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ORIGINAL RESEARCH

Mechanical evaluation of matrix type transdermal therapeutic systems containing captopril

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ABSTRACT

The objective of this study was to evaluate the mechanical properties of transdermal therapeutic systems (TTS) containing captopril together with synthetic and pH independent polymers, Eudragit RL 100 and RS 100. The formulations were characterized in terms of their adhesiveness and bioadhesiveness by using texture analyser. These optimum formulations were chosen according to the results of our previous study regarding *in vitro* dissolution and *ex vivo* diffusion rate studies through excised human skin by using *Franz Diffusion Cell.* Results indicated that the mechanical properties of the formulations were suitable to be used as a transdermal patch.

Keywords: captopril, transdermal therapeutic system, patch adhesiveness, patch bioadhesiveness, texture analyser

INTRODUCTION

Captopril (1-[(2S)-3-mercapto-2-methyl propionyl]-L-proline) is used in chronical treatment of hypertension and congestive heart failure as first agent, because of the absence of side effects in the majority of patients (1-6). The drug is considered as a drug of choice in antihypertensive therapy due to its effectiveness and low toxicity (7-10). It is an orally effective angiotensin I converting enzyme inhibitor (1). The drug is freely soluble in water (125–160 mg/ml, at pH 1.9) with pKa of 3.64 at 25°C and its partition coefficient is pH- dependent (11,12). It has a relatively short elimination half-life in plasma (1-3 h) and low oral bioavailability (% 60-75) (1,13-15). For these reasons, by applying this drug as a transdermal therapeutic system, dosing time intervals will be expanded so that patient compliance will be arised and side effects will be minimised. Candidate drug for transdermal drug delivery should have physicochemical properties such as low molecular weight, [217.29 Da], low polarity, low melting point (105-108ºC) and low daily therapeutic dose (50-75 mg) (2). Captopril possesses all these properties except for low polarity.

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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 (16). 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 alternatively (17).

The adhesive performance of a transdermal therapeutic system is a critical factor determining its drug delivery, therapeutic effect and patient compliance. It is essential to test the adhesive properties of a transdermal therapeutic system in its final form to ensure acceptable adhesive quality (16). Poor adhesion results in improper dosing of the patients, patches that fail to adhere for their prescribed time period must be replaced more often, thereby increasing the patient's cost. Lack of adhesion is also a safety issue. There is potential accidental dosing of children who may pick up fallen patches. Death and other serious medical problems have occurred when accidentally exposed to certain patches (18,19).

The aim of this study was to evaluate the mechanical properties of transdermal therapeutic systems (TTS) containing captopril. TTS formulations were developed by using synthetic and pH independent polymers, Eudragit RL 100 and RS 100. Optimum formulations were chosen according to the results of our previous study regarding *in vitro* dissolution and *ex vivo* diffusion rate studies through excised human skin by using *Franz Diffusion Cell*. Adhesiveness and bioadhesiveness of the TTS containing captopril were determined with texture analyser for the evaluation of mechanical properties of the patches.

MATERIALS

Captopril (Mustafa Nevzat Pharmaceuticals, Turkey), Eudragit RL 100 and Eudragit RS 100 (Evonik Röhm Pharma, Germany), polyethylene glycol 400 (Merck, Germany), acetone (Merck, Germany), polyisobutylene (BASF), hexane (Merck, Germany) and other materials were all of analytical grade.

Table 1. The composition of the formulations of transdermal therapeutic systems containing captopril with and without PIB

Formulation	Eudragit RL 100 (g)	Eudragit RS 100 (g)	PEG 400 (g)	Captopril (g)	Acetone (ml)	PIB (g)	n-hexane (ml)
FM1 (with PIB)	1.3	0.7	0.4	0.4	7 + 5	0.2	10
FM2 (with PIB)	1 + 1	-	0.2 + 0.2	0.2 + 0.1	7 + 5	0.2	10
FM1 (without PIB)	1.3	0.7	0.4	0.4	7 + 5	-	-
FM2 (without PIB)	1 + 1	-	0.2 + 0.2	0.2 + 0.1	7 + 5	-	-

METHODS

Preparation of Matrix Type Transdermal Therapeutic Systems Containing Captopril

Plasticiser (PEG 400) and polymer (Eudragit RL 100 and/or Eudragit RS 100) were dissolved in acetone, then captopril solution in acetone was added to the polymer-plasticiser mixture and stirred by using a mechanical shaker (Gerhardt, 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 minimum amount enough to solve the polymer and the drug. The formulations containing polyisobutylene (PIB) adhesive layer were prepared by adding the solution of PIB in hexane onto the prepared dry transdermal film and was allowed to dry at room temperature (20). The compositions of the formulations are listed in Table 1.

