INTRODUCTION

In the recent few years, a research interest has been evolved to design a wide variety of novel drug delivery systems (NDDS) using the existing drug molecules.1 Currently, transdermal drug delivery is considered as one of the most promising approaches for the implementation of NDDS.2 Topical dosage forms containing one or more therapeutic agents that can produce a systemic effect of the agent is termed as transdermal drug delivery system (TDDS).3 There are several advantages of TDDS like controlled release of the drug, steady blood-level profile, minimized systemic side effects, bypassing first-pass hepatic metabolism, self-administration, enhanced patient compliance, improved efficacy over any other conventional dosage forms.1 Transdermal system has been designed for delivering an effective amount of drug across the intact skin to accomplish both the local and systemic effects.4 Pain, hypertension, motion sickness, angina, nicotine addiction are the diseases which can be treated by the aid of transdermal delivery of drugs. Latest example of successfully using this system is healing of urinary incontinency and contraception.5 Transderm SCOP approved by Food and Drug Administration (FDA) in 1979, was the first transdermal system which was used to inhibit nausea and vomiting associated with motion sickness.1 Creams, ointments, pastes, gels, lotions, sprays, and patches are the most common transdermal formulations available in the market.
A transdermal patch is a user-friendly, convenient, and extensively accepted medicated adhesive device that distributes the drug through the skin for systemic effects in a controlled and programmed manner. Exposing of patch application site should be avoided from the external heat sources such as hot water bottles, hot water bags, etc. A higher body temperature may also elevate the rate of drug release. Here, the patch must be removed immediately. Restricting nature of skin is one of the significant drawbacks for passive delivery of drugs through transdermal patches. Transdermal patches are classified into three types as the drug (i) in a reservoir system, (ii) in adhesive, (iii) in matrix. The drug in matrix systems are developed by dispersing or dissolving the active pharmaceutical ingredient in a polymer matrix followed by adding an adhesive layer if desired. The polymer matrix regulates the rate of drug delivery. The selection of a polymer depends upon its physicochemical properties, compatibility with drug, optimization of the drug loaded into the matrix with other ingredients, skin contact, mode of drug release, and stability. Ideal drug candidates for transdermal patch that can readily permeate to the skin must have a low molecular weight, high therapeutic potency, be moderately lipophilic and being non-allergenic, and non-irritating. Tramadol hydrochloride is a 4-phenyl-piperidine analogue of the opioid drug codeine, 2-(dimethyl amino)-methyl)-1-(3′-methoxyphenyl) cyclohexanol hydrochloride, which was first synthesized in 1962. The drug is categorized as an analgesic and can be used to relieve from moderate to severe acute and chronic (cancer and non-cancer) pain, osteoarthritis. For treating dental pain, osteoarthritis flare pain, and chronic back pain, tramadol provides rapid onset and prolonged action along with acetaminophen. It has been evidenced that at small dosages, tramadol hydrochloride is an effective and safe treatment protocol for premature ejaculation, a common sexual disorder. The study out by Chandak and Verma indicated that the matrix type transdermal patches of tramadol fabricated with different grades and altered ratios of hydroxypropyl methylcellulose (HPMC) embraced adequate potential for transdermal delivery owing to controlled release pattern of drug from the patches and on the aegis of their in vitro and pharmacokinetic results. Recent experimental studies have demonstrated that the transdermal patch containing HPMC as a polymer in higher concentrations caused an increased drug release. This work focused on the development of an optimized sustained release transdermal patch of tramadol hydrochloride with suitable physicochemical properties and desired release kinetics.

