Research Article

Iontophoretic Permeation of Propranolol Hydrochloride Based Gellan Gum Gel Through Human Cadaver Skin

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Accepted on: 27-07-2014; **Finalized on:** 30-09-2014.

ABSTRACT

Hypertension is the most common cardiovascular disease; its prevalence increases with advancing age. Oral route has the drawbacks namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. Also injectable administration is invasive nature which may painful, requires skill, and may cause infection, therefore injection are not suitable for self or home sitting administration. Propranolol HCl is a nonselective, beta-adrenergic receptor-blocking agent indicated in the management of hypertension Propranolol is highly lipophilic and is almost completely absorbed after oral administration. However, it undergoes high first-pass metabolism by the liver and on average, only about 25% of propranolol reaches the systemic circulation. Gellan gum at concentration 0.6% w/w optimized. This showed a flux value of 32.814 μg/cm^2/hour and 3.039 μg/cm^2/hr at viscosity of 490.32 ± 6.01 cps. Propranolol HCL permeation through human cadaver skin via iotophoresis and passive application. It was observed that in comparison to passive permeation study, iontophoretic permeation exhibited more flux. Also, various permeation enhancers were combined with the iontophoresis to study the synergistic effect, but no increase in flux was recorded with them. From the results it was concluded that iontophoretic gellan gum based gel of propranolol HCl can be formulated for the management of hypertension.

Keywords: Iontophoresis, hypertension, beta blocker, Propranolol HCl, gellan gum gel, and permeation enhancer.

INTRODUCTION

Hypertension is the most common cardiovascular disease; its prevalence increases with advancing age. Elevated arterial pressure causes pathological changes in the vasculature and hypertrophy of the left ventricle. Hypertension is the principal cause of stroke, is a major risk factor for coronary artery disease and its complications, and is a major contributor to cardiac failure, renal insufficiency, and dissecting aortic aneurysm. Hypertension is defined as a sustained increase in blood pressure ≥140/90 mmHg, a criterion where the risk of hypertension related cardiovascular disease is high enough to worth medical attention.[1]

At present, the most common route for delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks– namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient.[2,3,4]

To overcome these difficulties there is a need for the development of a new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. Site specific), spatial and temporal placement within the body, thereby reducing both the size and number of doses. One of the methods most often utilized has been transdermal drug delivery, meaning transport of therapeutic substances through the skin for systemic effect.[5,6,7] Closely related is percutaneous delivery, which is transported into target tissues, with an effort to avoid systemic effects. The disadvantages of injectable administration are invasive nature which may painful, requires skill, and may cause infection, therefore injection are not suitable for self or home sitting administration. Oral therapy with antihypertensive agents is generally associated with severe GI side effects and low patient compliance also some of them has a high first pass metabolism.[8-11]

Therefore, development of a method of drug delivery that maintains the proper drug level for a prolonged period without adverse effects and should bypass first pass metabolism required. Thus, transdermal delivery has all the necessities that are required for delivery of classical antihypertensive agents. Propranolol HCl is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity. Propranolol HCL is indicated in the management of hypertension; it may be used alone or in combination with other antihypertensive agents.[12-14]

Propranolol is highly lipophilic and is almost completely absorbed after oral administration. However, it undergoes high first-pass metabolism by the liver and on average, only about 25% of propranolol reaches the systemic circulation. Recognizing the drawbacks of oral and injectable dosage forms for Propranolol HCL transdermal administration of Propranolol HCL is suitable, but significant limitation of passive transdermal administration is a slow onset of the action. This slow onset of action acts as a clinical limitation by two ways

first is a necessity to apply a patch several hours before to therapy timing and second one a slow acting transdermal patch cannot reasonably serve as an immediate acting medication form.[15,16,17]

The aim of study is study the passive and iontophoretic permeation of Propranolol HCL solution and factors affecting its permeation, to formulation and evaluation of transdermal gel containing Propranolol HCL, study the passive and iontophoretic permeation of Propranolol HCL gel formulation and factors affecting Propranolol HCL permeation, and study the effect of various permeation enhancers on permeation of Propranolol HCL gel and to study effect of concentration of permeation enhancer on permeation of Propranolol HCL gel formulation.

