Transdermal iontophoresis of Ranitidine: an opportunity in paediatric drug therapy

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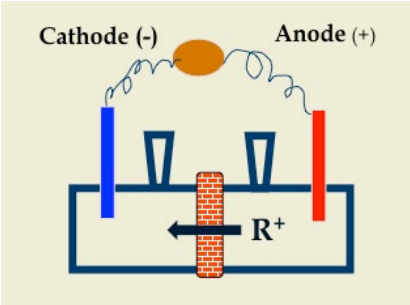

Abstract

The objective of this study was to examine the use of transdermal iontophoresis for the delivery of ranitidine hydrochloride in children. Constant, direct current, anodal iontophoresis of ranitidine was performed *in vitro* across dermatomed pig skin. The effect of donor vehicle, current intensity, and drug concentration were first examined using aqueous solutions. It was found that drug delivery was higher at pH 7 (donor: 5 mM Tris) than pH 5.6 (donor: water). In the presence of low levels of competing background electrolyte, ranitidine delivery increased linearly with applied current but was independent of the donor drug concentration. The second part of the study evaluated two Pluronic® F-127 gels as potential vehicles for ranitidine delivery. The formulations were characterised in terms of apparent viscosity, conductivity and passive permeation measurements. Iontophoretic delivery of ranitidine was only slightly affected when delivered from the gels relative to aqueous solutions. Overall the results demonstrated that therapeutic paediatric doses of ranitidine (neonates: 0.09-0.17 µmol/kg.h; 1 month to 12 years: 0.36-0.71 µmol/kg.h) could be easily achieved by transdermal iontophoresis with simple gel patches of practical surface area (0.2-1.5 cm^2/kg).

Keywords: Iontophoresis; ranitidine; paediatric drug delivery; topical gels; transdermal drug delivery

1. Introduction

Ranitidine is used extensively in paediatric medicine especially in intensive care. It is prescribed in a variety of clinical indications for which gastric acid reduction is necessary (British National Formulary for Children). This includes gastro-oesophageal reflux disease, benign gastric and duodenal ulcerations, prophylaxis of acid aspiration prior to surgery, and treatment as well as prophylaxis from stress-induced gastrointestinal ulcers and consequent haemorrhage. Methods of administration include oral and intravenous delivery. The oral bioavailability of ranitidine is highly variable between paediatric subjects especially in neonates (40-80% (Garg et al., 1983; Blumer et al., 1985; Vanhecken et al., 1982)). This is due to incomplete absorption of the drug from the gastro-intestinal tract as well as first-pass metabolism. The need for frequent dosing (2 to 4 times a day), due to the short half-life of the drug (2-3 hours (Blumer et al., 1985; Lugo et al., 2001)), and the bitter taste of the oral solution, reduce child compliance. In addition, some formulations contain up to 8% alcohol and no oral preparation is licensed for use in children under 3 years of age; parenteral delivery is only licensed for children over 6 months old (British National Formulary for Children) and has inherent pitfalls such as pain and distress, invasiveness, risk of infection, and technical difficulty.

The transdermal route can provide an alternative approach for the delivery of ranitidine. The relatively non-invasive nature of this administration method renders the application particularly attractive in paediatric medicine. Iontophoresis is an interesting option because it is possible to control delivery rates over extended periods of time. The technique involves passing a small electrical current (≤ 0.5 mA/cm^2) through conductive vehicles in contact with the skin. As a result, ions migrate through the skin towards the electrode of opposite charge (Phipps and Gyory, 1992). In addition, electroosmosis is induced due to the negative charge of the skin at physiological pH (Burnette and Ongpipattanakul, 1987; Luzardo-Alvarez et al., 1998; Kim et al., 1993), and this facilitates the transport of neutral and positively-charged molecules across the skin in the anode-to-cathode direction. Ranitidine hydrochloride is a potential candidate for iontophoresis. Target rates for therapeutic delivery (i.e., the recommended intravenous infusion rates currently used in clinical care (British National Formulary for Children)) are 0.09-0.17 μmol/kg.h in neonates, and 0.36-0.71 μmol/kg.h in children from 1 month to 12 years.

