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Research paper

Controlled non-invasive transdermal iontophoretic delivery of zolmitriptan hydrochloride *in vitro* and *in vivo*

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ABSTRACT

The objective was to investigate the transdermal delivery kinetics of zolmitriptan from an iontophoretic patch system in Yorkshire swine *in vivo*. Preliminary *in vitro* experiments showed that cumulative drug transport during a 6-h current application (0.25 mA cm^{-2}) was independent of patch load (263.7 ± 92.7, 357.2 ± 85.9, 374.9 ± 74.3 and 335.9 ± 27.7 μg cm^{-2} for 7.5, 15, 45 and 90 mg patch loads, respectively; ANOVA, $p < 0.05$); the steady-state flux was ~92 μg cm^{-2} h^{-1}. The *in vivo* studies used multistep current profiles to demonstrate (i) rapid drug uptake and (ii) the effect of superposing a bolus input on basal drug levels. In both studies, zolmitriptan was detected in the blood after 2.5 min; drug levels were 7.1 1.7 and 10.4 ± 3.5 ng ml^{-1} at t = 30min in Studies 1 and 2, respectively. In Study 2, increasing current intensity from 0.2 to 1.4 mA (0.05–0.35 mA cm^{-2}) at t = 180 min caused zolmitriptan levels to rise from 9.38 ± 0.93 ng ml^{-1} at t = 180 min to 13.57 ± 1.85 ng ml^{-1} at t = 190 min; a ~50% increase in 10 min. Extrapolation of these results to humans suggests the feasibility of delivering therapeutic amounts of zolmitriptan at faster rates than those from existing dosage forms.

1. Introduction

Zolmitriptan is a structural analogue of serotonin (5-HT); it contains a tertiary amine group (p*K*a ~ 9.52) and is thus positively charged under physiological conditions (Fig. 1; Table 1). It has strong affinities for the 5-HT_{1B} and 5-HT_{1D} receptors, pK_i 8.3 and 9.2, respectively [1], and it is used in the treatment of acute migraine [2]. Although several anti-migraine therapeutics are available for administration by different routes [3,4], there are still several unmet needs. The principal deficiencies in existing therapies cited by migrainers include (i) the time taken to provide pain relief (87%), (ii) incomplete pain relief (84%), and (iii) the prevalence of headache recurrence (71%) [5,6]. Ideally, the optimal drug would provide onset of relief within 30 min, complete pain relief within 2 h, reduce headache recurrence and alleviate other symptoms associated with migraine episodes (e.g., nausea).

In order to improve the efficacy of these medications and to reduce the onset time for therapeutic effect, a number of different pharmaceutical dosage forms have been developed for the different triptans. For example, sumatriptan is available as a subcutaneous injection, oral tablet (conventional and fast-dissolving) and as a nasal spray [7]; rizatriptan is administered as a fast-dissolving tablet [8] and zolmitriptan is available as a tablet and as a nasal spray [9]. Although subcutaneous administration of sumatriptan provides the quickest pain relief [4,7], the incidence of local site reactions and issues with patient compliance have restricted its use [10].

Therefore, there is a need to develop fast-acting, non-invasive delivery systems for anti-migraine therapeutics. Transdermal iontophoresis is a controlled delivery technology that would seem to be well-suited for addressing these needs [11]. Drug input kinetics can be modulated (and tightly controlled) by the current profile; short duration pulses of high current intensity can be used to deliver "bolus" drug inputs, whereas application of lower intensity currents of longer duration enables basal drug levels to be maintained. Transdermal iontophoresis of sumatriptan has been demonstrated *in vitro* and *in vivo* [12–15]. However, it is less potent than other triptans (Table 1), and transdermal delivery rates cannot match input kinetics of subcutaneous injection [4,7,14].

Zolmitriptan appears a very good candidate for iontophoresis since it is a low molecular weight cation that is completely ionized under physiological conditions, readily soluble in aqueous solution and available as a hydrochloride salt (making it amenable for use with Ag/AgCl anodal electrochemistry) (Fig. 1; Table 1). Moreover, it is potent; the oral dose is 2.5–5 mg and since its oral bioavailability is approximately 40–45%, this implies that only 1–2 mg actually enters the bloodstream; and it is well within the capabilities of iontophoresis to deliver these amounts of drug.

