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Research Article

TRANSDERMAL IONTOPHORESIS OF DILTIAZEM HYDROCHLORIDE: EFFECT OF CONCENTRATION AND ELECTRICAL FACTORS

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Abstract

The present work showed that the iontophoretic approach was feasible to enhance transdermal drug delivery of drug. *In vitro* horizontal cell has been developed to co-relate with *in vivo* iontophoretic drug delivery more closely. Two electrodes were positioned on the either side of the epithelial. Iontophoretic delivery of Diltiazem HCl across porcine ear skin increased proportional to (a) Increased initial donor concentration in the range of 0.024 M to 0.08 M (b) Increased current on/off ratio valued 30/30, 60/15 and 90/15 resulting in enhancement ratios 12, 20, and 26 respectively, initially applying 0.08 M Diltiazem HCl and (c) Increased current density valued 0.1, 0.2, 0.3 and 0.4 mA/cm obtaining enhancement ratios 6, 13, 25 and 34 respectively, initially applying 0.08 M Diltiazem HCl. The results demonstrated the feasibility of the iontophoretic approach to enhance and control the rate of transdermal delivery of Diltiazem HCl.

Key words: Current density, Diltiazem HCl, Iontophoresis, on/off ratio, Transdermal.

1. Introduction

Iontophoresis is one of transdermal approach in enhancement of transdermal permeation of many drug. Iontophoresis based on the principle that application of electric current provides external energy to drug ions for passage across the skin, thereby increasing drug permeability through the skin. Transdermal iontophoretic drug delivery provides steady state drug concentration in blood, elimination of hepatic first-pass effects, increased patient compliance and dose dumping never occurs. The present work employed a modified iontophoretic permeation cell. This modified cell

reflected the *invivo* iontophoretic drug delivery approach more closely. Both electrodes positioned on the either side of skin, as used in *invivo* study.[1,2,3]

Diltiazem hydrochloride, a benzothiazepine calcium channel antagonist agent has been widely used in the treatment of stable, variant and unstable angina pectoris, mild to moderate systemic hypertension and many other cardiovascular disorders, with a generally favorable adverse effect profile. Diltiazem hydrochloride is subjected to an extensive and highly variable hepatic first pass metabolism by CYP3A4 followed by an oral administration and the absolute bioavailability is approximately 40%, with a large inter individual variation. The interindividual variation may be explained by a variable first pass effect. The short half-life value of Diltiazem hydrochloride (3-5 hours), low molecular weight, pka value 7.7 and its extensive and highly variable first pass metabolism following oral administration make it a suitable candidate for administration by transdermal route to avoid hepatic first pass metabolism. [4,5,6] The aim of present work was to study the feasibility of iontophoretic drug delivery of Diltiazem HCl.

2. Materials and methods

2.1 Materials

Diltiazem HCl was obtained from Sneha Medicare Pvt. Ltd. as a sample. All other reagents were analytical grade and were purchased commercially. Deionized water was used to prepare all solutions. Porcine skin from the ear was obtained from slaughter of the animal, the tissue was stored, frozen and used within 3 days. Isotonic phosphate buffered saline pH 7.4 was prepared from sodium dihydrogen phosphate, disodium hydrogen phosphate and sodium chloride. pH of solution was adjusted with dilute HCl/NaOH solution. Silver wire of 2.34 mm diameter, silver plate of 1.2 cm diameter and 1.9 mm thickness were purchased commercially.

2.2 Electrodes

Silver/silver chloride coated silver electrodes were prepared from 8 cm long silver wire with 1.13 cm^2 Circular silver Plate, connected by Silver welding. The electrode was dipped in Nitric acid and cleaned with distilled water prior to use, also same process was repeated after each use. The electrode was then immersed in 0.1 N HCl and a current of 1 mA were applied for 6 h using a silver wire as a cathode.

