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Preparation of Transdermal Patch from Propranolol Base Prepared from Hydrochloric Salt and Evaluation of its Physical Parameters

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ABSTRACT

Propranolol is a beta-blocker.3 Beta-blockers affect the heart and circulation (blood flow through arteries and veins). Propranolol is a nonselective beta-adrenergic receptor blocker (beta-blocker) that is widely used for the therapy of hypertension, cardiac arrhythmias, angina pectoris and hyperthyroidism. Propranolol has yet to be convincingly associated with clinically apparent liver injury and is often used in patients with liver disease and cirrhosis. Traditional medication delivery methods, such as pills, capsules, liquids, powders, and intravenous needles, are often inefficient or invasive and can lead to undesirable side effects8. A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. The present study of preparation of Propranolol base from hydrochloric salt, which results white amorphous powder of Propranolol base and characterization of different parameters is done for its physiochemical properties. Also preparation of monolithic Transdermal patch from Propranolol hydrochloride and evaluation of different physical parameters.

Keywords: *Propranolol Hydrochloride, Solubility, Spectroscopic analysis, Transdermal Patch, Skin, Permeation.*

I. INTRODUCTION:

Propranolol is used to treat tremors, angina (chest pain), hypertension[8] (high blood pressure), heart rhythm disorders, and other heart or circulatory conditions. It is also used to treat or prevent heart attack, and to reduce the severity and frequency of migraine headaches.

Propranolol Hydrochloride is the hydrochloride form of propranolol, a synthetic beta-adrenergic receptor blocker with antianginal, antiarrhythmic, and antihypertensive properties. Propranolol competitively antagonizes beta-adrenergic receptors, thereby inhibiting beta-adrenergic reactions, such as vasodilation, and negative chronotropic and inotropic effects.

Transdermal patches are simple to use and constitute a simple albeit efficient idea for medication delivery. One side of the patch contains the medication, which is formulated into the skin contact adhesive. It is this side of the patch which is adhered to the skin. A person's skin is his or her largest organ. It covers and protects the body, regenerates when needed, and provides limited but essential permeation.

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. Drug delivery technologies are patent protected formulation technologies that modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance[1].

The skin has three layers. The first layer is called the epidermis. The second layer of the skin is called the dermis. It lies beneath the epidermis and contains connective tissue that gives the skin structure and strength. This layer of skin transmits medication from a patch into the deepest layer named as Hypodermis which contains blood vessels which also reach into the dermis and epidermis. These blood vessels are important in the transmission of medication from a patch to the bloodstream.

➢ **In vitro drug permeation study:-**

In vitro study was carried out to predict the delivery and permeation of the drug molecule through the skin surface in the body of the living animal. This was achieved by using a Franz diffusion cell.

➢ **Preparation of rat abdominal skin:-**

The male wistar rats weighing 170-190 g were sacrificed using anesthetic ether. The full thickness skin was removed from the abdominal region and abdominal hairs were removed by depilatory. The dermal side of the skin was washed thoroughly with distilled water to remove the blood vessels and adhering tissues. The skin of the test animal was then wrapped in aluminum foil and stored in freezer until further use. Prior to the experiment the skin was equilibrated for 15 minutes in the dissolution medium (phosphate buffer pH 7.4).

II. EXPERIMENTAL WORK

Preparation of Propranolol free base from official salt form:-

Firstly we prepared Propranolol base from hydrochloric salt. In 25 ml of distilled water, 1 gm of Propranolol hydrochloride was dissolved. Addition of Strong ammonia solution and pH was adjusted upto 9.4, and then Propranolol free base was precipitated out. Extraction and purification of base using solvent ether. Four times, the Extraction process was carried out using 25 ml ether. Ethereal phase was collected and evaporated at 60^{o}C. White amorphous powder of Propranolol base was obtained.

