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DEVELOPMENT AND CHARACTERIZATION OF KETOROLAC TRANSDERMAL PATCHES

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ABSTRACT
The objective of present study was to develop matrix type transdermal therapeutic systems of Ketorolac using various hydrophilic and hydrophobic polymers as matrix formers. Results revealed that prepared patches showed good physical characteristics, no drug-polymer interaction and no skin irritation was observed. The in vitro release study revealed that F7 formulation showed maximum release in 8 hrs. Formulation F7 was subjected for accelerated stability studies. The F7 formulation was found to be stable as there was no drastic change in the Physico-chemical properties of the patches, which was also confirmed by FTIR. Thus conclusion can be made that stable transdermal patches of Ketorolac has been developed. F8 formulations showed highest cumulative percentage drug release of 96.30% were obtained during in vitro drug release studies. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Based upon the in vitro dissolution data the F7 formulation was concluded as optimized formulation.

KEYWORDS: Ketorolac, Polymers, FTIR studies solvent casting technique, In-vitro drug release studies.

INTRODUCTION
Transdermal drug delivery systems (TDDS) are the devices which contains the active ingredients of defined surface area that delivers the predetermined amount of active ingredient to the surface of intact skin at predefined rate.[1,2] TDDS has many advantages over oral dosage forms like, it is a painless method to deliver the drug only by applying the drug on healthy skin, so the needle phobia can be avoided, it avoids gastric irritation, it avoids hepatic first pass metabolism and also increases bioavailability of drug, it improves the patient compliance by reducing the dosing frequency and also suitable the patients who are unconscious.[3] Ketorolac is a non-selective NSAID that works by inhibiting both the COX-1 and COX-2 enzymes that convert arachidonic acid to prostaglandins. Ketorolac Tromethamine are widely recommended to treat pain caused by osteoarthritis, ankylosing spondylitis, acute sciatica, rheumatoid arthritis and low back pain.[4] The drug is reported to be 90% oral bioavailable with a very low first pass metabolism.[5] Its short biological half-life (4-6 h) calls for frequent administration, and many adverse effects, such as upper abdominal pain and gastrointestinal ulceration restrict its long term oral use TDDS are extended release dosage forms that can offer a stable systemic drug concentration and avoid first pass metabolism. They can even avoid gastrointestinal problems associated with drugs and low absorption.[6,7] The objective of this study was to design and formulate TDDS of Ketorolac and to evaluate their extended release *in vitro*.

MATERIALS
Ketorolac was obtained from Hetero Labs, HYD. Ethyl cellulose and HPMC polymers were procured from SD Fine chemicals, Hyderabad, and other chemicals, and the reagents used were of analytical grade.

METHODOLOGY
Drug excipient compatibility
Compatibility studies of drug and the polymers were carried out by using Fourier Transform Infrared

Spectroscopy (FTIR). Fourier transform infrared spectra of the samples were obtained in the range of 4000 to 450 cm-1 using a FTIR by the KBr disc method.

