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ENHANCEMENT OF IONTOPHORETIC TRANSPORT OF ANTIMIGRAINE DRUGS (TRIPTANS) BY OPTIMIZATION OF PH AND ELECTRODE DESIGN

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ABSTRACT:
The purpose of the present study was to discover the inactive and electrically assisted transdermal transport of Rizatriptan Benzoate by iontophoresis. For improved bioavailability, enhanced patient compliance, and improved delivery of Rizatriptan Benzoate, an iontophoretic drug delivery system of a thermosensitive Rizatriptan Benzoate was formulated. The effects of pH, electrode design, and pulse rate on the Rizatriptan Benzoate permeation were investigated. Iontophoretic transport of Rizatriptan Benzoate was found to increase with a increase in the pH of the medium and an increase in the surface area of the electrode. Anodal pulsed iontophoresis with disc electrode significantly increased the Rizatriptan Benzoate skin permeation as compared with the passive controls. Transdermal iontophoresis is the administration of ionic therapeutic agents through the skin by the application of a low-level electric current. Transdermal iontophoresis appears to be a promising technique for the delivery of a variety of compound in a controlled and preprogrammed manner. Transdermal iontophoresis would be particularly useful in the delivery of hydrophilic drugs produced. However, because of the complex physicochemical properties of drug, many factors must be carefully considered for the proper design of an iontophoretic drug delivery system. Penetration of skin has been shown to increase the iontophoretic mediated delivery of a range of compounds both in vitro and in vivo, this study has shown, for the potential devices that remain in contact with the skin during the course of drug delivery.

Key words: Iontophoresis, TDDS, Rizatriptan Benzoate

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INTRODUCTION:

Triptans are attention to work by activating serotonin (5-HT) receptors on trigemino vascular nerve endings, inhibiting the release of neurotransmitters that cause painful cranial vasodilatation. Furthermore, Triptans produce active vasoconstriction and may relieve symptoms of migraine by stimulating 5-HT receptors on cranial vessels. [1] Rizatriptan Benzoatetriptan is the most widely prescribed Triptans, comprising roughly half of all Triptans prescriptions. [2]

The oral formulation offers ease of use but produces variable blood levels and incompatible response of drugs. Rebound happens with all three Rizatriptan Benzoate (RBZ) formulations. [3] This common trouble with reappearance is liable due to diligence of the original event with a time course exceeding the duration of action from the presently available formulations. This is mostly so because RZB has a serum elimination half-life of only 2 h and most of the API drug is eliminated within 4–6 h in the majority of patients. Therefore, a most favorable product would seek to provide the advantages of rapid, systemic RZB management found in the injection without the need for an injection and with a steady duration of action which exceeds the time course of the patient's migraine. These targets could be proficient, in theory, with sustained delivery systems.

Iontophoresis is a method which utilizes bipolar electrical fields to boost charged molecules across intact skin and into critical tissue. [4-5] Using this expertise, RZB is deliver through a thin, disposable, single-use device with an independent galvanic power battery resource and tiny, wafer thin lithium battery. The RZB formulation is attached to the skin with adhesive and is intended for systemic delivery of an unchanging quantity of RBZ, controlled by the design of the electrodes. Active (electronic) transdermal drug delivery can provide momentous advantages relative to conventional passive transdermal drug delivery. These consist of greater rate and control of delivery. This scheme is proposed to offer quick and consistent therapeutic blood levels without an injection over numerous hours with the goal of preventing frequent headaches. The RZB delivery of drug by using Iontophoretic patch is the one of most convenient method other than any of preparations.

MATERIAL AND METHOD

Materials

Rizatriptan Benzoate (RZB) was obtained gift sample from Cipla ltd. Mumbai, India, phosphate buffer pH 6.8, distilled water prepare in laboratory, microcontroller Atmel 89S51 was purchased from local market.

Methods

Preliminary studies

We were studied pre-formulation parameters like appearance, melting point, IR spectra, solubility, UV spectra, partition coefficient and DSC.

Differential Scanning Calorimetry (DSC):

Thermal behavior of RZB was examined by DSC. Accurately weighed sample of RZB (4.62 mg) was run at the scanning rate of 20°C/min over a temperature range of 150 to 200°C.

Construction of calibration curve: [6]

The 10mg of drug was accurately weighed and dissolved in 100 ml of phosphate buffer pH 6.8 to give the concentration 100 µg/ml (stock solution). It is then further diluted to give the serial

dilution from 1 to 10 µg/ml and absorbance was determine at 225 nm using double beam spectrophotometer (JASCO V-630). The graph was plotted between absorbance and concentration.

