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Original Research Article

Formulation and evaluation of transdermal patches containing dexketoprofen trometamol

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ABSTRACT

Dexketoprofen Trometamol is a NSAID, used as an analgesic and anti-inflammatory drug. It works by blocking the action of cyclo-oxygenase in the body. Conventional route of delivery has many drawbacks such as hepatic first-pass metabolism, reduced bioavailability, and fluctuating drug concentrations in the blood. These problems can be overcome by development of transdermal drug delivery system. The objective of this study was to develop and evaluate the transdermal patches of the drug Dexketoprofen Trometamol. The patches were prepared by solvent casting method using polymers; Ethyl cellulose, HPMC and ERS 100 in different ratios.

The prepared formulations were uniform in their physical characteristics**.** The formulation F6, combination of polymer (HPMC: EC in ratio 4:1) showed maximum release of 85.77% in 24 hours. The resultant data was fitted in to zero, first, Higuchi and Peppas model. The results specify that Dexketoprofen Trometamol transdermal patch can be designed for obtaining better therapeutic benefits.

1. Introduction

Transdermal drug delivery systems (TDDSs) is a self-contained distinct dosage forms which delivers the drug by means of transdermal patch through the epidermis of the skin at a predetermined and sustained rate with low biological half life. It provides systemic delivery of drug through increased bioavailability with reduced dosing frequency.[1,2]

The skin has a number of considerable advantages over other routes of administration when used as a site of drug delivery, including increased patient compliance, the ability to avoid gastric irritation, no hepatic first-pass metabolism thus enhancing the bioavailability, minimize the risk of systemic side effects by reducing plasma concentrations contrast to oral therapy, provide a sustained release of drug at the site of application; rapid termination of therapy by removal of the patch, the reduction of fluctuations in plasma levels of drugs, and avoid pain associated with parenterals. Thus TDDS has the potential of reducing side effects and improving patient compliance.[3]

Dexketoprofen Trometamol is chemically 2-Amino-2-(hydroxymethyl)-1,3-propanediol (S)-3- benzoyl-alpha-methylbenzeneacetate. The structure of Dexketoprofen trometamol is shown in Figure 1.[4]

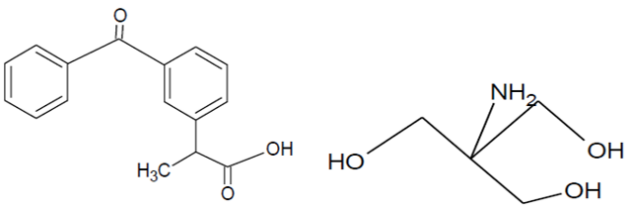

Fig. 1: Structure of Dexketoprofen trometamol

It belongs to a class of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). It is used as an analgesic and anti-inflammatory drug.

It works by blocking the action of cyclo-oxygenase in the body, which is involved in the production of prostaglandins

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in the body. Prostaglandins are produced in response to injury or certain diseases and may cause swelling, inflammation and pain. By blocking cyclo-oxygenase, it prevents the production of prostaglandins and therefore reduces inflammation and pain.[5]

The motive of the present work was to formulate and characterize the transdermal patches of Dexketoprofen Trometamol in order to investigate the practicability of this route of administration for prolonged action of drug in body and also increase the patient compliance and bioavailability.

2. Materials and Methods

2.1. Materials

Dexketoprofen Trometamol was received as a generous gift sample from Emcure Pharmaceuticals Limited, Pune, India. HPMC, Ethyl Cellulose and Eudragit RS 100 were procured from S. D. Fine Chemicals, Mumbai, India. Dialysis membrane was purchased from Hi-Media Laboratories Ltd., Mumbai, India. All other laboratory chemicals and reagents used in the study were of either pharmaceutical analytical grade.

3. Methods

1. Preformulation studies of drug.
2. Identification of drug.

3.1.

3.1.1. Organoleptic properties

Color, odor, taste, and state were determined.

3.1.2. Determination of melting point

The melting point was determined by the capillary method. The temperature at which the drug melted was recorded.

3.1.3. Determination of UV absorption maxima

The identification of drug was done by UV spectrophotometric method. From the spectra, λ_{max} of Dexketoprofen Trometamol was observed at 242 nm. The spectral data from this scan was used for the preparation of a calibration curve of Dexketoprofen Trometamol.[6]

3.1.4. Fourier transform infrared analysis

FTIR analysis of the sample was employed for compound identification (FTIR-8400S Shimadzu). The powdered drug was scanned from 400 to 4000 cm^{-1}.

3.1.5. Determination of solubility

The solubility analysis for Dexketoprofen Trometamol was done by solubility determination in different solvents like Water, Chloroform, DMSO, Ethanol, Methanol, etc.

3.1.6. Determination of partition coefficient

The partition coefficient was determined by dissolving 10 mg of drug in separating funnels containing 10 ml portion of each of n-Octanol and PBS pH 7.4. The separating funnels were shaken on mechanical shaker for 24 hours. Two phases were separated and aqueous phase was filter through Whatman filter paper and the amount of the drug in aqueous phase was determined spectrophotometrically at 242 nm.[7]

3.1.7. Calibration of dexketoprofen trometamol

Stock solution was prepared by dissolving 100 mg of Dexketoprofen trometamol in 100 ml methanol in a volumetric flask. An aliquot of desired concentration was prepared. The absorptivity coefficient of the drug at the 242 nm was determined.