2.3 *In vitro* permeation study[7]

The passive *in vitro* permeation studies were conducted in a specially designed permeation cell. The skin was sandwiched between two glass slides. The thickness of skin was measured before and after a permeation study. The thickness of the skin was calculated by subtracting the thickness of glass slides from the total thickness of the glass slides plus the skin. The receptor compartment was filled with buffer. Two pieces of skin were sandwiched between the donor receptor and reference receptor interface, respectively. After adding 2.0 ml buffer to the donor and the reference chamber respectively, the cell was stabilized for approximately 1 h on a circulating water bath. During the experiment 37°C temperature was maintained in receptor compartment and 25°C in donor and reference chamber.

The donor solution was replaced by Diltiazem solution prepared using deionized water. The samples were analysed by HPLC. Six replicates was conducted for each treatment. Pulsed direct current was applied by Mitutoyo digimeter, using a silver electrode (donor electrode) for anode and a silver chloride coated silver electrode for cathode in the reference chamber. The distance between two electrodes was 2.3 cm and the distance between the electrode and skin was approximately 5 mm. (Figure 1).

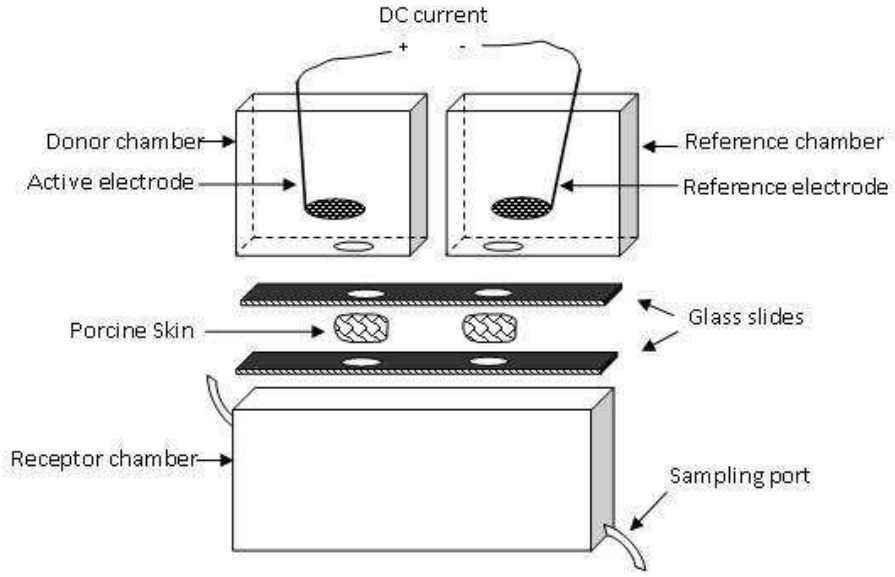

Figure-1: Schematic diagram of in vitro cell used in passive and Iontophoresis permeation study.

The leakiness of the mounted skin was investigated by applying 2 ml of 0.01% methylene blue solution to the donor and reference chamber. After 30 min receptor solution was visually inspected for blue coloration. No staining of receptor solutions was accepted.

2.4 Effect of initial drug concentration/ on-off ratio / current density[8,9,10,11,12]

Effect of initial drug concentration/ on off ratio / current density was evaluated by selecting conditions given in Table 1. An experimental condition, current density value of 0.4 mA/cm^2, an on/off value of 60/30 and a frequency value of 200Hz was maintain throughout the experimentally if not specified otherwise. The permeability study was carried out for 6 h. Hereafter, the donor and reference solution were collected for quantitative analysis. The passive permeability of 0.08 M Diltiazem HCl was also studied.

Table-1: Experimental variables to evaluate the effect of Initial drug concentration/ on off ratio / current density on Diltiazem HCl permeability by iontophoresis.

