# Bioadhesive Monolayer Film for the *In Vitro* Transdermal Delivery of Sumatriptan

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**ABSTRACT:** The work presented here aims to develop a bioadhesive monolayer film containing sumatriptan as adjuvant for the treatment of headache pain in a severe migraine attack. Permeation experiments were performed from the films prepared and from the respective solution, to evaluate the relevant permeation parameters. The effect of the penetration enhancers Transcutol®, 2-pyrrolidone, and polyethylene glycol 600 was evaluated. The results obtained show that Transcutol® and 2-pyrrolidone decreased sumatriptan permeation from solution, whereas a modest increase was produced by polyethylene glycol 600. The enhancers produced the same effects when they were included in the film. Compared to solution, the film showed a higher sumatriptan flux in the early times of the experiment. When the film was applied in occlusive conditions the profiles were much higher, indicating the importance of patch drying. Concerning skin retention, the bioadhesive film produced a reduction of the amount of sumatriptan remaining in the skin, but this can be advantageous in the control of drug input, since it reduces the reservoir effect in the skin and allows for an immediate interruption of drug input when the patch is removed.  J Pharm Sci 95:1561–1569, 2006

**Keywords:** transdermal drug delivery; patch; percutaneous; skin; permeation enhancers; transdermal

## INTRODUCTION

The current approach for antimigraine therapy is based on the use of potent serotonin 5-HT$1_B$/$1_D$ receptor agonists, collectively termed triptans. Sumatriptan was the first compound developed (late 1980s), and offers improved efficacy and tolerability over ergot-derived compounds (non-specific 5-HT receptor agonists). Many years of experience showed sumatriptan to be remarkably safe, highly effective, and the reference standard for "second generation" triptans developed and other triptans under investigation.

The absolute bioavailability of sumatriptan succinate is approximately 15%, 14%, and 96% after intranasal, oral dosing, and subcutaneous injection, respectively. The low bioavailabilities are primarily due to presystemic metabolism and partly due to incomplete absorption. All the newer triptans have higher oral bioavailability and longer half-life, even though these pharmacokinetic improvements seem to have ameliorated only marginally their efficacy in migraine.[1]

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Due to the low bioavailability after oral and intranasal administration and the inconveniences related to the parenteral administration, we aim to develop an alternative pharmaceutical form for the transdermal route, to be used as adjuvant for the treatment of headache in severe migraine attacks, in which one subcutaneous dose can be not enough to relief the pain.[2] Although the skin has become an important via for drug delivery, it is a remarkably efficient barrier, thus causing difficulties for transdermal delivery of therapeutic agents.[3,4] In order to enhance drug transdermal absorption, different methodologies have been investigated and developed. The use of chemical enhancers is a common approach in transdermal drug penetration enhancement.[5–10] We have demonstrated in a previous report that transdermal absorption of sumatriptan can be increased by skin pretreatment with chemical enhancers.[11]

We have recently presented an innovative transdermal therapeutical system, a bioadhesive film very thin, transparent, not adhesive in the dry state but bioadhesive when applied on wet skin, flexible, mechanically resistant, and permeable to water vapor.[12] The monolayer film, which includes the backing, the adhesive, and the drug-reservoir functions in one layer of material[12,13] can be used as a transdermal therapeutic system (TTS), in order to reach systemic therapeutic activity, or as a dermal therapeutic system (DTS), for topical effect.

The work presented here aims to develop a bioadhesive monolayer film containing sumatriptan for the treatment of severe headache pain in severe migraine attacks. According to the results obtained previously and because of the hydrophilic nature of the film, we used sumatriptan succinate and water soluble substances, Transcutol®, and polyethylene glycol 600, all assayed before as penetration enhancers.[14–20] Permeation experiments were performed from the films prepared and from the respective solutions, to evaluate the relevant permeation parameters. Rabbit ear skin was used as barrier in permeation experiments, because it can be considered as a reasonable model for human skin *in vitro* in passive conditions[21,22] and during transdermal iontophoresis.[22]