A. Characterization Parameters:-

The physiochemical properties of Propranolol free base were determined using following Parameters

➢ **Determination of Melting point:-**

Determination of melting point of drug was done by taking small amount of drug in a capillary tube closed at one end and placed in a melting point apparatus and the temperature at which drug melts was recorded. This was performed in triplicates and average value was noted.

➢ **Determination of partition co-efficient:-**

Using n-octanol as oily phase and phosphate buffer, pH 7.4, as aqueous phase, the partition co-efficient study was performed. The two phases were mixed in an equal quantity and were saturated with each other on a mechanical water bath shaker NSW-133 at 34^{o}C for 18 hr. The saturated phases were separated by centrifugation at 2000 rpm on a REMI R-23 centrifuge. Standard plots of drug were prepared for both, the phosphate buffer and octanol. Equal volumes (12.5ml each) of the two phases were taken in conical flasks and, to each; 100mg of weighed amount of drug was added. The flasks were shaken at 34^{o}C for 6hr to achieve a complete partitioning at 100rpm. The two phases were separated by centrifugation at 1000 rpm for 5min and they were then analyzed for respective drug contents by UV/VIS spectroscopy method. The partition co- efficient of drug K o/w was calculated using the following formula:

K o/w = (Concentration in octanol/ Concentration in phosphate buffer pH 7.4)

➢ **Solubility studies:-**

In phosphate buffer solution, pH 7.4, the solubility study of Propranolol base was performed in distilled water, methanol, chloroform, ether, alcohol (95%), acetone, toluene, glycerol, liquid paraffin, triethanol amine and silicone oil separately by adding excess amounts of drug in each case and keeping the excess drug containing flasks on a water bath shaker NSW-133 for 18hr at 34^{o}C.

➢ **UV /VIS Spectroscopic Analysis:-**

UV spectrum of Propranolol base was recorded on UV/VIS Spectrophotometer by scanning 5 µg/ml solution of Propranolol base in 0.01N hydrochloric acid and scanned between 200-400nm using UV/VIS Spectophotometer.

➢ **Infrared (IR) Spectroscopic Analysis:-**

Using potassium bromide (KBr) pellet method, Fourier Infrared (FTIR) spectrums of moisture free samples of Propranolol base was recorded on IR spectrophotometer. The scanning range was 4000 – 400 cm^{-1} and the resolution was 1 cm^{-1}.

➢ **Differential Scanning Calorimetry (DSC) Analysis:-**

DSC scans of the powered samples were recorded using DSC- Shimadzu 60 with TDA trend line software. Drug was weighed (7-10 mg) and heated at a scanning rate of 10^{o}C/min under dry nitrogen flow (100 ml/min) between 50-350^{o}C. Aluminium pans and lids were used for drug sample. Pure water and indium were used to calibrate the DSC temperature scale and enthalpy response.

III. PROCEDURE

The receptor compartment of the Franz diffusion cell was filled with 65 ml of phosphate buffer pH 7.4. The contents of the diffusion cell were stirred using a teflon coated bead at a constant speed of 50 rpm on a magnetic stirrer. The isolated rat skin was mounted on the diffusion cell and the transdermal patch was placed over the skin. The temperature of the medium in the receiver compartment was maintained at 37 ± 1ºC with the water jacket. The donor compartment was kept open to maintain the exposure of system to ambient conditions. The amount of drug permeated in the receptor solution was determined by withdrawing 1 ml at hourly intervals. Each time equal volume of buffer was supplemented in the receptor compartment to maintain sink condition. The samples were then diluted to 10 ml and analyzed for drug content at 236 nm using UV spectrophotometer. The permeation study was carried out for 11 hours.