MATERIALS AND METHODS

Tramadol hydrochloride was purchased from Emmennar Pharma Pvt. Ltd. (Visakhapatnam, India). Potassium dihydrogen orthophosphate, sodium hydroxide, triethyl citrate, HPMC E15, ethyl cellulose (EC), polyvinyl alcohol, potassium bromide, potassium chloride, polyethylene glycol (PEG) 400, n-octanol, calcium chloride (fused) were procured from Loba Chemie Pvt. Ltd. (Mumbai, India). HPMC E5 was provided by Colorcon Asia Pvt. Ltd. (Goa, India). Glycerol, propylene glycol, methanol was purchased from Merck Specialties Pvt. Ltd. (Mumbai, India). All these ingredients used were of analytical grade except n-octanol (high performance liquid chromatography grade) and potassium bromide [infrared (IR) spectroscopy grade].

Identification of drugs

Many monographic tests (Table 1) were employed as per IP to identify tramadol hydrochloride, which was used as the drug candidate for designing the formulations.

| Table 1. Specifications required for identification of drug |
|------------------------------------------------------------|
| **Tests** | **Specification** |
| Solubility | |
| In water | Freely soluble |
| In methanol | Freely soluble |
| In acetone | Very slightly soluble |
| Appearance of solution | |
| A 5.0% (w/v) solution of tramadol hydrochloride | Clear and colorless |
| Acidity | |
| 0.2 mL of methyl red solution and 0.2 mL of 0.01 M hydrochloric acid were added to 10 mL of 5.0% (w/v) solution of tramadol hydrochloride | Solution will be red |
| A specified amount of 0.01 M sodium hydroxide was added to change the colour from red to yellow | Not more than 0.4 mL |
| Loss on drying | |
| 1.0 g tramadol hydrochloride was dried in a hot air oven at 105°C for 3 h | Not more than 0.5% |
| Sulfated ash | Not more than 0.1% |
| Assay | |
| 0.18 g of tramadol hydrochloride was dissolved in 25 mL of anhydrous acetic acid and 10 mL of acetic anhydride. Then, it was then titrated with 0.1 M perchloric acid. The end point was determined potentiometrically. A blank titration was carried out (1 mL of 0.1 M perchloric acid is equivalent to 0.02998 g of tramadol hydrochloride) | - |
Compatibility of the drug with polymers
Compatibility between the drug and polymers was examined using Fourier transform IR spectroscopy (FT-IR) spectrophotometer. The IR spectra were recorded under a wave range between 4000-400 cm⁻¹.¹⁸,¹⁹

Preparation of backing membrane
To prepare the backing membrane, 3 g of polyvinyl alcohol was dissolved in 100 mL of distilled water warmed at a temperature 40°C. After filtering the solution, 2 mL filtrate was transferred to each glass mold. It was then placed in a tray dryer at 60°C for 6 hours to get dried.²⁰

Formulation of matrix type transdermal patches
A total 26 batches (F1-F26) of matrix type transdermal patches were fabricated using different ratios of HPMC and EC as a rate regulatory polymers (Table 2). PEG 400, glycerol, and triethyl citrate were used as plasticizers. Propylene glycol was added as an anti-crystalizing agent. The polymers and other excipients in different ratios (Table 2) were dissolved in methanol. Tramadol hydrochloride (50 mg) was added slowly to the polymeric solutions of individual batch and stirred on a magnetic stirrer until a uniform mixture was obtained. The mixture was then poured on the glass mold, which was covered with a glass funnel of appropriate size to govern evaporation.

Table 2. Composition of matrix type transdermal patches (F1-F26)

