Sumatriptan Succinate Transdermal Delivery Systems for the Treatment of Migraine

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ABSTRACT: We have successfully obtained sumatriptan transdermal systems with different polymer compositions: methyl cellulose (MC), polyvinyl pyrrolidone (PVP) and a polyvinyl pyrrolidone (PVP)-polyvinyl alcohol (PVA) mixture. The systems contained 1,2-propilenglycol (MC) or sorbitol as a plasticizer (PVP and PVP-PVA), methacrylate copolymer as an adhesive agent, and an occlusive liner. Azone® (5%, w/w) was incorporated into all the systems as a percutaneous enhancer. Transdermal systems are thin, transparent and non-adhesive when in a dry state. The permeation of sumatriptan succinate across pig ear skin was studied using the systems prepared. The formulation with MC polymer produced a statistically significant increment with respect to the PVP and PVP-PVA formulations ($p < 0.05$). Azone® incorporation into the systems produced an increment in the sumatriptan flux values of all three transdermal systems with respect to those of the controls ($p < 0.05$). In addition, the application of iontophoresis to the wet methyl cellulose-Azone® formulation produced a much higher increase of sumatriptan transdermal flux. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:2102–2109, 2008

Keywords: sumatriptan succinate; migraine; transdermal delivery systems; percutaneous absorption; iontophoresis; Azone®

INTRODUCTION

Current antimigraine therapy employs potent serotonin 5-HT_1 receptor agonists that are collectively termed triptans.[1] Sumatriptan was the first of these compounds to be developed, proving to be an effective and tolerable medication. Migraine headaches are the result of dilatation of the blood vessels in the head. Sumatriptan acts as a selective 5-HT_1 agonist, causing constriction of the extracerebral blood vessels and reducing neurogenic inflammation, thereby relieving the symptoms of migraine headache.[2]

Sumatriptan succinate can be administered orally (25 and 50 mg), intranasally (10 and 20 mg) or by subcutaneous injection (6 mg). The absolute bioavailability of this drug when received at these doses is approximately 14%, 15%, and 96%, respectively. Considering the low bioavailability after oral and intranasal administration, due to presystemic metabolism and incomplete absorption, in addition to the inconveniences associated with parenteral administration, the exploitation of an alternative route of sumatriptan delivery—such as transdermal administration—could be of benefit.[3,4] Skin is a natural barrier against the

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penetration of most drugs,[5] and, consequently, different methodologies have been applied in order to enhance the transdermal absorption of pharmacological products. The most common strategy is the use of chemical compounds,[3,4,6] while physical techniques such as iontophoresis aid drug transport across the skin by means of the application of a low-level electric current ($\leq$0.5 mA/cm^2).[5,7]

Our previous reports show that *in vitro* pretreatment of skin with chemical enhancers produces a significant increment of the transdermal permeation of sumatriptan with respect to that of a control.[8,9] Azone® has proved to be the greatest enhancer among those evaluated (sumatriptan transdermal flux values across human skin were approximately 460-fold higher than those observed in the control). Furthermore, the application of iontophoresis produces a much higher increment of transdermal flux than that achieved with chemical enhancers,[8,10] resulting in values that are 775.65 and 1403.92-fold those of the control when 0.25 and 0.50 mA/cm^2 are applied, respectively.

The aim of the present work was to prepare different transdermal systems (TS) with sumatriptan and to characterize sumatriptan transdermal absorption across pig ear skin. The following polymers were selected: methyl cellulose (MC), polyvinyl pyrrolidone (PVP) and a polyvinyl pyrrolidone (PVP)-polyvinyl alcohol (PVA) mixture. In order to improve the absorption of the drug, the TS were prepared with a backing layer, as we have previously confirmed that occlusion increases sumatriptan permeation.[11] Azone®, already demonstrated to be an effective penetration enhancer,[9,12] was included in the TS in order to analyze the effect of the enhancer on the transdermal absorption of sumatriptan. In parallel, the formulation with MC-Azone® was assayed with iontophoresis.

