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Research paper

In vitro and *in vivo* evaluation of the transdermal iontophoretic delivery of sumatriptan succinate

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Abstract

The objective was to evaluate the transdermal delivery of the 5-$HT_{1B/1D}$ agonist, sumatriptan from an iontophoretic patch system, *in vivo*. Initial *in vitro* experiments were conducted to optimize formulation parameters prior to iontophoretic delivery in Yorkshire swine. It was found *in vitro* that increasing drug load in the patch from 9.7 to 39 mg had no statistically significant effect on cumulative delivery (cf. 305.6 ± 172.4 vs. 389.4 ± 80.4 μg cm^{-2}, respectively). However, for a given drug load (39 mg) increasing formulation pH from pH 4.7 to 6.8 significantly increased the cumulative amount of sumatriptan delivered across the skin (389.4 ± 80.4 vs. 652.4 ± 94.2 μg cm^{-2}). A biphasic current profile comprising intensities of 1.8 mA from $t = 0$ to $t = 180$ min and 0.8 mA from $t = 181$ min to $t = 360$ min was used for the *in vivo* experiments. Drug levels in the blood were 13.7 ± 4.5 and 53.6 ± 10.2 ng ml^{-1} at the 30 and 60 min time-points, rising to 90–100 ng ml^{-1} during the 90–180 min time-period. The *in vivo* results show that the pharmacokinetics following transdermal iontophoretic delivery are comparable to those after oral, nasal or rectal administration, but do not match those upon subcutaneous injection.

Keywords: Transdermal; Iontophoresis; Migraine; Sumatriptan; $5HT_{1B/1D}$ agonist; Non-invasive; *In vivo*

1. Introduction

Sumatriptan is a selective serotonin 5-HT agonist at the 5-HT_{1B} and 5-HT_{1D} receptors (Fig. 1) used in the treatment of acute migraine episodes [1]. It was the first of the so-called ''triptan'' drugs which have had a significant impact on the treatment of acute attacks and it is available in several dosage forms including products for oral, nasal and rectal delivery [2]. However, patients cite limited efficacy, slow onset and incomplete prevention of recurrence as major shortcomings of current therapies [3]. There is a consensus that subcutaneous injection of sumatriptan provides the most rapid response at the 30 min time-point (63%) and complete relief at the 2 h time-point (67%) (conventional endpoint for evaluating treatment efficacy) [3,4]. Yet, from the patient's perspective, this is the least desirable modality of sumatriptan administration. In addition to the reluctance for self-injection, there are also reports of skin site reactions in more than 50% of patients [5].

Transdermal delivery offers a convenient alternative, particularly where nausea prevents administration of an oral dosage form. In addition, sumatriptan has a relatively poor oral bioavailability (only 14%) and a relatively short half-life ($T_{1/2} \sim 2$ h) [2]. However, based on the molecular properties of the weakly lipophilic sumatriptan base ($\log K_{o/w} = 0.93$

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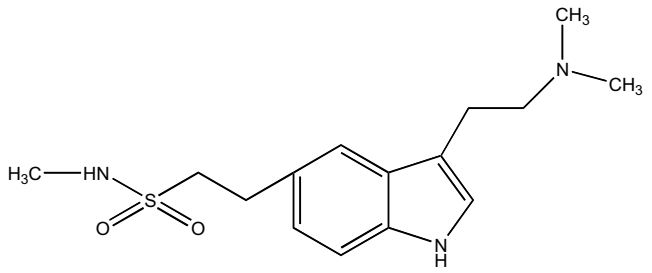

Fig. 1. Structure of sumatriptan ($MW = 295.5$ Da; $pK_a = 9.63$; $\log K_{o/w} = 0.93$ [6]; $\log D_{pH\ 7.4} = -1.3$).

