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Research Article

Formulation and Evaluation of Iontophoretic Transdermal Delivery of Diltiazem Hydrochloride

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ABSTRACT

The purpose of this research work was to develop and evaluate Iontophoretic Transdermal Delivery of Diltiazem Hydrochloride with various hydrophilic polymers HPMC, SCMC and PVA with propylene glycol as plasticizer by solvent casting method. The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy. Diltiazem hydrochloride patch were characterized by physicochemical characteristics like thickness, weight variation, drug content, folding endurance, percentage moisture loss, percentage moisture absorption, water vapour transmission rate, tensile strength and ex vivo skin permeation studies were performed using Franz's diffusion cell and *in vitro* permeation by using iontophoresis.. The formulations exhibited uniform thickness, folding endurance, weight and good uniformity in drug content. The prepared transdermal patches were subjected to *in vitro* drug permeation studies by using rat skin in Phosphate Buffer pH 7.2 for 24 hrs (passive and iontophoresis). On the basis of *invitro* drug release and ex *vivo* skin permeation performance, formulation F3 was found to be better than the other formulations. Electrodes for iontophoresis were made up of platinum wire and current density 0.5 mA/cm^2 has been used for permeation enhancement. The formulation F_3 was subjected to different current density from 0.4 mA/cm^2 to 0.6mA/cm^2 and it was found that permeability gradually increases with the increase in the current density. Kinetic data revealed that the drug release followed zero order non-fickian diffusion mechanism. The results of the study show that Diltiazem HCl could be administered transdermally by using iontophoresis through the matrix type TDDS for effective control of angina pectoris and hypertension.

Keywords: Diltiazem hydrochloride; Polymers; Transdermal patches; Iontophoresis; ex *vivo* skin permeation.

1. INTRODUCTION

Delivery of drugs into systemic circulation via skin has generated a lot of interest during the last decade as transdermal drug delivery systems (TDDS) offer many advantages over the conventional dosage forms and oral controlled release delivery systems notably avoidance of hepatic first pass metabolism, decrease in frequency of administration, reduction in gastrointestinal side effects and improves patient compliance (Robinson, J. R and Lee, H.L 1987). Matrix based transdermal formulations have been developed for a number of drugs such as metoprolol (Aquil M et al., 2003), nitrendipine (Ramesh G et al., 2007), ephedrine (Singh J et al., 1993), ketoprofen (Valenta, C. and Almasi-Szabo, 1995), propranolol (Krishna R et al., 1994), labetolol hydrochloride (Aquil M et al., 2005) and triprolidine (Shin, S. and Lee, H 2002).

Diltiazem hydrochloride**,** a calcium channel blocker, is widely used in the management of angina pectoris and hypertension. The apparent mean terminal elimination half life of diltiazem hydrochloride generally ranges from 3.6 to 6.6 h; the absolute bioavailability is approximately 40% due to a significant degree of first pass metabolism, In addition to pharmacokinetic properties, Diltiazem hydrochloride has high molecular weight (450.99), extensive first pass effect and hydrophilic nature. All the above properties are enough indicators that Diltiazem hydrochloride might be a good choice as a drug candidate for iontiophoretic transdermal delivery.

In spite of several advantages offered by transdermal route, only a few drug molecules are administered transdermally because the formidable barrier nature of stratum corneum. Two major approaches to increase transdermal permeation rate include physical techniques (iontophoresis, electroporation, sonophoresis, and microneedles) and use of chemical penetration enhancers (PE) such as solvents, surfactants, fatty acids, and terpenes.

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Iontophoresis is being explored for drugs whose delivery is not benefited by chemical enhancer. Iontophoresis may be defined as a method involving transfer of a charged substance in to tissue by the passage of a direct current through an ionized drug solution and into the patient, using appropriate electrode polarity. Iontophoresis is a non-invasive technique and is being investigated for localized and systemic therapy and an alternative drug delivery system.

Propylene glycol (PG) is the most commonly used pharmaceutical excipients and have been widely employed to enhance the transdermal flux of many drugs (B.J., Blake, 1990, Cho, Y.J 1998, Kim J et al., 2000, Panchangula R et al., 2001 and Manvi FV et al., 2003). Various mechanisms of action have been attributed to the PG for its penetration enhancement capabilities such as increased thermodynamic activity (Mollgaard, B. and Hoelgaard, A 1983), increased skin/vehicle partitioning of the drug (Barry BW, 1987), and alteration of barrier property by interacting with skin components. PG may reduce barrier property of skin by causing conformational changes either in lipid acryl chains (Rowe ES, 1985) or protein domains (Kurihara BT et al., 1990) or by partial lipid extractions (Kim YH et al., 1992).