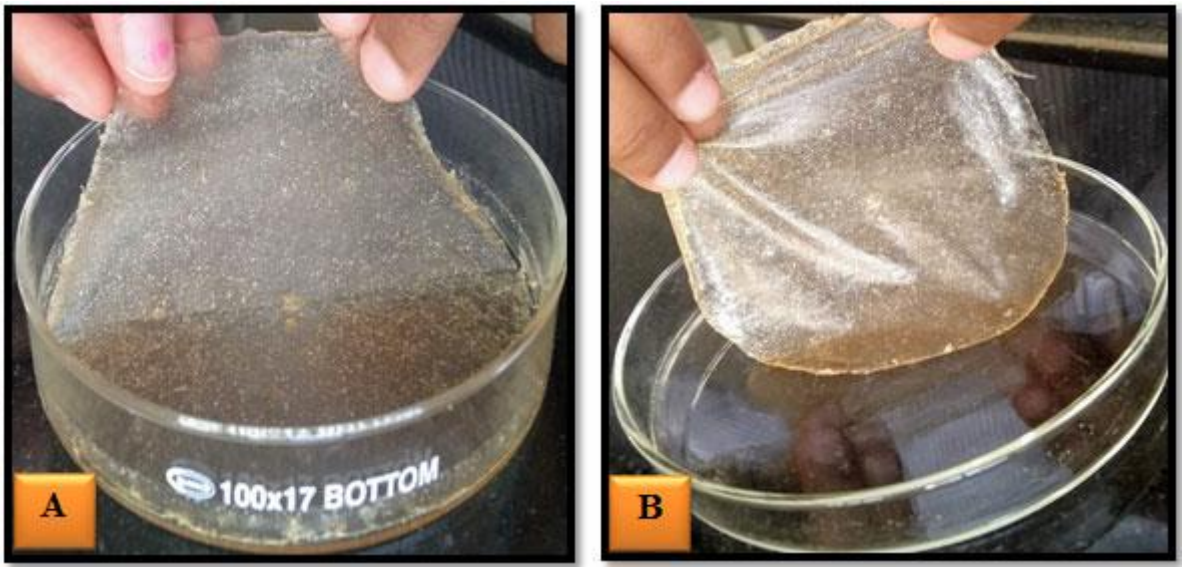
Formulation design

Preparation of transdermal patches[8]

Transdermal patches containing Ketorolac were prepared by the solvent evaporation technique. The drug Ketorolac was dissolved in suitable solvent . Polymers HPMC k 100 M , and Ethyl cellulose were taken. These polymeric solutions kept under magnetic stirrer after 1 hr. get viscous solution. After that drug add into the polymeric solution. Sufficient care was taken to prevent the formation of lumps. PEG was taken as a plasticizer and permeation enhancer like DMSO, and added to the mixture and mixed well. It was set aside for 2 hours to exclude any entrapped air and was then transferred into a previously cleaned Petri plate (40cm^2), drying of patches was carried out in vacuum oven at room temperature. Dried patches were packed in aluminum foil and stored in a desiccator for further evaluation.

Table-1: Formulation Design of Ketorolac Transdermal Patches.

S. No	F. code	Drug (mg)	Ethyl cellulose	HPMC k100M	PEG	DMSO
1	F1	10	100	-	1ml	0.1ml
2	F2	10	200	-	1ml	0.1ml
3	F3	10	300	-	1ml	0.1ml
4	F4	10	400	-	1ml	0.1ml
5	F5	10	-	100	1ml	0.1ml
6	F6	10	-	200	1ml	0.1ml
7	F7	10	-	300	1ml	0.1ml
8	F8	10	-	400	1ml	0.1ml



Evaluation of transdermal formulation

Physico- chemical evaluation[9,10,11]

Physical appearance

All the prepared transdermal films were observed for color, clarity, flexibility, and smoothness.

Weight uniformity

A specific part of a definite dimension is cut from various parts of the patch and weighed on a digital balance. The average weight and standard deviation values are then calculated.

Thickness of the patch

The thickness of the drug loaded patch is determined at different points by using a digital micrometer. The average thickness and standard deviation are then calculated from individual values.

Percentage Moisture content

The drug loaded patches are weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are reweighed. Determine the percentage moisture content from the below mentioned formula.

% moisture content = [Initial weight- Final weight/ Final weight] ×100.

Percentage Moisture uptake

The drug loaded patches are weighed and kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are reweighed and the percentage moisture uptake is determined from the below mentioned formula.

% moisture uptake = [Final weight- Initial weight/ initial weight] ×100.

Folding endurance

A strip of specific dimension is cut evenly and repeatedly folded at the same place until it breaks. The number of times the film could be folded at the same place without breaking indicates the magnitude of folding endurance. Usually the test is repeated for 5 patches selected at random. The average value and standard deviation are then calculated.

Uniformity of dosage unit test

An accurately weighed portion of the patch is cut into small pieces and transferred to a volumetric flask. Contents of the flask are dissolved in a suitable solvent and sonicated for complete dissolution of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was filtered using 0.2µm membrane filter and analyzed by suitable analytical technique (UV or HPLC).

Drug Content

A specified area of patch is to be dissolved in a suitable solvent in volumetric flask. The solution is then filtered through a filter medium and analyzed using suitable method (UV or HPLC technique).