[6]; $\log D_{pH\ 7.4} = -1.3$) it is unlikely that passive diffusion across the skin could deliver therapeutic amounts of drug from reasonably sized patches. Indeed, Femenía-Font et al. showed that the cumulative permeation of sumatriptan across porcine skin after 6 h from an aqueous solution was only ~1–2 μg cm^{-2} and although skin pre-treatment with *R*-(+)-limonene produced a >20-fold increase, cumulative delivery at the 6 h time-point was still only ~40 μg cm^{-2} [7]. Subsequent studies using bioadhesive films showed similar cumulative delivery of approximately 20 μg cm^{-2} at the 6 h time-point [8]. Based on the existing dosage forms (e.g., subcutaneous injection of 6 mg) and the known pharmacokinetics in man, it is probably necessary to deliver at least ~3–5 mg of drug across the skin [4]. Thus, passive delivery would neither deliver sumatriptan sufficiently rapidly nor in sufficient amounts to treat acute migraine attacks.

In contrast, transdermal iontophoresis is particularly suited to delivering polar and charged molecules across the skin [9]. In addition to the benefits of passive transdermal administration, iontophoresis improves drug input kinetics and enables rapid "bolus" drug inputs in response to patient need [10]. An investigation into the anodal iontophoretic transport of sumatriptan from buffered aqueous solutions (75 mM NaCl, 20 mM HEPES) across porcine skin *in vitro* showed that cumulative permeation at the 6 h time-point was ~270 and ~700 μg cm^{-2} at 0.25 and 0.5 mA cm^{-2}, respectively [11]. Furthermore, decreasing competition between charge carriers by lowering the NaCl concentration in the anodal compartment formulation to 25 mM produced a further increase in transdermal flux [11].

These experiments demonstrate that significant amounts of sumatriptan can be delivered across the skin from solution formulations by transdermal iontophoresis. The aim of the present study was to investigate sumatriptan electrotransport from an iontophoretic patch system and to determine whether therapeutically relevant delivery rates could be achieved under these conditions [12]. After an initial investigation of formulation parameters and their effect on sumatriptan transport across porcine skin *in vitro*, an *in vivo* feasibility study was conducted using an iontophoretic patch system in Yorkshire pigs.

2. Materials and methods

2.1. Chemicals

Sumatriptan succinate 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 two-compartment iontophoretic patch system was used during the studies (Fig. 2). 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 electrode compartment was separated from the sumatriptan succinate contained in the drug reservoir, made of polyvinylpyrrolidone (PVP, 15%; K-90F, BASF, Florham Park, NJ, USA), by a size-selective membrane (MW 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 placed on and 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 phase, which was replenished at a rate of 0.1 ml min^{-1}. A constant current of 0.25 mA cm^{-2} was used in all of the experiments; this is within the limits generally accepted for use in humans [13]. An AgCl electrode was employed as the cathode. Unless indicated otherwise sumatriptan succinate was dissolved in water at the appropriate concentration required for the desired patch loading and ~400 μl of the drug solution was introduced into the anodal drug reservoir (Table 1). A passive "no-current" control confirmed that there was negligible sumatriptan transport in the absence of an iontophoretic current.

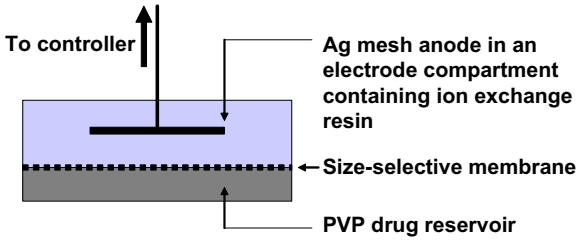

Fig. 2. Schematic representation of the anodal compartment from the two-compartment patch system.

Table 1
Composition of the formulations used in the *in vitro* and *in vivo* experiments

Study	Formulation	Drug reservoir	Drug loading (mg)	Initial pH	Final pH
In vitro					
Patch load	1	PVP[a]	9.7	4.8	5.0
	2	PVP	39	4.8	5.0
pH	3	PVP	39	6.8	7.1
In vivo					
Plasma profile	4	PVP	37	7.0	–

[a] Drug reservoir contained 15% PVP.

