

Research Article

FORMULATION AND EVALUATION OF TRANSDERMAL PATCH OF PROPRANOLOL HYDROCHLORIDE

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Abstract

The purpose of this research was to develop a matrix type transdermal patch containing Propranolol hydrochloride and combination of two hydrophobic Polymers Eudragit L-100 and Eudragit S-100 by Solvent Evaporation technique. Combination of two Plasticizers Glycerine and Dibutyl phthalate were used and their effect on drug release was studied by changing their concentration in each batch. Methanol and Dichloromethane solvent system was used in which methanol acts as a penetration enhancer. Since oral bioavailability of Propranolol Hydrochloride is poor due to high first pass metabolism transdermal patch is formed with the objective to get sustained release drug action with good bioavailability. The Physicochemical compatibility of the drug and polymers suggested by infrared spectroscopy suggested absence of any incompatibility. Formulated transdermal films were physically evaluated for thickness, weight variation, drug content, moisture and folding endurance. All prepared formulation indicated good physical stability. In vitro drug release studies were performed by using Franz diffusion cells and cellophane membrane. Sustained release drug action was achieved in optimized batches. The Drug irritancy study show that there was no any noticeable sign of erythema or oedema on rabbit skin throughout the period of 48 hrs.

Keywords: Propranolol, Eudragit L100, Eudragit S100, Hypertension, Bioavailability.

Introduction

Transdermal patches are defined as self-contained, discrete dosage forms which when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation. In other words Transdermal patches are adhesive, drug containing devices of defined surface area that deliver predetermined amount of drug to the surface of intact skin at preprogrammed rate. These systems provide drug systemically at predictable rate for extended period of time. Transdermal drug delivery has many advantages over the oral route of administration such as improving patient compliance in long term therapy, bypassing first-pass metabolism, sustaining drug delivery, maintaining a constant and prolonged drug level in plasma, minimizing inter- and intra-patient variability, and making it possible to interrupt or terminate treatment when necessary¹. Drugs can be delivered across the skin to have an effect on the tissues adjacent to the site of application in topical delivery or to have an effect after distribution through the circulatory system in Systemic delivery. There are many advantages to deliver drugs through the skin and the barrier properties of the skin provide specific challenge. By understanding the mechanisms by which compounds cross the skin it will possible to devise means for improving drug delivery². Some of many factors that influence the rate of delivery of drugs across the skin include the thermodynamic activity of drug in formulation; the interaction of the drug and formulation with the skin; Variations in the skin with age, race, anatomical region and disease. Research in transdermal drug delivery needs to address all these factors. Most of chronic disease has genetic, hereditary type of lifestyle borne like hypertension, asthma, diabetes, addiction etc. It is desirable from standpoint of pharmacodynamics to maintain the drug concentration in the plasma within therapeutic effective range for long periods. This approach is more pertinent in case of chronic disorders³. Transdermal delivery system of an antihypertensive drug has already been marketed. Other hypotensive drugs that have been explored for their transdermal delivery potential are propranolol, pinacidil, metopro-

lol, mipindolol, captopril, verapamil and others. Propranolol hydrochloride is a well-known anti-hypertensive drug. It is available in the market in the form of tablet, capsule, and i.v solution. Here is attempt to formulate transdermal patch of propranolol hydrochloride. Propranolol, the prototype of the beta-adrenergic receptor antagonists, in activity. Propranolol is a racemic compound; the l-isomer is responsible for adrenergic blocking competitive, non-selective beta-blocker similar to nadolol without intrinsic sympatho mimetic activity. Propranolol competes with sympathomimetic neurotransmitters such as catechol amines for binding at beta (1)-adrenergic receptors in the heart, inhibiting sympathetic stimulation⁴. This results in a reduction in resting heart rate, cardiac output, systolic and diastolic blood pressure, and reflex orthostatic hypotension. Propranolol HCL is selected drug for formulation of patch due to its short half-life i.e. 4hr, oral bioavailability is 30% oral dose is 160 to 260 mg daily, mol wt. is 259.35, melting point is 96°C. The present work is planned with the objective to prepare transdermal patch using various polymers and to obtain sustained Release drug action of the selected drug candidate⁵. The present work is planned with the objective to prepare transdermal patch using various polymers and to obtain sustained Release drug action of the selected drug candidate.

