IONTOPHORESIS OF RANITIDINE: AN OPPORTUNITY IN PAEDIATRIC DRUG DELIVERY

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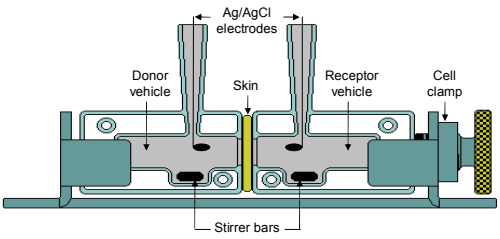
Introduction

- Ranitidine is used extensively in paediatric medicine especially in intensive care units.
- Clinical indications include reflux oesophagitis, benign gastric and duodenal ulceration, and other conditions where gastric acid reduction is beneficial.
- Delivery routes include oral and intravenous administration.
- Oral route suffers from considerable variation in bioavailability (39-88%), short half life and the need for frequent dosing (2-4 times a day), and the bitter taste of the oral solution.
- Intravenous route has inherited pitfalls such as pain and distress to the child, invasiveness, risk of infection, and technical difficulties.
- Transdermal route can provide an alternative approach to the delivery of ranitidine. Such approach is highly attractive owing to the large surface area available in the skin.
- Transdermal iontophoresis is a technique whereby the application of a small electrical current across the skin permits the non-invasive, continuous and rate-controlled delivery of drugs into the body. Several products have already been successfully marketed e.g. Ionsys®
- **The aim of this work, therefore, is to investigate transdermal iontophoresis as a drug delivery system of ranitidine in paediatric care. *In vitro* experiments were conducted to:**
  - **Examine the effects of the donor vehicle pH, drug concentration, and applied current on the iontophoretic delivery of ranitidine from solution-based vehicles.**
  - **Evaluate the performance of gelled formulations of ranitidine as delivery vehicles for transdermal iontophoresis.**

Methods



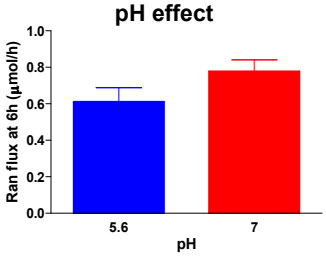
- Standard side-by-side diffusion cells (transport area: 0.78 cm^2). Dermatomed (~750 µm) abdominal pig skin. Constant direct current. Receptor solution: 154mM NaCl (pH ~6.5). Number of replicates ≥ 3.
- Ranitidine chlorhydrate (Ran, MW 350.9, pKa 8.2, logP 0.27) delivery flux determined from hourly sampling of the receptor vehicle into which Ran was transported by electromigration. All data are reported as mean ± SD.

1) **Solution-based donor vehicle:** Investigated the effects of pH ([5.6, water] vs. [7, 5 mM Tris], 25 mM Ran), current intensity (0.1-0.3mA, 50mM Ran in 5 mM Tris, pH 7), and drug concentration (25-150 mM Ran in 5 mM Tris, pH 7, 0.3 mA) on delivery flux of Ran. Current applied for 6 h. Passive diffusion control (150mM Ran).

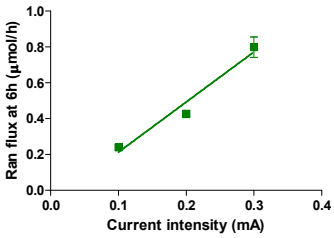
2) **Gel-based donor vehicle:** Pluronic F127, a gelling agent, was incorporated (0-30 %w/w) in 5 mM Tris solution (pH 7) containing 150 mM Ran, and used as donor vehicles for the iontophoretic delivery of Ran. Current applied for 10 h. Viscosity, conductivity, and iontophoretic efficiency of these vehicles were assessed at controlled temperature: 22.2 ± 0.9 °c. Passive diffusion (24 h).