2.3. Experimental procedure in vivo

The *in vivo* experimental protocol was approved by the local Ethics Committee. Three 18–19 kg (7–9 weeks) 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. Before applying the patches, the skin was gently wiped with warm water followed by an alcohol swab and patted dry. 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, the two-compartment iontophoretic patch system (with an active area of 4 cm^2 and where the PVP drug reservoir contained 37 mg of sumatriptan at pH 7.0), coupled to a programmable power source, was used to apply the current (Table 1). Two anodal patches were applied to each animal, that is, the total active surface area in contact with the skin was 8 cm^2. The cathode consisted of another two patches again with a total surface area of 8 cm^2. All three animals received the iontophoretic treatment involving application of a biphasic current protocol. In step 1, from $t = 0$ to $t = 180$ min, the current intensity was 1.8 mA (0.45 mA cm^{-2}); in step 2, from $t = 181$ to $t = 360$ min, a lower current intensity of 0.8 mA (0.2 mA cm^{-2}) was applied. From $t = 361$ min to $t = 480$ min, no current was applied although the patches were left in contact with the skin to investigate elimination of the drug from the bloodstream. At the end of the studies, the animals were euthanized.

Blood samples (2 ml) were drawn at 15 min intervals from $t = -15$ min to $t = 240$ min and at 30 min intervals from $t = 240$ min to $t = 420$ min and again at $t = 480$ min. The samples were collected into chilled 3 ml glass vacutainer tubes containing ethylenediaminetetraacetic 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.

2.4. Analytical methods

2.4.1. In vitro

Samples obtained from the *in vitro* experiments were assayed using reverse phase HPLC. 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 Zorbax 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, Palo Alto, CA, USA). The mobile phase comprising 15% acetonitrile and 85% 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. Sumatriptan was detected at 282 nm; the limit of detection was 1 μg ml^{-1}.

2.4.2. 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 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 by LC/MS/MS.

(ii) *Assay*. This was adapted from a published method [14]. Briefly, the LC system comprised a LC-10 AP pump and SCL-10M controller (Shimadzu Corporation, MD, USA); autoinjector (Waters 717plus 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 sumatriptan. The mobile phase (20% methanol and 80% 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 MS conditions, the spectrometer employed a heated ion nebulizer at 475 °C. The product ion had a molecular weight of 251.1 Da. The limit of quantification was 0.4 ng ml^{-1}.

3. Results

Fig. 3 shows that a 4-fold increase in patch load (9.7–39 mg) produced no statistically significant difference (t-test, $\alpha = 0.05$) in the cumulative amounts of sumatriptan delivered after current application for 6 h (305.6 ± 172.4 vs. 389.4 ± 80.4 μg cm^{-2}).

In the next *in vitro* study, the pH of the drug formulation was increased from pH 4.7 to pH 6.8. The former pH is close to the isoelectric point of the skin and hence there is only a limited contribution of electroosmosis to iontophoretic transport [15]. Fig. 4a shows that increasing the formulation pH by two units produced a statistically significant (t-test, $\alpha = 0.05$) increase of approximately 60% in cumulative sumatriptan delivery (389.4 ± 80.4 vs. 652.4 ± 94.2 μg cm^{-2}) [16]. It should be noted that the pH of the drug reservoir remained fairly constant during current application (Table 1). Fig. 4b presents the iontophoretic flux observed under these conditions. The flux at 6 h was 109.8 ± 14.4 and 153 ± 25.2 μg cm^{-2} h^{-1} at pH 4.7 and pH 6.8, respectively. At the higher pH, the steady state flux corresponds to transport number of 0.056, meaning that ~5.6% of the charge transferred during iontophoresis is carried by the sumatriptan cation. Since there is minimal competition from cationic species, it is evident that the predominant charge carrier in the system is the chloride ion from the receptor compartment towards the anode.

