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Research Article

Design and Development of Propranolol Hydrochloride Transdermal Patches: *In Vitro* and *Ex Vivo* Characterization

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Abstract

The main aim of this investigation is to design and develop matrix type transdermal patches of Propranolol Hydrochloride which is an anti-hypertensive drug. These matrix type transdermal patches were prepared by "Solvent Casting Technique" using drug, HPMC E15 and Eudragit L 100 in the ratio of 1:6, 1:6.5, 1:7, 1:7.5, 1:8, 1:8.5, 1:9, 1:9.5. All formulations carried 20%v/w of PEG-600 as plasticizer. The prepared patches were characterized for various physicochemical parameters like weight, thickness, folding endurance, drug content, percent moisture content, percent moisture absorption, and in vitro drug release and ex vivo permeation. Among this 1:9 ratio was found to be an Optimized formulation and patches were prepared by using permeation enhancers (lemon grass oil, Eucalyptus oil, and clove oil). The cumulative amount of drug release in 12hrs for F7 formulation showed maximum and used for that formulation skin permeation on Goat abdominal skin. FTIR studies show no interaction between drug, polymer and other excipients. The drug permeation kinetics followed "First order" and "zero order" profile with diffusion mechanism.

Keywords: solvent casting, dispersion method, diffusion, HPMC E15, eudragit L100, FTIR

Introduction

Transdermal drug administration generally refers to topical application of agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retension and metabolism of the drug in the skin. Transdermal drug delivery systems are defined as self-contained discrete dosage forms which applied on the intact skin, delivery the drugs through the skin, at controlled rate to systemic circulation. Transdermal drug delivery system has many advantages over the oral route of administration such as Improves absolute bioavailability due to avoidance of first pass hepatic and gastrointestinal metabolism, Enhance therapeutic efficacy, reduced side effects due to optimization of blood concentration-time profile, Rapid termination of drug action by removal of drug application from the surfaces of the skin, Therapeutic agents delivered at controlled rate through skin into systemic circulation.

Materials and Methods

Propranolol Hydrochloride, Methanol,Dichloromethane,HPMC E15,PEG-400,Potassium dihydrogen orthophosphate,Calcium chloride,Aluminium chloride,Sodium hydroxide, Dialysis membrane.

Methodology

Preformulations studies

Preformulation studies area unit primarily done to research the chemistry properties of drug and to determine its compatibility with different excipients.

Drug-Excipient Compatibility study

This was carried out by FTIR analysis of pure drug (Propranolol Hydrochloride) and pure polymer (HPMC E15) and their physical mixtures as used in formulations to study the possible interaction between drug and polymers.

FT-IR:

A Fourier Transform - Infra Red Spectrophotometer (FTIR Spectrum BX series 2.19 version) equipped with spectrum v2.19 software was used to study the non-thermal analysis of drug- excipient (binary mixture of drug: excipient 1:1 ratio) compatibility

Construction of calibration curve of Propranolol Hydrochloride in Phosphate buffer pH7.4

100mg of Propranolol Hydrochloride was accurately weighed and dissolved in pH 7.4 buffer to obtain a range of 1000µg/ml. From the above 10ml was withdrawn and diluted to 100ml to obtain a concentration of 100µg/ml. From this stock solution 1ml was diluted to 10ml to obtain a range of 10µg/ml and then aliquots of 1ml, 2ml, 3ml, 4ml, 5ml were diluted in 10ml volumetric flask with pH 7.4 buffer to give concentrations in range of 10µg/ml to 50µg/ml respectively, absorbance was measured at 221nm. Absorbance was determined by spectroscopy was taken on Y-axis, concentration taken X-axis, plotted a standard graph.