Evaluation Factor	Experimental variable
Effect of initial donor concentration	0.024 M 0.040 M 0.060 M 0.080 M
On/off ratio	30/30 60/15 90/15
Effect of current density	0.1 mA/cm^2 0.2 mA/cm^2 0.3 mA/cm^2 0.4 mA/cm^2

2.5 Quantitative determination of Diltiazem Hydrochloride by Ultra-violet spectroscopic method

The UV visible spectrophotometer used was a Perkin-Elmer, model λ-25, connected to a computer loaded with Perkin Elmer UVPC software. Spectra of diltiazem hydrochloride standard were obtained in the range from 200 to 400 nm using 1 cm quartz cuvettes in the fast scan speed (about 3200 nm/min), 2.0 nm data interval and 2 nm bandwidth. The drug release percentage was assayed at the wavelength of 237 nm. 10 µg/ml solutions of Standard Diltiazem hydrochloride RS and test samples were prepared in Phosphate buffer PH-6.8/ 0.1N Hydrochloric acid and sonicated for 30 min. absorbances was measured at ultra-violet wavelength, 237 nm.

2.6 Data analysis [7,14]

The steady state flux at time (t) was calculated from the linear part of the plot of cumulative amount of Diltiazem HCl in receptor chamber verses time according to

$Flux_J = \frac{Qt}{A\,(t-L)}$ ……. (1)

Q_t = Total cumulated amount of Diltiazem in receptor chamber at time t. A was the cross section area of donor-receptor opening and *L* the lag time obtained by extrapolation of the x-axis of linear part of the plot of cumulative amount of Diltiazem HCl in receptor chamber versus time. The time t varied from 240 min to 480 min. The presented value of steady state flux was calculated as the mean of $flux_J$. The apparent permeability Co efficient (P) were calculated using equation 2.

$P = \frac{dQ}{dt} \cdot \frac{1}{A \cdot Co}$ …….. (2)

Were dQ/dt signified the steady state rate of Diltiazem HCl in the receptor chamber. A, was the cross sectional area of the receptor-donor opening and C_o was represented the initial donor concentration. The experimental enhancement ratio was evaluated according to,

$$\text{Enhancement ratio} = \frac{\text{Iontophoretic P}}{\text{Passive P}} \text{…….. (3)}$$

Where iontophoretic P represents the p value obtained in the presence of iontophoresis and passive P value was obtain in the absence of current application. Results were presented as mean ± Standard deviation and *n* represented the number of replicates.

3. Results and Discussion

The developed *in vitro* iontophoretic permeation cell provided both electrodes positioned on the epithelial side of the skin, hereby reflecting the *in vivo* situation. In future *in vitro* iontophoretic permeation studies one might consider mounting a piece of skin on the reference–receptor opening instead of other side of skin. Permeation cell provided the unique possibility to examine the solution and tissue in reference chamber, i.e. pH measurement and quantitative analysis of appearance of test compound in the reference solution.[15, 16]

Porcine ear skin was selected as a model for human skin because it was comparable with respect to histology and permeability properties.[17,18,19] Thickness of the porcine skin measured before and after a permeation study resulted in 2.13 ± 0.42 mm (n=10) and 2.24 ± 0.57 mm (n=10). Results represents that there was increase in thickness of the skin

because of 6 h hydration (experimental condition). The effect of variable skin thickness was minimized by repeating the same experiment several times and taking mean value.

The silver / silver chloride-coated silver electrodes are generally considered ‘‘reactive’’, but depletion of chloride from a silver / silver chloride-coated silver electrode may turn it into an ‘‘inert’’ electrode causing electrolysis of water, hence creating alkalization. In the present work, pH of donor, receptor and reference solutions were found change by 0.8 units after 6 h. To avoid competitive ions an unbuffered donor solution was chosen and to introduce few ions a buffer with low buffer capacity was used in the receptor and reference chambers.

3.1. Effect of initial donor concentration

The cumulative amount of drug transfer to receptor compartment-time profiles of Diltiazem HCl across porcine skin during iontophoresis were given in Figure 2. The iontophoretic flux of Diltiazem HCl across porcine skin was found to increase proportional to the initial donor concentration in the range of 0.024–0.080 M Diltiazem HCl, applying 0.4 mA/cm^2 and on/off ratio valued 60/15 (Figure 3). The mean iontophoretic flux values ± S.D. of 1.16 ± 0.43 x 10^{-7}, 1.38 ± 0.44 x 10^{-7}, 2.01 ± 0.51 x 10^{-7}, and 2.33 ± 0.37 x 10^{-7} (mmol/cm s) were obtained at initial donor concentrations of 0.024, 0.04, 0.06, and 0.80 M Diltiazem HCl respectively (n=6). The passive mean steady state flux valued 7.58 ± 0.87 x 10^{-8} (mmol/cm s) (n =6) was obtained at initial donor concentration 0.080 M Diltiazem HCl.