The results from the *in vitro* delivery experiments were used to decide the conditions for the *in vivo* study. Fig. 5 shows sumatriptan plasma concentrations during iontophoretic current application and following subcutaneous injection in Yorkshire swine. A biphasic current profile was employed wherein a higher current of 1.8 mA (0.45 mA cm^{-2}) was applied for 3 h followed by 3 h at 0.8 mA (0.2 mA cm^{-2}). Blood levels of sumatriptan rose gradually upon current application, achieving 3.4 ± 3.1, 13.7 ± 4.5 and 53.6 ± 10.2 ng ml^{-1} at the 15, 30 and 60 min time-points and achieved fairly constant levels, of between 90 and 100 ng ml^{-1}, during the 90–180 min time-period. The current intensity was then decreased to 0.8 mA (0.2 mA cm^{-2}), during the 180–360 min period, and there was a concomitant decrease in drug levels in the blood. Current application was terminated at $t =$ 360 min, at which point, sumatriptan levels fell progressively as the drug was eliminated from the bloodstream, illustrating the control afforded by iontophoresis over drug delivery kinetics.

Visual inspection of the skin at the patch application sites after sumatriptan iontophoresis (and comparison of photographs of the sites before and after iontophoresis) did not reveal any significant erythema.

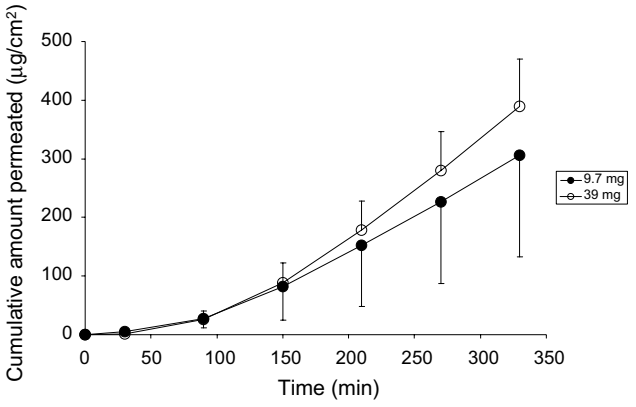

Fig. 3. Effect of a 4-fold increase in drug load on the cumulative amount of sumatriptan delivered across porcine skin *in vitro* with a 6 h iontophoretic current application (0.25 mA cm^{-2}) from a patch system with a PVP gel drug reservoir. Filled and hollow circles represent patch loadings of 9.7 and 39 mg, respectively (mean ± SD; $n = 4$).

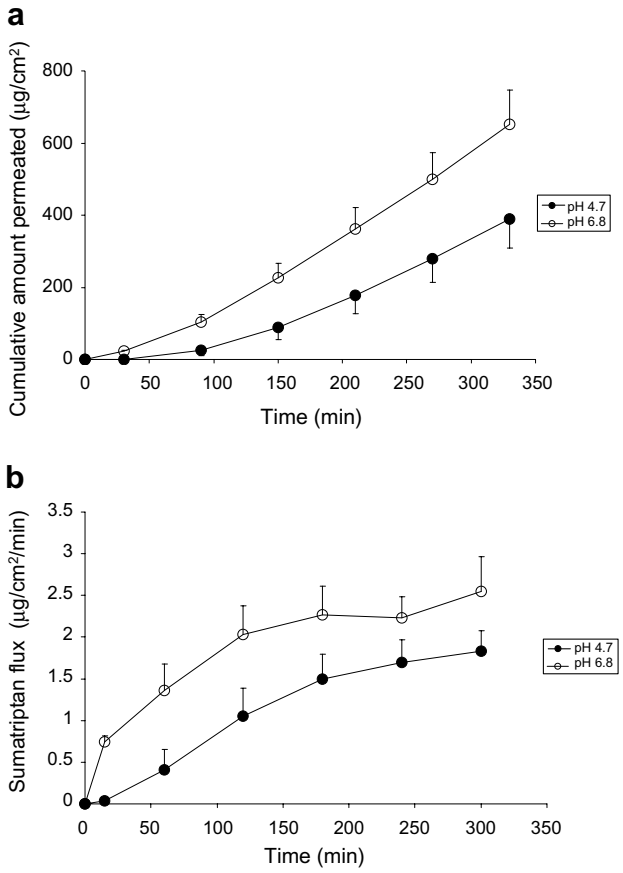

Fig. 4. Effect of increasing formulation pH from 4.7 to 6.8 on (a) the cumulative amount of sumatriptan delivered across porcine skin *in vitro* and (b) the corresponding drug flux, with a 6 h iontophoretic current application (0.25 mA cm^{-2}) from a patch system with a PVP gel drug reservoir containing 39 mg of drug. Filled and hollow circles represent formulation pH of 4.7 and 6.8, respectively (mean ± SD; $n = 4$).

