Iontophoretic Transdermal Delivery of Sumatriptan: Effect of Current Density and Ionic Strength

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ABSTRACT: Iontophoretic transdermal delivery of sumatriptan was investigated *in vitro*. Among the conditions tested, 0.25 mA/cm^2 and low ionic strength (NaCl 25 mM) was the best experimental condition to increase its transport across the skin. The flux increased 385-fold respective to passive diffusion, thus resulting in a transdermal flux of sumatriptan of 1273 ± 83 nmol/cm^2 h. © 2005 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 94:2183–2186, 2005

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INTRODUCTION

Although skin has become an important via for drug delivery for topical, regional, or systemic effects, its properties as a barrier,[1] force to use different methodologies in order to enhance transdermal drug absorption, among them iontophoresis, a technique based on the application of a low-level electric current ($\leq$0.50 mA/cm^2).[2]

The mechanisms by which iontophoresis enhances molecular transport across the skin are: (a) electrorepulsion, that implies that charged ions are repelled from an electrode with the same charge,[3–5] (b) electroosmosis, the convective flow of solvent that occurs in response to the preferential passage of counter ions when the electric field is applied,[3–10] and (c) current-induced skin permeability increment. The contribution of electroosmosis becomes greater in the transport of large cations,[3] that have low transport numbers due to the competition with smaller and more mobile ions comprising the background electrolytes. In fact, different parameters as background electrolytes, and current density have a great impact on iontophoresis efficacy.[12,13]

Sumatriptan succinate is used in the treatment of migraine. Its absolute bioavailability is approximately 15%, 14%, and 96% after intranasal, oral dosing, and subcutaneous injection, respectively, due to incomplete absorption and pre-systemic metabolism.[14] In this context, the development of new presentations, such as a transdermal delivery system, has reasonable importance.

Sumatriptan succinate is positively charged at pH 7.4, and has a molecular weight of 413.50, thus being a good candidate for iontophoretic delivery.[10–12]

The aim of this work was to investigate the iontophoretic transdermal delivery of sumatriptan and evaluate the effect of the current density applied as well as that of the ionic strength of the donor solution.

MATERIALS AND METHODS

Sumatriptan succinate (98.6%) [3-[2-(dimethylamino) ethyl]-*N*-methyl indole-5 methane-sulphonamide succinate (1:1)] (Eur. Ph. monograph 1573) was gifted by GlaxoSmithKline.

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NaCl, NaOH, and HCl analytical grade were purchased from Mallinckrodt Baker B.V., Deventer (Holland). HEPES (*N*-[2-hydroxyethyl]piperazine-*N*′-[2-ethanesulfonic acid]), silver chloride (99%), silver and platinum wire 1 mm (both 99.9%), were obtained from Sigma-Aldrich CO., St Louis.

Pig ears were collected immediately after sacrifice from a local slaughterhouse (Carnes Estellés, Paterna, Spain). The skin from the outer face was excised from the ear and then it was dermatomed to a thickness of 600 μm with a Aesculap-Wagner dermatome C. GA 176 (B. Braun Surgical S.A., Barcelona, Spain). It was stored at −20°C until use.

The electrical current applied on the skin was provided by a Kepco BHK-MG 0–2000 V power supply (Kepco, Inc., Flushing, NY).

Vertical diffusion cells, in which both electrode chambers are located on the epidermal side of the skin were used. The area of the skin exposed in each electrode chamber was 0.9 cm^2. The experiments were done at room temperature.

The donor cathodal solution was 75 mM NaCl buffered to pH 7.4 with HEPES 20 mM. The solution placed in the donor anodal compartment consisted in sumatriptan succinate 14.5 mM dissolved in the previously mentioned solution (final pH = 6.5). The receptor compartment solution was 150 mM NaCl buffered to pH 7.4 with HEPES 20 mM. The current density applied were 0.25 and 0.50 mA/cm^2, resulting in intensities of 0.225 and 0.45 mA, respectively.

One milliliter samples were taken from the receptor compartment hourly for 8 h, and replaced with the corresponding buffer. At that moment the donor solutions were also renovated.

For lower current density, analogue experiments were performed using lower ionic strength solutions. The sole difference with the above mentioned solutions was that the concentration of NaCl of the donor solutions was 25 mM.

At the different conditions assayed, passive diffusion experiments were also performed and used as controls.

At the end of the assays, the amount of sumatriptan retained in the skin was extracted by shaking the skin for 12 h with 3 mL of HEPES-buffered saline solution (pH 7.4). Previously, the efficiency of the drug extraction process was assayed and found to be over 98%.

The amount of sumatriptan in all samples was quantified using a previously validated HPLC method.[16]

Transdermal flux was estimated from the slope of the steady-state portion of the plot of the accumulated amount of drug versus time. When statistical differences were detected by means of the ANOVA test ($P < 0.05$) the permeation enhancing activities, ER_{flux}, were calculated as the ratio of the flux value obtained with iontophoresis to that found with the control.