Iontophoresis is an exciting technology that was initially investigated 250 years ago. Simply defined, it is the application of an electrical potential that maintains a constant electric current across the skin or barrier that enhances the delivery of ionized as well as unionized moieties.

In the past few years, different types of iontophoresis such as transdermal, ophthalmic, transungual, buccal, ural and transnasal iontophoresis have been reported. Transdermal iontophoresis is the application of an electrical potential that maintains a constant electric current across the skin and enhances the delivery of ionized as well as unionized moieties (Yiping et al., 2005). It offers various advantages such as easier termination of therapy, better control of drug delivery, improving delivery of polar drugs as well as high molecular weight substances, benefits of bypassing hepatic metabolism and reducing considerably the inter and intra-individual variability(Williams AC and Barry BW 1992 & Williams AC and Barry BW 1991) and ability to be used for systemic delivery or local delivery of drugs. Various studies have been conducted on cardiovascular drugs including antihypertensive drugs (calcium channel blockers and adrenoreceptor blockers) (Chesnoy S et al., 1999, Ganga S et al., 1996 and Kanikkannan N et al., 2000).

Antihypertensive drug hence require quick action but passive transdermal patch provides only sustained release of the drug. Also some part of the medication remains in the part of the system. Hence it was decided to further extend the study and develop an iontophoretic drug delivery system, which may facilitate quick release of drug by alteration of current. Also the dose of drug require for iontophoretic delivery system is comparative smaller than passive system. Permeability of the drug is enhanced by the increasing pore size of the skin. Iontophoretic system has inherently high dose efficiency that delivers 75% of the loaded dose. In order to attain effective blood level for a long period in a single dose and suppress side effects associated with conventional therapy.

Previously the diffusion-controlled transdermal delivery system of diltiazem hydrochloride has been reported (Ekapol, 2008). The results showed that the polymeric film composed of hydroxy propyl methyl cellulose (HPMC) and ethyl cellulose (EC) at the ratio of 8:2, dibutyl phthalate (DBP) as a plasticizer and Isopropyl myristate (IPM), Isopropyl palmitate (IPP), or Tween 80 as the permeation enhancer was suitable for developing a transdermal drug delivery system for diltiazem hydrochloride.

The aim of the present study was to prepare iontophorectic transdermal patches of Ditiazem hydrochloride using hydrophilic polymer and the purpose was to provide the delivery of the drug at a controlled rate through the skin.

2. MATERIALS AND METHODS

Materials

Diltiazem hydrochloride was obtained as a gift sample from Micro labs, Hosur, Tamilnadu, India. Polymers HPMC and SCMC were obtained as a gift sample from Colorcon Asia pvt Ltd, Goa, India. PVA and Propylene glycol were obtained as a gift sample from S.D. fine chem. Ltd, Mumbai, India.

2.1. Investigation of physicochemical compatibility of drug and polymer

Fourier transform-infrared spectroscopy

The physicochemical compatibility between Diltiazem hydrochloride and polymers used in the films was studied by using Fourier transform-infrared spectroscopy (Perkin Elmer spectrum RX1 FT-IR). The pellatization was done by the KBr pellet method. The FT-IR spectra were recorded in the wavelength region between 4000 and 400 cm-1. The spectra obtained for KTF and physical mixtures of Diltiazem hydrochloride with polymers were compared.

2.2 Preparation of transdermal patch

In the present study, drug loaded matrix type transdermal films of Diltiazem hydrochloride were prepared by solvent casting method. A mould of 5 cm length and 5 cm width with a total area of 25 cm2 as fabricated was used. The bottom of the mould was wrapped with aluminium foil, the casting solution was prepared by dissolving the polymer in distilled water to form a 2 %w/v solution and 120 mg of the drug were dispersed in the polymeric solution and propylene glycol as a plasticizer. The resulted uniform solution was cast on

the aluminium foil and dried at 40°C in the hot air oven for 24 h. An inverted funnel was placed over the mould to prevent fast evaporation of the solvent. After 24 h the dried films were taken out and stored in a desiccator for further studies. Compositions of different formulations are represented in Table 1.