Preparation of guinea pig Skin: [7]
Guinea pig which had been given free access to food and water were sacrificed by respiratory paralysis by chloroform immediately before experiment. The hairs of the guinea pig skin at dorsal side were removed with hair remover clipper 24 hr before experiment. The skin was carefully excised; adhering fat and other visceral debris were removed manually. Separated epidermis was washed with normal saline solution before starting the experiment.

In vitro passive permeation study:
A Modified Franz diffusion cell was used for diffusion studies. The donor phase was consisting of 10 mg RZB dissolved in 1ml of distilled water. The receptor compartment was consisting of 20ml of pH 6.8 phosphate buffer solution. The whole assembly was maintained at 37 ± 1^0 C. The solution in the receptor compartment was continuously stirred at 100 rpm. One ml of sample was withdrawn from receptor compartment and replaced with same amount fresh medium. The withdrawn samples were suitably diluted filtered through membrane filter and assayed spectrophotometrically at 225 nm.

Preparation of electrodes: [7]
Rod shape silver wire (1 mm diameter, 2 cm length 99.9% pure) was used as anode. For the preparation of silver chloride electrode (Cathode), silver chloride powder has melted in porcelain dish and another silver wire dipped in it.

Development of Electrical Circuit / Microcontroller bases power supply for Iontophorosis:
The power supply used is designed and constructed using microcontroller Atmel 89S51. The input to the power supply is through a 12 V DC mains adapter and the 5V DC regulated supply to the microcontroller is derived using L 7805 voltage regulator. As the application does not demand for high speed operation, 2MHz crystal is used to provide clock pulses required for the operation of microcontroller.
The experiment was designed keeping in view the provision for applying the voltage to the cell under the following conditions.

- Continuously ON
- ON for one second and OFF for one second
- ON for one second and OFF for two seconds
- ON for one second and OFF for four seconds.

This feature is implemented in program in the microcontroller and for selecting one of the above programs; a thumb wheal switch is used. The thumb wheal switch is connected to upper four bits of port i.e. PO.4 to PO.7 of the microcontroller. When the thumb wheel is set at '0' the output of the supply is continuous, when '1' is set, it is ON for 1 second and OFF for 1 second. Similarly thumb wheel position 2 and 3 provide the schedule 3 and 4 in the above list.
The microcontroller output port bit P3.5 is used to control the duration, as the microcontroller cannot source the required range of current this port pin is used to drive an electromagnetic

relay. The main driven by an IC ULN 2003 that works as a driver for the relay. Again this relay is driven by electromagnetic relay. Again this relay is driven by an IC ULN 2003 that works as a driver for relay. The main function of the microcontroller is to read the value set in thumb wheal switch and according to the scheduled selected, it switches the relay making the power available at the output of relay. For indicating the ON and OFF state of the power supply a LED (LIGHT EMITTING DOIDE) is provided which glows when the supply is ON and it does not glow when it is OFF. The timing of the circuit is calibrated and appropriate values are programmed in the microcontroller to provide the desired timing sequence.
The supply to the relay is taken directly from the 12V supply and to the output current, a potentiometer (1 KΩ) is used. The current level desired could be selected keeping the thumb wheal switch in position and adjusting the potentiometer to give the desired value of current through the cell. If it is needed to measure the current through the cell, a DC milliammeter or a multimeter with a range of 20 mA can be used in series with the supply. The block diagram of electrical circuit shown in fig. 1. [8]

