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IONTOPHORESIS OF FLUVASTATIN SODIUM: STUDY OF VARIOUS FACTOR AND *IN-VITRO* PERMEATION

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ABSTRACT: Fluvastatin sodium (FVS) is the first fully synthetic 3-hydroxy-3-methylglutaryl coenzyme (HMG-CoA) reductase inhibitors used for the treatment of hypercholesterolemia. It shows extensive first pass metabolism with short plasma half-life (3 hrs). The iontophoresis approach was used to determine the permeability of drug through isolated rat skin. *In-vitro* permeation of drug was determined by using glickfeld diffusion cell. Cathodal iontophoretic delivery was studied and optimized by evaluating donor compartment for the effect of pH, NaCl concentration, current density, pulsed depolarized DC current and drug concentration. Effectual permeation of FVS was obtained in phosphate buffer pH 5. Different concentration of NaCl showed negative effect on the iontophoretic permeation of drug. At higher current density, the rate of permeation was increased. Pulsed depolarized DC current showed higher flux (34.34 µg/cm^2/hr) compared to the continuous DC current (26.44 µg/cm^2/hr). With increasing concentration of drug, permeation was increased linearly. Comparison between human cadaver skin and rat skin showed that the permeation of drug was decreased from human cadaver skin (443.311±3.53 µg/cm^2) as compare to the isolated rat skin (483.841±4.68 µg/cm^2) but not showed statistically significant difference. Iontophoretic system containing 3mg/ml concentration of FVS with the area of 3.49cm^2 would be able to maintain input rate of drug for the period of 12 hrs.

INTRODUCTION: Hypercholesterolemia is one of the major risk factors for CHD. With the increase in aging populations and progressively sedentary lifestyles, the global burden of CHD is likely to increase in the future despite better preventive strategies. It is vitally important to manage hypercholesterolemia effectively because it is a modifiable risk factor.

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At present, there are several guidelines with differences in recommendations. Coronary heart disease (CHD) remains the number one cause of death for both men and women in developed countries, and the global burden of cardiovascular disease (CVD) is expected to rise. Globally, the world population is expected to rise from 5.71 billion in 1995 to 8.29 billion by 2025.

Combined with changes in the demographic profile and the increasing westernization of developing countries, this will result in large numbers of adults who are potentially vulnerable to CHD. CHD mortality has a linear relation with cholesterol. There is conclusive evidence from the literature to show that higher levels of serum

cholesterol contribute significantly to CHD and CVD. Conversely the risk of these conditions is reduced by lowering serum cholesterol. Therefore, prevention of CVD by treating hypercholesterolemia is an important step in reducing coronary morbidity and mortality [1, 2]. For the treatment of hypercholesterolemia statin drugs [3-hydroxy-3-methylglutaryl coenzyme (HMG-CoA) reductase inhibitors] are the most effective and best tolerated drugs currently in use.

Fluvastatin sodium (FVS) is the first fully synthetic HMG-CoA reductase inhibitors approved for clinical lipid lowering therapy. FVS is subjected to extensive first pass metabolism in the liver and the plasma half-life of the drug is approximately 3hrs.

The pharmacokinetics of FVS has demonstrated reductions in the rate of bioavailability from 40% to 60%. The physicochemical characteristics of drug like molecular mass (411.46 g/mol), log $P_{o/w}$ (3.24) & pKa (5.5) favors to mold it in iontophoretic type drug delivery system [3].

Iontophoresis implies the use of small amounts of physiologically acceptable electric current to drive ionic (charged) drugs into the body. By using an electrode of the same polarity as the charge on the drug, the drug is driven into the skin by electrostatic repulsion. The technique has been observed to enhance the transdermal permeation of ionic drugs several fold, and this can expand the horizon of transdermal controlled drug delivery for systemic medication.

Besides the usual benefits of transdermal delivery, iontophoresis presents a unique opportunity to provide programmed drug delivery. This is because the drug is delivered in proportion to the current, which can be readily adjusted. Such dependence on current may also make drug absorption via iontophoresis less dependent on biological variables, unlike most other drug delivery systems. For delivering positively charged and negatively charged ions, two iontophoretic approaches have been developed, namely anodal and cathodal iontophoresis [4, 5].