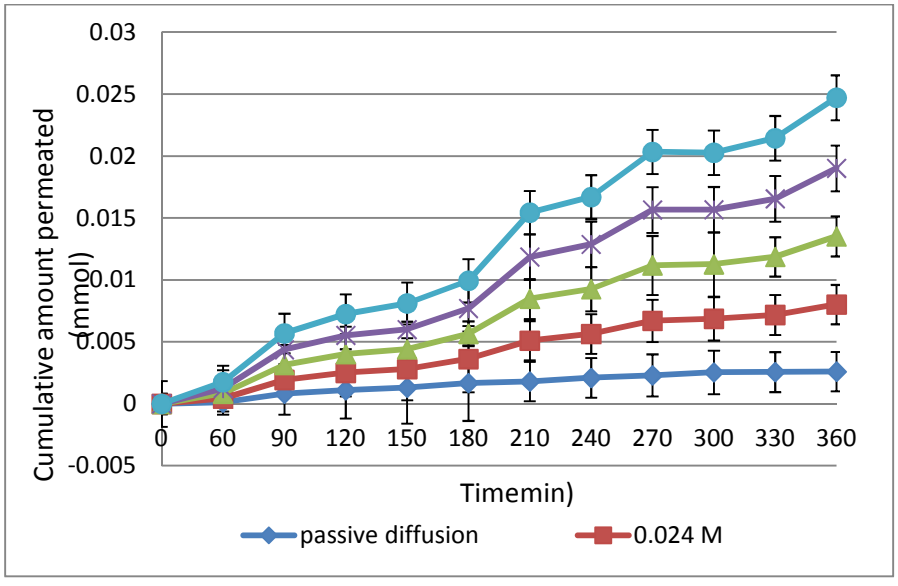

Figure-2: Plot of cumulative amount–time profiles of Diltiazem HCl permeated across porcine skin into receiver chamber during Iontophoresis.

