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(RESEARCH ARTICLE)

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Formulation and evaluation of Ketorolac tromethamine for transdermal drug delivery system

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as Ketorolac Tromethamine are widely recommended to treat pain caused by osteoarthritis, ankylosing spondylitis, acute sciatica, rheumatoid arthritis and low back pain. Modern drug delivery technology, such as transdermal patches, is mostly used in the treatment of numerous diseases. As first-pass metabolism is avoided. Transdermal drug delivery systems (TDDS) can efficiently enhance bioavailability and help with the planned and controlled release of drug molecules into the systemic circulation. The purpose of this work was to produce matrix-type Ketorolac tromethamine transdermal patches by solvent evaporation using different polymer ratios, such as HPMC 15 cps, HPMC E5, and Eudragit S 100. Along with solvents like methanol and chloroform, plasticizers like glycerine, propylene glycol, and PEG 200 are used in this formulation. According to the FTIR study, Ketorolac Tromethamine had no significant interactions with other excipients. The following evaluations are carried out such as thickness, weight variation, folding durability, moisture content, drug content, surface pH, and *In vitro* diffusion are all evaluated for the prepared patches.

Keywords: Transdermal drug delivery system; Ketorolac tromethamine; HPMC 15cps; Eudragit S100; HPMC E5

1. Introduction

Transdermal drug delivery systems (TDDSs) refer to self-contained discrete dosage forms that, when applied to undamaged skin, distribute medication(s) into systemic circulation over a protracted period of time at a predefined and consistent rate. The aim of transdermal dose design is to minimize drug retention and metabolism in the skin while maximizing flux through the skin into the systemic circulation. TDDS offers many advantages over conventional injection and oral methods[1]. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliance and minimizes harmful side effects of a drug caused from temporary overdose. It is convenient, especially notable in patches which require only once a day application. Such a simple dosing regimen aids in patient adherence to drug therapy[2,3].

In contrast to injectables and oral methods, transdermal administration has a significant advantage due to patient compliance and the avoidance of first pass metabolism, respectively.

A variety of physicochemical and biological qualities are necessary for the formulation of medicines into transdermal drug delivery systems. According to general consensus, the best drug candidates for passive adhesive transdermal patches must be non-ionic, have a low molecular weight (500 Da), be sufficiently soluble in water and oil (log P in the range of 1-3), have an adequate solubility in aqueous solution (>1 mg/ml), have a low melting point (200 °C), have an aqueous pH range of 5 to 9, and have good potency (dose in milligrams per day) Developed by ALZA Corp, the first

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transdermal patch, Transderm-Scop (scopolamine), was authorised by the FDA in 1981 for the control of motion sickness[4,5,6].

Ketorolac is a non-selective NSAID that works by inhibiting both the COX-1 and COX-2 enzymes that convert arachidonic acid to prostaglandins. The gastric mucosa, vascular endothelium, and platelets all contain the constitutively active COX-1 enzyme. The COX-2 enzyme, on the other hand, is induces and mediates inflammation, pain, and fever. As a result, inhibiting the COX-1 enzyme is linked to an increased risk of bleeding and gastric ulceration, whereas inhibiting the COX-2 enzyme is linked to the desired anti-inflammatory and analgesic properties[7,8].

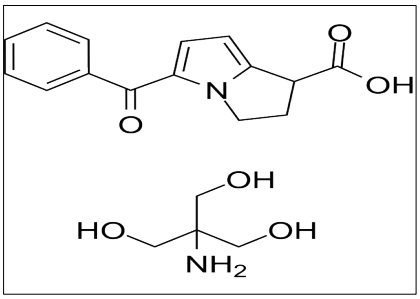

Figure 1 Structure of Ketorolac Tromethamine

2. Materials and methods

Ketorolac tromethamine was obtained as a gift sample from Divis Pharmaceuticals Pvt. Ltd, Hyd. HPMC, HPMC, Eudragit E100, glycerine, PEG-400, Methanol, chloroform from were obtained from fine chemicals, Mumbai.