## MATERIALS AND METHODS

### Materials

Sumatriptan succinate (Eur. Ph. monograph 1573) was obtained from a commercial source (Imigran®, GlaxoSmithKline, UK). Plastoid® E 35H was obtained from Rhom (Darmstadt, Germany). Polyvinyl alcohol 83400 (PVA) was obtained from Nippon Ghosei (Osaka, Japan) and polyethylene glycol 600 (PEG600) was purchased from Fluka Chemie (Buches, Switzerland). Transcutol® was a gift from Gattefossé (Gennevilliers, France) and 2-pyrrolidone from BASF (Soluphor®, Ludwigshafen, Germany). Sorbitol and HEPES (*N*-[2-Hydroxyethyl]piperazine-*N*′-[2-ethanesulfonic acid]) were obtained from Sigma-Aldrich Co. (St. Louis, MO). NaCl and ethanol (absolute) were purchased from Mallinckrodt Baker B.V. (Deventer, The Netherlands). All chemicals were of analytical grade.

Rabbit ears were collected immediately after animal death from a local slaughterhouse. The skin from the inner face was excised from the ear using a surgical blade. The full-thickness skin pieces were packed separately and stored until use at −20°C.

### Solubility Determination

An excess amount of sumatriptan succinate (100 mg) was added to 0.4 mL of solvent and left to equilibrate at room temperature under occasional stirring for 24 h. After filtration and dilution the samples were analyzed by high pressure liquid chromatography (HPLC).

### Film Preparation

Films containing different concentrations of sumatriptan succinate were prepared using a lamination technique.[23] Transcutol® and PEG600 were included in the formulation for a final concentration of 5% (w/w) after lamination and drying.

PVA was hydrated in the appropriate volume of hot water to a final concentration of 30% (w/w). The mixture was slowly stirred overnight using a magnetic stirrer. Plastoid® E 35H and sorbitol 70% (w/v) were then added to the mixture under continuous stirring. After that, Transcutol® and PEG600 were added to the formulation. Finally, sumatriptan succinate solutions were prepared from a commercial source (Imigran®, intranasal spray 20 mg/0.1 mL) and were incorporated to the mixture. The compositions of the mixtures prepared are outlined in Table 1.

All mixtures were laminated on siliconized paper using a film casting knife (BYK Gardner, Silverspring, MD—gap 600 μm) dried at room temperature in the dark for 24 h. After drying (final

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**Table 1.** Composition of the Different Mixtures Used for Film Preparation (% w/w)

| | Film 0.15% | Film 0.5% | Film 0.5% Transcutol® | Film 0.5% PEG600 |
|---|---|---|---|---|
| PVA 83400 | 18.60 | 18.60 | 18.60 | 18.60 |
| Plastoid® E 35H | 27.00 | 27.00 | 27.00 | 27.00 |
| Sorbitol 70% (w/w) | 4.00 | 4.00 | 4.00 | 4.00 |
| Sumatriptan succinate | 0.06 | 0.18 | 0.18 | 0.18 |
| Transcutol® | — | — | 0.80 | — |
| PEG600 | — | — | — | 0.80 |
| Ethanol | — | — | 1.50 | 1.50 |
| Water | 50.34 | 50.22 | 47.92 | 47.92 |

water content of 15% (w/w) approximately), the films (10 cm × 20 cm) were covered with a second siliconized paper and individually sealed in aluminum pouches. Samples of films of known weight were dissolved in water and sumatriptan concentration was determined by HPLC to measure sumatriptan succinate content in the finished products.

### *In Vitro* Diffusion Experiments

Transdermal permeation of sumatriptan was investigated at room temperature. Experiments were performed using vertical Franz flat flange joint type diffusion cells (DISA, Milan, Italy) with 0.64 $cm^2$ of diffusion area. The full-thickness rabbit ear skin was mounted on the cells with the stratum corneum facing the donor compartment. The receptor compartment (4.2 mL volume) was filled with HEPES (25 mM) buffered saline solution at pH 7.4. The following formulations were used in the donor compartment:

1. One milliliter of sumatriptan succinate solution (0.15% and 0.6% w/v);
2. One milliliter of sumatriptan succinate solution (0.6% w/v) containing Transcutol®, PEG600, or 2-pyrrolidone (5% w/w);
3. The prepared films (sumatriptan succinate concentration in the dried product 0.15% and 0.5% w/w). The application procedure of the film on the skin surface has been previously described by Padula et al.[12] In particular, since the film is not selfadhesive, the skin was prewetted with 15 μL/$cm^2$ of water before film application.

