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# Matrix Type Transdermal Patch of Aceclofenac: Formulation, Characterization and Optimization

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**ABSTRACT**

Aceclofenac is a BCS Class II drug possessing low solubility and high permeability. It belongs to NSAIDs category and is used in the treatment of pain and inflammation caused due to osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. The bioavailability of Aceclofenac is found to be poor, limiting its use for oral administration. In order to overcome this, the present study aimed at formulating a matrix type transdermal patch of Aceclofenac using solvent casting method. This will not only enhance the drug delivery of Aceclofenac transdermally but also, facilitate patient compliance due to its ease of application. To achieve these objectives, a transdermal therapeutic system containing Aceclofenac with different ratios of hydrophilic polymers in combination (Eudragit RS100, PEG 400) were prepared using solvent casting method. These prepared transdermal patches were evaluated for parameters like thickness, weight variation, folding endurance, drug content and in vitro drug release. The formulation batches were optimized using $3^2$ factorial designs, from the results obtained A5 formulation was found to be optimized formulation.

**Keywords:** Aceclofenac, Transdermal Patch, Solvent casting, In vitro Drug Release

## ABBREVIATIONS:

TDDS: Transdermal Drug Delivery System

NaCl: Sodium chloride

UV Vis: Ultraviolet visible spectroscopy

FTIR: Fourier Transform Infrared

ANOVA: Analysis of variance

PEG: Polyethylene glycol

## 1 INTRODUCTION

The first transdermal drug delivery system (TDDS) was developed in the 1970s for the treatment of motion sickness, and since then, numerous TDDS have been developed for a wide range of therapeutic applications. TDDS technology has advanced rapidly, and newer technologies such as iontophoresis, microneedles, and thermal ablation have been developed to enhance drug penetration and delivery across the skin. [1]

Transdermal drug delivery system:

TDDS is a non-invasive and convenient method of drug administration that has gained significant attention in recent years. TDDS is a promising alternative to traditional drug delivery methods and has several advantages, including improved patient compliance and sustained drug release. [2-6]

The purpose of the skin, which is our body's multi-layered outer layer, is to shield it from natural dangers including chemicals, heat, and toxins. [7] Each layer of this skin has characteristics

that prevent transdermal delivery, including the epidermis, which serves as a barrier for us, and the dermis, which houses blood vessels and produces skin cells. [8]

The Stratum Corneum (the non-living epidermis) and the active epidermis are additional divisions of the epidermis. The stratum lucidum, stratum granulosum, stratum spinosum, and stratum germinativum are the four layers that make up the active epidermis. The stratum corneum, the outer layer of the skin, which acts as a barrier against foreign objects, is where the protective quality of the epidermal skin is first found. The inhibitory effect is crucial for the transport of high molecular weight substances. [9]

The connection between the tissues surrounding the skin and the human vasculature may be seen in the dense layer of single endothelial cells that pierces the papillary loops of the upper arteriovenous plexus close to the dermal-epidermal region in the upper dermis. The skin's endothelium plays a comparable role to the body as a whole. Actively modifies in response to heat, osmotic pressure, chemokines, and cytokines maturation, resulting in either vasodilation or constriction [17]. In order to transport the medication to the skin tissue and pass through cellular and circulatory tissues to reach the target tissue, the main challenge of TDDS is to overcome the stratum corneum's inhibitory action. The issue is that skin tissue can only absorb a very little amount of the drug. [10][11]. (Figure 1 represents the structure of skin with transdermal patch).

**1.1 Factors affecting TDDS:**

**A. Drug:**

For the success of transdermal drug delivery system choice of the drug is very important step.

The drug should possess following properties:

1.Molecular weight should be less than 1000 Dalton.

2.It should be compatible in both hydrophilic and lipophilic phases.

3.Biological half-life should be short.

4.Medication should not cause any allergy.

5.Drug should have low melting point and daily dose should be less. [12]

**B. Polymer matrix:**

The chemical compound which regulates how much of the medicine will release. The polymer cannot be used in transdermal patches until the conditions listed below are satisfied.