And following parameters were estimated.[18-21]

Steady State Flux (J_{ss})

The cumulative amount of drug permeated per unit skin surface area (Q_8) was plotted against time and the slope of the linear portion of the plot was estimated as steady-state flux (µg/cm^2/hr).[22]

Permeability Coefficient (K_p)

It is calculated by following equation

$$K_p = \frac{J_{ss}}{C_d}$$

Where,
K_P = Permeability coefficient; J_{ss} = Steady state flux; and C_d = Initial concentration of drug in donor compartment.[23]

Enhancement Ratio (ER)

It is calculated by dividing iontophoretic steady-state flux with the corresponding passive steady-state flux.[24]

$$ER = \frac{\text{Iontophoretic flux}}{\text{Passive flux}}$$

Lag time (L_t)

Lag time was an X- intercept of the plot cumulative amount of drug permeated per unit skin surface area versus time.[24]

Single factor ANOVA

The single factor ANOVA applied to obtain data for statistical comparison.[25]

Skin drug content

For measurement of skin remained in skin after each experiment the skin was cut into the pieces and kept in phosphate buffer pH 7.4 for 24 hours. The solution was filtered by the Whatman filter paper and the concentration of Propranolol HCL was analyzed by UV spectrophotometer from this amount of drug remained in the skin was determined.[26-28]

MATERIALS AND METHODS

Material

Propranolol HCL (Cipla Ltd, Mumbai), gellan gum (Merck) and other chemicals were of analytical grade.

Preparation of electrode

Silver wire (diameter × length = 1mm × 2cm) was used as the anode and Ag| AgCl electrode- (4 cm length) as cathode in this study. Silver-silver chloride electrode (cathode) was prepared by electrode electrolysis in a 0.1 M HCl solution at 0.5 mA/cm^2 for 1 hour.[25]

Construction of calibration curve

The standard curve of Propranolol HCL was taken in pH 7.4 phosphate buffer. A stock solution was prepared by dissolving 10 mg of Propranolol HCL in 100 ml of 7.4 phosphate buffer in 100 ml volumetric flask to give stock solution of 100 µg/ml Dilutions of concentration 10, 20, 30, 40, and 50 µg/ml made by taking 1, 2, 3, 4, and 5 ml of the stock and volume made with 10 ml with pH 7.4 phosphate buffer respectively. Absorbance of these solutions was measured on UV spectrophotometer.[18]

Differential Scanning Calorimetry (DSC)

The thermal behavior of Propranolol HCL was examined by DSC, using a differential scanning calorimeter (Shimadzu DSC-60). The system was calibrated with a high purity sample of Indium. 3.4 mg Propranolol HCL was scanned at the heating rate of 20°C/min over a temperature range of 100 to 250°C. Peak transitions and enthalpy of fusion were determined for the sample using TA60 integration software.

Similarly, drug excipients compatibility (Gellan gum) done by taking the physical mixture of drug with polymers was prepared by triturating drug and polymer (1:1) in a dried mortar and stored for 1 month. After 1 month The Thermogram was recorded on DSC (Shimadzu DSC-60). The system was calibrated with high purity sample of Indium. Mixture of drug with polymer was scanned at the heating rate of 20°C/min over a temperature range of 100-250°C. Peak transitions and enthalpy of fusion were determined for the mixture of drug with polymer using integration software TA60.