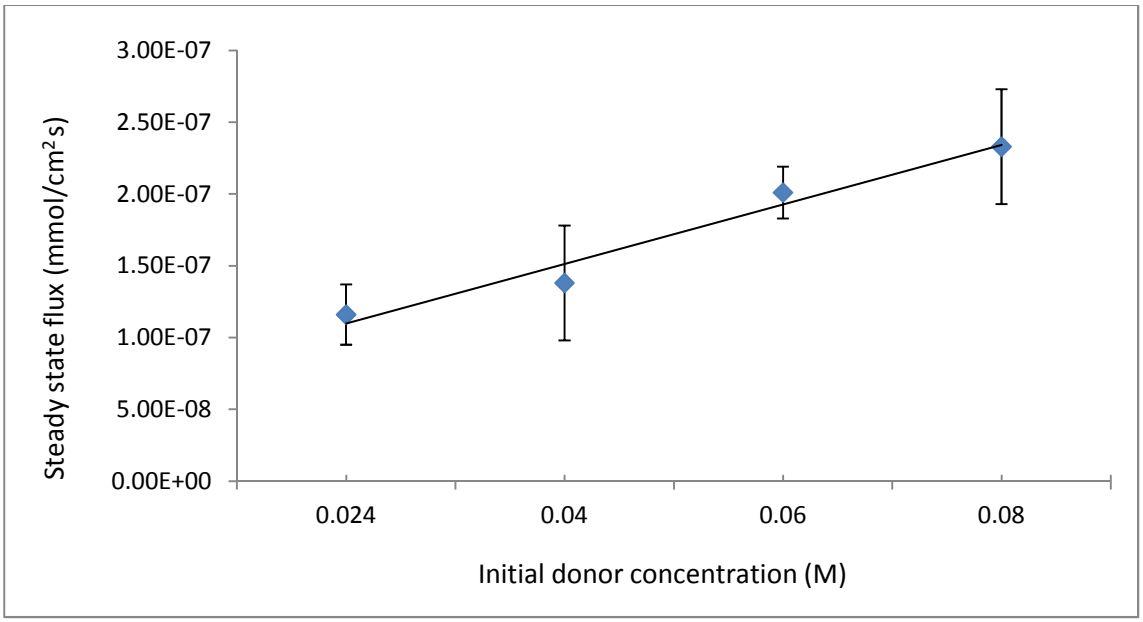

Figure-3: Plot of effect of initial donor concentration on delivery rate of Diltiazem HCl across porcine skin during Iontophoresis.

The initial drug concentration provides an easy way to control the rate of drug delivery. The effect of concentration may be predicted by the Nernst–Planck equation. The iontophoretic flux of Diltiazem HCl across porcine skin was found to be dependent on the initial donor concentration. A proportional increase in flux with increasing initial donor concentration observed. Similar relationship was reported by other workers.[20] It has been suggested that at higher drug concentrations, the transport may become independent of concentration, probably because of the "saturation layer'' at the donor side of the membrane relative to the donor bulk solution.[20]

3.2. Effect of on/off ratio

The iontophoretic *P* of Diltiazem HCl across porcine ear skin increased directly proportional to the increased on/off ratio (Figure 4). At on/off ratio 30/30, 60/15 and 90/15, the mean *P* values of 7.25 ±0.31x 10^{-7}, 12.34 ± 3.43 x 10^{-7} and 15.55 ±4.17 x 10^{-7} (cm/s) and enhancement ratios 12, 20, and 36 obtained respectively (*n* =6). The passive *P* valued 0.26 ± 0.053 x 10^{-7} (cm/ s) (*n* =6).

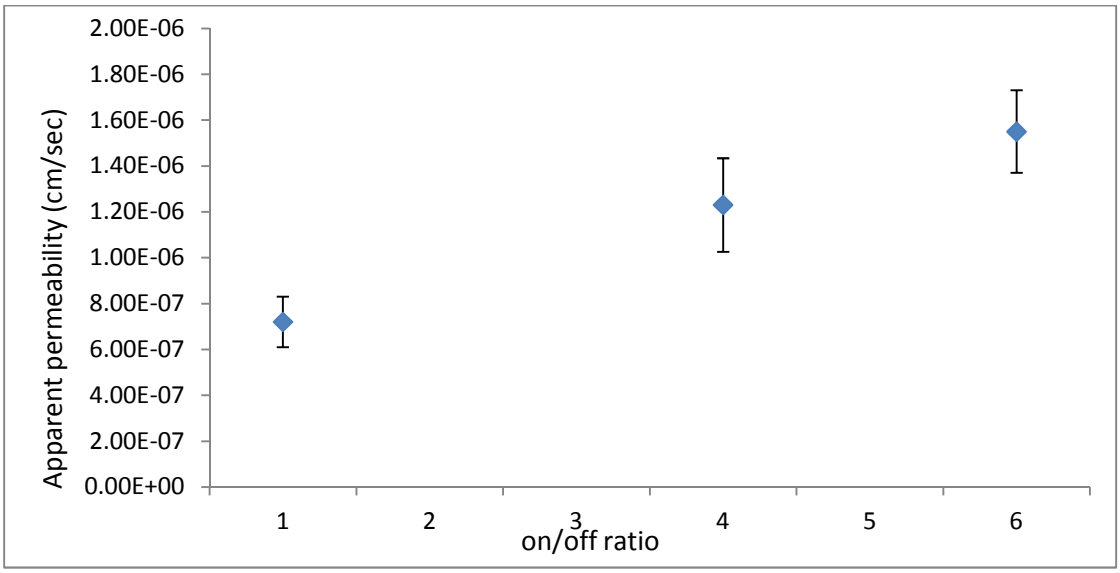

Figure 4: Plot of effect of on/ off ratio on delivery rate of Diltiazem HCl across porcine skin during Iontophoresis.

