Design, Characterization and Evaluation of Transdermal Patches of Zaltoprofen

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Abstract
The oral route of administering drugs has several drawbacks, such as limited bioavailabilitydue to to hepatic first-pass metabolism and a tendency to generate rapid, either high or low blood level spikes. In the current study, transdermal administration of Zaltoprofen was designed to circumvent first pass metabolism and reduce dose frequency compared to oral route. Matrix type transdermal patches were prepared using polymers such as Eudragit-L100, HPMCK 4M, and HPMCK 15M by employing solvent casting technique method. Propylene glycol and tween 80 were choosen as permeation enhancer and plasticizer respectively. F1 to F12 are designed at variable proportions of drug to polymer ratios. All the formulations were characterized. No drug-excipient interactions were found in FTIR studies. In *invitro* drug permeation studies, the F6 formulation exhibited 94.7% drug release over a period of 12-hours. Release kinetics of F6 has shown anomalous diffusion or non-fickian diffusion (swellable & cylindrical Matrix) and follows Peppa's method of drug release. Propylene glycol (PG) reduced skin irritation which is confirmed in skin irritation test. In stability studies the physical appearance and drug content of Zaltoprofen transdermal patch was found to be uniform.
Keywords: Zaltoprofen; Transdermal patch; Eudragit-L100; HPMCK 4 M and HPMCK15M.
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1.Introduction

Transdermal therapy systems are self-contained discrete dosage forms that deliver the drug(s) to the systemic circulation through the skin at a controlled rate when applied to intact skin. The substance Scopolamine was contained in the first transdermal drug delivery (TDD) system, Transderm-Scop, which was created in 1980 for the treatment of motion sickness[1]. This technique uses a microporous polypropylene film as the membrane. A membrane-moderated mechanism governs the transdermal patch [2,3].The thermal, cold, nutrient, skin care (a category that includes two major sub-categories: therapeutic or cosmetic), scent, weight reduction patches [4,5].

The gastrointestinal issues imposed by drugs, and poor absorption can be avoided with TDDS. Transdermal administration of drugs offers a number of benefits over traditional methods, such as the capacity to prevent issues with pH, emptying rate effects, and gastrointestinal irritation. It may also prevent hepatic first pass metabolism and certainly increases patient compliance.It offers systemic drugs delivery via decreasing dosage frequency and improving bioavailability [6, 7].

A non-steroidal anti-inflammatory medication (NSAID) is Zaltoprofen. It functions by preventing the production of specific chemical messengers that produce inflammation (redness and swelling), pain, and fever.Zaltoprofen restricts the activity of the B2-type bradykinin (BK) receptor in nerve terminals and prevents the generation of PGE2 at inflammatory locations.Zaltoprofen is used for fever, pain relief, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and gout [8].Designing and formulating TDDS of Zaltoprofen and evaluating their extended release were the goals of this study [9].

Zaltoprofen's transdermal patch increases patient compliance, lowers dosage frequency, prevents stomach discomfort, bypasses the first pass mechanism, and enhances local drug availability at the site of action.

2. Materials and Methods[10]

2.1 Materials of the Study

Based on its physical, chemical, and biological characteristics as well as its aptitude for transdermal drug delivery, Zaltoprofen was chosen as the model drug.As matrix-forming polymers, Eudragit-l100(mg), HPMCK4M, and HPMCK15M were selected [11].Propylene glycol and tween 80

were chosen as permeation enhancer and plasticizer, respectively.

2.2 Pre-formulation Studies[12]

Preformulation tests were conducted to determine physicochemical properties and its compatibility with various excipients.

2.2.1 Calibration curve of Zaltoprofen

In phosphate buffered saline with a pH of 6.8, UV spectrophotometric analysis was used to determine the Zaltoprofen content. The stock solution was scanned between 190 and 400 nm in the UV spectrum. The maximum absorbance was attained at 227 nm. Serial dilutions were made with various concentrations (5, 10, 15, 20, and 25 µg/ml) from stock solutions containing (20 g/ml) Zaltoprofen in phosphate buffer (pH 6.8), to create a calibration curve, the determined absorbance was recorded and plotted against concentration.