Table 1: Composition of Iontophoretic Transdermal Patches of Diltiazem Hydrochloride

Drug and polymer	F1	F2	F3
Diltiazem hydrochloride	120 mg	120 mg	120 mg
Hydroxy Propyl methyl cellulose	2% w/v	-	-
Sodium Carboxy methyl cellulose	-	2% w/v	-
Poly vinyl alcohol	-	-	2%w/v
Propylene glycol	0.12ml	0.12ml	0.12ml

2.3. Evaluation of transdermal patch

1. Physical appearance: All the prepared patches were visually inspected for color, clarity, flexibility and smoothness.

2. Film Thickness uniformity: The thickness of the formulated film was measured at 3 different points using a digital caliper and average thickness of three reading was calculated (GS. Sanap et al., 2008)

3. Film Weight variation: For each formulation, three randomly selected patches were used. For weight variation test, 3 films from each batch were weighed individually and the average weight was calculated (GS. Sanap et al., 2008).

4. Folding endurance: The folding endurance was measured manually for the prepared films. A strip of film (5 x 5 cm) was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance (GS. Sanap et al., 2008).

5. Percentage moisture absorption: The films were weighed accurately and placed in the desiccators containing 100 mL of saturated solution of potassium chloride, which maintains 80-90% RH. After 3 days, the films were taken out and weighed. The study was performed at room temperature (Y. Kasum Devi et al., 2003). The percentage moisture absorption was calculated using the formula:

$$\text{Percentage moisture absorption} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Initial Weight}} \times 100$$

6. Percentage moisture loss: The films were weighed accurately and kept in a desiccators containing anhydrous calcium chloride (Y. Kasum Devi et al., 2003). After 3 days, the films were taken out and weighed. The moisture loss was calculated using the formula:

$$\text{Percentage moisture loss} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Initial Weight}} \times 100$$

7. Water vapour transmission rate: Glass vials of 5 mL capacity were washed thoroughly and dried to a constant weight in an oven. About 1 g of fused calcium chloride was taken in the vials and the polymer films of 2.25 cm2 were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber of 80-90 % RH condition for a period of 24 h. The vials were removed and weighed at 24 h time intervals to note down the weight gain (Sivakumar A et al., 2010).

$$\text{Transmission rate} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Time} \times \text{Area}} \times 100$$

8. Tensile strength: Tensile strength of the film was determined with Universal strength testing machine (Hounsfield, Slinfold, Horsham, U.K.). The sensitivity of the machine was 1 g. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (4 × 1 cm2) was fixed between these cell grips and force was gradually applied till the film broke. The tensile strength of the film was taken directly from the dial reading in kg (Sivakumar A et al., 2010). Tensile strength is expressed as follows:

$$\text{Tensile strength} = \frac{\text{Tensile load at break}}{\text{Cross section area}}$$

9. Drug Content Uniformity of Films

The patches ($1cm^2$) were cut and added to a beaker containing 100 mL of phosphate buffered saline of pH 7.2. The medium was stirred with magnetic bead. The contents were filtered using whatmann filter paper and the filtrate was examined for the drug content against the reference solution consisting of placebo films (contains no drug) at 240 nm spectrophotometrically (GS. Sanap et al., 2008).

Preparation of rat skin

All experiment was conducted according to the protocol approved by the institutional animal ethics committee (IAEC), protocol number: SVCP/IAEC/ M.Pharm /04 /2008-09. The experiment was conducted according to the guidelines of CPCSEA (Committee for the purpose of control and supervision of experiment on animal).

The male abdominal rats were sacrificed by decapitation. The fresh abdominal skin was excised from male albino rat weighing 170-190 g. The abdominal skin of excised hairless rat skin was separated along the epidermal junction. The hair of skin was removed using depilatories. The process of the removal of hair did not alter the skin properties and delivery of the drug. It was kept at water bath maintained 60˚C for exactly 50 seconds. The heat treated skin was cleared of it subcutaneous fatty substance an immediately kept in refrige-

rator at 10˚C. This step maintained integrity and viability of the skin.