2.1. Analytical Method Development

2.1.1. Construction of Standard Graph of Ketorolac tromethamine

Accurately weighed amount of 100 mg Ketorolac tromethamine was transferred into a 100ml volumetric flask. 20 mL of distilled water was added to dissolve the drug and volume was made up to 100 mL with the same distilled water. The resulted solution had the concentration of 1mg/ml which was labeled as 'stock'. From this stock solution 10ml was taken and diluted to 100 mL with distilled water which has given the solution having the concentration of 100µg/ml. Necessary dilutions were made by using this second solution to give the different concentrations of Ketorolac tromethamine (2 to 10 µg/ml) solution. Using a UV spectrophotometer, the absorbance of thus prepared solutions was scanned between 200-700nm in comparison to a blank[9,10].

2.2. Drug-excipient compatibility studies by FT-IR

Infrared (IR) spectroscopy is an absorption method that is commonly used in both qualitative and quantitative evaluations. The electromagnetic radiation in the infrared region of the spectrum can change the vibrational and rotational states of covalent bonds in organic molecules. The IR spectrum of an organic compound is a unique physical property that can be utilized to identify unknowns by interpreting characteristic absorbances and comparing them to spectral libraries. Because of its sensitivity and selectivity, IR spectroscopy is also used in quantitative techniques. The method involves finely grinding a quantity of the drug with a specially purified salt, potassium bromide, to remove scattering effects from large crystals. This powder mixture is then pressed in a mechanical press to form a translucent pellet and then scanned between 400 and 4000 cm^{-1}. Drug excipient compatibility studies can be determined by FTIR. By analysing with pure drug and physical mixture of both drug and excipients[11,12,13].

2.3. Method of preparation of Ketorolac tromethamine transdermal patches

Matrix type transdermal patches containing Ketorolac were prepared by solvent evaporation technique, using different ratios of HPMCE5, HPMC15cps and Eudragit S 100 were weighted in requisite ratios for patch preparation and they are allowed for swelling for about 6hrs in a solvent mixture and plasticizer PEG 200 or Propylene glycol was added. After that, the drug solution was mixed with the polymeric solution. Casted on to petri plate, and it is allowed for air drying overnight followed by vacuum drying for 8-10hrs[14,15].

Table 1 Formulation table of Ketorolac tromethamine transdermal patches

Ingredients	K1	K2	K3	K4	K5	K6	K7	K8	K9	K10	K11	K12
Ketorolac tromethamine (mg)	10	10	10	10	10	10	10	10	10	10	10	10
HPMC 15 cps (mg)	26.3	26.3	-	-	13.15	13.15	-	13.15	6.57	6.57	13.15	13.15
HPMC E 5	-	-	26.3	-	13.15	-	13.15	6.57	13.15	6.57	13.15	-
Eudragit E 100 (mg)	-	-	-	26.3	-	13.15	13.15	6.57	6.57	13.15	-	13.15
Methanol (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Chloroform(ml)		0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Water (ml)	0.5	-	-	-	-	-	-	-	-	-	-	-
PEG 200 (ml)	0.05	-	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	-	0.05
Propylene glycol (ml)	-	0.05	-	-	-	-	-	-	-	-	0.05	-
Glycerin (ml)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05

2.4. Evaluation tests

2.4.1. Weight variation

The transdermal patch was cut into 2 cm squares to measure weight variation, and three pieces were weighed to calculate the average weight[16-20].

2.4.2. Thickness

A vernier caliper was used to measure the thickness of the three patches. Thickness was measured at three different points on the patch and the average value was recorded[16-20].

2.4.3. Folding endurance

A strip (2 cm x 2 cm) of a specific area was cut evenly and folded repeatedly until it broke at the same place. The number of times the film was not broken even when the film was folded at the same point was taken as the folding strength[16-20].