MATERIALS AND METHODS

Materials

Sumatriptan succinate [3-[2-(dimethylamino) ethyl]-*N*-methyl indole-5 methane-sulfonamide succinate (1:1)] (MW = 413.5) (Eur. Ph. monograph 1573) was obtained from a commercial source: Imigran® intranasal 20 mg (GlaxoSmithKline, UK). The excipients of drug are potassium dihydrogenphosphate, anhydrous disodium phosphate, sulfuric acid, sodium hydroxide, and water.

The chemical enhancer Azone® (1-dodecylazacycloheptan-2-one) was purchased from Netqem (Durham, NC).

MC (MH 1000 P2), polyvinyl pyrrolidone K90 (PVP), polyvinyl alcohol (PVA), cetrimide, 1–2 propylenglycol, lauric acid, glycerol and sorbitol (70%, w/w) were obtained from Guinama Laboratories (Alboraya, Spain). Adipic acid was purchased from Sigma-Aldrich Co. (Gillingham, UK) Eudragit® E100, used for the preparation of the adhesive Plastoid E® 35 L, was generously donated by from Degussa A.G. (Dusselford, German).

Scotchpack™ Backing 9733 layer and Scotchpak™ 1022 Release Liner were donated by 3M™ (USA).

HEPES (N-[2-Hydroxiethyl] piperazine-*N*′-[2-ethanesulfonic acid]) was purchased from Sigma-Aldrich Co. (St. Louis, MO). NaCl was obtained from Mallinckrodt Backer B.V. (Deventer, Holland). Ammonium *di*-hydrogen phosphate (96–102%, w/w) and ortophosphoric acid (85–88%, v/v) were purchased from Panreac Química S.A. (Barcelona, Spain). Acetonitrile was obtained from Rathburn Chemicals (Walkernburn, Scotland). All reagents were of analytical or HPLC grade. Ultrapure water was used in the preparation of solutions.

Pig ear skin, used for *in vitro* transdermal diffusion experiments, was acquired from a local slaughterhouse immediately following the death of the animal.

Silver Chloride 99% and silver and platinum wire 99.9% 1 mm, used to make the Ag/AgCl electrodes employed in the iontophoretic studies, were purchased from Sigma-Aldrich Co. (St. Louis).

Methods

Preparation of Transdermal Systems

Transdermal therapeutic systems containing sumatriptan succinate were prepared using MC (6%, w/w), PVP (28%, w/w) or PVP (28%, w/w)-PVA (28%, w/w; 1:2) polymeric mixture.

Plastoid E® 35 L adhesive solution was prepared according to the Degussa protocol: Eudragit® E100 (14.0%, w/w), lauric acid (8.4%, w/w) and adipic acid (1.7%, w/w) were added to hot water (66.0%, w/w) (temperature range, 78–82°C). The mixture was stirred 30 min, maintaining the temperature at 80°C in order to obtain a clear solution. Afterwards, glycerol (9.3%, w/w) was added to the solution. The mixture was then

poured into wide-necked plastic bottles and maintained at room temperature.

Polymers were dissolved in water at 60°C to obtain adequate concentrations and the previously prepared Plastoid E® 35 L adhesive solution was added.

The sumatriptan succinate was dissolved in water, and a plasticizer, either 1–2 propylenglycol or sorbitol, was added to the mixture. Azone® was also added at a concentration of 5% (w/w). Finally, this solution was added to the polymer dispersion. Compositions of the different formulations we prepared are outlined in Table 1.

The mixtures were laminated at 600 μm on Scotchpack™ 9733 backing layer and dried overnight at room temperature, in the dark. Subsequently, films were covered with Scotchpak™ 1022 Release Liner and sealed in aluminum pouches. Samples of the TS (1 cm^2) were dissolved in saline buffer pH 7.4 in order to determinate the amount of sumatriptan succinate (mg/cm^2) present in each transdermal system.

