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Propranolol Hydrochloride Transdermal Patch Design and Development: In Vitro and Ex Vivo Evaluation

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Introduction

In general, transdermal medication administration refers to the topical application of substances to healthy, intact skin for either systemic therapy or localized treatment of the tissues beneath the skin. The objective of dosage design for transdermal medicines is to limit drug retension and metabolism in the skin while simultaneously optimizing the flux through the skin into the systemic circulation. Transdermal drug delivery devices are self-contained, discrete dose forms that are placed to undamaged skin and allow the medications to enter the bloodstream at a regulated pace. When compared to oral administration, transdermal medication delivery offers numerous benefits. For example, it increases absolute bioavailability by avoiding first-pass hepatic and gastrointestinal processing. increased effectiveness of treatment, decreased adverse effects as a result of blood concentration-time profile modification, Therapeutic agents are given through the skin at a controlled rate into the systemic circulation, resulting in a rapid termination of drug action by removing the drug application from the skin's surfaces.

Materials and Procedures

Propranolol hydrochloride, sodium hydroxide, potassium dihydrogen orthophosphate, methanol, dichloromethane, HPMC E15, PEG-400, and calcium and aluminum chloride, as well as a dialysis membrane.

Techniques

Preformulations research

The main purpose of preformulation studies is to investigate the chemical characteristics of the medicine and ascertain whether it is compatible with various excipients.

Study of Drug-Excipient Compatibility

Propranolol hydrochloride, a pure medication, and HPMC E15, a pure polymer, as well as their physical mixes utilized in formulations, were subjected to FTIR analysis in order to investigate potential interactions between the two substances.

FT-IR: The non-thermal analysis of drug-excipient (binary mixture of drug: excipient 1:1 ratio) was conducted using a Fourier Transform-Infra Red Spectrophotometer (FTIR Spectrum BX series 2.19 version) and spectrum v2.19 software. compatibility

Building the Propranolol Hydrochloride Calibration Curve in pH 7.4 Phosphate Buffer 100 mg of Propranolol Hydrochloride was precisely weighed and dissolved in pH 7.4 buffer to yield a range of 1000µg/ml. To get a concentration of 100µg/ml, 10 ml was taken out of the above and diluted to 100 ml. To get concentrations in the range of 10µg/ml to 50µg/ml, aliquots of 1 ml, 2 ml, 3 ml, 4 ml, and 5 ml were diluted in a 10 ml volumetric flask with pH 7.4 buffer. The absorbance was measured at 221 nm. One milliliter of this stock solution was diluted to ten milliliters to get a range of 10µg/ml. Using spectroscopy, absorbance was measured on the Y-axis, concentration on the X-axis, and a standard graph was plotted.