Ranitidine (free base) has a molecular weight of 314.4 Da, is freely soluble in water, and has an octanol-water partition coefficient close to 2 (log P ~0.3) (Moffat et al. 2001). Ranitidine has two basic groups with pK_a values of 2.3 and 8.2 (Brittain, 2007) and therefore exists primarily as a monovalent cation between pH 4 and 7. Anodal iontophoresis of ranitidine within this pH range is therefore anticipated to be efficient, predominantly due to electromigration and supplemented with a smaller electroosmotic contribution.

In vitro investigations of transdermal iontophoresis are typically performed using solution-based vehicles because of easy preparation and manipulation. However, transdermal systems for clinical applications are invariably semi-solid or polymeric formulations, such as hydrogels. The latter are attractive because they provide sufficient rigidity to adhere well to the skin (without leakage) and their high water content provides a suitable conductive medium for iontophoresis. Nonetheless, it is important to test the *in vitro* delivery of the drug of interest from such preparations and to mimic *in vivo* use as closely as possible. Because non-liquid vehicles may retard drug transport, it is crucial to ensure that any formulation effects are resolved before development of a final product.

Pluronic® F-127 is a surface active gel-forming agent frequently used in topical skin applications (Collett, 2006; Escobar-Chavez et al., 2006). It is composed of triblocks of polyoxyethylene-polyoxypropylene copolymers at a ratio of 70% ethylene oxide (hydrophilic) and 30% propylene oxide (hydrophobic), and with an average molecular weight between 9840 and 14600 Da (Collett, 2006; Booth and Attwood, 2000; Cabana et al., 1997). With increasing F-127 concentration, or at higher temperatures, the entanglement of the polymer chains increases and the gel becomes more rigid. Pluronics® are favoured for transdermal iontophoresis because: (a) The non-ionic nature of the surfactant avoids competition with the drug to carry the applied current, and reduces potential interaction between the polymer and the active (Taveira et al., 2009; Fang et al., 2002; Al-Khalili et al., 2003; Gupta et al., 1994). (b) F-127 is safe as shown by its wide use in pharmaceutical preparations intended for

different routes of administration (Collett, 2006). (c) The thermo-reversible properties of the polymer are advantageous. At 15-30% w/w concentrations in water, F-127 exists in the liquid state at low temperature (≤ 5°C) but forms a semi-solid gel upon warming (> 15°C). These unique rheological properties facilitate easy fabrication and straightforward incorporation with the iontophoretic electrodes; they also enable firm application conforming to the skin contours and preventing material from running across the skin.

The purpose of this study was to investigate the potential of transdermal iontophoresis as a ranitidine delivery system for paediatric use. The rate of input of the drug when administered as a continuous intravenous infusion was used as a guide to determine the target transdermal flux necessary to achieve similar therapeutic levels. *In vitro* experiments were conducted to examine the effects of donor vehicle, drug concentration, and current intensity on the iontophoretic delivery of ranitidine from aqueous solutions. The most appropriate conditions were adopted in gelled formulations and their performance as potential delivery systems for ranitidine was evaluated.

2. Materials and methods

2.1 Chemicals

Ranitidine hydrochloride, silver (Ag) wire (99.99%), silver chloride (AgCl, 99.999%), and Pluronic® F-127 were purchased from Sigma Aldrich (Gillingham, UK). Tris base (α, α, α-Tris-(hydroxymethyl)-methylamine) and sodium chloride were obtained from Acros (Geel, Belgium). Acetonitrile, hydrochloric acid (HCl), glacial acetic acid, and triethylamine were provided by Fisher Scientific (Loughborough, UK). All reagents were at least analytical grade and highly purified deionised water (resistivity ≥ 18.2 MΩ.cm, Barnsted Nanopure Diamond™, Dubuque, IA) was used for the preparation of all solutions.