| Patches | Quantity/patch (mg) | Tramadol HCl | HPMC E5 | HPMC E15 | EC | PEG 400 | Glycerol | Propylene glycol | Triethyl citrate | Total weight (mg) |
|---------|---------------------|--------------|---------|----------|----|---------|----------|------------------|------------------|------------------|
| F1      | 50                  | -            | -       | 50       | 10 | -       | -        | 10               | 10               | 120              |
| F2      | 50                  | -            | -       | 100      | 10 | -       | -        | 10               | 10               | 170              |
| F3      | 50                  | -            | -       | 100      | 10 | 10      | -        | -                | 170              |
| F4      | 50                  | -            | -       | 100      | 20 | 10      | -        | -                | 180              |
| F5      | 50                  | -            | -       | 100      | 30 | 10      | -        | -                | 190              |
| F6      | 50                  | -            | -       | 100      | 20 | 20      | -        | -                | 190              |
| F7      | 50                  | -            | -       | 150      | 20 | 20      | -        | -                | 240              |
| F8      | 50                  | -            | -       | 200      | 20 | 20      | -        | -                | 290              |
| F9      | 50                  | 100          | -       | -        | 20 | 20      | -        | -                | 190              |
| F10     | 50                  | 150          | -       | -        | 20 | 20      | -        | -                | 240              |
| F11     | 50                  | 200          | -       | -        | 20 | 20      | -        | -                | 290              |
| F12     | 50                  | 100          | -       | 100      | 20 | 20      | -        | -                | 290              |
| F13     | 50                  | 150          | -       | 100      | 20 | 20      | -        | -                | 340              |
| F14     | 50                  | 200          | -       | 100      | 20 | 20      | -        | -                | 390              |
| F15     | 50                  | 200          | 100     | -        | 20 | 20      | -        | -                | 390              |
| F16     | 50                  | 200          | 200     | -        | 20 | 20      | -        | -                | 490              |
| F17     | 50                  | 200          | 125     | -        | 20 | 20      | -        | -                | 415              |
| F18     | 50                  | 200          | 125     | -        | 20 | 20      | 10       | -                | 425              |
| F19     | 50                  | 200          | 125     | -        | 20 | 20      | 20       | -                | 435              |
| F20     | 50                  | 200          | 125     | -        | 20 | 20      | 15       | -                | 430              |
| F21     | 50                  | 200          | 125     | -        | -  | 20      | 10       | -                | 405              |
| F22     | 50                  | 200          | 125     | -        | -  | 30      | 10       | -                | 415              |
| F23     | 50                  | 200          | 125     | -        | -  | 40      | 10       | -                | 425              |
| F24     | 50                  | 200          | 125     | -        | -  | 50      | 10       | -                | 435              |
| F25     | 50                  | 200          | 150     | -        | -  | 50      | 10       | -                | 460              |
| F26     | 50                  | 250          | 190     | -        | -  | 50      | 10       | -                | 550              |

HPMC: Hydroxypropyl methylcellulose, EC: Ethyl cellulose, PEG: Polyethylene glycol
rate of the solvent. The casting solvent was subsequently permitted to evaporate overnight at 40°C for attaining the dried patches. After drying, the patches were cut from the glass mold. Backing membrane was affixed with suitable adhesive and dried at the room temperature. The patches were then kept between sheets of wax paper and stored in desiccators for their evaluation followed by optimization.

Evaluation of matrix type transdermal patches

Planned patches were evaluated for different physicochemical parameters such as thickness, drug content, moisture content, moisture uptake, flatness, tensile strength, water vapor transmission (WVT) rate, folding endurance, etc.

Thickness

Thickness was measured using a digital screw gauge at five distinct portions of the patches from each batch and the mean value including standard deviation was calculated.

Weight variation

Randomly selected ten patches from each batch were subjected to weight variation test. A specified area of the individual patch was cut into different parts and weighed. Average weight and standard deviation were calculated from the weights measured individually.

Drug content

An accurately weighed (100 mg) section of transdermal patch was dissolved in 100 mL of phosphate buffer (pH 7.4) and the solution was then shaken continuously for 24 hours in a shaker incubator followed by sonication for about 15 min. After subsequent filtration and suitable dilution, the drug content in the solution was assessed using a ultraviolet (UV)-visible spectrophotometer at a wavelength of 275 nm.

