Formulation and Evaluation of Iontophoretic Delivery of Tanpentadol Pluronic Gel.

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Abstract:
The Intension of this research was to discover the passive and electrically triggered transdermal transport of Tapentadol hydrochloride (TPH) by iontophoresis. For better bioavailability, better patient compliance, enhanced delivery of TPH, an iontophoretic drug delivery system of a thermosensitive TPH gel was formulated using Lutrol F-127 Gel. The study was carried out by the help of silvers-silver chloride electrodes through hairless pig skin. The effects of polymer concentration, pH, electrode design, and pulse rate on the TPH permeation were explored. The relationship between temperature, viscosity, and conductance of TPH was correlated using conductometry. Iontophoretic transportation of TPH was found to be increasing with a decreasing 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 TPH skin permeation as compared with the passive controls.
KEYWORDS: Tapentadol Hydrochloride, Thermosensitive Gels, Conductance, Viscosity, Permeation, Pulsed current.

Introduction:

Iontophoresis may be defined as the facilitation of ionizable drug permeation across the skin by an applied electrical potential, the driving force of which may be simply visualized as electrostatic repulsion[1]. A typical iontophoresis device consists of a battery, microprocessor controller, drug reservoir and electrodes.The technique involves the application of a small electric current (usually 0.5 mA/cm^2) to a drug reservoir on the skin, with the similarly charged electrodes (on the surface of the skin) placed together in the drug reservoir producing a repulsion effect that effectively drives the solute molecules away from the electrode and into the skin[2].

Major concerns in the fabrication of devices are the mode of current delivery and type of current used. Continuous direct current may be useful for acute conditions and pulsed current may be preferable for chronic conditions dictated by chronopharmacology of the therapeutic agent and lesser propensity in causing skin irritation. Alternating current is reported to cause fewer 'skin burns' because of the reversal of polarity, which alternately generates hydrogen and hydroxyl ions thereby neutralizing the ions generated in one cycle[3].

Tapentadol hydrochloride is an Opioid analgesic used in the treatment of moderate to severe pain,cancer pain,post-operative pain with dose of 50mg - 150mg;Tablet has to be administered every 4-6 hours.Tapentadol HCL undergoes extensive first pass metabolism (97%) through liver and therefore its bioavailability is very less(32%). To avoid first pass metabolism and increase the bioavailability[4] *Iontophoretic Transdermal Drug Delivery System* for Tapentadol HCL was selected. Iontophoretic transport is weak for dry patch/film due to lack of skin hydration and poor conductance. Therefore to enhance the drug delivery, *Gel* of Tapentadol HCL was prepared.[5]

Material and Method

Tapentadol Hydrochloride was obtained as a gift sample from MSN labs Pvt. Ltd., Hyderabad, India. Lutrol F-127obtained as a gift sample from, Lupin ltd,Aurangabad,Maharashtra. Batch No. 10468348. Benzalkonium Chloride obtained from Research Lab Fine Chem Industries, Mumbai, India. Batch No. 6591203

Standard curve of Tapentadol HCL:

Standard curve ofTapentadol HCL was determined by using PBS pH 7.4. 50 mg of Tapentadol hydrochloride was dissolved in 100 ml of PBS pH 7.4. From this stock solution serial dilutions were done to get drug concentrations in the range of 50-350µg/ml. The absorbance of the resulting solutions were measured against PBS pH 7.4 as a blank at 273 nm, using double beam UV visible spectrophotometer. The graph of absorbance v/s concentration was plotted.

Preparation of Electrodes [6,7]

Ag/AgCl electrodes were used for their stability and reversibility. They prevent electrolysis of water, which may result in pH shifts. Two types of electrodes were prepared. The rod-shaped electrode which is used as cathode was prepared by dipping the silver wire (99.9%; 1mm diameter) into the molten silver-chloride. The disc shaped electrode was prepared as follows. Silver discs of 1 mm thickness with 1cm and 2 cm diameter each were lightly sanded with emery paper, washed in acetone and then cleaned in 1 M HCl for 20 min at 50^0C. After this it was thoroughly rinsed with distilled water and used as anode.

Preparation of Skin

Density of the hair on the human skin and that of pig skin is similar[8]. Hence pig skin was chosen for the permeation studies. Pig skin of 2-3 days old pig that has been killed by carotid bleeding was obtained from a local slaughter house. Muscles, fat layer and tissue remains were removed, hair was cut short and skin pieces were examined for pin holes. The skin was then cut into appropriately sized pieces and was used within 2 hrs.

Conductivity Study to Correlate Among pH, Ionization and Conductance [9]

Prior to measurements the instrument was calibrated using 0.05% NaCl, which has a conductivity of 1 mS/cm. Various solutions of different pH containing 25mg/ml of TapentadolHCL were prepared in distilled water. The solutions prepared were filtered through 0.2µ Millipore filter and conductivity was measured using Conductometer. Triplicate determinations of the conductivity were made for each solution.