2.2 Skin

Fresh pig skin was obtained from a local slaughterhouse, cleaned under cold running water, and stored in the fridge until the following day. Abdominal skin was cut into ~ 20 x 10 cm^2 pieces, dermatomed (Zimmer™ Electric Dermatome, Dover, Ohio. Nominal thickness 750 µm), wrapped individually in Parafilm™, and then kept in the freezer (-20°C) until use. Immediately prior to the permeation experiment, the skin was thawed at room temperature for a period of 30 minutes and excess hair was carefully cut away with scissors. The skin was then mounted onto the diffusion cells without any further treatment.

2.3 Iontophoresis set-up

Side-by-side two-compartment diffusion cells (active transport area = 0.78 cm^2, volume = 3 ml) were utilised in all experiments. The skin was mounted between the two chambers with the epidermal side oriented towards the anode compartment. The receptor chamber always held 154 mM sodium chloride solution (unbuffered, pH ~6) and was magnetically stirred (Multipoint-6 stirrer, Thermo Scientific Variomag, Cole-Parmer, London, UK) at 400 rpm throughout the experiment. Anodal, direct, constant current was delivered using Ag/AgCl electrodes and a power supply (KEPCO 1000M, Flushing, NY, USA). Hourly samples (0.5 ml) of the receptor phase were withdrawn and replaced with fresh solution. Separate passive diffusion, control experiments were also performed with samples taken every 2 hours for 10 hours and two final samples withdrawn at 22 and 24 h. Again each sample taken was replaced with 0.5 ml fresh solution.

2.3.1 Ranitidine delivery from aqueous solutions

Prior to the start of the transport study, the skin was left for 30 minutes in contact with the donor vehicle without drug, and 154 mM sodium chloride in the receptor chamber. Both compartments were then refreshed with new donor (now containing ranitidine) and receptor solutions. Experiments examined donor vehicle, drug concentration, and current intensity effects on the iontophoretic delivery of ranitidine. Specific conditions examined are summarised in Table 1.

2.3.2 Ranitidine delivery from gel formulations

Two gel formulations were prepared according to the “cold method” (Schmolka, 1996). Solutions containing 150 mM ranitidine in 5 mM Tris (pH 7) were cooled to ~3-5°C under continuous gentle agitation. F-127 (at 20 and 30% w/w) was then incorporated slowly into the solutions and the resulting formulations were stirred for 2 days to achieve complete homogeneity.

Table 1: *Experimental conditions performed to characterise ranitidine transdermal delivery from aqueous solutions.*

	Donor vehicle	[Ranitidine] (mM)	pH	Current intensity (mA)	n**
Donor vehicle	Water	25	5.6 (unbuffered)	0.3	5
	5mM Tris		7*		5
Current	5mM Tris	50	7*	0.1	5
				0.2	4
				0.3	5
Concentration	5mM Tris	25	7*	0.3	5
		50			5
		150			5
Passive diffusion	5mM Tris	150	7*	0	3

* pH adjusted to 7 with 1M HCl.

** number of replicates

For the permeation experiments, 3.3 grams of each formulation was added to the donor compartment and constant current (0.3 mA) was delivered for 6 hours. The voltage across each iontophoresis system was monitored regularly. All experiments were conducted at 22.2 ± 0.9°C, and both compartments were covered with Parafilm to avoid water evaporation.

2.4 Viscosity measurements

The apparent viscosities of the gel formulations were determined using a Bohlin rheometer (Malvern Instruments, Malvern, UK) equipped with a cone-plate system. The angle of the cone was 4° and the diameter of the plate was 40 mm. Three specific shear rates were tested (0.1, 1, or 10 1/s) with a gap size set at 150 mm. Readings were performed at 22.1 ± 0.2°C and gels were allowed to equilibrate on the plate for 5 minutes before the measurements were made. The viscosities of control formulations (without ranitidine) were also verified and all measurements were performed in triplicate.

2.5 Conductivity measurements

The conductivities of the gel formulations were measured (T-120 conductivity meter, Metrohm AG, Herisau, Switzerland; cell reference = 0.85) at 22°C. These were compared to the conductivity of ranitidine in aqueous solution. All measurements were performed in triplicate.