IV. RESULTS

Propranolol base prepared form hydrochloric salt was white amorphous powder, which showed following characteristics:

- **Melting point:-**

Melting point of Propranolol base was determined by capillary tube method and it was found to be 162^{o} C±1.502 (average of three readings). This value is same as that of the literature citation.[3]

- **Partition co-efficient:-**

Octanol and in vitro study fluid (here phosphate buffer, pH 7.4) are considered to be the standard system to determine drug partition coefficient between skin and in vitro study fluid. The logarithmic value of partition coefficient (log P) value was experimentally found to be 2.186. The results obtained also indicate that the drug possess sufficient lipophillicity, which fulfills the requirements of formulating it into a transdermal patch. Partition coefficient should be in the range of 1 to 4.

- **Solubility study:-**

Solubility of Propranolol base was evaluated in different solvent.

Table: Solubility of Propranolol base in different solvents

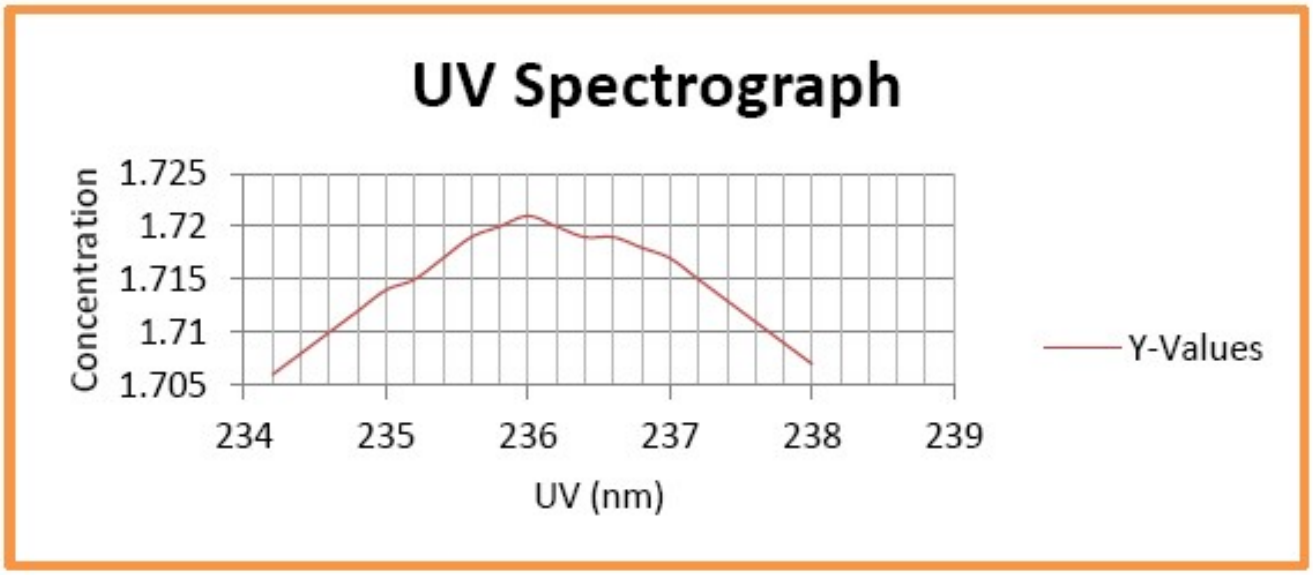
Solvent	Solubility
Phosphate buffer (pH 7.4)	Insoluble
Methanol	Freely soluble
Chloroform	Freely soluble
Alcohol (95%)	Freely soluble
Acetone	Freely soluble
Silicone oil	Insoluble
0.01N Hydrochloric acid	Soluble
Distilled water	Insoluble
Liquid paraffin	Soluble
Triethanolamine	Soluble
Ether	Freely soluble
Toluene	Freely soluble
Glycerol	Insoluble

An attempt was made at this point to learn whether the media phosphate buffer, pH 7.4, was able to maintain sink condition in diffusion as well as in permeation studies. Here form solubility studied data it was found that solubility of drug was poor in phosphate buffer, pH 7.4. Therefore it becomes difficult to maintain sink condition during diffusion study. Propranolol base was soluble in 0.01 N HCl and it was selected as a diffusion medium.