RESULTS AND DISCUSSION

Figure 1 represents the accumulated amount of sumatriptan in receptor compartment as a function of time for 0.25 and 0.50 mA/cm^2 (75 mM NaCl solutions) and the respective passive control. The steady-state flux values calculated for each condition are listed in Table 1. The application of a current density of 0.25 mA/cm^2 produces a statistically significant increment (78-fold) with respect to the passive control ($P < 0.05$, ANOVA followed by a multiple comparison Dunnett 3T test). Applying a larger current density (0.50 mA/cm^2), we observed a significant increase in the flux, not only respective to passive control (192-fold) but also to the 0.25 mA/cm^2 iontophoretic condition (2.4-fold). These results are consistent with previous reports:[13] doubling the current density doubles the transdermal flux.

Table 1 shows the amount of sumatriptan retained in the skin after 8 h of transdermal diffusion, 0.50 mA/cm^2 produced a statistically significant increment compared to the control ($P < 0.05$, Dunnet 3T test), but when considering the 0.25 mA/cm^2, the differences found were not statistically significant with respect to controls.

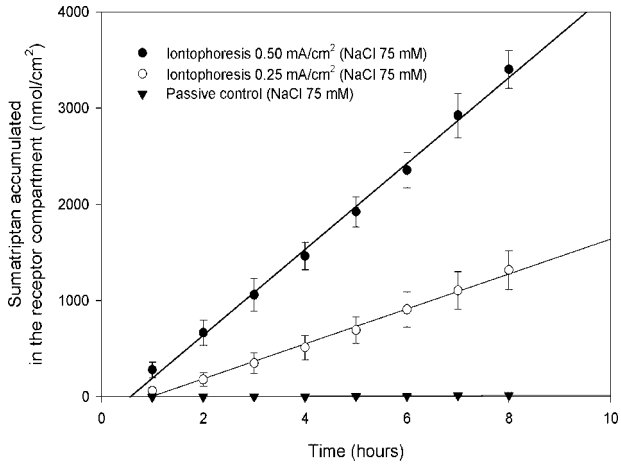

Figure 1. Effect of the current density applied on the accumulated amount of sumatriptan (nmol/cm^2) under high ionic strength iontophoretic conditions. Each point represents the mean ± standard deviation.

Table 1. Iontophoretic Sumatriptan Transdermal Fluxes, Enhancement Ratios and Amount of Sumatriptan Retained in the Skin After Transdermal Diffusion Experiments

Experimental Condition Assayed (n)	Sumatriptan Transdermal Flux [nmol/(cm^2 h)] (mean ± SD)	ER_{flux} Respective to Control (mean ± SD)	Sumatriptan Retained in Skin [μmol/(cm^2)] (mean ± SD)	Sumatriptan Transport Number (%)
Passive control (NaCl 75 mM) (12)	2.4 ± 0.9	—	0.21 ± 0.12	—
Iontophoresis 0.25 mA/cm^2 (NaCl 75 mM) (8)	187 ± 23[a]	78.3 ± 31.1	0.35 ± 0.08	2.46 ± 0.27
Iontophoresis 0.50 mA/cm^2 (NaCl 75 mM) (6)	459 ± 51[a]	192 ± 75	0.72 ± 0.39[a]	2.01 ± 0.25
Passive control (NaCl 25 mM) (6)	3.3 ± 0.8	—	0.12 ± 0.04	
Iontophoresis 0.25 mA/cm^2 (NaCl 25 mM) (6)	1273 ± 83[a]	385 ± 100	0.62 ± 0.16[a]	13.64 ± 0.89

Transport number of sumatriptan has been calculated in each iontophoretic condition. Passive controls have also been included for reference. The number in parenthesis corresponds to the number of experiments.

[a]Denotes statistical differences respective to its control (Dunnet T3 test, $P < 0.05$).

The reduction of the ionic strength of the donor compartment bathing solutions from 75 to 25 mM NaCl produced an important increment in the transdermal flux values of sumatriptan, that of 25 mM being 1273 ± 83 nmol/cm^2 h, which represents an ER_{flux} respective to control of 385 ± 100.

The results obtained confirmed the importance of the competition phenomena between the drug and ions of the background electrolyte in the transdermal transport of the drug, supporting previous reports.[7–9,11] The transport number of sumatriptan increased from 0.02 to 0.14. The reduction of the ionic strength to the lowest possible limit has greater impact than doubling the current density.

The amount of compound retained in the skin after applying 0.25 mA/cm^2, with a low ionic strength solution (NaCl 25 mM) is similar to that retained after employing iontophoresis at high current density (0.50 mA/cm^2) and high ionic strength (NaCl 75 mM).

Our previous reports have shown that skin pretreatment with chemical enhancers produced a significant increase in the transdermal flux values of sumatriptan. *R*-(+)-limonene was the best enhancer among the compounds tested, providing an increment in sumatriptan transdermal flux of 22-fold with respect to the control.[9] Nevertheless, in this work iontophoresis has been demonstrated to be more efficient, increasing sumatriptan transdermal flux 385-fold respective to its passive diffusion.

CONCLUSIONS

Iontophoresis is a very efficient enhancement technique for the transdermal delivery of sumatriptan. The application of iontophoresis at 0.25 mA/cm^2 with the use of low ionic strength (NaCl 25 mM) has shown the best capability to increase sumatriptan transport across the skin. The results obtained point out the importance of controlling the experimental conditions in order to optimize transdermal fluxes when applying iontophoresis.

The results obtained *in vitro* are promising and further work, *in vivo*, has to be made to ensure that therapeutic blood levels of sumatriptan can be achieved using this technology.

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