The objective of the study was to achieve iontophoretic permeation of FVS through skin membrane and to study the factors which improve the permeation of drug.

In order to achieve desired flux of FVS following factors have been examined in this present paper:

(1) Effect of donor compartment pH

(2) Effect of NaCl

(3) Effect of current density

(4) Effect of pulsed depolarized DC current

(5) Effect of drug concentration.

MATERIALS AND METHODS: Fluvastatin Sodium (FVS) was a gift sample from Biocon Limited, India. DC power source was purchased from C-Tech, Mumbai, India (0-25 V & 0 – 10 mA with resolution of 0.01mA). Modified Glickfeld diffusion cell obtained from Sabar Scientifics, Ahmedabad, India.

Silver wire (0.5mm diameter, 99.9%) and Silver chloride 99% were obtained from Sigma Aldrich Chemical, India. All the reagent and chemicals were of HPLC grade.

EXPERIMENTAL PROCEDURE:

Preparation and evaluation of drug solution: On the basis of pH and pKa value of drug, a pH range was selected where FVS remains in ionic form in maximum extent. Drug permeation study was carried out by using Phosphate buffer of different pH to identify a suitable solvent system of donor compartment.

Subsequently, various factors which may contribute or affect enhancement of drug permeation through isolated rat skin were studied and optimized was charged for stability study. Further, all the compositions were compared with passive diffusion amount of FVS by using flux enhancement ratio.

Effect of different pH conditions: Drug composition was prepared by adding previously prepared drug solution (in deionized water) in Phosphate buffer system (pH 5, 6 & 7) and placed in donor compartment.

TABLE 1: COMPOSITION OF DONOR SOLUTION

Composition of Donor solution (100ml)					
Composition Code	**Concentration of FVS (mg)**	**pH of donor solution**	**Concentration of NaCl (M)**	**Current Density (mA/cm^2)**	**Type of current**
CNT	100	-	-	-	-
FP1	100	5	-	0.25	Continuous
FP2	100	6	-	0.25	Continuous
FP3	100	7	-	0.25	Continuous
FI1	100	5	0.025	0.25	Continuous
FI2	100	5	0.05	0.25	Continuous
FI3	100	5	0.1	0.25	Continuous
FC1	100	5	-	0.1	Continuous
FC2	100	5	-	0.25	Continuous
FC3	100	5	-	0.5	Continuous
FM1	100	5	-	0.5	Pulsed
FM2	100	5	-	0.5	Continuous
D1	100	5	-	0.5	Pulsed
D2	200	5	-	0.5	Pulsed
D3	300	5	-	0.5	Pulsed

Effect of NaCl Concentration: From the study of effect of pH, the condition which shows maximum drug permeation was used for further screening of other factor. In this section the effect of different concentration of NaCl was studied. Different concentration of NaCl (0.025 – 0.1M) was added in selected drug containing buffer system and studied for in-vitro drug permeation.

Effect of Current Density: On the basis of the effect of NaCl concentration, suitable condition was selected for further experimentation. In this section, continuous DC current density (0.1, 0.25 & 0.5mA/cm^2) was evaluated for the maximum drug permeation by iontophoresis.

Effect of Pulsed Depolarized Current: Effect of pulsed depolarized current during *in-vitro* iontophoresis was studied by using continuous DC current supply and pulsed depolarized current supply individually.

In pulsed depolarized current supply experiments, currents were kept on 10 seconds on/off mode. Current density and selected solution compositions were kept constant during this study.

Effect of drug concentration: FVS composition were prepared with 1mg/ml, 2mg/ml & 3mg/ml drug concentrations and studied for *in-vitro* drug permeation. pH condition of buffer system, concentration of NaCl, type of the current and current density factors were selected on basis of previous experiments (with FVS composition FP1 to FM2) and were kept constant.

HPLC analysis of FVS: FVS analysis was carried out using RP-HPLC technique by using gradient system HPLC (Cyberlab, USA) with a C18 column (BDS HYPERSIL®, 150x4.6mm, 5µm). The mobile phase was prepared by Methanol: Phosphate buffer pH 3: Acetonitrile at the ratio of 5:3:2v/v. The pH of mobile phase was adjusted to 3.0 with phosphoric acid (85%). Prepared mobile phase was filtered under vacuum by using Millipore membrane (0.2 µm) and degassed using Sonicator. The mobile phase was pumped at a flow rate of 1.0 ml/min through the column at ambient temperature. 20µl samples were introduced by injection in the HPLC system with 235nm as a detection wavelength. Run time was kept at 10 minutes and retention time was 6.4min [6].