4. Discussion

The data showed that use of the two-compartment system resulted in sumatriptan transport rates that were independent of patch load (Fig. 3); this could be significant for costly therapeutics such as peptides. It has been shown

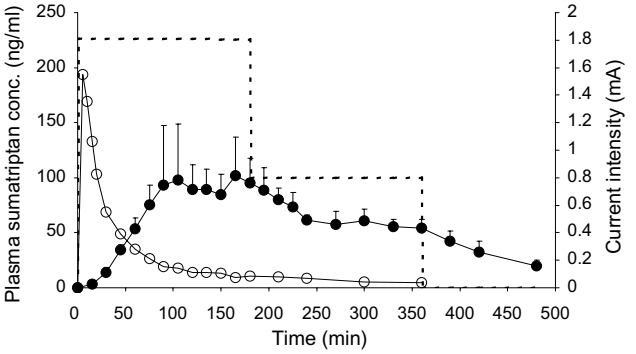

Fig. 5. Plasma concentration profiles of sumatriptan as a function of time during subcutaneous injection (6 mg; hollow circles) and anodal iontophoresis (filled circles) in Yorkshire swine using an iontophoretic patch system with an active area of 4 cm^2 and where the PVP drug reservoir contained 37 mg of sumatriptan at pH 7. Two patches were applied to each animal (total area = 8 cm^2). A biphasic current profile was applied (dashed line, secondary y-axis), in phase 1, 1.8 mA (0.45 mA cm^{-2}) for the $t = 0$–180 min time-period, then in phase 2, 0.8 mA (0.2 mA cm^{-2}) during the $t = 181$–360 min time-period. (C_{max}, T_{max} and AUC values were ~100 ng ml^{-1}, 105 min and 27,600 ng ml^{-1} min, respectively, for iontophoretic administration; cf. 194 ng ml^{-1}, 5 min and 8480 ng ml^{-1} min for the subcutaneous injection) (mean ± SD; $n = 3$).

that, in the absence of competing cations and with only a single monovalent anion in the receptor, the iontophoretic flux of a cationic drug depends on the respective mobilities of the drug and the anion and is independent of drug concentration in the formulation [17–20]. In these published studies, the drugs were hydrochloride salts with good aqueous solubility and did not require the addition of NaCl to provide chloride ions necessary for anodal electrochemistry. In the current study, sumatriptan was supplied as the succinate salt. Hence, we used a patch design wherein the electrode compartment contained a cation exchange resin and was separated from the drug-containing gel reservoir by a low molecular weight cut-off size-selective membrane (100 Da) to reduce the effect of competing cations.

The iontophoretic flux of sumatriptan across porcine ear skin *in vitro* was 2.6 ± 0.4 μg cm^{-2} min^{-1} (Fig. 4b). This was approximately 2.5 times less than that observed (6.3 ± 0.4 μg cm^{-2} min^{-1}) using the same current density and an aqueous formulation containing 14.5 mM sumatriptan succinate (and 25 mM NaCl) at pH 6.5 [11]. In other studies with low molecular weight cations, we have found that transport rates from patch systems were sometimes lower (by up to ~50%) than those observed using aqueous formulations (unpublished results).