2.2.2 Drug excipients interaction studies by FTIR

The KBr disc method was used to do IR spectral analysis utilising the FT-IR. Between wave numbers 4000.0 and 400.0 cm^{-1}, the pure drug, physical mixture of drug and excipients, as well as the drug loaded transdermal patches examined.

2.3 Methods

2.3.1 Preparation of Different Placebo Polymeric Films[13]

Different placebo patches are prepared by employing hit and trial method on various combinations of different polymers. From these various placebo patches, the ideal transdermal drug delivery system is selected for incorporation of drug. The combinations of polymers selected are as follows: Eudragit-L100, HPMCK4M and HPMCK15M in graded amount individually;Eudragit-L100, HPMCK4M in 1:1 ratio;Eudragit-L100, HPMCK15M in 1:1 ratio respectively[14].

2.3.2 Preparation oftransdermal patches of Zaltoprofen

Transdermal patches were made using solvent casting method. The appropriate amounts of Eudragit L100, HPMCK4M, and HPMCK15M were weighed, and using a magnetic stirrer, they were then dissolved in a solvent solution of dichloromethane and ethanol.The aforementioned dispersion was then supplemented with Zaltoprofen(300mg), Propylene glycol, and Tween 80 while being continuously stirred. The petri plate was filled with the homogeneous dispersion [15]. The rate of solvent evaporation was managed by placing a cut funnel upside down over the patches. The dry films were removed after 24 hours and placed in desiccators for storage. The details of formulations were shown in Table 1.

Table 1: Formulation of Zaltoprofen Transdermal Patches

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Drug (mg)	300	300	300	300	300	300	300	300	300	300	300	300
2	Eudragit-L100(mg)	100	150	200	-	-	-	-	-	-	100	100	-
3	HPMCK4M(mg)	-	-	-	100	150	200	-	-	-	100	-	100
4	HPMCk15M (mg)	-	-	-	-	-	-	100	150	200	-	100	100
5	Dichloromethane(ml)	8	8	8	8	8	8	8	8	8	8	8	8
6	Ethanol(ml)	8	8	8	8	8	8	8	8	8	8	8	8
7	Propylene glycol(ml)	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
8	Tween-80(ml)	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2

2.4 Evaluation of ZaltoprofenTransdermal Patch by Physical Methods[16]

Transdermal patches were examined for colour, clarity, flexibility, and smoothness.

2.4.1Thickness

Using screw gauze, the patches' thickness was measured three times. Three patches were chosen at random for each formulation**.**

2.4.2Weight variation

For a weight variation test, three 2x2 cm^2 discs were cut and weighed on an electronic scale. The test was carried out to examine weight

homogeneity and, consequently, batch-to-batch variance[17].

2.4.3Flatness

From each patch, longitudinal strips were cut out—one in the middle and two on either side. Each strip's length was measured, and the change in length due to flatness uniformity was determined by calculating the present constriction, with 0% constriction being equivalent to 100% flatness.

2.4.4 Folding endurance

Manual folding endurance testing was done on the preparation patch. The films were cut into 4x3 cm strips that were folded repeatedly until they shattered[18].

2.4.5 Moisture uptake

The patch's physical stability and integrity under highly humid conditions were examined using the % moisture absorption test. The patch's ability to absorb moisture was assessed in the current investigation in the following way. To achieve an internal humidity of 84% RH, the patches were placed in desiccators containing 200 ml of a saturated potassium chloride solution. After three days, the films were developed and weighed to determine the moisture uptake[19].

Percentage moisture absorbed= $\frac{\text{Final weight-Initial weight}}{\text{Initial weight}}$

2.4.6 Moisture content

Before each patch was put in a desiccator with fused calcium chloride and kept at 40°C for a whole day, it was weighed. The patches were weighed again until a constant weight was reached. The moisture content was calculated in percentage terms based on the difference between the initial and constant final weights of the patches.