***In vitro* drug permeation study & their Data Analysis:**

Preparation of rat skin: Ten to twelve week old male albino rat (250g) sacrificed by excess of ether inhalation. Skin hair was shaved with clippers and full-thickness of rat skin was surgically removed. Epidermis layer was isolated from whole skin and then carefully cleaned with normal saline. Finally fat tissue adhered to skin were removed by soaking the skin for 30 minutes in PBS buffer and dried under the vacuum. Dried epidermal layers were stored in the desiccators until further use.

Only the abdomen area was cut from it and square piece used for permeation experiment. Protocol for the use of animal for the above experiment was approved from the Institutional animal ethics committee, Noble Group of Institutions, Junagadh [7, 8].

Preparation of Human Skin: Human cadaver skin (epidermal part) from the chest, back, and abdominal regions were provided by the Parul Institute of Ayurveda (Baroda, India). The skin samples were stored at −20°C and thawed at room temperature prior to use [9].

In-vitro drug release study – Experimentation: Modified glickfeld diffusion cell was used for in-vitro iontophoresis study [10, 11, 12]. The assembly was set by using modified glickfeld diffusion cell. Now first, receptor compartment was filled with 30ml phosphate buffer pH 6.8. The excised skin samples were mounted on both donor compartments. Stratum corneum was faced upward on the donor compartment.

The drug solution of FVS was placed in Cathodal Chamber and Anodal chamber was filled with 5ml of normal saline solution. Anode and cathode wires were dipped in donor compartments by keeping 5 mm above mounted skin surface. Both electrodes were connected with power source at constant voltage and varied current density according to the need of optimization factor as described in **Table 1**.

Buffer present in receptor compartment was stirred continuously by using magnetic bead at 600 rpm. The water jacket surrounding the receiver chamber was kept at a constant temperature of 37°C±1°C. The permeation study was carried out for 12 hrs. After predetermined time period, 5ml solution was sampled from receptor compartment and substituted with fresh buffer.

The sample aliquot with drug was determined by RP-HPLC method. Triplicate observations of each sample were measured. Cumulative amount of drug permeated (µg/cm^2) through rat skin in receptor chamber was plotted as a function of time (hr).

In-vitro permeation profile of optimized composition was determined through human cadaver epidermis.

The cumulative amount of drug permeated through human skin in µg/cm^2 were plotted against time (hr) and compared against the permeation profile of optimized patch through rat skin. Data obtained from the *in-vitro* release study were fitted to different kinetic models (zero order & first order) to understand the release mechanism of selected composition.

Data Analysis: The data obtained from the in-vitro permeation study were further used for the determination of Flux (Jss), Permeability coefficient (Kp) and enhancement ratio (ER). The flux (Jss, µg/cm^2/hr) of drug was calculated from the slope of the plot of cumulative amount of drug permeated per square centimeter of skin at steady state against the time using linear regression analysis. Permeability coefficient (Kp) of prepared patch has been determined by following equation [13]:

$$Kp\ (cm/hr) = \frac{Jss}{C_d}$$

Where, Jss represents the flux of studied patch, C_d represents concentration of drug in donor compartment (µg/cm^2).

The Enhancement Ratio was determined by following equation;

Enhancement Ratio (ER) =

$$\frac{\text{Steady state of Flux by Iontophoresis}}{\text{Steady state Flux by Passive Permeation}}$$

Stability study: The Stability study was carried out according to ICH guideline at accelerated condition and flux was examined at predetermined interval. Temperature at 40°C±2°C and relative humidity at 75% ±5% RH was maintained for the period of 6 months [14].

Statistical analysis: The statistical evaluation were performed by one way analysis of variance (ANOVA) using GraphPad InStat, Version 3.01 software for the significant difference between the permeation profile of unconstrained FVS composition and the resulted *in-vitro* permeation profile after accelerated stability study. Difference were considered significant when $p<0.05$.

