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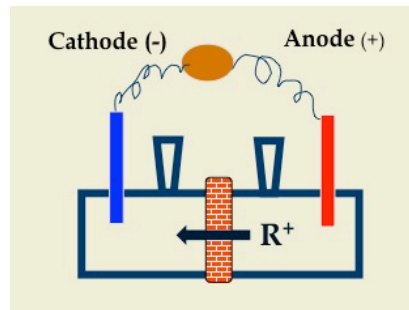
Transdermal iontophoresis of Ranitidine: an opportunity in paediatric drug therapy

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TOC graphic:



23 **Abstract**

24 The objective of this study was to examine the use of transdermal iontophoresis for the delivery of
25 ranitidine hydrochloride in children. Constant, direct current, anodal iontophoresis of ranitidine was performed *in*
26 *vitro* across dermatomed pig skin. The effect of donor vehicle, current intensity, and drug concentration were first
27 examined using aqueous solutions. It was found that drug delivery was higher at pH 7 (donor: 5 mM Tris) than pH
28 5.6 (donor: water). In the presence of low levels of competing background electrolyte, ranitidine delivery
29 increased linearly with applied current but was independent of the donor drug concentration. The second part of
30 the study evaluated two Pluronic® F-127 gels as potential vehicles for ranitidine delivery. The formulations were
31 characterised in terms of apparent viscosity, conductivity and passive permeation measurements. Iontophoretic
32 delivery of ranitidine was only slightly affected when delivered from the gels relative to aqueous solutions.
33 Overall the results demonstrated that therapeutic paediatric doses of ranitidine (neonates: 0.09-0.17 µmol/kg.h;
34 1 month to 12 years: 0.36-0.71 µmol/kg.h) could be easily achieved by transdermal iontophoresis with simple gel
35 patches of practical surface area (0.2-1.5 cm²/kg).

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

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40 1. Introduction

41 Ranitidine is used extensively in paediatric medicine especially in intensive care. It is prescribed in a variety
42 of clinical indications for which gastric acid reduction is necessary (British National Formulary for Children). This
43 includes gastro-oesophageal reflux disease, benign gastric and duodenal ulcerations, prophylaxis of acid
44 aspiration prior to surgery, and treatment as well as prophylaxis from stress-induced gastrointestinal ulcers and
45 consequent haemorrhage. Methods of administration include oral and intravenous delivery. The oral
46 bioavailability of ranitidine is highly variable between paediatric subjects especially in neonates (40-80% (Garg et
47 al., 1983; Blumer et al., 1985; Vanhecken et al., 1982)). This is due to incomplete absorption of the drug from the
48 gastro-intestinal tract as well as first-pass metabolism. The need for frequent dosing (2 to 4 times a day), due to
49 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
50 solution, reduce child compliance. In addition, some formulations contain up to 8% alcohol and no oral
51 preparation is licensed for use in children under 3 years of age; parenteral delivery is only licensed for children
52 over 6 months old (British National Formulary for Children) and has inherent pitfalls such as pain and distress,
53 invasiveness, risk of infection, and technical difficulty.

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

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

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

78 Pluronic® F-127 is a surface active gel-forming agent frequently used in topical skin applications (Collett,
79 2006; Escobar-Chavez et al., 2006). It is composed of triblocks of polyoxyethylene-polyoxypropylene copolymers
80 at a ratio of 70% ethylene oxide (hydrophilic) and 30% propylene oxide (hydrophobic), and with an average
81 molecular weight between 9840 and 14600 Da (Collett, 2006; Booth and Attwood, 2000; Cabana et al., 1997).
82 With increasing F-127 concentration, or at higher temperatures, the entanglement of the polymer chains
83 increases and the gel becomes more rigid. Pluronics® are favoured for transdermal iontophoresis because: (a)
84 The non-ionic nature of the surfactant avoids competition with the drug to carry the applied current, and reduces
85 potential interaction between the polymer and the active (Taveira et al., 2009; Fang et al., 2002; Al-Khalili et al.,
86 2003; Gupta et al., 1994). (b) F-127 is safe as shown by its wide use in pharmaceutical preparations intended for

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

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

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101 2. Materials and methods

