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FORMULATION AND EVALUATION OF TRANSDERMAL PATCH OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (CELECOXIB)

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ABSTRACT

The present study aimed to develop and evaluate Celecoxib-loaded transdermal drug delivery systems (TDDS) to overcome the limitations associated with oral administration of NSAIDs. Matrix-type transdermal patches were prepared using the solvent evaporation method with different polymeric combinations of HPMC E15, ethyl cellulose, and PVP K30. Preformulation studies revealed a melting point of 202–203°C, λmax at 234 nm, and excellent linearity (r^2 = 0.995). The calculated permeability coefficient and flux were found to be 4.4004 and 0.101 mg/cm²/hr, respectively, with a dose of 12.12 mg/10 cm²/12 hr. All formulations exhibited satisfactory physicochemical properties, including thickness (0.061–0.077 mm), drug content (89.16–95.04%), and folding endurance (99–125). In vitro diffusion studies showed a maximum drug release of 91.04% for formulation F1 over 12 hours, following the order F1 > F5 > F6 > F2 > F3 > F4. Release kinetics indicated non-Fickian diffusion with the optimized formulation best fitting the Higuchi model (r^2 = 0.9875). The study concludes that Celecoxib can be effectively formulated into transdermal patches to provide sustained

drug release, improve bioavailability, and minimize systemic side effects.

KEYWORDS: Transdermal drug delivery system, Celecoxib, NSAIDs, Matrix patch, In vitro diffusion, Release kinetics.

1. INTRODUCTION

Transdermal drug delivery systems (TDDS)

The transdermal drug delivery system (TDDS) is a novel approach for delivering therapeutic agents through the skin into the systemic circulation, offering several advantages over conventional dosage forms such as oral or injectable routes. It enables sustained and controlled release of drugs, avoids first-pass hepatic metabolism, reduces gastrointestinal irritation, and enhances patient compliance due to its non-invasive nature.[1] The human skin, being a natural barrier, limits the penetration of foreign substances; therefore, the design of transdermal systems requires understanding of skin anatomy and permeability characteristics. The outermost layer, the stratum corneum, composed of keratinized cells embedded in lipid matrix, serves as the primary barrier to drug diffusion.[2] Drugs must possess optimal physicochemical properties such as low molecular weight (<500 Da), adequate lipophilicity, and high potency to effectively traverse the skin and reach systemic circulation.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used therapeutic agents for the management of pain, inflammation, and fever. They act primarily by inhibiting the cyclooxygenase (COX) enzymes COX-1 and COX-2 thereby blocking the synthesis of prostaglandins responsible for inflammation, pain, and edema.[12] Commonly used NSAIDs include diclofenac, ibuprofen, ketoprofen, naproxen, indomethacin, and piroxicam. Although highly effective, traditional oral administration of NSAIDs often leads to gastrointestinal irritation, ulceration, and systemic side effects due to first-pass metabolism and fluctuating plasma drug levels.[13] These limitations have motivated the exploration of transdermal drug delivery systems (TDDS) as a safer and more effective alternative route of administration.

2. MATERIALS AND METHODS

- ***Chemicals***

Celecoxib was received as a generous gift sample from Dhamtec Pharma and Consultants,Navi Mumbai-410209, India. N-octanol, disodium hydrogen phosphate, sodium hydroxide, propylene glycol 400, sodium lauryl sulfate, dichloromethane, and

potassium dihydrogen phosphate were procured from Loba Chem Ltd., Mumbai, India. Colorcon Asia Pvt. Ltd., Mumbai, India was the chief supplier for HPMC E15, ethyl cellulose, and PVP K30. Methanol was purchased from HiMedia Laboratories India, Mumbai, India. All other chemicals and reagents used in the study were of analytical grade.

- ***Instrumentations***

Weighing balance (Shimadzu® AUW220D, Japan), Digital melting point apparatus (Jyoti® Instruments D113, India), UV-spectrophotometer (Shimadzu® UV-1800, Japan), Fourier transform infrared spectroscopy (Shimadzu® IRAffinity-1, Japan), Differential scanning calorimeter (Metter Tolado® DSC 60, UK), Powder X-ray diffractometer (Bruker-axs® D8-Advance, USA), USP type-II dissolution test apparatus (DBK® Instruments, India) were employed for this study.

- **Preformulation of drug**

1. Melting point

Using the digital melting point apparatus (Figure 1), which includes inserting a small quantity of Celecoxib in the device and comparing the results to standards, the melting point of Celecoxib was assessed.