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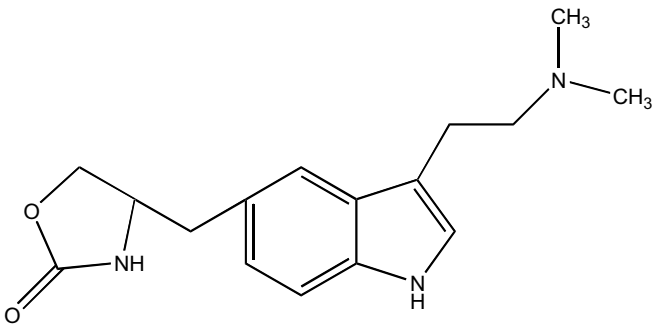

Fig. 1. Structure of zolmitriptan (M_W = 287.4, p*K*a = 9.52).

Table 1
Comparing physicochemical and pharmacological properties of sumatriptan and zolmitriptan

	Sumatriptan	Zolmitriptan
[a]M_W	295.4	287.4
[b]pK_a	9.49	9.52
[c]logP	0.667	1.644
[d]log$D_{pH7.0}$	−1.73	−0.78
[e]pI ($5HT_{1B}$)	7.8	8.3
[e]pI ($5HT_{1D}$)	8.5	9.2
Dosage forms	Oral: 25–100 mg SubQ: 6 mg Intranasal: 20 mg Rectal: 25 mg	Oral: 2.5–5 mg Nasal: 5 mg

[a] Molecular weight (Da).
[b] Dissociation constant.
[c] log (octanol/water) partition coefficient.
[d] Distribution coefficient were calculated using Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris (©1994–2006 ACD/Labs).
[e] Log receptor affinity [4].

The objectives of this study were to investigate zolmitriptan delivery kinetics from a transdermal iontophoretic patch system and to determine whether these could result in the delivery of therapeutic amounts of zolmitriptan. The first part of the study was conducted using porcine skin *in vitro* in order to optimize the formulation and iontophoretic conditions. The second part comprised two studies in Yorkshire swine *in vivo*. The first of these involved the application of a multistep current profile in order to increase the rate of zolmitriptan entry into the bloodstream. The second, which also involved application of a complex current profile, investigated the potential for delivering repeat bolus doses superposed on a basal input rate (as might be required to prevent headache recurrence).

2. Materials and methods

2.1. Chemicals

Zolmitriptan hydrochloride was custom synthesized (Natco Pharma Limited, Hyderabad, India); ketamine, xylazine and propofol were obtained from Henry Schein Inc. (Melville, NY, USA). Ammonium acetate (ACS reagent) was obtained from Sigma–Aldrich (St. Louis, MO, USA); acetonitrile, acetic acid and methanol (all HPLC grade) were obtained from (G.J. Chemical, Newark, NJ, USA).

2.2. Experimental procedure in vitro

Porcine skin was obtained from Thomas D. Morris, Inc. (Reistertown, MD, USA). The excised skin was dermatomed (∼500 μm) on the same day and stored at −20 °C for a maximum period of up to 1 week. A proprietary 2-compartment patch system was used during iontophoresis [14]. The electrode compartment comprised an Ag-mesh anode, a small amount of sodium chloride (0.06%) and an ion exchange resin (AMBERLITE™ IRP-69, Rohm & Haas, Perth Amboy, NJ, USA) that trapped Ag^+ ions preventing them from competing with drug ions to carry current. The anode initially functions using Ag/AgCl electrochemistry before switching to acting as an Ag-dissolution electrode with a concomitant increase in its operating voltage. The electrode compartment was separated from the drug reservoir, made of polyvinylpyrrolidone (PVP, 15%; K-90F, BASF, Florham Park, NJ, USA), and containing zolmitriptan hydrochloride, by a size-selective membrane (M_W cut-off 100 Da, SpectroPor; Rancho Dominguez, CA, USA). The active surface area of the anodal patch in contact with the skin was 4 cm^2. A vertical diffusion set-up was employed wherein the patch was directly in contact with the skin, which was placed on a polymeric support. A flow through system, built in-house, ensured that the drug did not accumulate in the receiver, which was replenished at a rate of 0.1 ml min^{-1}. A constant current of 0.25 mA cm^{-2} was applied for a maximum of 6 h. Unless indicated otherwise zolmitriptan hydrochloride was dissolved in water at the appropriate concentration required for the desired patch loading and ∼300–400 μl of the drug solution was introduced into the anodal drug reservoir. A passive "no-current" control confirmed that there was negligible zolmitriptan transport in the absence of an iontophoretic current.