Moisture content

The patches from the individual batch were weighed individually and stored in a dessicator installed with activated silica at room temperature for 24 hours. The patches were then weighed repeatedly until a constant weight was found. Percentage moisture content was measured using the following formula.

\[
\text{Percentage moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100
\]

Moisture uptake

A transdermal patch was weighed and placed in a dessicator containing a saturated solution of potassium chloride at room temperature for 24 hours. After the completion of the period, the patch was weighed repeatedly until a constant weight was found. Percentage moisture uptake was measured using the following formula.

\[
\text{Percentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100
\]

Flatness

A flatness test was performed to confirm that the developed patches retain a smooth surface and will not constrict with time. One longitudinal strip was cut from the center and two from either end of the patches which were individually measured. The variation in length caused by non-uniformity in flatness was checked by determining the percent constriction. Zero percent constriction is considered as equivalent to 100 percent flatness. Percentage constriction was calculated using the following formula.

\[
\text{Percentage constriction} = \frac{\text{Initial length of strip} - \text{Final length of strip}}{\text{Initial length of strips}} \times 100
\]

Folding endurance

Folding endurance of the patches was estimated by repeatedly folding a small section of the patch (2 × 2 cm) at the same place until it cracked. The number of times through which the patch could be folded at the same place without producing any crack line presented the folding endurance value. Three patches from each batch were considered for performing the test.

Tensile strength

Transdermal patches were cut into 1 cm² size and placed between two clamps of the tensiometer. Weight was gradually added so that the increasing pulling force could break the film. The force needed to break the patch was recognized as tensile strength expressed in the unit kg/cm².

Water vapor transmission rate

The quantity of moisture transmitted through unit area of patch in unit time is expressed as the WVT rate. Glass vials of equal diameter and volume were used as transmission cells, which were washed thoroughly. After drying the vials in a hot air oven, about 1 g of anhydrous fused calcium chloride was taken in each vial, and the patch was affixed over the edge of the vial using a suitable sticking plaster. The weight of the vial was noted and kept in a desiccator comprising a saturated solution of potassium chloride for maintaining 84% relative humidity. These cells were removed from the desiccators after 24 hours and re-weighed. The water vapor transmission rate was determined as follows.

\[
\text{WVT rate} = \frac{\text{Weight of water vapor transmitted} \times \text{Thickness of patch}}{\text{Surface area exposed in square meters}}
\]

In vitro permeation studies

Modified Franz diffusion cell was employed to conduct in vitro permeation studies. Mixed cellulose ester membrane was used as a dialysis (barrier) membrane which was previously soaked in distilled water for 24 hours. The transdermal patches were adhered to the dialysis membrane and the membrane was tied firmly to the donor compartment of the diffusion cell. The receptor compartment of the diffusion cell was filled with 85 mL of phosphate buffer (pH 7.4). The donor compartment
was lowered to the receptor compartment in such a way that the dialysis membrane only touched the media of the receptor compartment. This assembly was constructed on a magnetic stirrer with a heater. Temperature of the receptor compartment was maintained at 37 ± 2°C. The content of the diffusion cell was continuously stirred using a teflon-coated bead at a constant speed of 600 rpm. Samples were taken at specified intervals of time and the same amount of phosphate buffer (pH 7.4) was added to maintain the sink condition. After suitable dilution, the samples were examined for percent drug content using UV-visible spectrophotometer at a wavelength of 275 nm. In vitro permeation study was conducted for 6 hours.

**Ex vivo skin permeation studies**

In ex vivo skin permeation studies, goat skin was used as a dialysis (barrier) membrane which was obtained from a local slaughterhouse. The skin was thoroughly cleaned with running tap water followed by eliminating full thickness and non-dermatome skin using a scalpel. It was then soaked in an isotonic solution for 30 min. Ex vivo permeation study was conducted for 12 hours. Procedure mentioned for in vitro permeation studies was followed for performing these studies.

**Drug release kinetics study**

Data obtained from in vitro and ex vivo permeation studies were fitted to different mathematical models such as zero order, first order, and Higuchi release kinetics to define the kinetics and pattern of drug release. Statistical analysis was not used in this study.