Figure 1: Thiele's tube setup for melting point determination.

2. Quantitative solubility determination

Celecoxib solubility in methanol, ethanol, dimethyl fluoride, methyl chloride, and 0.1 N HCl was examined qualitative. To perform solubility experiments, excess Celecoxib was added to several beakers of the solvent. For 24 hrs, the mixture was stirred with a stirrer in continuous manner. The level of solubility was determined qualitatively.

3. Determination of λmax

0.1 g of the drug was dissolved in 100 ml of phosphate buffer (pH 7.4) [2.38 g disodium hydrogen phosphate, 0.19 g of potassium dihydrogen phosphate, 8 g of sodium chloride were mixed and stir until dissolved. Bring the volume to 1000 mL with distilled water and adjust the pH to 7.4] to prepare 100 mg/ml of solution. From this solution, 0.1 ml was withdrawn and the volume was made up to 10 ml with phosphate buffer (pH 7.4) for preparing the stock solution. The solution containing a concentration of 10µg/ml Celecoxib was scanned over the wavelength of 200 to 400 nm in UV-Vis spectrophotometer (Figure 2) to determine the wavelength of maximum absorbance.

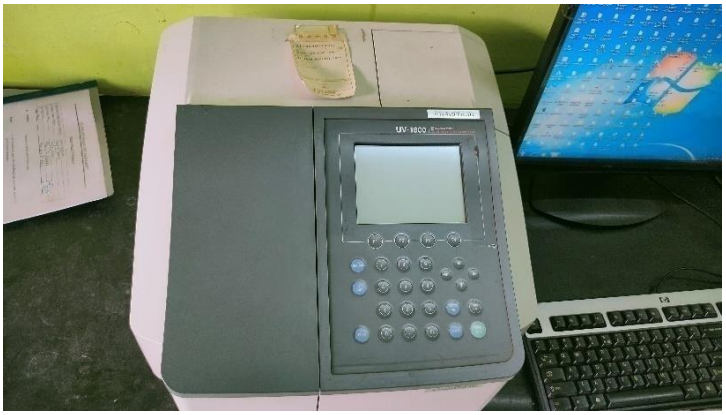

Figure 2: UV-Vis Spectrophotometer.

4. Compatibility study

The compatibility study of the drug and polymers is an essential requirement before formulating as if the drug will react with the polymers or excipients, will lead to a reduced shelf life of the product or may cause unwanted effects on the formulation. The incompatibility between the physical mixture of drug and polymers was determined by Fourier-transformed Infrared Spectroscopy (FT-IR) spectra. The FT-IR study was performed using KBr equipped Shimadzu® Affinity-1 FT-IR instrument (Figure 3). The overlapping peaks were identified for the drug, excipients, polymers, and physical mixture. Any new product or major change in the spectra was reported. The peaks were expressed as cm-1 in the range of 4000-400 cm-1.

Figure 4: FT-IR spectroscopy.

➢ ***Steps towards formulation development***

1. Calculation of flux and drug loading

The Potts and Guy showed to formulate an empirical relationship between Kp and two simple characteristics of the permeant; the octanol-water partition coefficient (Koct) and the molecular weight (MW).

$$log\ Kp(cm/hr) = -2.72 + 0.71\ log\ Koct - 0.0061\ MW \quad (1)$$

It must be realized that it is not the permeability coefficient alone that determines the efficiency of topical and transdermal delivery. It is the flux across the skin, which is the product of permeability coefficient and the drug concentration in the vehicle. The maximum achievable flux is, therefore, Kp multiplied by the aqueous solubility (Sw).

$$Flux = log\ Kp \times Sw \quad (2)$$

2. Calculation of dose

From equation **(1)**, the permeability coefficient was computed to be 4.4004, the determined flux was determined to be 0.101 mg/cm^2/hr, and finally, the dose was fixed to be 12.12 mg/10 cm^2/12 hr.