102 2.1 Chemicals

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

109 2.2 Skin

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

116 2.3 Iontophoresis set-up

117 Side-by-side two-compartment diffusion cells (active transport area = 0.78 cm^2 , volume = 3 ml) were utilised
118 in all experiments. The skin was mounted between the two chambers with the epidermal side oriented towards
119 the anode compartment. The receptor chamber always held 154 mM sodium chloride solution (unbuffered, pH
120 ~ 6) and was magnetically stirred (Multipoint-6 stirrer, Thermo Scientific Variomag, Cole-Parmer, London, UK) at
121 400 rpm throughout the experiment. Anodal, direct, constant current was delivered using Ag/AgCl electrodes and
122 a power supply (KEPCO 1000M, Flushing, NY, USA). Hourly samples (0.5 ml) of the receptor phase were
123 withdrawn and replaced with fresh solution. Separate passive diffusion, control experiments were also performed
124 with samples taken every 2 hours for 10 hours and two final samples withdrawn at 22 and 24 h. Again each
125 sample taken was replaced with 0.5 ml fresh solution.

126 2.3.1 Ranitidine delivery from aqueous solutions

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

132 2.3.2 Ranitidine delivery from gel formulations

133 Two gel formulations were prepared according to the “cold method” (Schmolka, 1996). Solutions containing
134 150 mM ranitidine in 5 mM Tris (pH 7) were cooled to $\sim 3\text{-}5^\circ\text{C}$ under continuous gentle agitation. F-127 (at 20 and
135 30% w/w) was then incorporated slowly into the solutions and the resulting formulations were stirred for 2 days
136 to achieve complete homogeneity.

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140 **Table 1:** Experimental conditions performed to characterise ranitidine transdermal delivery from aqueous
 141 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 |

142 * pH adjusted to 7 with 1M HCl.

143 ** number of replicates

144 For the permeation experiments, 3.3 grams of each formulation was added to the donor compartment and
 145 constant current (0.3 mA) was delivered for 6 hours. The voltage across each iontophoresis system was
 146 monitored regularly. All experiments were conducted at $22.2 \pm 0.9^\circ\text{C}$, and both compartments were covered with
 147 Parafilm to avoid water evaporation.

148 2.4 Viscosity measurements

149 The apparent viscosities of the gel formulations were determined using a Bohlin rheometer (Malvern
 150 Instruments, Malvern, UK) equipped with a cone-plate system. The angle of the cone was 4° and the diameter of
 151 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.
 152 Readings were performed at $22.1 \pm 0.2^\circ\text{C}$ and gels were allowed to equilibrate on the plate for 5 minutes before
 153 the measurements were made. The viscosities of control formulations (without ranitidine) were also verified and
 154 all measurements were performed in triplicate.

155 2.5 Conductivity measurements

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

159 2.6 Sample analysis

160 Quantification of ranitidine was performed by high performance liquid chromatography with UV detection
 161 (315 nm). The method was modified from a previous publication (Oo et al., 1995) and used a Jasco HPLC system
 162 comprising: a PU-980 pump with an AS-1595 autosampler, a UV-975 UV-VIS detector, and a HiQ-SilTM C18 (250 x
 163 4.6 mm, 5 μm) reverse-phase column (Jasco UK, Ltd., Dunmow, UK) thermostatted at 25°C . The mobile phase (pH
 164 3.8) consisted of a mixture of water, acetonitrile, acetic acid, and triethylamine (85:15:1.5:0.2, respectively in
 165 volume), and was pumped through the system at 1 ml/min.

166 2.7 Data analysis and statistics

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

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

174 The transference number (T) of ranitidine was computed according to Faraday's law [6]: $T = \{(J_{total} \cdot z \cdot F) / I\}$,
175 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
176 absolute value of the valence of the drug ion (~1).