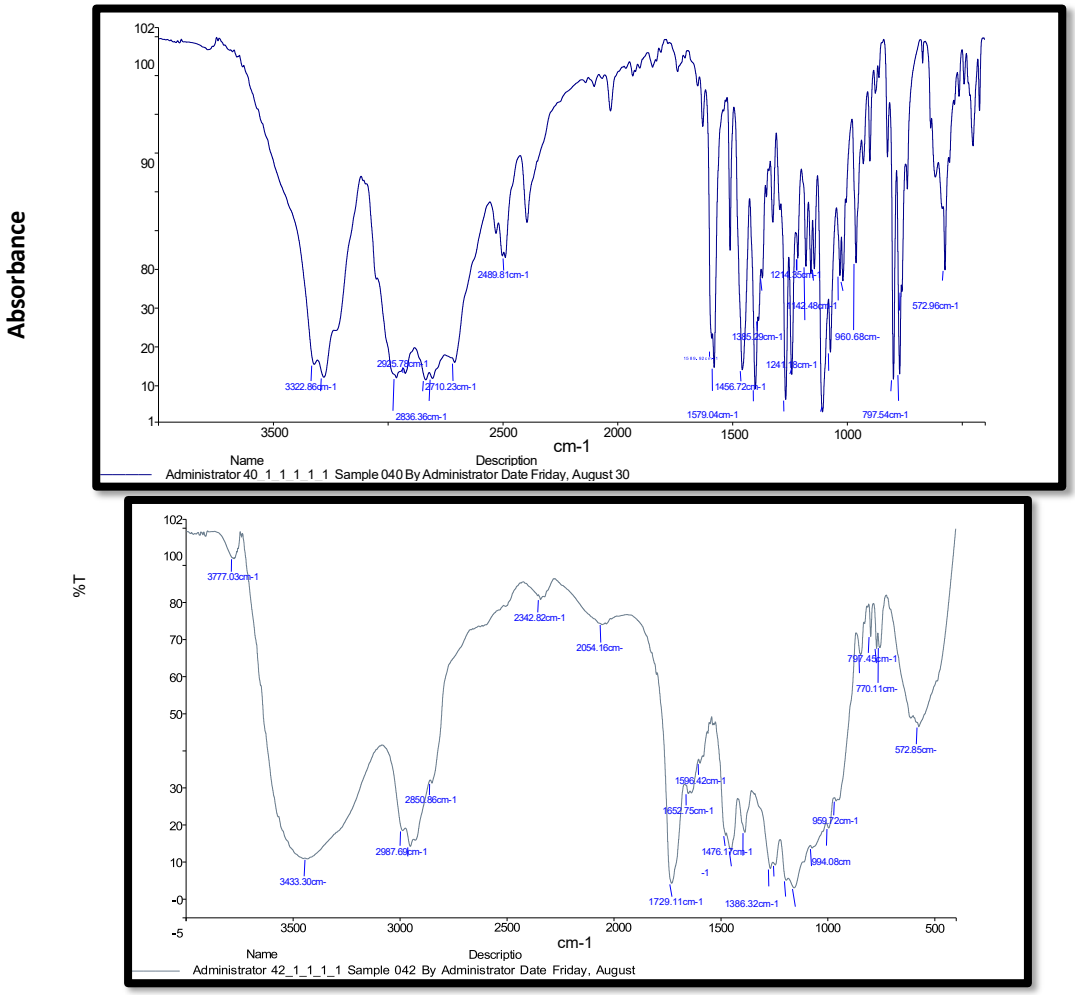
Formulation/Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hydrochloride (mg)	96.16	96.16	96.16	96.16	96.16	96.16	96.16	96.16	96.16
HPMC E15 (mg)	403.8	437.5	471.1	504.8	538.5	572.1	605.82	639.4	673.1
EUDRAGIT L-100 (mg)	173.0	187.5	201.9	721.2	230.7	245.2	259.6	274.0	288.4
Poly ethylene glycol 600(µL)	155	217	279	310	465	310	310	310	310
Methanol (mL)	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Dichloro methane (mL)	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5

Table: 1 Composition of Propranolol Hydrochloride Trasdermal patches

Results and Discussion Pre – Formulation Studies

Drug – excipient compatibility study by Fourier Transform Infrared spectroscopy

To investigate the non-thermal investigation of drug excipient compatibility (a binary mixture of drug and excipient 1:1



ratio), a Fourier Transform – Infra red spectrophotometer was employed. Compatibility tests were conducted between the pure medication (propranolol hydrochloride) and the drug with a physical mixture (excipient).

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Figure 2: FTIR Spectrum of Propranolol Hydrochloride + HPMC E15 + Eudragit L 100

IR Spectra	Peak Functional groups(cm^{-1})				
	O-H Stretching	Aromatic C=C Stretching	C- H Stretching	C-N Stretching	C-O

Drug	3322	1456	2710	1106	1192
Drug + HPMC E15 +Eudragit L100	3433	1652	2850	1156	1072

Table: 2 Excipient compatibility study – FTIR Analysis

There was no disappearance of any characteristics peak in FTIR spectrum of drug and the polymer used. This shows that there is no chemical interaction between drug and polymer used.

UV Spectroscopy (Determination of λ max)

On the basics of preliminary identification test and FTIR it was concluded that the drug complied the preliminary identification in pH 7.4 phosphate buffer. From the scanning of drug it was concluded that the drug had **λ max** of 221nm.