The selection of dose for oral dosage form was based on following:

- ***STEP 1:-*** *Calculation of permeability coefficient*

Log Kp (cm/h) = - 2.72 + 0.71 log koct - 0.0061MW

Log Kp (cm/h) = - 2.72 + (0.71 × log 3.12) – (0.0061 × 331.35)

Log Kp (cm/h) = 4.4004

- ***STEP 2:-*** *Calculation of Flux*

Flux = log Kp × SW Flux = 4.4004 × 0.023

Flux = **0.101 mg / cm^2 /hr**

- ***STEP 3:-*** *Calculation of dose for 10 cm^2 /12 hr*

Dose = flux × 10 × 12 Dose = 0.101 × 10 × 12

Dose = **12.12 mg / 10 cm^2 / 12 hr**

The patches were prepared on film former. The formula was calculated for the total area of patch spread on the film former:

Area of film spread = 270 cm^2 Dose calculated = 12.12 mg/10cm^2

Drug load = 270/10 = 27 x 12.12 = **327.24 mg / 270 cm^2**

All the other ingredients like SLS and PEG were calculated accordingly.

➢ **Preparation of Matrix Patch**

Celecoxib-loaded matrix transdermal patches were prepared using the solvent evaporation method with varying polymer ratios of HPMC E15, ethyl cellulose, and PVP K30 (3:1, 3:2, 2:1). Initially, HPMC was allowed to swell in a dichloromethane:methanol (2:1) solvent system for 1 hour. Ethyl cellulose was then added with continuous stirring, followed by incorporation of PEG 400 as a plasticizer and sodium lauryl sulfate as a permeation enhancer. Celecoxib was subsequently mixed into the uniform polymeric solution. The resulting homogeneous mixture was cast onto a film-forming surface and allowed to dry under controlled conditions. The dried films were cut into 10 cm² patches, wrapped in aluminum foil, and stored in a desiccator for further evaluation.

Table 1: Formulation Chart for Celecoxib Transdermal Films.

Ingredients	**F1 (3:1)**	**F2 (2:1)**	**F3 (3:2)**	**F4 (3:1)**	**F5 (2:1)**	**F6 (3:2)**
Celecoxib (in mg)	327	327	327	327	327	327
HPMC (in mg)	3750	3750	3750	3750	3750	3750
EC (in mg)	1250	1875	2500	-	-	-
PVP (in mg)	-	-	-	1250	1875	2500
DCM + Methanol (1:2) (in ml)	50	50	50	50	50	50
PEG 400 (in mg)	1000	1125	1250	1000	1125	1250
SLS (in mg)	100	112.5	125	100	112.5	125

➢ ***Evaluation of transdermal patch***

1. Physical appearance

All the prepared patches were visually inspected for color, clarity, flexibility, and smoothness.

2. Thickness uniformity

The thickness of the drug loaded patches was measured by using a screw gage micrometer at three different points on the patches. Average values and standard deviation values of the three readings were calculated for each drug loaded patch.

3. Weight uniformity

A specified area of the patches was cut carefully in different parts and afterward weighed in a digital balance. The average weight and standard deviation values were calculated from the individual weight.

4. Tensile strength

The tensile strength of the patch was evaluated by using the tensiometer. It consists of two load cell grips. The lower one was fixed and upper one was movable. Film strips with dimensions of 2x2 cm were fixed between these cell grips, and force was gradually applied till the film broke. The tensile strength was taken directly from the dial reading in kg.

5. Folding endurance

A patch on the specific area was cut evenly and repeatedly folded at the same place until it was broken. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

6. Percentage moisture content

The prepared transdermal films were weighed individually and kept in desiccators containing fused calcium chloride at room temperature for the duration of 24 hrs. After 24 hrs, the films were re-weighed and the percentage moisture content was determined by the given formula.

Percentage moisture content =Initial weight − Final weight/ Final weight × 100

7. Percentage moisture uptake

The individually weighed Transdermal films were kept in desiccators containing a saturated

solution of potassium chloride at room temperature for 24 hrs. After 24 hrs, the formed Piroxicam films were re-weighed and the percentage moisture uptake was measured from the below-mentioned formula:

Percentage moisture content = Final weight − Initial weight/ Initial weight × 100

8. Water vapor transmission rate

Water vapor transmission rate (WVTR) is defined as the quantity of moisture transmitted through unit area of film in unit time. Glass vials of equal volume and diameter were used as transmission cells. The cells were washed properly and dried in oven. Then, about 1 g of anhydrous fused calcium chloride was placed in each vial, and the patch was fixed over the brim of the vial with the help of an adhesive tape. These vials were then weighed and placed in desiccators containing saturated solution of potassium chloride to maintain 84% relative humidity. These cells were removed from the desiccators and weighed after 1st, 2nd, 3rd, 4th, 5th, 6th, and 7th day. The water vapor transmission rate was determined as follows:

$$W.\ V.\ T = WL/S$$

Where W is the weight of water vapors transmitted, L is the thickness of patch and S is the surface area exposed in square centimeter.