Method of preparation: Solvent casting technique

Matrix type transdermal patches containing Propranolol Hydrochloride were prepared by "solvent casting technique", using different ratios of HPMC E15. Weighed quantity of polymer and drug was dissolved in

25ml of solvent mixture 1:1 ratio (Methanol: Dichloromethane) allowed for swelling for about 6 hours, after 6 hours then add 20%v/w (of dry polymer weight) polyethylene glycol 400 was incorporated as plasticizer and the weighed drug dissolved in the solvent and added to the above solution and then vortexed for 5min. Further, it was set aside for some time to exclude any entrapped air and then transferred into previously cleaned Anumbra Petri plate. Drying of these patches is carried out at room temperature for overnight and then in vaccum oven at room temperature for 10-20 hours.

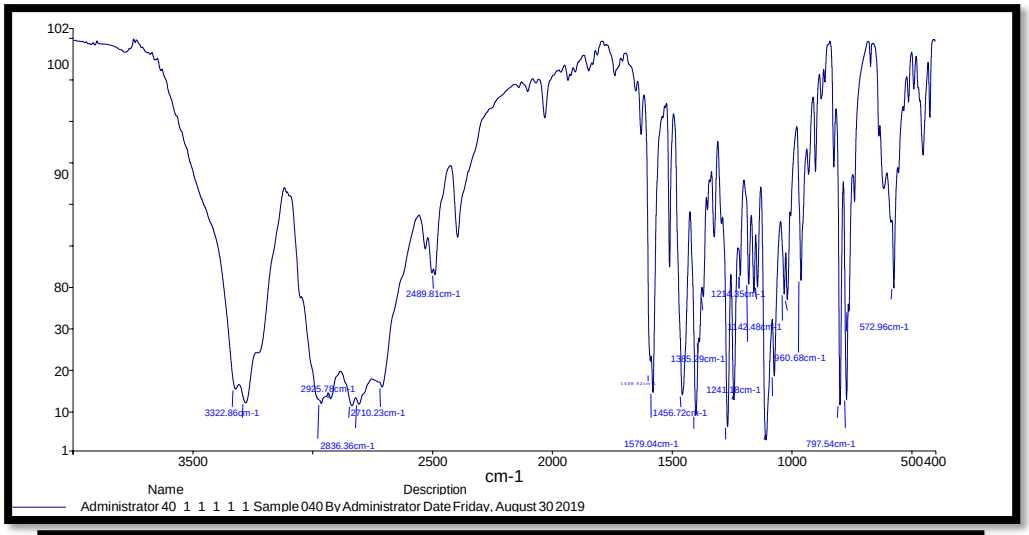
Formulation/Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hydrochloride (mg)	96.16	96.16	96.16	96.16	96.16	96.16	96.16	96.16	96.16
HPMC E15 (mg)	403.8	437.5	471.1	504.8	538.5	572.1	605.82	639.4	673.1
EUDRAGIT L-100 (mg)	173.0	187.5	201.9	721.2	230.7	245.2	259.6	274.0	288.4
Poly ethylene glycol 600(µL)	155	217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

A Fourier Transform – Infra red spectrophotometer was used to study the non- thermal analysis of drug excipient (binary mixture of Drug: excipient 1:1 ratio) compatibility. The Pure drug (Propranolol Hydrochloride) and drug with physical mixture (excipient) compatibility studies were performed.