2.6 Sample analysis

Quantification of ranitidine was performed by high performance liquid chromatography with UV detection (315 nm). The method was modified from a previous publication (Oo et al., 1995) and used a Jasco HPLC system comprising: a PU-980 pump with an AS-1595 autosampler, a UV-975 UV-VIS detector, and a HiQ-Sil^{TM} C18 (250 x 4.6 mm, 5µm) reverse-phase column (Jasco UK, Ltd., Dunmow, UK) thermostatted at 25°C. The mobile phase (pH 3.8) consisted of a mixture of water, acetonitrile, acetic acid, and triethylamine (85:15:1.5:0.2, respectively in volume), and was pumped through the system at 1 ml/min.

2.7 Data analysis and statistics

Data analysis and regressions were performed using Graph Pad Prism V.5.00 (Graph Pad Software Inc., La Jolla, CA, USA). Unless otherwise stated, data are represented as the mean ± standard deviation (SD). Transport fluxes were calculated as the amounts delivered during a permeation period divided by the length of that period.

Statistical significance was set at $p < 0.05$. Comparisons made between different sets of data were assessed by either a two-tailed unpaired t-test (for 2 groups) or a one-way ANOVA (for >2 groups) followed by Tukey's post-test. Comparison of ranitidine transdermal delivery from gel formulations relative to aqueous solution was made with a two-way ANOVA followed by Bonferroni post-tests.

The transference number (T) of ranitidine was computed according to Faraday's law [6]: $T = \{(J_{total} \bullet z \bullet F)/I\}$, where J_{total} is the total flux observed at 6 h, (I) is the current intensity applied, (F) is Faraday's constant, and z the absolute value of the valence of the drug ion (~1).

3. Results and discussion

3.1 Ranitidine delivery from aqueous solutions

The donor concentrations of ranitidine hydrochloride (25-150 mM) provided sufficient chloride ions for the Ag/AgCl electrochemistry at the anode. The passive diffusion flux of ranitidine from the highest donor concentration used (150 mM) was only 0.1 ± 0.04 nmol/h after 6 hours diffusion and was negligible relative to that achieved with iontophoresis.

3.1.1 Effect of donor vehicle

The first iontophoresis experiments used a donor solution containing only ranitidine hydrochloride (25 mM) in water. The pH of this unbuffered solution was around 5.6 and was low enough to ensure almost complete ionisation (93%) of the more basic group of ranitidine (pK_a 8.2). Ranitidine was the only cation present in the donor compartment, therefore, resulting in the maximum iontophoretic transport possible with the flux reaching 0.61 ± 0.08 µmol/h after 6 hours of current passage (Figure 1); this corresponds to a transference number of 5.47 (± 0.67)%.

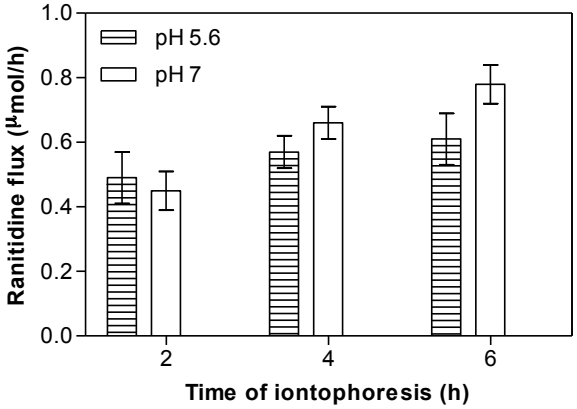

Figure 1: *Ranitidine iontophoretic transport (mean ± SD; applied current = 0.3 mA) as a function of time from donor solutions containing 25 mM drug at pH 5.6 (in water) and 7 (in 5 mM Tris buffer).*

The next donor vehicle examined contained 5 mM Tris buffer with the final pH adjusted to 7 with 1 M HCl. The iontophoretic fluxes were initially similar to those measured at pH 5.6, but attained a value (0.78 ± 0.07 µmol/h), after 6 hours of current passage, which was significantly higher ($p < 0.05$) (Figure 2), and corresponded to a transference number of 6.95 (± 0.58)%. Thus, even though the presence of Tris introduced co-ion competition with ranitidine (~4.6 mM of positively charged Tris at pH 7, pK_a 8.1), the higher pH of the donor solution enhanced the overall electrotransport of the drug (presumably a combination of a greater negative charge on the skin (pI~4.5 (Marro et al., 2001) and an enhanced electroosmotic flow) (Phipps and Gyory, 1992; Marro et al., 2001; Santi and Guy, 1996). This result is consistent with previous observations for other cations, including sodium (Sieg et al., 2004), verapamil (Wearley et al., 1989), and sumatriptan (Patel et al., 2007).