3.1.8. Drug- excipients compatibility studies

A small quantity of drug with an excipient was placed in a vial, and stoppered from above by rubber cork and sealed properly. A storage period of about 2 weeks at 60 °C and the same sample was retained for 2 months at 40 °C. After storage, the sample was observed physically for liquefaction, caking, odor or gas formation, discoloration.[8]

4. Formulation of Transdermal Matrix Patch

4.1. Preparation of casting solutions

The casting solutions were prepared by dissolving weighed quantities of polymers in a mixture of chloroform and methanol in 1:1 ratio. The drug, plasticizer and permeation enhancer were then added to the polymer solutions separately and systematically mixed to form a homogenous mixture. The resultant solution was kept aside without any disturbances to permit the entrapped air to bubble out.

4.2. Preparation of transdermal patches

About 3 ml of the above prepared casting solution were pipetted into circular glass moulds especially designed to hold contents, which is casted on mercury surface. The glass moulds containing the casting solutions were allowed for dry at room temperature for 24 hrs and the patches are dried in oven at 40-45° for about 30 minutes to remove the residual solvents. The patches were removed and cut into circular discs with 4.4 cm diameter (15.21 cm^2 surface area). These patches were wrapped in aluminum foil and stored in dessicator for further studies.[9]

4.3. Evaluation of transdermal patches

All the prepared transdermal patches were evaluated by the following parameters:

Table 1: Composition of transdermalpatches

S. No.	Formulation Code	Drug (mg)	Polymer	Ratio	Plasticizer Glycerol (% w/w)	Permeation Enhancer DMSO (% w/w)
1.	F1	20	EC : ERS 100	1:4	30	20
2.	F2	20	EC : ERS 100	4:1	30	20
3.	F3	20	HPMC : ERS 100	1:4	30	20
4.	F4	20	HPMC : ERS 100	4:1	30	20
5.	F5	20	HPMC : EC	1:4	30	20
6.	F6	20	HPMC : EC	4:1	30	20

4.4. Physical appearance

All the prepared patches were visually inspected for color, clarity, entrapment of any air bubble, flexibility and smoothness.[10]

4.5. Thickness

Thickness of the patch was measured by using digital thickness gauge at four different points and average thickness was determined.[11]

4.6. Weight variation

10 patches from each formulation were weighed individually and the average weight was calculated. The individual weight should not deviate significantly from the average weight.[12]

4.7. Drug content

A specified area 2x2 of patch was dissolved in mixture of chloroform and methanol. It was closed and shaked vigorously for 24 hours in a shaker. The resulting solution was filtered and the amount of drug present in the filterate was determined by using UV spectrophotometer at 242 nm.[13]

4.8. Flatness

Longitudinal strips from patches of each formulation were cut. One from the center and one from the other side of patch. The length of each strip was measured and the variation in length because of the non-uniformity of flatness was measured. 0% constriction was considered to be 100% flatness. Flatness was calculated using given formula.[14]

% Constriction =

$$\frac{I1\ (Initial\ length\ of\ each\ strip) - I2(Cutted\ film\ length)}{I2\ (Cutted\ film\ length)}\ x\ 100$$

4.9. Folding endurance

Folding endurance was determined by repeatedly folding a small strip of patches (approximately 2×2 cm) at the same place till it broke. The number of times patches could be folded at the same place, without breaking gave the value of folding endurance and it was recorded.[15]

4.10. Tensile strength

The patches were evaluated for its tensile strength to calculate their mechanical properties. It was determined by using a self designed assembly by the following formula.[16]

Tensile Strength =

$$\frac{Break\ Force}{a\ .\ b\ (1 + \Delta L/L)}$$

Where,

a = Width of the patch, b = Thickness of the patch, L = Length of the patch,

ΔL = Elongation of patch at break point, Break Force = Weight required to break the patch (Kg)

4.11. Moisture content

The patches were accurately weighed and kept in a desiccator containing calcium chloride 24 hrs. Then the concluding weight was noted. It can be calculated by following formula[17]

% Moisture content =

$$\frac{Final\ weight\ -\ Initial\ weight}{Initial\ weight}\ x\ 100$$

4.12. Moisture uptake

Prepared patches was kept in desiccators at room temperature for 24 h with silica gel and weighed and transferred to other desiccators to expose of 75% RH using a saturated solution of sodium chloride at 25°C. The moisture uptake capacity was calculated according to the given formula[18]

% Moisture uptake =

$$\frac{Wm\ -\ Ws}{Ws}\ x\ 100$$

4.13. In-vitro permeation study

The release studies from formulated patches were carried out by using Franz diffusion cell in order to determine delivery and permeation of drug from the skin in to the body.[19]

The drug release data of all formulations were fitted to various mathematical models such as zero order as cumulative % of drug released vs. time, first order as log cumulative % of drug remaining vs. time and Higuchi's model as cumulative % drug released vs. square root of time. To determine the mechanism of drug release from formulations, the data were fitted into Korsmeyer Peppas equation as log cumulative % of drug released vs. log time.[20]

4.14. Ex-vivo permeation study

Ex vivo permeation studies are conducted by using Franz diffusion apparatus to forecast the in vivo absorption of the drug. The rat skin was kept between the diffusion cells, with stratum corneum facing the donor compartment. The patch is applied above the stratum corneum (upper side) and a dialysis membrane was kept over the patch. The receiver phase (lower phase) was containing 24 ml of buffer stirred at 500 rpm on a magnetic stirrer.

