



## Original Research Article

# Design, development and characterization of ketorolac tromethamine-loaded transdermal patches

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## ABSTRACT

**Aim and Objective:** The aim of this study was to develop and evaluate ketorolac tromethamine-loaded transdermal patch, designed for sustained drug release and enhanced patient compliance in pain management.

**Introduction:** Pain management is a critical component of healthcare, especially in conditions requiring long-term treatment. NSAID, such as ketorolac tromethamine, is commonly prescribed for the relief of moderate to severe pain due to their potent analgesic and anti-inflammatory properties. However, the conventional forms of ketorolac can be associated with limitations and the need for frequent dosing.

**Materials and Methods:** Different combinations of polymers (HPMC K100 and PVP K30) and plasticizer (PEG 400) were used to prepare the transdermal patches by solvent casting method. The drug was dissolved in polymeric solution. The solution was poured into mould and allowed to dry to form a patch. After preparation of Transdermal patch evaluation tests were performed.

**Results:** The transdermal patches exhibited good physical characteristics with uniform thickness and weight variation. The folding endurance test indicated high mechanical strength, with patches enduring multiple folds without breaking. The moisture content was within acceptable limits, ensuring patch stability. The drug content was shown higher value with minimum batch variability. The *in vitro* drug release study showed that patches containing lower concentrations of HPMC K100 and higher concentration PVP K30 had the highest drug release rates, with up to 90% of the drug released over 8 hours.

**Conclusion:** The ketorolac tromethamine-loaded transdermal patches developed in this study demonstrated promising characteristics for sustained drug delivery. Formulations F3 batch provided optimal drug release profiles. These patches could potentially improve patient compliance in pain management by providing a non-invasive, sustained-release drug delivery system.

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## 1. Introduction

There has been a rise in interest in transdermal drug delivery systems (TDDS) and the administration of medications via the skin for both systemic and topical purposes, including topical delivery for the treatment of sick skin.<sup>1</sup> When it comes to a multitude of other drug administration routes, the skin offers several noteworthy advantages over others.

These include the capacity to prevent issues with gastric irritation, pH, and emptying rate effects. To circumvent hepatic first-pass metabolism, which enhances the drug's bioavailability, to minimize the risk of systemic side effects by reducing plasma concentrations in comparison, to oral therapy and to offer a sustained release of the drug at the site of application, quick therapy termination by eliminating the device or formulation, Less variation in medication plasma levels and prevention of injection-related discomfort. Additionally, pulsed entrance into the

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## 2.4. Evaluations of transdermal patches

### 2.4.1. Weight variation

The weight variation test is a critical quality control parameter in the development of transdermal patches. It ensures uniformity in drug content and patch composition, which is essential for consistent drug delivery and therapeutic efficacy.<sup>12</sup> The study was carried out on three patches obtained from casting solution. The mean weight of the patch as well as the deviation from the mean was obtained and the data was recorded. The weight of each patch was taken using electronic balance. The test was done to check the uniformity of weight and thus check the batch-to-batch variation.<sup>13</sup>

### 2.4.2. Thickness

The thickness of a transdermal patch is a crucial parameter that influences drug release rates, adhesive properties, and overall performance of the patch. Consistency in thickness across patches ensures uniform drug delivery and therapeutic efficacy. Measurement of patch thickness is an essential quality control step in the development and production of transdermal drug delivery systems.<sup>14</sup> The thickness of the patch was assessed by using micrometer screw gauge at different points of the patch. From each formulation three randomly selected patches were used. The average value for the thickness of a single patch was determined.<sup>15</sup>

### 2.4.3. Folding endurance

The folding endurance test involves repeatedly folding a patch at the same location until it breaks or shows visible signs of damage. The number of folds a patch can endure before failure is recorded as its folding endurance.<sup>16</sup> Randomly select patches from the batch. Fold each patch at the same point (typically the center) repeatedly by hand. Count the number of folds until the patch shows visible signs of damage (cracking, breaking, or loss of flexibility). Record the number of folds for each patch.<sup>17</sup>