Determination of the Adhesive Properties of Matrix Type Transdermal Therapeutic Systems Containing Captopril

The probe tack test was performed with the TA.XT plus Texture Analyser (Stable Micro Systems, UK, Godalming, Surrey) (Figure 1) with the following test parameters: test speed 0.05 mm/s, return speed 1.00 mm/s, applied force 300.0 g, contact time 0.01 s, n = 6. The spherical probe consisted of stainless steel with a diameter of 1 inch. The specimens of transdermal systems were placed on the working platform of the Texture Analyser with a double

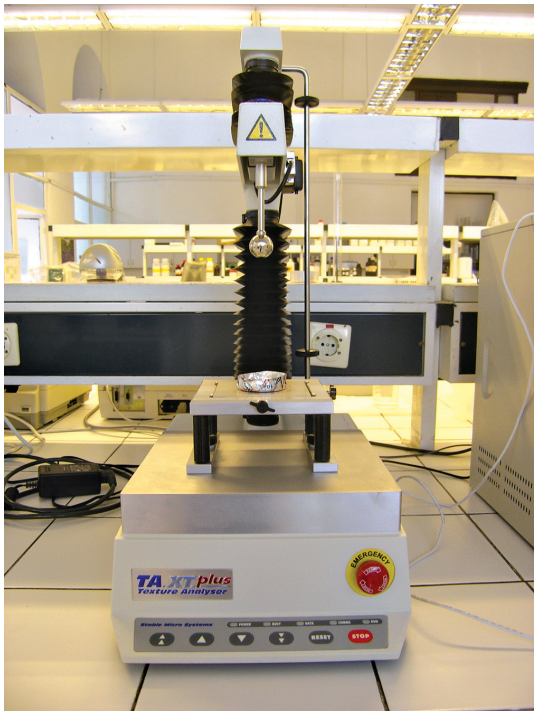

Figure 1. Texture Analyser (Stable Micro Systems, UK, Godalming, Surrey)

sided band. Using the test parameters above, the mean adhesive force (g) ± SD and the mean area under the curve (N.sn) ± SD were determined (21).

Determination of the Bioadhesive Properties of Matrix Type Transdermal Therapeutic Systems Containing Captopril

The probe tack test was performed with the TA.XT plus Texture Analyser (Stable Micro Systems, UK, Godalming, Surrey). Abdominal skin samples of Wistar albino rats were used for the determination of bioadhesive properties of matrix type transdermal therapeutic systems. Abdominal hair was removed using an electrical razor (Figure 2). Excised full thickness skin samples were placed on the working platform of the Texture Analyser with a double sided band. 50 µl normal saline solution at 37 ºC was applied on the surface of the skin just before the experiment. The cylindrical probe P10 Delrin was used for the test and the backing layer side of the transdermal patch was attached to this probe with the help of double sided band so that the release layer could contact with the skin during the test. The following test parameters were used: test speed 1.00 mm/s, return speed 1.00 mm/s, applied force 254.9 g, contact time 20 s, n = 6. The mean adhesive force (g) ± SD and the mean area under the curve (N.sn) ± SD were determined (22).

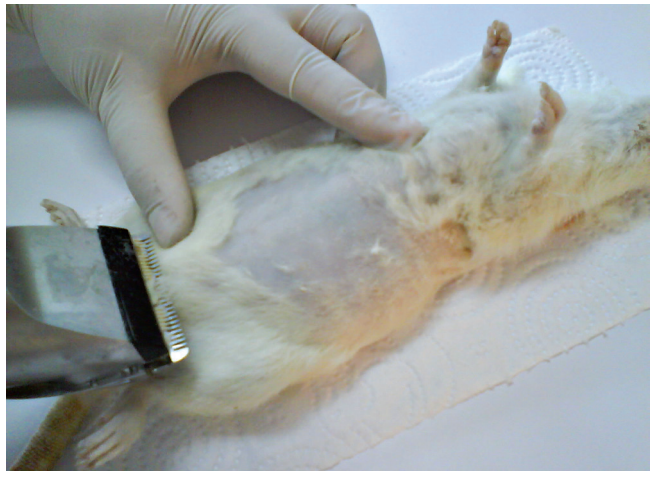

Figure 2. Removal of the rat abdominal hair with an electrical razor

Animals

All experimental protocols were approved by the Marmara University (MU) Animal Care and Use Committee. Approval date and number: 26.03.2010-14.2010.mar. Male or female Wistar albino rats (250- 300 g), supplied by the MU Experimental Animal Implementation and Research Center (DEHAMER), were kept at a constant temperature (22 ± 1º C) with 12 h light and dark cycles. All animals in the study were nourished with pellet diet and water ad libitum.