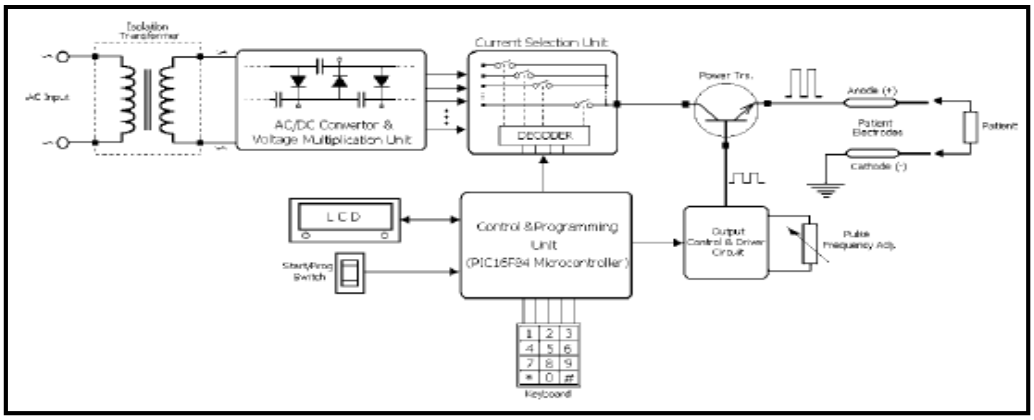


Figure 1: Block diagram of electrical circuit

In vitro Iontophoretic permeation study:
A Modified Franz diffusion cell was used for diffusion studies. The donor phase was consisting of 10 mg RZB dissolved in 1ml distilled water. The receptor compartment was consisting of 20 ml of pH 6.8 P.B.S. The whole assembly was maintained at 37±1ºC. It was kept on a magnetic stirrer (100rpm) and a current was applied as per study using silver–silver chloride electrode. Samples (1ml) were withdrawn from the receptor compartment at hourly interval for a period of 8 hr and assayed for drug content by U.V. at 225 nm.

Optimization studies
a) Current density:
For optimization of current density, permeation studies were carried out with pulsatile current of current density 0.2 mA/cm^2, 0.4 mA/cm^2 and 0.5 mA/cm^2.

b) Type of pulsatile current:
For optimization of type of current, permeation studies were carried out with pulsed direct current (pulsed DC) of 0.5 mA/cm^2 current density with ON: OFF ratio of 1:1, 1:2 and 1:4.

c) pH of Donor Medium:

The hairless guinea pig skin was mounted on vertical diffusion cells with the stratum corneum facing the donor compartment and the assembly were maintained at $37^0C \pm 1^0C$ using a hot water circulator. RZB in a concentration of 10 mg/ml was dissolved in pre-filtered buffer solutions of pH values 4.2, 6.8, 7.4 and distilled water pH 7. Exactly 1 ml of each RZB solution was placed in the donor compartment. The receiver solution for permeation studies was P.B.S. pH 6.8. Silver wire of 2.0cm was used as the anode and silver-silver chloride wire of 4.0 cm was used as the cathode. The anode was dipped in the donor solution and the cathode in the receptor solution, which was stirred using a Teflon-coated magnetic stirrer at 100 rpm. An optimized current density was applied for iontophoretic delivery. The use of silver–silver chloride electrode is because; it prevents the electrolysis of water which may result in pH shifts.

$$\% \, \boldsymbol{RZB\ ionized} = \frac{\mathbf{10}\,(\boldsymbol{pH-pKa})(\mathbf{100})}{\mathbf{1+10}(\boldsymbol{pH-pKa})}$$

Data analysis:

Dilution correction: [9]

After the removal of sample on the hourly basis it was analyze for the drug content. The dilution corrections were made using Hyton-Chien equation as follows.

Hyton-Chien equation

$$Cn^1 = Cn\ (V_T/V_T\text{-}V_S)\ (Cn^1\text{-}1/Cn\text{-}1)$$

Cn^1=Corrected concentration of n^{th} sample

Cn = Measured concentration of n^{th} sample

V_T = Volume of receptor compartment

V_S = Volume of sample withdraw

Cn-1= Measured concentration of (n-1)th sample

Cn^1-1= Corrected concentration of (n-1)th sample

Cumulative amount of drug permeated (CADP): CADP was calculated by using following equation. CADP at the end of 8^{th} hr. was given as Q_8

CADP = Total amount of drug permeated /Area of permeation

Steady state flux (*Jss*): [10]

The cumulative amount of drug permeated per unit skin surface area plotted against time and the slope of the linear portion of the plot is estimated as steady-state flux (µg/cm^2/hr).

Permeability coefficient (K_P):

It can be calculated by following equation.

$$\mathbf{K_P = \ Jss\ /\ Cd}$$

Where,

K_P = permeability coefficient.

Jss = steady state flux.

Cd = initial concentration of drug in donor compartment.

Enhancement Ratio (ER):
It is calculated by dividing CADP by iontophoretic study to the CADP by passive study or CADP by iontophoresis with penetration enhancer to the CADP by iontophoresis without penetration enhancer as per study.

ER = CADP with iontophoresis / CADP without iontophoresis

Statistical analysis:
Statistical analysis was done by using one way ANOVA followed by dunnet test using Prism software.

