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ORIGINAL ARTICLE

Formulation and characterization of a captopril ethyl ester drug-in-adhesive-type patch for percutaneous absorption

Darren R. Gullick[1], W. John Pugh[2], Matthew J. Ingram[3], Paul A. Cox[1] and Gary P. Moss[4]

[1]School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, UK, [2]Welsh School of Pharmacy, Cardiff University, Cardiff, Wales, UK, [3]School of Pharmacy & Biomolecular Sciences, University of Brighton, Brighton, UK and [4]School of Pharmacy, Keele University, Staffordshire, UK

Abstract

Background: The ethyl ester of captopril has been shown to exhibit enhanced permeation across human skin compared to the parent drug. A drug-in-adhesive patch formulation of a captopril ethyl ester was therefore developed for optimum drug release. *Method*: A wide range of transdermal patches were prepared using two commercially available bioadhesive polymers. Investigational screening was conducted on the patches using microscopy, texture profile analysis, and infrared spectroscopy. Drug release profiles of suitable patches were obtained using both polydimethylsiloxane (Silastic™) and porcine skin in vitro. *Results*: Diffusion results across Silastic™ showed a gradual plateau in flux with increased drug loading that may be attributable to intramolecular interactions while flux across porcine skin was seen to increase with increasing patch thickness and attained a therapeutic level. *Conclusions*: This study demonstrated that adhesion and drug loading are significant factors in optimizing a topical patch formulation for the delivery of a captopril prodrug.

Key words: *Captopril; drug-in-adhesive formulation; percutaneous absorption; texture profile analysis; transdermal drug delivery*

Introduction

Transdermal patches offer many benefits, including the potential for zero-order drug delivery, avoidance of first-pass metabolism and GI side effects, reduced side effects (because of lower peak plasma concentrations), increased safety (by allowing the application of an accurately known dose to a clearly defined area), and improved patient compliance. According to a recent report[1], the value of the global market for transdermal delivery was $12.7 billion in the year 2005 and is expected to increase to $21.5 billion in the year 2010 and $31.5 billion in the year 2015[2]. Hypertension remains a condition that affects a large proportion of the world's population and is currently treated by the numerous oral medications. However, there is currently no licensed UK equivalent to the US antihypertensive Catapres-TTS® (ALZA Corporation, Vacaville, CA, USA).

Captopril (Figure 1) is a well-established antihypertensive that is available in oral dosage form and could benefit from transdermal drug delivery. Although now superseded by other angiotensin-converting enzyme (ACE) inhibitors, it was selected by us for conversion into a transdermal therapeutic not only because it remains clinically relevant (due to the zero-order kinetics associated with the transdermal route that would benefit the delivery of ACE inhibitors such as captopril) but in the context of proof-of-concept developments in understanding the nature of topical prodrugs[3,4] it also contains functional groups that make it a relatively straightforward molecule to chemically modify for such uses. The captopril derivatives prepared previously[3] were initially designed as prodrugs using a quantitative structure–permeability relationship (QSPR) approach, with the ester anticipated to hydrolyze back to the parent

Address for correspondence: Dr. Gary P. Moss, PhD, School of Pharmacy, Keele University, Staffordshire ST5 5BG, UK. Tel: +44(0) 1782 734 776. E-mail: g.p.j.moss@mema.keele.ac.uk

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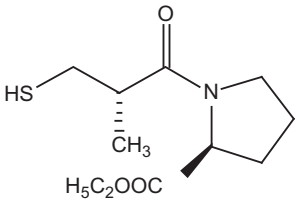

Figure 1. Chemical structure of the captopril carboxyl ester.

drug upon entering the skin[4]. The synthesis was driven via the acid chloride intermediate and afforded an extremely high yield, usually >99% because of the in situ synthesis method employed. Skin permeation studies[3] on six *n*-carboxyl esters of captopril (C_1–C_6) found that the derivatives offered greater skin permeability than the parent drug, but the subsequent metabolism studies[4] showed that *n*-carboxyl C_1–C_4 esters were relatively stable to hydrolysis by skin esterases but ultimately underwent hydrolysis via pseudo first-order kinetics. Furthermore, in vitro pharmacological investigations[4] found that the captopril ester derivatives displayed substantial ACE-inhibitory activity, because two of the three structural moieties necessary for inhibition of the active site of ACE (the sulfhydryl and carbonyl groups) were still present in the esters. These investigations demonstrated that the methyl ester derivative of captopril displayed 10-fold greater therapeutic activity than the parent drug in vitro. Ultimately, however, the ethyl ester derivative of captopril was selected for formulation development studies as it showed optimal flux through porcine skin[3] and similar ACE-inhibitory activity to captopril[4].