The amount of the drug transferred was estimated by taking 5ml of the sample at graded time intervals up to 24 hrs. The absorbance was measured at 242 nm spectrophotometrically. The graph was plotted between Cumulative amounts of drug transferred in $\mu g/cm^2$ against time.[20,21]

4.15. Drug flux

The drug flux (μg /hr/ cm^2) at steady state was determined by dividing the slope of the linear portion of curve by area of the exposed skin surface. The flux calculated by the following formula[22]

$$J_{Target} = \frac{C_{ss} Cl_T BW}{A}$$

Where,

A = effective surface area of the transdermal patch, BW = average human body weight of 70 kg,

C_{ss} = the steady state plasma concentration of drug, Cl_T = documented total clearance of drug

4.16. Lag time (Tlag)

The lag time (T_{lag}) was determined by extrapolating the linear portion of the cumulative amount permeated versus time curve to the abscissa.[23]

4.17. Enhancement factor

The effectiveness of various permeation enhancers was determined by comparing drug flux in the presence and absence of each permeation enhancer, and obtained ratio was known as the enhancement factor (EF).[24]

$$EF = \frac{Drug\ flux\ with\ enhancer}{Drug\ flux\ without\ enhancer}$$

4.18. Skin irritation test

To determine the irritant effect or any chance of edema with the use of transdermal patches, primary skin irritancy test was evaluated according to Draize test. Transdermal patches were applied on to the dorsal skin of albino rats which was shaved on the previous day of the study. The rats were divided into five groups (six animals in each group). The patch is to be removed after 24 hr and the skin was observed and classified into 5 grades (0 to 4) on the basis of the severity of skin injury.

The scores were given for erythema from 0 to 4 depending on the degree of erythema as follows: 0 = no erythema, 1= slight erythema (barely perceptible- light pink), 2 = moderate erythema (dark pink), 3 = moderate to severe erythema (light red), 4 = severe erythema (extreme redness).

The edema scale was: 0 = none, 1 = slight, 2 = well defined, 3 = moderate and 4 = severe.[25]

4.19. Stability study (As per ICH guidelines)

Stability studies of formulations was conducted according to ICH guidelines by storing at 40 °C and 75% RH for 3 months. The samples were withdrawn at 30, 60 and 90 days and evaluated for physical appearance and drug contents. The ex vivo permeation study was performed after 90 days and compared with fresh batch.[26]

5. Results and Discussion

5.1. Preformulation studies

The preformulation study was performed in order to assure the accuracy of drug sample and determination of various parameters for formulation of transdermal patch.

5.2. Identification of drug

5.2.1. Organoleptic properties

Organoleptic properties of the drug were found within limits as shown in Table 2.

Table 2: Organolepticproperties of the drug

S. No.	Properties	Inference
1.	Color	White to off-white
2.	State	Crystalline powder
3.	Odor	Odorless

5.3. Melting point

Melting point of drug was found to be 106 ± 1 °C which compared with previously reported value (105 to 107 °C) indicated that the drug sample was pure.

5.4. UV absorption maxima

The maximum absorbance of drug in methanol was found to be at λ_{max} 242 nm.

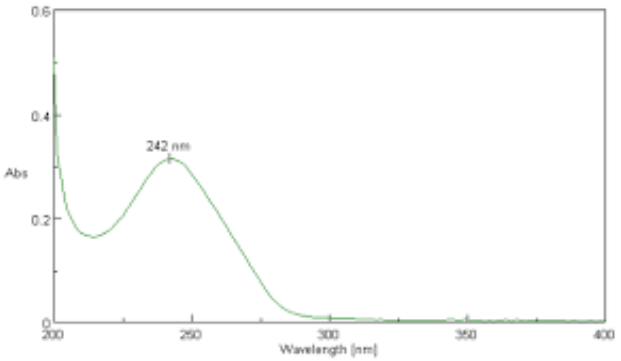

Fig. 2: UV spectra of Dexketoprofen trometamol in methanol

5.5. Fourier transform infrared analysis

The FTIR analysis of the drug was carried out for compound identification. The powdered drug was placed carefully over sample holder for scanning. The FTIR spectrum for pure drug is shown in Figure 3.

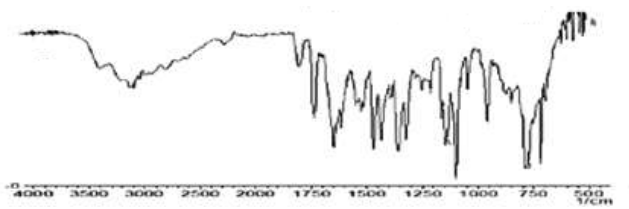

Fig. 3: FTIR spectra of pure drug (Dexketoprofen trometamol)

5.6. Solubility

The solubility study revealed that the drug sample was freely soluble in water and DMSO and sparingly soluble in methanol.