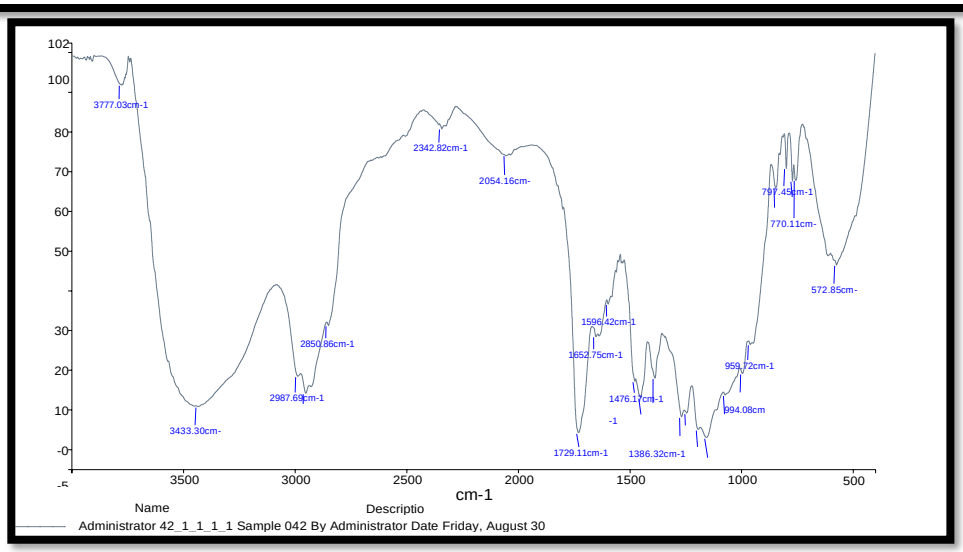


Figure 2: FTIR Spectrum of Propranolol Hydrochloride + HPMC E15 + Eudragit L 100

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.

Concentration (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)

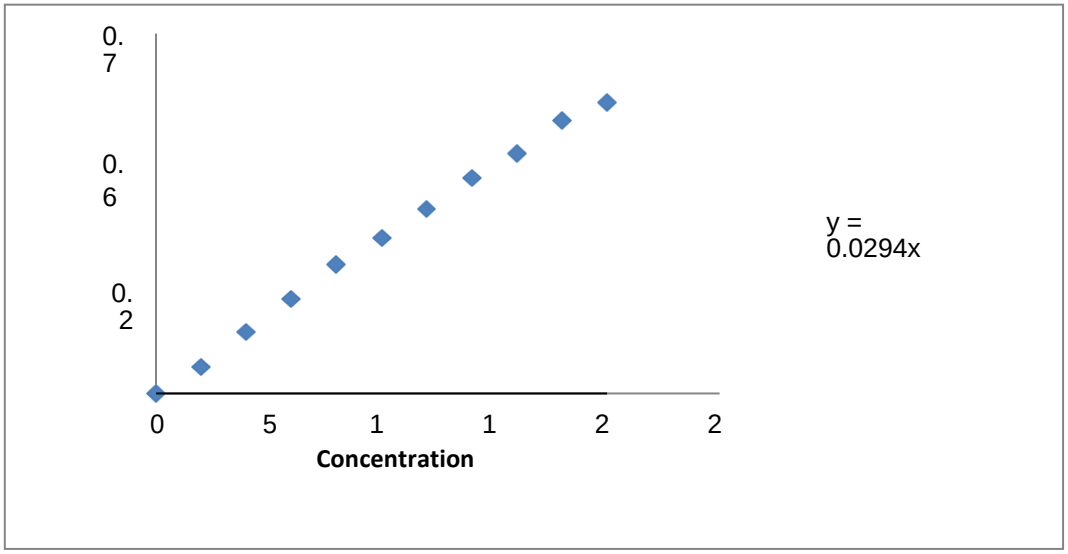


Figure 3: Standard graph of Propranolol Hydrochloride in pH 7.4 phosphate buffer Physicochemical properties

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 were almost 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