The polymer needs to be stable and safe. In stratum devices, the following polymers may be helpful: Gelatine made of cellulose, wax, natural rubber, starch, and other natural polymers are examples. Polybutadiene, hydrin rubber, polysiloxane, nitrile, propenonitrile, styrene butadiene rubber, etc. are some examples of synthetic elastomers. Polyvinyl alcohol, Polyvinyl chloride, synthetic resin, plastic, polyacrylate, polyamide, polyurea, polyvinyl pyrrolidone, polymethylmethacrylate, epoxy, etc. are examples of synthetic polymers. [13] **C. Membrane:**

It regulates the drug's release by dispersing it through an inert polymer matrix. The drug moiety was physically combined with the polymer powder, and the mixture was then physically moulded into the appropriate form with the necessary thickness and surface area. [14]

**D. Permeation enhancer:**

Substances that facilitate the absorption of medications administered topically are sometimes known as absorption promoters, accelerants, or penetration enhancers. To increase the diffusivity and solubility of pharmaceuticals through the skin and reversibly lower the skin's barrier resistance, penetration enhancers are added to a formulation. Consequently, permit the medicine to reach the living tissues and enter the bloodstream.

**Desirable Properties of Penetration Enhancers:**

i. It should not cause irritation, sensitization, phototoxicity, or comedogenicity.

ii. The action should start quickly, and its duration should be predictable and repeatable.

iii. Not pharmacologically active (i.e., not bind to the receptor site) in the body.

iv. The upper layer should completely and instantly regain its usual barrier property when the enhancer has been removed.

v. The skin's barrier function should only decrease in one direction. Endogenous material shouldn't diffuse out of the skin and be lost to the environment.

vi. All medications and adjuvants to be included in topical treatments and devices shall be chemically and physically compatible with the accelerants. vii. It must be cheap, flavorless,

and colorless. viii. It must easily be synthesized into dermatological medicines. ix. It should have a desired solubility parameter that resembles skin.

x. On the skin, it should feel good and adhere and distribute evenly. Many other kinds of substances, such as water, hydrocarbons, alcohols, acids, amines, amides, esters, surfactants, terpenes, terpenoids, essential oils, sulfoxides, lipids, and other substances, such as cyclodextrin derivatives, chitosan, etc., are examples of the often-employed classical enhancers. [15]

**E. Pressure-sensitive adhesive:**

Pressure sensitive adhesive has so far been able to speed up transdermal systems. In TDD devices, polyisobutylene, polyacrylate, and silicones are the three adhesives that are most frequently utilized. [15]

**F. Backing laminates:**

When designing the baking layer, the following factors must be taken into account:

i. Need to be adaptable.

ii. Having a low water vapor transmission rate to encourage skin hydration and hence increase drug skin permeability. iii. Transdermal system should be compatible as it is still in use while applying. iv. Need to be chemical resistant.

v. Having an excellent tensile strength. vi.

Non irritating.

Polyethylene, polyester, and polyolefin films, as well as an aluminum vapor coated layer, are examples of backings laminate. [16]

**G. Release liner:**

The patch is stored with a protective liner until it is utilized. Because the release liner is in close contact with the transdermal system and must be both physically and chemically inert, it should be removed and discarded only before applying the patch to the skin. The release liner is made up of a base layer that may be non-occlusive (like paper fabric) or occlusive (like polyethylene, polyvinyl chloride), and a release coating layer comprised of silicon or Teflon. Polyester foil and metalized laminate are additional materials utilized as release liners in transdermal patches. [17]

**H. Other excipients like plasticizers and solvents:**

**Plasticizers:** Between 5% and 20% (w/w, dry basis), plasticizers have been utilized in numerous formulations. It is also in charge of the film's brittleness, ductility, adhesiveness to other surfaces or membranes, and improvement in film strength. Examples include phosphate, phthalate esters, fatty acid esters, and glycol derivatives like PEG 200 and PEG 400. Glycerol or sorbitol, at 15%, w/w, dry basis, is another example.

**Solvents:** A variety of solvents, including acetone, dichloromethane, methanol, chloroform, and isopropanol, are employed to produce drug reservoirs. [18].