5.7. Partition coefficient

The logarithmic value of partition coefficient value was experimentally found to be 4.55. This revealed the hydrophobic nature of Dexketoprofen trometamol and further indicated that it is a suitable candidate for transdermal drug delivery.

5.8. Calibration of Dexketoprofen Trometamol

Table 3: Data for Calibration curve ofDexketoprofen trometamol in methanol

S. No.	Concentration (μg / ml)	Absorbance
1.	0	0
2.	4	0.155
3.	8	0.313
4.	12	0.468
5.	16	0.621
6.	20	0.774

5.9. Drug-excipients compatibility studies

No significant changes were observed.

6. Evaluation of Transdermal Patches

6.1. Physical appearance

The formulated patches were found to be clear, smooth, uniform, flexible in their physical appearance and free from entrapment of air bubble.

6.2. Thickness

The thickness of the prepared patches varies between 0.120 ± 0.007 to 0.184 ± 0.013. Low standard deviation values shows uniformity of the patches [Table 4].

6.3. Weight variation

The weight of the prepared transdermal patches for different formulations ranged between 286 ± 0.008 to 566 ± 0.017 mg. The variation in weight uniformity of the prepared patches was within acceptable range [Table 4].

6.4. Drug content

The drug content was found to be ranging between 90.00 ± 0.28 and 97.83 ± 1.42 mg [Table 4].

6.5. Flatness

The results showed that none of the formulations have variation in the strip lengths before and after longitudinal cut, indicating 100% flatness and 0% constriction, and thus they can maintain a even surface when applied to the skin [Table 4].

6.6. Folding endurance

Folding endurance values varied between 47 ± 3.63 and 60 ± 5.12. The result was found satisfactory indicating that the patches would not break and would maintain their integrity when used [Table 4].

Table 4: Physico-chemical evaluation of Dexketoprofen trometamol patches

S. No.	Formulation Code	Thickness (mm) ± S.D	Weight Variation (mg) ± S.D	Drug Content (%) ± S.D	Flatness (%)	Folding Endurance ± S.D	Tensile Strength (kg/mm^2) ± S.D
1.	F1	0.134 ± 0.043	525 ± 0.001	94.65 ± 0.34	100	49 ± 4.84	0.309 ± 0.035
2.	F2	0.184 ± 0.013	566 ± 0.017	92.26 ± 1.56	100	54 ± 2.54	0.326 ± 0.071
3.	F3	0.144 ± 0.003	361 ± 0.002	91.39 ± 0.91	100	47 ± 3.63	0.386 ± 0.055
4.	F4	0.150 ± 0.008	318 ± 0.001	90.00 ± 0.28	100	51 ± 3.91	0.394 ± 0.046
5.	F5	0.135 ± 0.006	286 ± 0.008	96.61 ± 0.39	100	54 ± 4.18	0.404 ± 0.057
6.	F6	0.120 ± 0.007	322 ± 0.006	97.83 ± 1.42	100	60 ± 5.12	0.438 ± 0.036

6.7. Tensile strength

The values varied between 0.309 ± 0.035 to 0.438 ± 0.036 kg/mm^2. Thus, this is the required mechanical strength to protect the formulation [Table 4].

6.8. Moisture content and moisture uptake

The results are depicted in Table 5.

Table 5: Moisture content and Moisture uptake ofDexketoprofen trometamol patches

S. No.	Formulation Code	Moisture Content (%) ± S.D	Moisture Uptake (%) ± S.D
1.	F1	1.24 ± 0.570	1.99 ± 0.025
2.	F2	2.77 ± 0.160	4.97 ± 0.004
3.	F3	2.14 ± 0.190	3.45 ± 0.002
4.	F4	5.77 ± 0.009	6.93 ± 0.083
5.	F5	4.36 ± 0.009	5.67 ± 0.009
6.	F6	7.55 ± 0.007	9.88 ± 0.009

The percentage moisture content and percentage moisture uptake is found to be high for the patches formulated with HPMC:EC when compared to the patches formulated with HPMC:ERS100 and EC:ERS100. The reason behind this might be the higher proportions of hydrophilic polymer, HPMC along with EC; whereas patches with HPMC:ERS100 combination shows lesser moisture content and moisture uptake because of the highly hydrophobic polymer, ERS100.

6.9. In-vitro Permeation study

The cumulative percentage of the drug released in 24 h was found between 12.02% (F1) to 85.77% (F2) for transdermal films. The percentage of drug release order was as follows:

F6>F5>F4>F3>F2>F1

The formulation F6 showed a better in vitro drug release profile across the cellulose membrane, when compared to the other formulations. This might be attributed to the nature of polymer; plasticizers and even the permeation enhancer used. Thus formulation F6 is considered as optimized formulation. The results are depicted in Table 6.

6.10. Kinetic analysis of diffusion data

The in vitro permeation data of all formulations was analyzed by fitting the release data in to various kinetic models to elucidate permeation profile (Table 7 and Figures 4, 5, 6 and 7)

It was observed that the in vitro permeation profiles of all the different formulations of transdermal patches did not fit to Higuchi's equation. But for the all formulations the r^2 values were higher when fitted to zero order kinetics which states that the drug release rate from the formulation is independent of the concentration of the drug. The n values from drug release for all formulation ranged from 0.867 to 1.504.