2.4.7 Swelling study

3.83 cm^2 membranes that had been completely dried were weighed and placed in desiccators for 24 hours. They were taken out and placed in desiccators with relative humidity levels of 75% and a saturated sodium chloride solution. Single pan balance was weighed repeatedly until a steady weight was attained[20]. The percentage increase in membrane weight over the initial weight of the specimen was used to calculate the swelling capacity of the membranes (in weight %). The trials were performed in triplicate, and the computation was based on the average results. The degree of swelling (DS) in terms of % was computed as

$$DS\ (\%) = W_s\text{-}W_d/W_d \times 100$$

Where, $W_s$and $W_d$indicate the weight of the swollen and dry membranes respectively.

2.5 Drug Content Determination

A 3.83 cm^2 patch was cut, and it was dissolved in PBS pH 7.4. The mixture was then mixed with solvents ethanol and dichloromethane to make the polymer soluble, and the residual volume was filled with PBS pH 7.4 to 100 ml in a 100 ml volumetric flask [21]. Then 1 ml of the solution was taken out and diluted to 10 ml. The concentration was determined by measuring the solution's absorbance at 310 nm. The medication content was determined after accounting for the dilution factor.

2.6*In vitro* Permeation Studies

Franz diffusion cells were used for permeation research. The donor and receptor compartments are located within the Franz diffusion cell. The receptor compartment measures 5 mm and has a 15 ml capacity[22]. The receptor compartment is connected to a collecting tube, making it simple to take hourly samples while diffusion is taking place. While diffusion tests were being conducted, the donor and receptor compartments were held together by a clap and the diffusion cell was set up on a magnetic stirrer. The total area of the receptor compartment that is exposed to the Transdermal patch for permeation is 3.83 cm^2.

Using a Franz diffusion cell and the abdomen skin of a male wistar rat weighing 200–250 g, an in vitro permeation study was conducted. Using an electrical clipper, the hair in the stomach area was carefully removed. To get rid of any tissue or blood vessel adhesion, the dermal side of the skin was properly cleaned. Before starting the experiment, it was equilibrated for an hour in a pH 7 phosphate buffer saline solution. The heater, which was thermostatically controlled, kept the cell temperature at 37±0.5 °C.The rat skin fragment was positioned in the space between the diffusion cell compartments, with its epidermis facing the donor compartment. The 1 ml sample volume was taken out of the receptor compartment at intervals of 1, 2, 3, 4, 6, 8, 10, 12, hours, and an equivalent volume of fresh medium was added. After passing through the whatman filter, the samples were examined for Zaltoprofen at 255 nm using a UV-Visible spectrophotometer.

2.7 Kinetic Modelling of Drug Release

For the purpose of describing the kinetics of drug release, various models were tested. The acquired data were fitted into the zero-order, first-order, Higuchi, and Korsmeyer-Peppas release models to analyse the mechanism of the drug release rate kinetics of the dosage form[23,24]. It is a zero order release if n is equal to 0.89. The release is best explained by Fickian diffusion if n is equal to 0.45; however, if n is between 0.45 and 0.89, the release is best explained by anomalous diffusion or non-Fickian diffusion (Swellable& Cylindrical Matrix).A plot of log (Mt/M) versus log (time) in this model is linear [25,26].

2.8 Skin Irritation Studies

A skin irritation study isdone on healthy rabbits (average weight: 1.2 to 1.5 kg). The rabbit's dorsal surface (50 cm^2) was cleaned[27,28].The hair from the smooth dorsal surface is removed, cleaned with rectified spirit, and then the patches are applied to the skin. After 24 hours, the patch is removed, and the skin was examined.5 groups were prepared each of 6 rats per group[29].Score of erythema was recorded and was compared with standard. The study design was accepted by the Institutional Animal Ethical Committee(IAEC-1648/PO/Re/S/12/CPCSEA), Geethanjali College of Pharmacy, Telangana India.