***In vitro* drug release studies**

This test was performed using franz diffusion cell. The dissolution medium used was phosphate buffer (pH 7.4). Samples were withdrawn maintaining sink conditions and were evaluated for drug content using suitable analytical techniques.

In vitro drug release kinetics[12]

To study kinetics, data obtained from the in-vitro release were plotted in various kinetic models.

Zero-order equation

$\%R = Kt$

This model represents an ideal release profile to achieve prolonged pharmacological action.

First-order equation

$\text{Log}\%\text{ unreleased} = Kt / 2.303$

This model applies to studying hydrolysis kinetics and studying the release profiles of pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices.

Higuchi equation

$\%R = Kt^{0.5}$

This model applies to systems with the drug dispersed in the uniform swellable polymer matrix in patch with the water-soluble drug.

$\%\ R = Kt^{n}$

Korsmeyer-Peppasequation

This model is widely used when the release phenomenon could be involved. The end value could be used to characterize different release mechanisms.

Stability studies[13]

Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°c and 75±5% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content.

RESULTS AND DISCUSSION

Drug - excipient compatibility studies (FT-IR)

The compatibility between the drug and the selected polymers and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-polymer mixture, which confirmed the absence of any chemical interaction between the drug, polymer and other chemicals.

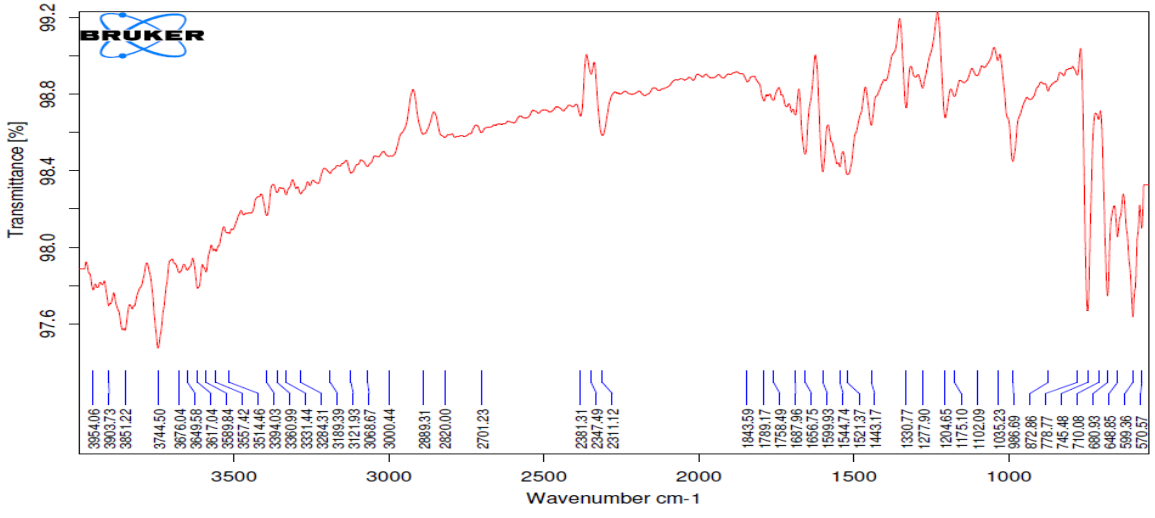


Fig-1: FT-IR Sample for Ketorolac.