6.11. Ex-vivo Permeation study

The above-obtained results of the drug (Dexketoprofen Trometamol) through the rat abdominal skin confirmed that the formulation is well suitable for human skin.

6.12. Skin irritation test

The skin irritation score (erythema and edema) was found to be less than 2. According to Draize et al. compound which producing score of less than 2 are considered negative. Hence, the prepared transdermal patches of Dexketoprofen Trometamol were free of skin irritation.

6.13. Stability study (As per ICH guidelines)

After three months stability study of optimized formulation F6 was determined, values of all physico-chemical parameters were almost similar to the initial values. The % drug release and diffusion profile was just same of the initial one. There were not any significant changes in any values so the formulation was stable and able to provide an effective therapy for prolonged period of time.

7. Conclusion

Transdermal patches of Dexketoprofen Trometamol have been successfully by solvent evaporation technique. Evaluation of the prepared patches in terms of physical appearance, weight, thickness, flatness, tensile strength

Table 6: In vitro release of dexketoprofen trometamol from transdermal patches

Time (h)	Cumulative % drug release ± SD					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	0.08 ± 1.13	1.59 ± 1.66	0.29 ± 1.43	2.11 ± 1.96	0.29 ± 1.43	4.65 ± 1.15
2	0.40 ± 1.52	2.01 ± 1.95	0.81 ± 1.42	4.47 ± 1.06	0.44 ± 1.42	6.20 ± 1.86
3	1.04 ± 1.13	2.60 ± 1.69	1.62 ± 1.25	6.26 ± 1.78	3.46 ± 1.83	10.29 ± 0.95
4	1.68 ± 1.76	3.28 ± 1.80	2.07 ± 1.54	7.24 ± 1.64	5.01 ± 1.54	12.17 ± 1.85
5	2.08 ± 1.53	4.12 ± 1.87	3.03 ± 1.55	9.03 ± 1.06	6.04 ± 1.80	14.45 ± 1.19
6	2.80 ± 1.61	4.62 ± 1.74	4.00 ± 1.83	11.72 ± 1.34	7.67 ± 1.75	16.01 ± 1.65
7	3.44 ± 1.62	5.38 ± 1.95	5.55 ± 1.01	13.02 ± 1.16	8.92 ± 1.55	18.29 ± 1.25
8	4.08 ± 1.38	6.47 ± 2.15	6.88 ± 1.80	14.57 ± 1.13	10.4 ± 1.25	24.50 ± 1.93
10	4.57 ± 1.15	7.15 ± 2.18	8.15 ± 1.89	15.71 ± 1.93	11.87 ± 1.01	28.26 ± 1.78
12	5.21 ± 1.52	8.49 ± 2.71	9.48 ± 1.75	16.93 ± 1.72	13.79 ± 1.89	30.87 ± 1.15
24	12.02 ± 1.56	23.72 ± 2.44	26.22 ± 1.43	47.86 ± 1.32	52.66 ± 1.43	85.77 ± 1.63