(Group 1- Normal; Group 2- Control; Group 3– 0.8% v/v aqueous solution of Formalin; Group 4- transdermal patch without drug (blank), Group 5- Transdermal patch with a drug).

2.9 Stability Studies

Transdermal patches which shown better drug content and drug release i.e.F6 and F7 have selected for stability studies were conducted at 0°C and at 75% RH for a period of 60 days.

3. Results

Calibration curve of Zaltoprofen was constructed (Table 2, Figure 1). All the Transdermal patches were visually inspected for colour, clarity, flexibility. All the Transdermal patches were found to be flat without any foam (Figure 2).Utilizing FTIR, tests on the compatibility of drug excipients were conducted, and it was shown that there were no interactions (Figure 3&4).The prepared Zaltoprofen transdermal patches were evaluated by physical methods such as physical appearance, flatness, weight variation, thickness, folding endurance, drug content, moisture uptake and moisture content and all the results were found to be within the pharmacopeial limits.The results are presented in the Table 3.

Table 2.Standard graph of Zaltoprofen

Concentration (µg/ml)	Absorbance
5	0.123
10	0.210
15	0.320
20	0.411
25	0.501

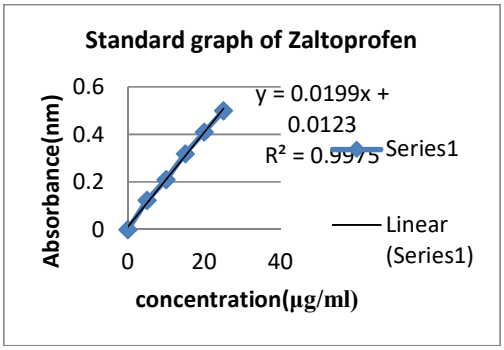


Figure1. Standard graph of Zaltoprofen

A

B

Figure 2. (A) Trandermal patch of Zaltoprofen (B) Flatness test

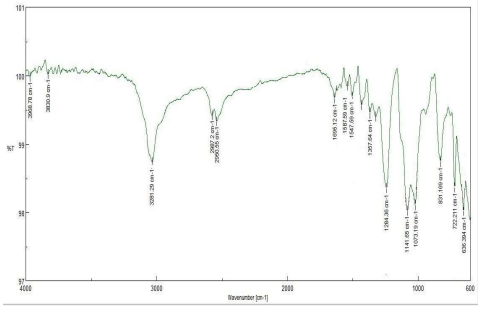


Figure 3. FTIR of Pure drug

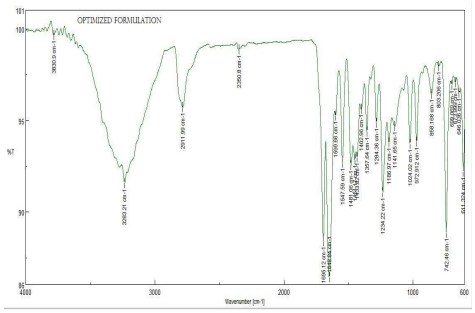


Figure 4. FTIR of Optimized formulation (F6)

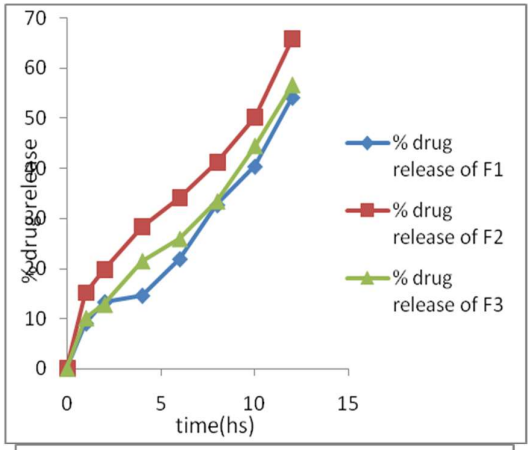
Table3. Evaluation of Zaltoprofen Transdermal Patch