In Vitro Diffusion Studies

Experiments were performed employing vertical Franz-type diffusion cells (DISA, Milan, Italy) with a diffusion area of 0.6 cm^2.

Skin from the outer side of pig ears used in the experiments was excised from the ear using a surgical blade. Afterwards it was dermatomed, using an Aesculap-Wagner dermatome C. GA 176 (B. Braun surgical S.A., Barcelona, Spain) to a thickness of a 600 μm. Dermatomed skin samples were packed and stored at −80°C.

Pig ear skin was defrosted and then placed between both sides of the cell so that the stratum corneum faced the donor compartment. The previously prepared transdermal therapeutic systems of sumatriptan succinate were placed in the donor compartment. Since the systems were not self-adhesive, their application onto the skin surface was carried out using a procedure previously described by Padula et al.[13] (skin was prewetted with 15 $\mu L/cm^2$ of water).

The receptor compartment (4 mL volume) was filled with HEPES/NaCl (20/150 mM) saline buffer (pH 7.4), thermostated at 37°C and stirred to prevent boundary layer effects.

Iontophoresis studies were carried out with wet MC-Azone® formulation. In order to ensure the passage of current during the assay in the preparation of the gel we added 7.5 mg of NaCl/10 g gel. Using Ag/AgCl electrodes connected to a Kepco BHK-MG 0–2000 V power supply, (Kepco, Inc., Flushing, NY), a constant current (0.5 mA/cm^2) was applied to the skin for 8 h.

At predetermined time intervals, samples of 200 μL were taken from the receptor chamber. The sample volume taken was replaced with buffer pH 7.4. The sumatriptan succinate contained in each sample taken was analyzed by HPLC in order to calculate the accumulative amount of drug in the receptor compartment.

At the end of the *in vitro* experiments, transdermal systems were peeled off and diluted in saline buffer (pH 7.4) to determine the residual concentration of sumatriptan succinate.

The sumatriptan succinate retained in the skin was extracted by shaking the skin during 12 h in 2 mL of the saline buffer (pH 7.4), according to Femenía-Font et al.[8]

Sumatriptan transdermal fluxes in steady-state (J_{ss}) and the lag time of diffusion (t_0), when applying the transdermal systems, were estimated by fitting the empirical diffusion equation derived from the Fick's second law of diffusion to the accumulated amounts of sumatriptan *versus*

Table 1. Composition (%, w/w) of the Different Wet Mixtures Used to Prepare the Sumatriptan Transdermal Systems

	MC	MC-Azone®	PVP	PVP-Azone®	PVP-PVA	PVP-PVA-Azone®
MC 6 % (w/w)	73.70	73.70	—	—	—	—
PVP K90 28 % (w/w)	—	—	62.0	62.0	20.70	20.70
PVA 28 % (w/w)	—	—	—	—	41.30	41.30
Plastoid E® 35L	13.2	13.2	25.60	25.60	25.60	25.60
1,2-propylenglycol	3.90	3.90	—	—	—	—
Sorbitol 70% (w/w)	—	—	4.00	4.00	4.00	4.00
Sumatriptan succinate	2.40	2.40	2.40	2.40	2.40	2.40
Azone®	—	5.00	—	5.00	—	5.00
Water	6.80	1.80	6.00	1.00	6.00	1.00

MC, methyl cellulose; PVP, polyvinyl pyrrolidone; PVA, polyvinyl alcohol.

time.[11] The fitting was performed using Win Nonlin 4.1 Software (Pharsight corp., Mountainview, CA).

The data from iontophoresis application were fitted using the empirical diffusion equation derived from the Fick's First Diffusion Law.

The J_{ss} values obtained were compared using the one-way ANOVA, followed by the Scheffe post-hoc test.