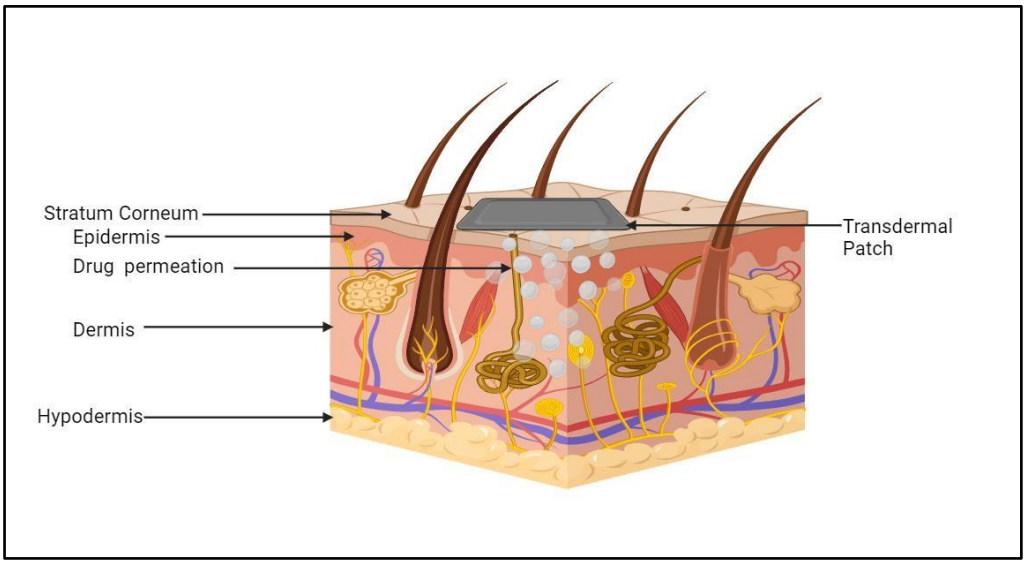



**Figure 1: Structure of the skin with transdermal patch**

## 2 MATERIALS AND METHODS

Experimental studies were carried out using following materials and methods.

### 2.1 Materials:

Aceclofenac (Yarrow Chem Product, Mumbai), Methanol (Modern Industries, Sinnar), Chloroform (Research Lab Fine Chem Industries, Mumbai), PEG 400 (Modern Industries, Sinnar), SPAN 80 (Modern Industries, Sinnar), Eudragit RS 100 (Research Lab Fine Chem Industries, Mumbai), Ethanol (Sanjivani factory, Kopargaon).

### 2.2 Method:

### 2.2.1 Preformulation studies:

#### 2.2.1.1 Fourier Transform Infrared Spectroscopy (FTIR) Spectra of pure drug:

The FTIR spectra of pure drug was taken using FTIR spectrophotometer (Shimadzu).

#### 2.2.1.2 Determination of λmax and calibration curve of Aceclofenac:

**Preparation of Phosphate Buffer pH 7.4:**

0.19 g of potassium dihydrogen phosphate, 2.38 g of disodium hydrogen orthophosphate, and 8.0 g of Sodium chloride (NaCl) was dissolved in distilled water, and the volume was made up to 1000 ml with distilled water. The pH of the buffer was adjusted to 7.4.

The calibration of Aceclofenac was done using Phosphate buffer pH 7.4 at λmax 274 nm. The dilutions were prepared and absorbance was taken using UV Vis spectrophotometer (Shimadzu 1800). The calibration curve was plotted and the linearity was demonstrated by $R^2$ value. [20]

### 2.2.2 Formulation of Aceclofenac Transdermal Patch:

The solvent casting method was utilized to prepare transdermal patch. Methanol and Ethanol were weighed accurately and mixed properly. Then to this mixture, Eudragit RS-100, Polyethylene Glycol 400, SPAN 80 was added. Finally, Aceclofenac was added to this mixture with constant stirring and the resulting mixture was centrifuged for 30 minutes. [19]

The method of preparation of Aceclofenac transdermal patch is diagrammatically represented in (Figure 2).