9. Drug content determination

For determining the drug content, an area of 10 cm2 of the patch was cut and dissolved in 10 ml of phosphate buffer (pH 7.4). After that 0.1 ml volume was withdrawn from the solution and diluted with the phosphate buffer to 10 ml in a volumetric flask. The absorbances of the solutions were taken at 335 nm by using UV spectrophotometer (Shimadzu® UV-1800), keeping the pure drug (0.1 g) as the standard solution.

- ***In-vitro* drug diffusion study**

1. Preparation of goat skin

The skin of the goat was utilized for in vitro diffusion studies of the transdermal patch. For the preparation, goat skin was selected. The hair was shaved carefully with a safety razor and further cleaned with wet cotton to remove the stitched hairs. The procured skin was then cleaned thoroughly with distilled water and stored in Ringer solution with proper aeration.

2. *In-Vitro* Diffusion Cell Study

The in vitro drug diffusion study was conducted using Franz diffusion cells to evaluate drug permeability across the transdermal patch. Goat abdominal skin was mounted between the

donor and receptor compartments and secured with clamps. Phosphate buffer (pH 7.4) was used as the receptor medium, maintaining a constant volume of 6 ml. The system was stirred at 100 rpm using a magnetic stirrer and temperature was maintained at 37±1°C. The study was carried out for 12 hours, with 1 ml samples withdrawn at hourly intervals and analyzed spectrophotometrically at 335 nm. An equal volume of fresh buffer was replaced each time to maintain sink conditions.

3. Release kinetics

For determining the drug release mechanism(s) from the transdermal patch, the data acquired from the in vitro drug release studies were plotted in various kinetic models of Zero-order, First order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models were used. Based on the goodness-or fit test, the most appropriate model was chosen. The correlation coefficient (r2) and release exponent

(n) were expressed for each model in correlation to the drug kinetics.

3. RESULTS

- **Preformulation**

The preformulation parameters such as melting point was correctly estimated, solubility profile was determined, λmax was confirmed, and was studied.

1. Melting point

With a digital melting point instrument, the melting point was found showed characteristic melting over the range 202°C-203°C (Table 2).

Table 2: Melting point determination.

S. No.	Reading	Average ± SEM
1.	202°C-204°C	202°C-203°C ± 1.66
2.	203°C-204°C	
3.	202°C-203°C	

2. Quantitative solubility determination

Celecoxib was practically insoluble in distilled water whereas soluble nature was ethanol, methanol, acetone, and ethyl acetate, in qualitative determination. High soluble characteristics of Celecoxib were observed in chloroform and petroleum ether (**Table 3**).

3. λ max determination

The λ max was detected at 234 nm (Figure 5), which indicated UV absorption characteristic feature of quercetin.

Table 3: λmax determination.

S. No.	Reading	Average ± SEM
1.	234 nm	234 nm ± 1.33
2.	235 nm	
3.	234 nm	

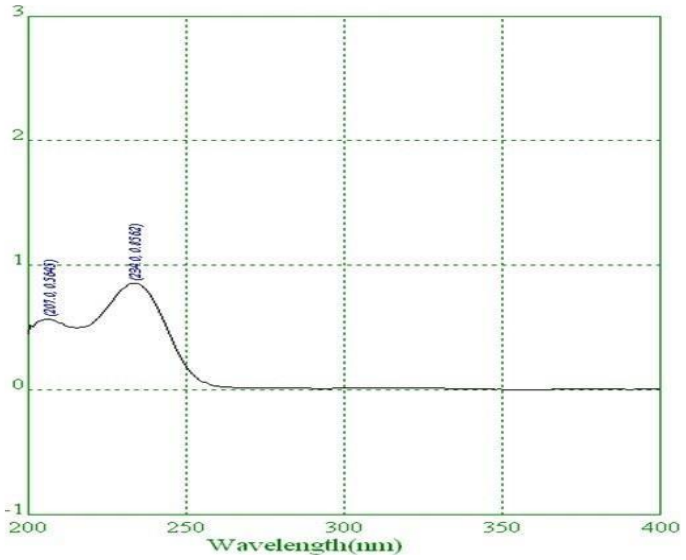

Figure 5: λmax of Celecoxib.

