FORMULATION AND EVALUATION OF TRANSDERMAL PATCH OF ESMOLOL HYDROCHLORIDE

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Abstract

The purpose of this study was to create a transdermal drug delivery system with reduced adverse effects in comparison to alternative painkillers and enhanced drug absorption through the identification of the best transdermal formulas patches made with different amounts of plasticizer.The transdermal patch was prepared using solvent evaporation method which contains esmolol hydrochloride and polymers such as HPMC and carbopol. Plasticizers such as Glycerine and PEG were employed by varying their concentration in each batch their impact on drug release was investigated. Ethanol serves as a penetration enhancer in the solvent system

consisting of water and ethanol. Drug delivery from different polymer based transdermal patches would be improved by a good penetration enhancer. The transdermal therapeutic system allows for a sustained, predetermined rate of drug release through intact skin into systemic blood stream over an extended period of time.

Weight fluctuation, thickness, drug content, moisture content, moisture uptake, flatness and invitro drug release were all evaluated for each prepared formulation.

Keywords: Carbopol, Dissolution, Erosion, Calibration, Esmolol, Hepatic metabolism.

1. Introduction

Transdermal patches are characterized as independent, distinct dose forms that, when administered to the intact skin, administer the medications through the skin at regulated pace to the circulation of the body. In other transdermal patches are drug-adhesive.[1] These transdermal formulations are an additional drug delivery method. The administration that has undergone significant development in order to deliver of many active ingredients. Transdermal application can stop the first-pass effect, which has fewer adverse effects than oral getting ready.[2] The ability to avoid issues with gastric irritation, pH, and emptying rate effects, avoid hepatic first-pass metabolism which increases the drugs bioavailability, lower the risk of systemic side effects by minimizing plasma concentrations compared to oral therapy provide sustained release of drug at the site of application that the skin offers as a drug delivery site.[3] The formulations components including the chosen polymers and excipients have a big impact on the patch physical characteristics, drug release and applicability. The characteristics of the active ingredient or substances must also be taken into account as a significant influencing factor when developing the composition.[4]

1.1 Basic Components of Transdermal Drug Delivery System

1.1.a Drug:

For effectively creating a transdermal medication delivery system, the medication should be carefully selected. The subsequent are a few of a medications ideal qualities for transdermal delivery.

- The medications molecular weight ought to be lower than roughly a thousand Daltons.
- The drug melting point should be low.[5]

1.1.b Polymers:

Polymers serve as the carrier for the drug, forming a matrix or reservoir that holds and stabilizes the drug. It regulates how quickly and how long a drug is released.[6]

1.1.c Permeation Enhancer:

These substances increase the permeability of the skin by changing the skin to act as a barrier to a desired penetrants flow.[7]

1.1.d Plasticizer:

Plasticizers improve the polymer films elasticity and flexibility while decreasing brittleness, which makes the patch more comfortable and long lasting.[8]

1.1.e Solvents:

These substances may improve penetration by fluidizing lipids or ingesting the polar pathway. For example; Water alcohols include ethanol and methanol.[9]

This is try to create an esmolol hydrochloride transdermal patch. Brevibloc is a common trade name for esmolol, a cardio selective beta-1-receptor blocker. At prescribed therapeutic dosages, it exhibits q quick onset but brief duration of action without producing notable intrinsic sympathomimetic effects. By inhibiting the beta-adrenergic receptors in the heart, it lowers the force and frequency of cardiac contractions.[10] The goal of current project is to transdermal patches are prepared using a variety of polymers and to produce a medication with sustained release acti on of the chosen medication candidate.[11]

2. Materials and Methods

Every chemical and material used came from a laboratory grade. The chemicals and reagents used are Esmolol Hydrochloride, Ethanol, HPMC, Carbopol, Glycerine, PEG. The drug is obtained as gift sample.[12]

Table. No 2.1: List of materials used

S. No	Drug and Excipients
1	Esmolol HCl
2	HPMC
3	Carbopol
4	Glycerine
5	PEG
6	Ethanol

3. Determination of λ max and preparation of calibration curve for Esmolol HCl

The standard calibration curve of Esmolol HCl was determined in pH 7.4 buffer. It was discovered that the λmax was 465 nm. So, the standard calibration curve of Esmolol HCl was developed at this wavelength. The calibration curve was linear between 10–50 µg/ml. Results were tabulated in Table No.3.1 and plotted in Fig No.3.1. The R^2 value in pH 7.4 was found to be 0.990 respectively.

Table No. 3. 1 Standard curve data of Esmolol HCl in 7.4pH buffer at 465 nm

S. No.	Concentration (µg /ml)	Absorbance
1	10	0.092
2	20	0.248
3	30	0.389
4	40	0.469
5	50	0.621

The procedure for standard calibration curve of Esmolol HCl in 7.4 pH buffer at 465 nm was discussed and the results were shown here.