Infrared Red (IR) spectroscopy

The FTIR spectrum of PROPRANOLOL HCL was recorded by using an infrared spectrometer (SHIMADZU Prestige-21). The desiccated drug sample was placed in the FTIR sample holder and scanned over the range 400- 4000 cm^{-1}. Likewise FTIR spectrum of Propranolol HCL and polymers in 1:1 stored for 1 month was recorded to screen for the compatibility

Preparation of human cadaver skin

The abdominal skin of human cadaver was used for permeation studies. The skin was stored at temperature -20°C in sterile cotton gauze soaked in normal phosphate

buffer pH 7.4 and wrapped with aluminum foil, then thawed just before use. Subcutaneous fat was removed from the skin with the aid of scalpels and epidermis was peeled off from dermis carefully with scissors and a scalpel. Hairs were removed using scissors, and then it was washed with normal phosphate buffer pH 7.4 before the start of the experiment.

Skin permeation experiments

The excised human cadaver skin was mounted on a modified Franz diffusion cell (surface area available for permeation was 4.9 cm^2). Sonicated phosphate buffer pH 7.4 was used as the receptor medium (18 ml, maintained at 32 ± 2°C) and it was stirred continuously with a magnetic stirrer at 300 RPM (Whirlmatic-Mega, Spectralab).

Aliquots of 5 ml were withdrawn periodically from receptor medium at sampling intervals of 1, 2, 3, 4, 5, 6, 7, and 8 hour. The sink condition was maintained by replenishing the medium with 5 ml of phosphate buffer pH 7.4. The withdrawn samples were analyzed by developed UV spectroscopic method at λ_{max} 289.0 nm

Preparation and evaluation of gel containing Propranolol HCL.

An attempt was made to prepare gels of Propranolol HCL using gellan gum. The gel was prepared by the adding of 0.2, 0.4, and 0.6% gellan gum in the required volume of distilled deionzied warmed water containing 2mg/gm Propranolol HCL respectively. It was constantly stirred using a magnetic bead. To the stirring solutions of drug and gellan gum a 1mg NaCl was added to form a gel. Resultant gel was subjected to evaluation. Also the optimum viscosity of gel was tested for *In vitro* permeation through human cadaver skin.

Evaluation of gel formulations

The gel formulations containing Propranolol HCL were evaluated for pH, clarity, consistency, drug content (UV spectrophotometer), viscosity and other rheological properties.

pH

The pH of the gel formulations containing Propranolol HCL was measured. The gel formulation was diluted in ratio 1:25 using distilled water. The pH was monitored using previously calibrated digital pH meter (Cyber Scan 1000). The diluted gels were kept in contact with the pH electrode for 10 min until stable pH value obtained. The gel was tested in triplicate to obtain mean pH values. The electrode was thoroughly washed after each pH determination.

Clarity

All the gel formulations were visually inspected by naked eyes. The clarity of the gel formulations was observed.

Viscosity and other rheological properties

The viscosity of the gel formulations containing Propranolol HCL was determined by Brookfield R/S plus Rheometer and spindle no. C75-1. Other rheological properties of gel like Torque (mNm), Shear Stress (Pa), Shear Rate (1/s), and thixotropic behavior were estimated.

***In vitro* passive permeation and iontophoretic studies of Propranolol HCL using gel formulation**

Propranolol HCL permeation from gel formulation via a passive and iontophoretic process was studied by mounting human cadaver skin on Franz diffusion cell (area 4.9 cm^2). Gel formulation (5 gm) was applied to the epidermal side of the membrane and direct continuous current of 0.5 mA/cm^2 was. The experimental setup and drug analysis on calibration curve.

***In vitro* iontophoretic permeation studies of Propranolol HCL to study the effect of gel viscosity on permeation of Propranolol HCL.**

The effect of gel viscosity on iontophoretic permeation of Propranolol HCL studied by changing the viscosity of the gel in the donor compartment at 100, 490 and 1000 cp constant continuous current 0.5 mA/cm^2 for 8 hour applied. Drug content analyzed on the calibration curve.