2.3. Experimental procedure in vivo

The *in vivo* experimental protocol was approved by the local ethics committee.

Three 15–20 kg (7–9 weeks old) prepubescent female pigs were used in the study. The weight of the animals was measured and recorded before the start of each experiment. Animal hair at the site of patch application was clipped the night before the experiment. The skin was gently wiped with warm water followed by an alcohol swab and patted dry before patch application. The animals were placed on a surgical table under general anaesthesia and jugular, ear vein and arterial catheters were placed either percutaneously or surgically.

Anaesthesia was induced by intramuscular administration of ketamine (11 mg kg^{-1}) and xylazine (2 mg kg^{-1}); it was maintained by continuous infusion of propofol (12–20 mg kg^{-1} h^{-1}). Arterial blood pressure, end tidal CO_2 volume, rectal temperature and ECG measurements were recorded during all procedures. Respiratory rate and quality was monitored visually. Body temperature was maintained by (i) placing a circulating water heating pad under the animal and (ii) a thermal blanket over the pig to retain body heat.

As with the *in vitro* studies, a proprietary iontophoretic patch system (with an active area of 4 cm^2 and where the anode contained 15 mg of zolmitriptan at pH 4.5) coupled to a programmable power source was used to apply the current. In Study 1, three animals received the iontophoretic treatment involving application of a multi-phase current protocol. In step 1, from t = 0 to 10 min, the current intensity was 1.4 mA (0.35 mA cm^{-2}); in step 2, from t = 11 to 30 min, the current intensity was decreased to 1.0 mA (0.25 mA cm^{-2}); in step 3, from t = 31 to 180 min, the current intensity was further reduced to 0.4 mA (0.1 mA cm^{-2}) and in step 4, from t = 181 to 360 min, the current intensity was 0.2 mA (0.05 mA cm^{-2}).

In Study 2, three animals again received the iontophoretic treatment. The controller was programmed to deliver "Pulse-train 1" with a current intensity of 1.4 mA (0.35 mA cm^{-2}) for the first 10 min, which was then decreased to 1.0 mA (0.25 mA cm^{-2}) for the next 20 min (t = 11–30 min) and further reduced to 0.2 mA (0.05 mA cm^{-2}) for the next 2.5 h (t = 31–180 min). A second higher intensity pulse was applied after the first 3 h "pulse-train" with a slightly different profile. In "Pulse-train 2", a current of 1.4 mA

(0.35 mA cm^{-2}) was applied for the first 10 min (t = 181–190 min); this was decreased to 1.0 mA (0.25 mA cm^{-2}) for the next 20 min (t = 191–210 min); no current was applied during the next 2.5 h (t = 211–360 min) although the patches were left in contact with the skin.

In Study 1, blood samples (2 ml) were drawn every 2.5 min from t = 0 to 10 min; at 5-min intervals from t = 10 to 45 min; every 15 min from t = 45 to 180 min and at 30-min intervals from t = 180 to t = 360 min. In Study 2, blood draws were made at 2.5-min intervals from t = 0 10 min and from t = 180 to 190 min; every 5 min from t = 10 to 30 min and from t = 190 to 210 min; at 15-min intervals from t = 15 to 180 min and from t = 210 to 360 min. At the conclusion of the studies, the animals were euthanized.

The samples were collected into chilled 3 ml glass vacutainer tubes containing ethylenediaminetetracetic acid tripotassium salt (K_3EDTA) (BD, Franklin Lakes, NJ, USA). The tubes were immediately placed on ice and centrifuged at 4 °C (1600 g for 15 min). The contents were then split into two samples and stored in Nalgene cryopreserve vials (VWR, Westchester PA, USA). The plasma samples were stored at −70 °C.

3. Analytical methods

In vitro: Samples obtained from the *in vitro* experiments were assayed using the following reverse phase HPLC method. The HPLC system comprised a 600 E Controller pump, an Autosampler Injector 717-plus, and a 486 tunable UV Detector (Waters, Milford, MA, USA) and was equipped with a Luna RX c18 column with guard and prefilter (4.6 mm internal diameter, 25 cm in length and with a 5 μm particle size) (Agilent Technologies, CA, USA). The mobile phase (19% acetonitrile and 81% 0.5 M ammonium acetate buffered pH 4.9 solution with 1% trifluoroacetic acid (TFA)) was delivered at a flow rate of 1 ml min^{-1}. The injection volume was 50 μl. Zolmitriptan was detected a 282 nm. The limits of detection and quantification for the analysis of the *in vitro* samples were 0.2 and 0.5 μg/ml, respectively.