10. In vitro drug release studies

Skin permeation studies were performed by using a modified Franz diffusion cell with a receptor compartment capacity of 20 mL. The synthetic cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were cut into size of 2.3 cm^2 and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.2. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 37 ± 0.50C. The samples were withdrawn at time intervals upto 24 h, analyzed for drug content spectrophotometrically at 240 nm (GS. Sanap et al., 2008).

11. *In vitro* drug release studies using Iontophoresis

In vitro permeation studies were carried out by using a diffusion cell with a diffusion surface area of 2.3 cm^2 and act as donor compartment. Rat skin along with loaded polymeric film was tied and placed into7.2 phosphate buffer solution which acts as a receptor compartment, under agitation, at 37ºC, in order to assess sink conditions during the release studies.

The anode was placed in the donor compartment and the cathode was placed in the receptor compartment. Current 0.5 mA/cm^2 was applied for period of 2hrs by using platinum electrode. At different time intervals, samples were collected and the Diltiazem hydrochloride released determined by UV-Visible Spectrophotometer at 240 nm.

12. Skin irritation studies

Skin irritation studies were performed on healthy male albino rat (average weight: 170g to 190g). The dorsal surface (50cm^2) of the rat was cleaned, and the hair was removed by shaving. The skin was cleansed with rectified spirit. A representative patch (F3) was placed over the skin with the use of adhesive tape and was removed after 24 h. The skin was examined for erythema/odema (GS. Sanap et al., 2008).

Release Kinetics

In order to understand the mechanism and kinetics of drug release, the results of the *invitro* drug release study were fitted to various kinetics equations like zero order (%cumulative drug release vs. time), first order (log %cumulative drug remaining vs. time), Higuchi matrix (% cumulative drug release vs. square root of time) (Yadav KS et al., 2007). In order to define a model which will represent a better fit for the formulation, drug release data were further analyzed by Peppas equation, $Mt/M\infty = ktn$, where Mt is the amount of drug released at time t and $M\infty$ is the amount released at ∞, $Mt/M\infty$ is the fraction of drug released at time t, k is the kinetic constant and n is the diffusional exponent, a measure of the primary mechanism of drug release. r^2 values were calculated for the linear curves obtained by regression analysis of the above plots.

3. RESULTS AND DISCUSSIONS

The present work efforts have been made to develop iontophoretic transdermal delivery of diltiazem hydrochloride prepared by solvent casting method employing HPMC, SCMC; PVA used for controlled the release of drug, propylene glycol as plasticizer and distilled water as solvent.

Physicochemical compatibility of drug and polymer

The FT-IR spectral analysis of Diltiazem hydrochloride alone showed that the principle peaks were observed at wave numbers 1024.84, 1178.19, 1743.09, 1291.67, and 1606.27 cm^{-1}, confirming the purity of the drug. In the FT-IR spectra of the physical mixture of HPMC, SCMC and PVA the major peaks of Diltiazem hydrochloride were observed at wave numbers 1024.84, 1178.19, 1743.09, 1291.67, and 1606.27 cm^{-1}. However, some additional peaks were observed with the physical mixture, possibly because of the presence of polymers.

Table 2: Evaluation of formulated patches

Formulation Code	Thickness (mm)	Folding endurance	Weight variation (mg)	% Moisture absorbed	% Moisture loss	Water vapour transmission rate	Tensile strength (Kg/mm 2)	% Drug content
F_1	0.46±0.07	178±8.1	0.156± 0.005	2.27±0.10	1.46±0.03	0.0045 ± 0.0002	3.29 ± 0.045	92.35± 0.223
F_2	0.52±0.10	157±5.5	0.165±0.0 04	7.34±0.18	5.68±0.28	0.0030 ± 0.0004	3.45 ± 0.079	89.42± 0.235
F_3	0.35±0.12	200±2.6	0.152±0.0 04	1.91±0.04	1.15±0.12	0.0037 ± 0.0003	3.842± 0.125	98.38± 0.175

* All values are expressed as mean ± S.D, n= 3

Table 3: In Vitro % Drug Permeation Data for Iontophoretic Transdermal Patches of Diltiazem Hydrochloride