4. Calibration curve

The calibration curve of the drug displayed a high linearity with r^2 value of 0.995 where a linear relationship was observed within the concentration range.

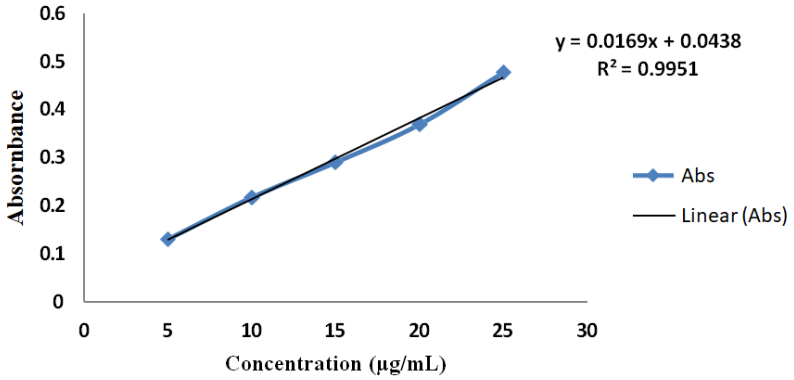

Figure 6: Calibration curve of Celecoxib.

5. Permeability study

The permeability of Celecoxib after 12 hrs duration was determined to be 26.65%.

6. Compatibility study

There was no incompatibility observed between the drug, excipients, and polymers as indicated from the FT-IR studies. The FT-IR spectra demonstrated the presence of characteristic peaks of drugs and polymers. The chief peaks of the drug were 3450 cm-1, 3066 cm-1, 2931 cm-1, 2521 cm-1, 1745 cm-1, 1629 cm-1 and for polymers 3473 cm-1, 2974 cm-1, 2922 cm-1, 2611 cm-1, 2430 cm-1, 1639 cm-1, 1629 cm-1, 1529 cm-1, 1460 cm-1, 1425 cm-1 (Figure 7), respectively. The physical mixture exhibited distinctive drug peaks in the spectra along with the polymer peaks, confirming that the drug remains in inert form with the excipients.

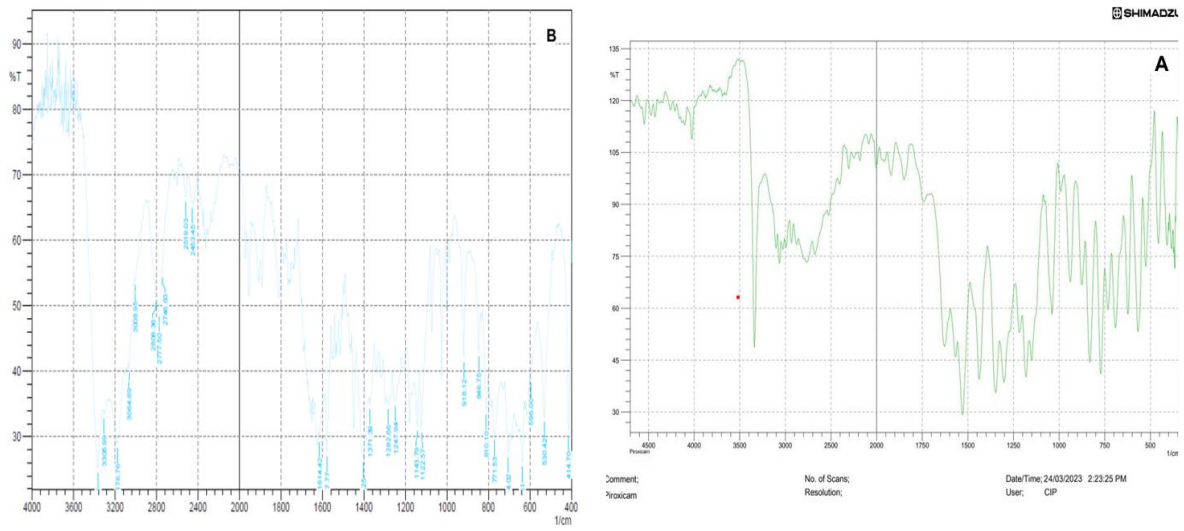

Figure 7: FT-IR spectra: (A) Celecoxib; (B) Celecoxib + Polymer (HPMC E15 + Ethyl cellulose + PVP K30).

➢ Evaluation of transdermal patches

The Celecoxib transdermal patches were fabricated by the solvent evaporation technique with an aim to improve the bioavailability of Celecoxib. All the fabricated films were evaluated for their physical parameters (weight, thickness, folding endurance, diameter, and in vitro diffusion).