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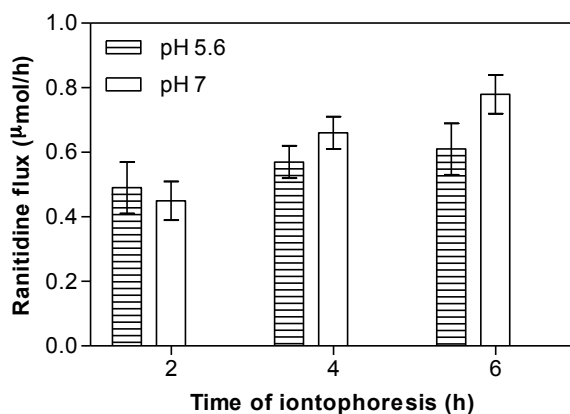
179 **3. Results and discussion**

180 **3.1 Ranitidine delivery from aqueous solutions**

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

185 **3.1.1 Effect of donor vehicle**

186 The first iontophoresis experiments used a donor solution containing only ranitidine hydrochloride (25 mM)
187 in water. The pH of this unbuffered solution was around 5.6 and was low enough to ensure almost complete
188 ionisation (93%) of the more basic group of ranitidine (pK_a 8.2). Ranitidine was the only cation present in the
189 donor compartment, therefore, resulting in the maximum iontophoretic transport possible with the flux reaching
190 0.61 ± 0.08 $\mu\text{mol/h}$ after 6 hours of current passage (Figure 1); this corresponds to a transference number of 5.47
191 (± 0.67)%.

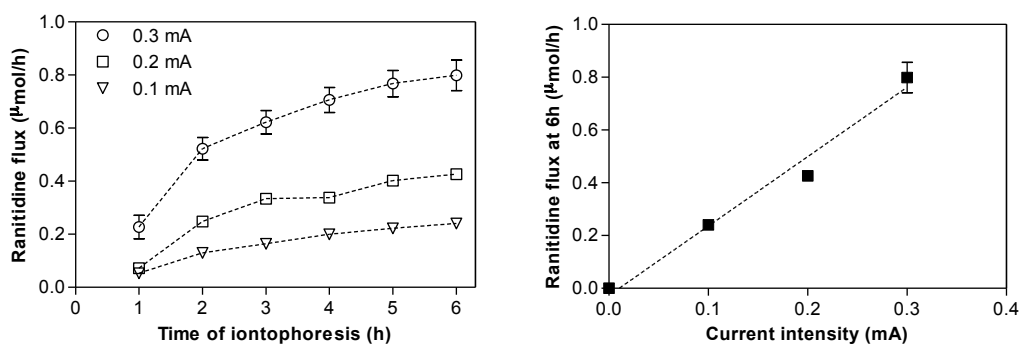


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200 **Figure 1:** Ranitidine iontophoretic transport (mean \pm SD; applied current = 0.3 mA) as a function of time from
201 donor solutions containing 25 mM drug at pH 5.6 (in water) and 7 (in 5 mM Tris buffer).

202
203 The next donor vehicle examined contained 5 mM Tris buffer with the final pH adjusted to 7 with 1 M HCl.
204 The iontophoretic fluxes were initially similar to those measured at pH 5.6, but attained a value (0.78 ± 0.07
205 $\mu\text{mol/h}$), after 6 hours of current passage, which was significantly higher ($p < 0.05$) (Figure 2), and corresponded
206 to a transference number of 6.95 (± 0.58)%. Thus, even though the presence of Tris introduced co-ion
207 competition with ranitidine (~ 4.6 mM of positively charged Tris at pH 7, pK_a 8.1), the higher pH of the donor
208 solution enhanced the overall electrotransport of the drug (presumably a combination of a greater negative
209 charge on the skin ($pI \sim 4.5$ (Marro et al., 2001) and an enhanced electroosmotic flow) (Phipps and Gyory, 1992;
210 Marro et al., 2001; Santi and Guy, 1996). This result is consistent with previous observations for other cations,
211 including sodium (Sieg et al., 2004), verapamil (Wearley et al., 1989), and sumatriptan (Patel et al., 2007).