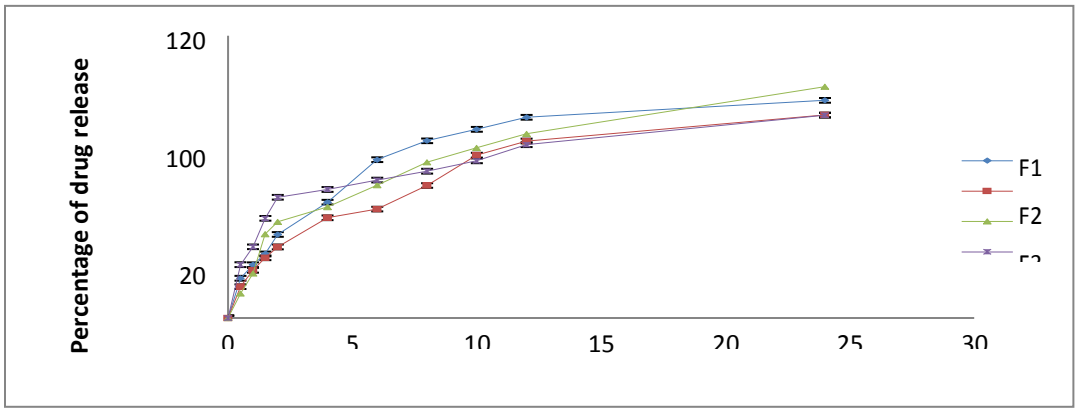
Table 5: Drug content, %Moisture absorbed and %Moisture content of Propranolol Hydrochloride Transdermal patches. (Mean ±S.D, n=3).

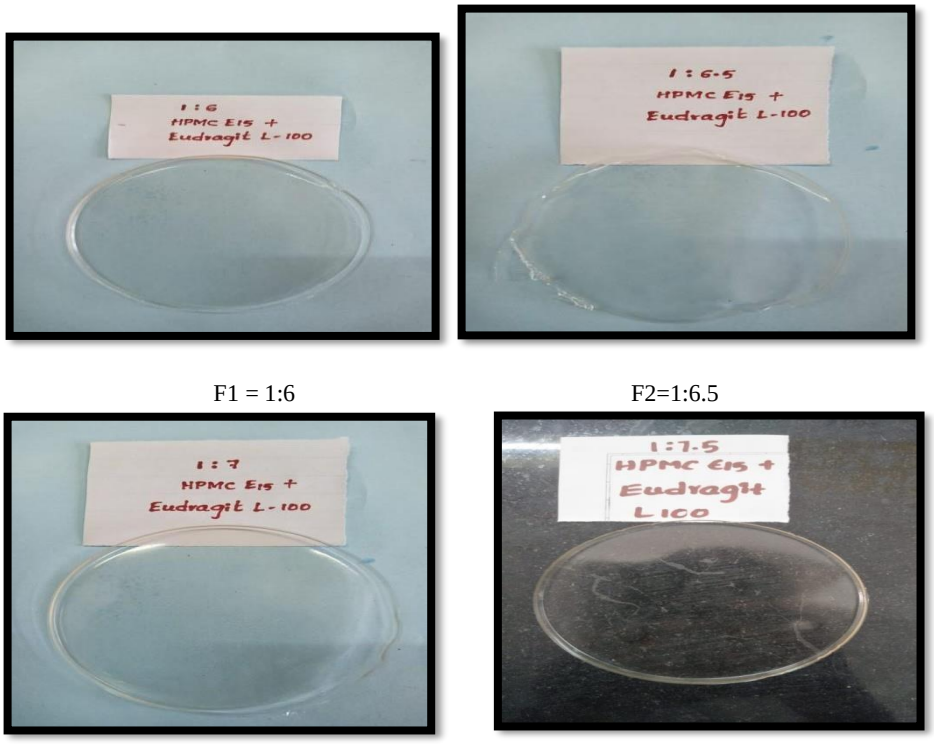
In vitro drug release studies from transdermal patches

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)