### 2.4.4. Percentage of moisture content

The moisture content can be measured using a gravimetric method, where patches are weighed before and after drying to a constant weight.<sup>18</sup> Randomly select patches from the batch. Weigh the patches individually to obtain the initial weight (W1). Dry the patches in an oven at a specified temperature (typically 60°C to 80°C) until a constant weight is achieved. Weigh the dried patches to obtain the final weight (W2). Calculate the percent moisture content using the formula.<sup>19</sup>

### 2.4.5. Determination of surface pH

The patches were allowed to swell by keeping them in contact with 1 ml of distilled water for 2 h at room temperature and pH was noted down by bringing the

electrode in contact with the surface of the patch, allowing it to equilibrate for 1 min.<sup>16</sup>

### 2.4.6. Percent elongation

When stress is applied, a patch sample stretches and this was to as strain. Strain is basically the deformation of patch divided by original dimension of the sample. Generally, elongation of patch increases as the plasticizer content increases. It is calculated by using following formula.<sup>7</sup>

### 2.4.7. Drug content

The drug content of a transdermal patch is an essential evaluation to ensure uniformity and accuracy in drug dosage. Cut a specified area of the transdermal patch (1 cm<sup>2</sup>) to ensure uniformity. Place the weighed patch in a volumetric flask containing 25 ml of phosphate buffer pH 7.4 was added gently heated to 45°C for 15 minutes, and kept for 24 hours with continuous stirring on magnetic stirrer. Then, the volume was made up to 50 ml with phosphate buffer of pH 7.4. After that, allow the solution to settle, and filter it using filter paper to remove any insoluble components of the patch. Take the filtered solution and dilute it with the solvent to bring the drug concentration within the detection range of the spectrophotometer. Analyse the diluted sample using a UV-Visible spectrophotometer at 366 nm wavelength.<sup>20</sup>

### 2.4.8. In vitro release study

*In vitro* release studies were carried out using Franz diffusion cell 10 ml capacity. Cellulose Acetate membrane was isolated and used for the study. Accurate size of patch was kept on the Cellulose Acetate membrane.<sup>18</sup> The Cellulose Acetate membrane was clamped between donor and receptor compartment. The receptor compartment was filled with 10 ml pH 7.4 Phosphate Buffer maintained at 37°C and stirred by using magnetic stirrer. 1ml sample was collected at suitable time interval (i.e., for every 2 hrs. Until complete drug was released) and replaced with fresh buffer. The collected samples were analysed for drug content by UV visible Spectrophotometer at 366nm.<sup>21</sup>

## 3. Results

Ketorolac tromethamine loaded transdermal patches were prepared by solvent casting method using HPMC K100 and PVP K30 in different concentrations.

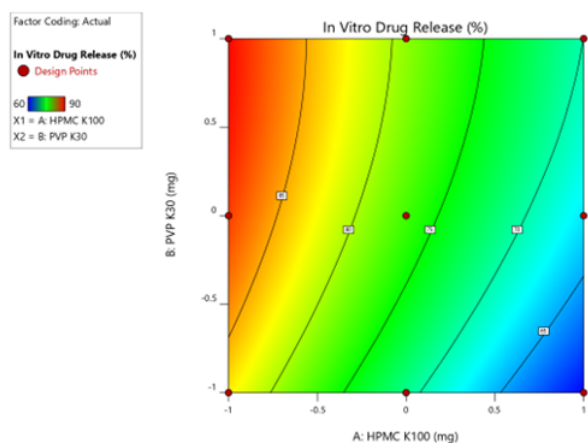
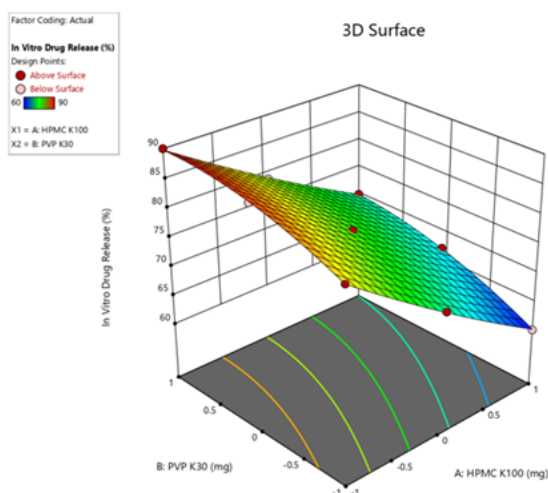
### 3.1. Factorial design

The results of Design of Experiment (DOE) were shown in (Table 3), (Figures 1 and 2). The variables being analyzed are the amounts of HPMC K100 (X<sub>1</sub>) and PVP K30 (X<sub>2</sub>) used in the formulation.