***In vitro* iontophoretic permeation studies of Propranolol HCL to study the effect of permeation enhancers on permeation of Propranolol HCL gel.**

The effect of permeation enhancer on iontophoretic permeation of Propranolol HCL was studied by adding three permeation enhancer in gel, i.e. menthol, ethanol (95 per cent) and propylene glycol (PG) in 1% v/w and constant continuous current 0.5 mA/cm^2 for 8 hr applied respectively Drug content analyzed on the calibration curve.

***In vitro* iontophoretic permeation studies of Propranolol hcl to effect of concentration of permeation enhancer on permeation of propranolol hcl gel.**

The effect of concentration of permeation enhancer on iontophoretic permeation of PROPRANOLOL HCL studied by taking ethanol (95 per cent) in different concentrations viz. 1, 2.5, and 5% v/w and constant, continuous current 0.5mA/cm^2 for 8 he applied respectively Drug content analyzed on the calibration curve.

RESULTS AND DISCUSSION

Construction of calibration curve

The standard calibration curve (Figure 1) of Propranolol HCL showed the linearity in the range of 10- 50 µg/ml with a correlation coefficient of 0.99906. All standard solutions obeyed Beer- Lambert's law.

DSC

Propranolol HCL featured a single sharp melting endotherm; having a peak temperature of 165.97°C. DSC

thermogram melting endotherm complying with reported melting endotherm hence PRP was pure. The DSC study of the Propranolol HCL with gellan gum (peak 163.94°C) illustrated no significant deviation in the endothermic peak as compared to the DSC of Propranolol HCL alone (peak 165.97°C) as shown in Figure 2 Hence, from DSC study it can be concluded that the Propranolol HCL is compatible with gellan gum DSC.

Infrared Red (IR) spectroscopy

IR spectrum of Propranolol HCL was recorded as shown in Figure 3, and Table 1 and functional group ranges were found listed in the which same as reported suggesting Propranolol HCL was pure.

Evaluation of gel formulations

It demonstrated to increase the concentration of gellan gum increases the viscosity and thixotropic behavior gels containing 0.2, and 0.4% w/w gellan gum has good clarity and acceptable pH but their viscosity was low which was unable to hold in electrode cavity. 0.6% w/w gellan gum forms a clear, consistent and excellent viscosity 490.32 ± 6.01 cp gel which can be easily held in electrode cavity when applied to the skin hence it was selected as optimized concentration Table 2. The optimized G3 batch showed the shear thinning (pseudo plastic) type of flowing behaviour.

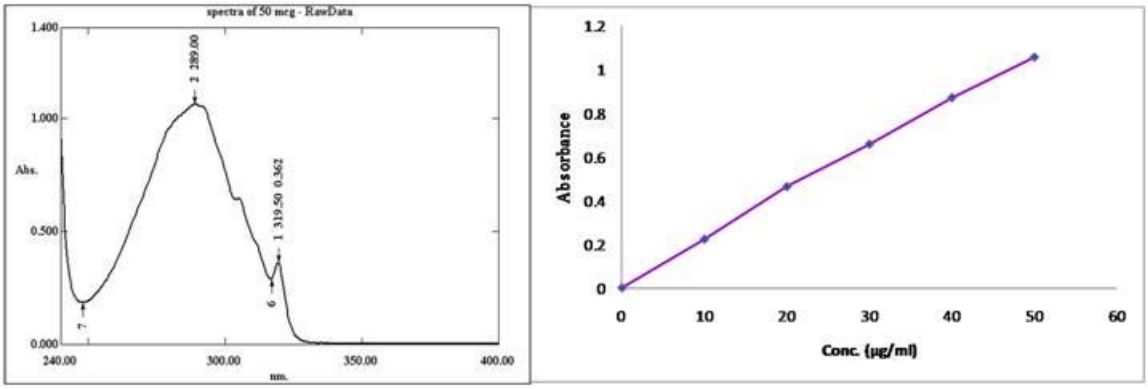

Figure 1: Absorption maxima and standard calibration curve of Propranolol HCl in Phosphate buffer 7.4