RESULTS AND DISCUSSION:

Effect of pH: According to Henderson-Hasselbalch equation, pH is the determining factor governing the amount of drug present in the ionized state. For optimum permeation through iontophoresis it is highly desired to have a relatively large proportion of the drug in the ionized state. The effect of pH is a critical variable in iontophoresis because it affects the skin charge and electro-osmotic flow.

Based on the pH, pKa and % ionization of FVS, the permeation profile was studied at three different pH (5, 6 & 7), by using phosphate buffer. The current density was kept constant at 0.25 mA/cm^2 and continuous current was applied. For in-vitro permeation study phosphate buffer pH 6.8 was kept as a receptor media to maintain the sink condition.

In-vitro iontophoresis results have shown that the maximum Q_{12} (cumulative amount of drug released per unit area at the end of 12hrs) was obtained at pH 5 (FP1, 233.63±5.41 µg/cm^2). Likewise, the flux (21.43 µg/cm^2/hr) & permeability coefficient (0.00429 cm/hr) were also highest at pH 5 compared to other pH (Table 2). As compared to the passive diffusion which was determined without the application of any current, iontophoresis provided 26.13 fold permeation enhancement at pH 5 (FP1).

The iontophoretic flux followed the trend of pH 7 < pH 6 < pH 5 for the *in-vitro* permeation of FVS, since the pKa value of FVS was 5.5 and the maximum change in the % of ionization of FVS was obtained at pH 5. Iontophoresis is more effective at pH values where drug is mainly ionized [15]. The pH of drug solution affects not only the ratio of ionized and non-ionized forms, but also the properties of skin surface.

Usually, the skin is having minimum charge density at a pH value of about 3 - 4, which is the isoelectric point of keratin. As the pH reaches this value, the skin becomes positively charged and it favors the transport of negatively charged species. Due to this the transdermal iontophoresis favors permeation of anionic molecules at lower pH values, which resulted in the highest permeation amount of FVS at pH 5, approximately which is the isoelectric point of the skin [16].

Effect of NaCl: The experiment was conducted by giving the continuous constant current of 0.25mA/cm^2. The pH of donor compartment was kept constant at 5. The results showed that as the concentration of NaCl increased, Jss (flux) decreased from 17.393 µg/cm^2/hr (FI1) to 11.83 µg/cm^2/hr (FI2) & 9.626 µg/cm^2/hr (FI3) (**Table 2**). Similarly permeability coefficient and enhancement ratio also decreased (Table 2).

TABLE 2: RESULT OF *IN-VITRO* SKIN PERMEATION STUDY OF ALL COMPOSITION CODE

Composition of Donor solution (100ml)					
Composition Code	**Concentration of FVS (mg)**	**pH of donor solution**	**Concentration of NaCl (M)**	**Current Density (mA/cm^2)**	**Type of current**
CNT	100	-	-	-	-
FP1	100	5	-	0.25	Continuous
FP2	100	6	-	0.25	Continuous
FP3	100	7	-	0.25	Continuous
FI1	100	5	0.025	0.25	Continuous
FI2	100	5	0.05	0.25	Continuous
FI3	100	5	0.1	0.25	Continuous
FC1	100	5	-	0.1	Continuous
FC2	100	5	-	0.25	Continuous
FC3	100	5	-	0.5	Continuous
FM1	100	5	-	0.5	Pulsed
FM2	100	5	-	0.5	Continuous
D1	100	5	-	0.5	Pulsed
D2	200	5	-	0.5	Pulsed
D3	300	5	-	0.5	Pulsed

*Cumulative amount of drug released per unit area at the end of 12hrs

The flux of Composition Code FI1 (17.393 µg/cm^2/hr) also decreased as compared to the flux of Composition Code FP1. The effect of concentration of NaCl on FVS permeation followed the trend of 0.0>0.025>0.05>0.1 M NaCl.

The presence of ion with the similar charge as the drug, which is known as co-ion results in competition between the drug and the co-ion. It might have reduced the fraction of the current carried by the drug and have shown a reduction in the transdermal iontophoretic flux of the drug [17]. The electrochemical decomposition of water with the production of H^+ ions at the anode and OH^- ions at the cathode is a common phenomenon when utilizing silver wires as the electrodes [18]. Such a reaction causes the pH of the donor compartment to be increased during the cathodal iontophoresis in the present study.