The ANOVA for Response Surface Quadratic model and Model summary statistics- influence of formulation

**Table 3:** Factors and response

Formulation Code	HPMC K100 (X1)(mg)	PVP K30 (X2) (mg)	In vitro Drug Release (Y1)(%)
F1	150	150	83.2±1.3
F2	150	200	88.3±1.2
F3	150	250	90.7±1.1
F4	200	150	71.4±1.4
F5	200	200	77.2±1.4
F6	200	250	79.2±1.4
F7	250	150	60.7±1.5
F8	250	200	67.2±1.3
F9	250	250	70.1±1.3

**Figure 1:** 2D Contour plots for evaluating influence of HPMC K100 (X1) and PVP K30 (X2) on In vitro Drug Release (Y1)**Figure 2:** 3D Response surface plots for evaluating influence of HPMC K100 (X1) and PVP K30 (X2) on In vitro drug release (Y1)

variables on the response factors for Ketorolac Transdermal Patch were shown in (Table 4).

### 3.2. Anova for quadratic model

#### 3.2.1. Response 1: In vitro drug release

Factor coding is Coded. Sum of squares is Type III – Partial. The Model F-value of 2458.37 implies the model is significant. P-values less than 0.0500 indicate model terms are significant. In this case  $X_1$ ,  $X_2$ ,  $X_1X_2$ ,  $X_1^2$ ,  $X_2^2$  are significant model terms.

### 3.3. Evaluations of ketorolac tromethamine transdermal patch

Different evaluation parameters like weight variation, Thickness, Folding Endurance, Moisture Content, pH, Percent Elongation and Drug Content were tabulated in (Table 6).

#### 3.3.1. Weight variation

The Average weight variation of transdermal patches from F1 to F9 was found in the range of  $4.3 \pm 0.4$  to  $6.7 \pm 0.4$ .

#### 3.3.2. Thickness

The thickness of transdermal patches from F1 to F9 was found in the range of 0.19 mm to 0.23 mm.

#### 3.3.3. Folding endurance

The Folding Endurance of transdermal patches from F1 to F9 was found in the range of  $139 \pm 3$  to  $169 \pm 3$ .

#### 3.3.4. Moisture content

The Moisture Content was found to be very less in F2, F6 and F8 Formulation i.e., 4%, 5% and 4% respectively and F1, F3, F4, F5, F7 and F9 formulation contain 11%, 10%, 8%, 10%, 9% and 9% moisture respectively.

#### 3.3.5. pH determination

The pH of transdermal formulations was found in the range of pH 5.8 to 6.2 which indicates skin capability.

#### 3.3.6. Percent elongation

The Percent Elongation of transdermal patches was found in the range of  $56 \pm 2.1$  to  $89 \pm 3.1$ .

#### 3.3.7. Drug content

The drug content analyses 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. The drug content was found between  $84.3 \pm 0.02\%$  to  $95.2 \pm 0.03\%$ .

**Table 4:** ANOVA for response surface quadratic model

ANOVA for response surface quadratic model for ketorolac transdermal patch					
Response Factor	Model F-Value	P -Value	Mean	Lack of fit	C.V. %
In vitro Drug Release	2458.37	< 0.0001	76.11		0.3345

In Vitro drug release (Y1) = 76.89-10.67X<sub>1</sub>+4.17X<sub>2</sub> +0.7500X<sub>1</sub>X<sub>2</sub>+0.6667X<sub>1</sub><sup>2</sup>-1.83X<sub>2</sub><sup>2</sup> Eq (1)

**Table 5:** Model summary statistics- influence of formulation variables on the response factors for ketorolac transdermal patch

Model summary statistics- influence of formulation variables on the response factors for Ketorolac Transdermal Patch						
Response Factor	Source	Standard Deviation	R2	Adjusted R2	Predicted R2	Adequacy Precision
In vitro Drug Release	Quadratic	0.2546	0.9998	0.9993	0.9972	142.7175