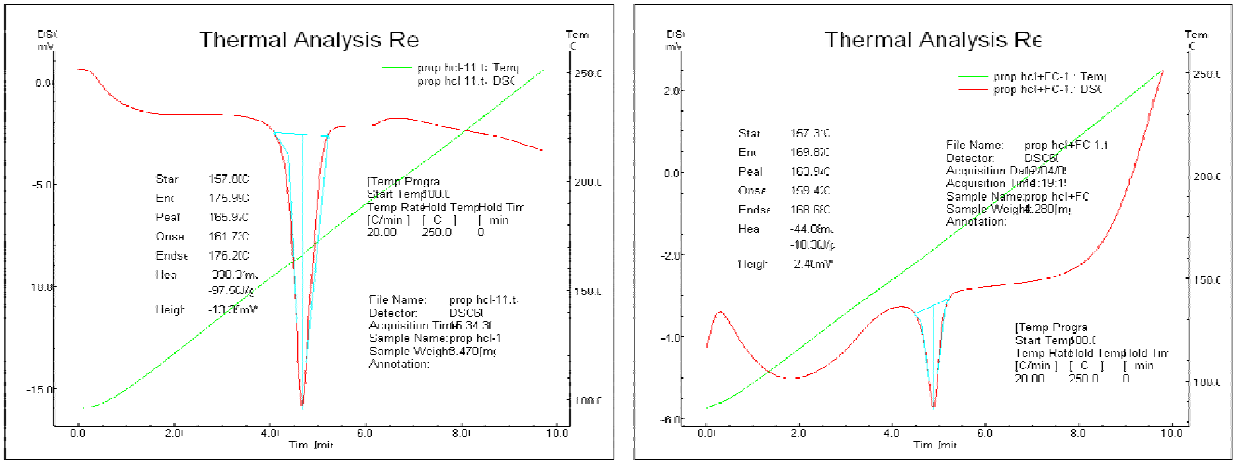

Figure 2: DSC thermogram of pure propranolol HCl and Gellan gum and Propranolol HCl Physical mixture

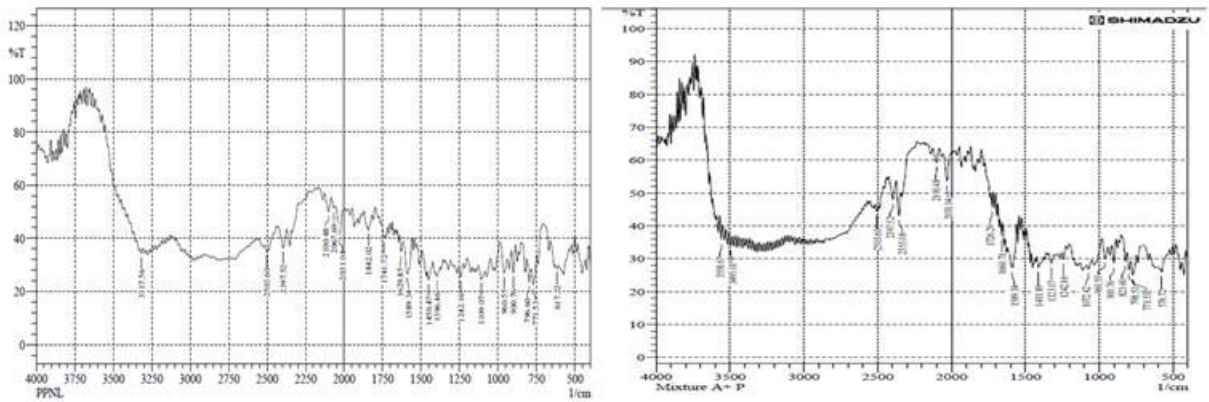

Figure 3: FTIR spectrum of Propranolol HCl and Propranolol HCl and gellan gum mixture.