Ex-Vivo Permeation Study for Optimizing pH of Donor Medium[9,10]

The hairless pig skin was mounted on vertical diffusion cells which were maintained at 37±1°C using a hot water circulator. The skin was mounted on the diffusion cell with the stratum corneum facing the donor compartment. Tapentadol HCL in the concentration of 25mg/ml was dissolved in pre filtered buffer solutions (prepared as per USP) of pH values 4.2, 5.5, 6.4, and 7.4. 2 ml of each above prepared Tapentadol HCL solution was placed in the donor compartment. The receiver solution for permeation studies was of pH 7.4 saline phosphate buffer solution. A constant DC current of 0.5 mA was applied for iontophoresis using silver–silver chloride electrodes. They prevent electrolysis of water, which may result in pH shifts. Silver wire of 1.5 cm 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 teflon coated magnetic stirrer at 600 rpm. Passive permeation was tested without application of any current.

Preparation of Thermosensitive Gel for Optimizing The Concentration of Lutrol F-127

Solutions of the Lutrol F-127 of 18, 20 and 22% were prepared by using cold method.[10, 11, 12] Weighed amounts of Lutrol F-127 were slowly added to cold water with gentle mixing. These Lutrol F-127 solutions were then

allowed to hydrate and disperse overnight at 5^0C. The prepared gels were further subjected to viscosity determination.

Preparation of Thermosensitive Gel to Investigate Effect of pH and Tapentadol HCL on Lutrol Gel

Gel A having 20%w/v Lutrol F-127, in distilled water and Gel B having 20%w/v Lutrol F-127, in pH 4.2 phosphate buffer were formulated without incorporation of drug.

Gel C containing 25mg/ml TapentadolHCLand 20% Lutrol F-127 was prepared in pH 4.2 phosphate buffer. These Lutrol F-127 solutions were then allowed to hydrate and disperse overnight at 5^0C. The prepared gels were further subjected to viscosity determination.

Viscosity Determination:[13]

Viscosity of the gels was determined using a cone and plate viscometer. Sufficient amount of gel was placed on the sample plate of the viscometer and allowed to stand for 5 min to reach equilibrium temperature. Viscosity of gels was determined at 20, 25, 30 and 32^0C. For each measurement, readings were recorded at 10 rpm for 30 s.

Conductivity Study to Investigate Effect of Temperature and Viscosity on the Conductance of Tapentadol HCL

Lutrol gel containing 20% Lutrol F127 was prepared in prefiltered pH 4.2 phosphate buffer with and without 25mg/ml of Tapentadol HCL. Along with this conductance of plain 20% Lutrol F127 gel prepared in distilled water was also measured. Conductivity of gels was measured using Conductometer at 15, 20, 25, 30, 32 and 37^0C. Triplicate determinations of the conductivity were made for each Gel.

Preparation of Medicated Thermosensitive Gel[13,12]

Gels were prepared by cold method[14,15]. After optimization, Gel containing Tapentadol HCL and Lutrol F-127, and lecithin was prepared as follows. 25mg/ml of Tapentadol HCLand 0.02%w/v Benzalkonium Chloride was dissolved in a phosphate buffer pH 4.2 and solution was maintained at 5^0C using a freezing mixture. It was constantly stirred using a teflon coated magnetic bead. 20%w/v of Lutrol F-127 was dispersed slowly to this drug solution phosphate buffer pH 4.2 to obtain gel, and the resulting mixture was then refrigerated at 5^0C for 48 hrs to get a completely hydrated, homogeneous and clear gel.

EVALUATION OF FORMULATION

The prepared medicated thermosensitive gel was evaluated for clarity, drug content, viscosity and *ex-vivo* permeation study.

Appearance

The developed formulations were inspected visually under florescent light against white and black background for clarity of solution and gel.

Drug Content

Each formulation (2 gm) was taken in a 25 ml volumetric flask diluted with PBS pH 7.4 and shaken to dissolve the drug in PBS pH 7.4. The solution was further diluted with PBS pH 7.4 upto the mark. The content of the drug was estimated spectrophotometrically by using standard curve plotted at 273 nm.

Ex-Vivo Permeation Study Using Thermosensitive Gel [9,13,15]

The same experimental setup used for ex-vivo permeation studies for optimizing pH of donor medium was used. 2 ml of medicated thermosensitive gel was filled in the donor compartment. A constant DC current of 0.5 mA was appliedfor iontophoresis using Ag/AgCl electrodes. Silver wire of 1.5 cm was used as the anode and silver–silver chloride wire was used as the cathode. Passive permeation was tested without application of any current. Same experiment was repeated by using disc electrode of 1cm and 2cm as an anode, using 0.5 mA constant DC current and pulsed current having ON:OFF ratio of 1:1, 2:1 and 3:1.