Samples of the receptor chamber were taken hourly for the first 8 h and at 22 h, 23 h, and 24 h. The sample volume taken was replaced with the saline buffer (pH 7.4).

At the end of the diffusion experiments, the exhausted films were peeled off and diluted in the appropriate volume of water to determine the residual concentration of sumatriptan. In the solution experiments, a sample from the donor solution was taken at 24 h in order to determine the residual concentration of drug.

The amount of sumatriptan retained in the skin was extracted by shaking the skin during 12 h with 3 mL of the saline buffer (pH 7.4), according to Femenia-Font et al.[11] The mass balance demonstrated a total recovery (permeated plus accumulated plus residual) higher than 95%.

The permeation profiles obtained from solutions were fitted to Eq. 1[24]:

$$Q = (KH)C_{\text{veh}}\left[\frac{D}{H^2}t - \frac{1}{6} - \frac{2}{\pi^2}\sum_{n=1}^{\infty}\frac{(-1)^n}{n^2}\exp\left(\frac{-Dn^2\pi^2 t}{H^2}\right)\right] \quad (1)$$

where $Q$ is the cumulative amount of drug permeated per unit area at time $t$, $C_{\text{veh}}$ is the concentration of the drug in the donor vehicle, $K$ is the stratum corneum/vehicle partition coefficient, $D$ the diffusion coefficient, and $H$ the diffusion pathlength. The fitting was performed using KaleidaGraph 3.6.2 (Synergy Software) running on a MacIntosh Power Book G4.

The permeability coefficient $P$ was calculated as:

$$P = KH \times \frac{D}{H^2} \quad (2)$$

and steadystate flux ($J_{ss}$) as:

$$J_{ss} = P \times C_{\text{veh}} \quad (3)$$

$J$ values using enhancer were compared with the control (0.6% solution) by means of student $t$-test. When statistically differences were detected ($p < 0.05$) the permeation enhancing activities, expressed as enhancement factor (EF), were calculated as the ratio of permeability coefficient with and without enhancer (control).

Amount of sumatriptan retained in skin were log-transformed for normality assessment. Afterwards the values were compared by means of the one-way ANOVA. Multiple comparison tests were carried out with the Scheffe test. Each experiment was replicated 8–12 times.

### Analytical Method

The amount of sumatriptan in the samples was quantified by HPLC using a Perkin Elmer liquid chromatograph (Perkin Elmer, Norwalk, CT) which included a UV detector, set to 283 nm and an analytical Kromasil C18 column, (4 mm × 250 mm), purchased from Análisis Vínicos (Tomelloso, Spain). A mixture of monobasic ammonium phosphate water solution (0.05 M, pH 3.3)-acetonitrile (84:16, v/v) was used as mobile phase, at a flow rate of 1 mL/min. Injection volume was 50 μL. The method has been previously validated.[25]

## RESULTS AND DISCUSSION

Sumatriptan succinate permeation across the skin is not favored by the hydrophilic nature of the drug ($\log P_{\text{pH 7.4}} = -1.5$). Previous studies on pig ear skin showed that passive permeation was very low, but iontophoresis application improved sumatriptan flux to a considerable extent (EF approx. 500).[26] Skin pretreatment with chemical enhancers, such as terpenes improved sumatriptan permeation,[11] although to a limited extent. The enhancers chosen in the present work were all water soluble, namely Transcutol®, 2-pyrrolidone, and PEG600, in view of their inclusion in the bioadhesive film, which represents the final formulation studied. For the same reason, a soluble salt of sumatriptan, namely its succinate, was used.

### Permeation of Sumatriptan from Solutions

Initially, the permeation of sumatriptan was studied from solutions of the drug with different concentration (0.15% and 0.6% w/v) and, for the more concentrated solution, in the presence of penetration enhancers.