The aim of this work was to develop a suitable transdermal formulation that would deliver a therapeutic dose of the captopril ethyl ester across porcine skin in vitro, using the known minimum therapeutic concentration of captopril (0.5 mg/mL)[5].

Materials and methods

Materials

Captopril was a gift from Bristol-Meyers Squibb PRI (Wallingford, CT, USA). Duro-Tak® 387-2054 and 387-2516 were gifts from Henkel (Zutphen, the Netherlands). Ethyl acetate (general reagent grade) was purchased from Fisher Chemicals Co. Ltd., Loughborough, UK. Scotchpak 1109 SPAK 1.34 MIL Heat-sealable polyester film (ID number 70-2005-4809-0) and Scotchpak 1022 release liner 3.0 MIL (ID number 70-2005-4805-8) were gifts from 3 M (St. Paul, MN, USA). A template for applying the formulations to the heat-sealable film was produced in-house by the University of Portsmouth engineering department (stainless steel frame to leave an exposed central area of $100 \times 100 \times \times 5$ mm). Patches were stored in air-tight conditions using polyethylene bags that were supplied with a 'Princess' vacuum bag sealer (RKW; Stoke-on-Trent, Staffordshire, UK). Patch thicknesses were measured with a micrometer (Mitutoyo Ltd., Kawasaki, Japan). Uniform patch samples were cut using a cork borer (6 mm diameter; Fisher Scientific Ltd., Loughborough, UK) and standard bench vice. Infrared spectroscopy was performed using a Research Series Fourier-transform infrared spectroscopy (FT-IR) (Mattson Instruments Inc., Madison, WI, USA). Adhesion analysis was performed using a texture analyzer, model TA-XT plus (Stable Micro Systems Limited, Surrey, UK) with a muco-adhesion rig and 10-cm diameter polypropylene probe. Franz-type diffusion cells (10-mm aperture, 3 mL receptor volume and 1 mL donor volume; Soham Scientific, Cambs, UK) were used to characterize the drug delivery of the formulations. Silastic™ membrane (polydimethylsiloxane transparent sheet, 0.3-mm thickness, hardness 60) was purchased from Samco Silicone Products Ltd. (Warwickshire, UK). Porcine skin was harvested from deceased weanling pigs (up to 4 months old) and treated in accordance with previous studies[3]. Analysis of captopril ethyl ester in the Franz-type cell receptor solution was performed by high-performance liquid chromatography (HPLC) using an Agilent 1100MSD (Agilent Ltd., Wokingham, UK) equipped with an octadecylsilyl column (Hichrom, 15 cm × 4.6 mm i.d.). Disposable HPLC sample vials with incorporated 0.4 μm polytetrafluoroethylene filter (Whatman Mini-Uni Prep) were purchased through Fisher Chemicals Co. Ltd.

Methods

Transdermal patch preparation

A range of formulations with differing drug loading were prepared with two pressure-sensitive self-curing acrylate-based adhesives (Duro-Tak® 387-2054 and 387-2516) in a method similar to those previously described[6,7]. Appropriate amounts of the drug, pressure sensitive adhesive (PSA), and ethyl acetate were mixed and sonicated. The mixture was cast onto the backing membrane (Scotchpak® 1109) using the template and dried under conditions of constant temperature (20°C) and humidity (30% RH) for 8 hours. The dried film was then laminated with release liner (Scotchpak® 1022) and stored in airtight re-sealable bags. Samples (6-mm diameter) were cut from the laminate before each experiment using a cork borer.

Preformulation

Microscopical examination was performed on the initial formulations (0–10%, w/w, drug loading) to investigate formulation's supersaturation. Infrared spectra

using sodium chloride plates were recorded for the neat oil, the adhesive, and the formulations with 1.5%, 3.0%, 4.4%, 5.8%, 7.1%, 13.3%, 23.5%, 31.5%, and 38.0% (w/w) drug loading.