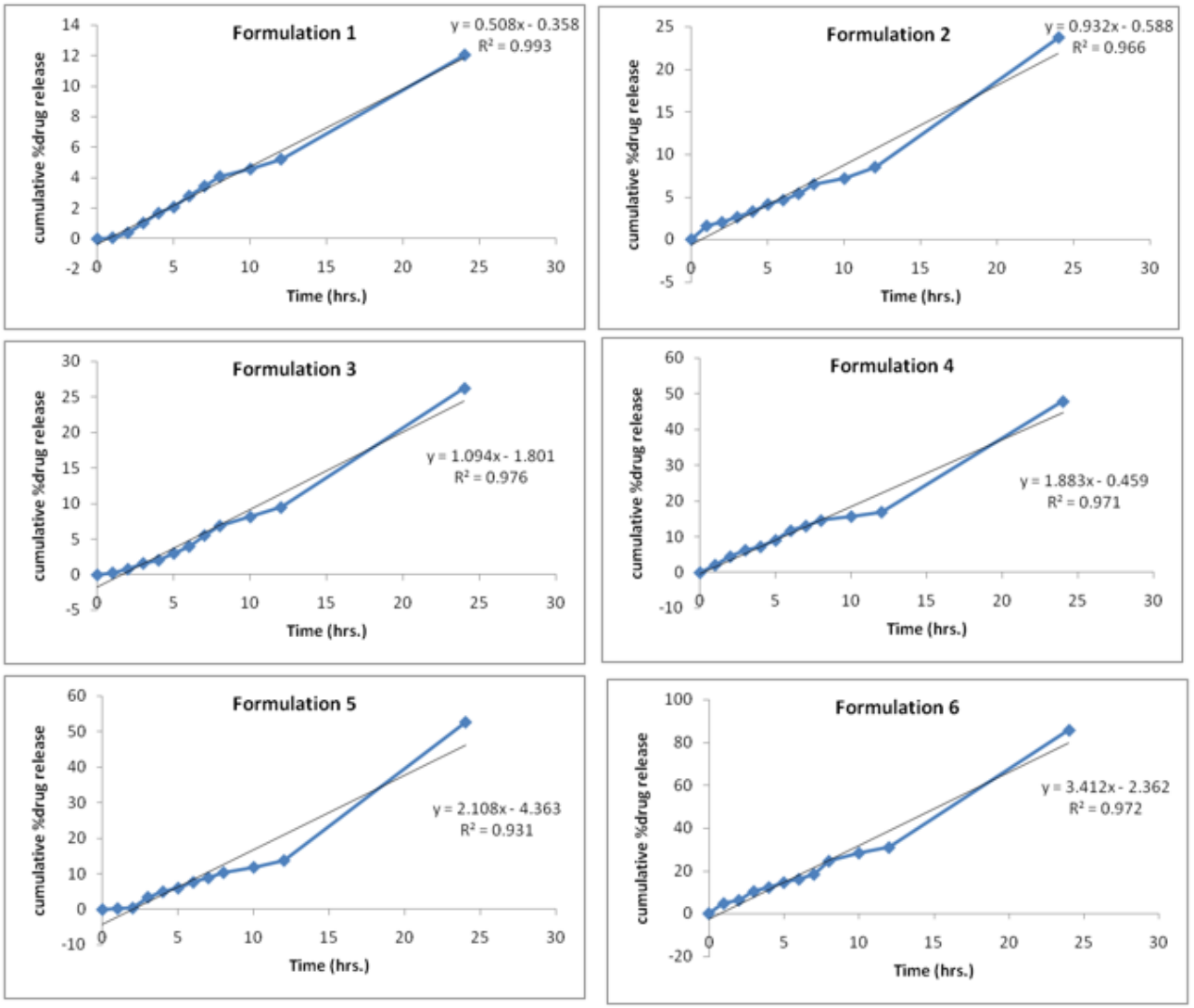

Fig. 4: Zero order release kinetics (Zero order release kinetics of Formulations)

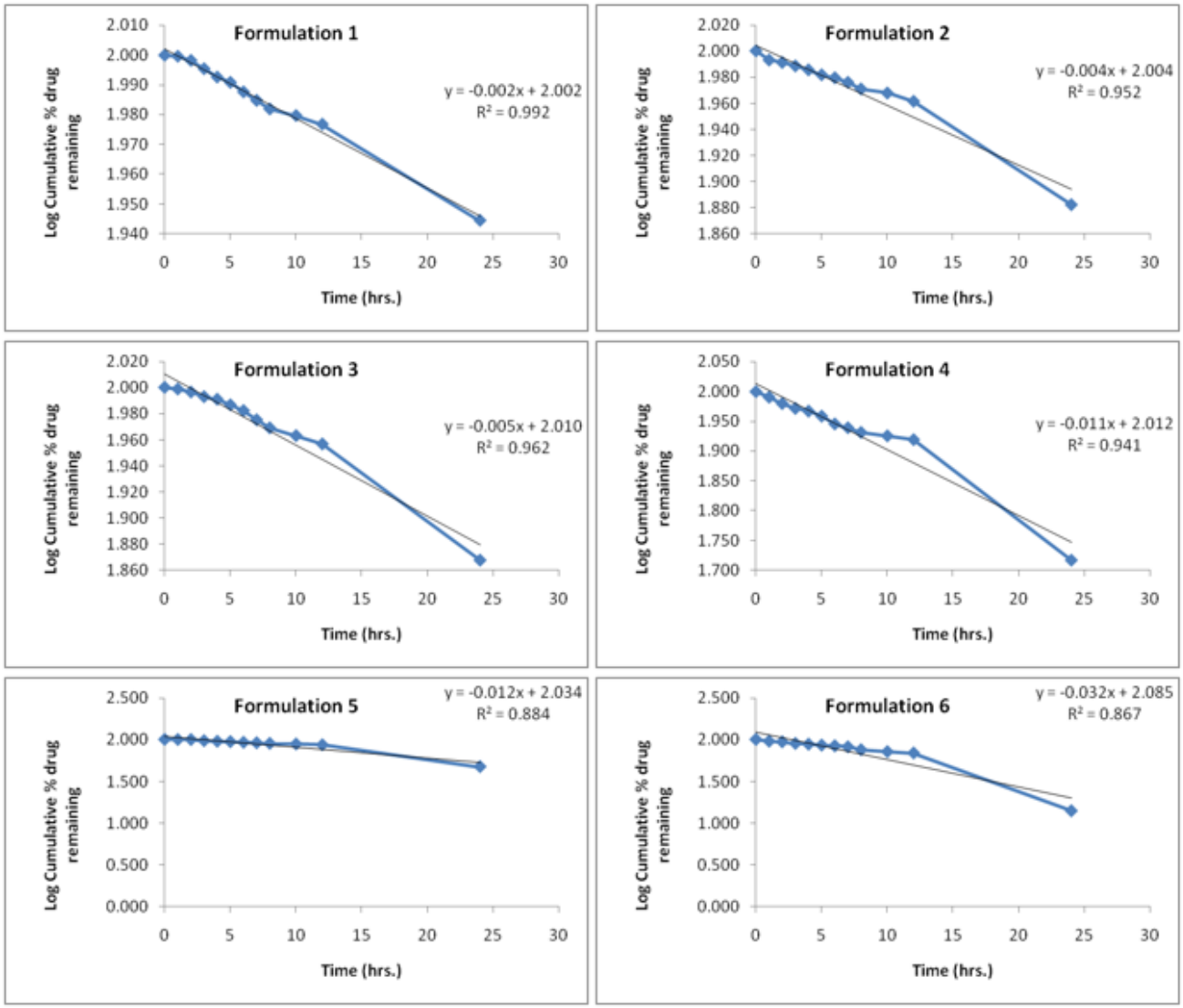

Fig. 5: First order release kinetics (First order release kinetics of Formulations)