- **UV/VIS Spectroscopic analysis:-**

The UV maxima of resultant solution were measured with Shimadzu, Japan UV/VIS Spectophotometer. The UV maxima of Propranolol base in the solution was found to be 236.0 nm, which was suitable for the preparation of standard curve and estimation of Propranolol base from various formulations. Figure shows the UV spectrograph of Propranolol base in 0.01N HCL.

Fig: UV spectrograph of Propranolol in 0.01N HCl



Sr. No.	UV (nm)	Concentration	Sr. No.	UV (nm)	Concentration	Sr. No.	UV (nm)	Concentration
1	238	1.707	8	236.6	1.719	15	235.2	1.715
2	237.8	1.709	9	236.4	1.719	16	235	1.714
3	237.6	1.711	10	236.2	1.72	17	234.8	1.712
4	237.4	1.713	11	236	1.721	18	234.6	1.71
5	237.2	1.715	12	235.8	1.72	19	234.4	1.708
6	237	1.717	13	235.6	1.719	20	234.2	1.706
7	236.8	1.718	14	235.4	1.717			

➢ **Infrared (IR) Spectroscopic Analysis**

Propranolol was subjected for FTIR spectroscopic analysis, to characterize drug. FTIR Spectra for base was compared with that given for FTIR spectra of official salt form. Diagnostic peaks and finger print regions were identical. These characteristics peaks are useful in drug excipients compatibility study.

Fig: FT-IR Spectra of pure drug (Propranolol)