2.4.4. Surface pH

A 2 cm square film was placed in 0.5 ml of double distilled water in a glass tube for about 1 hour and the pH of the film was calculated using a pH meter[16-20].

2.4.5. Drug content

Place the 2 cm square film into a mixture of 20 mL of methanol and 80 mL of phosphate buffer (pH 7.4) in a 100 mL volumetric flask and stir using a magnetic stirrer for 24 hours. Drug solutions were scanned by UV spectroscopy and drug content was calculated[16-20].

2.4.6. Percentage of moisture content

Films of 2 cm square are weighed individually and stored in a desiccator for about 24hrs at room temperature and moisture content was calculated using formula[16-20.]

Moisture content = initial weight – final weight / final weight ×100

2.4.7. In vitro drug diffusion studies

In vitro drug release studies is performed by using Franz diffusion cell. It consists of receptor compartment of 22.5ml capacity and it also contains donor compartment. The receptor compartment was filled with pH 7.4 phosphate buffer cellophane membrane was Placed between the donor and receptor compartment. The prepared transdermal patch was placed on cellophane membrane. The whole assembly was fixed on a magnetic stirrer and continuously stirred at 50rpm.The temperature was maintained at 32 ± 0.5 ºC. The samples were withdrawn at different time intervals and

analyzed in UV spectroscopy. The receptor chamber was replenished with an equal amount of pH 7.4 phosphate buffer to Maintain sink conditions. A graph was plotted between cumulative percentages of drug permeation per square cm of patches against time[21,22].

3. Results and discussion

3.1. UV spectrum analysis

The maximum absorption of Ketorolac Tromethamine in distilled water was found to be 323nm.

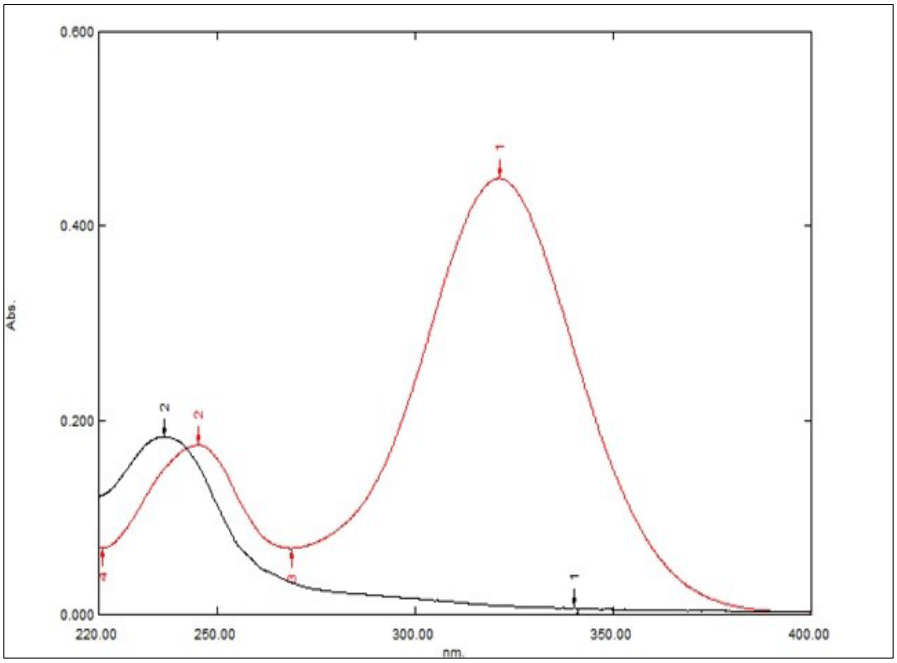

Figure 2 Ketorolac Tromethamine Maximum absorption

3.1.1. UV Calibration of Ketorolac Tromethamine

In the concentration range of 0-12 mg/ml, the drug calibration curve followed Beer Lambert's law (R^2 = 0.991), with the results depicted below