In vivo: (i) Extraction: The drug was extracted by protein-precipitation. The plasma samples were first allowed to thaw at room temperature. After vortexing, 100 μl of sample was transferred into 2 ml Eppendorf tubes. Then, 10 μl of MeOH:H_2O (1:1 mixture) was added to the plasma samples containing sumatriptan. After the addition of 300 μl of acetonitrile and vortexing for a few seconds, the mixture was centrifuged at 1200*g* for 10 min. Then, 300 μl of the resulting supernatant was transferred to 16 × 100 mm clean culture tubes and evaporated to dryness under nitrogen at 35 °C (this took approximately 20 min). The samples were then reconstituted with 100 μl of mobile phase and vortexed before being transferred to injection vials and assayed using an LC/MS/MS system. (ii) Assay: The LC system comprised a LC-10 AP pump and SCL-10M controller (Shimadzu Corporation, MD, USA); autoinjector (Waters 717-plus autosampler, Waters Corporation, MA, USA) and was equipped with an Inertsil ODS2 column (4.6 mm internal diameter, and 15 cm in length with 5 μm particle size) (Keystone Scientific, Inc. PA, USA). Perkin Elmer API 365 and API 3000 detectors were used to detect zolmitriptan. The mobile phase (30% methanol and 70% 10 mM ammonium acetate buffered pH 4.0 solution) was delivered at a flow rate of 1 ml min^{-1}. The injection volume was 10 μl. With respect to the conditions for MS/MS, the spectrometer employed a heated ion nebuliser at 475 °C. The limit of quantification was 0.4 ng ml^{-1}.

3.1. Statistical methods

Data were expressed as mean ± SD Outliers, determined using the *Grubbs test*, were discarded. The results were evaluated statistically using analysis of variance (ANOVA); Student's *t*-test was used to compare two data sets. The level of significance was fixed at $p < 0.05$.

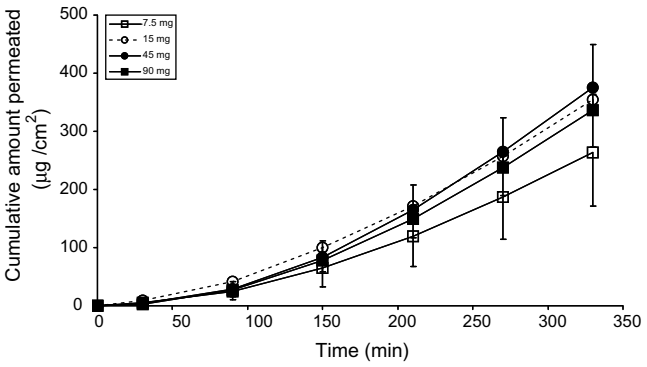

Fig. 2. Effect of increasing zolmitriptan loading in the patch from 7.5 to 90 mg on the cumulative amount of zolmitriptan delivered across porcine skin *in vitro* with a 6 h iontophoretic current application (0.25 mA cm^{-2}) from a patch system with a PVP gel drug reservoir. No statistically significant difference in the cumulative amounts permeated was observed (ANOVA, $p < 0.05$). (Mean ± SD; $n \geqslant 6$).

4. Results

The objective of the initial *in vitro* experiments was to optimize the formulation and iontophoretic conditions for the subsequent experiments *in vivo*. As shown in Fig. 2, a 12-fold increase in patch loading from 7.5 to 90 mg did not produce a statistically significant increase in the cumulative amount of zolmitriptan delivered across the skin during a 6-h current application (263.7 ± 92.7, 357.2 ± 85.9, 374.9 ± 74.3 and 335.9 ± 27.7 μg cm^{-2} for 7.5, 15, 45 and 90 mg patch loads, respectively; ANOVA, $p < 0.05$). For the lowest patch loading (7.5 mg), this corresponds to a delivery efficiency of ∼14% (that is, 14% of the applied drug load was administered during current application). Using the steady-state flux (J_{SS}) obtained from the linear portion of the graph, it is possible to calculate the zolmitriptan transport number (t_{SS}) at steady-state from

$$t_{SS} = \frac{J_{SS}F}{I} \quad (1)$$

where I and F represent the current intensity and Faraday's constant, respectively. The steady-state flux (for the 15 mg patch load) calculated from the linear portion of Fig. 2 is ∼92 μg cm^{-2} h^{-1}; thus, for a 4 cm^2 patch, this corresponds to a drug input rate of ∼368 ± 99 μg h^{-1}. Insertion of the appropriate values reveals a t_{SS} of ∼0.03. Thus, approximately 3% of the charge passed during current application was transported by the drug; the principal charge carrier was chloride ion moving from the receiver compartment towards the anode.