Construction of calibration curve of Propranolol Hydrochloride

- The standard graph of Propranolol Hydrochloride in PH 7.4 phosphate buffer have shown good linearity over a concentration range of 2-20µg/ml with R^2 of 0.9962.
- It obeys "**Beer- Lamberts** law".
- This graph was utilized in the estimation of Propranolol Hydrochloride samples.

oncentration (µg / mL)	Absorbance (at 221 nm)
2	0.051
4	0.120
6	0.183
8	0.251
10	0.302
12	0.359
14	0.420
16	0.467
18	0.531
20	0.566

Table: 3 Standard plot of Propranolol Hydrochloride in PH 7.4 phosphate buffer (λ max 221nm)

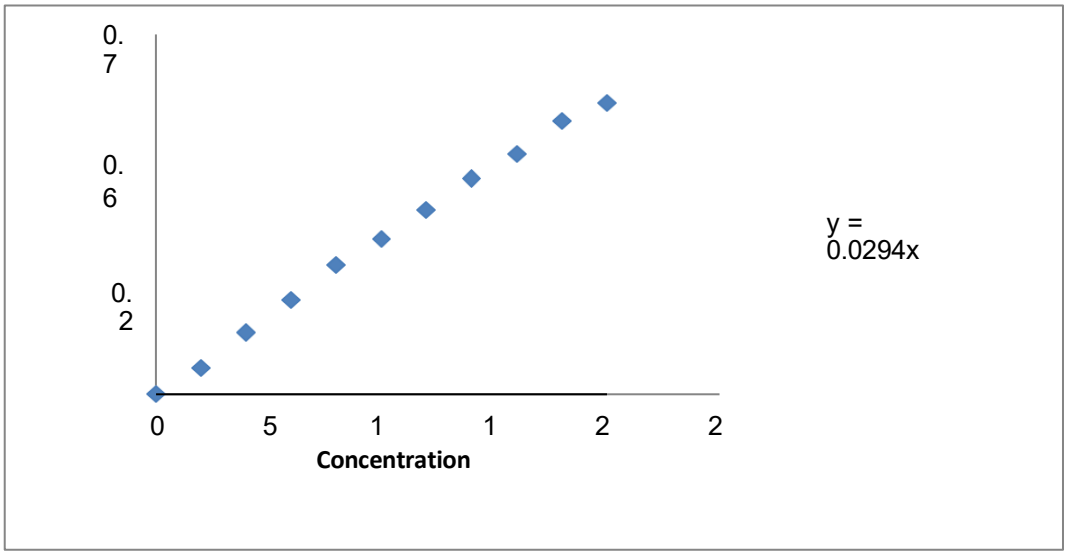


Figure 3: Standard graph of Propranolol Hydrochloride in pH 7.4 phosphate buffer Physicochemical properties

The patches prepared by general procedure were evaluated for the following properties

Weight variation test:

The results of weight variation test for various transdermal patches were shown in table 15 results of weight variation test indicated uniformity in weight of patches, as evidence by SD values, which were less than 2.0 for all formulations. In formulations the weights of the patches werealmost same.

Thickness variation test:

In thickness variation test, the thickness was found to be uniform. The thickness increase withincrease in HPMC E15 and Eudragit L 100 concentrations. The SD values were less than 2 for all formulations, an indication of more uniform patches. The results of thickness variation test for various transdermal patches were shown in table 10

Folding endurance number:

The folding endurance numbers of HPMC E15 and Eudragit L 100 containing patches has in the range of 90 and for the formulations prepared with permeation enhancers as in the range of 100 to 128 were shown in table 10. The folding endurance number gives the mechanical property of the patches, high folding endurance number indicate that has high mechanical property. The folding endurance number was increased with increasing in HPMC E15 and Eudragit L 100 content. These results indicated that the patches would not break and would maintain their integrity with general skin folding when applied.

Formulation	Weight(mg)	Thickness(mm)	Folding endurance
F1	81.66 ±0.15	0.25 ±0.012	90 ±4.2
F2	92.68 ±0.31	0.26 ±0.015	92 ±2.2
F3	96.98 ±0.34	0.28 ±0.016	100 ±4.5
F4	100.18 ±0.16	0.30 ±0.019	102 ±5.2
F5	103.98 ±0.19	0.31 ±0.031	103 ±4.2
F6	104.32 ±0.11	0.33 ±0.032	105 ±5.3
F7	123.25 ±0.35	0.34 ±0.034	106 ±5.4
F8	126.2 ±0.37	0.35 ±0.005	108 ±5.5

Table 4: Weight, Thickness, Folding endurance, of Propranolol Hydrochloride Transdermal patches (Mean ±S.D. n=3)