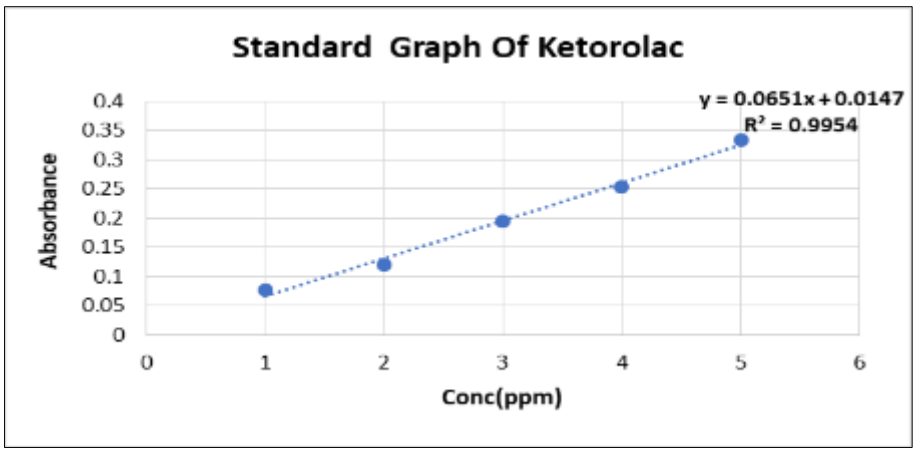

Figure 3 Standard Graph of Ketorolac Tromethamine

3.2. FTIR Analysis

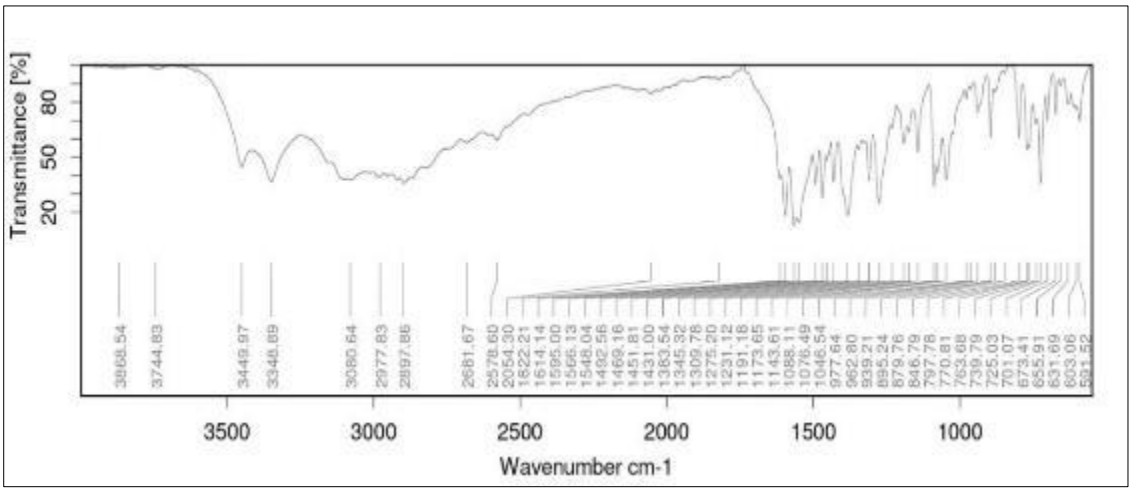

Figure 4 FTIR of Ketorolac Tromethamine Pure Drug

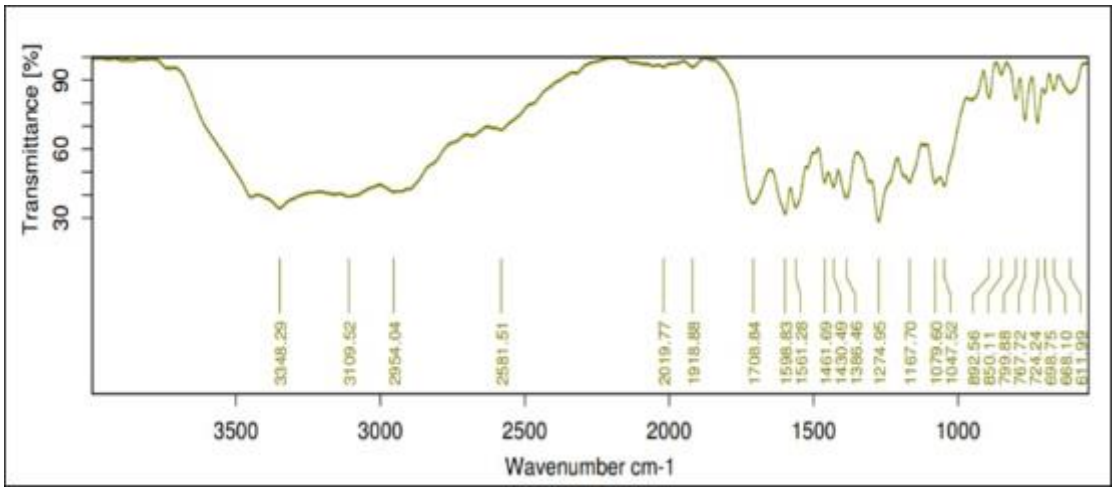

Figure 5 Topical Ketorolac Tromethamine Hydrogel formulation (HF4) spectrum

Table 2 FTIR Comparative Studies of Ketorolac Tromethamine Drug and Formulation

Wavelength cm^{-1}	Group	Compound Class
3900-3300	O-H stretching	Alcohol
3300-2700	N-H stretching	Amine salt
2700-2500	C-H stretching O-H stretching	Alkane Carboxylic acid
2500-2000	C=C=C stretching	Allene
2000-1500	C=O bending	Aromatic Compound
	C=C bending	Alkene
	C=N bending	Nitriles Carbene

3.3. Evaluation tests

Thickness was measured for all the formulations and thickness was found to be in the range of 0.18 ± 0.04 to 0.29 ± 0.05values of thickness are shown in the table 4.Folding endurance was measured for all the formulations and Folding endurance was found to be in the range of 115 ± 9 to 226 ± 12values of Folding endurance are shown in the table 3.Surface pH was measured for all the formulations and surface pH was found to be in the range of 5.25± 0.28 to 6.91± 0.32 values of surface pH are shown in the table 4.Drug content was measured for all the formulations and drug content was found to be in the range of 92.12±2.31 to 99.23±4.02 values of drug contents are shown in the table 4.