So, the ionic strength should be high enough to give sufficient buffering capacity which can avoid pH drift. Salt was added to resist pH drift in donor compartment but it exhibited negative influence on Fluvastatin Sodium *in-vitro* iontophoresis. It was observed that Na^+ has a slower ionic velocity in an electrical field since sodium ions attract more water of hydration resulting in a larger hydrated diameter of sodium ions [19]. Due to this effect inter ionic interference between Fluvastatin negative ion and Na^+ increased after the addition of NaCl so that the rate of permeation of FVS was decreased.

Effect of current: The skin is known to produce a large electrical resistance to charge molecules which are driven through skin under an applied electrical potential [20]. The effect of current on the permeation of drug was determined at three different **current densities**: 0.1 mA/cm^2, 0.25 mA/cm^2 & 0.5 mA/cm^2. Here the highest current density kept at 0.5mA/cm^2, which is the safe current for cathodal iontophoresis. In the experimental study continuous current was applied and the donor solution was kept at constant pH 5.

The resulted data showed that as the current density increased, Q_{12} increased from 235.69±2.44 µg/cm^2 (FC2, 0.25 mA/cm^2) to 287.66±3.72 µg/cm^2 (FC3, 0.5 mA/cm^2) (Table 2). Similarly, the flux (Jss) and permeability coefficient (Kp) was also increased as the current density increased (Table 2).

The Composition code FC3 showed the enhancement ratio of 32.18 as compared to the control permeation of FVS.

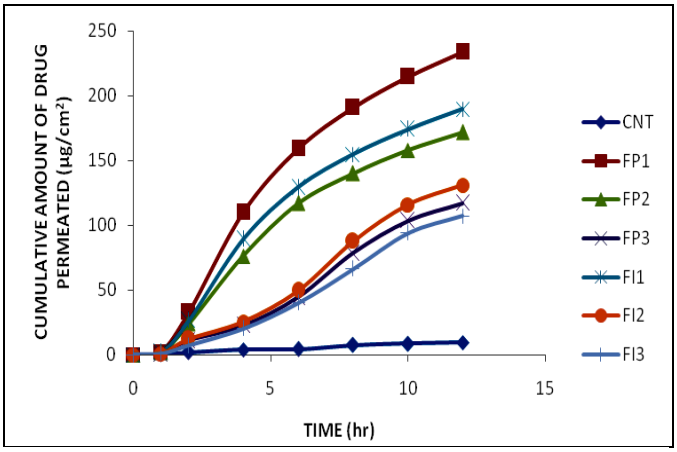

FIGURE 2: GRAPHICAL REPRESENTATION OF *IN-VITRO* PERMEATION PROFILES OF COMPOSITION CODE CNT, FP1 TO FP3 & FI1 TO FI3

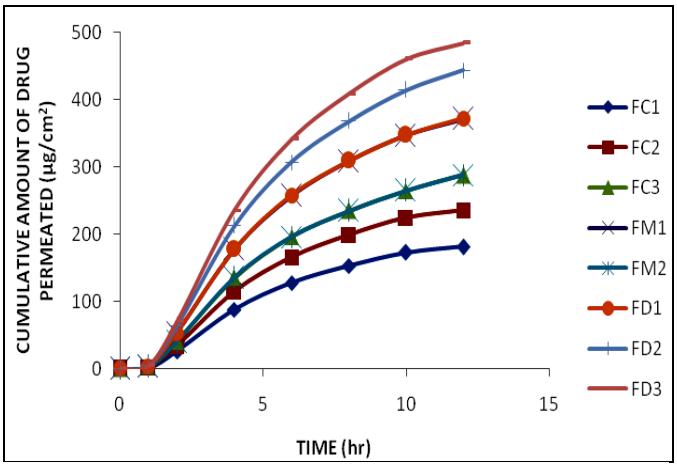

FIGURE 2: GRAPHICAL REPRESENTATION OF *IN-VITRO* PERMEATION PROFILES OF COMPOSITION CODE FC1 TO FC3, FM1, FM2 & FD1 TO FD3

Effect of pulsed depolarized DC current: To induce the penetration of ionic molecules in to the skin, an electrical field with DC mode is used but it may show electrochemical polarization of the skin. Such a polarization works against the applied electrical field and greatly reduces the magnitude of the input current. Therefore, the effective current declines across the skin when a constant DC voltage is applied [21].