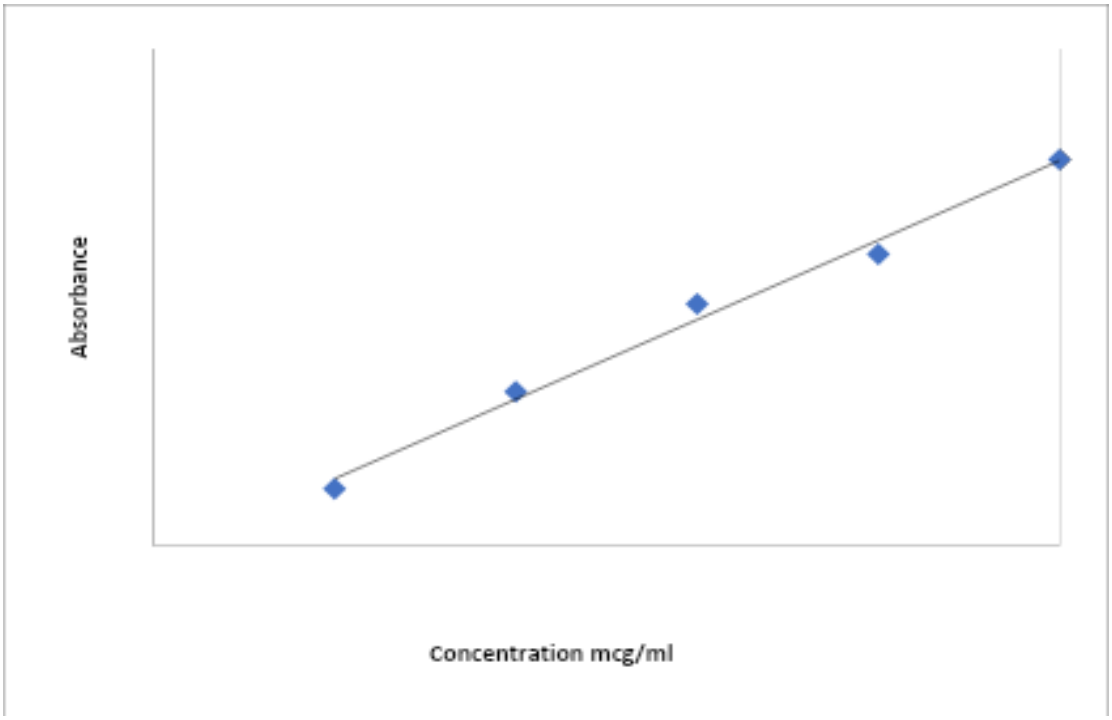

Fig No.3.1 Calibration Curve of Esmolol HCl

4. Formulation of Transdermal Patch

4.1 Solvent Evaporation Method:

To prepare the transdermal patch by using solvent casting method of six different formulas(table-4.1). This process entails breaking down polymers and additional ingredients in a solvent, then transferring the resultant mixture into mold and the solvent is evaporated, leaving only the active ingredients within the patch.

The polymers like HPMC and carbopol were taken in required quantity as shown in table no-4.1. About 20ml of solvent mixture of ethanol and water (1:1) was added and shacked to prevent the formation of lumps and then kept aside for swelling of polymers. And after complete solubilization of polymers in mixture of solvents, then add required quantity of glycerine to the mixture and stir well to dissolve homogenously. Finally weighed quantity of esmolol hydrochloride added to the polymer solution and mixed well. It was kept aside for some time and then transferred into a petri plate containing small amount of glycerine. A glass funnel was flipped over the petri plate to regulate the rate of solvent evaporation. The transdermal patches were successfully prepared for compositions given in table no-4.1. The patches were cutted of required batch size and stored in aluminium pouch then preserved for evaluation studies.[13]

Table.No.4.1: Composition of Esmolol HCl Transdermal Patch

Ingredients	Formulations Code					
	F1	F2	F3	F4	F5	F6
Esmolol HCl(mg)	500	500	500	500	500	500
Carbopol (mg)	100	200	400	-	-	-
HPMC(mg)	-	-	-	100	200	400
Glycerine (ml)	4	4	4	4	4	4
Ethanol (ml)	10	10	10	10	10	10
Water (ml)	10	10	10	10	10	10
PEG 400 (ml)	1	2	4	1	2	4

5. Evaluation of Transdermal Patches of Esmolol Hydrochloride

5.1 Weight Variation

The individual weights of randomly to selected films are determined. The weight of the can be measure. It is not different from the individual weight. The Patch weight can be measure using analytical balance. Limit of Weight Variation is 30-49.[14]

5.2 Thickness

The Patch thickness can be measure by micrometer screw gauge at five different point of the Patch i.e. It is possible to calculate the mean thickness of the middle and four corners. Sample with air bubble, tear having means thickness variation of greater than 5% are excluded from analysis. It is essential for the uniformity of thickness is directly related to the accuracy of dose in the Patch.[15] Limit of Thickness is 0.05-0.09.

5.3 Folding Endurance

The Transdermal Patch can be measured by hand.The Patch can be repeatedly folded at the same place till it breaks. The number of times Patch could be folding at the same place without breaking gives the value of folding endurance.[16] Limit of Folding Endurance is 98-128.

5.4 Moisture content (Loss on drying)

The stability of dosage forms may be impacted by the intrinsic moisture content of the material, particularly if it contains a medicine that is water-sensitive. The moisture content that results in a weight loss during the process is determined using the absolute approach. Three patch from each batch (3.14 cm^2), were weighed individually and the average weight was calculated. This weight was considered as an Initial weight. After that, all of the patches were stored for 24 hours at room temperature in desiccators with active silica.

The final weight was noted when there was no further change in the weight of individual patch.[17] The percentage moisture absorption was calculated as a difference between initial and final weight with respect to final weight. Limit of Moisture content is 2.632-2.854.

$$\% \text{ Moisture content} = (\text{Initial weight} - \text{Final weight}) \times 100$$

5.5 Drug content

Drug content determination of the Patch was carried out by dissolving the Patch of 2 cm2 in 100 ml of pH 7.4 phosphate buffer using magnetic stirrer for 1 hour. The drug concentration was then evaluated spectrophotometrically at λmax of 465 nm. The determination was carried

out in triplicate for all the formulations and average with standard deviation was recorded and reported and results were tabulated in table no.12 Limit of content uniformity is 78-89%.

5.6 *In-vitro* drug penetration studies

To study the *in-vitro* drug release of Esmolol HCl from transdermal patch, a modified Franz Cell apparatus (Perm Gear, USA) was fabricated. The initial stage involved attaching an artificial membrane between the Franz Cell apparatus's donor and receptor compartments.
As a receptor solvent, phosphate buffer pH 7.4 was used. Five milli liters of the receptor solvent were added to each receptor compartment.

The membrane was cut into such piece that the diffusion area was $2cm^2$.The transdermal patch was fixed on then membrane in such a way that the drug layer of the patch was facing to the artificial membrane and was then fixed in between the donor and receptor compartments of the Franz Cell apparatus.[18-20] The temperature of receptor solvent was maintained at 32°C ± 1 °C with constant circulation of hot water. Samples of each 2 ml were withdrawn from the receptor compartments at specific time interval and were immediately replaced with fresh receptor solvent already maintained at the same temperature. The samples were filtered through a membrane filter [0.45µm] and were analyzed for the drug concentrations by using UV-Visible spectrophotometer at a detection wave length of 465 nm.

5.7 Kinetics of drug release

The mechanism of drug release from the Esmolol HCl from transdermal patch during the dissolution test in dissolution medium, (pH-7.4 buffer) was determined using zero order and first order.

5.7a Zero order equation

It describes systems where the release rate is independent of the concentration of the dissolved species. The zero order equation fits the dissolution data.

$Q = Q0 - K0t$ (1)
Q = Amount of drug released at times'
Q0 = Amount of drug released initially (often considered zero)
K0 = Zero order rate constant

A concentration vs. time graph would show a straight line with a slope of K0 that intercepts the axes' origin. Plotting the cumulative percentage of medication dissolved against time yields zero order graphs.