Analysis of Samples

The amount of sumatriptan in the samples was quantified by high pressure liquid chromatography (HPLC) using a previously validated method.[14] A Waters 600 Controller was used for the analysis and was equipped with a quaternary pump which included a diode-array detector (Waters 996 Photodiode Array Detector, Barcelona, Spain). Separation was carried out using an ammonium *di*-hydrogen phosphate water solution (0.05 M, pH 3.3)-acetonitrile (84:16 v/v) mixture as mobile phase, at a flow rate of 1 mL/min, and an analytical reverse-phase Kromasil C-18 column (4 mm $\times$ 250 mm) (Análisis Vínicos, Tomelloso, Spain). Analysis was performed at room temperature. The wavelength of detection was 282.7 nm. Aliquots of 50 μL were injected.

RESULTS

We have successfully obtained sumatriptan TS with different polymer compositions based on MC (Fig. 1), PVP and PVP-PVA polymeric mixtures.

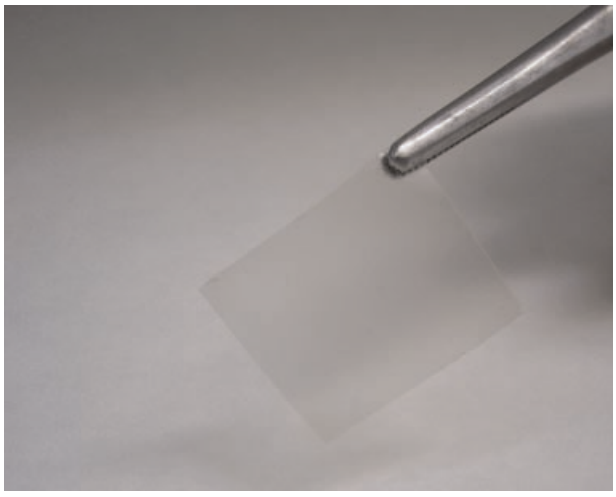

Figure 1. Sumatriptan succinate transdermal delivery system with methyl cellulose polymer.

The systems contained 1, 2-propylenglycol (MC) or sorbitol as a plasticizer (PVP and PVP-PVA), methacrylate copolymer as an adhesive and an occlusive liner (Tab. 1). Both plasticizers permitted a sufficiently flexible and elastic system, and the adhesive copolymer used allowed adaptation for application to skin.

The systems were thin, transparent and non-adhesive in a dry state. They become bioadhesive in the presence of water, and remained adhered to the skin throughout the assay.

The incorporation of the drug and enhancer into the TS did not seem to cause any modification of the patch, while the flexibility and adhesion capacity of the TS did not appear to change either.

Permeation of Sumatriptan from the Transdermal Systems

The permeation of sumatriptan succinate across pig ear skin was studied using the prepared sumatriptan TS. Figure 2 shows the permeation profiles obtained in the *in vitro* experiments. Comparing the permeation profiles from the different transdermal sumatriptan systems, it can be observed that the amount of sumatriptan in the receptor compartment was modified by the different polymers contained in the formulations. As can be observed in Table 2, the amount of sumatriptan obtained in the receptor compartment at the end of the experiments was much

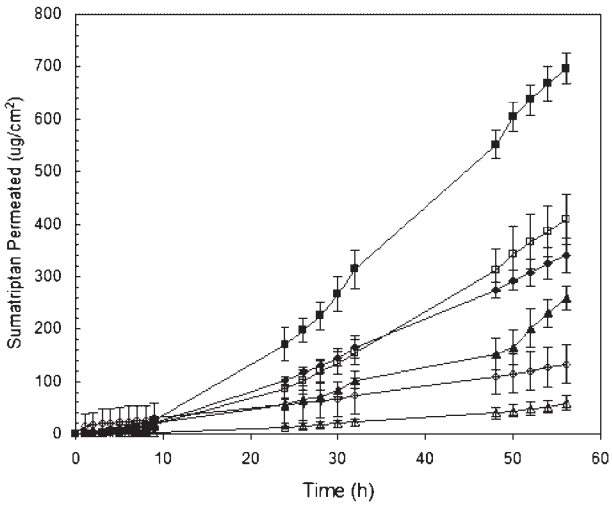

Figure 2. Permeation profiles of sumatriptan succinate from the transdermal systems: MC (□), MC-Azone® (■), PVP (◇), PVP-Azone® (◆), PVP-PVA (△), PVP-PVA-Azone® (▲). Average values ± SD, $n \geq 3$. MC, Methyl cellulose; PVP, polyvinyl pyrrolidone; PVA, polyvinyl alcohol.