**RESULTS AND DISCUSSION**

**Identification of drugs**

Several monographic tests were performed (Table 3) to check the identity of tramadol hydrochloride. Obtained results matched satisfactorily with their corresponding specification required. Hence, monographic tests confirmed the identity of tramadol hydrochloride.

**Fourier transform infrared spectroscopy**

The drug and polymeric materials were found to be physically compatible with each other. The characteristic absorption peak obtained from FT-IR spectra of tramadol hydrochloride (Figure 1) resembled almost the same with the spectra of standard sample of that. It was evidently manifest that the individual characteristics bands of tramadol hydrochloride (Figure 1), and the polymers HPMC E5 (Figure 2), HPMC E15 (Figure 3), EC (Figure 4) at the particular wavenumbers were also present in the FT-IR spectra analyzed for the physical mixtures of the drug along with these polymers (Figure 5, Table 4). Interpretation from the FT-IR studies directed that the drug was pure and chemically compatible with the polymers used. HPMC, as a hydrophilic polymer and EC, as a water insoluble polymer were used in the formulations.

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**Table 3. Identification of drug by performing several monographic tests**

| Tests          | Obtained result                        |
|----------------|----------------------------------------|
| **Solubility** |                                        |
| In water       | Freely soluble                         |
| In methanol    | Freely soluble                         |
| In acetone     | Very slightly soluble                  |
| **Appearance of solution** |                          |
| A 5.0% (w/v) solution of tramadol hydrochloride | Clear and colorless |
| **Acidity**    |                                        |
| 0.2 mL of methyl red solution and 0.2 mL of 0.01 M hydrochloric acid were added to 10 mL of 5.0% (w/v) solution of tramadol hydrochloride | Red color solution was formed |
| A specified amount of 0.01 M sodium hydroxide is added to change the colour from red to yellow | A yellow color appeared after adding 0.3 mL |
| **Loss on drying** |                                      |
| 1.0 g Tramadol hydrochloride was dried in a hot air oven at 105°C for 3 h | 0.3% |
| Sulfated ash   | 0.087%                                 |
| **Assay**      |                                        |
| 0.18 g of tramadol hydrochloride was dissolved in 25 mL of anhydrous acetic acid and 10 mL of acetic anhydride. Then, it was titrated with 0.1 M perchloric acid. The end point is determined potentiometrically. A blank titration was then carried out (1 mL of 0.1 M perchloric acid is equivalent to 0.02998 g of tramadol hydrochloride) | 98.13% |
Evaluation of matrix type transdermal patches

Based on the observations found from the physical appearance of all batches (F1-F26) of transdermal patches (Table 5), only eleven batches were nominated for evaluation.

Physicochemical parameters

Thickness of the patches ranged from 0.47 to 0.57 mm (±0.003 to ±0.007) while the average weight of the patches varied from 289.89 to 558.16 mg (±0.40 to ±0.48) (Table 6). These minimum SD values assured that the method of preparation was skilled to develop patches with least intrabatch variability. Satisfactory
percentage of drug content with minimum SD value (Table 6) was found throughout all patches. Table 6 displays that increased amounts of HPMC caused an increase in the percentage of moisture content and moisture uptake of the transdermal patches due to hydrophilic properties of HPMC. Patel et al.\textsuperscript{23} reported that a higher percentage of HPMCs results in a higher moisture content. However, lower percentage of moisture content of the batches was capable of prevent the patches from microbial contamination and retarding their bulkiness. Flatness of the transdermal patches shown in Table 6 indicated a minimum level constriction just close to zero percent.\textsuperscript{1} Folding endurance value was found to be greater than 200 in all batches with minimum SD value (±0.51 to ±0.58) (Table 7) which proved that the prepared transdermal patches were flexible enough, able to withstand mechanical pressure and proficient to retain the integrity with skin folding after its application. From Tables 6 and 7, it was reported that decreasing in the thickness of the patches accomplished a higher folding endurance value. The patches containing higher amounts of HPMC showed greater tensile strength, whereas an increasing amount of EC lowered the strength. Limpongsa and Umprayn\textsuperscript{34} also reported that the addition of EC resulted in the lower tensile strength. Due to the hydrophilic properties of HPMC, the films containing a higher proportion of HPMC showed greater WVT rate and addition of EC lowered it.