%Moisture content was measured for all the formulations and % Moisture content was found to be in the range of 1.12 ± 0.16 to 2.18 ± 0.07 values of % moisture content is shown in the table 3.

Table 3 Evaluation tests of Ketorolac tromethamine transdermal patches

Code	Weight Uniformity SD ± n=3	Thickness(mm) SD ± n =3	Folding enduranceSD ± n=3	Surface pH SD ± n=3	Drug content SD ± n=3	%Moisture content SD ± n = 3
K1	5.83 ± 0.16	0.29 ± 0.05	217 ± 12	6.21± 0.34	98.49±1.03	2.18 ± 0.07
K2	6.32 ± 0.47	0.28 ± 0.06	186 ± 15	5.88± 0.13	92.12±2.31	2.11 ± 0.06
K3	5.31 ± 0.32	0.27 ± 0.04	204 ± 16	5.72± 0.05	97.23±3.12	1.42 ± 0.02
K4	6.23± 0.71	0.26 ± 0.08	210 ± 10	6.12± 0.23	95.54±2.28	2.16 ± 0.13
K5	5.99 ± 0.59	0.19 ± 0.07	115 ± 9	6.03± 0.18	99.23±4.02	1.86 ± 0.21
K6	5.34± 0.04	0.21 ± 0.04	212 ± 13	6.05± 0.19	92.76±1.49	1.12 ± 0.16
K7	5.98± 0.05	0.23 ± 0.06	204± 7	6.23± 0.23	95.12±1.48	1.22 ± 0.17
K8	6.16± 0.24	0.19 ± 0.02	211 ± 11	5.89± 0.03	98.54±2.05	1.78 ± 0.11
K9	5.32 ± 0.86	0.20 ± 0.03	226 ± 12	5.86± 0.11	96.67±1.86	1.21 ± 0.16
K10	5.48± 0.32	0.18 ± 0.04	217 ± 3	5.96± 0.15	92.34±2.19	1.45 ± 0.13
K11	6.17± 0.45	0.20 ± 0.05	208 ± 3	5.25± 0.28	94.79±1.03	1.59 ± 0.32
K12	6.09 ± 0.72	0.21 ± 0.03	219 ± 3	6.91± 0.32	98.93±2.42	1.25 ± 0.09