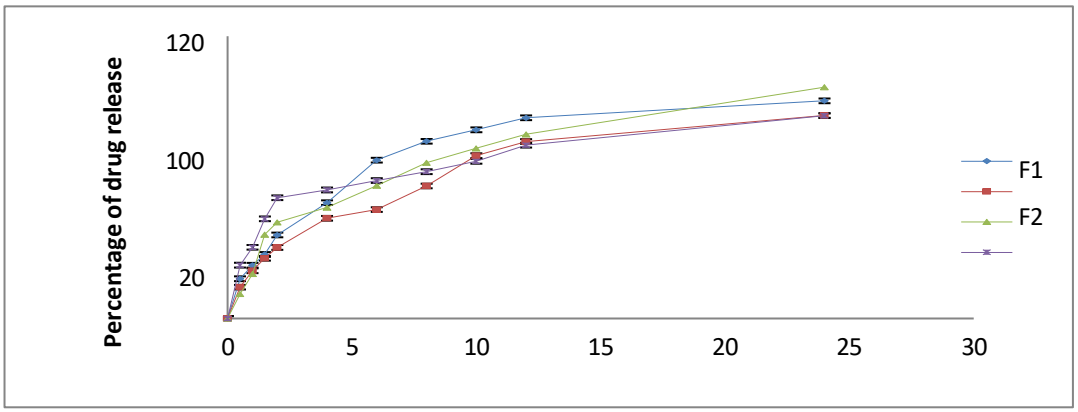
Estimation of drug content in polymeric patches:

Good uniformity in drug content was observed in all transdermal patches as evidenced by low SD values. The drug content is ranged 90.5% to 98.5%. The results of drug content for various transdermal films were shown in Table 11.

Moisture absorption and Moisture content study:

The results of moisture content and moisture absorption studies were shown in table 11. The moisture content in the patches for F1, F2, F3, F4, F5, F6, F7, F8 are 8.78, 9.45, 9.61, 9.99,

10.17, 10.74,14.3,and 15.2. The moisture absorption in the patches for F1, F2, F3, F4, F5, F6, F7, and F8 are 3.81, 3.86, 4.54, 4.74, 4.92, 5.23,
5.41 and 5.60. The results revealed that the moisture absorption and moisture content was found to be increase with increasing concentration



of polymer HPMC E15 and Eudragit L 100.The small moisture content in the formulations help them to remain stable and from being a completely dried and brittle patch.

Formulation	Drug content (%)	% Moisture absorbed	% Moisture content
F1	90.4±0.45	8.78±0.95	3.81±0.52
F2	91.3±0.46	9.45±0.39	3.86±0.37
F3	92.5±0.34	9.61±0.57	4.54±0.95
F4	93.2±0.42	9.99±0.32	4.74±0.45
F5	94.9±0.25	10.17±0.49	4.92±0.48
F6	96.8±0.41	10.74±0.56	5.23±0.52
F7	97.9±0.42	14.3±0.42	5.41±0.55
F8	98.2±0.24	15.2±0.43	5.60±0.49

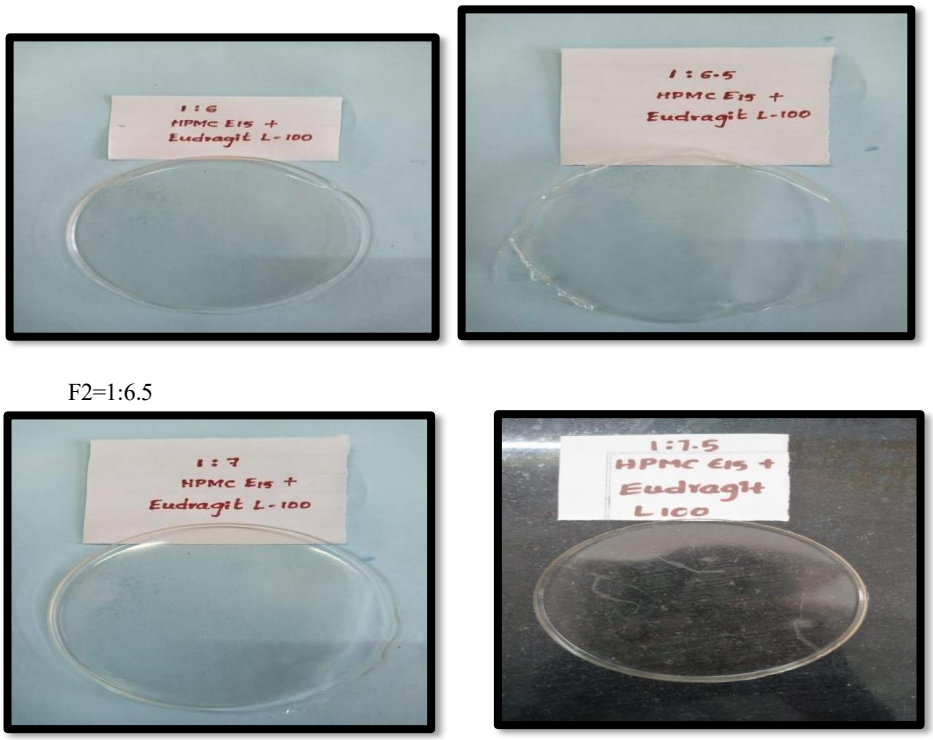
Table 5: Drug content, %Moisture absorbed and %Moisture content of Propranolol Hydrochloride Transdermal patches. (Mean ±S.D, n=3).