1. Physical appearance

The fabricated film was found to be uniform, flexible, smooth, and transparent.

2. Weight uniformity

The weight of the formed transdermal patches of different formulations was in the range of 143.9±2.12 mg and 218.2±2.23 mg. The films exhibited excellent weight uniformity among the various fabricated batches. The uniformity of weight indicates that the polymer solution of the drug is well dispersed on a flat surface. However, a little variation in weight among the formulation F1 to F6 was observed in the range of 41 mg to 82 mg which may attribute to the variation in polymeric content. An increase in the weight of the fabricated formulation (F1 to F3) was seen with an increase in the EC concentration. This may be due to the fact that EC is having a low water permeability nature that prevents water evaporation and hence retains the mass considerably. The batch F5 (2:1 ratio) demonstrated the highest weight variability of 85 mg while the batch F1 exhibited the lowest weight variability of 41 mg.

3. Thickness uniformity

The thickness of the patches of different formulations ranged from 0.061±0.0019 mm to 0.077±0.0013 mm. The thickness of the transdermal patches was found to be proportional to the concentration of the polymers. The value of low standard deviation represented that the preparation of transdermal formulation is quite reproducible with similar weight and thickness (Table 4). The batch F5 (2:1 ratio) demonstrated the best thickness uniformity as compared to other 5 batches.

Table 4: Evaluation Characteristics of Celecoxib Transdermal Films.

Formulations	Weight Uniformity (in mg)	% Drug Content	% Moisture Content	% Moisture Uptake	Folding Endurance
F1	41	95.04	2.41	1.32	112
F2	53.3	94.48	3.16	1.51	125
F3	43.3	91.84	2.21	1.54	99
F4	68	89.16	1.73	2.15	101
F5	82	94.27	1.89	2.19	105
F6	63	94.38	1.23	2.64	103

4. Drug content

All formulations exhibited slight variation in drug content ranging from 89.16% to 95.04%. Formulation F1 shows highest drug content of 95.04% while the batch F4 presented the lowest drug content of 89.16%. All formulations found to be satisfactory with reference to the drug content.

5. % Moisture content and % moisture uptake

The % moisture content was found to be in the range of 1.23 -3.16% in the formulation F1 to F6 (Figure 5.4). With the increase in the polymer concentration (HPMC, EC, and PVP), the content of moisture was observed to escalate. Small moisture content in the formulation helps them to remain stable and prevent from being a completely dried and brittle. It has been observed that the optimized ratio of 2:1 for HPMC: EC/PVP lead to an increased retention of moisture to the formulation. The high ratios of hydrophilic concentration in F2 resulted in increased % moisture preservation. The moisture uptake rate was found to be in the range of 1.32-2.64%. A low moisture uptake protects the material from microbial contamination and bulkiness of the patch. The formulations F1 and F4 displayed the lowest moisture absorption attributes as a result of decrease in water permeability of the polymer ethyl cellulose. The absorption of moisture is an imperative aspect which influences the drug diffusion as it extends into the water uptake of the patch from the body tissues as well as from the environment during the application period. It is a vital parameter which helps to maintain mechanical integrity.

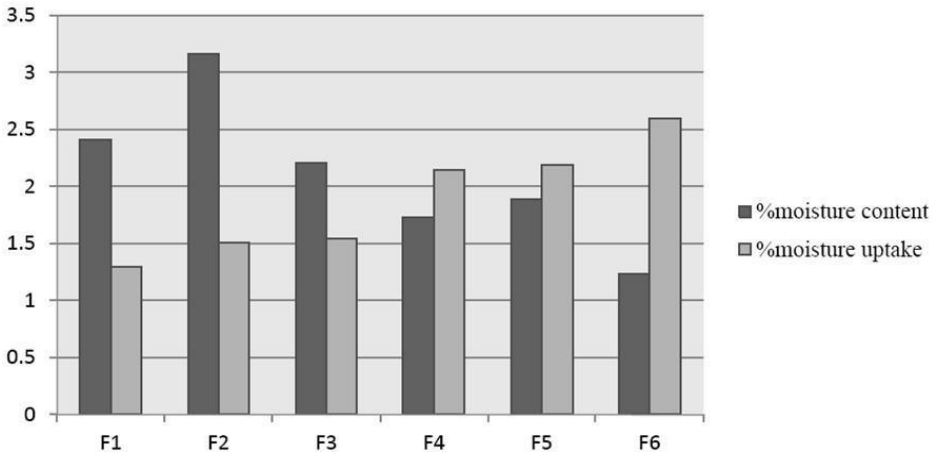

Figure 8: % moisture content and % moisture uptake by the fabricated transdermal formulations.