5.7b First order equation

The release from systems where the concentration of the dissolving species affects the rate of dissolution is described by the first order equation.
The dissolution data of tablet formulations in dissolution medium that is water containing PH-6.8 phosphate buffer were plotted in accordance with the first-order equation, i.e., the logarithm of the percent remained as a function of time. Log C = Log C0 – Kt / 2.303 (2)
C0 = Initial concentration of the drug
C = Concentration of drug at time's K = First order constant t = Time

5.7c Higuchi model

In order to investigate the release of water-soluble and low-soluble medications integrated into semisolid and solid matrices, Higuchi created models in 1961 (Higuchi 1961) and 1963 (Higuchi 1963). The relationship found when studying the dissolution from a planer system with a homogenous matrix was;

A = [D (2C-Cs) Cst] 1/2 (3)

where D is the drug molecules' diffusivity in the matrix material, C is the initial drug concentration, and Cs is the drug's solubility in the matrix media,and A is the amount of drug released in time per unit area. For instance, this connection can be used to illustrate how a medicine dissolves in suspension from ointment bases. In order to investigate the dissolution from a planer in a spherical heterogeneous matrix system, where the drug's solubility is greater than its concentration in the matrix and its release takes place through matrix pores, the following relationship was found:

$A = D\varepsilon/\tau\ (2C-\varepsilon Cs)\ Cst$ (4)

where τ is the capillary system's tortuosity factor, ε is the matrix porosity, and A, D, C, Cs, and all have the same meaning as in equation (4). In general way Higuchi model can be simplified (generally known as the simplified Higuchi model) as,

A= KH t½ (5)

Where KH is the Higuchi dissolution constant. Higuchi describes drug release as a diffusion process based in the Flick's law, square root time dependent. Example: Drug dissolution from some modified release dosage forms as in case of some transdermal systems and matrix tablets with water soluble drug s follows the above relationship as described in equation (5).

5.7d Korsmeyer-Peppas model

In 1983 Korsmeyer et al developed a simple, semi-empiric model, when diffusion is the main drug release mechanism, relating exponentially the drug release to the elapsed time (t).

$At/A\infty = atn$ (6)

Where 'a' is the constant incorporating structural and geometrical characteristic of the dosage form, n is the release exponent , indicative of the drug release mechanism and the function of 't' is $At/A\infty$.

This n value was utilized by Pappas in 1985 to describe various release mechanisms, coming to the conclusion that values for a slab of n = 0.5 for fiction diffusion and between 0.5 and 1.0 or n = 1.0 for mass transfer using a non-fiction model are appropriate. For anomalous transport, $0.5 < n < 1.0$. The location of the release curve where $At/A\infty < 0.6$ should be the sole one utilized to calculate the exponent "n." In situations where the release mechanism is unclear or when many release phenomena may be at play, this model is typically utilized to assess the release of polymeric dosage forms.

When there is the possibility of a burst effect, the equation (6) becomes.

$At/A\infty = atn + b$ (7)

Where 'b' is the burst effect. The Korsmeyer equation i.e. equation (6) were considered inappropriate since the introduction of the lag period was essential to describe the accurately the quantity of drug released. An equation

$At/A\infty = [k (t-l) n + k' (t-l) 2n]$ (8)

Incorporating a lag period (l), kinetic constant (k and k') for diffusion and erosion controlled release and a diffusion exponent (n) produced the best fit of the data. The kinetic constants were not normally additive, k' becoming increasingly negative with increase in temperature.

5.7e Hixson – Crowell model

In 1931, Hixson-Crowell identified a way to assess medication release as the diameter and surface area of the particles or tablets changed and recognized as the that the cubic root of the particle's volume determines its regular area, the equation given as $A\ 0\ 1/3 – At1/3 = kst$ (9) where ks is a constant that incorporates the surface volume relation, A0 is the starting amount of medication in the dosage form, and At is the amount of drug that is left in the dosage form at times". For instance, if the tablet's dimensions decrease proportionately in a way that maintains the original geometrical form at all times, the dissolving will take place in planes parallel to the drug surface. In this instance, the cubic root of the unreleased percentage of the medication vs. time will be visually portrayed as linear if equilibrium requirements are not satisfied and the geometrical shape of the dose form diminishes correspondingly with time.
This model is used by assuming that release rate is limited by the drug particles dissolution rate and not by the diffusion.[21-22]

The procedure for kinetics of drug release of Esmolol HCl transdermal patches was discussed and the results graphs were shown here. Correlation coefficient (r^2) Values for different kinetic models for all formulations in Table No.7

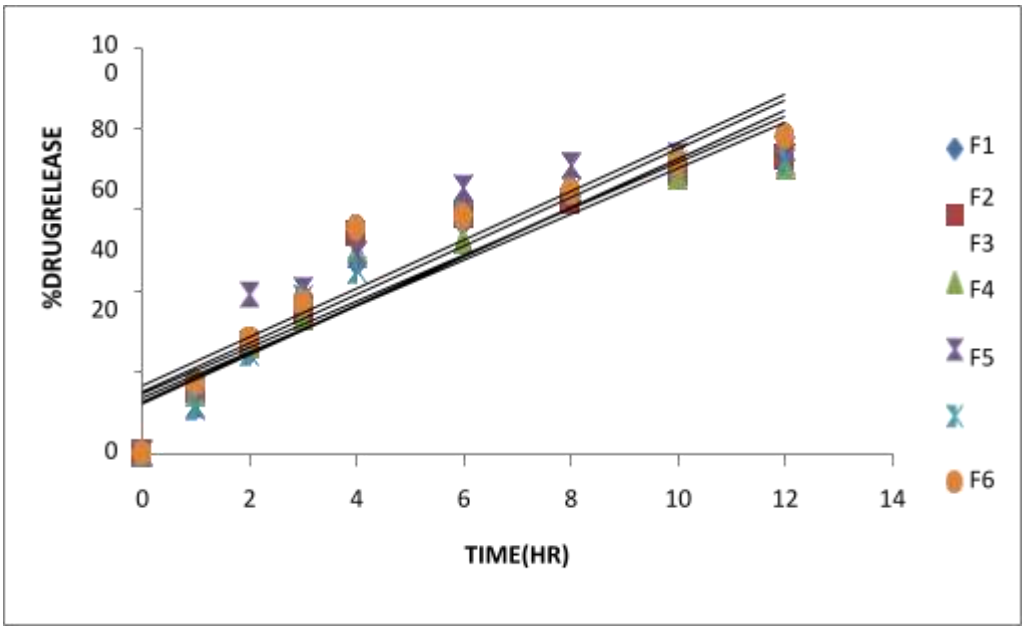

Fig No.5.7a Zero order release of formulations (F1-F6)