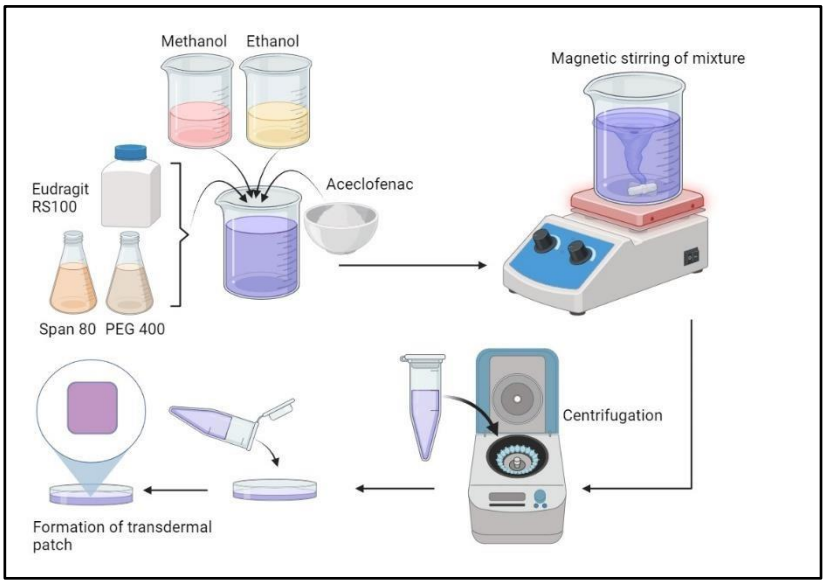



**Figure 2: Diagram representing formulation of Aceclofenac transdermal patch**

### 2.2.3 Optimization of Formulation:

Design Expert (Version 13 Stat Ease) was used to design the formulation batches. A $3^2$ factorial design was applied and regression analysis was performed for optimization of the Eudragit Rs 100 concentration, and Polyethylene glycol 400 concentration. The independent factors, i.e., Eudragit Rs 100 concentration (X1), and Polyethylene glycol 400 concentration (X2) were set at Low, Medium and High levels. Percentage drug release was taken as a dependent variable. The data obtained was analyzed using analysis of variance (ANOVA). The 3-D response surface methodology was studied to test the interaction of Eudragit Rs 100 (Y1) and Polyethylene glycol 400 (Y2).

## 3. EVALUATION OF TRANSDERMAL PATCH:

The components of transdermal patches have profound effect on the physical and mechanical characteristics, the release and permeation of drugs. Formulated dried transdermal patches of 3.77 $cm^2$ area were examined as follows:

### 3.1 FTIR Analysis:

In order to evaluate the integrity of the pure drug, optimized formulation, the FTIR spectra was obtained using FTIR Spectrophotometer (Shimadzu).

### 3.2 Thickness:

The thickness of patches was measured at three different places using a micrometer and average was calculated.[19]

### 3.3 Weight Variation:

The patches were subjected to mass variation by individually weighing randomly selected patches. [19]

### 3.4 Folding endurance:

It was counted manually for different prepared patches in which three patches of each formula with size (1 cm × 2 cm) were cut using a sharp blade. The folding endurance of films was measured by frequently folding a strip at the same point till it is was broken or folding up to 200 times at one point until it breaks which gave folding endurance of film. [20]

### 3.5 Drug content:

The uniformity of drug content of the transdermal patch was determined, based on dry weight of drug and polymer used, by means of a UV-Vis spectrophotometer method. The formulated patch was cut into pieces and dissolved in 10 ml of methanol. The resulting solution was transferred to a volumetric flask, appropriate dilutions were made with phosphate buffer pH 7.4, filtered and analyzed for aceclofenac content at 271.1 nm by a UV-visible spectrophotometer. [20]

### 3.6 In vitro drug release:

A Franz diffusion cell was utilized for performing the drug release test. The transdermal patch was placed over the cell containing a cellophane membrane above it. A receptor compartment of a cell contained a phosphate buffer solution with pH 7.4. The temperature was maintained at 37 ± 1 °C and stirred continuously. At predetermined time intervals, the sample was withdrawn. The fresh medium was added immediately after each sample withdrawal to maintain the sink condition. The samples were analyzed spectrophotometrically at 274 nm wavelength and percentage drug release was calculated. **4. Results and Discussions**

### 4.1 FTIR Analysis:

From the spectra obtained of FTIR, the values of peaks were found at 3170, 1520.6, 1360, and 1270.5 $cm^{-1}$ for drug and in the same ranges for the formulation indicating the compatibility of drug with excipients. The (Figure 3) shows the FTIR spectrum of pure drug and the optimized formulation.