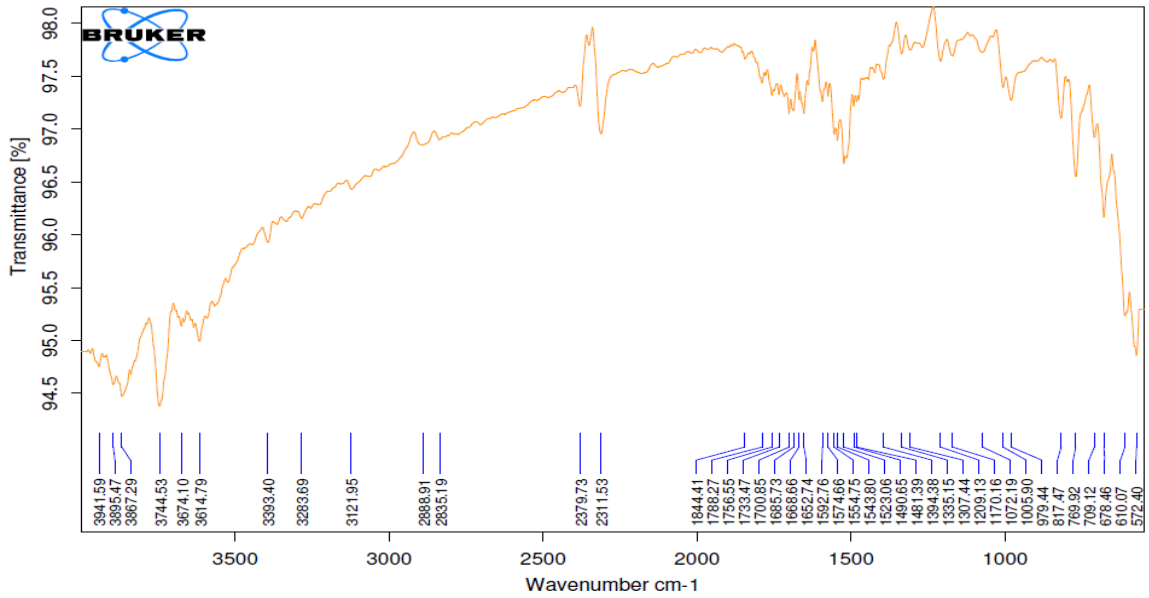


Fig-2: FT-IR Sample for Optimized Formulation.

Evaluation of Transdermal formulation

Physical appearance

The prepared patches were found to be uniform, smooth, flexible and homogenous.

Folding endurance

The folding endurance numbers of all the Ketorolac patches are 33 – 41. 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 the Polymer content. These results indicated that the patches would not break and maintain their integrity with general skin folding when applied.

Thickness of the film

Thickness was changed from batch to batch in individual strips of medicated patch carry uniform thickness, which indicates that total medicated patch carry uniform thickness.

Weight uniformity

The mean weights of all the prepared patches are shown in table . The weights are in the range of 138-148. The F7 formulation patches showed maximum weight.

Drug content

The drug content analysis of the prepared formulations have shown that the process employed to prepare the patches was capable of giving uniform drug content with minimum batch variability. All the patches were found to have drug content in the range of 89 – 100%. So the method employed i.e. solvent evaporation method is satisfactory for the preparation of Ketorolac transdermal patches.

Table-2: Physicochemical evaluation of Ketorolac patches.

Formulation code	Weight (mg)	Thickness (mm)	Folding endurance	Drug content (%)	% moisture loss	% moisture absorption
F1	142	0.21	35	90.37	7.2	8.9
F2	146	0.24	38	92.16	7.8	8.8
F3	140	0.26	40	91.42	8.2	9.0
F4	138	0.28	33	93.25	7.7	8.7
F5	145	0.27	41	89.32	8.1	8.9
F6	143	0.30	36	92.96	8.3	9.2
F7	148	0.25	39	93.80	7.9	9.1
F8	139	0.20	33	91.28	8.3	9.3

***In vitro* drug release study**

Phosphate buffer pH 7.4 containing 0.5% SLS was used as medium for the release studies and good linearity was observed in the plotted standard graph with a correlation coefficient of 0.999. The drug release profiles of Ketorolac patches containing different ratios of polymers Ethyl cellulose, HPMCK100M. It was cleared from the release profiles of formulations, that the drug release was governed by polymer nature and content.

Table-3: *In vitro* drug release profiles of Ketorolac transdermal patch (F1-F8).