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

Preparation and Optimisation of Matrix Type Transdermal Therapeutic Systems Containing Captopril

TTS formulations were developed by using synthetic and pH independent polymers, Eudragit RL 100 and RS 100. All the formulations that are mentioned in our previous study (20) were evaluated for their macroscopic properties (general appearance, transparency, color, softness, homogeneity and flexibility), thickness and captopril content. Optimum formulations (FM1 and FM 2) were chosen according to the results of our previous study regarding *in vitro* dissolution and *ex vivo* diffusion rate studies through excised human skin by using *Franz Diffusion Cell.*

Table 2. The mean adhesive and bioadhesive forces (g) ± SD and the mean area under the curve (AUC) (N.sn) ± SD of the formulations

Formulation codes	The mean adhesive force (g) ± SD	The mean area under the curve (AUC) (N.sn.) ± SD	The mean bioadhesive force (g) ± SD	The mean area under the curve (AUC) (N.sn.) ± SD
FM 1 (with PIB)	590.341 ± 44.386	3.108 ± 0.531	290.952 ± 39.980	2.601 ± 0.552
FM 2 (with PIB)	718.050 ± 51.738	4.033 ± 0.514	149.401 ± 30.505	1.796 ± 0.517
FM 1 (without PIB)	458.196 ± 113.724	0.416 ± 0.142	-	-
FM 2 (without PIB)	515.274 ± 95.113	0.591 ± 0.211	-	-

Adhesive and Bioadhesive Properties of Matrix Type Transdermal Therapeutic Systems Containing Captopril

The mean adhesive force (g) ± SD and the mean area under the curve (AUC) (N.sn) ± SD of the formulations are seen in Table 2. The best adhesive force (g) ± SD and the mean area under the curve (AUC) (N.sn) ± SD were obtained with the FM 2 formulation containing PIB (Figure 3). However, the bioadhesive property of FM 1 with PIB (Figure 4) was higher than FM 2 with PIB formulation (Figure 5). According to this result, further pharmacodynamic studies were processed with FM1 (23).

There are numerous studies in the literature regarding the adhesiveness and bioadhesiveness of transdermal patches (21, 22, 24-26). Sezer AD et al. used chicken back skin as a model tissue to study the bioadhesion of fucoidan-chitosan films. The measurement was conducted with a texture analyser equipped with a 5-kg load cell and bioadhesion test rig. Bioadhesion values of the films they formulated, ranged from 0.076 to 1.771 mJ/cm^2. They also found out that all formulation factors were effective on bioadhesion and the films' bioadhesive property was increased with increase of polymers and lactic acid concentrations in the membrane formulation ($P < 0.05$) (24). In another study, adhesive properties of the model patches containing guarana extract were determined using a Stable Micro Systems TA-XT2 Texture Analyser in the tension mode. They determined the adhesive properties of the model patches on two substrates, porcine skin and an artificial membrane (dialysis tubing). They found out that the porcine skin provided greater reproducibility. They also found out that the differences were not great and the trends were very similar (25). Yener G. et al. prepared transdermal patches containing meloxicam and lornoxicam. They cut circle pieces with 4 cm diameter from films and their tensile strengths were determined by using TA-TX2 Texture Analyser Apparatus (U.K.) equipped with a 0.25" spherical probe (P/0.25 s). Their texture analyser results showed that strength of films under the force was in a

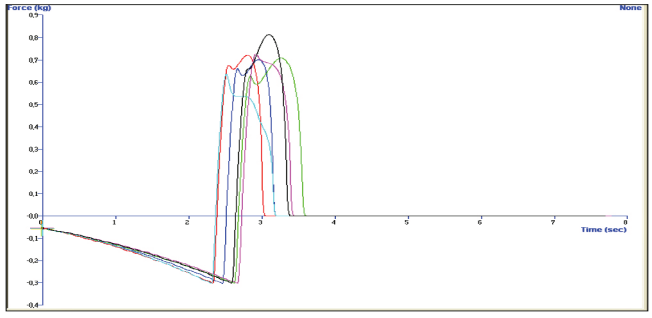

Figure 3. The adhesion graphic of FM2 with PIB
test parameters: test speed 0.05 mm/s, return speed 1.00 mm/s, applied force 300.0g, contact time 0.01 s, n = 6. The spherical probe consisted of stainless steel with a diameter of 1 inch.