**In vitro and ex vitro permeation studies**

Because of their long-term release pattern, only F14, F18, F23, and F26 batches were selected (Table 8) for ex vivo skin permeation and kinetics study. The results obtained from in vitro permeation studies showed controlled drug release as the concentration of EC decreased. The formulation F26 containing the higher amounts of HPMC E5, HPMC E15 as polymers

| Table 5. Physical appearance of the planned transdermal patches (F1-F26) |
|-----------------------------|---------------------------------|-----------------|
| Formulation code | Observation | Remarks |
| F1 | Patch was not formed | Rejected |
| F2 | Patch was formed, but became brittle on drying | Rejected |
| F3 | Patch was brittle; crystallization occurred on drying | Rejected |
| F4 | Patch was not formed | Rejected |
| F5 | Showed crystallization and enhanced brittleness | Rejected |
| F6 | Crystallization has occurred | Rejected |
| F7 | Patch was formed firmly | Selected |
| F8 | Patch was formed firmly | Selected |
| F9 | Patch was not formed | Rejected |
| F10 | Patch was formed, but crystallization occurred | Rejected |
| F11 | Better than F10, crystallization occurred in negligible amounts | Selected |
| F12 | Better than F10, crystallization occurred in negligible amounts | Selected |
| F13 | Patch was not formed | Rejected |
| F14 | Better than F11 and F12 | Selected |
| F15 | Patch was formed firmly | Selected |
| F16 | Patch was formed, but enhanced crystallization was found | Rejected |
| F17 | Patch was formed, but slightly brittle | Rejected |
| F18 | Patch was formed firmly | Selected |
| F19 | Patch was sticky | Rejected |
| F20 | Patch was sticky | Rejected |
| F21 | Patch was more brittle than F17 | Rejected |
| F22 | Patch was more brittle than F17 | Rejected |
| F23 | Patch was formed firmly | Selected |
| F24 | Patch was formed firmly | Selected |
| F25 | Better patch from all respects | Selected |
| F26 | Better patch from all respects | Selected |
### Table 6. Evaluation of physicochemical parameters of the selected transdermal patches

| Formulation code | Thickness* (mm) ± SD | Weight variation* (mg) ± SD | Drug content* (%) ± SD | Moisture content* (%) ± SD | Moisture uptake* (%) ± SD |
|------------------|----------------------|-----------------------------|-----------------------|---------------------------|-------------------------|
| F7               | 0.49 ± 0.006         | 289.89 ± 0.41               | 99.23 ± 0.79          | 1.19 ± 0.07               | 2.29 ± 0.07             |
| F8               | 0.57 ± 0.003         | 299.42 ± 0.41               | 99.33 ± 0.61          | 1.18 ± 0.05               | 2.28 ± 0.05             |
| F11              | 0.51 ± 0.004         | 299.91 ± 0.48               | 98.93 ± 0.77          | 1.29 ± 0.07               | 4.42 ± 0.03             |
| F12              | 0.51 ± 0.006         | 300.18 ± 0.40               | 99.13 ± 0.65          | 1.22 ± 0.07               | 4.34 ± 0.03             |
| F14              | 0.48 ± 0.006         | 398.77 ± 0.41               | 98.91 ± 0.78          | 1.81 ± 0.06               | 4.94 ± 0.03             |
| F15              | 0.55 ± 0.005         | 399.60 ± 0.43               | 99.09 ± 0.84          | 2.19 ± 0.04               | 6.76 ± 0.03             |
| F18              | 0.50 ± 0.003         | 434.47 ± 0.47               | 99.27 ± 0.81          | 2.56 ± 0.09               | 6.94 ± 0.03             |
| F23              | 0.56 ± 0.007         | 434.50 ± 0.43               | 99.40 ± 0.72          | 2.59 ± 0.05               | 6.97 ± 0.01             |
| F24              | 0.51 ± 0.006         | 443.53 ± 0.46               | 98.96 ± 0.76          | 2.58 ± 0.06               | 6.98 ± 0.02             |
| F25              | 0.53 ± 0.007         | 468.28 ± 0.47               | 99.02 ± 0.82          | 3.08 ± 0.06               | 7.81 ± 0.08             |
| F26              | 0.47 ± 0.004         | 558.16 ± 0.42               | 99.41 ± 0.60          | 3.52 ± 0.04               | 9.94 ± 0.03             |