Generally, use of pulsed direct current compared to constant direct current improved iontophoretic drug delivery by allowing the tissue to depolarize during the ‘‘off time’’. An increased ‘‘on time’’ offered an increased amount of current for drug delivery resulting in an increased flux. Similar results were also reported by other workers. The obtained enhancement ratios demonstrate that the on/off ratio is one of the important electrical factors to be optimized to obtain a controlled rate of drug delivery. An upper limit of ‘‘on time’’ is not determined in present work.

3.3. Effect of current density

The iontophoretic P of Diltiazem HCl across porcine skin increased directly proportional to the increased current density (0.1-0.4 mA/cm). At current densities 0.1, 0.2, 0.3, and 0.4 mA/cm, the mean P ± S.D. values of 3.66 ± 0.93 x 10^{-7}, 7.71 ± 5.90 x 10^{-7}, 15.10 ± 4.38 x 10^{-7} and 20.26 ± 3.10 x 10^{-7} (cm/ s) and enhancement ratios 6, 13, 25, and 34 were obtained respectively (n =6). The iontophoretic P values were significantly different from passive P value.

Electrical factors (Current density and on/ off ratio) were capable of controlling the drug delivery rate. The results were in accordance with previous reports on other compounds.[20] The enhancement ratios indicated that the quantity of iontophoretic delivery of Diltiazem HCl depended on electrical factors such as on/off ratio and current density, also depends on the concentration gradient created by various initial donor concentrations.

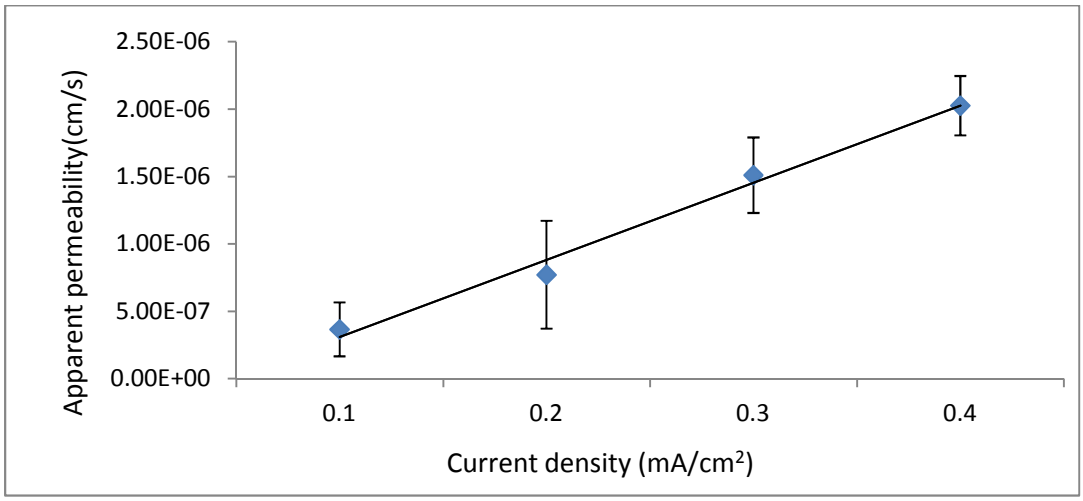

Figure-5: Plot of effect of current density on delivery rate of Diltiazem HCl across porcine skin during Iontophoresis.

4. Conclusion

The present work showed that the Iontophoretic approach was feasible to enhance and control the rate of transdermal drug delivery of Diltiazem HCl. Iontophoretic enhancement ratios valued above 30 were obtained. The Iontophoretic delivery increased proportional to the increased initial donor concentration, on/off ratio and current density. The results showed that the enhancement ratio depended on the electrical factors and concentration gradient. By optimizing these factors it is possible to deliver Diltiazem HCl through Iontophoresis.

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