3.1.2 Effect of current intensity

These experiments were designed (a) to confirm that iontophoresis provides a controllable means to deliver ranitidine, and (b) to determine whether acceptably small current intensities can are able to provide therapeutic drug doses. While a current density of up to 0.5 mA/cm^2 is considered tolerable by adult subjects, it is clearly desirable to use lower levels in children, and especially neonates, to reduce discomfort and improve compliance. Three current intensities were examined: 0.1, 0.2, and 0.3 mA, (0.13, 0.26, and 0.39 mA/cm^2) at a fixed drug donor concentration (50 mM).

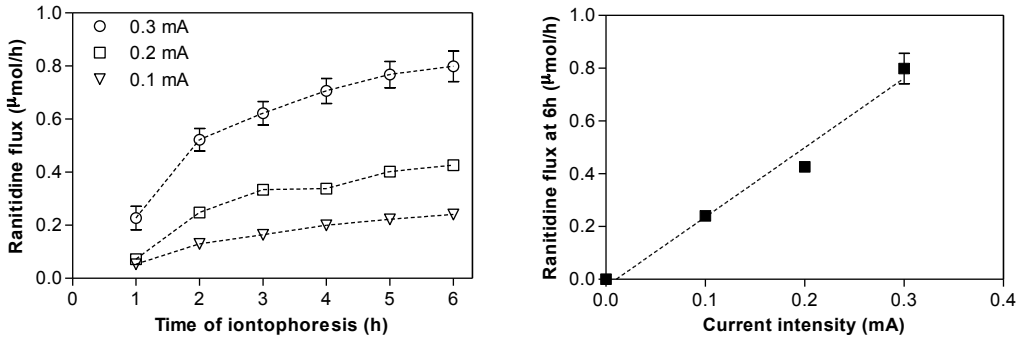

Figure 2: *Iontophoretic delivery of ranitidine (mean ± SD) from a 50 mM donor solution (containing 5 mM Tris, pH 7) as a function of time (left) and current intensity (right), with which the flux at 6 hr was highly correlated (r^2 = 0.97, p < 0.0001).*

As expected, and in agreement with Faraday's law and several earlier publications (e.g., Green et al., 1992; Padmanabhan et al., 1990; van der Geest et al., 1997; Singh et al., 1999)), the current intensity directly determined the permeation of ranitidine across the skin (Figure 2). The drug's transference number, calculated from the slope of the linear dependence of flux at 6 hr against current intensity, was 7.05 (± 0.33)%; in good agreement with that determined in the first series of experiments using half the ranitidine concentration in the donor.

At the lowest current density used (0.13 mA/cm^2), the delivery rate of ranitidine was 0.31 (±0.02) µmol/h.cm^2. This flux is sufficient to satisfy the recommended intravenous infusion dose of ranitidine for neonates (0.09-0.17 µmol/kg.h), and for children older than 1 month (0.36-0.71 µmol/kg.h) (British National Formulary for Children, 2008), with patch application areas (anode + cathode) of only 0.6-1.1 cm^2/kg for neonates and 2.3-4.6 cm^2/kg for older children. Obviously, with increasing current density, the area required is proportionately reduced, as illustrated in Figure 3.