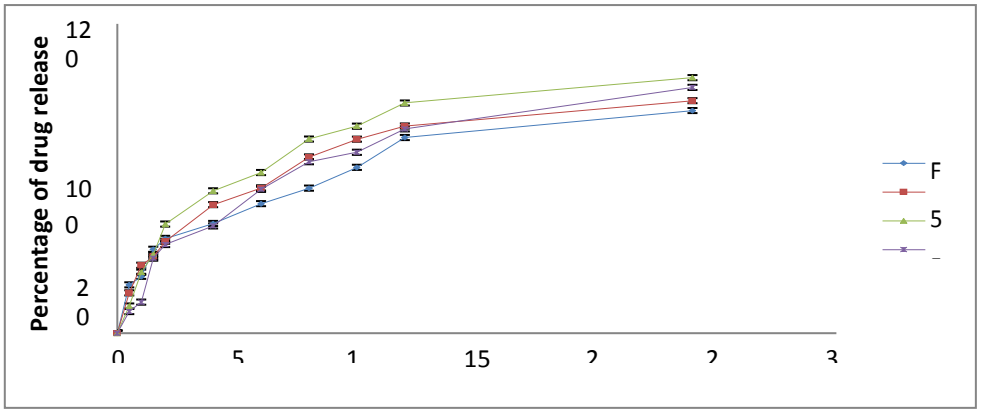


Figure 6: *In vitro* drug release studies of Propranolol hydrochloride transdermal patches (F5, F6 F7, F8)

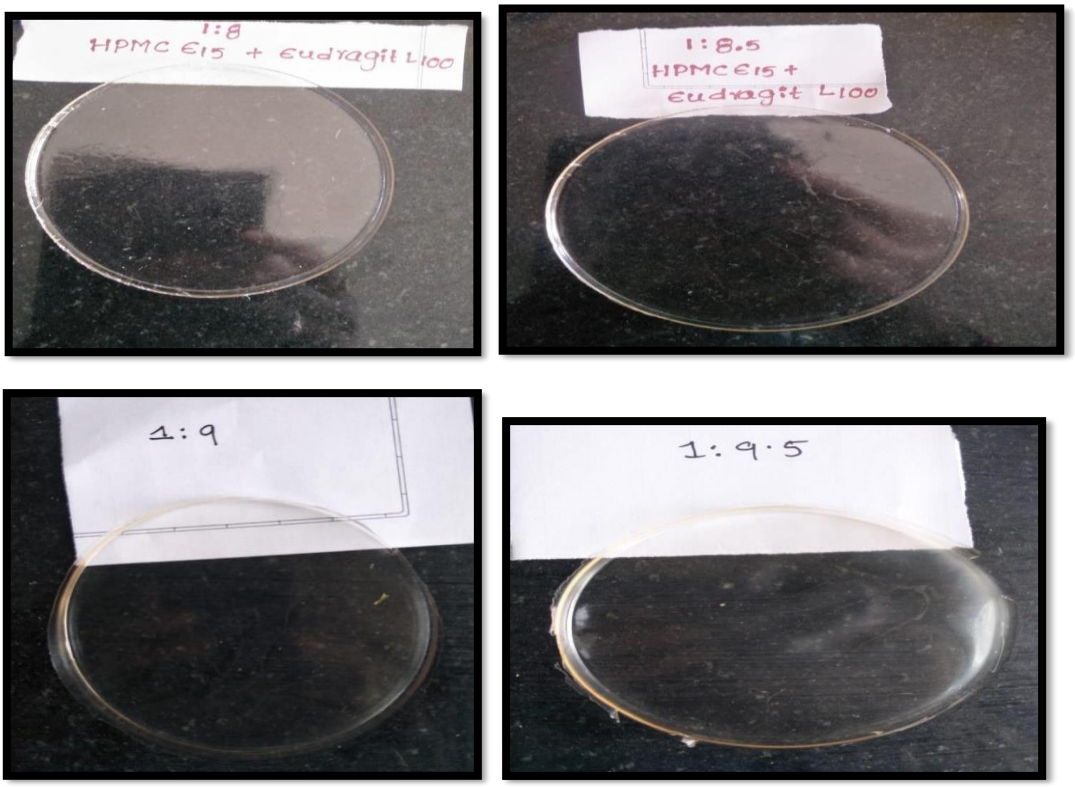


Figure 7: Transdermal patches with different polymer ratios (1:8, 1:8.5, 1:9, 1:9.5)