In vivo study: [11]
Female Sprague–Dawley rats (250–300 g) were housed in the CBP college, Latur. The rats were divided into three groups of six rats each, viz., first group served as negative control, second group was passive drug applied and third group was iontophoretic drug applied. In the case of transdermal permeation studies, the rats were fixed supinely and an animal hair clipper was used to remove the abdominal hair and the skin was wiped with dilute isopropyl alcohol. The teflon rings (1.532 cm i.d.) were fixed to the rat's body using polyacrylate glue and the distance between the two rings was 10 mm. The formulation (2 ml) was applied using a positive pressure pipette to one of the teflon compartments, while to the other compartment, a blank was applied. The platinum electrodes were kept in place using tight fit caps on the teflon ring to make contact with the formulation and the current was applied using a constant power supply. The anode was placed in the drug compartment, while the cathode was placed in the other compartment. In the passive treatment group, no current was applied. The enhancer was then removed using a tissue paper and the skin was washed with water. To the cleaned skin surface, drug was applied and either passive or iontophoretic permeation was carried out. The blood samples (0.3ml) were withdrawn from the retro-orbital plexus periodically up to 8 h and the plasma was separated by centrifugation. One aliquot of the plasma was used for estimation of RZB.

RESULT AND DISCUSSION
The results of preliminary studies were found in limit shown in table no. 1.
Table no. 1: Results of preliminary studies

Sr. No	Preformulation Parameter	Observation	Inference (w.r.t. standards of suppliers datasheet)
1	Appearance	White, crystalline powder	Complies as per standards
2	Melting point	178^{o}C to 179 ^{o}C	Reported melting point was 178^{o}C -180^{o}C, so indicated that drug was in pure form.

3	IR spectra	Characteristics peaks were observed as follows C=N-1567 cm^{-1} , N-H-3400 cm^{-1} , C-N -1354 cm^{-1} , C-H- 1949 cm^{-1}	Confirmed that supplied sample was of RZB and it was in pure form.
4	Solubility	Soluble in water	Complies as per standards
5	UV spectra	The absorbance maximum in phosphate buffer pH 6.8 was found at wavelength 225 nm	A reported UV spectrum was same confirmed that given sample was of RZB.
6	Partition Coefficient	In octanol/water system was found to be 0.7.	It indicated that given sample was hydrophilic (moderately lipophilic).

Differential Scanning Calorimetry (DSC):

The thermogram of RZB shows a melting endothermic at 185ºC (fig.2).

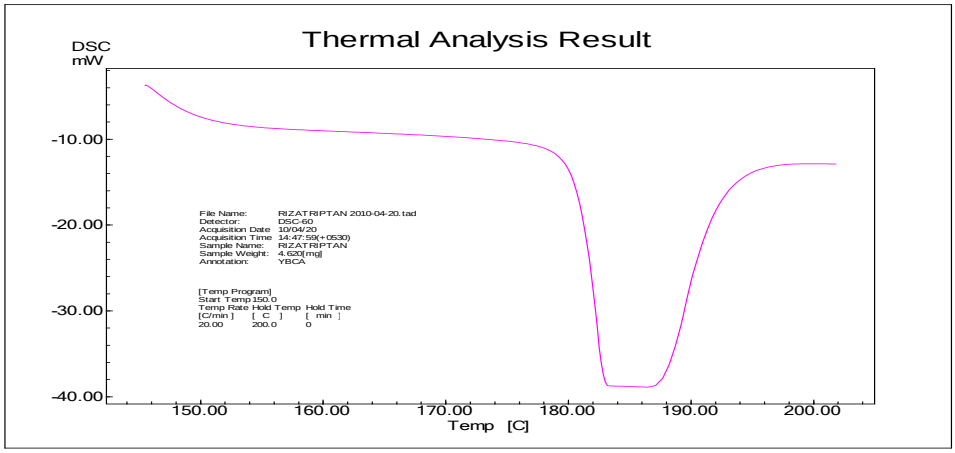


Figure 2: Differential Scanning Thermogram of RZB

Calibration curve

Calibration curve was studied by preparing standard solution at different concentration levels. Standard stock solution of RZB was further diluted to get concentration in the range of 1-10 µg/ml. The resultant absorbances of the solutions were measured at 225 nm against phosphate buffer pH 6.8 as blank. The calibration curves were constructed by plotting absorbances versus concentrations of the drug and the regression equations were calculated (figure 3). These results shown there was an excellent correlation between absorbance and analyte concentration (table 2)