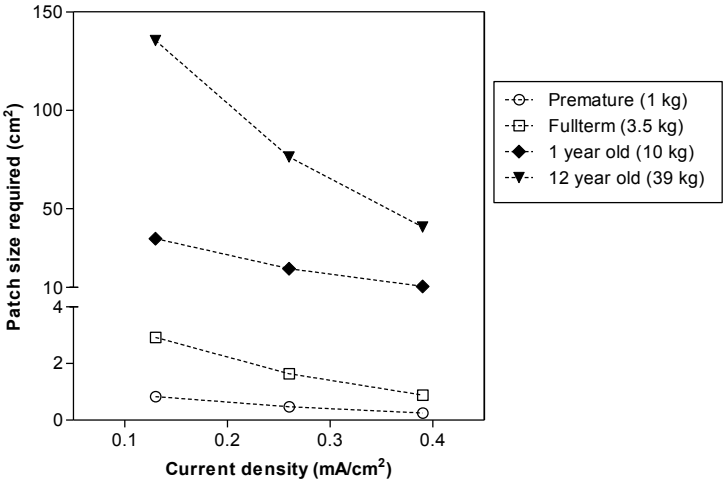

Figure 3: *Estimated patch areas required to achieve therapeutic input rates of ranitidine, as a function of the iontophoretic current density applied. 4 age groups are used to illustrate The range of areas necessary in four illustrative paediatric populations are shown.*

3.1.3 Effect of drug concentration

The delivery of ranitidine as a function of donor concentration is shown in Figure 4. No significant impact was observed and the flux only increased from 0.78 (±0.07) to 0.90 (±0.10) µmol/h despite a six-fold increase in drug concentration in the donor. This is because the molar fractions of drug used in the three experiments are not that different (being 0.84, 0.91 and 0.97 for 25, 50 and 150 mM drug, respectively).

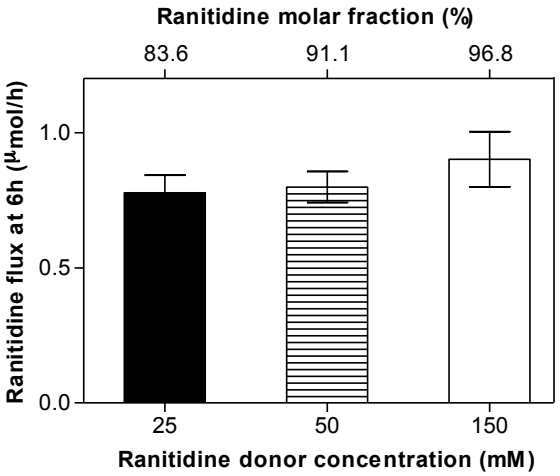

Figure 4: *Ranitidine flux (mean ± SD) after 6 h of iontophoresis as a function of donor concentration and molar fraction.*

3.2 Ranitidine delivery from gel formulations

Pluronic® F-127 (at 20 or 30% w/w) as used to produce gel formulations containing ranitidine at 150 mM in 5 mM Tris buffer (pH 7). The current intensity employed was 0.3 mA. The highest concentration of drug was chosen to counteract, as much as possible, any potential effects that gelation of the vehicle might have on the electrotransport of ranitidine.

3.2.1 Apparent viscosity measurements

Figure 5 displays the apparent viscosity of each gel formulation with and without ranitidine. The values were unaffected by the presence of the drug, implying that it did not interfere with the micellisation/entanglement/packing of the F-127. The formulations were semi-solid at 22°C but the viscosity of that containing 30% w/w polymer was significantly greater than that with less (e.g., at an applied shear rate of 0.1 s^{-1}, the apparent viscosity of the 20% w/w F-127 was 863 (±67) Pa.s, while that with 30% w/w polymer was 5139 (±302) Pa.s). The 20% gel structure was "soft" relative to the more rigid semi-solid consistency of the 30% formulation, which would be more appropriate for transdermal applications. The flow curves of the gel formulations conformed (with r^2 values of ≥0.98) to the Ostwald-De Waele power law (Macosko, 1994; Malkin, 1994; Goodwin and Hughes, 2008): $\eta = K \bullet \dot{\gamma}^{n-1}$, where η is the apparent viscosity measured at a particular shear rate ($\dot{\gamma}$), K is the flow consistency index, and n is the power-law index.