In vitro drug release studies from transdermal patches

In vitro Diffusion studies

Time(hr)	F1	F2	F3	F4
0.5	16.6±1.24	16.1±0.14	19.3±1.72	20.1±1.74
1	24.6±1.48	24.8±0.52	23.8±2.03	26.8±2.33
1.5	33.3±1.98	31.4±1.69	36.8±0.82	32.8±1.39
2	53.2±0.85	50.4±1.53	39.6±0.32	37.3±0.47
4	66.6±0.94	65.8±0.79	44.5±0.76	38.8±0.68
6	75.2±0.64	85.8±0.45	55.5±1.75	46.8±0.82
8	78.8±0.89	79.4±1.13	70.7±0.72	55.1±0.59
10	85.6±0.86	85.9±0.42	84.9±1.12	67.9±1.05
12	97.3±1.66	93.6±0.78	89.3±1.12	81.5±0.64
24	98.3±1.72	95.1±0.98	96.6±1.08	96.3±1.41

Table 6: Percentage of drug release of formulation (F1, F2, F3, F4). (Mean ±S.D, n=3).



F1 = 1:6 F2=1:6.5

F3=1:7 **F4=1:7.5**

Figure 5: Transdermal patches with different polymer ratios (1:6, 1:6.5, 1:7, 1:7.5)

Time(hr)	F5	F6	F7	F8
0	**0**	**0**	**0**	**0**
0.5	21.8±1.89	20.8±0.89	**19.9±1.72**	8.92±0.77
1	26.7±2.32	25.6±0.03	**23.4±2.13**	12.8±1.13
1.5	29.2±2.54	28.3±1.34	**35.4±1.81**	31.5±1.89
2	31.2±2.71	30.2±0.17	**40.8±1.42**	38.6±1.16
4	48.9±1.05	45.9±1.06	**49.6±0.56**	46.1±1.28
6	56.3±0.83	59.7±0.84	**53.6±0.54**	63.3±0.22
8	69.8±0.63	63.7±0.64	**70.7±0.72**	74.6±0.75
10	75.4±1.65	79.8±1.85	**79.9±1.88**	78.9±0.77
12	86.3±0.58	89.8±0.98	**94.2±0.17**	84.9±1.12
24	96.2±0.97	97.4±0.58	**99.6±1.62**	90.8±0.92

Table 7: Percentage of drug release of formulation (F5, F6, F7, F8)