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	13.25	12.96	13.21	14.25	15.28	16.02	17.10	16.99
2	25.39	26.34	27.11	24.20	26.45	28.09	27.18	28.04
3	36.74	37.52	38.20	37.11	39.32	39.22	38.52	37.23
4	46.25	49.25	48.79	46.92	49.21	48.66	50.07	49.99
5	53.18	55.22	52.21	57.20	60.15	61.20	63.33	62.32
6	68.35	67.91	68.42	68.21	71.22	72.35	73.18	72.25
7	73.25	74.59	75.51	78.27	82.31	83.22	84.25	83.10
8	89.55	91.24	90.12	92.39	94.27	95.08	96.30	94.98

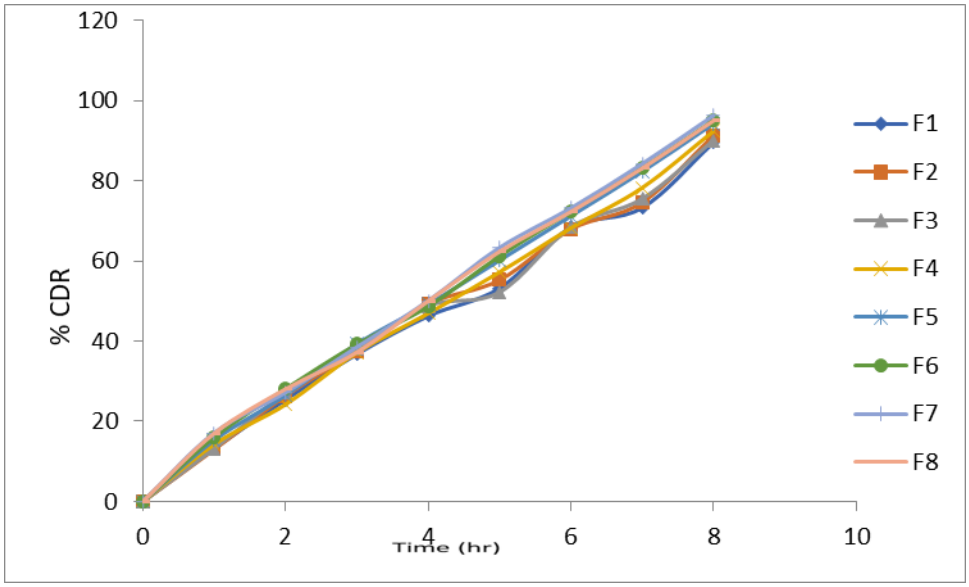


Fig-3: Drug release for all formulations.

Release kinetics

Kinetics and mechanism of drug release from all formulation was evaluated on the basis of zero order, Higuchi equation and Pappas model. Correlation coefficient (r^2) and slop value for each equation was calculated from Microsoft excel. Zero order plot for all formulations were found to be linear in both dissolution medium. That indicates it may follow zero order mechanism. Higuchi plot was found to be linear, which indicates diffusion may be the mechanism of drug release for each formulation. Peppas plot was found good linear, n > 0.5 for all formulations, indicated that drug release may follow anomalous diffusion. Zero order plot for F7 formulation was found to be linear in both dissolution medium, it considered as a best fit for drug release.

Zero order kinetics

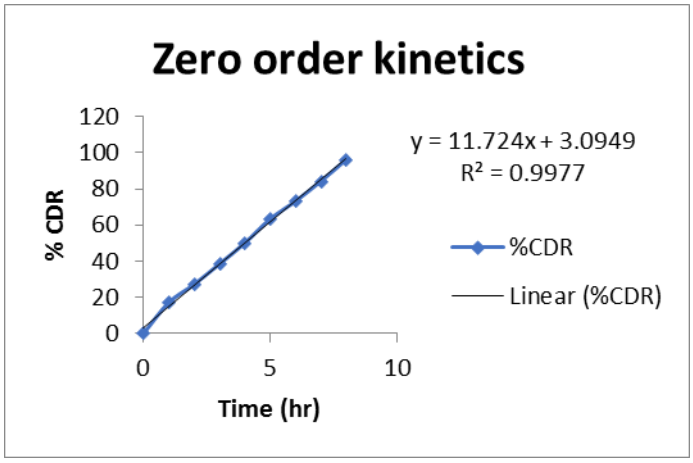


Fig-4: Zero order kinetics.