Adhesion analysis

Adhesion properties were characterized as Work of Adhesion (peak area, N mm)[6,8,9]. The settings used were as follows: approach speed of probe to patch, 0.2 mm/s; application (compression) force, 5.0 N; duration of applied force, 30.0 seconds; velocity of probe detachment, 2.0 mm/s; distance of probe detachment, 10.0 cm. Preliminary experiments were performed using the standard polypropylene probe contacting the unprotected patch surface to determine peak reproducibility upon detachment (n = 4). Subsequent adhesion analysis was performed by measuring the detachment (work of adhesion) of patch samples from porcine skin. Frozen porcine skin (10 × 2.5 cm) was thawed, washed, and then shaved using a guarded electric shaver to remove hair while avoiding damage to the *stratum corneum*. The prepared skin was carefully mounted on a mucoadhesion rig to expose the test area of skin (3 cm^2). Measurements (n = 4) were taken using a fresh skin surface for every analysis. The formulations that displayed similar adhesive properties compared to the Nicorette® benchmark were selected for subsequent analysis by in vitro drug transport experiments.

Drug transport experiments

Flux was initially determined using a Silastic™ membrane, as its uniformity gives the precision necessary for initial interformulation comparison[6]. Subsequent diffusion analysis was performed using porcine skin. Full thickness skin was taken from the back of the weanling pigs within 24 hours of death. Subcutaneous fat was carefully removed, the hair was clipped and then shaved using an electric shaver with a metal guard, and the skin was stored at −20°C for a maximum of 6 months. Franz-type diffusion cell studies were based on the method reported previously[3,10] where static diffusion cells were employed, along with a protocol employing periodic removal and replacement of the receptor media.

Analysis of receptor samples from diffusion experiments using Silastic™ membrane was performed by UV, as described previously[3]. Briefly, a λ_{max} value of 202 nm was determined for the captopril ethyl ester in water, and a calibration curve was prepared using standards of ethyl ester in water in the range 0.9–133 mg/mL for which the relationship was linear (r^2 = 0.992), and the absorbance values were recorded for each receptor sample at 202 nm. The relationship between absorbance and ethyl ester concentration was used to construct a diffusion profile for each cell. Flux was determined using the gradient of the straight-line portion of the profiles, and permeability values were calculated by application of Fick's first law. Analysis of receptor compartment samples from diffusion experiments using porcine skin membrane was performed via liquid chromatography-mass spectrometry (LC-MS) using the method developed previously for diffusion studies[3]. Briefly, the LC-MS conditions included use of an octadecylsilyl stationary phase, methanol:water (50:50) mobile phase with isocratic elution at a flow rate of 0.3 mL/min, and sample size 10 µL. Electrospray conditions were left unchanged from diffusion studies, specifically these were fragmentor (40 V), nitrogen drying gas flow rate (10 L/min), nebulizer pressure (35 psi), drying gas temperature (300°C), and capillary voltage (3000 V). A calibration curve was generated for this analysis whereby a linear relationship was recorded (r^2 = 0.9851) between MS-positive ion peak area and ethyl ester concentration, within a range of 0.009–0.1063 mg/mL.

Treatment of results

All results are reported as mean values, plus or minus standard deviation, of four replicates (adhesion studies), three replicates (Silastic™ permeation studies), and six replicates (porcine skin studies). Work of adhesion values for the initial screen using the polypropylene probe were subjected to two-way analysis of variance, followed by a Dunnett's test, using drug loading and adhesive concentration as factors. This was performed to determine statistical differences between the Work of Adhesion values and to investigate both the influence of drug loading and the concentration of adhesive on the Work of Adhesion values. Minitab® version 15.1.3 was used for all figure generation and statistical analysis. For all tests a probability of 0.05 or less was taken to indicate a significant difference between groups.

Results and discussion

Preformulation

Microscopical observations indicated supersaturation of formulations containing more than 13.3% (w/w) drug loading. This appeared as unbound, free drug. As the captopril ethyl ester is a liquid at room temperature, this resulted in small amounts of liquid drug visibly present on the surface of the patches.