MATERIALS AND METHODS

All materials and chemicals used were of laboratory grade. Distilled water was prepared in the laboratory using all glass distillation apparatus. The chemicals and reagents used are Propranolol HCL,

Eudragit L-100, Eudragit S-100, Methanol, Dibutyl phthalate, Glycerine, Potassium hydrogen phosphate, Sodium hydroxide, Cellophane membrane. The drug is obtained as a gift sample from Dr.Reddy's laboratories, Goa while excipients are obtained from Loba chemicals, Mumbai.^{5, 6}

1) Determination of λ max of propranolol in phosphate buffer pH 7.4 solution-

A) Preparation of propranolol HCL std stock solution (100 μ g/ml) in phosphate buffer pH 7.4 solution-

Standard stock solution of propranolol was prepared by dissolving accurately weighed 10 mg of propranolol in little quantity of phosphate buffer pH 7.4 and then adjust volume upto mark in 100ml volumetric flask. Std stock solution of 100 μ g/ml is obtained.

B) Scanning of propranolol by UV spectrophotometer in phosphate buffer (pH 7.4) solution. From the standard stock solution, 3ml was diluted to 10ml with phosphate buffer solution (pH 7.4). The resulting solution containing 30 μ g/ml was scanned between 200 to 400 nm.¹¹

2) Calibration curve of propranolol in phosphate buffer solution (pH 7.4)-

Stock solution of 100 μ g/ml was prepared in phosphate buffer pH 7.4.

Using this solution dilutions were done and solutions of concentration 10, 20, 30, 40, 50 μ g/ml were prepared and their absorbance was measured in UV spectrophotometer at λ max 290nm¹¹.

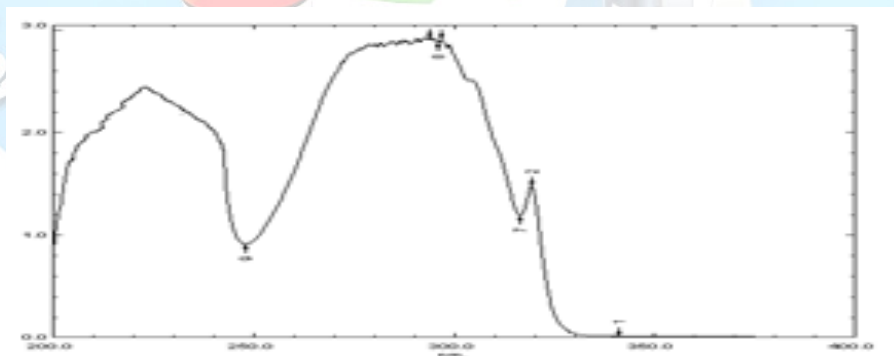


Fig.no1: UV spectrum of propranolol in phosphate buffer pH 7.4 solution (100 μ g/ml)

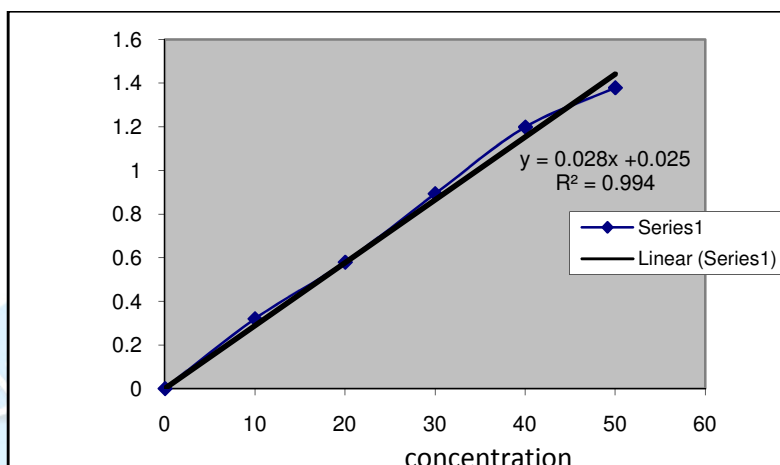


Fig.no2 : Calibration curve of propranolol in pH 7.4 phosphate buffer solution.(100 µg/ml

Preformulation studies-

1) Melting point-Melting point of propranolol was found to 96°C .which is same as literature review.⁷

2) Solubility-Propranolol hydrochloride has high degree of aqueous solubility due to presence of hydrochloride salt moiety, whereas the base compound has limited aqueous solubility. The solubility of Propranolol hydrochloride in different solvents is represent as below.⁷