212 **3.1.2 Effect of current intensity**

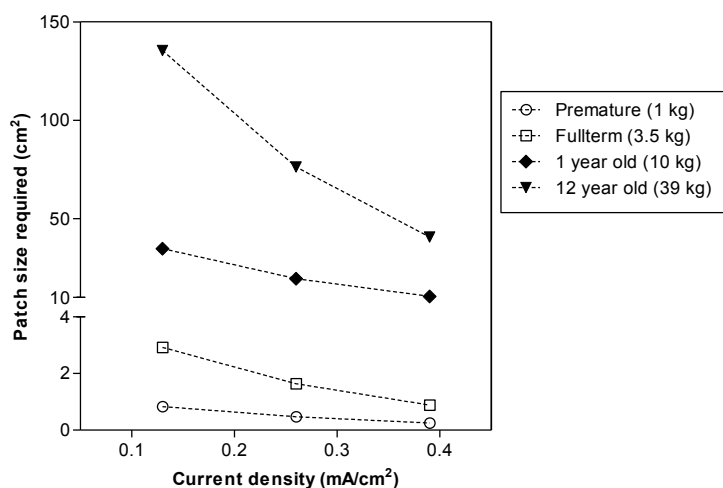
213 These experiments were designed (a) to confirm that iontophoresis provides a controllable means to deliver
214 ranitidine, and (b) to determine whether acceptably small current intensities can are able to provide therapeutic
215 drug doses. While a current density of up to 0.5 mA/cm² is considered tolerable by adult subjects, it is clearly
216 desirable to use lower levels in children, and especially neonates, to reduce discomfort and improve compliance.
217 Three current intensities were examined: 0.1, 0.2, and 0.3 mA, (0.13 , 0.26 , and 0.39 mA/cm²) at a fixed drug
218 donor concentration (50 mM).



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226 **Figure 2:** Iontophoretic delivery of ranitidine (mean \pm SD) from a 50 mM donor solution (containing 5 mM Tris, pH
227 7) as a function of time (left) and current intensity (right), with which the flux at 6 hr was highly correlated ($r^2 =$
228 0.97, $p < 0.0001$).

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

235 At the lowest current density used (0.13 mA/cm²), the delivery rate of ranitidine was 0.31 (\pm 0.02)
236 $\mu\text{mol/h}\cdot\text{cm}^2$. This flux is sufficient to satisfy the recommended intravenous infusion dose of ranitidine for
237 neonates (0.09-0.17 $\mu\text{mol/kg}\cdot\text{h}$), and for children older than 1 month (0.36-0.71 $\mu\text{mol/kg}\cdot\text{h}$) (British National
238 Formulary for Children, 2008), with patch application areas (anode + cathode) of only 0.6-1.1 cm²/kg for neonates
239 and 2.3-4.6 cm²/kg for older children. Obviously, with increasing current density, the area required is
240 proportionately reduced, as illustrated in Figure 3.

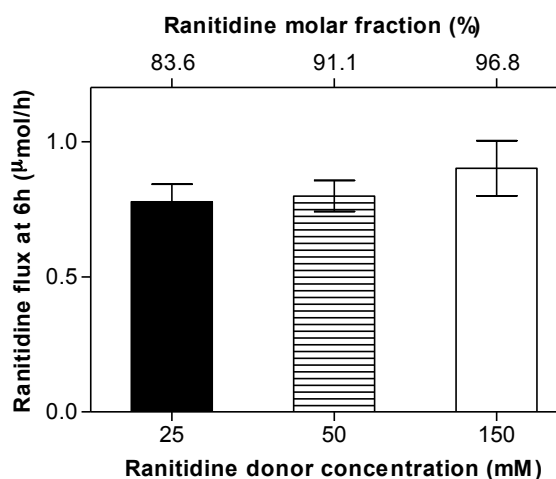


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249 **Figure 3:** Estimated patch areas required to achieve therapeutic input rates of ranitidine, as a function of the
250 iontophoretic current density applied. 4 age groups are used to illustrate The range of areas necessary in four
251 illustrative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

252 3.1.3 Effect of drug concentration

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

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

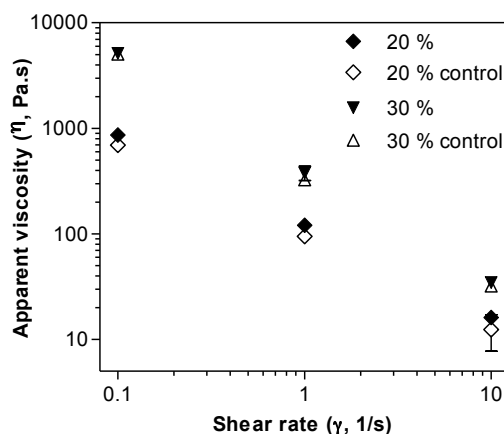
267 3.2 Ranitidine delivery from gel formulations