Weight variation was measured for all the formulations and weight variation was found to be in the range of 5.31 ± 0.32 to 6.32 ± 0.47 values of weight variation are shown in the table 4.

Table 4 *In vitro* drug diffusion studies of K1 to K6

TIME(hrs)	K1	K2	K3	K4	K5	K6
1	14.21±0.01	13.51±0.02	12.51±0.01	13.31±0.01	10.52±0.02	15.33±0.03
2	35.61±0.03	32.52±0.01	30.52±0.04	23.15±0.04	17.51±0.03	25.21±0.02
3	45.61±0.05	43.61±0.04	41.53±0.05	33.23±0.03	29.03±0.01	35.42±0.03
4	66.23±0.03	63.71±0.05	56.32±0.03	40.31±0.04	33.16±0.04	45.22±0.01
6	98.52±0.01	76.14±0.03	64.51±0.01	54.26±0.02	39.26±0.05	55.60±0.05
8		97.87±0.01	77.45±0.03	62.15±0.05	43.17±0.01	66.35±0.02
12			98.54±0.02	73.81±0.03	50.17±0.02	80.12±0.03
16				98.54±0.01	56.8±0.03	96.19±0.01
24					98.16±0.02	

Table 5 *In vitro* drug diffusion studies of K7 to K12

TIME (hrs)	K7	K8	K9	K10	K11	K12
1	16.31±0.41	14.71±0.03	15.62±0.32	13.52±0.01	14.61±0.63	17.41±0.45
2	46.75±0.05	35.14±0.44	34.21±0.04	32.53±0.03	16.73±0.03	21.22±0.47
3	63.51±0.52	44.32±0.31	42.53±0.15	46.72±0.52	34.51±0.09	35.14±0.41
4	73.23±0.03	54.61±0.45	63.31±0.63	68.65±0.04	44.83±0.08	46.21±0.19
6	88.02±0.31	60.52±0.41	75.33±0.45	81.54±0.35	56.82±0.06	59.24±0.71
8		76.55±0.13	95.52±0.02	94.62±0.02	67.85±0.04	77.54±0.41
12		90.23±0.64			76.93±0.03	98.12±0.34
16					92.65±0.51	
24						