Time (hrs)	Cumulative Percentage of Drug Permeation							
	F1 (Passive)	F2 (Passive)	F3 (Passive)	F1 (0.5 mA/cm2)	F2 (0.5 mA/cm2)	F3 (0.4 mA/cm2)	F3 (0.5 mA/cm2)	F3 (0.6 mA/cm2)
0	0	0	0	0	0	0	0	0
0.25	3.091	1.360	4.328	5.935	5.688	5.812	6.677	8.112
0.50	6.203	3.100	6.088	9.685	9.683	7.211	9.690	11.01
0.75	8.347	4.481	7.365	12.22	11.72	9.856	12.22	15.46
1	10.75	6.118	12.23	15.51	15.51	12.27	15.02	18.03
2	13.29	12.46	16.52	21.07	18.70	18.53	21.80	23.22
4	16.59	15.51	17.49	29.98	21.30	24.09	24.17	28.07
6	19.92	18.71	21.32	33.39	24.78	28.83	29.77	31.84
8	25.00	22.17	24.67	36.58	29.89	32.73	35.28	38.11
10	27.26	24.17	28.54	43.00	35.40	37.76	39.59	42.32
12	32.01	30.26	32.44	48.10	39.71	42.71	45.04	50.63
14	37.91	31.94	38.83	51.75	44.54	48.18	50.78	56.77
16	41.87	36.85	43.66	59.50	52.62	55.91	59.76	63.44
18	45.85	39.81	47.28	63.72	63.22	62.82	67.32	71.15
20	49.85	47.11	50.92	73.90	72.16	71.14	75.54	80.39
22	55.24	51.13	57.18	81.92	76.83	79.02	85.92	88.69
24	58.69	53.18	60.64	87.76	81.90	87.07	92.16	96.68

Evaluation of prepared transdermal patches

The prepared transdermal patches were evaluated for their physicochemical characteristics such as weight variation, thickness, folding endurance, % moisture loss, % moisture absorption, water vapour transmission rate, tensile strength and drug content (Table 2). The results of all these tests were found to be satisfactory. The thickness of the transdermal patches was uniform in all formulations and they were found to be flexible and smooth. The thickness of the all film value ranged from 0.35±0.12 to 0.52±0.10. The results were found to be uniform with low SD value. The folding endurance of the all film value ranged from 157±5.5 to 200±2.6. The weight variation of the all film value ranged from 0.176±0.004 to 0.240±0.005. The results were found to be less weight variation. The percentage moisture absorption of the all film value ranged from 1.91±0.04 to 7.34±0.18. The results were found to be less moisture absorption. The percentage moisture loss of the all film value ranged from 1.15±0.12 to 5.68±0.28. The results were found to be less moisture loss. The tensile strength measures the ability of a patch to withstand rupture. The mean value was found to vary between 3.29 ± 0.045 to 3.84 ± 0.125 kg/mm2. Drug content was also found to be uniform among the all formulations and ranged from 89.42±0.23 to 98.38±0.17.

***In vitro* permeation studies**

Release studies are required for predicting the reproducibility of rate and duration of drug release. The importance of polymer dissolution on drug release from matrices has been known for ensuring the sustained release performance. *In vitro* permeation studies were carried out as a carrier on male albino rat skin in a diffusion cell. The cumulative percentage drug release was found to be 58.69 %, 53.18 %, and 60.64 % for formulation F_1, F_2, and F_3 respectively. The studies indicated that this film were permeable to drug diltiazem hydrochloride showed lesser permeable.

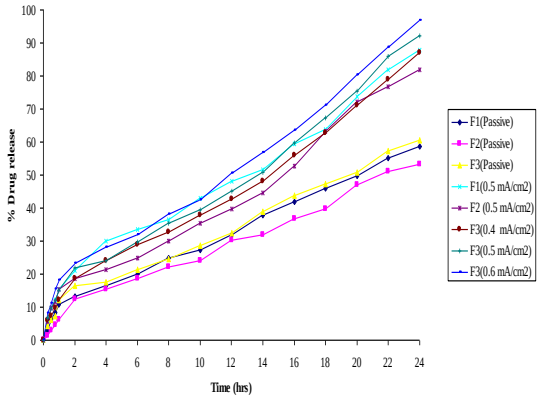

Figure 1: Comparative in vitro release profiles of diltiazem hydrochloride TDDS

***In vitro* permeation studies using Iontophoresis**

In vitro permeation studies were carried out on rat skin in a diffusion cell by using iontophoresis (0.5mA/cm^2) for 2hour with direct current. This method is further supported by the earlier work done on Enhanced Skin Permeation of diclofenac by Iontophoresis (Elizabeth Varghese, 1996). Iontophoresis of diltiazem hydrochloride Increase pore size of the skin and help in an easy permeation of drug through skin. The cumulative percentage drug permeation was found to be 87.76%,

81.90%, and 92.16 % for formulation F1, F2, and F3 respectively. Figure.1 shows the comparative *in vitro* release profiles of diltiazem hydrochloride TDDS. Table 3 shows the *in vitro* percentage drug permeation data for Iontophoretic Transdermal Patches of Diltiazem Hydrochloride.