RESULTS AND DISCUSSION

CONDUCTIVITY STUDY TO CORRELATE RELATIONSHIP BETWEEN pH, IONIZATION AND CONDUCTANCE

As defined above, Iontophoresis may be defined as the facilitated movement of ions of soluble salts across a membrane under an externally applied potential difference[16]. So the number of ionized species in the solution remains an important factor. As seen in Equation 2, ionization is a function of pH of the surrounding medium. As depicted in **Figure 1** and **Table 1**, as the pH of the drug solution decreased, ionization of the Tapentadol HCl increased. Tapentadol HCl was completely ionized at pH 4.2.

Conductance of the drug depends upon number of ionic species present in the medium. Solutions of different pH contain different buffering ions along with drug which carry charge. Therefore Equation 1 was used to know the exact conductance made by the drug alone. Therefore as seen in the **Figure 1**, conductance of the Tapentadol HCl increased as pH of the solution decreased and ionization increased.

EX-VIVO PERMEATION STUDY FOR OPTIMIZING pH OF DONOR MEDIUM

The effect of pH on iontophoretic transport of Tapentadol HCl was investigated. Iontophoresis markedly improved the transdermal permeation of Tapentadol HCl. On ionization Tapentadol HCl acquires positive charge. On iontophoresis, positive charge of anode pushes positively charged Tapentadol HCl ions into the skin due to which its transport across the skin is increased as compared to passive diffusion. As seen in the **Figure 2** and **Table 2**, as the pH of the solution is decreased the permeation of Tapentadol HCl is increased. With the pH of donor solution at 4.2, the $flux_{ss}$ was 15.40 mg/cm^2 hr while it was only 8.72 mg/cm^2 hr (ER = 1.62) when the donor pH was 7.4 (t-test, $p<0.05$).

As seen in equation 2, ionization is a function of pH of the surrounding medium. Tapentadol HCl being a very weak acid (pKa 9.60-10.28), 100% ionization at pH 4.2 was observed. Therefore increased ionization and greater repulsion resulted in increased permeation. In addition to this, it is generally accepted that the stratum corneum possesses a net negative background charge[17,18]. pH 4.2 neutralizes skin's negative charge and avoids the interruption of skin charge during iontophoretic permeation. Therefore further studies were carried out using pH 4.2 phosphate buffer medium.

OPTIMIZING THE CONCENTRATION OF LUTROL F-127

Gels are clinically acceptable delivery systems for iontophoresis in terms of stability, ease of handling and refilling of iontophoretic patches. Lutrol F-127 (Poloxamer 407) is a non-ionic block copolymer which is an intermediate between hydrophilic and hydrophobic polymers[19]. It forms a themoreversible hydrogel[20] of polyoxy(ethylene oxide)-b-poly(propylene oxide)-poly(ethylene oxide). Its three dimensional network provides sufficient rigidity while the highly hydrated microscale environment facilitates mass transfer[21]. Thermoreversible gel carries additional advantages over conventional gels. Lutrol F-127 was selected as it forms a thermoreversible gel at the optimized iontophoretic conditions with acceptable viscosity and release characteristics[22,23].

Concentration of Lutrol F-127 in the gel was optimized to maintain it in liquid state so that it can be poured into the electrode cavity. On application of this electrode to skin, the polymeric solution must immediately gel in order to avoid any spillage. The viscosity of the polymeric solutions containing 18, 20 and 22%w/v of Lutrol F-127 in phosphate buffer pH 4.2 was determined at different temperature to assess their gelling characteristics. **Table 3 and Figure 3** demonstrates that increase in concentration of Lutrol increases the gelling property of the gel at lower temperature. Polymeric solution containing 22%w/v of Lutrol gelled at 25^0C with a high viscosity. Solution containing 18%w/v of Lutrol remained in a liquid state at 25^0C and gelled at 30-32^0C with a very low viscosity that indicates poor gelling. At 20%w/v of Lutrol concentration, the gelling property of the gel gradually increased as the temperature increased with a good viscosity of 18.437 Pascal at 32^0C. Thus concentration of Lutrol which is optimized to have a gel having sufficient viscosity that would hold the formulation in the electrode cavity on its application to the skin. In order to determine effect of lecithin on viscosity, gel containing lecithin was prepared using optimized concentration of Lutrol (20%).

EFFECT OF pH AND TAPENTADOL HCl ON LUTROL GEL

Viscosity of gel A, B ,C and D was determined to investigate the influence of pH and the drug Tapentadol HCl on the gelling property and viscosity of gel. **Table 4** indicates that gel B exhibits no significant effect of pH on the viscosity (*t* test, P>0.05) but after addition of Tapentadol HCl in the gel, there was a fall in viscosity (3.237 P) at 25^0C as the polymeric solution did not form a gel. As temperature increased to 30^0C, there was spontaneous gelling indicated by sudden increase in the viscosity (16.250 P). At 32^0C polymeric solution showed good gelling with a viscosity of 17.500 Pascal. The gel formation is a result of micellar entanglement and packing with an outer aqueous environment (hydrated PEO chains) and inner hydrophobic core (PPO chains); making it suitable for the delivery of both hydrophilic and hydrophobic drugs[24]. In gel C at 25^0C, possibly due to presence of hydrophilic Tapentadol HCL, Lutrol might be unable to form micellar entanglement (formation of PEO chains) resulting into non-gelling and low viscosity. Therefore presence of Tapentadol HCl in the gel further enhances the flow property of the polymeric solution as it remains in the liquid state at room temperature. Further studies were carried out using 20% w/v Lutrol F-127 gel. Addition of lecithin (D) significantly increased viscosity of gel and highest viscosity was found at 32^0C.