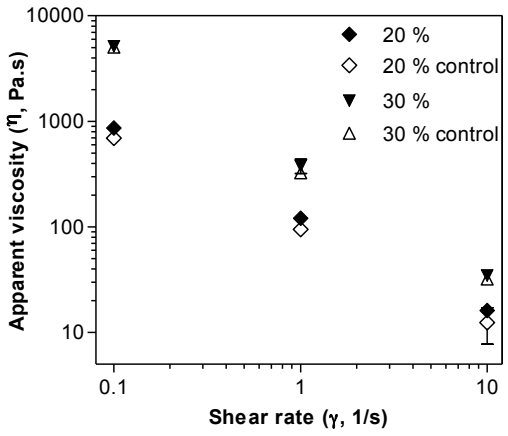

Figure 5: *Apparent viscosities of F-127 gels measured at different shear rates. Regression of the data yielded the following parameters from the power law relation: (a) for the 20% w/w gel, K and n were, respectively, 119 (±1) and 0.14 (±0.01) with drug, and 91 (±5) and 0.11 (±0.03) without; (b) for the 30% w/w gel, K and n were, respectively, 405 (±8) and -0.07 (±0.01) with drug, and 375 (±8) and -0.10 (±0.01) without.*

The *n* index values of all formulations were below 1 indicating pseudoplastic behaviour; further, the inverse relationship between the apparent viscosity and the applied shear rate shows that the gels are shear-thinning fluids. Even at high shear rates, the apparent viscosity of the gels remained in the linear regime of the power law suggesting that the internal network structure of the formulations was stable.

3.2.2 Conductivity measurements

The conductivity of the high concentration drug formulation without gelation was 7.9 (±0.1) mSi/cm; with 20 and 30% w/w F-127, the conductivities were significantly less (4.3 (±0.03) and 2.9 (±0.02) mSi/cm, respectively) and significantly different from one another. In accordance with Stoke's law (Kuhn et al., 2008), these observations suggest that ion mobility (and hence conductivity) and formulation viscosity are inversely related.

3.2.3 Voltage measurements

The voltage across the diffusion cells was monitored throughout the iontophoresis experiments at an applied current of 0.3 mA and the average results (±SD) are shown in Figure 6. The voltage was highest at the start of iontophoresis because skin resistance is greatest at this point; it then fell off as ions were driven into the membrane, which became progressively more conductive. It is apparent, furthermore, that the nature of the donor formulation also contributed to the total resistance of the iontophoretic circuit, and that this contribution increased with the viscosity of the gels used (being higher for the 30% w/w polymer than the one containing 20%). However, the 2-fold increase observed would be of trivial significance in terms of the feasibility and practicality of an in-use iontophoretic device.

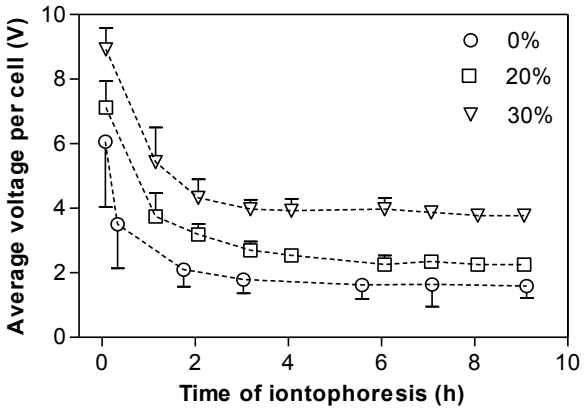

Figure 6: *Average voltage applied (mean ± SD) across the diffusion cells as a function of time of current application (0.3 mA) for an aqueous donor solution (0%) and for the two F-127 gels examined (20% and 30%).*

3.2.4 Permeation studies

Figure 7 (left panel) shows the passive diffusion profiles of ranitidine from donor formulations containing 0 (control), 20 and 30% w/w of the gelling agent F-127. After 24 hours, cumulative amounts of 18.6 (±6.9), 15.6 (±4.7), and 9.2 (±4.6) nmol/cm^2, respectively, had permeated through the skin. At most, therefore, these values suggest that the gelling agent at its highest concentration only leads to a 50% reduction in the passive skin permeation rate. From a practical standpoint, this effect is of little consequence, given the much greater delivery rates achieved with iontophoresis, as shown in Figure 7 (right panel).