In the next experiment, the pH of the formulation was increased from 4.5 to 7.0; the objective was to increase the contribution of electroosmosis to zolmitriptan delivery. However, and somewhat surprisingly, there appeared to be no statistically significant increase in transport rates upon increasing pH (*t*-test, $p < 0.05$) (see Fig. 3).

Based on the results from the *in vitro* experiments, it was decided to conduct the *in vivo* studies (in Yorkshire swine) using a relatively modest patch loading of 15 mg zolmitriptan dissolved in an aqueous unbuffered solution (pH 4.5); this was used in preference to the 7.5 mg loading to avoid the risk of drug depletion in the reservoir. The objective of the first *in vivo* study was to rapidly achieve and maintain target zolmitriptan levels in the bloodstream. In order to do this, a complex multistep current profile was programmed into the controller (see Section 2 and Fig. 4). Typ-

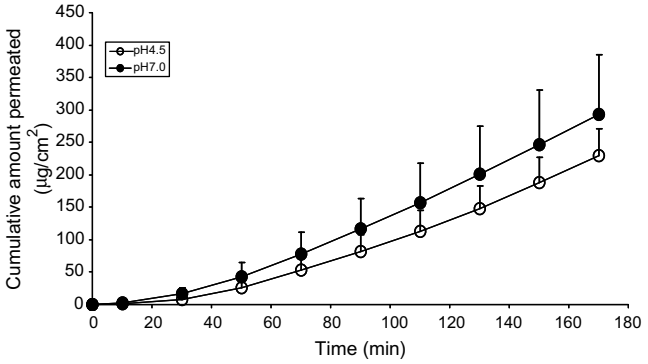

Fig. 3. Effect of increasing formulation pH from 4.5 to 7.0 on the cumulative amount of zolmitriptan delivered across porcine skin *in vitro* with a 6 h iontophoretic current application (0.25 mA cm^{-2}) from a patch system with a PVP gel drug reservoir containing 90 mg of drug. Hollow and filled circles represent formulation with a pH of 4.5 and 7.0, respectively. No statistically significant difference in the cumulative amounts permeated was observed (*t*-test, $p < 0.05$). (Mean ± SD; $n = 6$).

ically, upon commencing iontophoretic current application, there is an unsteady state period as drug flux across the skin gradually increases before steady state is attained and a constant flux is achieved [16]. *In vivo*, this translates into a hyperbolic plasma concentration profile as a function of time. The objective of this *in vivo* study was to achieve a "step-function" increase in zolmitriptan concentrations in the bloodstream; hence, the use of different current intensities during the first 30 min of current application.