CONDUCTIVITY STUDY TO INVESTIGATE EFFECT OF TEMPERATURE AND VISCOSITY ON THE CONDUCTANCE OF TAPENTADOL HCl

As reported in many studies[25, 26], amongst different factors influencing iontophoretic drug delivery system, one of the prime factor is the charge carried by the co-ions. The extraneous species present in the medium compete with the drug for carrying the current. Due to this less charge is available for drug, resulting into decreased iontophoretic transport. Also several studies[27,28] have reported that an increase in the viscosity results in a decrease in the formulation conductivity. Therefore to investigate the influence of Lutrol and the viscosity of gel on the charge carrying capacity of Tapentadol HCl, conductance study was carried out. **Table 5** depicts that, Tapentadol HCl in gel showed 10 fold greater conductance as compared to plain Lutrol gel and lutrol gel containing lecithin (t-test, p<0.05). This difference indicates that charge carried by extraneous ions is very minor and will not significantly influence the iontophoretic transport of Tapentadol HCl. Also, conductance gradually increased with the increase in the temperature/viscosity of the gel. This is possibly because, as temperature increases, the free energy of the Tapentadol HCl ions increases leading to increased mobility and ultimately the conductance. This indicates that viscosity of the 20% Lutrol gel does not interfere with the mobility of ionized Tapentadol HCl which carry charge.

Since the gel containing 20%w/v Lutrol F-127 showed good gelling property, viscosity and conductance it was considered as optimum for iontophoretic drug delivery and further ex-vivo permeation studies were carried out on the same.

EVALUATION OF FORMULATIONS

EX-VIVO PERMEATION STUDY USING THERMOSENSITIVE GEL

Passive permeation profile of Tapentadol HCl gel in **Table 6** shows significant decrease (t-test, $p<0.01$) in the permeation rate of Tapentadol HCl as compared to passive permeation of Tapentadol HCl from the solution of pH 4.2. This indicates that although the viscosity of the gel does not influence the conductance of Tapentadol HCl, it significantly decreases the permeation rate of Tapentadol HCl. Therefore Tapentadol HCl diffusion through the thermoreversible matrix may be a rate determining step. On iontophoresis, permeation rate of Tapentadol HCl from the gel was significantly increased with a flux of 8.96 mg/cm^2 h. To further increase the permeation rate, permeability study was carried out using 1 cm and 2 cm disk electrode, since surface area and permeation rate are directly proportional. As seen in the figure 15, permeation rate was markedly enhanced by disk electrodes as compared to wire electrodes (t-test, $p<0.01$). Approximately 100% of Tapentadol HCl was permeated within 10, 7 and 6 hrs using wire electrode, 1 cm and 2 cm disk electrodes respectively. Maximum flux$_{ss}$ of 11.44mg/cm^2 hr was seen when 2 cm disk electrode was used. ER of 1.46 was observed between flux$_{ss}$ of 2 cm disk electrode and passive permeation while ER of 1.40 was observed between 2 cm disk electrode and wire electrode. Instant electronic repulsion and enhanced iontophoretic transport is observed at the disk electrode due to increased surface area. Permeation profile of passive permeation at pH 7.4 in Figure 11 reflects a lag time of 1 hr which has been gradually decreased with the decrease in pH. The initial slope of the permeation curve was markedly enhanced using disk electrodes as well. Therefore to have an immediate pharmacological effect, disk electrode will provide maximum initial flux$_{ss}$ as compared to wire electrode.

EFFECT OF PULSED CURRENT ON EX-VIVO PERMEATION STUDIES

Use of continuous direct current may result in skin polarization which can reduce the efficiency of iontophoretic delivery proportional to the length of direct current application[28]. The build up of this polarizable current can be overcome by using pulsed direct current which is delivered periodically[29]. Therefore to further increase the permeation rate and the flux of Tapentadol HCl across the skin, pulsed iontophoresis using disk electrodes was carried out. As seen in **Table 7**, permeation profile of Tapentadol HCl at pulsed iontophoresis of ON:OFF pulse ratio 2:1 and 3:1 was similar to that of the continuous current (t-test, $p>0.05$). Using pulse current rate 1:1, However, the permeation rate was significantly increased at the pulse rate 1:1 having flux of 13.66 mg/cm^2 hr and ER of 1.18 as compared to continuous current (t-test, $p<0.05$). The use of pulse current allows the skin to depolarize and return to its initial electric condition when current phase is put off for a fraction of time.