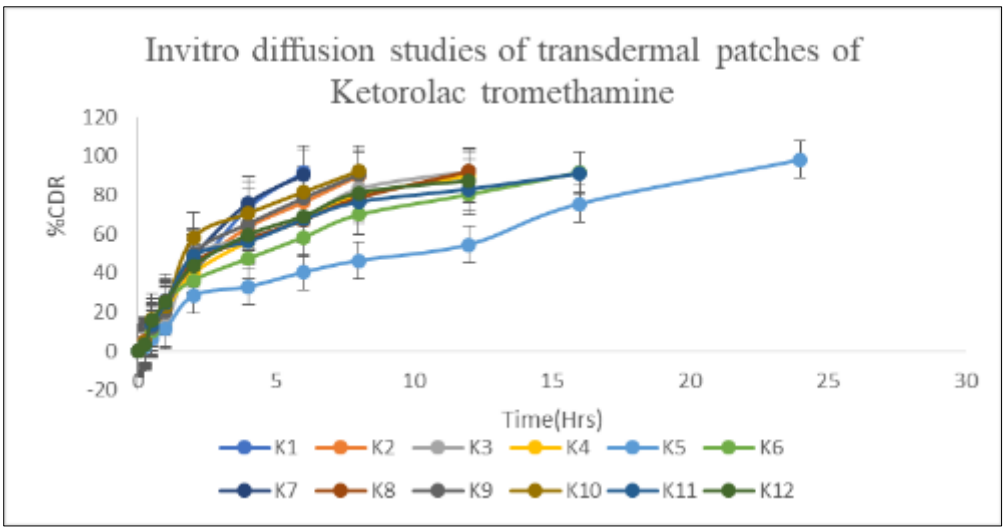

Figure 6 *In-vitro* drug diffusion studies of K1 to K12

The data obtained from the *In vitro* drug diffusion studies is shown in the table 4 and 5 and fig-6. *In vitro* drug diffusion studies are performed for 24 hours. All the prepared patches have shown controlled release for 8 hrs except K5 (24hrs).*In-vitro* drug diffusion studies are carried out using pH 7.4 phosphate buffer at 323nm. Among them K5 shows highest drug release at the end of 24th hour with zero order diffusion type of drug release which is confirmed by the obtained R^2 value of various kinetic models shown in Fig-7 to 10. Hence, K5 formulation chosen as the best formulation as it releases the drug at a slow rate for prolonged duration of time.