6. Folding Endurance

Folding endurance was evaluated manually to assess the flexibility and mechanical strength of the prepared patches. It was determined by repeatedly folding the film at the same point until it broke, and the number of folds required to cause breakage was recorded as the folding endurance value. All formulations showed satisfactory folding endurance in the range of 99 to 125, indicating good flexibility. Among the batches, F2 and F1 exhibited higher folding endurance values of 125 and 112, respectively, suggesting better mechanical performance

compared to F3 and F4, which showed values of 99 and 101. Formulations F5 and F6 demonstrated moderate folding endurance of 105 and 103. The results indicate that increasing the concentration of hydrophilic polymers enhances elasticity, thereby improving the folding endurance of the patches.

7. *In vitro* Diffusion Study

In vitro diffusion studies were performed on patches (F1-F6) containing the permeation enhancer SLS to evaluate drug release behavior. Among all formulations, F1 exhibited the highest drug diffusion (91.04%) after 12 hours, while F4 showed the lowest release (84.66%). Overall, the variations in drug permeation among the formulations were not significant. However, formulations F1, F2, F5, and F6 demonstrated comparatively higher cumulative drug release than F3 and F4. The order of drug diffusion rate was observed as: F1 > F5 > F6 > F2 > F3 > F4. The results indicate that both the type and concentration of polymer influence drug release, with higher polymer concentration leading to a reduction in diffusion rate.

Table 5:* In-vitro *drug diffusion from various formulations of transdermal patches.

Time (hrs)	% Cumulative drug release					
	F1	F2	F3	F4	F5	F6
1	26.21	22.98	17.72	30.99	30.36	34.04
2	36.10	35.66	34.76	35.65	33.20	35.06
3	41.87	36.06	37.93	36.35	35.89	36.02
4	43.33	36.35	41.37	37.31	36.14	38.69
5	45.05	41.66	42.89	43.06	49.41	46.05
6	49.95	51.29	53.32	49.39	51.92	50.81
7	56.17	56.40	57.92	56.06	58.53	59.69
8	64.64	62.95	64.82	62.20	63.29	64.58
9	74.63	72.69	69.96	65.15	71.21	71.33
10	81.33	80.46	75.56	75.38	88.51	86.44
11	86.23	82.44	81.41	81.23	89.17	87.46
12	91.04	89.34	86.64	84.66	90.99	90.46

One of the most likely reasons that can be considered for the highest diffusion of the drug from formulation F1 was the concentration of hydrophilic polymer and hydrophobic polymer. Higher concentration of these two polymers (HPMC and EC); it forms a strong viscous gel on contact with the aqueous media that hinders the diffusion of the drug from the formulation (Dangre *et al.*, 2016). Therefore, it has been detected that the formulations F3 and F2 demonstrated less *in vitro* drug diffusion as compared to formulation F1 at 12 hrs. In contrast, the formulations F4 to F6, containing polymer PVP,

the drug diffusion was observed to be non-consistent in nature where the diffusion did not follow any linearity and a phenomenon of polymer concentration-dependent release was not seen during the 12 hrs of study. The formulation F5 and F6 presented a good *in vitro* drug release from the patch due to burst effect of PVP and also more solubility in aqueous media.