Results: 1) Solution-based donor vehicle

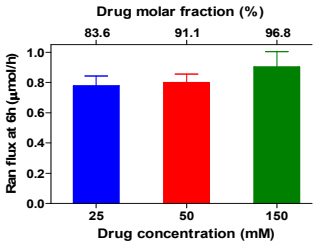
pH effect



Current effect



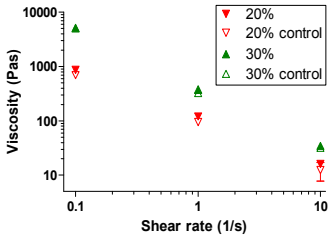
Drug concentration effect



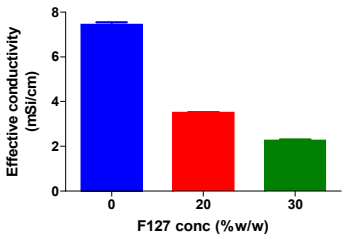
- Ran iontophoretic delivery at pH 7 is significantly higher than at pH 5.6 (unpaired t-test, $p<0.01$)).
- Changes in drug concentration (25 mM-150mM) had little effect on the drug molar fraction (82.9%-96.7%) and consequently on iontophoretic fluxes (ANOVA test, $p>0.05$).
- Passive diffusion flux from a 150 mM Ran solution was 1.8 ± 0.6 nmol/h at steady state.

Results: 2) Gel-based donor vehicle

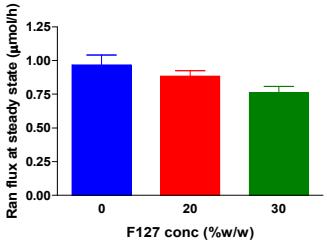
Viscosity of gel formulations



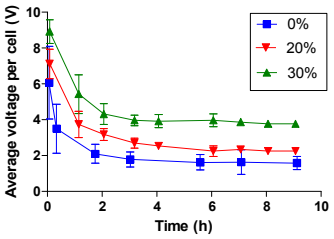
Ran effective conductivity in different gel formulations



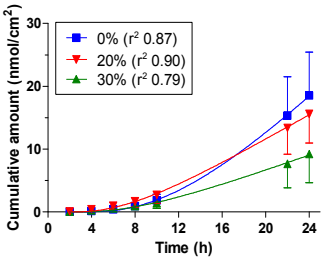
Iontophoresis



Average voltage per iontophoresis cell



Ran Passive diffusion data fitted with Fick's second law



F127 (%w/w)	10^3 . KH (cm)	D/H^2 (h^-)	10^6 . K_p (cm/h)	$J_{ss,\ passive}$ (nmol /h.cm^2)
0%	1.1 ± 0.4	0.01 ± 0.002	11.9 ± 4	1.8 ± 0.6
20%	0.4 ± 0.1	0.02 ± 0.01	6.8 ± 1.1	1 ± 0.2
30%	0.3 ± 0.2	0.02 ± 0.004	4.3 ± 2.2	0.7 ± 0.3

F127 (%w/w)	$J_{ss,\ iontophoresis}$ (µmol/h)	~ Time to reach steady state (h)	Area of patch required (cm^2)**
0%	1 ± 0.1	4	0.2 - 45
20%	0.9 ± 0.04	3	0.2 – 50
30%	0.8 ± 0.04*	3	0.2 – 55

* Significantly different from the other formulation values.
** Area of patch (Anode + cathode) required to reach therapeutic doses as when given intravenously [0.1-28 µmol/h as i.v. infusion (doses for neonates to children up to 12 years of age)]

Conclusions

- Ranitidine was efficiently transported by transdermal iontophoresis using solution- and gel-based formulations as delivery vehicles.
- Iontophoresis can deliver therapeutic doses of ranitidine to the paediatric population. The variability in oral absorption and the disadvantages associated with the parenteral route can, thus, be avoided. Further, the wide range of doses required by the different age groups can be easily obtained by current and patch area manipulation.

[The diffusion cell diagram was adapted from: http://www.permegear.com/sbsassy.htm]

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