The pulse DC mode is a DC voltage which periodically alternates with the "on" and "off" of the applied voltage. In the state of "on", charged ionized drug molecules are forced into skin and due to that stratum corneum become polarized.

On the opposite side, in the state of "off", no external current or any stimulation is present and due to that stratum corneum become depolarized. The number of on/off cycles is controlled by the frequency of time of interval chosen. Over here on/off ratio was kept at 10 sec interval. The experiment was conducted at constant pH 5 and current density kept at 0.5 mA/cm^2. The result showed that in the pulsed depolarized DC type of current, Q_{12} increased from 288.24±2.86 µg/cm^2 (FM2, Constant current) to 371.51±2.89 µg/cm^2 (FM1, Pulsed current). Likewise, flux and permeability coefficient also increased from 26.44 µg/cm^2/hr (FM2) to 34.34 µg/cm^2/hr (FM1) and from 0.00529 cm/hr (FM2) to 0.00687 cm/hr (FM1). The enhancement ratio of Composition code FM1 was found to be 41.87 as compared to control diffusion.

Effect of Drug Concentration: Increased uptake by the skin during and after iontophoresis with an increase in drug concentration has been reported by some researcher [17]. However, this is based on the assumption that the drug concentration in the donor compartment is equivalent to the drug concentration present in the aqueous transport pathways within the membrane. The rate of permeation of ionized drug increases until a plateau level is reached at which no further increase in the rate of permeation is observed.

So to determine the effect of drug concentration on iontophoretic permeation three different concentrations 1 mg/ml (FD1), 2 mg/ml (FD2) & 3 mg/ml (FD3) was studied. Experiment was carried out at pulsed current of 0.5 mA/cm^2 with 10 sec on/off interval and the donor compartment was kept at pH 5.

The result showed that as the drug concentration increased from Composition Code FD1 to FD3, Q_{12} increased from 372.25±3.08 µg/cm^2 (FD1) to 443.77±3.82 µg/cm^2 (FD2) & 483.84±4.68 µg/cm^2 (FD3). The flux also increased from 34.4 µg/cm^2/hr (FD1) to 41.01 µg/cm^2/hr (FD2) & 45.12 µg/cm^2/hr (FD3). But the permeability coefficient of ionized drug decreased from 0.00688 cm/hr (FD1) to 0.00410 cm/hr (FD2) & 0.00301 cm/hr (FD3) might be due to the higher concentration of drug in the donor compartment which showed the saturation of the permeation site of stratum corneum.

The highest permeation was shown by composition code FD3, which showed the enhancement ratio of 55.02 as compared to the passive or control permeation of FVS. First order release kinetic (R^2 = 0.9516) was found to be predominant over zero order (R^2 = 0.9301) for iontophoresis of FVS by composition FD3.

The comparison of enhancement ratio (**Figure 3**) showed that highest enhancement was shown by formulation code FD3 which was obtained at 3mg/ml concentration of drug containing pH 5 in the donor compartment with the applied pulsed depolarized current of 0.5mA/cm^2 at 10 sec on/off interval so that as compared to other preparation, the Formulation Code FD3 could be considered as optimized formulation.

The cumulative *in-vitro* permeation of optimized composition FD3 was determined by using human cadaver epidermis showed the release of 443.311±3.53µg/cm^2 at the end of 12 hrs. Likewise, permeability coefficient and enhancement ratio were also decreased but they were non-significant (**Table 3**). This decreased situation of permeation might be due to the presence of less hair follicle on human cadaver skin as compared to rat skin. Higher number of hair follicles on rat skin facilitated the pore formation by iontophoresis and because of that drug permeation was more. This composition FD3 was charged for the determination of stability study at accelerated condition.