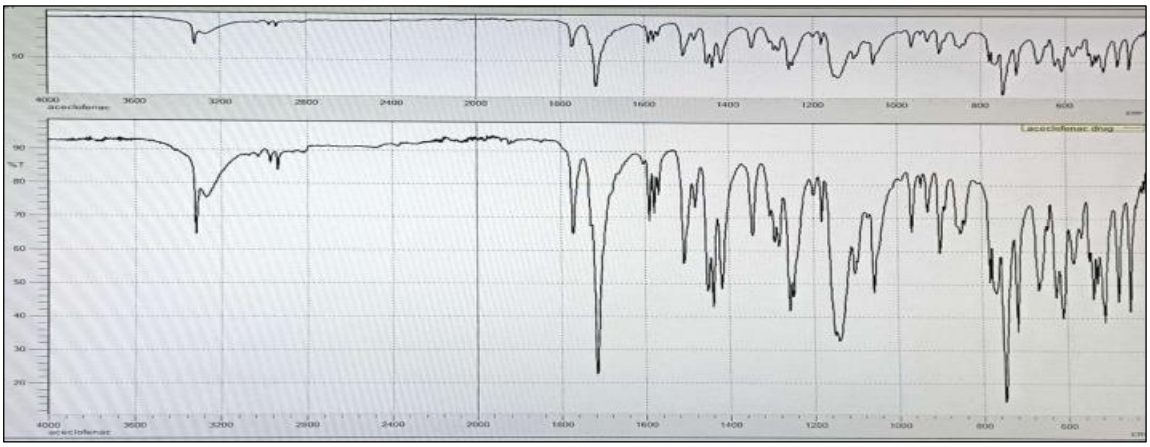


**Figure 3: FTIR spectra of pure drug and optimized formulation**

### 4.2 Calibration Curve of Aceclofenac:

The values obtained for absorbance for dilutions were used to determine the unknown concentration (Table 1). The calibration curve of Absorbance Vs Concentration was plotted with $R^2$ value of 0.999 (Figure 4).

| Sr no. | Concentration(µg/ml) | Absorbance(nm) |
|---|---|---|
| 1 | 5 | 0.122 |
| 2 | 10 | 0.296 |
| 3 | 15 | 0.456 |
| 4 | 20 | 0.652 |
| 5 | 25 | 0.796 |
| 6 | 30 | 0.987 |

**Table 1: Calibration curve readings**

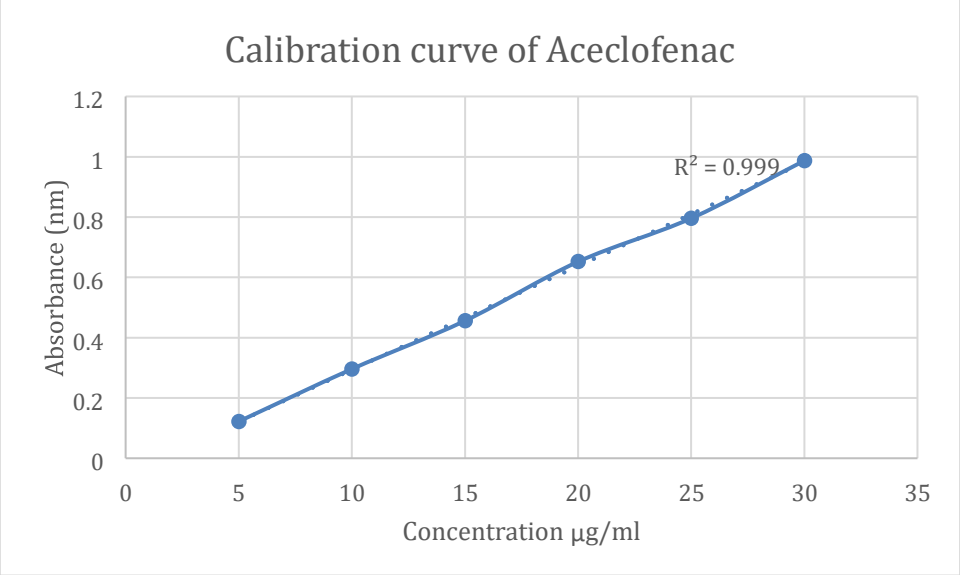



**Figure 4: Calibration Curve of Aceclofenac**

### 4.3 Results for thickness, weight variation, folding endurance and drug content:

Thickness and folding endurance were minimum for A5 formulation and maximum for A9 formulation. The drug content was found to be maximum for A6 formulation. There was not much variations among the patches for drug content and weight. The results obtained are given in (Table 2).