Table 1. Conductivity Study to Correlate Relationship between pH, Ionization and Conductance

Sr. no	Buffer pH	Conductance (mMhos)*	% Tapentadol HCl Ionized
1	7.4	4.28±0.01	98.09
2	6.4	4.64±0.01	99.85
3	5.5	5.07±0.01	99.95
4	4.5	5.15±0.01	99.98
5	4.2	5.19±0.005	100.00

* indicates n=3, SD ≤ 0.2

Table 2. Ex-vivo Permeation Study for Optimizing pH of Donor Medium

Time (Hrs)	Percentage Cumulative Amount of Tapentadol HCl Permeated* (%)				
	pH 7.4 PP	pH 7.4 IP	pH 6.4 IP	pH 5.5 IP	pH 4.2 IP
0	0.000	0.000	0.000	0.000	0.000
1	1.018±2.25	4.794±2.23	6.435±2.13	7.349±2.36	9.118±1.22
2	4.086±2.78	12.457±2.36	15.158±2.12	17.378±2.45	22.928±1.42
3	7.283±2.36	20.922±2.31	24.505±2.21	25.639±2.61	38.377±1.2
4	16.675±2.36	34.335±2.69	38.936±2.59	51.902±2.78	65.293±3.00
5	27.899±2.45	47.877±2.69	52.023±2.69	92.553±2.56	96.426±3.10
6	35.194±2.63	69.084±2.63	76.803±2.63	93.170±2.30	93.162±3.12
7	46.498±2.56	93.420±2.78	95.027±2.36	92.350±3.1	94.435±2.24
8	72.263±2.36	90.564±2.78	93.622±2.23	91.353±2.56	93.360±2.69
9	88.748±2.34	91.524±2.66	94.200±2.17	92.572±2.36	92.682±2.59
10	97.503±2.77	90.780±2.44	92.738±2.69	92.330±2.58	92.901±2.78
11	96.174±2.16	-	-	-	-

* indicates n=3, SD ≤ 3

Table 3. Viscosity Determination for Optimizing the Concentration of Lutrol F-127.

Temperature (^{0}C)	Viscosity (Pascal)*		
	18% L	20% L	22% L
20	2.27±0.47	2.27±0.51	4.689±0.51
25	2.755±0.48	9.375±0.45	17.59±0.49
30	9.980±0.41	15.50±0.60	19.5±0.52
32	10.755±0.46	18.437±0.77	20.805±0.67

* indicates n=3, SD ≤ 1.0

Table 4. Effect of pH and Tapentadol HCl on Viscosity of 20%w/v Lutrol Gel and Pluronic Lecithin Gel.

Temperature (^{0}C)	Viscosity (Pascal)*		
	A	B	C
20	3.250±0.59	2.382±0.50	2.450±0.43
25	9.482±0.56	9.375±0.63	3.237±0.62
30	14.480±0.63	15.750±0.51	16.250±0.60
32	17.020±0.63	16.837±0.57	17.500±0.51

Where, A = Gel prepared in distilled water, B= Gel prepared in PBS pH 4.2, C = B gel containing Tapentadol HCL. * indicates n=3, SD ≤ 1.0

Table 5. Conductivity Study to Investigate Effect of Temperature and Viscosity on the Conductance of Tapentadol HCl

Temperature (^{0}C)	Conductance (mMhos)	
	A*	B†
15	2.580±0.1	0.170±0.01
20	2.850±0.07	0.195±0.008
25	3.100±0.11	0.285±0.03
30	3.495±0.004	0.349±0.007
32	3.580±0.02	0.364±0.012
37	4.189±0.015	0.399±0.006

Where, A = Conductance of Tapentadol HCl in Medicated Thermosensitive gel, B = Conductance of 20%w/v Lutrol gel prepared in distilled water. n= 3; *SD ≤ 0.2 and †SD ≤ 0.02

Table 6. Ex-vivo Permeation Study of Medicated Thermosensitive Gel

Time (Hrs)	Percentage Cumulative Amount of Tapentadol HCl Permeated*				
	Lutrol gel				
	Sol PP	Gel PP	Gel 1.5cm wire IP	Gel 1cm disc IP	Gel 2cm disc IP
0	0.000	0.000	0.000	0.000	0.000
1	1.865±2.55	0.926±0.62	1.973±0.73	2.147±1.79	8.785±1.42
2	8.820±1.57	2.100±0.77	3.250±1.56	13.312±1.79	22.460±1.42
3	12.510±2.91	4.988±1.77	7.675±2.05	22.800±1.6	34.625±2.73
4	31.500±2.28	11.548±2.25	18.718±2.55	45.420±2.33	55.402±2.27
5	41.689±2.44	22.475±2.2	24.286±2.26	63.853±1.38	81.812±2.48
6	60.789±2.22	32.315±2.48	35.557±1.53	86.493±1.24	93.628±1.49
7	86.950±2.1	41.558±2.88	51.670±2.66	96.454±1.6	94.951±1.39
8	92.420±1.91	65.779±2.33	72.526±2.9	91.596±1.22	91.252±1.15
9	90.580±2.1	81.767±1.11	85.921±2.9	92.848±1.45	92.162±1.16
10	86.930±2.12	84.556±1.92	94.228±2.48	91.252±1.02	91.766±2.6