Table 2. Cumulative Amount of Sumatriptan in Receptor Compartment at the End of Experiments (Q; μg/cm^2), Transdermal Flux of Sumatriptan Succinate Across Pig Skin Calculated at the Steady-State (J_{ss}; μg/cm^2 h), Sumatriptan Retained in the Skin (μg/cm^2) and Lag Time (t_0; h)

Transdermal Systems Assayed	Cumulative Amount (Q; μg/cm^2)	Sumatriptan Transdermal Flux (J_{ss}; μg/cm^2 h) (Mean ± SE)	Sumatriptan Retained in Skin (μg/cm^2) (Mean ± SD)	Lag Time (t_o) (h) (Mean ± SD)
MC	408.72 ± 48.98	11.00 ± 0.20	114.90 ± 10.10	19.24 ± 0.70
MC-Azone®	696.78 ± 28.99	17.20 ± 0.30	110.30 ± 7.90	15.21 ± 0.52
MC-Azone®-iontophoresis	2083.30 ± 183.20	284.60 ± 26.10	326.70 ± 21.80	0.008 ± 0.004
PVP	133.05 ± 37.81	2.34 ± 0.09	292.30 ± 39.10	0.08 ± 1.17
PVP-Azone®	340.12 ± 32.86	7.26 ± 0.15	224.60 ± 23.80	9.66 ± 0.71
PVP-PVA	59.62 ± 14.20	1.42 ± 0.08	297.10 ± 16.90	17.74 ± 1.71
PVP-PVA-Azone®	259.40 ± 23.50	5.73 ± 0.60	227.20 ± 13.80	16.44 ± 3.30

MC, methyl cellulose; PVP, polyvinyl pyrrolidone; PVA, polyvinyl alcohol.

lower in the case of the PVP and PVP-PVA systems than in that of the MC system.

The steady-state flux values calculated for each formulation are listed in Table 2. The formulation with MC polymer produced a statistically significant rise with respect to the PVP and PVP-PVA formulations ($p < 0.05$). When Azone® (5%, w/w) was incorporated into the systems an increase in the sumatriptan flux values with respect to controls ($p < 0.05$) was noted in all formulations.

Table 2 also lists the amounts of sumatriptan retained in the skin, extracted after the transdermal diffusion experiments, and shows how the amount of sumatriptan retained in the skin decreased as the amount accumulated in the receptor compartment increased.

Iontophoresis Study of Permeation of Sumatriptan from the Methyl Cellulose Transdermal Formulations

Since the MC system resulted in the highest level of sumatriptan transdermal permeation, we decided to apply iontophoresis to the formulation. Iontophoresis was carried out for less time than the passive diffusion studies in order to replicate real conditions as much as possible. Figure 3 shows the permeation profile of sumatriptan succinate from the MC-Azone® formulation with iontophoresis application (0.5 mA/cm^2). The flux tends to drop with time (the concentration in the receptor compartment at the end of the experiments is about 15% of that in the donor), nevertheless the linear regression of the data is significant, $p < 0.0001$.

The enhancement ratios calculated with respect to those of the corresponding control system have been outlined in Figure 4. As can be observed, the application of iontophoresis to the wet MC formulations increased the transdermal flux of sumatriptan and produced a much higher increment of transdermal flux with respect to that seen in the control system than did the chemical enhancer Azone®.