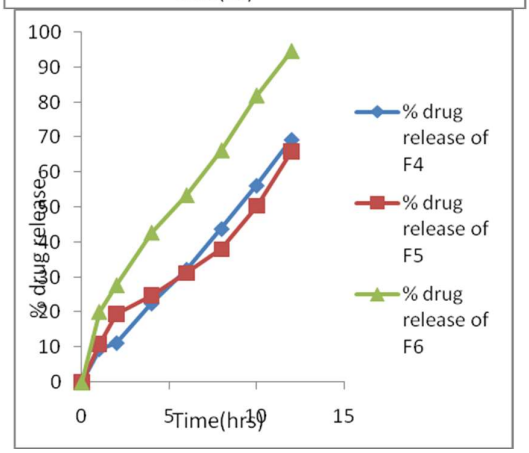
Formulation	Thickness (mm)	Weight variation	Folding endurance	Drug content (%)	Moisture uptake (%)	Moisture content (%)
F1	0.3569± 0.03	413 ±0.08	60± 1.23	45± 2.67	7.98 ±1.29	3.77 ±1.75
F2	0.3520± 0.01	455 ±0.07	65± 1.56	65± 3.12	12.05±0.56	4.21 ±1.42
F3	0.3470±0.05	505 ±0.05	67± 2.21	57.5 ±2.76	13.09±0.98	5.16 ±0.98
F4	0.3496±0.03	415 ±0.09	64± 1.54	60± 2.19	15.63±0.87	5.66 ±1.05
F5	0.3460±0.01	461 ±0.08	70± 1.09	67.5 ±3.24	11.73±0.43	6.87 ±1.26
F6	0.3517±0.05	512 ±0.07	72± 1.02	92.5 ±2.05	19.65±0.28	7.67 ±1.02
F7	0.3478±0.04	411 ±0.04	80± 2.12	90.7 ±3.28	9.42 ±0.58	3.43 ±1.46
F8	0.3437±0.02	452 ±0.07	67± 1.89	85± 2.93	10.87±1.04	4.72 ±0.78
F9	0.3503±0.03	501 ±0.06	64± 1.51	55± 2.81	16.44±1.35	6.62 ±0.92
F10	0.3532±0.02	415 ±0.05	69± 2.45	62.5 ±3.1	13.08±0.76	6.17 ±0.58
F11	0.3546±0.04	461 ±0.04	66± 2.09	85± 2.52	11.63±1.21	4.94 ±1.19
F12	0.3503±0.05	510 ±0.06	61± 1.98	82.5 ±1.98	15.73±1.01	6.55 ±1.32

Mean ± SD; $n = 3$; $p > 0.05$

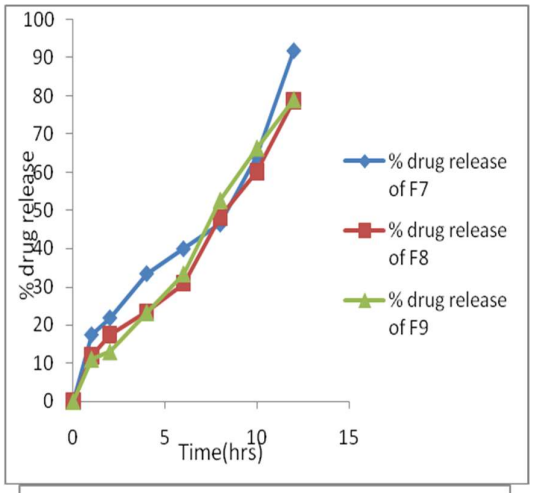
The prepared Zaltoprofen transdermal patches were evaluated for *in-vitro* permeation studies.Out of the 12 formulations tested, the F6 formulation containing 200 mg of HPMC K4M exhibited a cumulative drug release rate of 94% in under 12 hours. Additionally, HPMC K4M displayed a superior drug release profile than HPMC K15M. Table 4 presented the findings. The *in-vitro* permeation studies' release profiles were displayed (Figure 5).