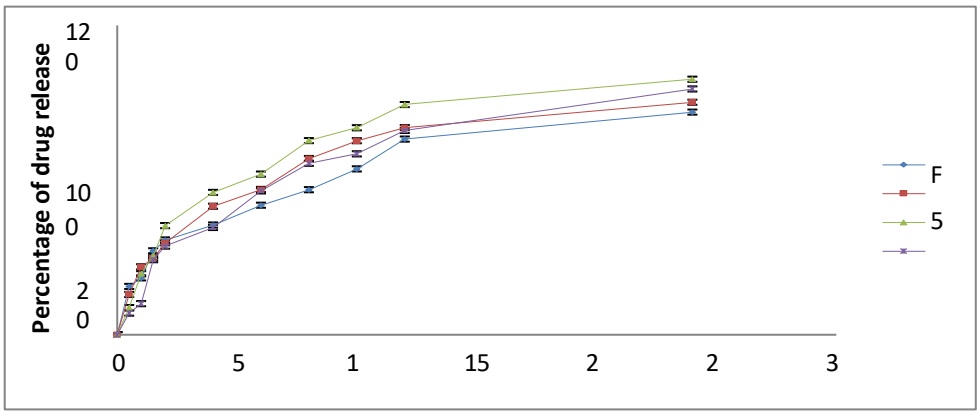
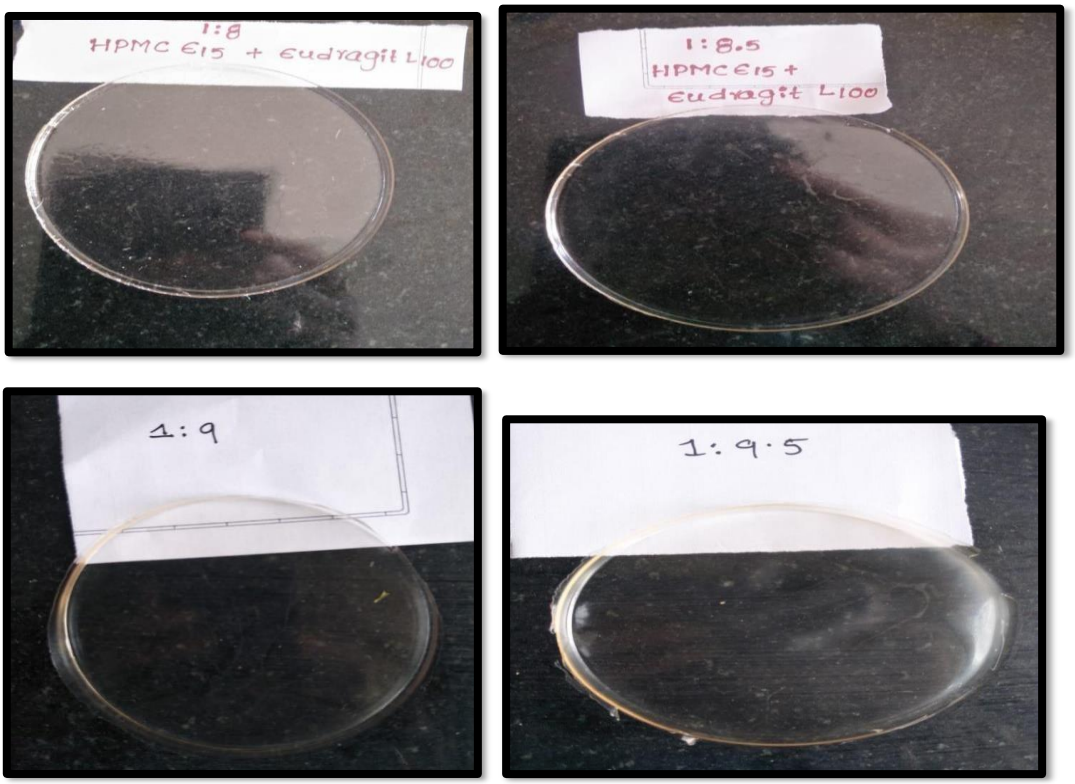


Figure 6: *In vitro* drug release studies of Propranolol hydrochloride transdermal patches (F5, F6 F7, F8)



Formulation code	Zero order equation(r^2)	First order equation(r^2)	Higuchi model(r^2)	Korsmeyer peppa's model	n value
F1	0.7432	0.9256	0.9621	0.9601	0.6387
F2	0.8255	0.9933	0.9820	0.9383	0.9345
F3	0.8360	0.9643	0.9811	0.9347	0.9965
F4	0.7849	0.9099	0.9270	0.9965	0.7666
F5	0.7677	0.9892	0.9694	0.9722	0.8281
F6	0.8022	0.9565	0.9771	0.9998	0.8002
F7	**0.9115**	**0.9746**	**0.9833**	**0.9624**	**0.7515**
F8	0.8235	0.9946	0.9802	0.9249	0.6251

Table 8: Drug release kinetics of Propranolol Hydrochloride Transdermal patches

gastric irritation produced by oral administration of drugs. Transdermal

1. From the above kinetics studies, for F7 the r2 value of zero order plot 0.9115 were greater than the r2 value of first order plot 0.9746 and the r2 value of Higuchi plot 0.9833.The r2 values reveals that the drug release pattern was found to follow “zero order” and through “diffusion” process, as it was evident from the release exponent (n) which was found to be 0.7515 indicating the drug release was anomalous (non- fickian) diffusion.