First order kinetics

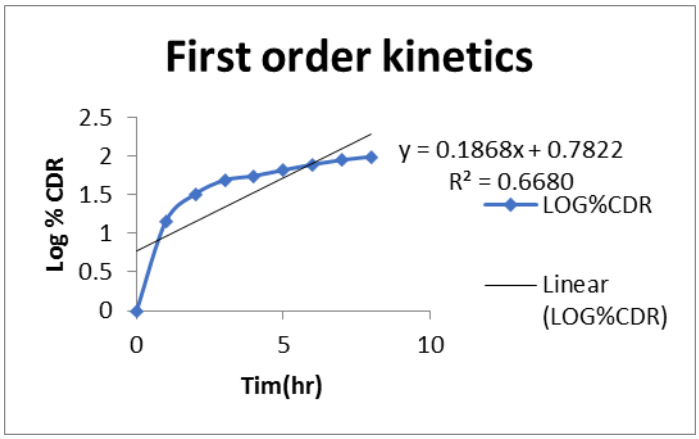


Fig-5: First order kinetics.

Higuchi model

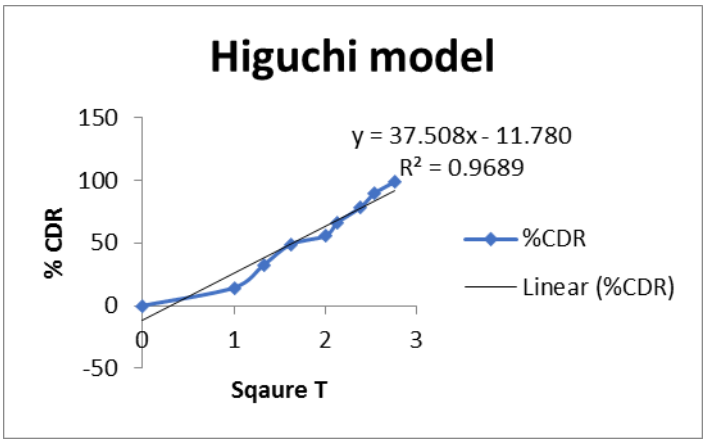


Fig-6: Higuchi model.

Krosmeyer peppas

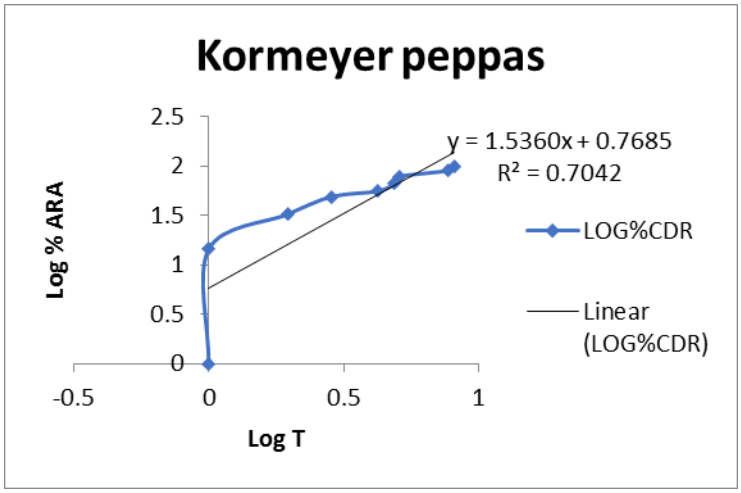


Fig-7: Krosmeyer peppas.

Stability Studies

Optimized formulations F7 was selected for accelerated stability studies as per ICH guidelines. The patches were observed for color, appearance and flexibility for a period of three months. The folding endurance, weight, drug content, % cumulative drug release of the formulation was found to be decreasing. This decrease may be attributed to the harsh environment (40^0C) maintained during the studies.

Table-4: Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months.

Time in days	Drug content (%)	Folding endurance	Physical appearance	% Cumulative drug release
0	93.80	39	No change in color	96.30
90	92.85	38	Slight yellowish color	95.28
180	91.25	37	Slight yellowish color	94.95

CONCLUSION

The F7 formulation was found to be stable as there was no drastic change in the Physico-chemical properties of the patches, which was also confirmed by FTIR. Thus conclusion can be made that stable transdermal patches of Ketorolac has been developed. F7 formulations showed highest cumulative percentage drug release of 96.30% were obtained during *in vitro* drug release studies after 8 hrs. Based upon the *in vitro* dissolution data the F7 formulation was concluded as optimized formulation.

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