ($p > 0.05$), both contain Eudragit RS 100 and PIB layer and increase in the amount of Eudragit RS 100 did not cause a significant effect (Fig. 4a and b).

Diffusion studies

The best *in vitro* release profiles according to duration of effect and release rate per hour were obtained with formulations containing PIB layer. For this reason, these formulations (F10 - F14) were chosen to be examined for their diffusion properties through different types of synthetic membranes (hydrophilic and hydrophobic) with different pore size and thickness (Tab. 2). Diffusion profiles of captopril from the transdermal therapeutic systems are shown in Figure 5a-d. When using HAWP membrane the diffusion rate of captopril was lower than with VCWP membrane (Fig. 5a). This result may be attributed to the thickness of the HAWP membrane (Tab. 2). Diffusion rates of captopril when using hydrophobic membranes (GVHP and FHLP) were slower than the rates found when using hydrophilic membranes (HAWP and VCWP). Effective concentration of captopril was not achieved as it can be seen from the diffusion profiles (Fig. 5b).

Formulations F15, F16, F17 and F18 were prepared by reducing the amount of PIB in order to achieve sufficient release of captopril. Formulation F15 was prepared by reducing PIB amount to 0.2 g while keeping other ingredients of F14 constant. Formulations F16 and F17 were again prepared by reducing PIB amount to 0.2 g while keeping other ingredients of F11 and F10 constant, respectively. F18 formulation was prepared without using PIB while keeping other ingredients of F11 constant. The reduced amount of PIB in the formulations (F15, F16, F17) affected the diffusion profiles both when using hydrophobic (Fig. 5c) and hydrophilic (Fig. 5d) membranes.

Diffusion of captopril from human epidermis was investigated with formulations F15, F16 and F18. Formulation F17, containing 0.1 g PIB, was not used because of its poor adhesive property to the skin. F18 formulation was used in diffusion studies both with synthetic membranes and human epidermis in order to investigate the effect of PIB as a rate limiting layer. Diffusion studies conducted with for-

mulations F15 and F16 by using synthetic membranes and human epidermis showed that effective concentration of captopril can be obtained (Fig. 6).

Data analysis

Apparent diffusion coefficients calculated according to the equation of Higuchi can be seen in Table 4. The highest diffusion coefficient was observed with formulation F9 by using human epidermis. The lowest diffusion coefficient was observed with formulation F16 by using HAWP membrane. Diffusion rates of captopril when using hydrophobic membranes (GVHP and FHLP) were slower than the rates found when using hydrophilic membranes (HAWP and VCWP) (Fig. 5a,b). Diffusion coefficient data were also lower when hydrophobic membranes were used and higher when hydrophilic membranes were used. The effect of reduced amount of PIB observed in diffusion rate graphics were also observed in the diffusion coefficient data.

CONCLUSION

The best *in vitro* release profiles according to duration of effect and release rate per hour were obtained with formulations containing PIB layer. For this reason, these formulations (F10, F11, F12, F13 and F14) were also examined for their diffusion properties through synthetic membranes with different nature (hydrophilic and hydrophobic), different pore size and different thickness. According to diffusion study results, new formulations were developed and the best of them were also investigated with human epidermis. Type of the membrane used and the composition of the formulation affected the diffusion profiles of captopril from the transdermal therapeutic systems. Finally, it can be concluded that the captopril containing transdermal therapeutic systems were successfully prepared and especially with the formulations F15 and F16, captopril can be administered *via* skin. Animal studies should be carried out to assess these results before going into clinical trial.

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Declaration of interest

The authors report no declarations of interest.

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