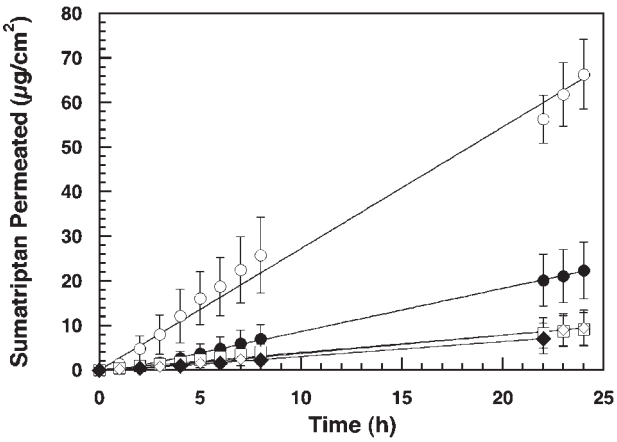


**Figure 1.** Permeation profiles of sumatriptan from water solutions containing sumatriptan succinate at 0.15% (◇), 0.6% (●), 0.6% plus 5% PEG600 (○), 0.6% plus 5% Transcutol® (□), 0.6% plus 5% 2-pyrrolidone (◆). Average values ± SD, $n = 6–10$. The data were fitted using Eq. 1.

Sumatriptan permeation profiles across rabbit ear skin, reported in Figure 1, increased with drug donor concentration. The inclusion of PEG600 produced a remarkable increase of sumatriptan permeation while Transcutol® and 2-pyrrolidone reduced its permeation. The addition of a penetration enhancer, such as 2-pyrrolidone, Transcutol®, or PEG600, albeit at low concentration (5% w/w), can in principle alter the solubilization properties of the donor solution, thus modifying the thermodynamic activity of sumatriptan. To clarify the solvent role of the enhancers, the solubility of sumatriptan succinate in the solutions used as donor vehicles was determined experimentally and the results are reported in Table 2, together with the respective degrees of saturation. All enhancers used slightly decreased the solubility of sumatriptan succinate, thus producing a non-significant increase in the degree of saturation of

**Table 2.** Permeation Parameters of Sumatriptan Across Rabbit Ear Skin from Solutions (Mean Values ± SEM)

| Enhancer | Solubility (mg/mL)[a] | $KH \times 10^3$ (cm) | $D/H^2$ (per h) | $P \times 10^4$ (cm/h) | $J_{ss}$ (μg/cm²·h) |
|---|---|---|---|---|---|
| None[b] | 205 (0.007) | 3.33 ± 0.60 | 0.13 ± 0.02 | 3.88 ± 0.61 | 0.42 ± 0.07 |
| None[c] | 205 (0.029) | 3.50 ± 0.56 | 0.09 ± 0.02 | 2.43 ± 0.25 | 0.99 ± 0.11 |
| PEG600[c] | 185 (0.032) | 5.05 ± 1.86 | 0.22 ± 0.04* | 7.86 ± 0.95** | 3.37 ± 0.41** |
| Transcutol®[c] | 187 (0.032) | 0.24 ± 0.08** | 0.70 ± 0.24* | 0.63 ± 0.15** | 0.32 ± 0.10** |
| 2-Pyrrolidone[c] | 190 (0.033) | 0.73 ± 0.32** | 0.19 ± 0.04* | 0.87 ± 0.44** | 0.37 ± 0.19** |

Significantly different from control (*$p<0.05$; **$p<0.01$).
[a]Sumatriptan succinate solubility in the donor vehicle; in parentheses the degree of saturation of the donor solution.
[b]Solution (0.15%).
[c]Solution (0.6%).

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the donor solution. In particular, the effect of PEG600, the only enhancer which increased sumatriptan permeation across the skin, was the same as Transcutol® and 2-pyrrolidone, suggesting that the effect produced by the enhancers was not due a variation of the thermodynamic activity of the drug. To try to explain the effect of the enhancers, the permeation parameters $KH$ and $D/H^2$ were calculated, by fitting the experimental data to a solution of Fick's law, which does not assume the achievement of steadystate[24] (Eq. 1). The parameter $KH$ gives indications as to the stratum corneum/vehicle partitioning of the molecule, while $D/H^2$ represents the diffusive parameter across the skin. Although the presence of a penetration enhancer can gradually alter the barrier function of the skin, thus changing the diffusion coefficient of the permeant and/or its penetration pathlength, these parameters have been used to estimate the effect of $K$ and $D$ on the total flux across the skin.[21,27]

The values obtained are reported in Table 2. The partitioning parameter $KH$ obtained using a water solution of sumatriptan succinate at 0.15% w/v was $3.3 \times 10^{-3}$ cm, compatible with the hydrophilic nature of the molecule. The value of $KH$ was not significantly different for the two concentrations of sumatriptan in the donor compartment and was not changed significantly by the presence of PEG600 either. The addition of Transcutol® or 2-pyrrolidone decreased in a significant way the partitioning parameter and this reduction can be explained assuming that the enhancer penetrates the skin and modifies the solubility of the hydrophilic permeant into the stratum corneum.[6,28]