Formulation characterization by FT-IR was performed (using the adhesive as reference) to observe any interaction (i.e., hydrogen bonding) that may have occurred between the captopril ester derivative functional groups and those on the acrylate/vinyl acetate

Table 1. Wavenumbers of peaks observed in the carbonyl region of the IR spectra for captopril ethyl ester prodrug and formulations, showing shift of carbonyl peak and addition of a new primary amide peak for both formulations. Samples were blanked against adhesive.

IR assignments (cm^{-1})	Peaks corresponding to captopril ethyl ester neat oil (cm^{-1})	Peaks corresponding to 7.1% (w/w) prodrug formulation (cm^{-1})	Peaks corresponding to 43.4% (w/w) prodrug formulation (cm^{-1})
C=O stretch	1741	1735	1737
C=O stretch (primary amide)	1640	1647	1644
	—	1617	1617

copolymer adhesive[11]. Shifting of the amide I peak was observed from 1640 cm^{-1}in the neat oil to ~1650 cm^{-1} and ~1617 cm^{-1} in the formulations. The concentration effect is also shown because of peak magnitude. Table 1 lists the respective wavenumbers.

Acrylate-based adhesives are those commonly found in, for example, PSA tapes and first-aid plasters. They are typically copolymers of C_4–C_8 alkyl acrylates with acetonitrile or acrylamide and are generally used as single-component systems with no need for additional excipients such as plasticizers, stabilizers, or tackifiers.

The suitability of a candidate adhesive was a key point in the formulation study for the captopril ethyl ester prodrug. Polysiloxane adhesives were considered unsuitable because of the irritation that these formulations can induce, and polyiobutylenes (PIBs) were eliminated because of the potential drug–skin–excipient interactions[12–14]. Therefore acrylate-based self-curing adhesives were selected. Two Duro-Tak® self-curing acrylate-based adhesives (387-2516 and 387-2054) were chosen, as these have been used previously by other investigators[7,15]. Furthermore, these materials were readily compatible with the drug and adhesive, as well as the patch materials. Adhesion studies showed Duro-Tak® 387-2054 to be the PSA more compatible with the captopril ethyl ester drug than 387-2516, because it showed a lesser plasticizing effect, and subsequent studies used only this adhesive.

Adhesion analysis

Adhesion analysis was performed using the TA-XT Plus Texture Analyser in the tensile mode (Stable Micro Systems Ltd., Godalming, Surrey, UK). This allowed work of adhesion to be estimated for formulations, and the study was divided between the use of a standard polypropylene probe and the use of porcine skin. Although the use of polypropylene probes, among others, is common to adhesion testing[16,17], the use of porcine skin is comparable to an 'in-use' situation and therefore was the most applicable technique to employ. Other methods, such as rheology, would be able to provide more detailed information about each formulation (e.g., regarding viscosity, shear stress, and shear thinning)[18]. However, the main purpose of this study was to benchmark the captopril ester formulations against a marketed product with accepted and well-tolerated adhesion properties. For this reason Nicorette® (Pharmacia Ltd., Sandwich, Kent, UK) patch was employed as such a benchmark. The tensile testing of formulations involves applying stress to the material to test for failure and measuring the load/elongation curve. The speed of analysis has a great effect on the results obtained. As the test speed is increased, the polymer would take a shorter time (or distance) to break and the tensile strength would rise. In this study, a detachment speed of 2 mm/s was chosen as an adequate speed. This speed allowed both the more brittle and the more flexible patches to be analyzed.

Results for formulations containing Duro-Tak® 387-2054 using a conventional polypropylene probe (Figure 2) showed a general increase in adhesion with increasing adhesive concentration. Adhesion was seen to reach an optimum at 13.3% (w/w) drug loading, after which the additional drug in the formulations had the effect of decreasing the work of detachment. This could be because of a plasticizing effect of the drug, which is an oil at room temperature. Indeed, this may also be because of the nature of the interaction of the drug with the polymer, as observed using IR spectroscopy and listed in Table 1. Previous studies have indicated the possibility of such interactions between drugs and excipients[19]. It is also clear from Figure 2 that, although increasing the adhesive concentration in patches clearly results in an increase in adhesion, such an increase is dependent upon the drug loading. At concentrations greater than 13.3% (w/w) drug loading, a significant decrease in adhesion was observed. This decrease became more pronounced as the drug loading was increased to 38% (w/w).