Table 7: Kinetic model for in vitro drug permeation studies

S. No.	Formulation Code	Zero order Regression value (R^2)	First order Regression value (R^2)	Higuchi model Regression value (R^2)	Korsmeyer Peppas model Regression value (R^2)	Korsmeyer Peppas model (Slope)
1	F1	0.993	0.992	0.861	0.820	1.262
2	F2	0.966	0.952	0.788	0.960	0.867
3	F3	0.976	0.962	0.784	0.939	1.263
4	F4	0.971	0.941	0.820	0.960	1.046
5	F5	0.931	0.884	0.712	0.907	1.504
6	F6	0.972	0.867	0.798	0.902	1.110

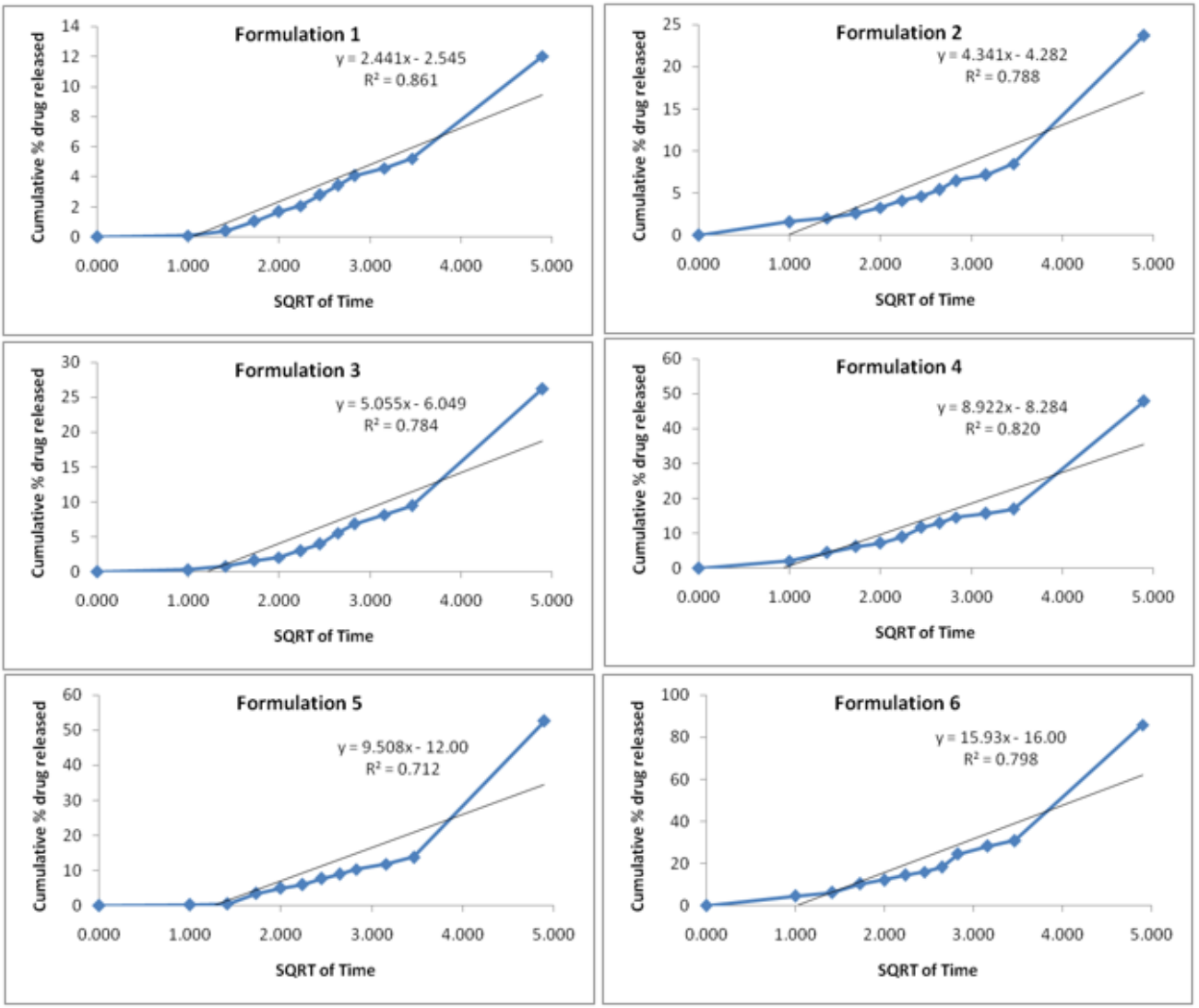

Fig. 6: Higuchi model release kinetics (Higuchi model release kinetics of Formulations)

Table 8: Permeation study of Dexketoprofen Trometamol from optimized transdermal patch F6 formulation