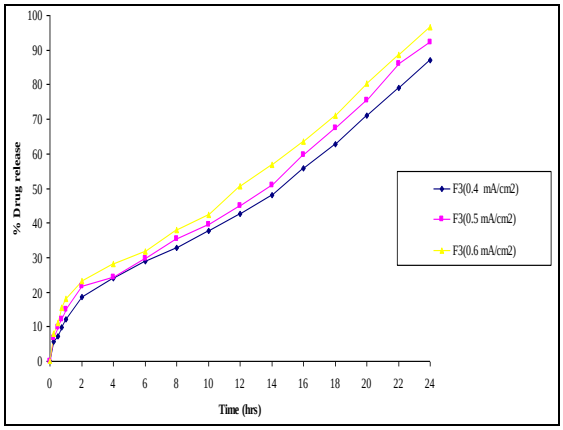

Figure 2: In vitro % drug permeation of formulation F3 by using different current density

In this respect formulation F3 showed best result among all formulation. Formulation F3 showed better rate controlling membrane as after application of current of 0.5mA/cm^2 on the transdermal patch. The formulation F3 was subjected to different current density viz 0.4mA/cm^2 and 0.6mA/cm^2. Figure.2 shows the I*n vitro* % drug permeation of formulation F3 by using different current density

Permeability gradually increased and cumulative percentage drug permeation was found to be 87.07%, 96.16% and 96.68 % respectively. The rate of drug delivery was found to be proportional to the current flowing through circuit. Previously it has been reported that the drug delivery is proportional to applied current (Vikram Kotwal, 2007).

The results of the diffusion studies indicate that the polymer concentration is having a substantial effect on the drug release from the patches. The polymer concentration increase proportional decrease drug release.

Mechanism of drug release

In order to understand the complex mechanism of drug release from the passive and iontophoretic transdermal patches, the *in vitro* Diltiazem hydrochloride release data were fitted to korsmeyer-peppa's release model and interpretation of release exponent values (n) enlightens in understanding the release mechanism from the dosage form. The release exponent values thus obtained were from 0.563 to 0.666. Based on these values we can say that the formulations F_1 to F_3 (passive and iontophoresis) exhibited (non-fickian transport) diffusion mechanism. The drug release was diffusion controlled as the plot of Higuchi's model was found to be linear (r>0.9104). While the formulations F_1 to F_3 (passive and iontophoresis) showed higher R^2 values for zero order plot indicating that drug release followed zero order kinetics.

The drug release kinetics studies showed that the majority of formulations were governed by Peppas model and mechanism of release was non-Fickian mediated. Regression analysis of the *in vitro* permeation curves was carried out. The slope of the curve obtained after plotting the mean cumulative amount released per patch versus time was taken as the *in vitro* release for diltiazem hydrochloride.

4. CONCLUSION

In conclusion, controlled release TDDS patches of Diltiazem hydrochloride can be prepared using various polymers such as HPMC, SCMC and PVA with propylene glycol as plasticizer. The results of the experimental study confirm that the results of the *in vitro* drug release study were fed in to various kinetic models to understand the possible mechanism of drug release. The formulations F_1 to F_3 (passive and iontophoresis) exhibited zero order non-fickian diffusion. In this respect formulation F_3 showed best result among all formulation. The formulation F_3 was subjected to different current density from 0.4 mA/cm^2 to 0.6 mA/cm^2 permeability gradually increases with increase in current density. The overall this study concludes that Diltiazem hydrochloride, being more hydrophilic, is more effectively transported iontophoretically under *in vitro* condition. Iontophoresis markedly improved transderamal penetration of diltiazem hydrochloride compared to passive penetration. Further, *in vivo* studies have to be performed to correlate with *in vitro* release data.

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