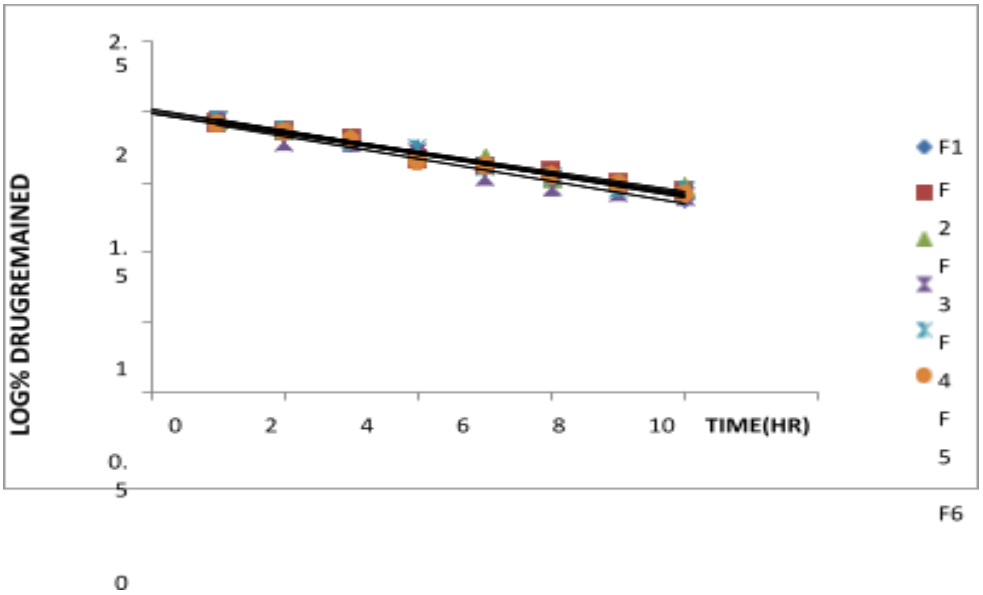

Fig No.5.7b First order release of formulations (F1-F6)

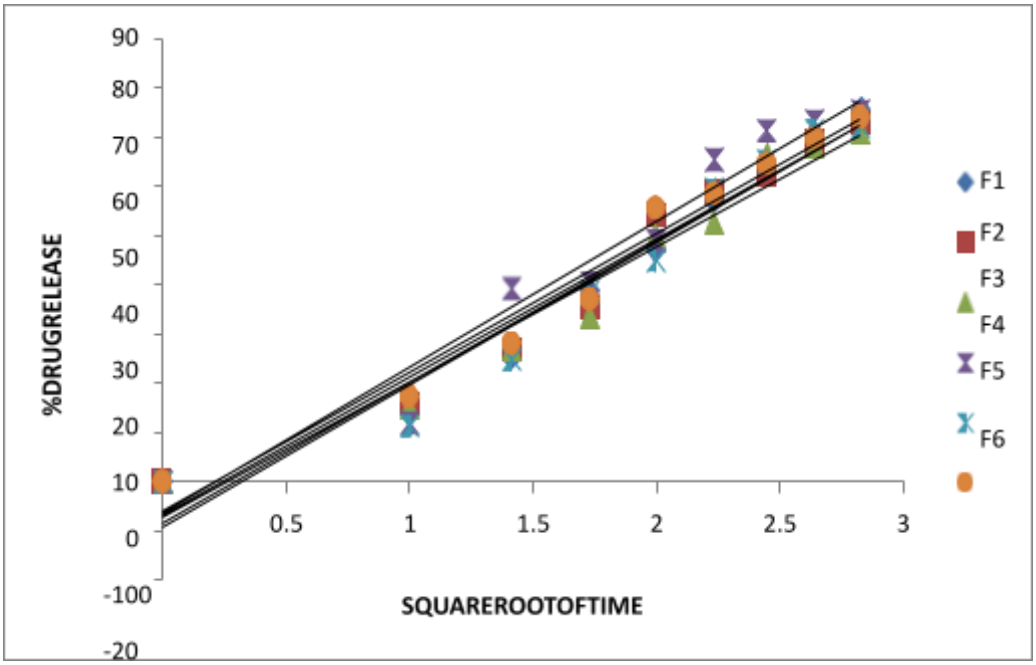

Fig No.5.7c Higuchi model release of formulations (F1-F6)

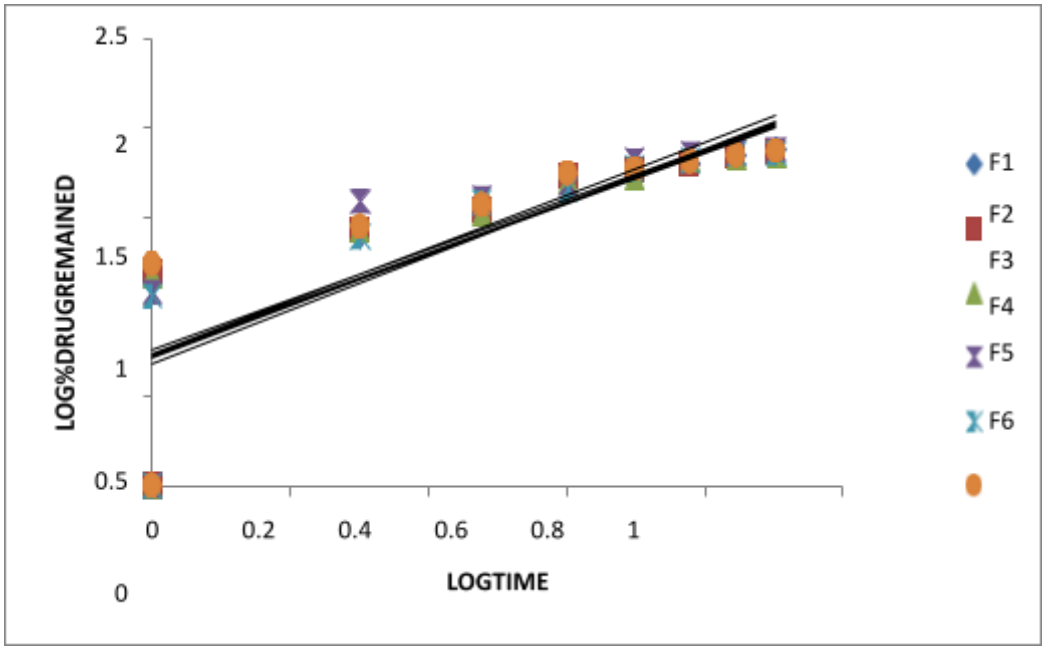

Fig No.5.7d Korsemeyer peppas release of formulations (F1-F6)