* indicates n=3, SD ≤ 3

Table 7. Effect of Pulsed Current on Ex-vivo Permeation

Time (hrs)	Percentage Cumulative Amount of Tapentadol HCl Permeated*			
	Lutrol gel			
	Continuous (Current)	On:Off ratio of Pulsed Current		
		1:1	2:1	3:1
0	0.000	0.000	0.000	0.000
1	9.710±2.04	16.220±1.74	11.938±2.31	10.856±2.87
2	20.869±2.74	25.422±1.16	23.112±1.73	21.957±2.31
3	35.240±2.88	47.754±1.72	41.230±2.88	39.524±2.89
4	57.419±2.88	67.189±3.4	61.821±2.88	60.230±2.88
5	81.212±2.89	96.038±2.3	80.744±2.31	81.277±2.89
6	95.628±2.88	94.814±2.33	96.577±2.29	94.649±2.30
7	94.955±2.30	95.610±1.73	94.454±1.74	93.329±2.30
8	93.257±2.29	93.749±1.73	92.372±1.74	92.561±2.30
9	92.834±1.45	94.289±1.92	93.186±1.92	93.649±2.89
10	92.506±2.03	93.707±2.35	93.158±1.46	93.770±1.72

* indicates n=3, SD ≤ 3

Figure 1. Conductivity study to correlate relationship between pH, ionization and conductance. Conductance data represents n=3, mean ± S.D.

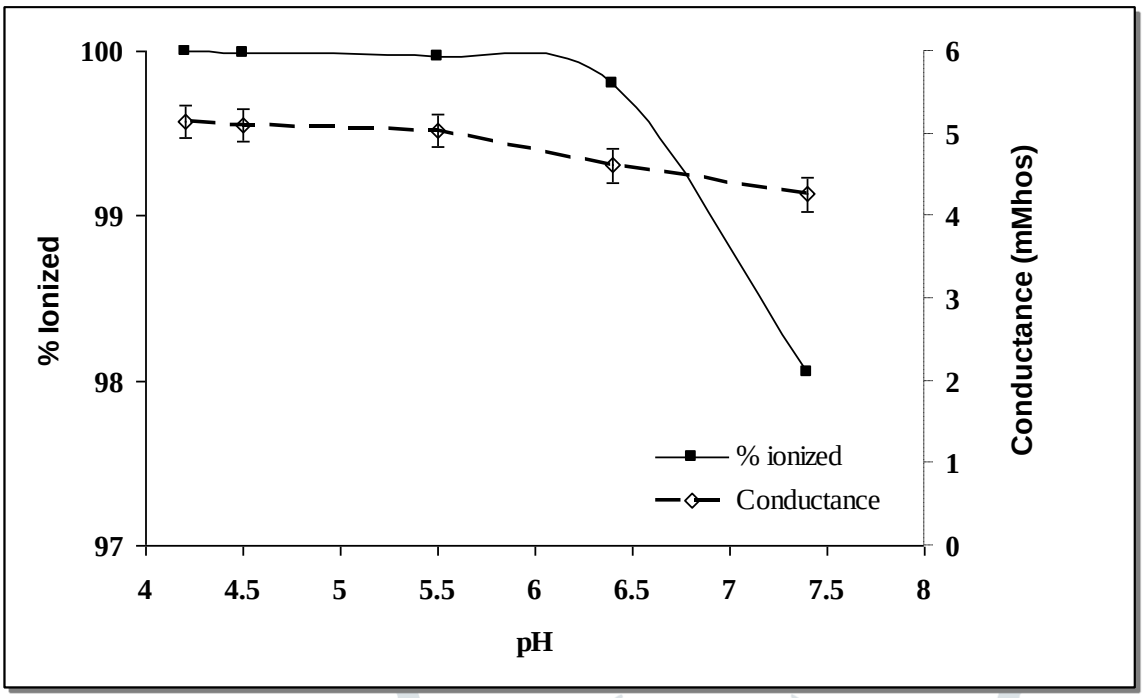


Figure 2. Effect of pH on the iontophoretic permeability of Tapentadol HCL. Where PP = Passive permeation, IP = Iontophoretic permeation. Data represents n=3, mean ± S.D.