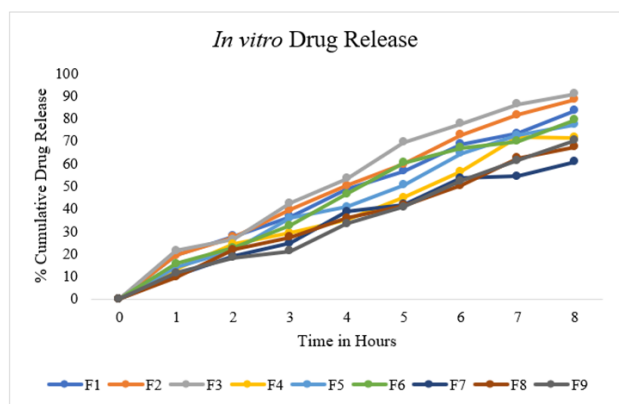
**Table 6:** Evaluations of ketorolac tromethamine-loaded transdermal patches

Characteristics	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight Variation (%)*	5.2±0.5	6.7±0.4	5.6±0.6	6.5±0.5	5.5±0.8	4.8±0.5	6.2±0.6	4.3±0.4	5.8±0.5
Thickness (mm)	0.22	0.21	0.19	0.19	0.20	0.22	0.21	0.22	0.23
Folding Endurance*	162±6	157±2	163±3	140±2	169±3	155±4	164±7	139±3	148±5
Moisture content (%)	11	4	10	8	8	5	9	4	9
pH	6.2	5.9	5.8	6.1	5.9	6.2	5.8	6.0	5.9
Percent Elongation*	59±1.2	89±1.1	58±3.2	56±2.1	68±3.2	71±2	69±2.1	84±2.2	70±3.1
Drug content (%)*	87.2±0.02	91.4±0.04	95.2±0.03	86.1±0.03	90.2±0.06	92.3±0.04	84.3±0.02	86.5±0.05	89.1±0.01

\*All values are mean ± SD, n = 3

### 3.3.8. In vitro drug release

The *in vitro* drug release of Ketorolac tromethamine loaded transdermal patch was performed by Franz diffusion cell by using cellulose acetate membrane. F1- F9 shows the drug release of 83.2±1.3, 88.3±1.2, 90.7±1.1, 71.4±1.4, 77.2±1.4, 79.2±1.4, 60.7±1.5, 67.2±1.3, 70.1±1.3 respectively as shown in (Table 7) & (Figure 3).

**Figure 3:** Percent cumulative drug release

## 4. Discussion

The DOE results indicate that the optimal formulation for maximum drug release involves lower concentrations

of HPMC K100 and higher concentration PVP K30. This information is crucial for formulating an effective transdermal patch with the desired drug release profile. The Predicted R<sup>2</sup> of 0.9972 is in reasonable agreement with the Adjusted R<sup>2</sup> of 0.9993; i.e. the difference is less than 0.2. Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Here ratio of 142.718 indicates an adequate signal. This model can be used to navigate the design space (Table 5). The mathematical modelling of prepared transdermal patch was carried out and following equations were obtained.

Lower weight variation indicates better uniformity in the amount of drug and excipients distributed across the patch. Patches with higher weight variation might need process optimization to ensure uniformity, which is crucial for consistent drug release and efficacy.

Consistent thickness is important for uniform drug release. The slight variations suggest good control during manufacturing, ensuring that the patches have consistent physical dimensions, which is essential for predictable performance.

Higher folding endurance values (e.g., 169 ± 3) suggest that the patches are more flexible and less prone to cracking or breaking when applied to the skin. Lower values may indicate brittleness, which could lead to patch failure during use. Patches with higher folding endurance are generally preferred for their robustness during handling and application.