3) Partition coefficient-

The partition coefficient of drug is a measure of lipophilicity of that compound, and is expressed as the ratio of solute distribution between lipophilic and hydrophilic phase. Propranolol hydrochloride has relatively high oil-water partition coefficient and show high degree of lipid solubility. The partition coefficient for propranolol in octanol/water (phosphate buffer pH 7.4) was found to be 3.37 at 30°C of temperature.⁸

4) pH-

1% w/v solution of propranolol hydrochloride in water has pH of 5.5.⁹

5) Dissociation constant-

The pKa of the drug is the negative log concentration of the Ka and its value is equivalent to pH at

which 50% of the drug is ionized. Propranolol is weakly basic drug and has pKa9.45.¹⁰

FORMULATION OF TRANSDERMAL PATCH

Solvent Evaporation method-

The polymers, Eudragit L100 and Eudragit S100, were taken in required quantity as shown in the table no.1. About 20 ml of solvent mixture of dichloromethane: methanol (1:1) was added and shaken to prevent the formation of lumps and then kept aside for swelling of polymers. And after complete solubilization of polymers in mixture of solvent, added required quantity of dibutyl phthalate to this mixture, followed by glycerin and vortexed. Finally weighed quantity of propranolol hydrochloride added to the polymer solution and mixed well. It was set aside for some time to exclude any entrapped air and was then transferred into a previously cleaned Petri plate containing Bangles wrapped with aluminum foil and then this was kept aside for solvent evaporation. The rate of solvent evaporation was controlled by inverting a glass funnel over the petri plate. The transdermal patches were successfully prepared for compositions given in table no.1. The prepared patches were stored in aluminum pouch and preserved in desiccator for further studies.^{5,6}

Table no 1: Formulation of Transdermal Patches

Ingredients	F6	F7	F8	F9	F11	F12	F13
Propranolol hydrochloride (mg)	350	350	350	350	350	350	350
Eudragit-l 100 (mg)	650	650	650	650	650	650	650
Eudragit-s 100 (mg)	350	350	350	350	350	350	350
Dichloromethane(ml)	10	10	10	10	10	10	10
Methanol (ml)	10	10	10	10	10	10	10
Dibutyl phthalate(% w/v)	5	10	15	20	5	10	15
Glycerin (% w/v)	5	5	5	5	10	10	10

EVALUATION OF TRANSDERMAL PATCHES OF PROPRANOLOL-

1) Physical appearance-

The patches formed were smooth and transparent/translucent in appearance.¹²

2) Thickness-

The Thickness of patch was measured with the help of Vernier caliper at three different places and average thickness was noted. Thickness results are given in the table no.3. Low value of standard deviation shows that thickness of patch is uniform. Batch F6 has lowest thickness while batch F11 has highest thickness. The order of the thickness of batches is F6<F7<F13<F9<F8<F12<F11¹².

3) Weight uniformity-

Drug loaded patches (1×1cm²) were tested for uniformity of weight and the results of weight uniformity are given in table no.3. Low value of standard deviation shows that weight of patch is uniform. Batch F9 has lowest weight while batch F11 has highest. The order of weight of patches is F9<F8<F6<F7<F12<F13<F11.¹²

4) Folding endurance-

Folding endurance of patch is measured manually by folding patch at one place number of times till it break. This gives value of folding endurance. The recorded folding endurance of the patches was shown in table no.3. As there is low value of stan-

dard deviation it means that folding endurance is uniform. It deficits all formulations have good film properties. The folding endurance of patches are in the following order F8<F11<F6<F12<F9<F13<F7. Batch F8 has lowest folding endurance while batch F7 has highest.¹³

5) Percent moisture Absorption-

The recorded percentage moisture absorption of the patches was shown in table no.3. The percent moisture absorption of the prepared patches are in following order F6<F7<F8<F9<F11<F12<F13. Batch F6 has lowest moisture absorption while F13 has highest. The results show the moisture absorption of all patches are within acceptable unit.¹²

6) Percent moisture loss-

The recorded percentage moisture is shown in table no.3. The percent moisture loss of prepared patches are in the following order F13<F12<F7<F11<F6<F8<F9. Batch F13 has lowest moisture loss as compared to other batches while Batch F9 has highest.¹²