Discussion:

Conventional systems of medication that require multi-dose therapy which are having several challenges. The controlled drug delivery is a novel way to distribute medicine into systemic circulation at a predetermined rate. Our technology should imitate continuous intravenous infusion, which not only skips hepatic first pass elimination but also maintains a consistent, extended and therapeutically effective drug level in body. TDDS ensure direct therapy at the illness site, preventing the drug delivery could potentially be used to prolong the drug delivery. Propranolol hydrochloride is an anti – hypertensive medication.

The present study was aiming to create and construct matrix type Propranolol hydrochloride. In this matrix type of TDDS of Propranolol attempted by utilizing HPMC E15 and Eudragit L100 polymer with different ratios. Polymer HPMC is a suitable thickness as well as matrix forming agents.

FTIR research demonstrates that the medicine Propranolol hydrochloride is compatible with polymers utilized. There was no drug – excipient interaction in the physical combination. It also shows that the medications did not undergo any degradation or interaction through the whole of the patch production process.

The method adopted for patches preparation in this investigation was solvent casting process employing varied ratios of HPMC E15 and Eudragit L100 (F1-F8) and employing clove, eucalyptus, and lemon grass oils as penetration enhancers (F9-F16). In the formulation above, 20% v/w PEG-600 was added as a plasticizer. Weight, thickness, folding durability, drug content estimation, moisture absorption, moisture content determination, in vitro drug release tests, and ex vivo drug penetration investigations via goat abdomen skin were among the characteristics of the produced patches that were assessed.

The weight variation test result showed that the weight of the patches was uniform, as shown by the SD values, which for all formulations were less than 2.0. Because the patches were manufactured with the same ratio of medicine to polymer—that is, drug: HPMC E15 and Eudragit L100—the weight of the patches is nearly the same in all formulations. Physical evaluation revealed that the thickness was consistent. As the concentrations of HPMC E15 and Eudragit L100 rose, so did the thickness. For every formulation, the SD values are less than 2.0, indicating more homogeneous patches.

The folding endurance numbers of HPMC E15 and Eudragit L100 including patches have in the range of 90 .The folding endurance number gives the mechanical property of patches, high folding endurance number gives the mechanical property. As the concentrations of HPMC E15 and Eudragit L100 grew, so did the folding endurance number. The outcome showed that patches would not shatter and would keep their integrity. Low SD values showed that the drug content of each patch was quite uniform, ranging from 90.5% to 98.5%. Patches for F1, F2, F3, F4, F5, F6, F7, and F8 had moisture contents of 8.78, 9.45, 9.61, 9.99, 10.17, 10.74, 14.3, and 15.2.

Absorption was 7.9%, 8.6%, 8.9%, 9.8%, 12.9%, 13.2%, 13.8%, and 14.3% in patches for F1, F2, F3, F4, F5, F6, F7, and F8. The findings showed that it was discovered that as the concentration of hydrophilic polymer (HPMC E15) and Eudragit L100 increased, so did the moisture content and absorption. The formulation's tiny amounts of moisture prevent the patch from becoming entirely dry and brittle.

In conclusion

Transdermal drug delivery systems (TDDS) of the propranolol hydrochloride matrix type were made by film casting with Hydroxy propyl methyl cellulose E15 and Eudragit L100 in the following ratios: 1:6, 1:6.5, 1:7, 1:7.5, 1:8, 1:9, and 1:9.5. Polyethylene Glycol -400 20%vw is used as a plasticizer. The produced TDDS was thoroughly tested for moisture content, moisture absorption, and in vitro release. FTIR, or spectroscopy. Fourier Infrared Spectroscopy (FTIR) was used to examine the physicochemical interactions between

propranolol hydrochloride and HPMC E15 and Eudragit L 100.

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