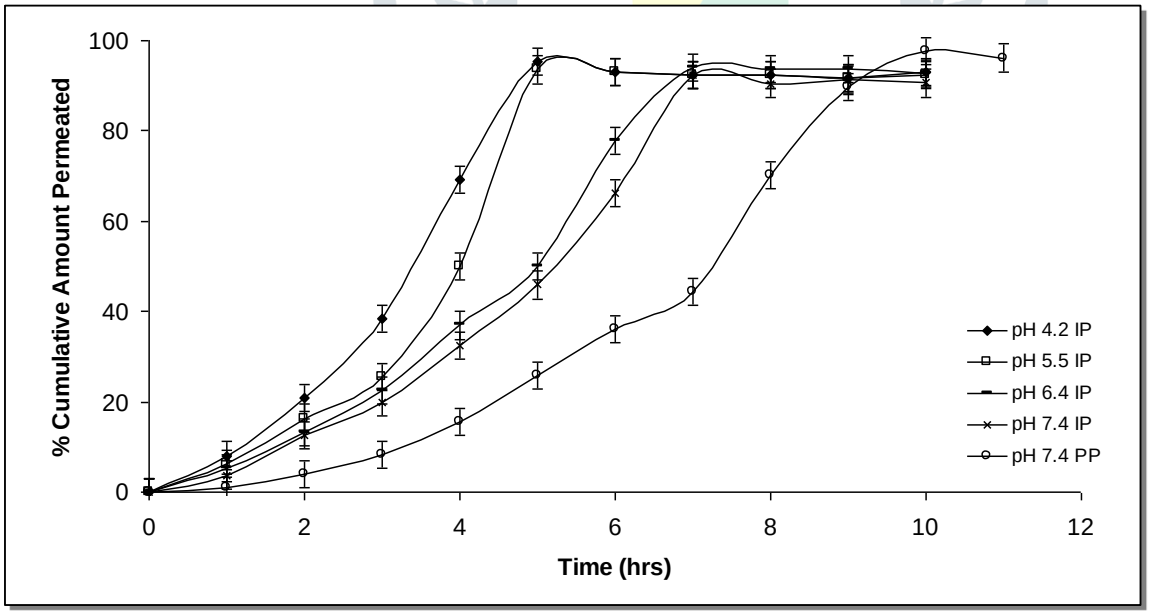
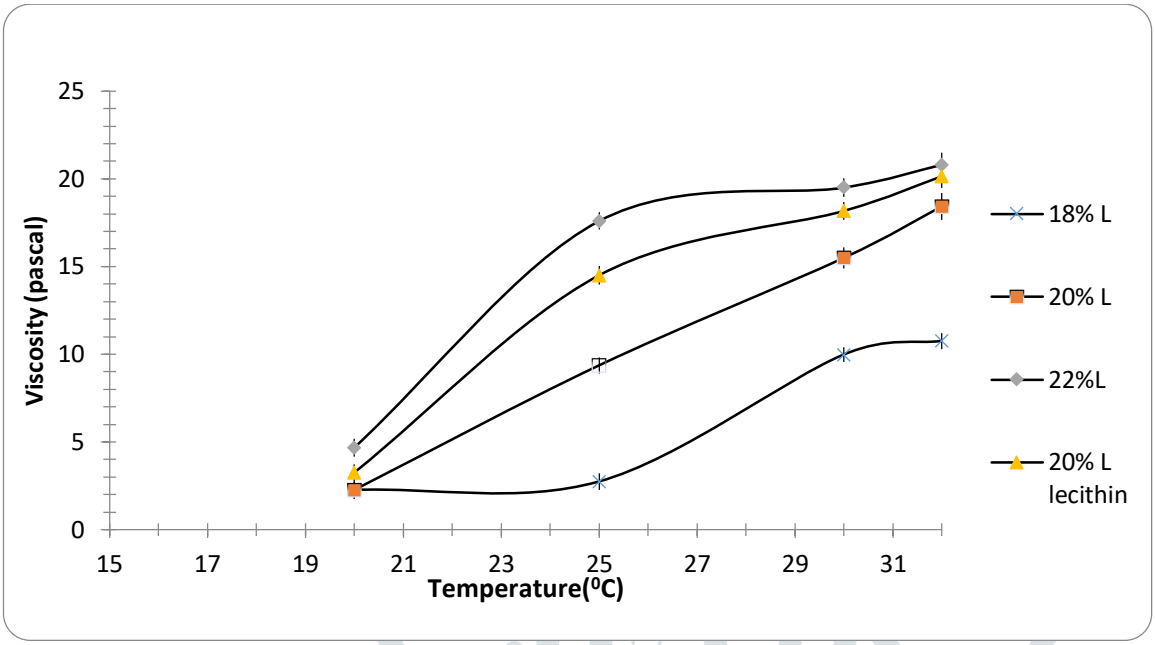


Figure 3. Effect of Polymer concentration on the viscosity of the gel.
Data represents n=3, mean ± S.D.