7) Drug content uniformity-

Drug content of the patch was carried out to ascertain that drug is uniformly distributed into the formulation. The results obtained are represented in table no.3. The drug content was in the following order F13<F12<F11<F7<F6<F8<F9. Batch F13 has lowest drug content while batch F9 has highest. From the results obtained and low standard deviation values it was clear that there was proper dis-

tribution of propranolol in film formulations. Hence it was concluded that drug was uniformly distributed in all the formulations.¹²

8) In vitro release studies-

In Vitro release of propranolol patches were carried out in Franz diffusion cell using cellophane membrane for permeation. Phosphate buffer pH 7.4 is used as diffusion medium. The release data is given in table no.4 for patches F6 to F13. Formulation of Batch F1 to F6 was in absence of glycerin and concentration of Dibutyl phthalate was 5% in F1 batch and increased by same concentration for further batches. These batches were not formed properly. In F1, F2, F3 batch only solid mass was formed while F4 and F5 batch patches were fragile in nature. so there in vitro release studies was not carried out. It is observed that as concentration of dibutyl phthalate increases release of drug increases. In batch F6 where both glycerin and dibutyl phthalate were taken 5% in concentration 73.87% release was obtained in 12 hrs. Then in F7 batch concentration of glycerin was constant i.e. 5% and concentration of dibutyl phthalate was increased to 10% in this case release of drug increase to 75.81%. In next batch F8 by increasing concentration of dibutyl phthalate by 5% Release of drug increased up to 78.75%. In batch F9 drug release drastically increased up to 97.14%. In this batch concentration of glycerin was 5% and that of dibutyl phthalate was 20%. In further batch F11 concentration of glycerin was increased up to 10% and dibutyl phthalate was reduced up to 5%, in this case there was sudden decrease in drug release it drop up to 77.28%. Now in batch F12 as concentration of dibutyl phthalate increased up to 10% and glycerin is used in same concentration there was little increase in drug release up to 78.08%. In batch F13 79.18% drug release was obtained where glycerin concentration was 10% while dibutyl phthalate was 15% in concentration.

From overall drug release studies it was observed that F9 batch shows greater release while F6 batch shows slower release as compared to other batches.¹²

9) Stability studies-

Stability studies were carried out for 60 days at room temperature, temperature of 25-30°C 60% RH and 45-50°C 75% RH. The patches were observed for physical change and drug content. It was found that, when patches were stored at 25-30°C, 60% RH, the loss of drug was approx. 2-3% at the end of 60 days. However, the amount of drug loss was found to be much higher (14-18%) when stored at 45-50°C, 75% RH. From this it was concluded that as temperature and humidity increases drug loss increases.¹⁴

10) Skin irritancy study-

Result of skin irritancy study revealed that neither blank patch nor patch containing propranolol HCL caused any noticeable sign of erythema or oedema on rabbit skin throughout the period of 48 hrs. Hence the patches were found to be compatible with the skin.¹⁴

RESULTS & DISCUSSION

Drug-Excipients compatibility studies-

The Fourier transform infrared Spectroscopy studies were carried out for pure drug alone and with polymers. IR spectra of propranolol, Eudragit L-100, Eudragit S-100, alone and with their combinations are shown in fig. below

- 1) IR spectrum of propranolol hydrochloride
- 2) Eudragit L-100
- 3) Eudragit S-100
- 4) Mixture of Drug and polymer

The characteristic peaks were not affected and prominently Observed in IR Spectra of propranolol along with polymers, Shown in **figure**. This indicates there is no interaction between Propranolol and polymers. As there is no shifting of the peak or disappearance of peak in mixture drug is compatible with polymer.