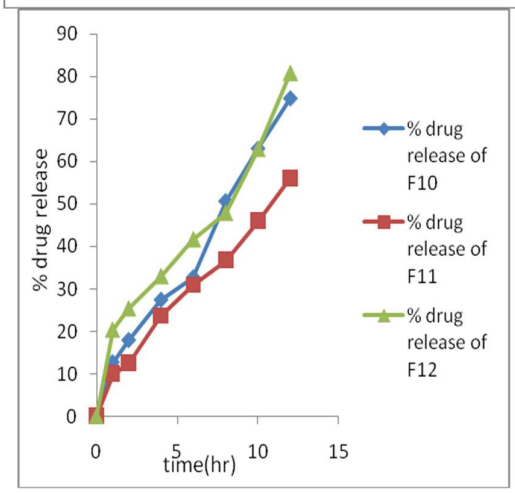
The study evaluated the drug release kinetics from *in-vitro* permeation studies of the F6 formulation. The regression coefficient value of 0.98 for the Korsmeyer-Peppas release model was found to be high. Additionally, it was discovered that the n value was 0.6203, indicating that non-Fickian diffusion was the drug release pattern. Table 5 presented the findings. There were reported kinetic investigations of Zaltoprofen transdermal patches(Figure 6, 7&8).





(A) (B)





(C)

(D)

Figure 5. Release Profile of Trandermal Patch Of Zaltoprofen in In-Vitro Permeation Studies (A) F1 to F3 (B) F4 to F6 (C) F7 to F9 (D) F10 to F12

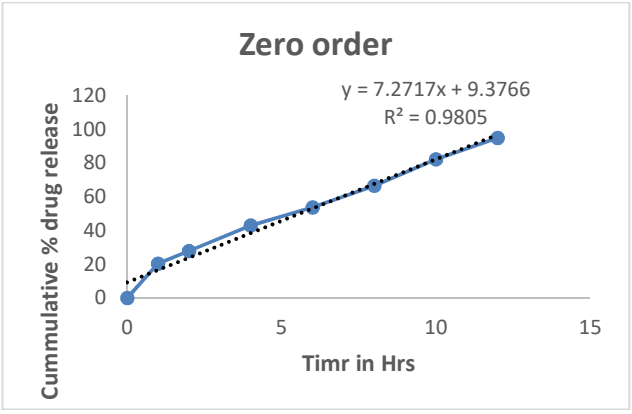


Figure 6. Zero order kinetics

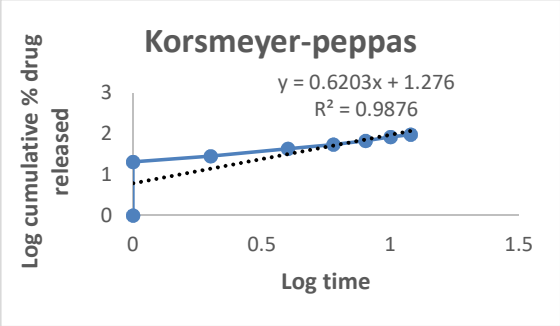


Figure7. Peppas plot

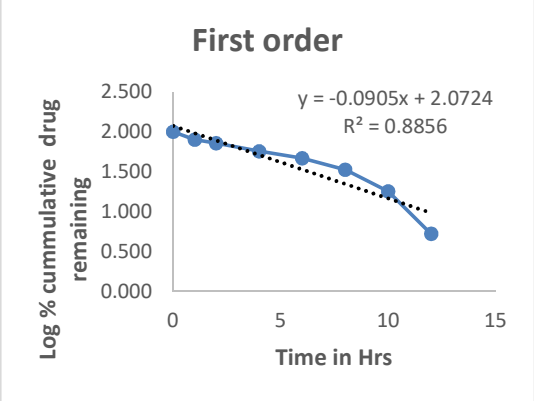


Figure 8. First order kinetics

Table 4. % Drug release of Trandermal patch of Zaltoprofen in *In-vitro* Permeation Studies