Table 1: FTIR peaks in Propranolol HCl and gellan gum mixture.

Functional group	IR peak range (cm^{-1}) of Propranolol HCL	IR peak range (cm^{-1}) of mixture
-OH	3317.56	3495.01
$N\text{-}H_{bend}$	1589.34	$3558.67_{str.}$, 1589.34_{bend}
C-O	1242.16	1242.16
C-N	1396.46	1323.17
$C{=}C_{aro.}$	1629.85	1589.34
$=C\text{-}H_{bend\ oop}$	796.60	798.53
$C\text{-}H_{bend}$	771.53	771.53

Table 2: Evaluation of Propranolol HCL gel

Formulation code	Conc. of gellan gum (% w/w)	pH*± S. D	Viscosity* (cp) ± S. D	Thixotropy* (Pa/s) ± S. D	Clarity
G1	0.2	7.34 ±0.12	125.54 ± 4.58	1267.11 ± 29.91	++
G2	0.4	7.22 ±0.14	281.46 ± 7.09	324.45 ± 1.99	++
G3	0.6	7.39 ±0.11	490.32 ± 6.01	2207.32 ± 162.62	+++

* = Mean of triplicate, S. D= Standard Deviation, + = Poor, ++ = Good, +++ = Excellent

***In vitro* passive permeation and iontophoretic studies of propranolol HCL using gel formulation**

The study revealed that significant difference was observed with passive permeation to iontophoretic permeation the flux was reported 3.039 and 32.814 $\mu g/cm^2/hr$, respectively (**Error! Reference source not found.**). The flux significantly reduced for iontophoresis study using a gel formulation as compared to the solution. This drastic reduction in the flux may due to the increased resistance to diffusion due to cross linked gelling agent.

The single factor ANOVA showed significant differences between passive flux from gel and passive flux from solution ($F>F_{crit.}$) also iontophoretic permeation from the gel and iontophoretic permeation from solution significantly different ($F>F_{crit.}$).

***In vitro* iontophoretic permeation studies of Propranolol HCL to study the effect of gel viscosity on permeation of Propranolol HCL.**

Viscosity is an important parameter for the permeation of the drug it is a function of the cross linking in gelling agent. This may be the barrier for the drug permeation by creating the physical resistance to the drug movement. The present study also showed the inverse proportionality relation between viscosity and flux, i.e. at lower viscosity (105±20 cp) flux was higher than, higher viscosity (996±29.5 cp) as shown in the **Error! Reference source not found.**.

However, viscosity 490±25 cp was considered as the optimized viscosity of Batch gel G3 which can hold the electrode cavity well than remaining another. Statistically permeation from gel viscosity 490 cp found significantly ($F>F_{crit.}$) greater than permeation from gel viscosity 996 cp.

***In vitro* iontophoretic permeation studies of Propranolol HCL to effect permeation enhancer on permeation of Propranolol HCL gel.**

Penetration enhancers combined with the iontophoresis results shows that a combination of enhancers and iontophoresis did not further increase permeation but actually decreased it slightly compared with iontophoresis alone as showed in Table 5.

Table 3: Comparisons of permeation parameters of PROPRANOLOL HCL through solution and gel formulation

Concentration of co ions (mg)		Q_8* ± S. D ($\mu g/cm^2$)	J_{ss}* ± S. D ($\mu g/cm^2/hr$)	K_p* ± S. D	L_t*± S. D (Hr.)	E_r	S. D. C (mg/cm^2)
Gel	Passive	14.276±8.97	3.039±8.97	$3.0\times10^{-4}\pm7.8\times10^{-3}$	0.49±0.73	0.59	0.281964
	Ionto.	112.283±7.10	32.814±7.10	3.2×10-3±9.1×10-3	1.29±0.89	10.8	0.369433
Solution	Passive	28.735±1.67	5.114±1.67	$5.1\times10^{-3}\pm3.6\times10^{-3}$	2.24±0.01	-	0.449
	Ionto.	467.545±6.784	73.533±6.784	$7.35\times10^{-3}\pm4.6\times10^{-3}$	0.70±0.02	14.3	0.491