Table no. 2: Calibration studies of RZB

Sr. No.	Concentration (µg/ml)	Absorbance	Standard Deviation
1	0	0	0
2	1	0.2731	± 0.01113
3	2	0.5107	± 0.00775
4	3	0.7545	± 0.00751
5	4	0.9954	± 0.01534
6	5	1.2059	± 0.01831
7	6	1.4760	± 0.02502
8	7	1.7329	± 0.00934
9	8	1.9791	± 0.02067
10	9	2.2418	± 0.02016
11	10	2.5321	± 0.01207

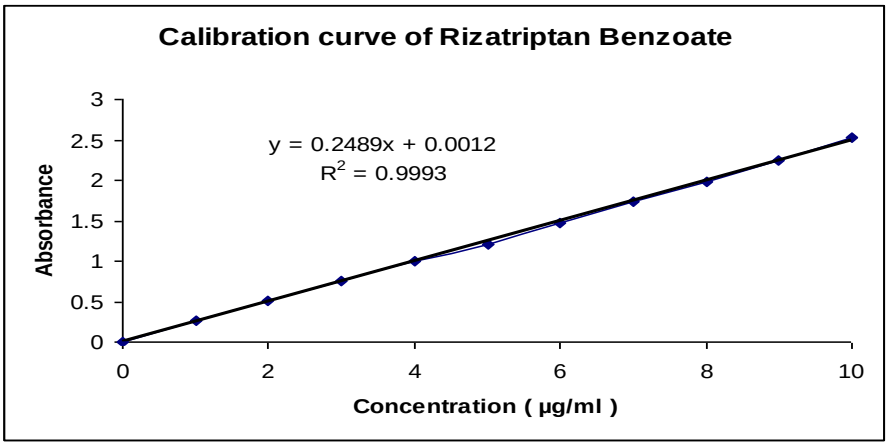


Figure 3: Calibration Curve of RZB

In vitro passive permeation study:

In the in vitro passive permeation study the Q_8 (cumulative RZB permeated at the end of 8th hr.) was found to be only 230.57±2.34 µg/cm^2 which is not sufficient to show the desired effect. So there was need to enhance the permeation by iontophoresis. The diagrammatic representation is given in figure 4.

Figure 4: Passive permeation study

In vitro Iontophoretic permeation study:

The diagrammatic representation is given in figure 5.

Figure 5: Iontophoretic permeation study

Optimization studies

a) Current density:

For optimization of current density, permeation studies were carried out with pulsatile current of current density 0.2 mA/cm^2, 0.4 mA/cm^2 and 0.5 mA/cm^2. The current density optimization study showed that as current density increases the Q_8 also increases. In solution RZB gets ionized and acquires positive charge. The positive electrode in the donor compartment repels the positively charge RZB ions into the epidermis, so the permeation gets increased. The Q_8 was found to be 432.28±3.54 µg/cm^2, 554.67±4.99 µg/cm^2 and 667.82±5.16 µg/cm^2 at 0.2 mA/cm^2, 0.4 mA/cm^2 and 0.5 mA/cm^2 current density. The statistical analysis of data was performed by ANOVA followed by Dunnet test which showed that there was no significant difference ($p>0.05$) in the Q_8 for passive permeation and iontophoretic permeation at 0.2 mA/cm^2 but significant increase ($p<0.05$, $p<0.001$)) in the Q_8 was observed at 0.4 mA/cm^2 and 0.5 mA/cm^2. This is in compliance with results reported by Banga, et al., (1988). [12] So, we select the 0.5 mA/cm^2 as a current density for further studies. The results are shown in the figure 6. The permeation parameters are given in Table no. 3.