References

1. Vyas SP, and Khar RK. *Contolled drug delivery-Concepts and advances*, ed 1,Vallabh prakashan Delhi, India, 2005; 411-25.
2. Roberts MS, Lai PM, Cross SE, Yoshida NH. *Mechanism of transdermal drug delivery*. Marcel Dekker, Newyork, 1997; 291-49.
3. Howard JP, Drake TR, Kellogg DL: Effect of alternating current iontophoresis on drug delivery. *Arch Phy Med Rehabil.* 1995, 76:463.
4. Naresh C, Shahid Mohammad S,Niranjan Babu M. Formulation and Evaluation of Tapentadol Immidiate Release Tablets. *International research journal of pharmacy*.2013;4(1),4-10.
5. Nadkarni S S,Abraham J,Khatri K,Mittal V. Pharmaceutical Invention of Tapentadol.World Intellectual patent office .WIPO,W02013011477(A1),2013
6. Doliwa A, Santoyo S, Ygartua P. Effect of passive and iontophoretic skin pretreatments with terpenes on the in vitro skin transport of piroxicam. *Int J Pharm*. 2001;229:37–44.
7. Oh SY, Jeong SY, Park TG, Lee JH. Enhanced transdermal delivery of AZT (Zidovudine) using iontophoresis and penetration enhancer. *J Control Release*.1998;51:161–168.
8. https://pubchem.ncbi.nlm.nih.gov/compound/57369748.
9. Singh P, Boniello S, Liu P, Dinh S. Transdermal iontophoretic delivery of methylphenidate HCl in vitro: *Int J Pharm*. 1999;178:121–128.
10. Schmolka IR. Artificial skin. I. Preparation and properties of pluronic F-127 gels for treatment of burns. *J Biomed Mater Res.* 1972;6:571–582.
11. Lutrol F 127, Technical information, BASF, Germany; 1999.
12. Vinod Nair, Ramesh Panchagnula. Poloxamer gel as vehicle for transdermal iontophoretic delivery of arginine vasopressin: evaluation of in vivo performance in rats. *Pharmacological Research* 47 (2003) 555–562.

13. Fang JY, Huang YB, Lin HH, Tsai YH. Transdermal iontophoresis of sodium nonivamide acetate. IV. Effect of polymer formulations. *Int J Pharm*. 1998;173:127–140.
14. Banga AK. *Electrically assisted transdermal and topical drug delivery*. London, PA:Taylor and Francis; 1998.
15. Fang JY, Huang YB, Wu PC, Tsai YH. Transdermal iontophoresis of sodium nonivamide acetate. II. Optimization and evaluation on solutions and gels. *Int J Pharm*. 1996c;145:175–186.
16. Banga AK. *Electrically assisted transdermal and topical drug delivery*. London, PA:Taylor and Francis; 1998.
17. Aguilella V, Belaya M, Levadny V. Passive Transport of Small Ions Through Human Stratum Corneum. *J Control Release*.1997;44:11–18.
18. DeNuzzio J, Dberner B. Electrochemical and Iontophoretic Studies of Human Skin. *J Control Release*.1990;11:105–112.
19. Wu HLS, Miller SC. In vitro release of nicotinic acid alkyl esters from poloxamer vehicles, *Int J Pharm*. 1990;66:213–221.
20. Anderson BC, Pandit NK, Mallapragada SK. Understanding drug release from poly(ethylene oxide)-b-poly-(propylene oxide)-b-poly(ethylene oxide) gels, *J Control Release*. 2001;70:157–167.
21. Zhang I, Schung KK, Edwards DA. Hydrogels with enhanced mass transfer for transdermal drug delivery, *J Pharm Sci*. 1996;85:1312–1316.
22. Chen-Chow P, Frank SG. In vitro release of lidocaine from pluronic F-127 gels. *Int J Pharm*. 1981;8:89–100.
23. Miyozaki S, Takeuchi S, Yokouchi C, Takada M. Pluronic F-127 gels as a vehicle for topical administration of anticancer agents. *Chem Pharm Bull*. 1984;32:4205–208.
24. Moore T, Croy S, Mallapragada SK, Pandit NK. Experimental investigation and mathematical modeling of pluorinc F127 gel dissolution: drug release in stirred systems, *J Control Release*. 2000;67:191–202.
25. Banga AK, Chien YW. Iontophoretic delivery of drugs: fundamentals developments and biomedical applications. *J Control Release*.1988; 7:1–24.
26. Singh P, Maibach HI. Iontophoresis: an alternative to the use of carriers in cutaneous drug delivery. *Adv Drug Del Rev*. 1996;18:379-394.
27. Ho HO, Huang FC, Sokoloski TD, Sheu MT. The influence of cosolvents on the in-vitro percutaneous penetration of diclofenac sodium from a gel system. *J Pharm Pharmacol* 1994;46: 636–642.
28. Lawler JC. Davis MJ, Griffith E. Electrical characteristics of the skin: The impedance of the surface sheath and deep tissues. *J Invest Dermatol*. 1960;34:301-308.
29. Banga A, Chein YW. Iontophoretic delivery of drugs: fundamentals, developments and biomedical applications. *J Control Release*. 1988;7:l-24.