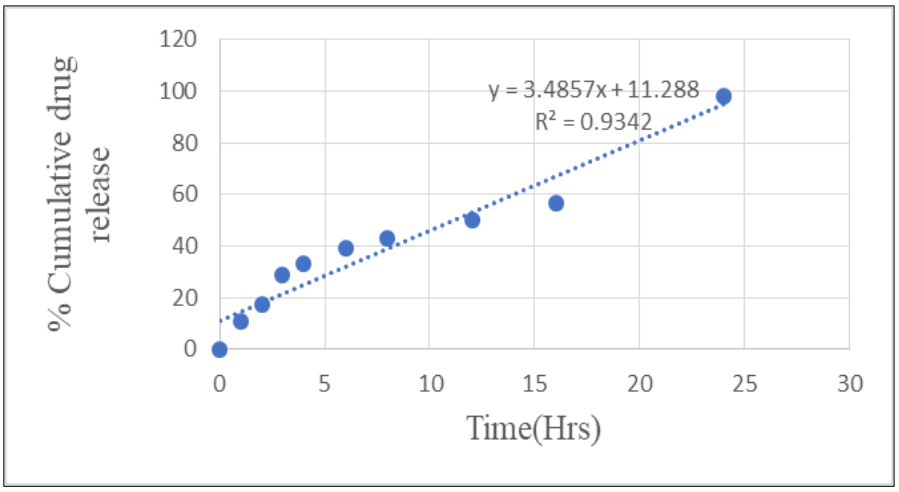

Figure 7 Zero order Model kinetic for K5

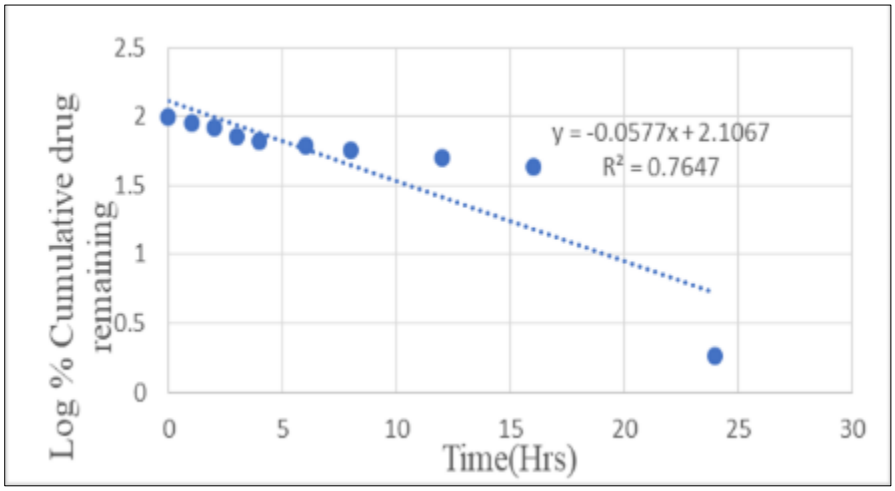

Figure 8 First order Model kinetic for K5

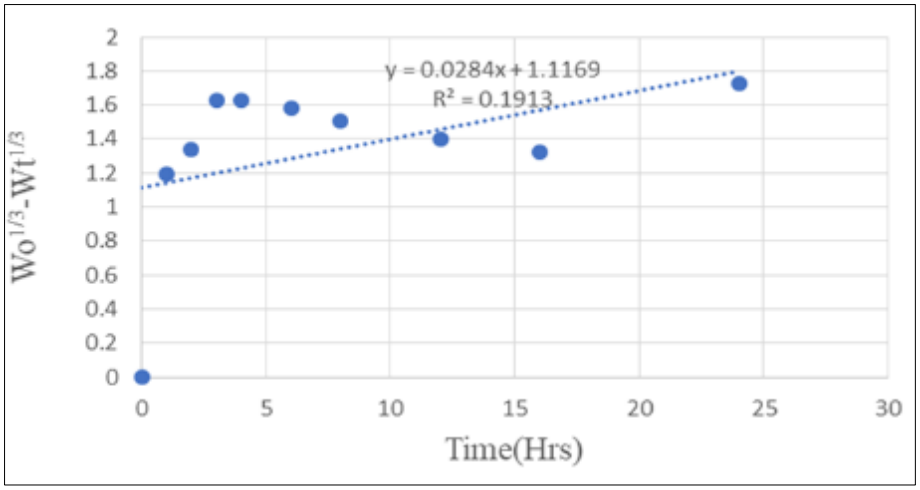

Figure 9 Hixson Crowell Model for K5

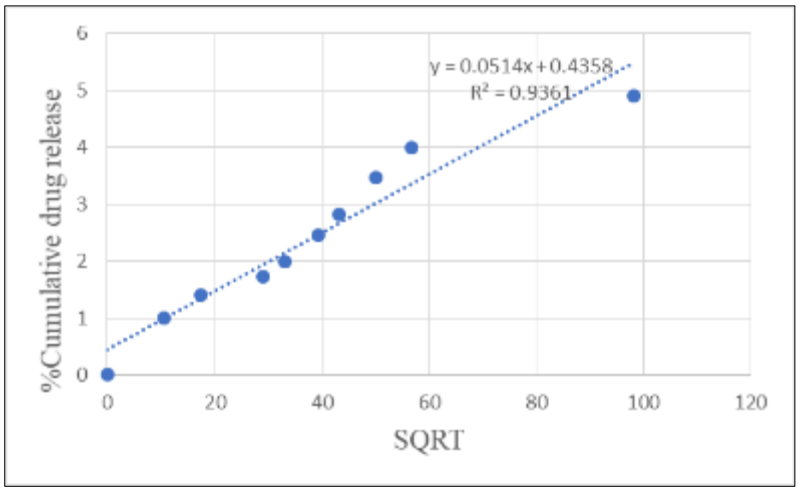

Figure 10 Higuchi Model for K5

4. Conclusion

Among all the formulations prepared K5 shows best results. All the physicochemical properties of K5 were found to be satisfactory. The patch exhibit - controlled release over 24 hours with zero order diffusion type of mechanism. The results of the study shows that Ketorolac can be delivered by Transdermal patches. The results of the current investigation suggest that the transdermal patch containing Ketorolac may have great promising for effective doses to systemic circulation.

Compliance with ethical standards

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Disclosure of conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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