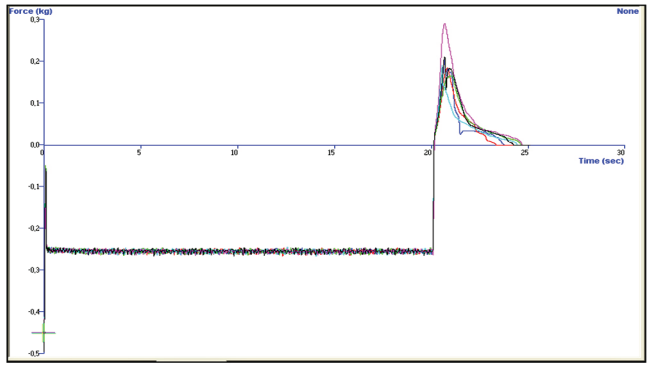

Figure 4. The bioadhesion graphic of FM1 with PIB
test parameters: test speed 1.00 mm/s, return speed 1.00 mm/s, applied force 254.9 g, contact time 20 s, n = 6. The cylindirical probe P10 Delrin was used for the test.

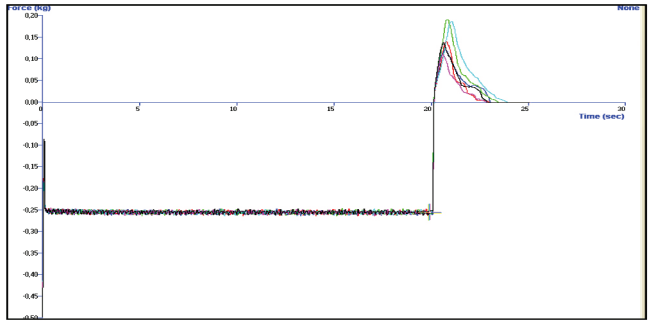

Figure 5. The bioadhesion graphic of FM 2 with PIB
test parameters: test speed 1.00 mm/s, return speed 1.00 mm/s, applied force 254.9 g, contact time 20 s, n = 6. The cylindirical probe P10 Delrin was used for the test.

range of 0.293—0.365 kg/s. They observed that there was a reverse relationship between tensile strength and molecular weight of semi-synthetic cellulosic polymers such as CMC and HPMC (21). Abdul Rasool BK. et al. prepared bioadhesive film for transdermal delivery of propranolol hydrochloride (PPL). They evaluated bioadhesive strength of PPL films by using a texture analyser (TA.XT2, Stable Micro System, UK). They applied the prepared films on excised rat skin in vitro for 8 hours during permeation studies and they found out that the prepared films firmly attached to the skin, indicating good adhesion properties for clinical use (26).

CONCLUSION

Adhesiveness and bioadhesiveness results of the formulations measured by texture analyser indicated that TTS containing captopril prepared with synthetic and pH independent polymers, Eudragit RL 100 and RS 100, can be considered as a transdermal therapeutic system for chronical treatment of hypertension and congestive heart failure. They firmly attached to the skin, indicating good adhesion properties for clinical use.

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Kaptopril içeren matriks tipindeki transdermal terapötik sistemlerin mekanik özelliklerinin değerlendirilmesi

ÖZET

Bu çalışmanın amacı sentetik ve pH'dan bağımsız polimerler olan Eudragit RL 100 ve RS 100 ile beraber kaptopril içeren transdermal terapötik sistemlerin (TTS) mekanik özelliklerinin değerlendirilmesidir. Formülasyonlar tekstür analiz cihazı kullanılarak adeziflik ve biyoadeziflik açısından karakterize edilmişlerdir. Optimum formülasyonlar daha önceki çalışmamızdaki in vitro dissolüsyon ve Franz difüzyon hücresinin kullanıldığı kesilerek ayrılmış insan derisinden geçirilerek yapılan ex vivo difüzyon hızı çalışmalarının verilerine göre belirlenmiştir. Sonuçlar formülasyonların mekanik özelliklerinin transdermal yama kullanımı açısından uygun olduğunu göstermiştir.

Anahtar kelimeler: kaptopril, transdermal terapötik sistem, yama adezifliği, yama biyoadezifliği, tekstür analiz

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