Time (hrs)	% Drug release											
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
1	9.05±0.06	15.1±0.02	10.1±0.04	9.49±0.06	10.9±0.06	20.2±0.04	17.5±0.06	12.0±0.04	11.1±0.06	12.7±0.02	10.0±0.04	20.4±0.02
2	13.3±0.04	19.8±0.04	12.8±0.06	11.3±0.03	19.6±0.04	27.8±0.06	21.9±0.02	17.5±0.06	13.0±0.04	17.9±0.04	12.5±0.05	25.4±0.04
4	14.6±0.02	28.3±0.02	21.5±0.02	22.6±0.06	24.9±0.06	42.8±0.04	33.5±0.06	23.4±0.04	23.3±0.06	27.4±0.06	23.6±0.06	33.0±0.05
6	21.9±0.04	34.1±0.06	25.9±0.06	32.3±0.04	31.2±0.04	53.5±0.03	40.0±0.04	30.9±0.03	33.4±0.04	32.7±0.04	30.9±0.04	41.7±0.04
8	32.7±0.02	41.1±0.08	33.4±0.06	43.9±0.03	38.0±0.02	66.3±0.02	46.5±0.03	48.1±0.06	52.7±0.05	50.6±0.05	36.7±0.06	47.9±0.06
10	40.4±0.06	50.1±0.04	44.5±0.04	56.3±0.06	50.3±0.04	82.0±0.04	64.2±0.04	60.0±0.05	66.4±0.04	63.0±0.06	45.9±0.04	63.0±0.06
12	54.2±0.04	65.8±0.06	56.7±0.02	69.4±0.04	65.9±0.06	94.7±0.04	91.9±0.06	78.7±0.06	79.1±0.05	74.8±0.03	56±0.06	80.9±0.04

Mean ± SD; $n = 3$; $p > 0.05$

Table 5.Drug Release Kinetics of F6 Formulation from In-*Vitro*Permeation Studies

Cumulative (%) release Q	Time (T)	Root (T)	Log (%) release	Log (T)	Log (%) remain	Release rate (cumulative % release/t)	1/cum% release	Peppas log Q/100	% drug remain	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
20.2356	1	1.000	1.306	0.000	1.902	20.236	0.0494	-0.694	79.7644	4.642	4.305	0.337
27.80759	2	1.414	1.444	0.301	1.858	13.904	0.0360	-0.556	72.19241	4.642	4.164	0.478
42.87958	4	2.000	1.632	0.602	1.757	10.720	0.0233	-0.368	57.12042	4.642	3.851	0.790
53.59293	6	2.449	1.729	0.778	1.667	8.932	0.0187	-0.271	46.40707	4.462	3.594	1.048
66.38743	8	2.828	1.822	0.903	1.527	8.298	0.0151	-0.178	33.61257	4.642	3.227	1.414
82.0877	10	3.162	1.914	1.000	1.253	8.209	0.0122	-0.086	17.9123	4.642	2.616	2.025
94.7055	12	3.464	1.976	1.079	0.724	7.892	0.0106	-0.024	5.294503	4.642	1.743	2.899

For the skin irritation test, visual inspection was carried out. It was noted that the amount of erythema and edema in group 5 was quitelower than the group that received treatment with the standard irritant, aqueous Formalin solution 0.8% v/v. Therefore, it may be stated that the formulation has very little to no skin irritation.
In stability studies, the physical appearance and drug content was uniform throughout the stability studies. The results were presented in Table 6.