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

From the above kinetics studies, for F7 the r^2 value of zero order plot 0.9115 were greater than the r^2 value of first order plot 0.9746 and the r^2 value of Higuchi plot 0.9833.The r^2 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 many problems. The controlled drug delivery is a newer approach to deliver drug into systemic circulation at a predetermined rate. Our system should duplicate continuous intravenous infusion, which not only bypasses hepatic first pass elimination but also maintains a constant, prolonged and therapeutically effective drug level in body. TDDS ensure direct treatment at the disease site, preventing the gastric irritation produced by oral administration of drugs. Transdermal drug delivery could also be used to prolong the drug delivery. Propranolol hydrochloride is an anti – hypertensive drug.

The present study was aimed to design and develop matrix type Propranolol hydrochloride. In this matrix type of TDDS of Propranolol attempted by using HPMC E15 and Eudragit L100 polymer with different ratios.

Polymer HPMC is a good thickness as well as matrix forming agents.

FTIR analysis shows that the drug Propranolol hydrochloride is compatible with polymers used. There was no drug – excipient interaction in the physical mixture. It also suggests that the drugs did not undergo any degradation or interaction through the whole of the patch making process.

The method employed for patches preparation in this study was solvent casting method using different ratios of HPMC E15 and Eudragit L100

(F1-F8) and using lemon grass oil, Eucalyptus oil, and Clove oil as penetration enhancer (F9-F16), in the above formulation 20%v/w PEG-600 was incorporated as plasticizer. The prepared patches were evaluated for the following properties such as weight, thickness, folding endurance, estimation of drug content, moisture absorption, moisture content determination, *in vitro* drug release studies & *ex vivo* drug permeation studies through goat abdominal skin.

Result of weight variation test indicated uniformity in weight of patches as evidenced by SD values, which are less than 2.0 for all formulations. In all formulations the weight of the patches are almost same because the patches were made with same ratio of drug and polymer i.e., Drug : HPMC E15 and Eudragit L100.In physical evaluation the thickness was found to be uniform. The thickness increased with increased in HPMC E15 and Eudragit L100 concentration. The SD values are lower than 2.0 for all formulations, as indication of more uniform patches.

The folding endurance numbers of HPMC E15 and Eudragit L100 containing 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. The folding endurance number was increased with increased in the concentration of HPMC E15 and Eudragit L100. The result indicated that patches would not break and would maintain their integrity .Good uniformity in drug content was observed in all patches as evidenced by low SD values the content ranged from 90.5%-98.5%.

The moisture content in patches for F1, F2, F3, F4, F5, F6, F7, F8 and were 8.78, 9.45, 9.61, 9.99, 10.17, 10.74, 14.3, and 15.2.The moisture absorption in patches for F1, F2, F3, F4, F5, F6, F7, F8 were 7.9%, 8.6%, 8.9%, 9.8%, 12.9%, 13.2%, 13.8%, 14.3%. The results revealed that the moisture absorption and moisture content was found to increase with increasing the concentration of hydrophilic polymer (HPMC E15) and Eudragit L100. The small amounts of moisture in formulation help them to remain stable and from being completely dried and brittle patch.

Conclusion

The Propranolol hydrochloride matrix type transdermal drug delivery systems (TDDS) were prepared by film casting technique using Hydroxy propyl methyl cellulose E15 and Eudragit L100 in the ratio of 1:6,1:6.5,1:7,1:7.5,1:8,1:9,1:9.5. Polyethylene Glycol -400 20%v\w is incorporated as a plasticizer .The prepared TDDS were extensively evaluated for in vitro release, moisture absorption, moisture content. The Spectroscopy (FTIR).

physicochemical interaction between Propranolol hydrochloride and HPMC E15 and Eudragit L 100 were investigated by Fourier Infrared Spectroscopy (FTIR).

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