Concerning the diffusive parameter ($D/H^2$), its value was independent of drug donor concentration, but increased ($p < 0.05$) when Transcutol®, 2-pyrrolidone, or PEG600 were added. The reason for this increment, which has been observed also for haloperidol and melatonin with PEG400,[29,30] is the interaction of the enhancer with the stratum corneum. The permeability coefficient of sumatriptan was decreased by Transcutol® and 2-pyrrolidone, owing to the marked reduction of $KH$, and increased by PEG600 and so did the steadystate flux. Overall, PEG600 produced an EF of 3.4.

The skin retention of drug at the end of the various permeation experiments (except those with 2-pyrrolidone) is reported in Figure 2. The amount of sumatriptan recovered in the skin increased with increasing drug donor concentration from 5.4 μg/cm$^2$ to 29.7 μg/cm$^2$ for 0.15% (data not shown) and 0.6%, respectively. The presence of either Transcutol® or PEG600 in the donor solution increased significantly ($p<0.01$) the amount of sumatriptan retained in the skin.

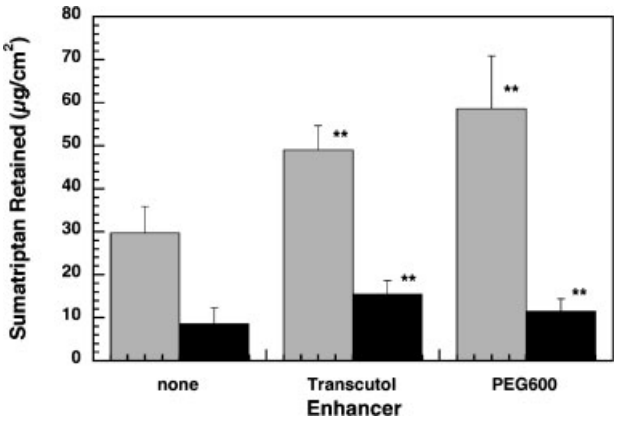


**Figure 2.** Sumatriptan retained in the skin at 24 h. Black bars represent the values obtained from the bioadhesive 0.5% film, gray bars from 0.6% solution. Average values ± SD, $n = 6–10$. **Significantly different ($p < 0.01$) from no enhancer control.

Taken together, flux and accumulation data on Transcutol® support the hypothesis that the enhancer is taken up into the skin where it alters the solubility of sumatriptan succinate (reduces its stratum corneum/vehicle partitioning) and facilitates the diffusion of the permeant. The net result is an increase in the global skin retention and a reduction in flux compared to the control water solution. 2-Pyrrolidone produces the same effects, probably for the same reasons. Concerning PEG600, the enhancement observed is due to the facilitated diffusion across the stratum corneum, which is accompanied also by an increase in skin retention.

Finally, comparing these results with the ones obtained using pig skin as barrier,[11] it looks like rabbit ear skin is slightly more permeable than pig skin (sumatriptan flux across rabbit ear skin was approx. twice compared to pig skin). Skin retention data were, however, higher for pig skin both with and without PEG600. The differences in thickness and structure of the two skin types probably account for these differences in permeation and retention.

### Permeation of Sumatriptan from the Bioadhesive Films

The next step was to examine the permeation of sumatriptan from the bioadhesive film. Different

films were produced (Tab. 1), with sumatriptan succinate loading of either 0.15% or 0.5% (w/w); the high loading films contained also either Transcutol® or PEG600 as enhancers. 2-Pyrrolidone was not used for film preparation since the results obtained with solution were similar to Transcutol®.

Figure 3 reports the permeation profiles obtained from the bioadhesive films. As observed already with other actives,[12,13,31,32] the permeation profiles were not linear with time, but showed a decreasing permeation rate over time. The inclusion of enhancers in the formulation produced an effect that was similar to what observed with solution: Transcutol® reduced sumatriptan flux while PEG600 enhanced it. Comparing the permeation profiles from solution and from the film (Figs. 1 and 3) it can be also observed that the total amount of sumatriptan permeated in a given condition (sumatriptan concentration, enhancer) was similar, even though the two formulations were completely different. In fact, the bioadhesive film is mainly composed of the polymer PVA (approx. 60% on dry basis) and is applied with only a small amount of water (15 μL/cm$^2$). Additionally, the experiments with solutions can be considered in infinite dose condition (sumatriptan succinate applied: 6 mg), while with the film they are in finite dose conditions (sumatriptan succinate applied: 0.4 mg).