MiniTab® (v.15) was used to statistically analyze the results of this study. A two-way analysis of variance was employed to investigate the effect of changing drug loading and adhesive concentration in patches. In general, both drug and adhesive affect the work of adhesion ($P < 0.001$). Furthermore, interaction plots suggest that although both drug and adhesive affect the parameters measured, interactions between the drug and the adhesive suggest that the effect is not additive, but that the interaction does vary with drug loading. In particular, the low P-value obtained shows that differences in drug loading and adhesive concentration exert a highly significant influence on the measured mechanical properties of the patches. The trends in adhesion analysis

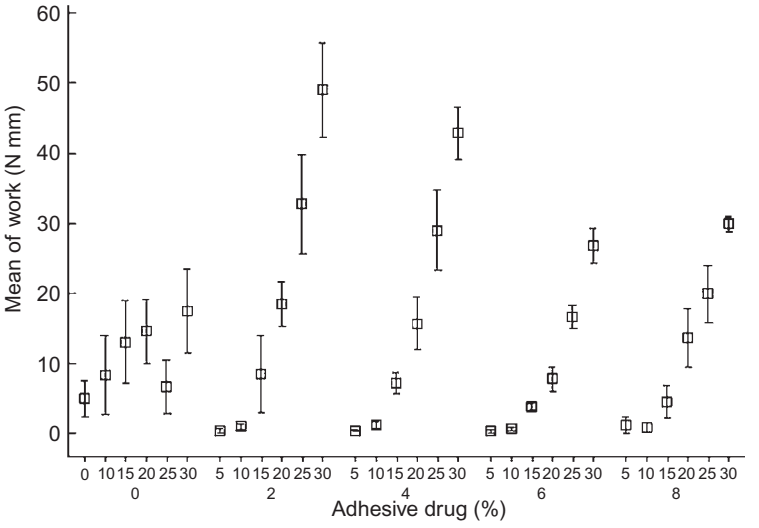

Figure 2. Effect of combinations of adhesive (before evaporative losses) and drug (as %, $n = 4$; shown as mean ± 95% confidence limits). The effect of drug loading on adhesion is clearly seen to reach an optimum between 2.0% and 4.0% (w/w) with adhesive at 30% (w/w).

showed that the formulated transdermal patches had optimal adhesive properties with 1.5%, 3.0%, 4.4%, 5.8%, 7.1%, 13.3%, 23.5%, 31.5%, and 38.0% (w/w) drug loading. These formulations were then selected for diffusion studies.

In vitro diffusion studies

Flux results of captopril ethyl ester patch formulations of increasing drug loading through Silastic™ membrane are summarized in Figure 3. An increase in flux with increased drug loading is observed up to a loading of 13.3% (w/w), and a plateau in flux is observed thereafter. This is possibly because of saturation of drug within the self-cured polymer matrix and may be indicative of the formulation issues observed by microscopy, and discussed above.

Diffusion profiles showed an initial burst of drug release, followed by a steady-state gradient indicating zero-order drug delivery up to 24 hours. The latter portion of the diffusion profile was used to determine the flux of each formulation examined.

Further investigations were performed into the effect of patch thickness (matrix effects) on diffusion. Figure 4 shows a comparison between flux values from patches of various drug loading but which were 0.2- and 0.7-mm thick. These results indicate no difference in flux values between thick and thin patches with up to 5.8% (w/w) drug loading, but a significantly greater flux was observed for the 13.3% (w/w) thicker patch. This may possibly be due to the donor phase depletion of the thin patch.