*All reading was taken in triplicate and represented as mean ± S. D

Table 4: Permeation parameters showing the effect of gel viscosity on permeation of the Propranolol HCL

Viscosity (cp) ± .S. D	Q_8* ± S. D ($\mu g/cm^2$)	J_{ss}* ± S. D ($\mu g/cm^2/hr$)	L_t*± S. D (Hr.)	K_p* ± S. D	S. D. C (mg/cm^2)
105±20	46.263±8.67	40.075±8.67	1.287±0.83	$3.28\times10^{-3}\pm8.9\times10^{-3}$	0.213
490±25	112.283±7.10	32.814±7.10	1.29±0.89	3.2×10-3±9.1×10-3	0.189

996±29.5	45.242±3.69	30.297±3.69	0.098±0.79	$40.1\times10^{-4}\pm7.9\times10^{-3}$	0.173

*All reading was taken in triplicate and represented as mean ± S. D

Table 5: Combination of iontophoresis with permeation enhancers

Penetration enhancer	Q_8* ± S. D (µg/cm^2)	J_{ss}* ± S. D (µg/cm^2/hr)	K_p* ± S. D	L_t*± S. D (Hr.)	E_r	S. D. C (mg/cm^2)
Continuous current	467.545±6.784	73.533±6.784	$7.35\times10^{-3}\pm4.6\times10^{-3}$	0.70±0.028	14.39	0.49
Menthol 1% v/w	117.387±3.75	46.819±3.75	$4.7\times10^{-3}\pm5.54\times10^{-3}$	1.881±0.87	0.64	0.13
Ethanol 1% v/w	122.878±8.97	54.074±8.97	$5.4\times10^{-3}\pm6.89\times10^{-3}$	3.275±0.31	1.15	0.12
PG, 1% v/w	39.034±4.70	31.681±4.70	$3.2\times10^{-3}\pm8.4\times10^{-3}$	3.879±0.51	0.59	0.23

*All reading was taken in triplicate and represented as mean ± S. D

However, when compared between permeation enhancer the flux was found to be higher with ethanol (54.074 µg/cm^2/hr) than menthol (46.819 µg/cm^2/hr) and Propylene Glycol (PG) (31.681 µg/cm^2/hr) this may be due ethanol increase the solubility of the Propranolol HCL in water, but this only results in a modest increase in the amounts transported across the skin into the receptor compartment. Menthol precipitated in donor compartment due to solvent evaporation hence caused lower permeation. Lowest permeation with PG attributed to decrease in the conductivity of the drug solution as well as a decrease in electro-osmotic flow. Single factor ANOVA has given significant greater permeation was found with continuous current than the combination of current with permeation enhancers ($F>F_{crit.}$) but among the permeation enhancer 1%v/w ethanol showed significant ($F>F_{crit.}$) greater flux than menthol and PG. Hence, in gel ethanol was added.

CONCLUSION

Gellan gum at concentrations of 0.2, 0.4, and 0.6% w/w was selected as a gelling agent for further development of gel formulation. From these concentrations 0.6% w/w optimized. The optimum gellan gum matrix gel (0.6% w/w) formulation G3 containing Propranolol HCL (2 mg/g) showed a flux value of 32.814 µg/cm^2/hr and 3.039 µg/cm^2/hr at viscosity of 490.32 ± 6.01 cp. Propranolol HCL permeation through human cadaver skin via passive and iontophoretic application. It was observed that in comparison to passive permeation study, iontophoretic permeation exhibited more flux. Also, various permeation enhancers were combined with the iontophoresis to study the synergistic effect, but no increase in flux was recorded with them.

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Source of Support: Nil, **Conflict of Interest:** None.