To better appreciate the differences in kinetics between the film and the solution, the average flux was calculated for each sampling interval and the

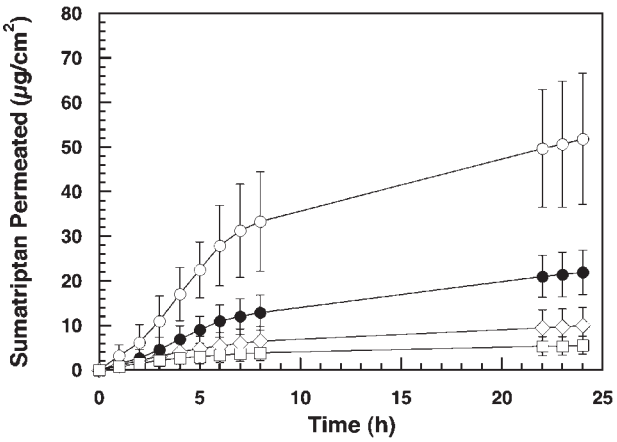


**Figure 3.** Permeation profiles of sumatriptan from the films containing sumatriptan at 0.15% with no enhancer (◇) and at 0.5%: no enhancer (●), PEG600 5% (○), Transcutol® 5% (□). Average values ± SD, $n$ = 6–10.

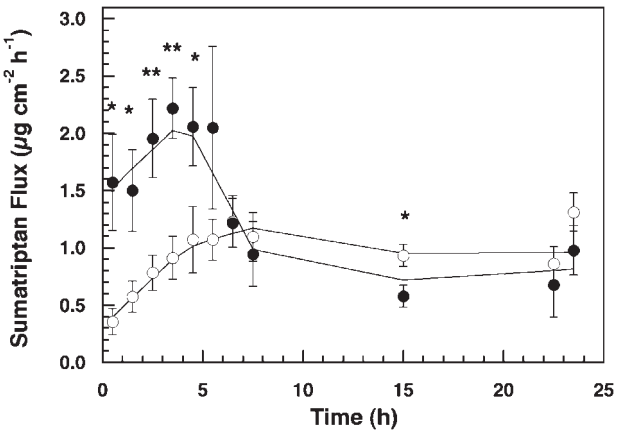


**Figure 4.** Sumatriptan fluxes across the skin from the 0.5% bioadhesive film (●) with no enhancer and from 0.6% water solution (○). *Significantly different ($p < 0.05$); **significantly different ($p < 0.01$).

results are reported in Figure 4. It can be observed that the bioadhesive film produced significantly higher fluxes in the time interval 0–5 h, but then the fluxes were superimposable to the ones obtained from the solution. The reason for the higher fluxes with the film can be the formation of a supersaturated solution of sumatriptan, in analogy with caffeine.[31]

Concerning skin retention (Fig. 2), the same relative effect of PEG600 and Transcutol® was observed, although the total amount of sumatriptan retained in the skin was much lower with the film compared to the solution. The reason for this lower skin retention is not known, but can be advantageous in the practical application on the skin, since it guarantees a lower reservoir effect in the skin and allows for an immediate interruption of drug input when the patch is removed.

If compared to other permeants, such as lidocaine and caffeine, the flattening of the permeation profiles over time was more evident for sumatriptan. While with other drugs it was possible to linearize the data representing them against the square root of time, in the case of sumatriptan this was not possible, since the fitting was very poor. We have supposed that drug depletion[12,32] and/or the formation of a supersaturated solution of the drug on the skin surface[31] were the reasons for this unusual permeation profile for caffeine. However, in the case of sumatriptan drug depletion is only marginally involved, since after 24 h only 10% of the drug