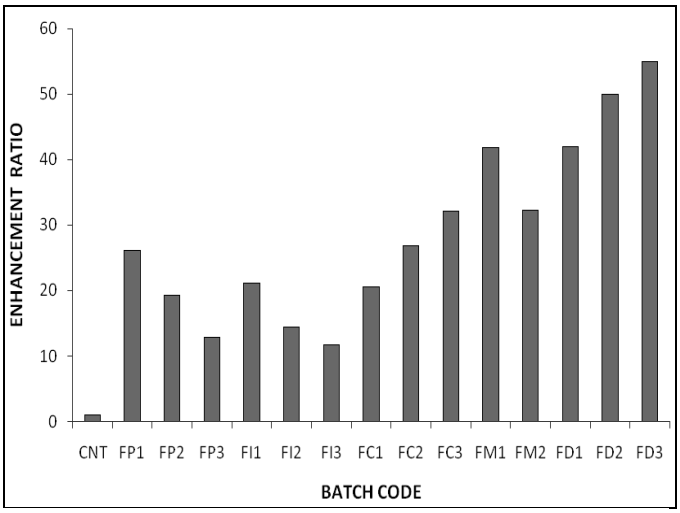

FIGURE 3: COMPARISON OF ENHANCEMENT RATIO OF ALL COMPOSITION STUDIED FOR THE IONTOPHORESIS OF FVS

TABLE 3: COMPARISON OF IN-VITRO PERMEATION PROFILE OF OPTIMIZED COMPOSITION OF FVS THROUGH HUMAN CADAVER SKIN AGAINST THE PERMEATION PROFILE THROUGH RAT SKIN

Partitioning Membrane for *in-vitro* permeation study	*Q_{12} (µg/cm^2)	Jss (µg/cm^2/hr)	Kp (cm/hr)	ER
RAT SKIN	483.841±4.68	45.12	0.00301	55.0
HUMAN SKIN	443.311±3.53	41.34	0.00276	50.4

*cumulative amount of drug released per unit area at the end of 12hrs

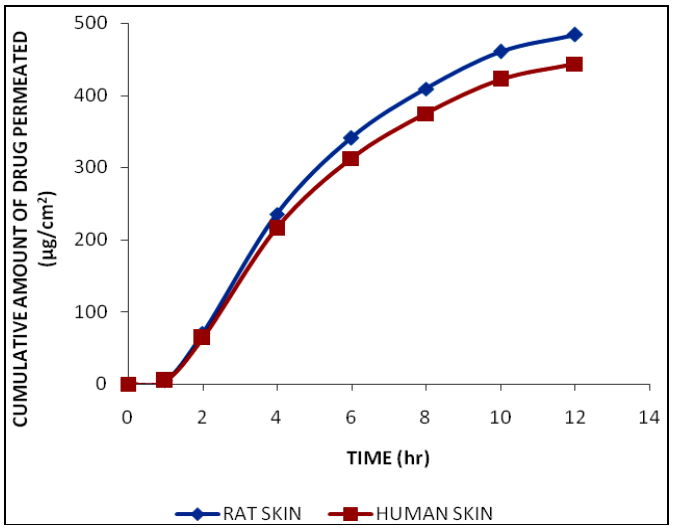

FIGURE 4: GRAPHICAL REPRESENTATION OF COMPARISON OF IN-VITRO PERMEATION PROFILE FOR IONTOPHORESIS OF FVS THROUGH RAT SKIN AND HUMAN CADAVER SKIN

Stability study: Stability study for the Composition code FD3 showed that the at the end of 180days flux was decreased from 45.12±0.27 µg/cm^2/hr to 43.93±0.47 µg/cm^2/hr. In-vitro permeation profile of accelerated conditioned donor solution at the end of 180 days was compared against the in-vitro permeation profile of unconstrained donor solution by ANOVA showed no significant difference in their release pattern ($p>0.05$considered not significant). Result of stability study showed good stability of donor solution at the temperature 40^{o}C ± 2^{o}C, so that it can be stored at this temperature or at Room temperature.

CONCLUSION: Iontophoretic delivery of Fluvastatin Sodium (first fully synthetic HMG-CoA reductase inhibitors) is possible by using 0.5 mA/cm^2 pulsed depolarized DC current. Phosphate buffer with pH 5 was found to be optimum conditions for saline buffer composition containing 3 mg/ml concentration of drug in donor compartment. Iontophoretic system of optimized composition provides its possibility to formulate in the area of 3.49 cm^2 to attain and maintain input rate of Fluvastatin sodium over a period of 12 hrs.

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