268 Pluronic® F-127 (at 20 or 30% w/w) as used to produce gel formulations containing ranitidine at 150 mM in
269 5 mM Tris buffer (pH 7). The current intensity employed was 0.3 mA. The highest concentration of drug was
270 chosen to counteract, as much as possible, any potential effects that gelation of the vehicle might have on the
271 electrotransport of ranitidine.

272 3.2.1 Apparent viscosity measurements

273 Figure 5 displays the apparent viscosity of each gel formulation with and without ranitidine. The values
274 were unaffected by the presence of the drug, implying that it did not interfere with the
275 micellisation/entanglement/packing of the F-127. The formulations were semi-solid at 22°C but the viscosity of
276 that containing 30% w/w polymer was significantly greater than that with less (e.g., at an applied shear rate of 0.1
277 s⁻¹, the apparent viscosity of the 20% w/w F-127 was 863 (\pm 67) Pa.s, while that with 30% w/w polymer was 5139
278 (\pm 302) Pa.s). The 20% gel structure was “soft” relative to the more rigid semi-solid consistency of the 30%
279 formulation, which would be more appropriate for transdermal applications. The flow curves of the gel
280 formulations conformed (with r^2 values of \geq 0.98) to the Ostwald-De Waele power law (Macosko, 1994; Malkin,
281 1994; Goodwin and Hughes, 2008): $\eta = K \cdot \dot{\gamma}^{n-1}$, where η is the apparent viscosity measured at a particular shear
282 rate ($\dot{\gamma}$), K is the flow consistency index, and n is the power-law index.

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

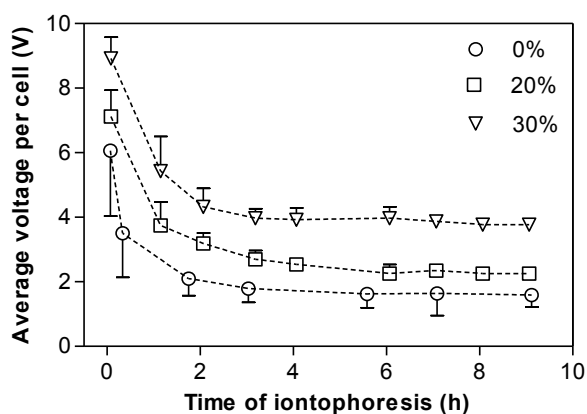
295 The n index values of all formulations were below 1 indicating pseudoplastic behaviour; further, the
296 inverse relationship between the apparent viscosity and the applied shear rate shows that the gels are shear-
297 thinning fluids. Even at high shear rates, the apparent viscosity of the gels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

299 3.2.2 Conductivity measurements

300 The conductivity of the high concentration drug formulation without gelation was $7.9 (\pm 0.1)$ mSi/cm; with
301 20 and 30% w/w F-127, the conductivities were significantly less ($4.3 (\pm 0.03)$ and $2.9 (\pm 0.02)$ mSi/cm, respectively)
302 and significantly different from one another. In accordance with Stoke's law (Kuhn et al., 2008), these
303 observations suggest that ion mobility (and hence conductivity) and formulation viscosity are inversely related.

304 3.2.3 Voltage measurements

305 The voltage across the diffusion cells was monitored throughout the iontophoresis experiments at an
306 applied current of 0.3 mA and the average results (\pm SD) are shown in Figure 6. The voltage was highest at the
307 start of iontophoresis because skin resistance is greatest at this point; it then fell off as ions were driven into the
308 membrane, which became progressively more conductive. It is apparent, furthermore, that the nature of the
309 donor formulation also contributed to the total resistance of the iontophoretic circuit, and that this contribution
310 increased with the viscosity of the gels used (being higher for the 30% w/w polymer than the one containing
311 20%). However, the 2-fold increase observed would be of trivial significance in terms of the feasibility and
312 practicality of an in-use iontophoretic device.