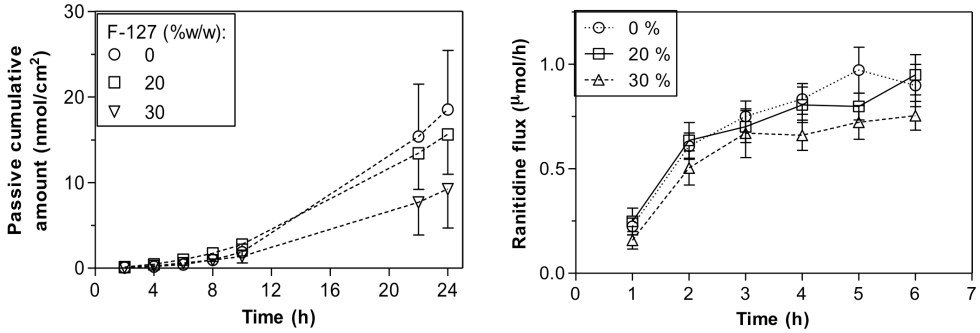

Figure 7: *Passive diffusion (left panel) and iontophoretic delivery (right panel) of ranitidine from an aqueous solution and from two F-127 gel formulations and liquid solution. Data are expressed as mean ± SD.*

The electrotransport of ranitidine after 6 hr of current passage was 0.90 (±0.10) µmol/h from aqueous solution, and 0.95 (±0.10) and 0.75 (±0.07) µmol/h, respectively from the 20% and 30% w/w F-127 gels. Two-way ANOVA tests on the fluxes from the 4th hour of iontophoresis indicated that delivery from the 30% polymer formulation was significantly lower, albeit by only ~20% (i.e., a difference of little practical importance). The calculated transference numbers of ranitidine from the control, and from the 20 and 30% w/w F-127 formulations were 8.05 (±0.91), 8.48 (±0.87), and 6.73 (±0.63)%, respectively.

Assuming that the flux rates achieved with the gel formulations are achievable *in vivo*, the patch areas required to achieve therapeutic input levels of ranitidine were estimated and are summarised in Table 2. From these results, it would appear that the F-127 gel formulations may be able to iontophoretically deliver therapeutically effective fluxes from acceptable patch application areas.

4. Conclusions

Transdermal iontophoresis of ranitidine enhanced its delivery significantly relative to the passive diffusion. The manipulation of different parameters allowed the drug's iontophoretic delivery to be optimised so that target therapeutic levels with both solution and gel formulations might be attained. In particular, a gel formulation comprising 30% w/w F-127 polymer showed promise, having an appropriate viscosity for transdermal application, an acceptable electrical conductivity, and achieving the desired iontophoretic efficiency. Specifically, the results obtained suggest that therapeutic levels of ranitidine in children up to the age of 12 years might be achievable with a total patch area of only 0.2-1.5 cm^2/kg.

Table 2: *Calculated iontophoresis gel patch sizes necessary to achieve target systemic levels of ranitidine in different paediatric populations.*

	Target input rate (µmol/h.kg)[(1)]	*In vitro* transdermal rates achieved[(2)] (µmol/h.cm^2)	Total area of patch required (cm^2/kg)
Neonate	0.09 – 0.17	Solution: 1.16 (±0.13)	0.1 – 0.3 0.1 – 0.3
		Gel 20%: 1.22 (±0.13)	0.2 – 0.4
1 month – 12 years	0.36 – 0.71	Gel 30%: 0.97 (±0.09)	0.6 – 1.2 0.6 – 1.2 0.7 – 1.5

[(1)]: Typical intravenous infusion rates.

[(2)]: Fluxes achieved after 6 hour iontophoresis (at a current density of 0.39 mA/cm^2, and a donor formulation containing 150 mM drug (pH 7)).

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