DISCUSSION

Sumatriptan succinate is highly soluble in water (water solubility at 20°C = 101 mg/mL), and the partition coefficient of the sumatriptan base in n-octanol/water ($P_{o/w} = 0.65$) is very low. According to its characteristics, we selected three hydrophilic matrixes to prepare the TS. The

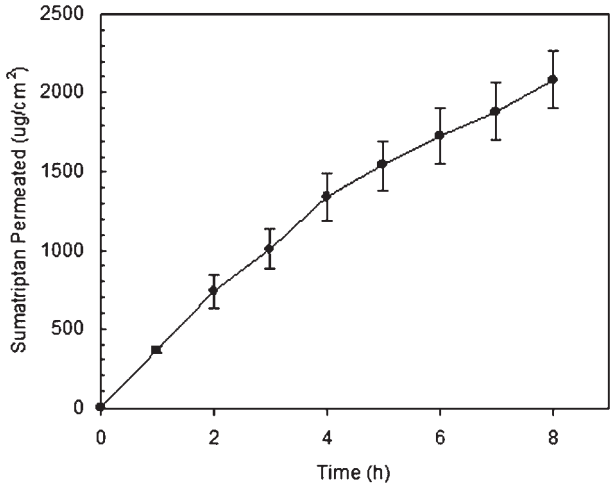

Figure 3. Permeation profile of sumatriptan succinate from the methyl cellulose—Azone® formulation with iontophoresis application (0.5 mA/cm^2). Average values ± SD, $n = 4$.

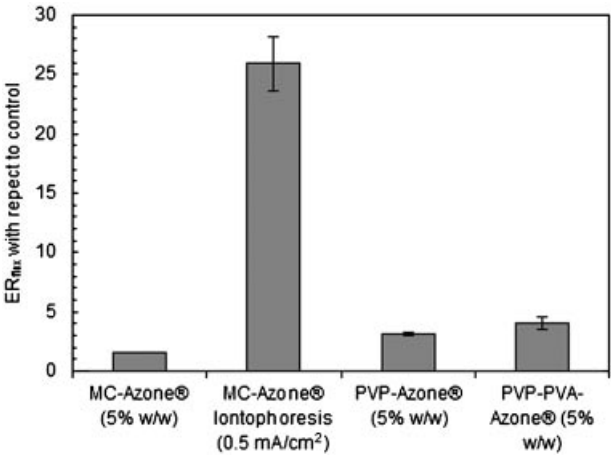

Figure 4. Enhancement ratio values (ER_{flux}) calculated with respect to transdermal control systems. MC, methyl cellulose; PVP, polyvinyl pyrrolidone; PVA, polyvinyl alcohol.

concentration of each of the polymers used to prepare the different TS was the minimum required to prepare a gel (6% MC, and 28% of PVP and PVA). The flux of sumatriptan across the skin was higher in the matrix with the lowest concentration of the gel agent. In this way, the MC net appeared to be less rigid than that obtained with PVP and PVP-PVA.

Our results demonstrate that Azone® is an effective transdermal absorption enhancer that can be incorporated into different hydrophilic TS systems. It has previously been demonstrated that the maximum enhancing effect of this compound is reached when used at concentrations between 1% and 5%, w/w. We selected a concentration of 5%, w/w based on studies using the same MC system into which we incorporated 1–10% of this substance.[15] The incorporation of Azone® into the TS did not affect their appearance. Logically, the effect of this substance was higher in the system that provided the lower basal flux of sumatriptan PVP-PVA (see Fig. 4).

Total body clearance of sumatriptan in humans is about 70 L/h, and the maximum concentration reached after a subcutaneous injection is 72 ng/mL. To reach that plasma concentration, an input of 5.04 mg/h is needed. Considering the *in vitro* flux that we obtained, the minimum surface necessary for the TS to be effective would seem to be 293 cm^2 for a TS prepared with MC and Azone®, or even 2–3 times that value (taking into account that our values were obtained using pig skin, and its permeability is twofold that of human skin,[9] and considering that permeability *in vivo* is lower than *in vitro*). Anyway, that would lead us to a nonrealistic situation.

Moreover, practically all the TS prepared showed a significant lag time of diffusion that represents an obstacle to their use in acute attacks of migraine.