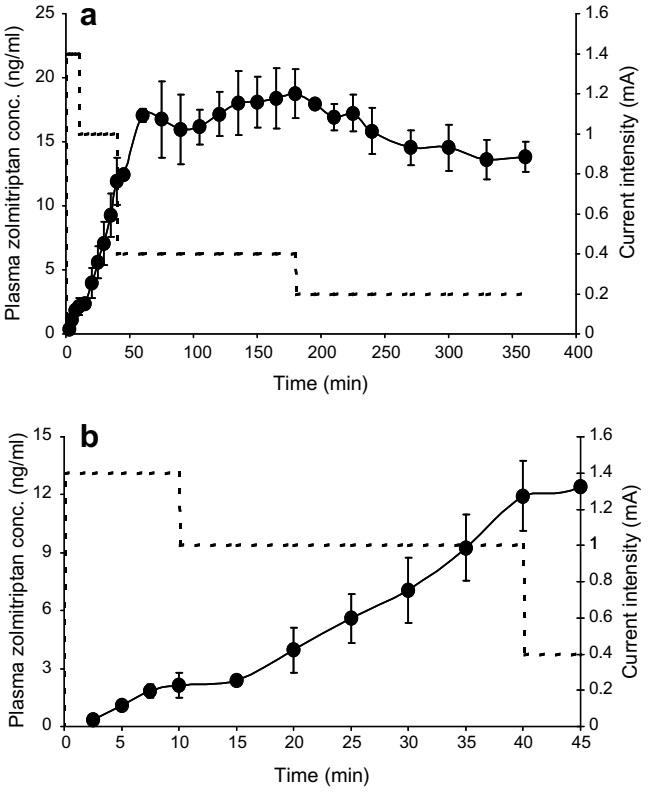

Fig. 4. (a) Plasma concentration profile of zolmitriptan as a function of time during iontophoretic delivery in Yorkshire swine. A multistep current profile was applied (secondary *y*-axis, dashed line) in order to achieve a rapid increase in drug levels in the bloodstream. In phase 1 ($t = 0$–10 min) – 1.4 mA (0.35 mA cm^{-2}); then in phase 2 ($t = 11$–30 min) – 1.0 mA (0.25 mA cm^{-2}); in phase 3 ($t = 31$–180 min.) – 0.4 mA (0.1 mA cm^{-2}); and finally, in phase 4 ($t = 181$–360 min) – 0.2 mA (0.05 mA cm^{-2}). (b) The initial increase in drug levels in the plasma during the first 45 min of current application. (Mean ± SD; $n = 3$).

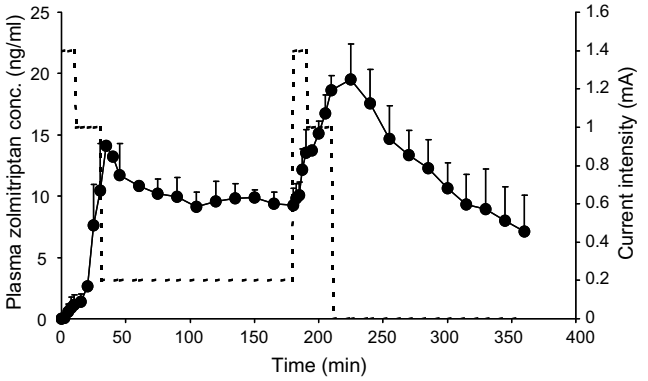

Fig. 5. Plasma concentration profiles of zolmitriptan as a function of time during iontophoretic delivery in Yorkshire swine. A multistep current profile was applied (secondary *y*-axis, dashed line) in order to simulate the effect of providing two bolus inputs; the second being superimposed on a low level or "maintenance" drug input rate. In phase 1 ($t = 0$–10 min) – 1.4 mA (0.35 mA cm^{-2}); then in phase 2 ($t = 11$–30 min) – 1.0 mA (0.25 mA cm^{-2}); in phase 3 ($t = 31$–180 min) – 0.2 mA (0.05 mA cm^{-2}); in phase 4 ($t = 181$–190 min) – 1.4 mA (0.35 mA cm^{-2}); then in phase 5 ($t = 191$–210 min.) – 1.0 mA (0.25 mA cm^{-2}); no current was applied between $t = 211$ and 360 min Plasma levels were tightly controlled and closely mapped the applied current intensities. (Mean ± SD; $n = 3$).

Zolmitriptan was detected in the bloodstream after 2.5 min and drug levels were 7.1 1.7 and 11.9 2.0 ng ml^{-1} at $t = 30$ and $t = 40$ min, respectively; indicating relatively fast drug uptake (Fig. 4b). Zolmitriptan concentrations were tightly controlled and showed only limited inter-animal variability; furthermore, they remained in a narrow range (between ~17 and 18.8 ng ml^{-1} for almost 3 h during the $t = 60$–225 min period even after the decrease in current input. Although zolmitriptan levels subsequently fell in response to a further decrease in the applied current, they remained significant (13.8 ± 1.3 ng ml^{-1}) throughout the $t = 180$–360 min period indicating that after the initial "bolus", high levels of zolmitriptan can be maintained using a lower current input.