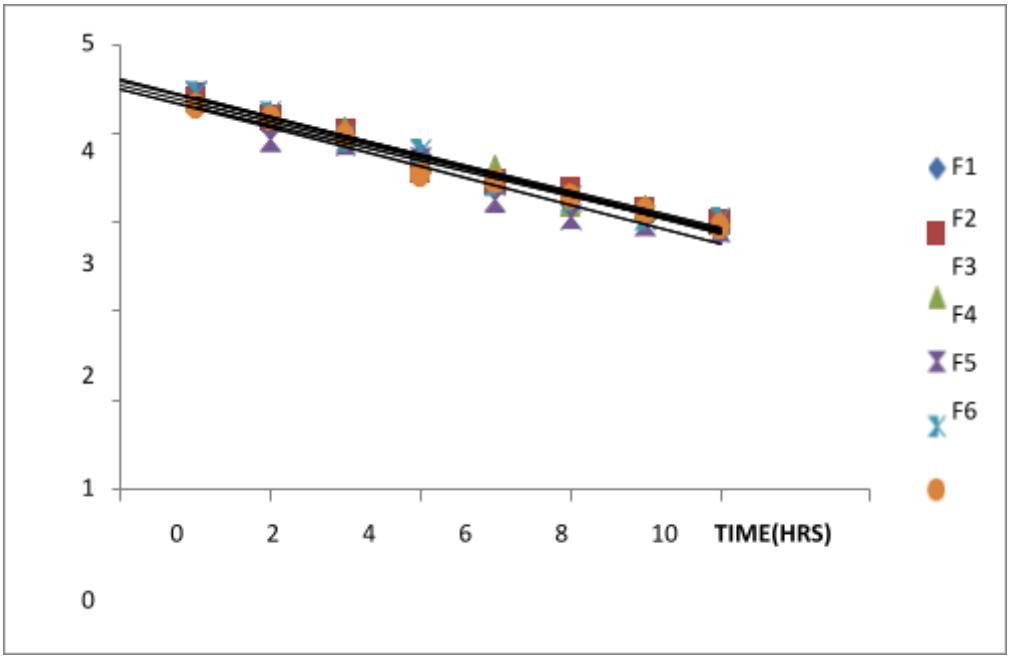

Fig No.5.7e Hixson Crowell Model release of formulations (F1-F6)

Table No.5: Correlation coefficient (r^2) Values for different kinetic models for all formulations

Formulation	r2	r2	r2	r2	r2
	Zero order	First order	Higuchi	Korse meryer papers	Hixson Crowell
F1	0.9992	0.9998	0.9844	0.9988	0.9995
F2	0.9947	0.9983	0.991	0.9992	0.9973
F3	0.9978	0.9998	0.9898	0.9934	0.9847
F4	0.9766	0.986	0.9763	0.9581	0.9995
F5	0.9999	0.9964	0.9766	0.9992	0.9977
F6	0.9999	0.9962	0.9946	0.9922	0.9947

6. Results and Discussion

6.1 Preparation of Transdermal patches

The Transdermal patches of Esmolol HCl was formulated to enhance effectiveness and to avoid side effects of the drug. The controlled releases of esmolol Hcl are provided by transdermal patches. The Transdermal patches of Esmolol HCl was formulated by using polymers HPMC

and Esmolol HCL by employing solvent evaporation technique. The prepared Transdermal patches of Esmolol HCl were characterized by FT-IR techniques. They were evaluated for weight variation, drug content uniformity, *in- vitro* drug permeation studies.

6.2 Fourier transforms infrared spectroscopy (FT-IR)

The FTIR spectra of Esmolol HCl, excipients and Transdermal patches are compared. From the obtained spectra of Transdermal patches it was observed that all characteristics peak of Esmolol HCl were also present in the Transdermal patches indicating that there are no interaction between the excipients and the drug.