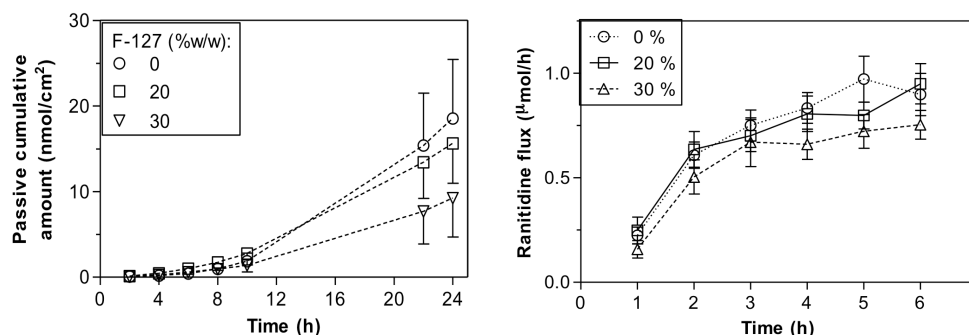


320 **Figure 6:** Average voltage applied (mean \pm SD) across the diffusion cells as a function of time of current
321 application (0.3 mA) for an aqueous donor solution (0%) and for the two F-127 gels examined (20% and 30%).

322

323 3.2.4 Permeation studies

324 Figure 7 (left panel) shows the passive diffusion profiles of ranitidine from donor formulations containing 0
325 (control), 20 and 30% w/w of the gelling agent F-127. After 24 hours, cumulative amounts of $18.6 (\pm 6.9)$, 15.6
326 (± 4.7) , and $9.2 (\pm 4.6)$ nmol/cm², respectively, had permeated through the skin. At most, therefore, these values
327 suggest that the gelling agent at its highest concentration only leads to a 50% reduction in the passive skin
328 permeation rate. From a practical standpoint, this effect is of little consequence, given the much greater delivery
329 rates achieved with iontophoresis, as shown in Figure 7 (right panel).



330
 331 **Figure 7:** Passive diffusion (left panel) and iontophoretic delivery (right panel) of ranitidine from an aqueous
 332 solution and from two F-127 gel formulations and liquid solution. Data are expressed as mean \pm SD.

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

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

343 4. Conclusions

344 Transdermal iontophoresis of ranitidine enhanced its delivery significantly relative to the passive diffusion.
 345 The manipulation of different parameters allowed the drug's iontophoretic delivery to be optimised so that target
 346 therapeutic levels with both solution and gel formulations might be attained. In particular, a gel formulation
 347 comprising 30% w/w F-127 polymer showed promise, having an appropriate viscosity for transdermal application,
 348 an acceptable electrical conductivity, and achieving the desired iontophoretic efficiency. Specifically, the results
 349 obtained suggest that therapeutic levels of ranitidine in children up to the age of 12 years might be achievable
 350 with a total patch area of only 0.2-1.5 cm²/kg.

351
 352 **Table 2:** Calculated iontophoresis gel patch sizes necessary to achieve target systemic levels of ranitidine in
 353 different paediatric populations.
 354

| | Target input rate (μ mol/h.kg) ⁽¹⁾ | <i>In vitro</i> transdermal rates achieved ⁽²⁾ (μ mol/h.cm ²) | Total area of patch required (cm ² /kg) |
|-----------------------|---|--|---|
| Neonate | 0.09 – 0.17 | Solution: 1.16 (\pm 0.13) | 0.1 – 0.3 |
| | | Gel 20%: 1.22 (\pm 0.13) | 0.1 – 0.3 |
| | | Gel 30%: 0.97 (\pm 0.09) | 0.2 – 0.4 |
| 1 month – 12 years | 0.36 – 0.71 | | 0.6 – 1.2 |
| | | | 0.6 – 1.2 |
| | | | 0.7 – 1.5 |

355 ⁽¹⁾: Typical intravenous infusion rates.

356 ⁽²⁾: Fluxes achieved after 6 hour iontophoresis (at a current density of 0.39 mA/cm², and a donor formulation containing 150
 357 mM drug (pH 7)).

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