Figure 6: Optimization of current density

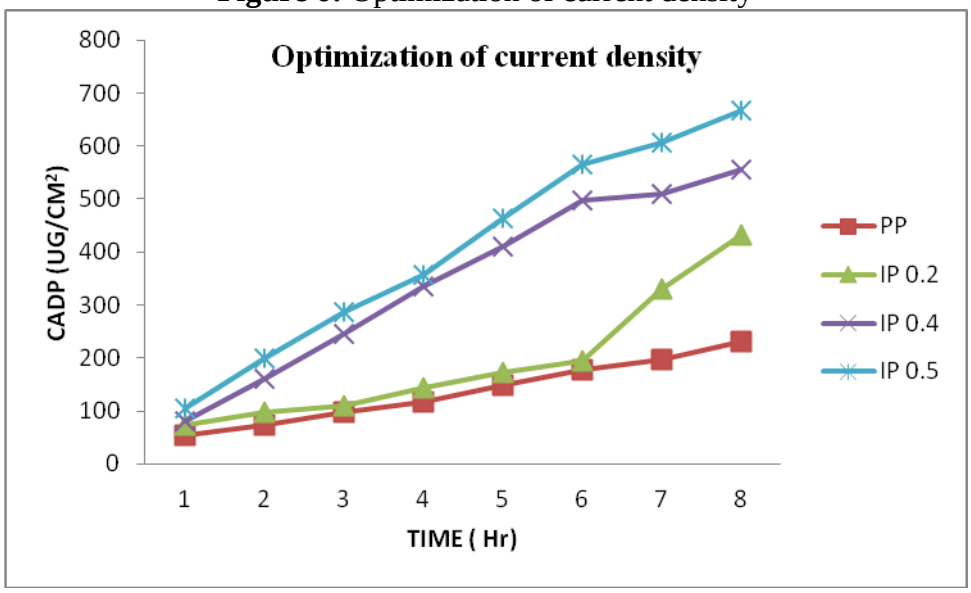


Table 3: Permeation parameters for optimization of current density

Sr.no.	Permeation study	Q_8, (µg/cm^2)	Jss(µg/cm^2/hr)	Kp,	ER	DR (mg)

1	Solution PP	**230.57±2.34**	25.38	2.5	1	0.501
2	IP0.2mA/cm^2	**432.28±3.54**[a]	47.86	4.7	1.87	0.436
3	IP0.4mA/cm^2	**554.67±4.99**[b]	70.21	7.0	2.40	0.398
4	IP0.5mA/cm^2	**667.82±5.16**[c]	82.40	8.2	2.89	0.102

Note: PP and IP=passive and iontophoretic permeation respectively. Jss=steady state flux, Kp = permeability coefficient, Q_8=Cumulative drug permeated at the end of 8th hr. ER is the enhancement ratio. DR: drug retain in skin. All the values are given in mean±SD, n=3. a= no significant difference (p>0.05) from solution PP, b= significant difference (p<0.05) from solution PP, c = significant difference (p<0.001) from solution PP

b) Type of pulsatile current:

For optimization of type of current, permeation studies were carried out with pulsed direct current (pulsed DC) of 0.5 mA/cm^2 current density with ON: OFF ratio of 1:1, 1:2 and 1:4.

Optimization of type of current studies reveals that the pulsed DC of 0.5mA/cm^2 with 1:1 ON: OFF ratio gives more permeation compared with continuous DC at 0.5 mA/cm^2. Use of continuous DC for long period of time results in skin polarization, this can reduce the efficiency of iontophoretic delivery proportional to the length of continuous DC application. This can be overcome by using pulsed DC. It allows the skin to depolarize and return to its original electrical condition when current put OFF for fraction of second.

As shown in Figure A, the permeation profile of RZB at pulsed iontophoresis of ON:OFF pulse ratios 1:2 and 1:4 was similar to that of the continuous current .This may be because of the skin remain in polarized condition for more time as in continuous current. However, the flux was increased at the pulse rate 1:1, The use of pulse current allows the skin to depolarize and return to its initial electric condition when the current phase is put off for a fraction of time. Therefore, the remaining studies were performed using pulse rate 1:1.

The Q_8 was found to be with continuous current (0.5mA/cm^2), pulsed dc 1:1, pulsed dc of 1:2 and pulsed dc of 1:4 667.82±5.16 µg/cm^2 1124.68±5.54µg/cm^2, 965.24±3.24µg/cm^2 and 756.35±2.94 µg/cm^2 respectively. The results are shown in the fig 7. From the above results 0.5 mA/cm^2 1:1 ON: OFF ratio pulsed dc was selected for further studies. Permeation parameters are given in table 4.