Time (h)	**Cumulative amount of drug permeated (μg/cm^2) {Formulation F6}**
0	0
1	6.41 ± 2.13
2	32.34 ± 3.72
3	87.85 ± 12.43
4	110.32 ± 23.61
5	143.87 ± 22.35
6	180.30 ± 17.86
7	257.31 ± 36.20
8	314.89 ± 30.39
10	484.24 ± 58.34
12	666.23 ± 52.39
24	806.86 ± 60.25

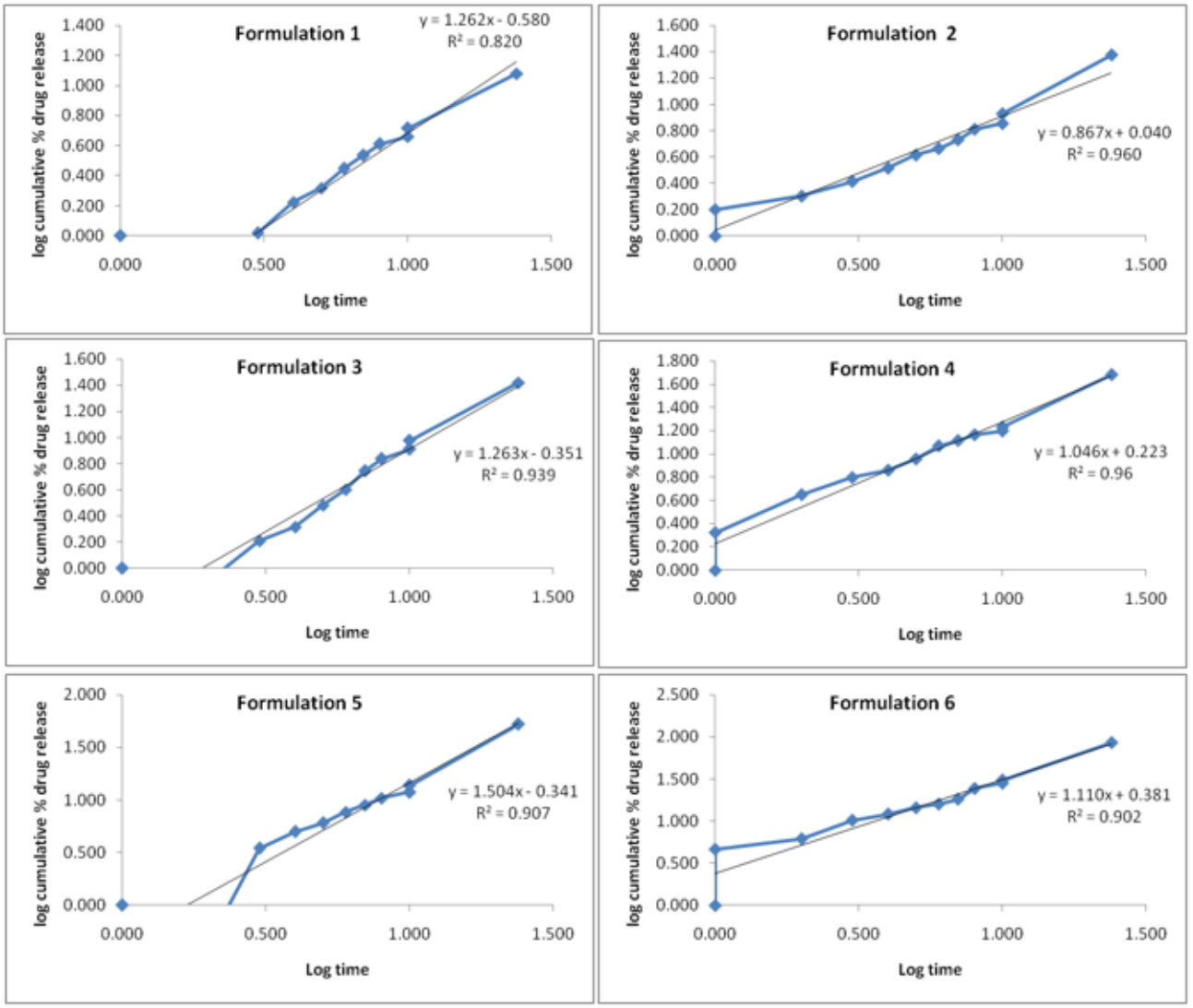

Fig. 7: K*o*rsmeyer Peppas model release kinetics (K*o*rsmeyer Peppas model release kinetics of Formulations)

Table 9: Drug flux, lag time & enhancement fact*o*r

Formulation Code	Drug Flux	Lag time (T_{lag})	Enhancement Fact*o*r
F6	36.70 ± 2.63 μg /hr/ cm^2	0.95 ± 0.36 hours	3.64

moisture absorption, moisture uptake and drug content uniformity recommend that the method employed for formulation of the transdermal patches was reproducible and assured outstanding quality and uniformity in patch characteristics with least variability. Further, in vitro and ex vivo drug release studies for all the formulations exhibited the drug release and nearly complete release (85%) was achieved in 24 h. These results show that transdermal delivery of Dexketoprofen Trometamol can have probable applications in therapeutic areas providing advantages by reducing dosing frequency, improving patient compliance, non-invasive character, improved bioavailability, and easy termination of therapy.

8. Source of Funding

None.

9. Conflicts of Interest

There are no conflicts of interest.

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