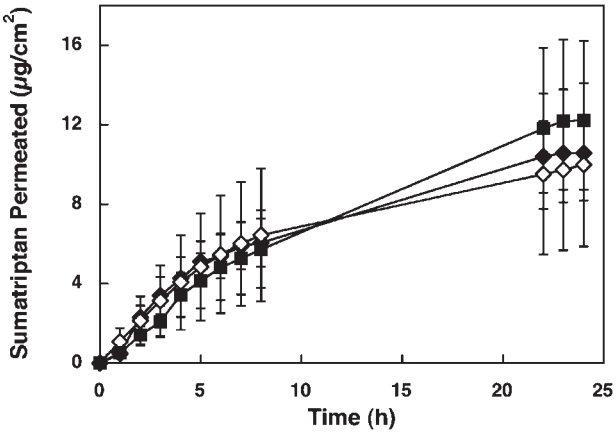


**Figure 5.** Permeation profiles of sumatriptan from the 0.15% film, applied with 7.5 μL/cm$^2$ (◆), 15 μL/cm$^2$ (◇), or 30 μL/cm$^2$ (■) of water. Average values ± SD, $n = 6–10$.

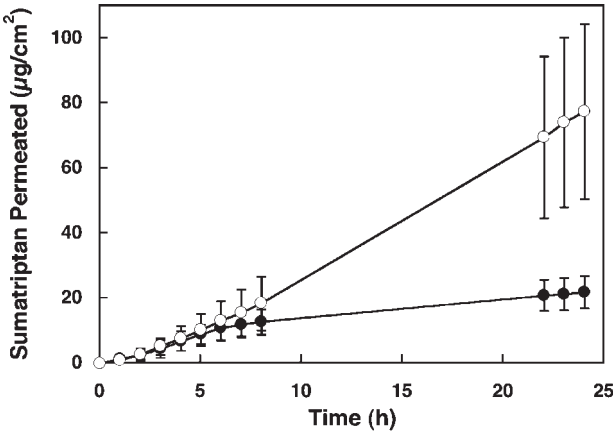


**Figure 6.** Permeation profiles of sumatriptan from the film containing sumatriptan at 0.5%, in nonocclusive (●) and occlusive (○) conditions. Average values ± SD, $n = 6–10$.

loaded had permeated the skin from the best performing formulation (it was 50% for caffeine after 24 h). On the other hand, drug diffusivity into the film should be similar for lidocaine and for sumatriptan, since they have comparable molecular weight, same charge (positive), and are both freely water soluble when present as salts. It is possible that the bioadhesive film containing sumatriptan succinate dries more quickly on the skin surface, compared to the film containing lidocaine or caffeine, and then sumatriptan diffusion within the dry patch is more difficult. In fact a previous study on caffeine[32] reports that water evaporation takes place in the first hour after patch application, but drying kinetics can be influenced by the nature of the drug included. Sumatriptan 0.15% film was then applied on the skin surface in the presence of different amounts of water, namely 7.5 μL/cm$^2$, 15 μL/cm$^2$ (the amount used in all other experiments), and 30 μL/cm$^2$. The permeation profiles obtained, reported in Figure 5, indicate that the amount of water used to apply the film of the skin surface is not critical for sumatriptan permeation. To further investigate the effect of film drying over the course of the experiment, the film containing 0.5% of sumatriptan succinate without enhancers was applied on the skin in occlusive conditions, that is, was covered with an impermeable backing. The profiles obtained, reported in Figure 6, show that in occlusive conditions sumatriptan flux is much higher, although highly variable, than in nonocclusive conditions and the decline observed in the latter is not present, confirming the importance of patch drying.

## CONCLUSIONS

From the results obtained in the present work it can be concluded that the bioadhesive film can be a promising and innovative therapeutic system for the transdermal administration of sumatriptan succinate. The film shows the advantage of a rapid permeation, compared to solution, in the early times of the experiment. If the film is applied in occlusive conditions the profiles were much higher, indicating the importance of patch drying. The inclusion of penetration enhancers, such as PEG600 and Transcutol®, had the same effect on solution and on the bioadhesive film. In particular, Transcutol® reduced sumatriptan flux and PEG600 increased it. Although the EF obtained is relatively small if compared with iontophoresis, this work demonstrates the suitability of the bioadhesive film as potential drug delivery system for the transdermal administration of sumatriptan. Finally, the bioadhesive film produced a reduction of sumatriptan retained in the skin, and this can be advantageous in the control of drug input, since it reduces the reservoir effect in the skin and allows for an immediate interruption of drug input when the patch is removed.

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