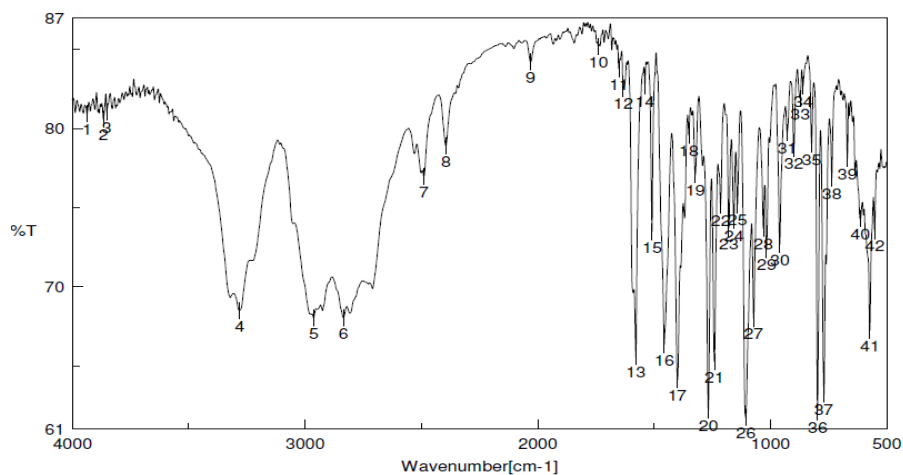
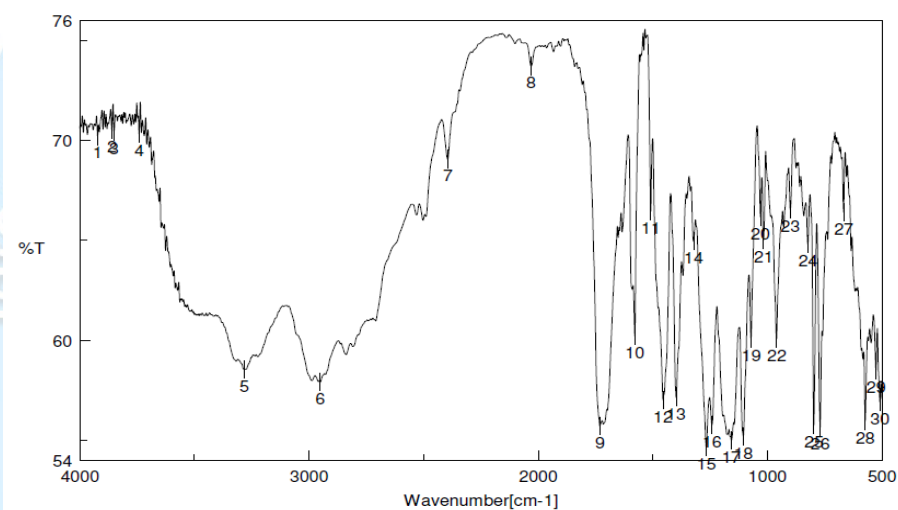
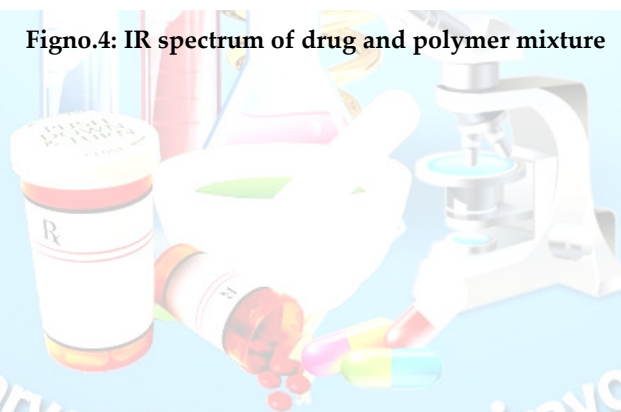
**Fig.no.3: IR spectrum of propranolol Hydrochloride****Fig.no.4: IR spectrum of drug and polymer mixture**

Table no.3: Evaluation of transdermal patches of propranolol

Formulation codes	Thickness	Weight uniformity	Folding endurance	Percent moisture absorption	Percent moisture loss	Drug content uniformity
F6	0.1733±0.005	0.446±0.003	82±4.89	1.46±0.25	12.643±1.991	2.51±0.0141
F7	0.18±0.000	0.453±0.001	98±6.027	1.72±0.19	8.6016±1.862	2.50±0.0141
F8	0.1866±0.005	0.442±0.002	72.66±4.932	2.92±0.12	13.541±1.804	2.52±0.008
F9	0.1833±0.005	0.434±0.002	89.33±3.511	3.38±0.32	14.583±3.608	2.55±0.008
F11	0.21±0.001	0.464±0.003	76.66±3.055	5.23±0.13	10.20±0.27	2.49±0.034
F12	0.19±0.000	0.453±0.002	88.33±4.509	7.75±1.342	7.48±0.34	2.48±0.0129
F13	0.18±0.000	0.462±0.003	97.33±3.055	7.842±1.697	7.24±0.32	2.46±0.0141