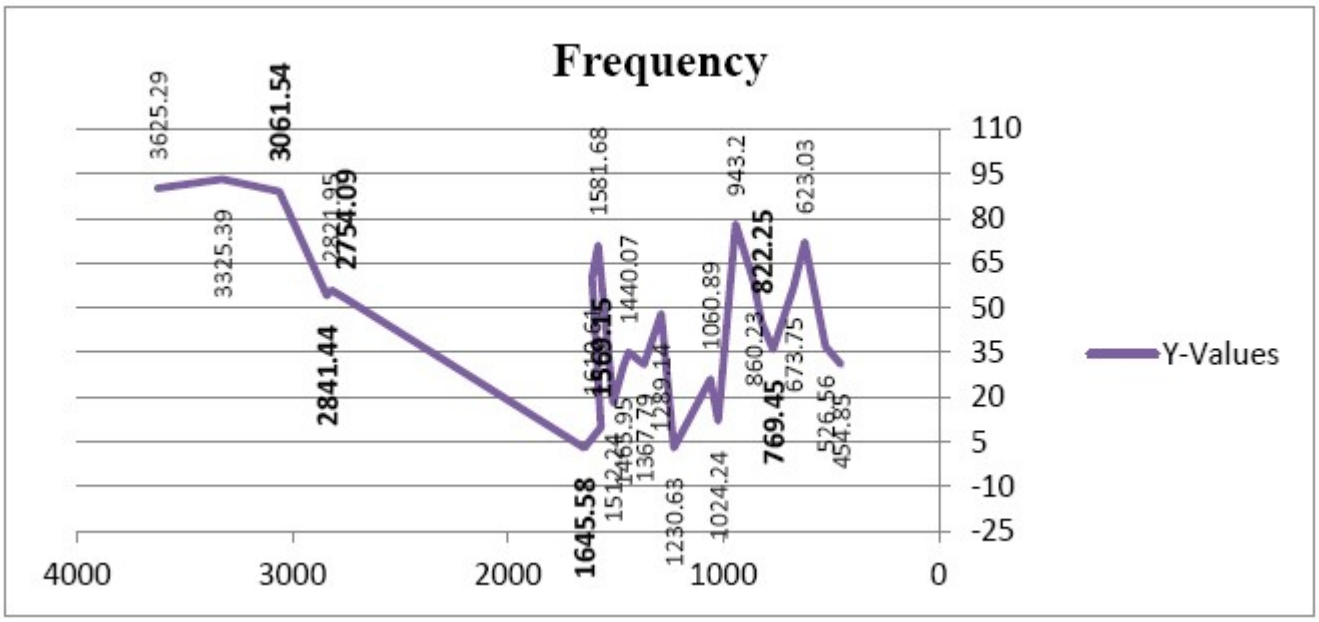


Table: FT-IR Spectral data of Propranolol

Frequency (cm^{-1})	Assignment
3061.54	Aromatic C-H stretch
2841.44	Aliphatic C-H stretch
2754.09	O-CH_3 C-H stretch
1645.58	Acetate C = O stretch
1569.15	Lactam C = O stretch
822.25	o-substituted aromatic C-H out of-plane deformation
769.45	p-substituted aromatic C-H out of-plane deformation

➢ **Differential Scanning calorimetry (DSC) analysis**

DSC enables the quantitative detection of all processes in which energy is required or produced. Pure powered Propranolol showed a melting endotherm at 158°C. DSC study is useful for further drug excipients interaction study to check suitability of polymer[6].

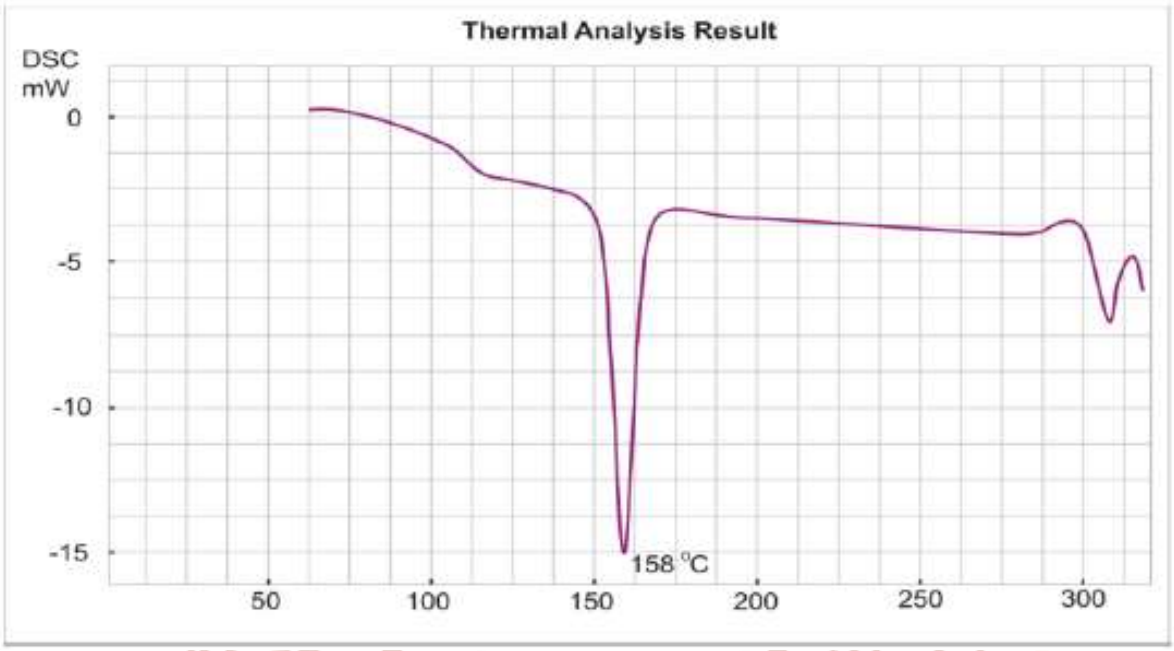


Figure: DSC thermogram of Propranolol

The monolithic transdermal patches of Propranolol hydrochloride using ethyl cellulose and polyvinyl pyrrolidone were prepared by solvent evaporation and solvent casting technique and were flexible, smooth and transparent.