| Formulation | Thickness (mm) | Weight Variation (mg) | Folding Endurance | Drug content ($mg/cm^2$) |
|---|---|---|---|---|
| A1 | 0.15 ± 0.02 | 10.61 ± 0.31 | 154 | 2.38 |
| A2 | 0.15± 0.05 | 12.51 ± 0.37 | 152 | 2.39 |
| A3 | 0.16± 0.09 | 14.97 ± 0.44 | 150 | 2.43 |
| A4 | 0.16± 0.02 | 15.28 ± 0.48 | 151 | 2.44 |
| A5 | 0.15 ± 0.01 | 16.68 ± 0.53 | 155 | 2.50 |
| A6 | 0. 16± 0.03 | 18.95 ± 0.60 | 154 | 2.53 |
| A7 | 0.17 ± 0.04 | 13.65± 0.56 | 151 | 2.47 |
| A8 | 0.17 ± 0.08 | 12.78 ± 0.25 | 150 | 2.47 |
| A9 | 0.18 ± 0.01 | 14.23 ± 0.35 | 153 | 2.36 |

**Table 2: Results of thickness, weight variation, folding endurance and drug content**

### 4.4 In vitro drug release study:

From the results obtained, it was found that A4 formulation had shown the maximum drug release of 85.54%. The values of maximum drug release range within 76 to 86 % for all the formulations. The values obtained for drug release of each transdermal patch are given in (Table 3).

| **Time (hours)** | **Drug release (Percentage)** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | A1 | A2 | A3 | A4 | A5 | A6 | A7 | A8 | A9 |
| 1. | 25.02 | 28.25 | 29.55 | 27.89 | 34.78 | 32.78 | 38.24 | 22.36 | 21.77 |
| 2. | 31.23 | 31.22 | 33.89 | 29.13 | 40.99 | 37.41 | 43.31 | 28.21 | 24.98 |
| 3. | 37.27 | 36.58 | 37.00 | 33.32 | 44.97 | 41.89 | 48.12 | 35.99 | 28.25 |
| 4. | 43.42 | 40.39 | 41.26 | 37.54 | 48.33 | 45.78 | 55.68 | 39.02 | 33.20 |
| 5. | 50.67 | 45.69 | 45.77 | 43.89 | 54.89 | 48.53 | 60.18 | 43.44 | 38.24 |
| 6. | 55.74 | 53.21 | 49.89 | 49.78 | 59.17 | 53.48 | 61.68 | 48.31 | 43.98 |
| 7. | 58.21 | 59.24 | 53.10 | 55.65 | 61.79 | 57.58 | 64.54 | 52.44 | 49.57 |
| 8. | 61.58 | 62.34 | 59.11 | 59.17 | 66.78 | 62.96 | 66.00 | 55.68 | 53.21 |
| 9. | 65.20 | 66.73 | 63.21 | 63.21 | 71.19 | 66.85 | 70.35 | 60.24 | 58.48 |
| 10. | 69.64 | 71.36 | 67.13 | 67.21 | 75.34 | 71.88 | 73.23 | 66.41 | 63.47 |
| 11. | 73.96 | 74.98 | 72.85 | 79.25 | 79.24 | 76.28 | 78.12 | 74.21 | 70.35 |
| 12. | 78.00 | 83.23 | 79.45 | 85.54 | 85.43 | 82.67 | 84.43 | 79.88 | 76.56 |

**Table 3: Result for in vitro drug release study**

### 4.5 Optimization of formulation:

The formulation batches obtained after applying $3^2$ factorial design with concentration of Eudragit RS 100(gm) and PEG 400(% w/w) along with percent drug release of each are given in (Table 4).

The **Model F-value** of 6.51 implies the model is significant. **P-value** less than 0.0500 indicate model terms are significant (Table 5).