Table 6. Stability studies of selected formulations (F6 and F7)

Formulation	Time Interval	Drug content (%)
F6	0	92.5±2.35
	30 Days	92.3±2.14
	60 Days	91.6±1.25
F7	0	90.7±2.46
	30 Days	90.2±2.12
	60 Days	89.8±1.43

Mean ± SD; $n = 3$; $p > 0.05$

4. Discussion

In this work, transdermal patches of Zaltoprofen were prepared by using solvent casting method. Twelve formulations were developed by using Matrix-forming polymers, such as Eudragit-L100 (F1-F3), HPMCK 4(F4-F6), and HPMCK 15 (F7-F9); combination of two matrix forming polymers in 1:1 ratio such as Eudragit-L100and HPMCK 4 (F10), Eudragit-L100 and HPMCK 15(F11) and HPMCK 4 and HPMCK 15(F12) . Propylene glycol and tween 80 were chosen as permeation enhancer and plasticizer respectively.

Physico chemical characteristics such as weight variationflatness, folding endurance, moisture uptake, moisture content and swelling study were reported satisfactory in all the formulations. Drug content was found to be more in F6, F7and F12. The thickness and overall appearance of the prepared patches remain intact despite the addition of penetration enhancers. Transdermal patch thickness affects drug diffusion via skin, drug release, penetration, and retention. The thickness of the films varied from 0.34-0.35mm in all formulations.The folding endurance was found to be in the range of 20-40. The formulations prepared withHPMCK 4 and HPMCK 15 has improved the folding endurance and increasing concentration of hydrophilic polymers showed increasing folding endurance and has the ability to be accord to the skin without breaking the patch.

The formulated transdermal patches having Eudragit-L100 have shown the low moisture uptake and moisture content when compared with formulation with HPMCK 4 and HPMCK15. It is due to the hydrophobic nature of Eudragit-L100. The increase in moisture uptake and content for F4-F9 is because of hygroscopic nature of the polymers. When combinations of polymers are used as in F11-F13, moisture uptake and contents were found to be less especially with F11. It was found that the prepared patches with the highest concentrations of HPMC K4 polymer showed higher moisture content.

Drug content was found to be more in F6; it indicates that HPMCK 4 improved the drug content in transdermal patch than HPMCK 15 and Eudragit-L100. In *invitro* diffusion studies, F1, F2, F3 containing Eudragit-L100 showed 55-60% drug release within 12hrs. Formulations F4, F5, F6 having increased concentration of HPMCK 4 have exhibited 65-95% of drug release, among them F6 has shown 94.7% of drug release over 12 hrs.Formulations F7, F8, F9 having increased concentration of HPMCK 15 have exhibited 65-95% of drug release in-between 79%-92% which indicates that optimum drug release was observed when HPMCK 4 and HPMCK 15 were used as polymers. Formulation with combination of Eudragit-L100 and HPMCK 4(F10); and HPMCK 4andHPMCK 15(F12) have shown 74.8 and 80.9 respectively whereas Formulation with Eudragit-L100 and HPMCK 15((F11) has shown only 56% of drug release which indicated that the viscous nature of the HPMCK 15 influenced the drug release pattern.

Formulation with higher concentration of HPMCK 4(F6) has shown better drug release pattern.The kinetics of *In-vitro* permeation studies for F6 formulation exhibits non-fickian diffusion. Hence, polymer swelling and dissolution influences the drug release process.Propylene glycol reduces skin irritation and increases viscosity and hygroscopicity and is confirmed in skin irritation test, where all the formulations have shown no skin irritation [30]. The physical appearance and drug content was uniform throughout the stability studies

6. Conclusion

Zaltoprofen's transdermal delivery system was designed for this study in order to avoid first-pass metabolism and reduce dosage frequency when compared to the oral route. Out of the 12 formulations tested, the F6 formulation containing 200 mg of HPMC K4M exhibited a cumulative drug release rate of 94% in under 12 hours.

Additionally, HPMC K4M displayed a superior drug release profile than HPMC K15M.

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Conflict of Interest

The authors declare no conflict of interest

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