Drug release studies through a polydimethylsiloxane (Silastic™) membrane showed an increase in flux with

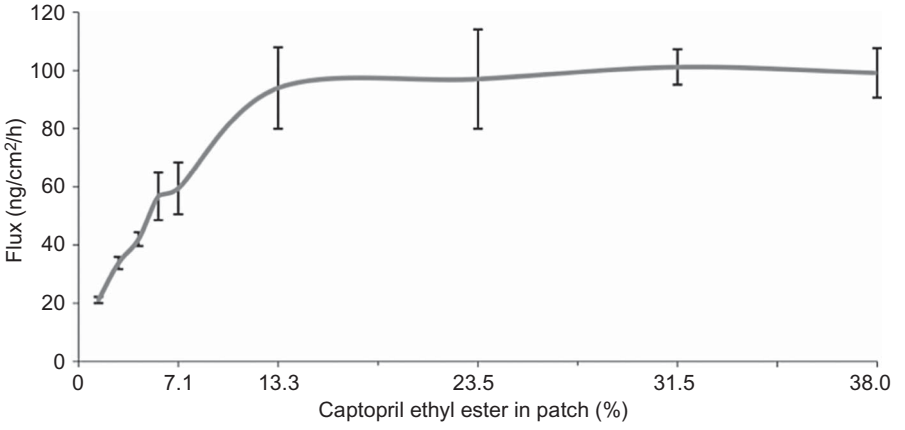

Figure 3. Trend in flux of captopril ethyl ester through Silastic™. Mean values ($n = 3$) ± SD.

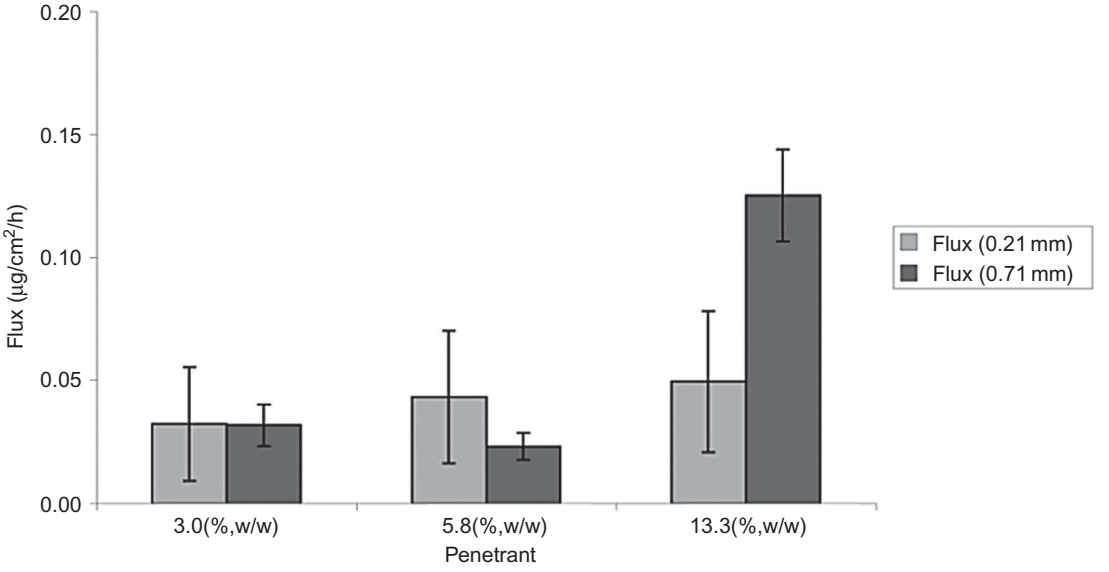

Figure 4. The effect of thin (0.2 mm) and thick (0.7 mm) patch on flux through frozen porcine skin. Mean values ($n = 6$) ± SD.

prodrug concentration reaching a maximum of approximately 90 ng/cm^2/h for the 13.3% (w/w) patch. Sink conditions were maintained during the diffusion experiments, because of the protocol employed of periodic removal of the entire receptor phase. Saturation of the matrix did not occur as this would give rise to surplus oil resting on the surface of the patch, or other signs of saturation such as a striated cloudy appearance, as previously observed with patches containing higher drug loading than the 13.3% (w/w) formulation. It is more likely that the plateau in drug delivery through Silastic™ membrane is because of the drug binding, or cross-linking, with the adhesive. This effect is supported by IR spectroscopy studies summarized in Table 1. The splitting/shifting of the amide I peak from ~1640 to ~1650 cm^{-1} and ~1617 cm^{-1}indicates hydrogen bonding between prodrug and adhesive[20]. The additional peaks suggest the presence of two different hydrogen bonds in the formulation, which may be due to the hydrogen bonding occurring between the amide and the functional groups in the adhesive, as well as possible intramolecular hydrogen bonding[20]. Donor phase depletion was not the cause of the plateau in flux, as mass balance calculations indicate that an average of 40.3% of prodrug remained in the patches when using Silastic™, and an average of 85.5% captopril ethyl ester remained in the patch following porcine skin diffusion studies. Indeed, this further supports the inference that passage of drug through the formulation may have been hindered in some way, possibly by rheological or steric effects through the polymer matrix, or by hydrogen-bonding effects as discussed above.