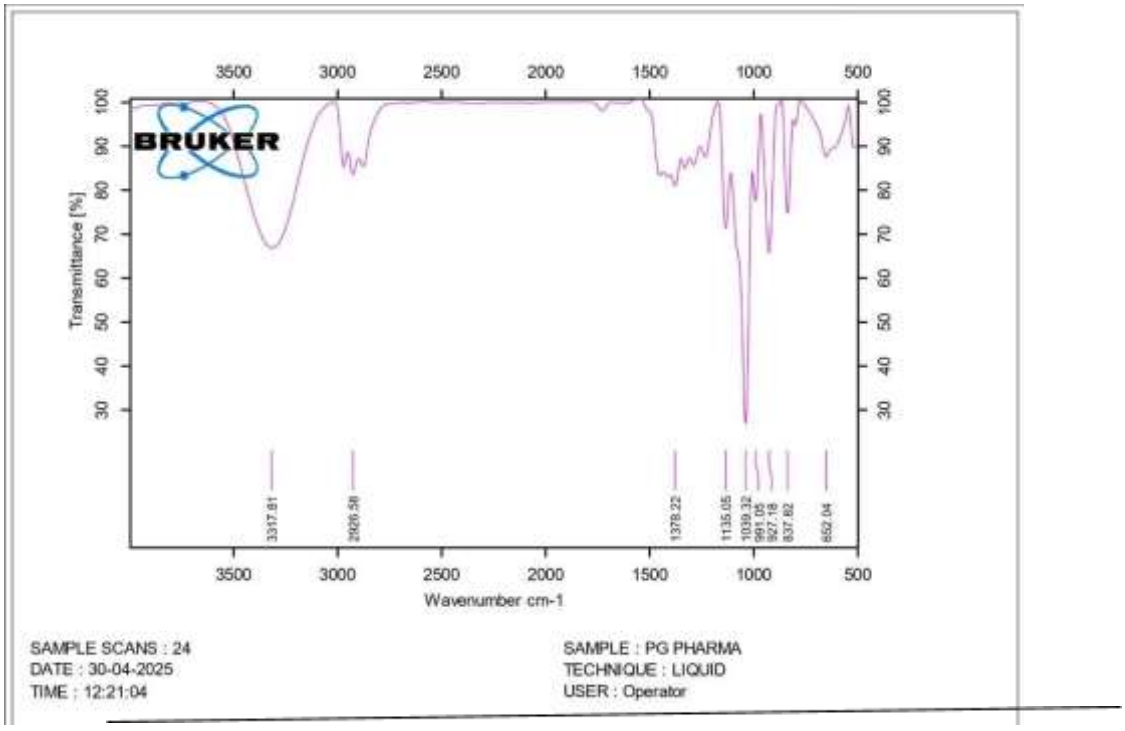

Fig No.6.2a FTIR Spectra of Esmolol HCl

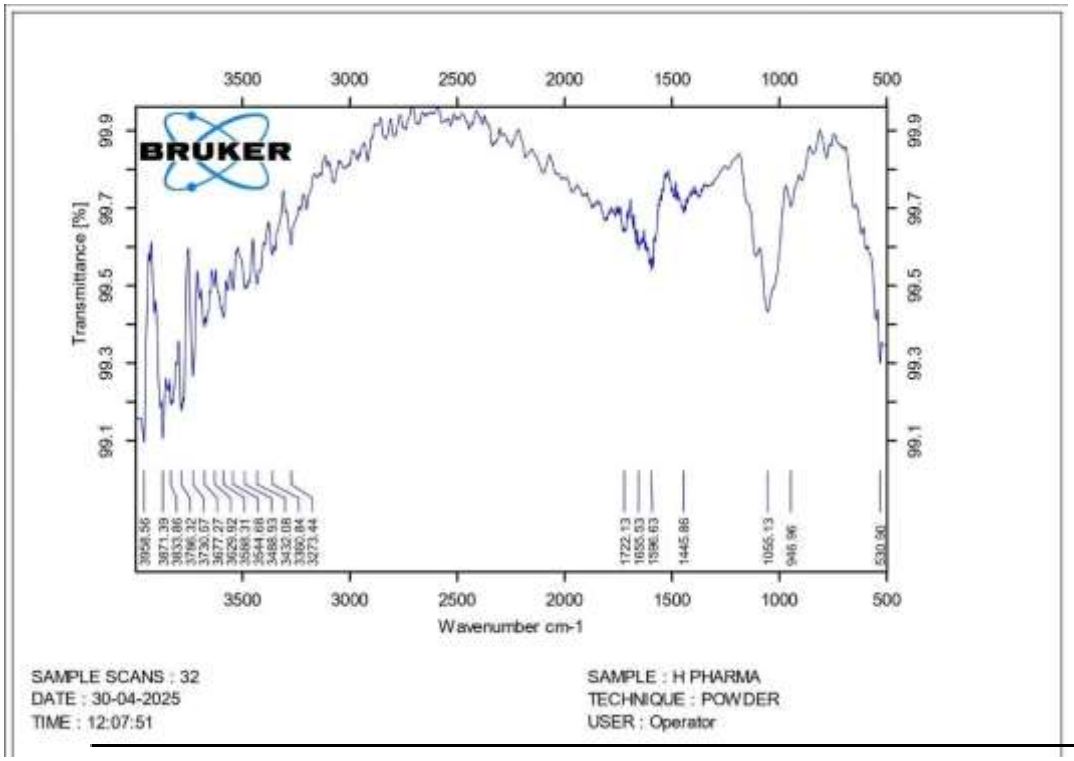

Fig No.6.2b. FTIR Spectra of HPMC

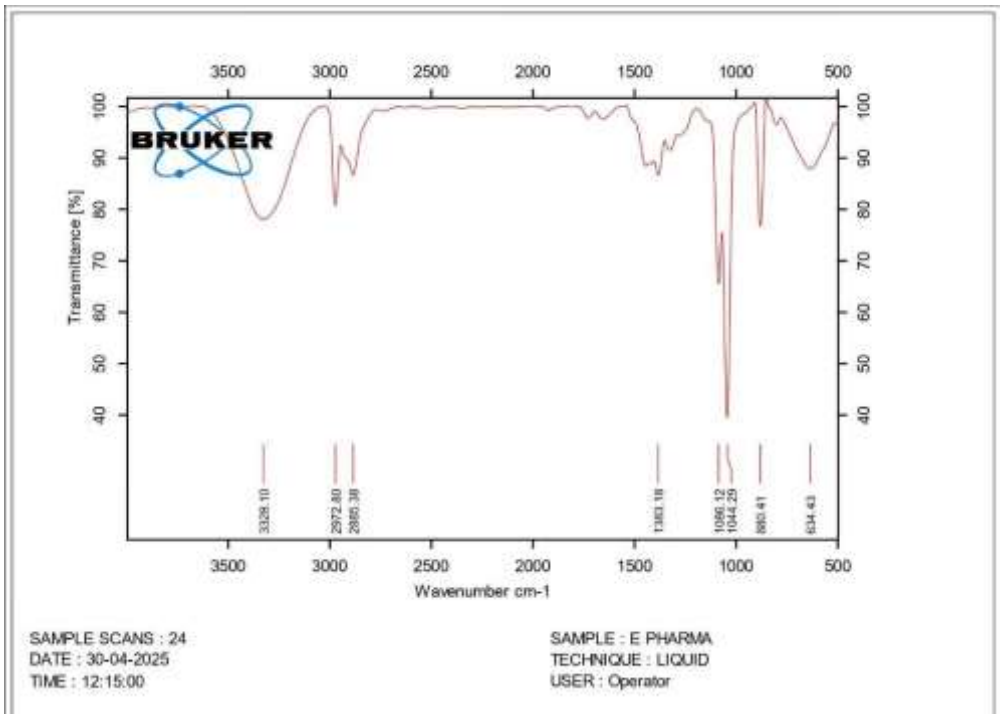

Fig No.6.2c. FTIR Spectra of Carbopol

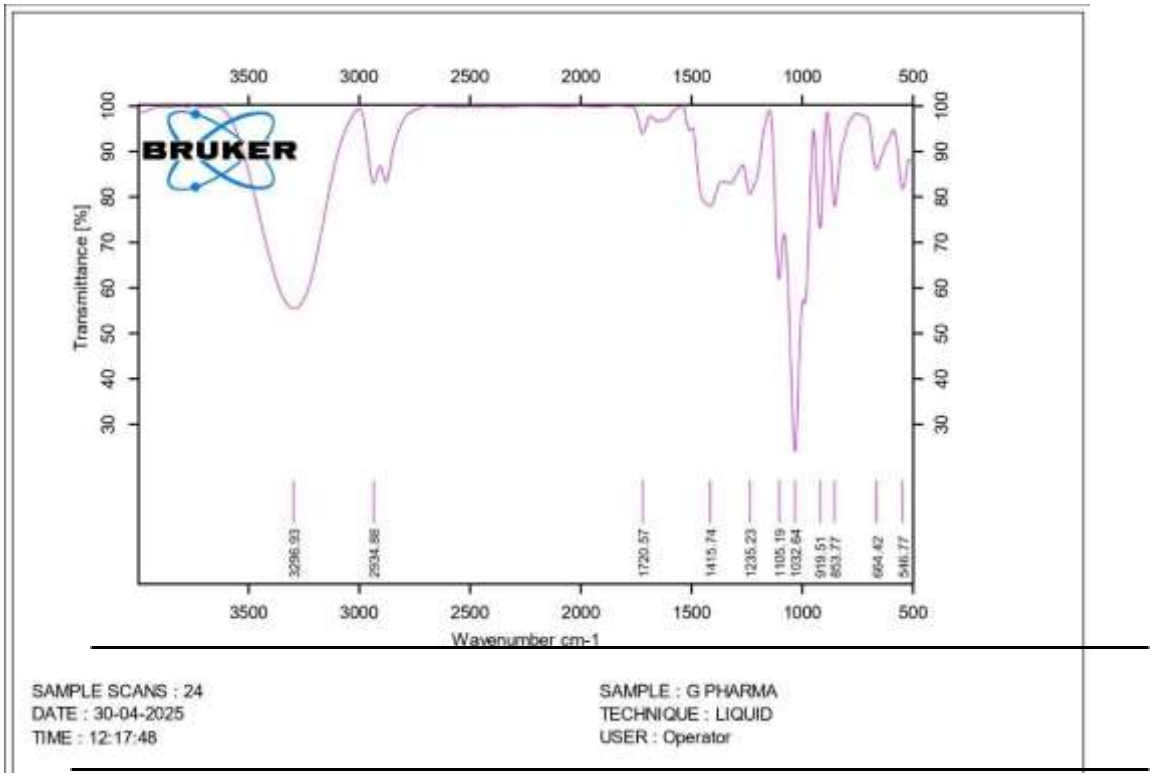

Fig No. 6.2d. FTIR Spectra of optimized formulation F6

6.3 Evaluation of Esmolol HCl Transdermal patches

All the prepared patches were found to be non irritant. Three patches each of 2×2 cm2 were cut at three different places from the casted patch and weight variation was determined. Weight variation varies from 39±1.58 to 57±0.05 mg was shown in Table No. 6.

Since the amount of polymers in each formulation varies, the thickness increased gradually as the amount of polymers increased. All the patch formulations were found to have thickness in the range of 0.02±0.004 to 0.08±0.001 mm. The results show gradual increase in the thickness shown in Table No. 6.

Folding endurance of patch was found to be in the range of 94±0.75 to 154±0.97 the prepared patch formulations were assayed for drug content. Results of drug content showed the uniformity of the drug and less loss of drug content in Tran's dermal patches was shown in Table No.6.

Depending on their composition, the formulations invitro drug diffusion profiles in ph 7.4 exhibit variations. A rapid diffusion of all the patch preparations was observed by the diffusion test, in which approximately 76.54% of Esmolol HCl diffused. F6 showed highest drug release.

Table No. 6 EVALUATION OF TRANSDERMAL PATCHES

Formulations	Weight variation (%)	Thickness (mm)	Moisture content (%)	Folding endurance	Drug Content (%)