In the second *in vivo* study, the objective was to demonstrate the effect of an initial bolus, followed by a maintenance input rate and a subsequent second bolus on zolmitriptan levels in the blood (Fig. 5). Zolmitriptan was again detected in plasma after 2.5 min and levels of 10.4 ± 3.5 ng ml^{-1} were achieved within 30 min. C_{max} for the first bolus was 14.1 ng ml^{-1} and achieved at $t = 35$ min. Plasma levels remained in a narrow range of 9.2–10.2 ng ml^{-1} during the maintenance phase ($t = 75$–180 min). At $t = 180$ min, the second pulse train was initiated and the current increased from 0.2 to 1.4 mA (0.05–0.35 mA cm^{-2}). In response, plasma levels rose from 9.38 ± 0.93 at $t = 180$ min to 13.57 ± 1.85 and 15.13 ± 1.00 at $t = 190$ and 200 min, respectively. Thus, there was an almost 50% increase of zolmitriptan levels in the blood in the space of 10 min upon raising the current intensity. Drug levels continued to increase and peaked at ~19.5 ng ml^{-1} ($t = 225$ min). As in Study 1, there was little inter-animal variation and blood levels were tightly controlled by the current. Drug was eliminated following the termination of the current application.

5. Discussion

As described above, the drug reservoir was separated from the electrode compartment in the iontophoretic patch by a size-selective membrane (M_W ~100 Da). This meant that, in addition to reducing the effect of competing ions, a smaller amount of drug was required and this can be an important factor when dealing with more costly therapeutic agents; for example, peptide and protein drugs. Thus, although approximately equivalent amounts of zolmitriptan were delivered from the iontophoretic patches with

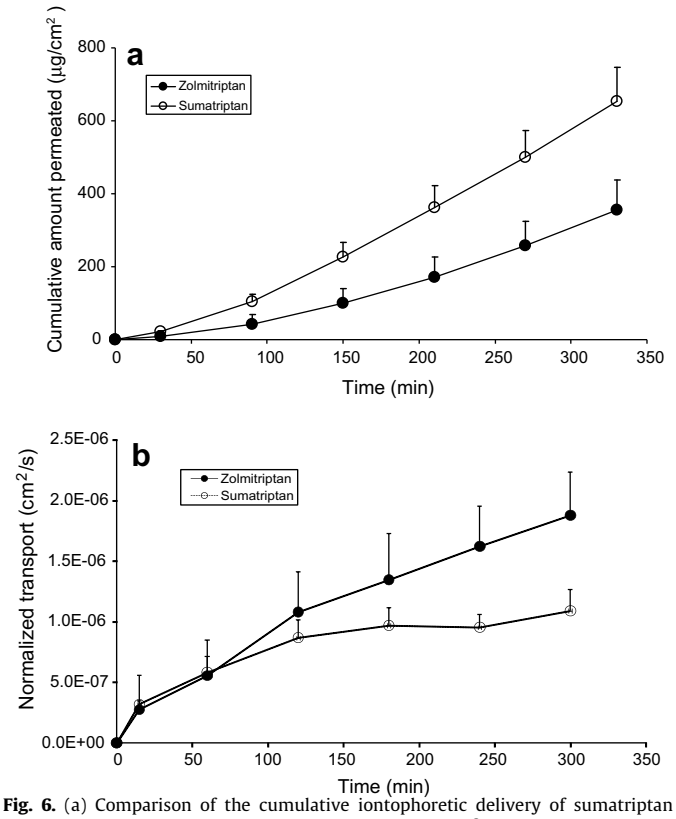

Fig. 6. (a) Comparison of the cumulative iontophoretic delivery of sumatriptan ([14]; PVP gel reservoir, 39 mg load, pH 6.8, 0.25 mA cm^{-2}) and zolmitriptan (PVP gel reservoir, 15 mg load, pH 4.5, 0.25 mA cm^{-2}) as a function of time across porcine skin *in vitro*. (b) Comparison of the normalized transfer rates taking into account the different drug loadings in the patches. (Mean ± SD; $n \geqslant 4$).

15 and 90 mg loads (1.43 ± 0.34 and 1.34 ± 0.11 mg, respectively), the fraction of the drug load delivered, in effect, the dose efficiency was significantly different (9.5% and 1.5%, respectively). Thus, the two-compartment iontophoretic system can be considered a "*D*ose *E*ffective *P*atch" (DEP) system.