Where n=3

Table no.4: In-Vitro drug Release studies for propranolol patches

Time	% Drug Release						
	Batch f6	Batch f7	Batch f8	Batch f9	Batch f11	Batch f12	Batch f13
0	0	0	0	0	0	0	0
1	12.6	10.54	14.05	13.92	10.34	12.04	13.92
2	19.33	18.59	20.53	20.32	22.69	22.79	22.18
3	26.86	27.48	28.70	28.50	28.00	28.08	28.00
4	30.13	30.32	36.90	54.78	30.85	31.22	33.02
5	34.44	34.65	39.77	39.74	36.93	37.71	39.93
6	38.28	38.30	44.65	50.85	44.63	44.89	49.34
7	46.92	48.71	52.57	57.74	53.51	54.65	56.67
8	57.13	54.87	59.53	68.26	59.65	60.36	68.14
9	63.62	60.62	67.27	71.47	65.14	67.18	72.22
10	67.77	65.08	71.19	78.92	71.16	69.65	73.44
11	71.73	71.16	75.28	85.73	73.14	74.26	76.46
12	73.87	75.81	78.75	97.14	77.28	78.08	79.18

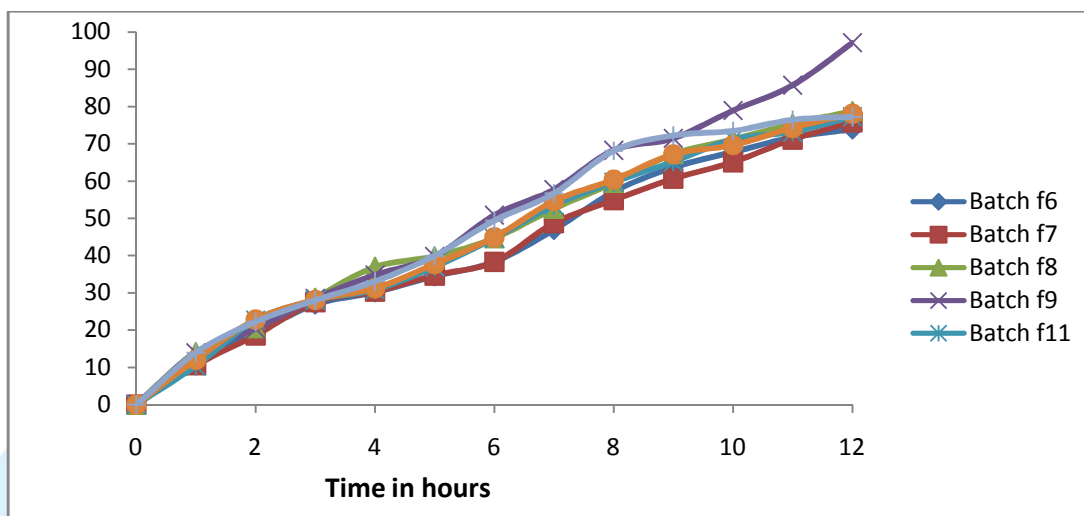


Fig. 5: Graph of time Vs % cumulative drug release

CONCLUSION

In the present investigation an attempt has been made to design and develop the formulation of propranolol hydrochloride patches using Eudragit L-100 and Eudragit S-100 by solvent evaporation method. The drug used is the best studied for therapy in treating hypertension. Selected drug complies with physicochemical properties required to permeate the skin. The preformulation studies involving description, solubility, melting point, partition coefficient of the drug were found to be comparable with the standard. Propranolol hydrochloride was successfully formulated as a Sustained release transdermal patches which prevents the frequency of administration and gives good patient compliance. The patches were subjected to following evaluation parameters such as physical appearance, thickness, folding endurance, drug content, percent moisture absorption, percent moisture loss, diffusion studies and skin irritation studies. All these parameters were within limits. From the Experimental results obtained F6 formulation is selected as the best formulation among all formulations. The in vitro drug diffusion study from formulation was found to be Sustained release. All the evaluation parameters obtained from formulation was found to be satisfactory. The formulation method used was simple, reliable and inexpensive. Based on the observations, it can be concluded that the attempt of formulation and evaluation of the propranolol hydrochloride patches was found to

be successful in the release of drug for an extended period of time. Further detailed investigations and elaborate in-vivo studies need to be carried out and an in-vitro in-vivo correlation need to establish to guarantee the efficiency and bioavailability of the formulation..

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