All values are expressed as mean SD, \(^a\): 10, \(^b\): 5; SD: Standard deviation

### Table 7. Evaluation of physicochemical parameters of selected transdermal patches

| Formulation code | Flatness* (%) ± SD | Folding endurance* (%) ± SD | Tensile strength* (kg/cm\(^2\)) ± SD | WVT studies* (g/m\(^2\)/24 h) ± SD |
|------------------|-------------------|-----------------------------|-------------------------------------|-----------------------------------|
| F7               | 99.87 ± 0.002     | 202 ± 0.54                  | 0.51 ± 0.03                          | 1.84 ± 0.02                       |
| F8               | 99.88 ± 0.004     | 200 ± 0.55                  | 0.46 ± 0.05                          | 1.81 ± 0.01                       |
| F11              | 100.03 ± 0.004    | 201 ± 0.52                  | 0.63 ± 0.08                          | 1.93 ± 0.05                       |
| F12              | 99.91 ± 0.001     | 200 ± 0.58                  | 0.52 ± 0.02                          | 1.85 ± 0.07                       |
| F14              | 99.97 ± 0.003     | 205 ± 0.52                  | 0.57 ± 0.03                          | 1.91 ± 0.04                       |
| F15              | 100.07 ± 0.002    | 200 ± 0.56                  | 0.68 ± 0.01                          | 2.21 ± 0.08                       |
| F18              | 99.93 ± 0.001     | 201 ± 0.55                  | 0.70 ± 0.05                          | 2.29 ± 0.07                       |
| F23              | 99.89 ± 0.004     | 200 ± 0.57                  | 0.69 ± 0.04                          | 2.33 ± 0.08                       |
| F24              | 99.96 ± 0.002     | 200 ± 0.51                  | 0.69 ± 0.03                          | 2.31 ± 0.05                       |
| F25              | 100.00 ± 0.003    | 200 ± 0.57                  | 0.73 ± 0.06                          | 2.73 ± 0.04                       |
| F26              | 100.01 ± 0.001    | 207 ± 0.58                  | 0.87 ± 0.08                          | 3.12 ± 0.08                       |

All values are expressed as mean SD, \(^a\): 10, \(^b\): 5; SD: Standard deviation, WVT: Water vapor transmission

### Table 8. In vitro permeation study of matrix type transdermal patches

| Time (min) | Percentage cumulative drug release |
|------------|-----------------------------------|
|            | F7 | F8 | F11 | F12 | F14 | F15 | F18 | F23 | F24 | F25 | F26 |
| 0          | 0  | 0  | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   |
| 30         | 49.51 | 26.74 | 49.76 | 31.46 | 27.22 | 36.62 | 29.68 | 34.57 | 40.21 | 32.36 | 21.46 |
| 60         | 85.43 | 41.87 | 91.48 | 68.63 | 38.64 | 51.62 | 40.12 | 42.55 | 48.19 | 45.62 | 30.26 |
| 120        | 98.52 | 69.49 | 90.13 | 88.67 | 52.58 | 68.32 | 54.54 | 61.31 | 66.95 | 62.74 | 42.10 |
| 240        | 97.78 | 86.31 | -    | 87.31 | 69.83 | 87.82 | 72.46 | 80.35 | 83.56 | 85.12 | 60.28 |
| 360        | -   | 93.78 | -    | -    | 78.24 | 101.87 | 83.22 | 88.77 | 94.41 | 99.63 | 71.96 |
showed a rate regulatory drug-release pattern compared to the other formulations. As a plasticizer, effect of glycerol was most satisfactory with increased concentration of HPMC in the formulation F26, which showed the controlled in vitro drug release.