Comparison of the *in vitro* transport data for zolmitriptan with published results for sumatriptan [14] shows that the cumulative permeation of the latter was greater (Fig. 6a) – due to the superior transport number (0.03 vs. 0.056). However, normalization of the flux by patch load (yielding a "diffusivity" parameter (cm^2/s)), to take into account the 2.6-fold higher loading of the sumatriptan patch (39 vs. 15 mg in this study) provides a different perspective. Now, transport of zolmitriptan is seen to be initially equivalent and then, after $t = 180$ min, superior to that of sumatriptan (Fig. 6b). In view of the similar physicochemical properties of the two molecules (e.g., M_W and pK_a; Table 1), the similarity of the transport rates is to be expected. However, zolmitriptan's superior potency means that increased pharmacological effect is achieved for the same mass transport.

For the *in vivo* scenario, if a constant input rate (K_0) is assumed (this is contingent upon the fact that steady-state flux is achieved fairly quickly [16]), then

$$K_0 = \mathrm{CL} \times C_{SS} \quad (2)$$

where CL and C_{SS} represent the clearance and steady-state concentration of zolmitriptan, respectively. Thus, from Fig. 4, using the average plasma concentration between $t = 60$ and 180 min of 17.4 ng ml^{-1}, and using the clearance observed in man (193 ml min^{-1} [3], we have previously found that the clearance for the structural analogue, sumatriptan, in Yorkshire swine was very similar to that in humans [14]), we obtain an input rate *in vivo* (K_0) of 336 μg h^{-1}.

It should be noted that earlier studies have confirmed that, in general, porcine skin is an excellent model for human skin both in terms of its biophysical properties and with regard to its function as a barrier to permeants [17,18]; although Femenía-Font et al. recently reported that the iontophoretic permeation of sumatriptan across porcine ear skin was 2-fold higher than that across human skin *in vitro* [13]. Since barrier function in the two membranes is comparable, it is possible to extrapolate the results obtained here to the human scenario and estimate, to a first approximation, whether the iontophoretic delivery rates are relevant from a therapeutic standpoint. The total blood volume in Yorkshire swine is on the order of 2–2.5 l; therefore, assuming a typical blood volume of ~5 l in humans, it is possible to scale the zolmitriptan concentrations in the Yorkshire swine and estimate the corresponding values in humans.

Pharmacokinetic studies following oral administration of 2.5 and 5 mg zolmitriptan tablets have reported C_{max} values of 3 and 5–9 ng ml^{-1}, respectively; the corresponding T_{max} values were 1.5 –2.5 h [9,19,20]. In this study (Fig. 4), the zolmitriptan levels after 40 min (11.9 2.0 ng ml^{-1}) and 1 h (17.0 3.0 ng ml^{-1}) would compare favourably to the values in man (assuming a proportionality factor of 0.4, the *projected* levels in man at the corresponding time-points would be ~4.8 and 6.8 ng ml^{-1}) and would be achieved more rapidly, perhaps enabling more rapid onset of therapeutic effect. The pharmacokinetics of the recently developed intranasal formulation have also been investigated in humans and although the drug is detected within 5 min in the bloodstream (cf. 15 min for the 2.5 mg tablet), the plasma concentrations at 30 and 60 min are ~2 and ~3 ng ml^{-1} [9], again suggesting that an iontophoretic delivery platform might provide increased drug input as compared to the existing dosage forms.

The plasma concentration profile obtained in Study 2 (Fig. 5) underlines the control provided by iontophoresis and its unique ability to rapidly change drug input rates; the profile shown in Fig. 5 is not possible with other transdermal delivery technologies and realistically could only be achieved by using an infusion pump, which is obviously far more invasive. The zolmitriptan concentration measured at the 35 min time-point (14.1 ng ml^{-1}) compares very favourably to the blood levels in man when scaled to the human scenario.

6. Conclusion

The results show that zolmitriptan is ideally adapted to iontophoresis, and has the balance of physicochemical characteristics and potency that renders it suitable for administration by this delivery platform. The *in vivo* data demonstrate that transdermal iontophoresis of zolmitriptan can effect the delivery of therapeutic amounts of zolmitriptan in a short timeframe. Extrapolation of drug levels achieved in Yorkshire swine suggests that the corresponding levels in humans would compare favourably with those achieved by the oral or nasal routes. Selection of an appropriate current profile enables fast entry of drug into the bloodstream (to improve efficacy in treating the initial attack), steady delivery of a low level maintenance dose to combat the recurrence of migraine and the provision of further bolus doses as deemed appropriate by the migraineur. The results presented here were used in the design of a Phase I clinical study to investigate drug pharmacokinetics following transdermal iontophoresis of zolmitriptan in human volunteers. The study has been successfully completed, and the results will be published after appropriate analysis.

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