➢ **Drug excipient interaction study:-**

The transdermal patches were also evaluated for the physical parameters[5,7] Table: Physical parameters and drug content of transdermal patches

Batch codes	Physical appearance	*Weight (mg)	*Thickness (mm)	*Drug content	*Surface pH	*Folding endurance	Flatness (%)	%Swellability
F1	++	7.5 ± 0.002	0.169± 0.001	96.9 ± 0.30	6.2± 0.15	289± 0.52	100	11.9
F2	++	7.9 ± 0.050	0.172± 0.001	97.5 ± 0.10	6.9± 0.10	296± 0.01	100	14.3
F3	++	8.15 ± 0.001	0.170± 0.005	97.9 ± 0.52	6.2± 0.11	295± 0.57	100	15.5
F4	++	9.16 ± 0.001	0.172± 0.007	98.5 ± 0.11	6.8± 0.10	297± 0.15	100	17.92

++Satisfactory; *Average of three determinations for each parameter

➢ ***In vitro* permeation studies:-**

The permeation study was carried out for 11 hours and maximum permeation was obtained for formulation F4 (97.42) and minimum permeation was obtained for formulation F1 (65.54). Formulation F1 contained higher proportion of Ethyl cellulose and it showed comparatively sustained release pattern. Hence for obtaining sustained release high concentration of ethyl cellulose is required[5]. The cumulative percentage of drug permeated for all the formulations have been shown in the plot of cumulative percent of drug permeated v/s time has been shown in Figure:

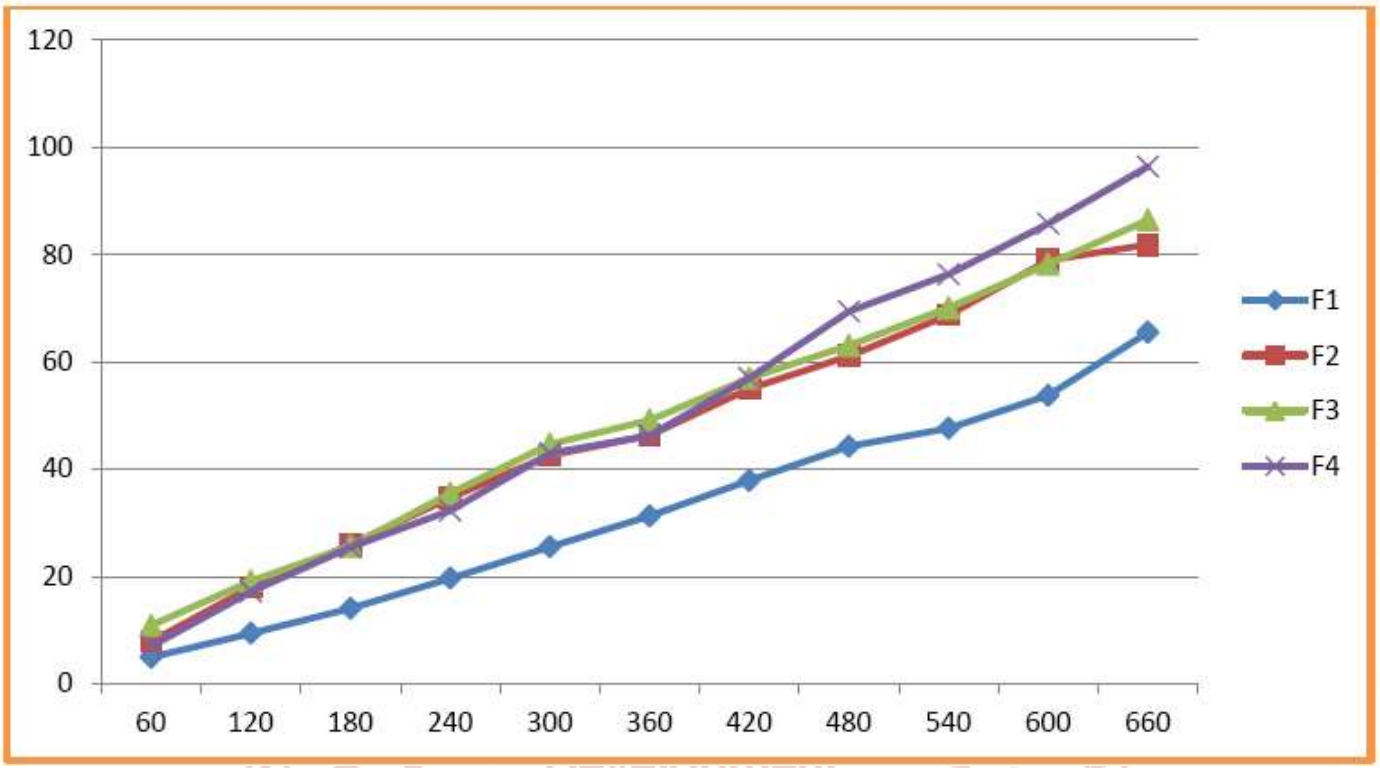


Fig: % Cumulative drug permeated vs time (min) for the formulations F1 –F4

Time (min)	Cumulative % of Drug permeated (F1)	Cumulative % of Drug permeated (F2)	Cumulative % of Drug permeated (F3)	Cumulative % of Drug permeated (F4)
60	4.932	7.89	10.9	6.99
120	9.415	17.99	19.2	17.2
180	14.05	25.98	25.69	25.44
240	19.69	34.7	35.53	32.28
300	25.52	42.56	44.68	42.99
360	31.28	46.32	49.15	46.23
420	37.9	55.01	57.01	56.99
480	44.25	61.12	63.09	69.42
540	47.63	68.78	70.1	76.34
600	53.76	78.95	78.23	85.78
660	65.54	81.88	86.46	97.42

➢ **Drug release kinetics:-**

The *in vitro* permeation data obtained for all the formulations was fitted to various kinetic models to elucidate the permeation profile. The drug permeation profile for all the formulations was found to follow zero order kinetics as evidenced by the straight line and higher regression value depicted in Figure. Thus the release rate was independent of the concentration of the drug. The kinetic models for various formulations have been shown in the table below[5,7].

Table: Value of R^2 for different kinetic models for formulations F1-F4

Formulation Code	R^2				
	Zero order	First order	Higuchi	Korsemeyer Peppa's	n value
F1	0.985	0.866	0.866	0.982	0.119
F2	0.989	0.921	0.921	0.982	0.109
F3	0.988	0.925	0.925	0.971	0.101
F4	0.990	0.889	0.889	0.955	0.699

V. CONCLUSION

Propranolol base was prepared from its official hydrochloride salt and characterized using different parameters. Melting point was determined to check purity of drug. From solubility study it was found that 0.01N HCl was able to maintain sink condition, so it was suitable as a diffusion medium. The results obtained from Partition co-efficient study revealed that the drug possessed sufficient lipophillicity, which fulfills the requirements of formulating it into a transdermal patch. Differential scanning calorimetry and Fourier transform infrared spectroscopy gave idea regarding chemical structure of pure drug. UV/VIS Spectroscopic data are useful for the preparation of standard curve and estimation of Propranolol base released from various formulations.

Formulated patches were found to be smooth flexible and transparent and exhibited good physicochemical properties. The in vitro permeation study indicated increase in the permeation rate with the increase in the concentration of hydrophilic polymer and formulation F4 was found to depict maximum release as compared to other formulations. The release kinetics was found to follow zero order and non fickian diffusion. The results of evaluation studies indicated that the formulated patches of Propanolol hydrochloride shows better compliance than conventional drug delivery system. Studies have depicted promising results and it holds scope for further pharmacokinetic and pharmacodynamic evaluation to filter out the potential of this delivery system.

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