**Equation for drug release:**

$$Drug\ release = +83.40444 + 0.884167 \times Eudragit\ RS\ 100 - 1.31333 \times PEG\ 400$$

The positive sign for coefficient Eudragit RS 100 (+0.884167×Eudragit RS 100) indicates that the higher concentration of Eudragit RS 100 in the formulation has a positive effect on the drug

release of the formulation. The negative sign for coefficient PEG 400 (-1.31333× PEG 400) showed that the concentration of PEG 400 affects negatively on the drug release of the formulation significantly. $R^2$ value was found to be 0.997 for drug release. The contour plot of drug release and response surface graph illustrates the effect of the independent variable on the response (Figure 5 and Figure 6).

| Formulation | Eudragit RS 100 concentration (gm) | PEG 400 concentration (%w/w) | % Drug release |
|---|---|---|---|
| A1 | 4 | 6 | 78.00 |
| A2 | 2 | 2 | 83.23 |
| A3 | 2 | 6 | 79.45 |
| A4 | 6 | 4 | 85.54 |
| A5 | 4 | 2 | 85.43 |
| A6 | 4 | 4 | 82.67 |
| A7 | 6 | 2 | 84.43 |
| A8 | 6 | 6 | 79.88 |
| A9 | 2 | 4 | 76.56 |

**Table 4: Optimization of formulation**

| **Source** | **F-value** | **p-value** | |
|---|---|---|---|
| Model | 6.51 | 0.0314 | significant |
| A-Eudragit RS 100 | 4.06 | 0.0905 | |
| B-PEG 400 | 8.96 | 0.0242 | |