**Table 7:** Percentage cumulative drug release

Time(Hrs)	1	2	3	4	5	6	7	8
F1	19.4±1.3	27.7±1.3	36.4±1.1	48.5±1.3	56.5±1.3	68.4±1.4	73.2±1.4	83.2±1.3
F2	19.2±1.2	27.4±1.4	39.5±1.3	50.2±1.2	59.7±1.4	72.6±1.2	81.4±1.2	88.3±1.2
F3	21.4±1.1	26.3±1.5	42.4±1.6	53.2±1.5	69.3±1.0	77.5±1.1	86.2±1.3	90.7±1.1
F4	13.2±1.6	24.3±1.1	29.2±1.7	35.1±1.2	44.8±1.1	56.3±1.2	71.5±1.2	71.4±1.4
F5	14.04±1.1	21.5±1.2	35.7±1.2	40.6±1.1	50.4±1.2	64.3±1.3	72.4±1.1	77.2±1.4
F6	15.6±1.3	22.6±1.2	32.4±1.1	46.5±1.0	60.2±1.2	66.8±0.7	69.7±1.1	79.2±1.4
F7	10.4±1.5	18.8±1.5	24.6±1.3	38.6±0.8	41.8±1.5	53.5±1.9	54.3±1.6	60.7±1.5
F8	9.5±1.2	21.8±1.2	27.2±1.4	35.7±1.2	41.4±1.4	50.2±1.7	62.4±1.0	67.2±1.3
F9	11.4±1.0	18.3±0.9	21.1±1.1	33.2±1.4	40.6±1.2	52.3±1.4	61.3±1.2	70.1±1.3

Moisture content influences the stability and adhesion of the patch. Lower moisture content (e.g., 4%) suggests better stability, reducing the risk of microbial growth or degradation of the patch materials. Higher moisture content (e.g., 11%) could affect the patch's mechanical properties and shelf life, potentially requiring moisture-resistant packaging.

The pH values are slightly acidic, which is generally suitable for skin application. This range is close to the skin's natural pH, minimizing the risk of irritation or discomfort. Consistent pH values across formulations indicate stable chemical properties and compatibility with the skin.

Percent elongation of F2 and F8 formulation was found to be good, which indicates good tensile strength. Percent elongation is an indicator of the patch's flexibility and ability to stretch without breaking. Higher values (e.g., 89% ± 1.1) indicate that the patch can stretch significantly, which is beneficial for patches applied to areas of the body that move frequently. Lower values suggest that the patch may be less flexible and more prone to breaking or losing adhesion.

Batch F3 has the highest drug content (95.2±0.03%), suggesting it is the most efficient in incorporating the drug, possibly due to better uniformity in preparation and mixing. F7 has the lowest drug content (84.3±0.02%), which might indicate some loss of drug during the formulation process, or possibly insufficient drug dispersion. Formulations F2, F3, F5, and F6 exhibit higher drug content (above 90%). These batches are promising candidates for further development as they show better drug incorporation and minimal loss during preparation.

Formulation F3 shows maximum drug release i.e. 90.7±1.1 % of drug at 8 hrs. The maximum drug release of F3 formulation indicates that lower concentration of HPMC K100 and higher concentration of PVP K30 influences the release of drug.

## 5. Conclusion

In this research, we successfully formulated and evaluated ketorolac tromethamine-loaded transdermal patches, aiming to provide a controlled and sustained release of the drug for effective pain management. The transdermal

patches were prepared using different polymers and evaluated for various physicochemical properties, including thickness, weight variation, folding endurance and moisture content. The results demonstrated that the formulated patches exhibited acceptable physicochemical properties with uniform thickness in the range from 0.19 mm to 0.23 mm, minimal weight variation i.e. 4.3±0.4 to 6.7±0.4 %, high folding endurance which found in a range 139±3 to 169±3, appropriate moisture content which was 4 to 11 %, pH was found between 5.8 to 6.2 and % elongation found between 56±2.1 to 89±1.1. The drug content of a transdermal patch is an essential evaluation to ensure uniformity and accuracy. The drug content of all formulations was obtained in range from 84.3 ± 0.02 and 95.2 ± 0.03 %. The drug release studies indicated a sustained release profile, which is desirable for maintaining therapeutic drug levels over an extended period. Out of all formulation F3 batch shows maximum drug release i.e. 90.7±1.1 % of drug at 8 Hours. Moreover, the transdermal patches showed good mechanical properties, flexibility, and stability, which are crucial for ensuring their durability and performance during application. The incorporation of suitable permeation enhancers significantly improved the drug permeation rate, highlighting the potential of these formulations for clinical use.

## 6. Source of Funding

None.

## 7. Conflict of Interest


None.

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