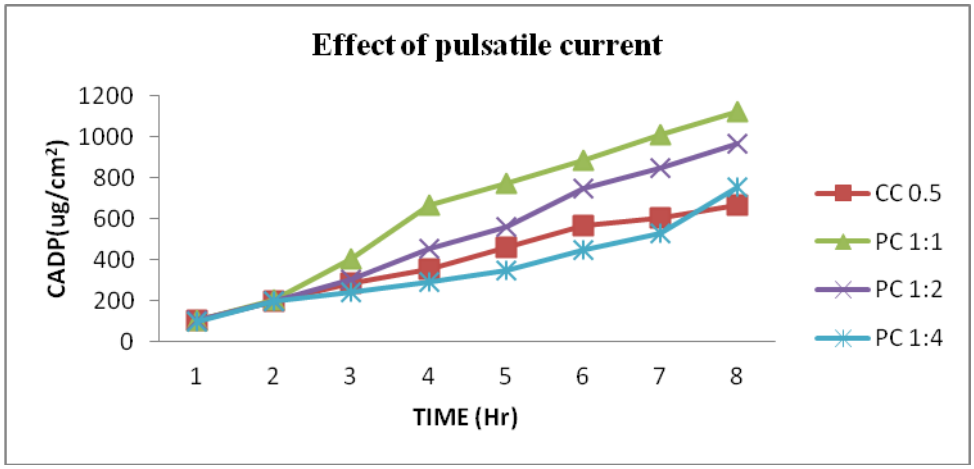


Fig. 7: Optimization of type of current

Table 4: Permeation parameters for optimization of type of current

Sr. no.	Permeation study	Q_8, (µg/cm^2)	Jss, (µg/cm^2 /hr)	Kp	ER	DR (mg)
1	CC 0.5	667.82±3.16	82.40	8.2	1	0.501
2	PC 0.5 (1:1)	1124.68±5.54[a]	152.03	15.2	1.68	0.102
3	PC 0.5 (1:2)	965.24±3.24[a]	127.76	12.7	1.44	0.489
4	PC 0.5 (1:4)	756.35±2.94[a]	82.83	8.2	1.13	0.371

Note: CC=Continuous current, PC= Pulsatile current. Jss=steady state flux, Kp=permeability coefficient, Q_8=Cumulative drug permeated at the end of 8th hr. ER=enhancement ratio. DR: drug retain in skin. All the values are given in mean±SD, n=3. a= no significant difference (P >0.05) from CC 0.5.

c) pH of Donor Medium:

The percent drug ionized depends on the pH of media, so the permeation studies were carried out with donor compartment of various pH. Q_8 was found to be more at pH 7.4. It might be because of the fact that at this pH more than 99% RZB was ionized (Table 5). There was no significant difference ($p<0.05$) observed in RZB permeation at pH 7.4 and distilled water pH

7 (Fig. 8) because the percent RZB ionized was almost similar at both pH. The Q_8 at pH 4.2, 6.8, 7 and 7.4 was 564.24±4.61µg/cm^2 678.25±4.86 µg/cm^2, 1310.89±5.54 µg/cm^2 and 1401.87±.6.14µg/cm^2 respectively. So to avoid the effect of ions present in the buffer solution we chose to study the further parameters by preparing the donor solution using distilled water. The other permeation parameters are given in table 6.

i.e. $\%\ \boldsymbol{RZB\ ionized\ (pH\ 4.2)} = \frac{\mathbf{10\ (4.2-3.01)(100)}}{\mathbf{1+10(4.2-3.01)}} = \mathbf{92.24}$

Table 5: %RZB Ionized study

Sr. no.	pH	% RZB ionized
1	4.2	92.24
2	6.8	97.42
3	7	99.98
4	7.4	99.99

Table 6: Permeation parameters for optimization of pH

Sr.no.	Permeation study	Q_8, (µg/cm^2)	Jss, (µg/cm^2/hr)	Kp,	ER	DR (mg)
1	pH 4.2	564.24±4.61	67.16	6.7	1	0.489
2	pH 6.8	678.25±4.86[a]	80.20	8.0	1.2	0.468
3	pH 7	1310.89±5.54[a]	169.21	16.9	2.32	0.426
4	pH 7.4	1401.87±.6.14[b]	186.01	18.6	2.48	0.365

Note: Jss=steady state flux, Kp=permeability coefficient, Q_8=Cumulative drug permeated at the end of 8th hr. ER=enhancement ratio. DR: drug retain in skin. All the values are given in mean±SD, n=3. a= no significant difference (P >0.05) from pH 4.2, b= significant difference (p<0.05) from pH 4.2