TS prepared from hydrophilic gel systems allow the formulas to be combined with iontophoresis. From the three systems prepared, we selected that which provided the highest flux of sumatriptan. Iontophoresis, applied to the MC formula, provided a flux of sumatriptan 25-fold that obtained with the MC TS, with the total amount of the compound in the receptor chamber amounting to 2100 $\mu g/cm^2$ after 8 h of assay.

Sumatriptan transdermal flux obtained after application of iontophoresis to the MC gel was 284.7 ± 23.9 $\mu g/cm^2$ h. Accordingly, the above mentioned plasma concentration could be provided by means of a patch of a reasonable surface area (around 17 cm^2). On the other hand, no lag time was observed with iontophoresis (Tab. 2). The results obtained confirm those recently published by Patel et al.[16] and endorse the potential of an iontophoretic TS in the treatment of migraine. These authors assayed a transdermal system prepared with a PVP drug reservoir, coupled with iontophoresis. The TS provided an *in vitro* flux of sumatriptan of 153 $\mu g/cm^2$ h (half of that obtained in the present study), and reached a peak drug concentration of 100 ng/mL in Yorkshire swine when a 4 cm^2 patch was employed.

Figure 5 shows a simulation of the sumatriptan plasma profiles that could be obtained using a 25 cm^2 system that provides a transdermal flux of 284.7 ± 23.9 $\mu g/cm^2$ h, considering that there would be no lag time, and with an iontophoresis session lasting 20 min ($\tau = 1$ h).

The plasma levels considered in our first approach were those provided by the available oral formulation (40 ng/mL). Nevertheless, the commercially available formulation for intranasal administration, with a dose of 20 mg, provides a maximum plasma concentration of 12.9 ng/mL.[17] Thus, the question arises of whether one or two 20 min sessions of iontophoresis would be required, assuming that this level is sufficient for migraine treatment. In our opinion, the system that we propose can be refined in order to obtain a system capable of providing therapeutic levels of this antimigranous agent within a reasonable time span.

In a similar way, an iontophoretic, fentanyl HCl patient-controlled transdermal system has been

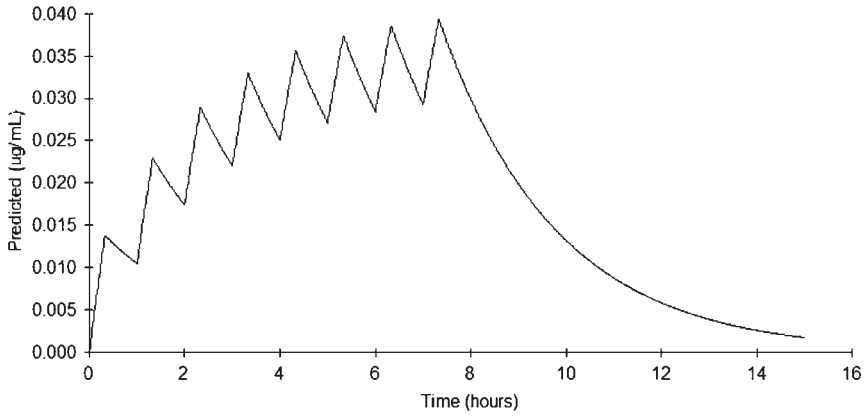

Figure 5. Simulation of the sumatriptan plasma profiles that could be obtained using a 25 cm^2 system, applied by means of 20 min session of iontophoresis that provides a transdermal flux of 284.7 ± 23.9 $\mu g/cm^2 h$, with no lag time ($\tau = 1$ h).

developed for acute postoperative pain management. The on-demand dosing of this system differentiates it from the passive transdermal formulation of fentanyl designed for the management of chronic pain. Clinical studies have shown that the fentanyl HCl system is effective in the management of acute postoperative pain, and have also demonstrated that it is safe and well-tolerated by patients.[18]

In conclusion, our results support the possibility of developing a transdermal system for sumatriptan capable of providing therapeutic levels of this antimigranous agent comparable to those obtained after subcutaneous injection, in a reasonable time span.

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