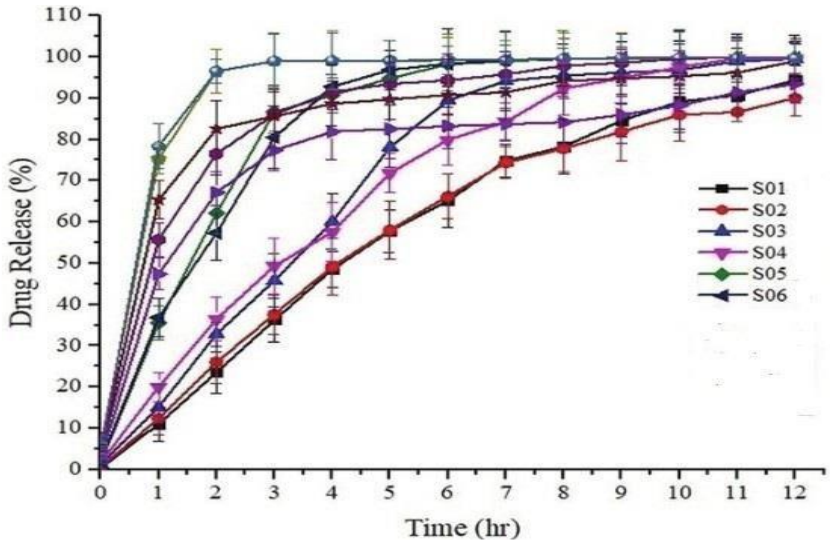

Figure 9: *In-vitro* drug diffusion.

9. Release Kinetics

The mechanism of drug release from swellable matrix systems involves several physicochemical processes, including water uptake by the polymer, gel layer formation, and relaxation of polymer chains. Different kinetic models were applied to evaluate the release behavior of the formulations. The correlation coefficient (r^2) and release exponent (n) values indicated that all formulations followed non-Fickian (anomalous) diffusion, suggesting that drug release is governed by a combination of diffusion and polymer relaxation mechanisms.

The optimized formulation, which showed the highest drug release, was best fitted to the Higuchi model, with a release exponent (n) value of 0.5168. This indicates a controlled and consistent drug release pattern over time from a matrix system of constant geometry until equilibrium of the polymer structure is achieved. Overall, the drug release mechanism was controlled by both diffusion and erosion processes, confirming the involvement of swelling and matrix degradation in drug transport.

Table 6: Release kinetics data of optimized formulation 1.

Value	Zero Order	First Order	Higuchi's model	Korsmeyer-Peppas model
r^2	0.9086	0.9595	0.9875	0.9504

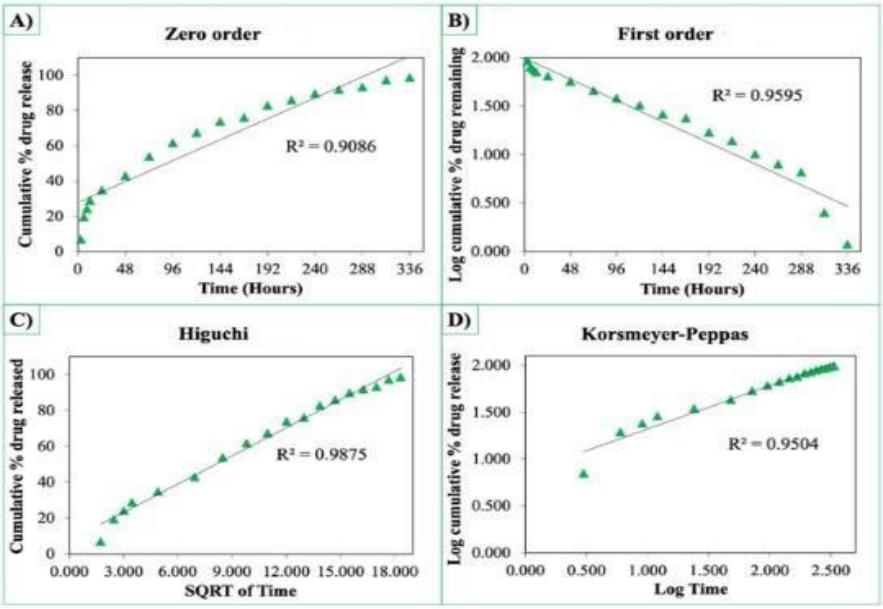

Figure 10: Release kinetics of optimized transdermal patch.

4. CONCLUSION

In this study, the mixture of HPMC K15, PVP, and EC was found to be completely compatible with the drug molecule and the designed formulation release the drug in a sustained fashion over a prolonged period of time. The transdermal patches of Celecoxib were prepared using the combination of polymers, HPMC, PVP, and EC in different concentration with SLS as the permeation enhancer and polyethylene glycol 400 as the plasticizer were used for formulation of TDDS which demonstrated sustained release of drug through the patches. In a thorough study of the evaluation parameters, the highly optimized parameters were observed for formulation F2. Hence, it can be concluded that Celecoxib can be successfully formulated as the transdermal patch that can release the drug for the extended period of time up to 12 hrs in a sustained manner. Such a drug delivery system can be used to avoid the side effects associated with the therapy and can safely deliver the drug for treating of pain with better patient compliance.

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