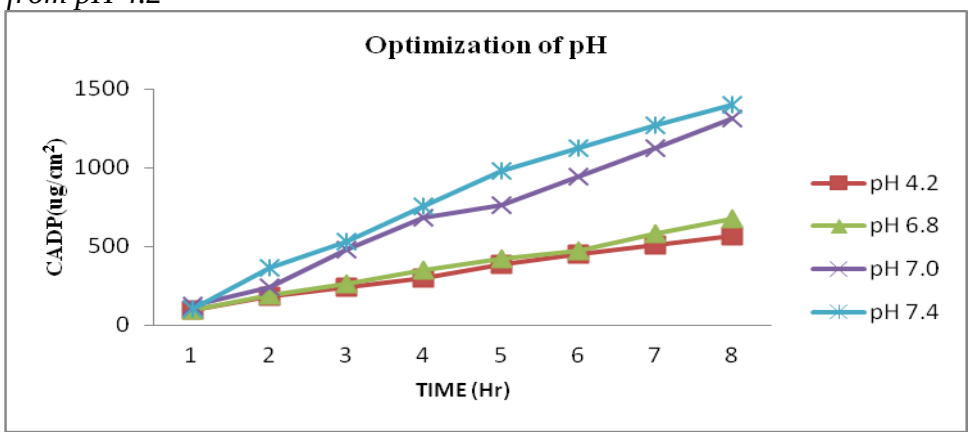
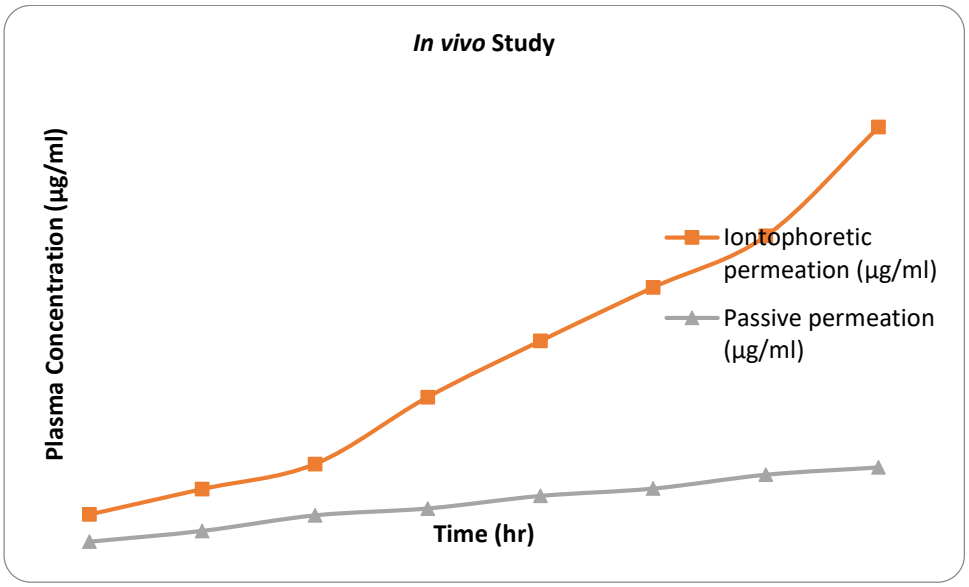


Fig 8: Optimization of pH of donor media

In vivo study

In vivo pharmacokinetic study was performed in Female Sprague–Dawley rats. The pharmacokinetic was directly obtained from the plasma concentration time curve (fig. 9). Passive or iontophoretic permeation was found to be with 198µg/ml and 986µg/ml for 8h and 26µg/ml and 89µg/ml for 1h respectively. An increase of about 5 times was evident in the permeation of drug in iontophoretic permeation to the passive pure drug points to the increased residence time of drug in biological system. After topical administration, RZB undergoes rapid and extensive absorption, reaching peak plasma concentration in less than an hour. The optimized iontophoretic permeation displayed a remarkable increase in bioavailability due to prolonged plasma residence as evident from the pharmacokinetic parameters. Thus we may conclude that effectively the dosing frequency can be reduced.



CONCLUSION

The present study highlighted transdermal drug delivery by forming Iontophorosis patch with the loading of Rizatriptan Benzoate. In particular, it was found that an increase in drug delivery from the skin by exchange of electrodes. Penetration of skin has been shown to increase the iontophoretic mediated delivery of a range of compounds both in vitro and in vivo, this study has shown, for the potential devices that remain in contact with the skin during the course of drug delivery. Furthermore, it has been shown that the application of electric current enables the permeation of macromolecules from the entire drug delivery. As such, future studies will focus upon the incorporation of Iontophoretic components into polymeric devices and their

potential for efficient, electrically controlled pulsatile delivery of macromolecules from drug loaded.

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