Diffusion experiments using porcine skin showed that the 'thin' (ca. 0.2-mm thickness) patch with the same concentration displayed a flux of 0.049 μg/cm^2/h whereas the 'thicker' (0.7-mm thickness) formulation gave a flux of 0.125 μg/cm^2/h (Figure 5). Control experiments indicated that the backing membrane employed in patch construction was impermeable after 7 days and that the captopril ester did not absorb into that membrane.

Conclusions

Adhesion values increased with derivative loading up to 13.3% (w/w), but these fell at concentrations above this possibly because of the plasticizing effect of the derivative. The 30% (w/w) adhesive range of formulations displayed optimal adhesive properties when compared with a Nicorette® patch and were selected for in vitro drug release studies. Diffusion studies using a Silastic™ membrane showed maximal flux at 90 ng/cm^2/h for the 13.3% (w/w) ethyl ester concentration formulation, reaching a plateau thereafter. Infrared spectroscopy experiments have shown that the plateau in drug flux may be due to hydrogen-bonding interactions between the derivative and the polymer matrix. Similar in vitro diffusion studies using porcine skin showed optimal flux at 0.125 μg/cm^2/h for the 13.3% (w/w) ethyl ester concentration thicker formulation.

Therefore, this study has demonstrated that adhesion and drug loading are significant factors in optimizing a topical patch formulation for the delivery of a captopril prodrug. Although the use of such a study may

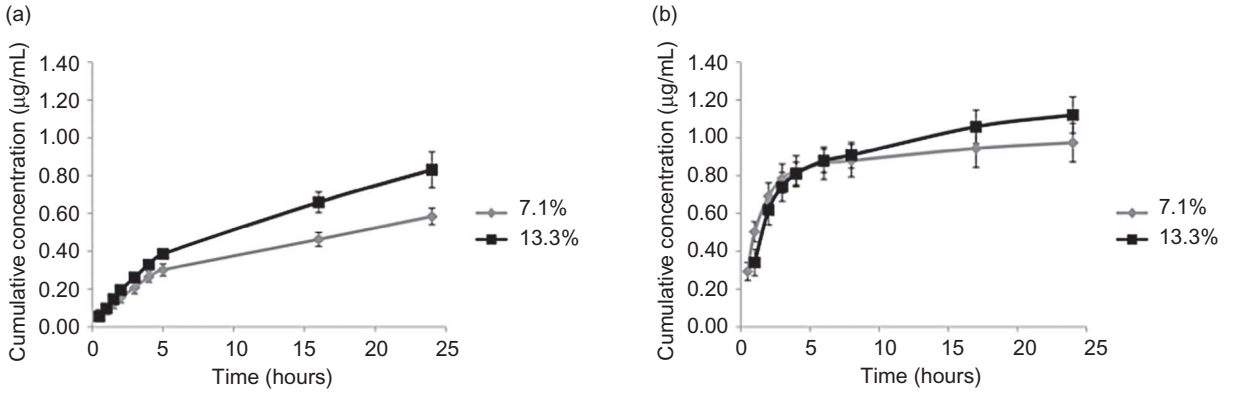

Figure 5. Diffusion profiles of 1% and 2% (w/w) captopril ethyl ester patches to compare Silastic™ (a) and porcine skin (a) membranes at 37°C $n = 3$ (Silastic™), and $n = 6$ (skin) ± SD.

be considered as a 'proof-of-concept' study, it is clear that the principles explored herein have application to other studies. Indeed, the use of esters, many of which are oils at room temperature, may present challenges to the production of stable and viable formulations, and as such the results obtained herein may have implications for similar studies with other such prodrugs.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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