The drug input rate *in vivo*, K_0 (mg min^{-1}), at steady state was estimated using Eq. (1):

$$K_0 = CL \cdot C_{SS}, \tag{1}$$

where CL is the clearance (ml min^{-1}) and C_{SS} is the concentration at steady state (mg ml^{-1}). The half-life and clearance ($T_{1/2} \sim 120$ min and CL ~172 ml min^{-1}, respectively, determined using a one-compartment model) were in reasonable agreement with the corresponding values in humans [2,4]. Using the above clearance and assuming C_{SS} to be ~100 ng ml^{-1} (average value between $t = 90$ and 180 min, Fig. 5), Eq. (1) then predicts that K_0 is ~1.0 mg h^{-1}. Eq. (2) enables calculation of the sumatriptan delivery efficiency *in vivo*, as measured by its transport number ($t_{in\ vivo}$):

$$t_{in\ vivo} = \frac{zFK_0}{I}. \tag{2}$$

Thus, upon insertion of the appropriate values, calculation shows that $t_{in\ vivo}$ was ~0.05, similar to that seen *in vitro*. As noted above, the sumatriptan iontophoretic flux *in vitro* (at pH 6.7) was ~0.15 mg cm^{-2} h^{-1}; therefore for an 8 cm^2 patch, the estimated *in vitro* delivery rate would be ~1.2 mg h^{-1} (cf. 1.0 mg h^{-1} *in vivo*).

Inspection of the patch application site did not reveal any erythema; this is notable since one of the principal side effects after subcutaneous injection of sumatriptan is local irritation [5]. In contrast, during a study into the iontophoretic delivery of alniditan, another 5-HT_{1D} agonist, (0.2 mA cm^{-2}, formulation pH 9.5) in human volunteers, investigators noted the presence of local erythema at the anode for up to 48 h, perhaps due to the elevated pH or a drug–skin interaction at the application site [21].

Upon oral administration in humans (tablets containing 25 and 100 mg sumatriptan), C_{max} was reported to be 16 and 54 ng ml^{-1}, respectively; T_{max} was 1.5 h for both doses [2,4]. Since it is known that the total blood volume in Yorkshire swine is of the order of 2–2.5 l, it is possible to extrapolate the results obtained in this study to the human scenario to estimate (to a first approximation) whether they are therapeutically relevant. Peak drug levels achieved here ($C_{max} \sim 90$–100 ng ml^{-1}) would be comparable to those seen in humans following oral delivery (assuming human blood volume of 5 l and hence using a scaling factor of ~0.4); furthermore, T_{max} is ~1.75 h, again similar to that observed in man. However, sumatriptan transport kinetics have recently been reported as being ~2-fold higher across porcine skin than human skin *in vitro* [22]. If this is the case *in vivo*, then the C_{max} observed in this study would probably be closer to the lower range of peak values seen in humans. In contrast to subcutaneous (and oral) administration, the iontophoretic patch enables drug levels to be maintained (if necessary) and also provides the possibility of administering a second bolus dose if required. Nevertheless, using the conditions employed in this study, sumatriptan iontophoretic delivery kinetics did not provide the rapid T_{max} (~10 min) observed following subcutaneous injection, which would be a key factor in determining usefulness as a therapeutic system. The time required to attain therapeutic levels following iontophoretic administration depends on both the physicochemical properties of the drug, which determine mobility through the skin, and the pharmacological potency. Sumatriptan is less potent than the other triptans, which are effective at lower doses; thus,

they may be better candidates for transdermal iontophoresis even if they possess similar electric mobility.

5. Conclusion

The *in vivo* data confirm that transdermal delivery of therapeutic amounts of sumatriptan is feasible using an iontophoretic patch system. The transport kinetics observed using the Yorkshire swine model suggest that transdermal delivery in humans, using an iontophoretic patch system, could result in blood levels similar to those seen after oral, nasal and rectal delivery [4]. Moreover, no irritation was observed at the patch application site. However, iontophoretic delivery kinetics were not comparable to those seen after subcutaneous injection (as indicated by the respective C_{max} and T_{max}). In the next phase of our studies we will investigate the iontophoretic transport of more potent antimigraine therapeutic agents that require delivery of smaller amounts of drug to achieve a pharmacologic effect.

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