F1	53±1.92	0.04±0.001	3.47±0.22	94±0.75	75.68
F2	46±0.54	0.02±0.004	3.57±0.33	145±0.96	73.57
F3	57±0.05	0.03±0.001	3.49±0.54	132±0.19	76.54
F4	51±0.98	0.06±0.003	3.56±0.51	142±0.16	55.53
F5	39±1.58	0.08±0.001	3.87±0.64	143±0.19	76.05
F6	51±0.25	0.05±0.002	3.43±0.61	154±0.97	73.53

***In-Vitro* diffusion**

The procedure for *in-vitro* diffusion of Esomolol HCl transdermal patches was discussed and comparative diffusion of formulations was shown in Fig No.7. The result has shown here.

Table No. 7. *IN-VITRO* DIFFUSION OF TRANSDERMAL PATCHES F1-F6

Time (hr)	F1	F2	F3	F4	F5	F6
1	14.24±0.43	12.97±0.32	13.43±0.21	14.51±0.21	12.56±0.76	16.78±0.87
2	21.09±0.54	21.45±0.43	25.65±0.43	35.31±0.41	21.53±0.28	29.87±0.56
3	36.43±0.43	33.21±0.32	31.46±0.64	41.32±0.56	36.21±0.17	33.43±0.65
4	43.65±0.69	51.32±0.43	47.91±0.39	47.32±0.87	43.46±0.87	51.45±0.57
5	49.63±0.13	54.46±0.32	51.56±0.64	64.35±0.64	57.90±0.76	56.76±0.87
6	59.31±0.24	61.44±0.65	64.36±0.75	69.21±0.76	62.56±0.76	63.65±0.34
7	69.54±0.76	64.65±0.65	64.61±0.77	71.31±0.54	73.57±0.26	68.98±0.76
8	71.32±0.65	71.87±0.43	71.46±0.34	74.16±0.32	74.78±0.21	76.08±0.72

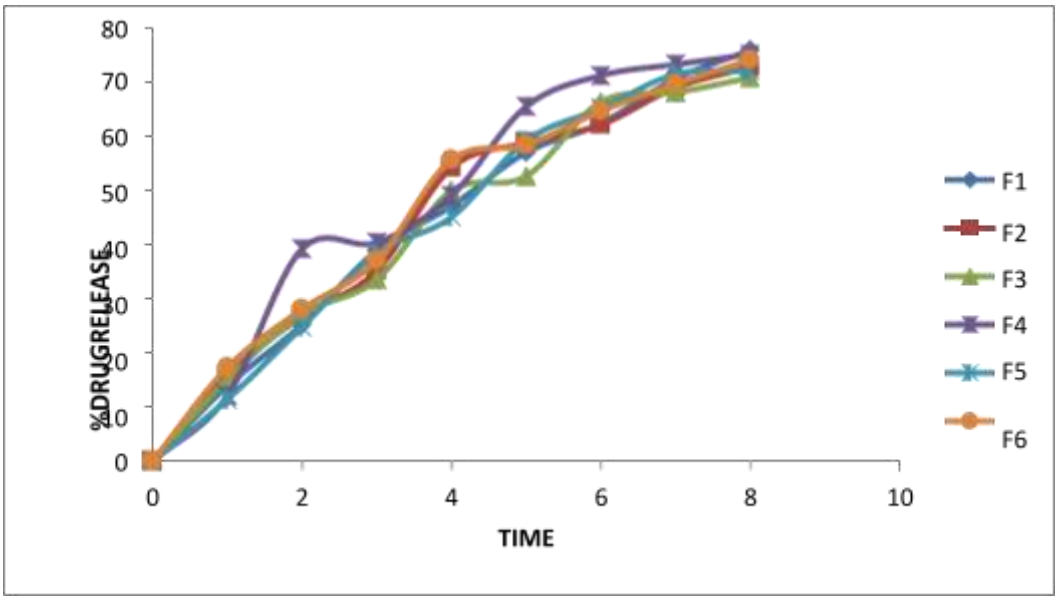

Fig No.6.3a: *In-Vitro* diffusion of Esmolol HCl formulations (F1-F6) in pH7.4

7. Summary and Conclusion

Developing new formulations for compounds with low aqueous solubility is very difficult. Esmolol HCl was selected as a model drug for the research work because it has a poor solubility, short elimination t1/2, low oral bioavailability, rapid extensive hepatic metabolism while high permeability.