**Table 5: Values obtained**

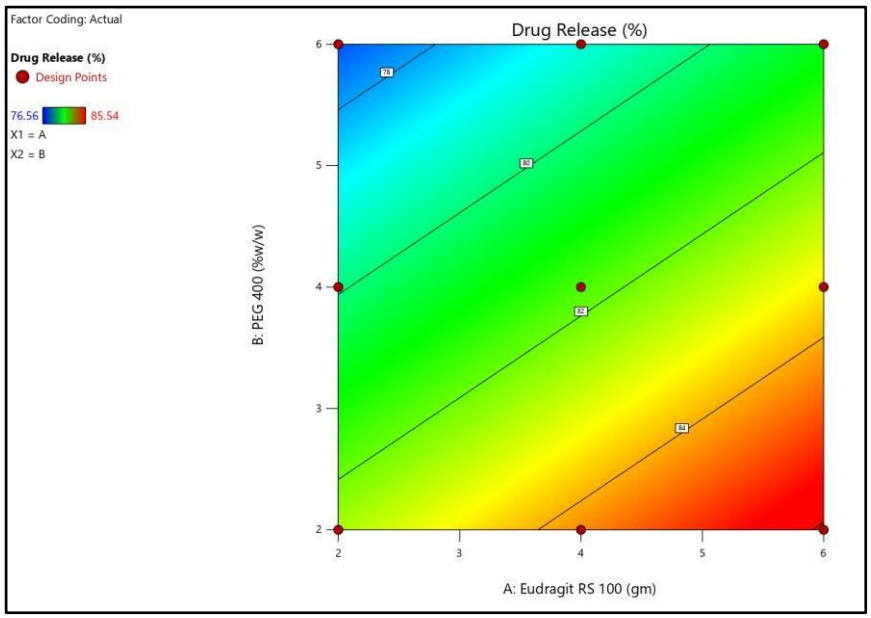



**Figure 5: Contour Plot of % drug release**

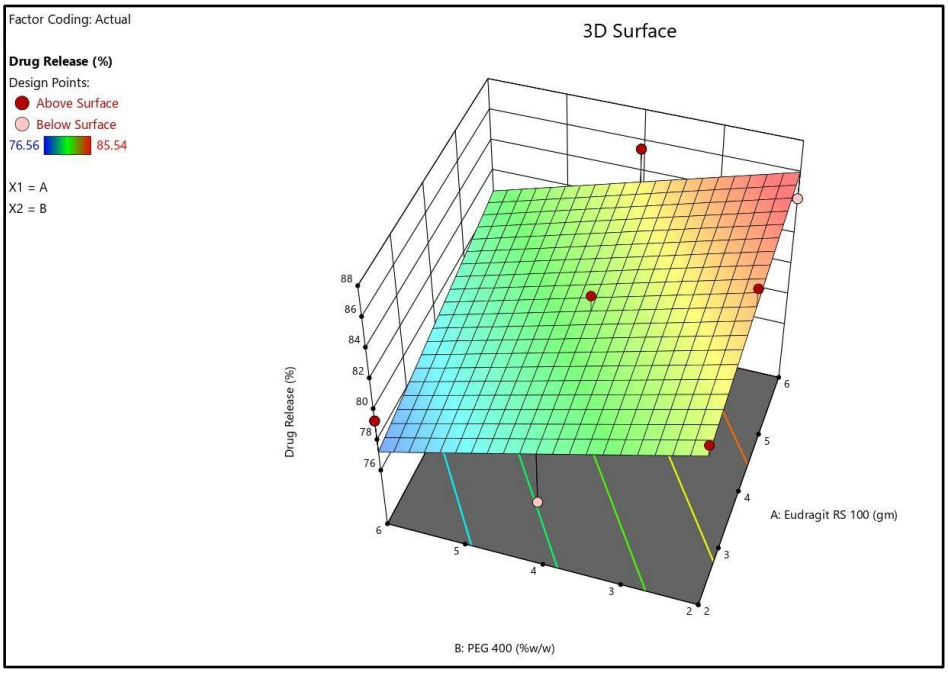
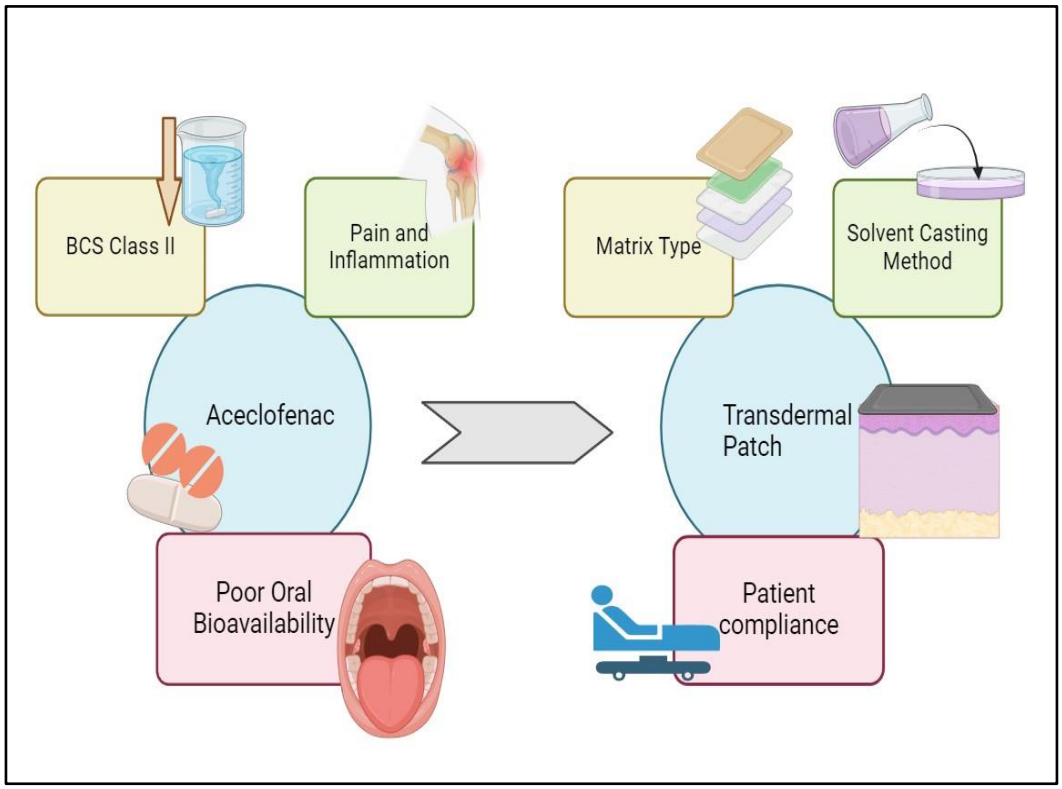



**Figure 6: Response Surface Graph of % drug release**




**Graphical abstract**

## 5. Conclusion

The formulated transdermal patches with different concentration of Eudragit RS 100 and PEG 400 were evaluated for various parameters like thickness, weight variation, drug content and in vitro drug release and was found to be efficient for drug delivery. Thus, it can be concluded that, aceclofenac formulated into the transdermal matrix type patches can be efficiently used by sustaining its release characteristics and offers an alternative route of administration for pain management with improved patient convenience and therapeutic outcomes. **Conflict of interest**

The authors declare no conflict of interest.

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