The effect of polymers and plasticizers on the results of ex vivo permeation studies was the same as the ingredients that influenced the results of in vitro permeation studies. Percentage cumulative drug release from the formulations was found to be more than 60% after 12 hours (Table 9), which was considered satisfactory. In vitro (Table 8) and ex vivo drug release profiles (Table 9) of the mentioned batches were fitted into different kinetic models (Figures 6 and 7). The data obtained from Table 10 explained that the selected batches except F23 were best fitted to Higuchi release kinetics for in vitro permeation studies. The rate of permeation of the drug through goat skin was slower and in a sustained manner compared to in vitro release profile. This could be explained by comparing the thickness of the goat skin membrane with that of dialysis membrane used. However, the data obtained from Table 11 clarified that the selected batches were best fitted to Higuchi release kinetics for ex vivo permeation studies.

### Table 9. Ex vivo permeation study of matrix type transdermal patches

| Time (min) | Percentage cumulative drug release (%) |
|------------|----------------------------------------|
|            | F14                 | F18                 | F23                 | F26                 |
| 0          | 0                   | 0                   | 0                   | 0                   |
| 30         | 11.15               | 15.87               | 19.67               | 12.78               |
| 60         | 20.88               | 24.83               | 28.56               | 18.42               |
| 120        | 34.82               | 35.78               | 45.71               | 29.25               |
| 240        | 52.07               | 52.776              | 58.51               | 42.17               |
| 360        | 60.48               | 63.98               | 69.87               | 50.11               |
| 480        | 68.61               | 72.66               | 80.78               | 57.26               |
| 720        | 71.98               | 75.87               | 83.71               | 65.51               |

### Table 10. Values of correlation coefficient of different kinetics models for in vitro permeation study

| Release kinetics | F14 | F18 | F23 | F26 |
|------------------|-----|-----|-----|-----|
| Zero order       | 0.840 | 0.849 | 0.827 | 0.905 |
| First order      | 0.964 | 0.980 | 0.984 | 0.983 |
| Higuchi          | 0.986 | 0.990 | 0.981 | 0.999 |

### Table 11. Values of the correlation coefficient of different kinetics model for ex vivo permeation study

| Release kinetics | F14 | F18 | F23 | F26 |
|------------------|-----|-----|-----|-----|
| Zero order       | 0.837 | 0.845 | 0.825 | 0.887 |
| First order      | 0.924 | 0.937 | 0.947 | 0.961 |
| Higuchi          | 0.969 | 0.978 | 0.973 | 0.993 |

**Figure 6.** Fitting the data obtained from in vitro permeation study to a different kinetics model.
Depending upon the results obtained from physicochemical evaluations performed and particularly based on the sustained release profile, F26 was designated as the optimized formulation. For this formulation, the best kinetics model was the Higuchi equation, whereas the plots exposed great linearity with highest \( R^2 \) values (Figures 6 and 7), suggesting the process of diffusion. Hence, it was confirmed that the formulation was capable of exhibiting matrix type drug delivery.

CONCLUSION
To achieve better bioavailability and improved patient compliance, optimized matrix type novel transdermal patches containing tramadol hydrochloride were developed with higher amounts of HPMC as rate regulating polymer. As per ex vivo drug release, the concern was that the optimized formulation permeated only 65.51% drug through goat skin within 12 hours (Table 9). This indicated a window for using a permeation enhancer in the formulation to improve the drug permeation rate through the goat skin. However, further ex vivo permeation studies must be conducted to determine the suitable permeation enhancer.

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