Esmolol HCl is antiarrhythmic agent that is a competitive antagonist of the β-1-adrenergic receptors primarily in the myocytes. Esmolol HCl belongs to class II drug in BCS classification i.e low. solubility and high permeability. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Suitable analytical method based on UV-Visible spectrophotometer was developed for Esmolol HCl λmax of 465nm was identified in pH 7.4.

Transdermal patch of Esmolol HCl was prepared with Esmolol HCl, HPMC and carbopol in different ratios in order to improve the drug diffusion. Esmolol HCl has formulated Transdermal patches were prepared by solvent evaporation technique.

Drug and polymers has been characterized by FT-IR. The FTIR spectra studies of formulation shows that no interaction between drug and excipient.

The evaluation of Transdermal patches of Esmolol HCl were performed mainly for their Physical parameters such as Weight variation, Thickness, Folding endurance test and also for their Drug content and In-vitro drug diffusion studies. The above mentioned tests were performed using the official procedures and with modified testing procedures collected from

various research articles. Results revealed that the patch of all formulations have acceptable physical parameters.

The patch prepared by solvent evaporation technique passes the prepared patch were found to be non irritant, weight variation was found in the range 39±1.58 to 57±0.05 mg, thickness in the range of 0.02±0.004 to 0.08±0.001 mm, Folding endurance of patches was found to be in the range of 94 ±0.75 to 154±0.97, drug content uniformity was in between 55.53 to 76.54 %. Depending on their composition, the formulations invitro drug profiles in ph 7.4 exhibit variations..

The diffusion test revealed transdermal patches of each preparation. It was also observed that F6 showed highest drug release**.**

8. References

[1] Kardile D, and Firodiya S.R.Ghule P.J. “FORMULATION AND EVALUATION OF TRANS-DERMAL PATCH OF PROPRANOLOL HYDROCHLO-RIDE”. *International Journal of Pharmaceutics and Drug Analysis*, vol. 5, no. 4, Mar. 2017, pp. 144-52.

[2] Jamaludin, Wahyudin Bin, Rahmi Muthia, Kartini Kartini, Finna Setiawan, Siti Juhrah, and Nuril Yulida. "Formulation and evaluation of transdermal patches from Eleutherine bulbosa Urb. bulb extract with plasticizer variations." *International Journal Of Applied Pharmaceutics* 16, no. 1 (2024): 94-97.

[3] Prajapati, Shailesh T., Charmi G. Patel, and Chhagan N. Patel. "Formulation and evaluation of transdermal patch of repaglinide." *International Scholarly research notices* 2011, no. 1 (2011): 651909.

[4] Zsolt H, Katalin KP, István B, Zoltán U, Eszter SD, Dóra K, Ádám H, Ágota P. Formulation and Evaluation of Transdermal Patches Containing BGP-15.

[5] *Rakesh P. Patel, Grishma Patel, Hitesh Patel , Ashok Baria. Formulation and Evaluation of Transdermal Patch of Aceclofenac. Research J. Pharma. Dosage Forms and Tech. 2009; 1(2): 108-115.*

[6] chatgpt

[7] *Rakesh P. Patel, Grishma Patel, Hitesh Patel , Ashok Baria. Formulation and Evaluation of Transdermal Patch of Aceclofenac. Research J. Pharma. Dosage Forms and Tech. 2009; 1(2): 108-115.*

[8] chatgpt

[9] *Rakesh P. Patel, Grishma Patel, Hitesh Patel , Ashok Baria. Formulation and Evaluation of Transdermal Patch of Aceclofenac. Research J. Pharma. Dosage Forms and Tech. 2009; 1(2): 108-115.*

[10] Drug bank.Safety data for HydroxyPropylMethylCellulose.2024

[11] *Rakesh P. Patel, Grishma Patel, Hitesh Patel , Ashok Baria. Formulation and Evaluation of Transdermal Patch of Acclofenac. Research J. Pharma. Dosage Forms and Tech. 2009; 1(2): 108-115.*

[12] Kardile.D, and Firodiya S.R.Ghule P.J. “FORMULATION AND EVALUATION OF TRANS-DERMAL PATCH OF
PROPRANOLOL HYDROCHLO-RIDE”. *International Journal of Pharmaceutics and Drug Analysis*, vol. 5, no. 4, Mar. 2017, pp. 144-52.

[13] Kardile D, and Firodiya S.R.Ghule P.J. “FORMULATION AND EVALUATION OF TRANS-DERMAL PATCH OF
PROPRANOLOL HYDROCHLO-RIDE”. *International Journal of Pharmaceutics and Drug Analysis*, vol. 5, no. 4, Mar. 2017, pp. 144-52.

[14] Bharkatia M., Nema R. K., Designing and Evaluation of Transdermal Patches of Nimesulide, Asian J. Pharm. 1(1), 2006, 46-48.

[15] Gupta S. P., Jain S. K., Effective and controlled transdermal delivery of metoprolol tartarate, Indian J. Pharm. Sci., 67(3), 2005, 346-350.

[16] Panchangula R., Bokalial R., Sharma P., Khandavilli S., Transdermal delivery of naloxone: skin permeation, pharmacokinetic, irritancy and stability studies, Int.J.Pharm, 293, 2005, 213-223.

[17] Schurad B., Tack J., Lipp R., Evaluation of the Transdermal Permeation behavior of Proterguride from Drug in Adhesive Matrix Patches through hairless Mouse Skin, Drug. Dev. Ind. Pharm**.,** 31(6), 2005, 505 – 513**.**

[18] Kanikkannan N., Andega S., Burton S., Babu R. J., Singh M. , A Formulation and In Vitro Evaluation of Transdermal
Patches of Melatonin, Drug Dev. Ind. Pharm, 30(2), 2004, 205 – 212

[19] Mehdizadeh A., Toliate T., Rouini M. R., Design and in vitro evaluation of new drug-in-adhesive formulation of fentanyl transdermal patches, Acta Pharm., 54, 2004, 301-317.

[20] Murthy S. N., Hiremath S. R., Clinical pharmacokinetic and pharmacodynamic evaluation of transdermal drug delivery systems of salbutamol sulfate, Int. JPharm. Sci., 287, 2004, 47-53.

[21] Aquil M., Asgar A., Monolithic matrix type transdermal drug delivery systems of Pinacidil monohydrate: in vitro characterization, European J. Pharm.Biopharm., 54, 2002, 161-164.

[22] Jamakandi V.G., Mulla J.S., Vinay B.L., Formulation, characterization and evaluation of matrix type transdermal patches of a model antihypertensive drug. Asian J. Pharm., 1, 2009, 59-65.