EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 12
Issue: 10
Year: 2025

DEVELOPMENT OF A SUSTAINED-RELEASE TRANSDERMAL SYSTEM FOR PAROXETINE

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DOI: https://doi.org/10.5281/zenodo.17221688

Article Received on 29/07/2025 **Article Revised on 28/08/2025** **Article Accepted on 08/09/2025**

ABSTRACT
Paroxetine, a selective serotonin reuptake inhibitor (SSRI), is associated with poor bioavailability due to extensive first-pass metabolism and gastrointestinal side effects when administered orally. This study aimed to develop sustained-release transdermal patches of paroxetine to overcome these limitations. Patches were prepared using hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and ethyl cellulose by solvent casting technique, and evaluated for physicochemical properties, folding endurance, tensile strength, moisture content, drug content uniformity, and in vitro release using Franz diffusion cells. FTIR confirmed drug–excipient compatibility, while calibration studies were conducted to standardize paroxetine estimation. The optimized formulation demonstrated desirable mechanical properties, uniform drug content, and sustained release over 24 h, best fitting Higuchi kinetics. This work highlights the potential of transdermal paroxetine delivery as a non-invasive, sustained-release alternative to oral therapy, potentially improving patient compliance and reducing systemic side effects.

KEYWORDS: Paroxetine, Transdermal patch, Sustained release, Drug delivery, Pharmacokinetics.

1. INTRODUCTION
Depression and anxiety disorders are among the most prevalent psychiatric conditions worldwide, affecting millions of individuals and contributing to substantial socioeconomic burden. Paroxetine, a selective serotonin reuptake inhibitor (SSRI), is frequently prescribed for the management of depression, generalized anxiety disorder, panic disorder, and related conditions. Despite its clinical efficacy, oral administration of paroxetine is associated with significant drawbacks, including extensive first-pass hepatic metabolism, gastrointestinal side effects, variable absorption, and short half-life, all of which can compromise therapeutic efficacy and patient adherence.

Transdermal drug delivery systems (TDDS) have emerged as a promising alternative to oral administration. By bypassing the gastrointestinal tract and hepatic first-pass metabolism, TDDS can enhance systemic bioavailability, reduce fluctuations in plasma drug concentrations, and minimize adverse gastrointestinal effects. Furthermore, sustained drug release from transdermal patches can improve patient compliance by reducing dosing frequency, an important consideration in chronic psychiatric conditions.

Advantages of TDDS
- First pass metabolism of drugs was altered at the site of action through treatment and it can deliver combination of drugs for a lengthened time period.
- It can achieve better patient compliance and can lessen the side effects in case of inter and intra-patient.
- Gastric and intestinal fluids degradation of drug may alter blood levels and thus difficult to control for longer period of time. The intravenous infusion release parameters of drug is proportional to TDDS.

Disadvantages of TDDS
- Application at site of action may be complicated.
- The drug having water solubility have low penetration rate

The characteristics of drug for TDDS
Drug contains various desirable properties i.e. physicochemical properties and biological properties.
Drug properties: The drug used for TDDS effect on the basis of physicochemical properties i.e. molecular weight. The mol weight of drug must be less than approx 1000 daltons with low melting point and it should be soluble in both lipophilic and hydrophilic media.

Dosing efficiency: The dose of the drug substances should be less as few mg/day on daily basis. It should have small half-life (t½) with non-skin irritation properties. Drug also should have non allergic reaction with less hepatic first-pass metabolism or not be degraded in the Gastro intestinal tract.

Transdermal patch

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. In this system medicated adhesive patches are prepared which deliver therapeutically effective amount of drug across the skin when it placed on skin. They are available in different sizes & having more than one ingredient. Once they apply on unbroken skin they deliver active ingredients into systemic circulation passing via skin barriers. A transdermal patch containing high dose of drug inside which is retained on the skin for prolonged period of time, which get enters into blood flow via diffusion process.

This study was undertaken to formulate and evaluate sustained-release paroxetine transdermal patches using polymeric matrices. The objectives included preformulation studies, patch development using solvent casting, physicochemical characterization, in vitro release evaluation, and kinetic modeling. The ultimate aim was to establish the feasibility of paroxetine transdermal delivery as a more effective and patient-friendly alternative to conventional oral formulations.

Figure. 1: Transdermal Patches.

2. MATERIALS AND METHODS

2.1 Materials

Paroxetine was used as the model drug. Hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and ethyl cellulose served as film-forming polymers. Plasticizers such as propylene glycol and dibutyl phthalate were used to enhance flexibility.

2.2 Preformulation Studies

Organoleptic evaluation, solubility determination, partition coefficient measurement, and melting point determination were performed. FTIR analysis was carried out to assess possible drug–excipient interactions.

2.3 Patch Preparation

Transdermal patches were prepared using the solvent casting method. Drug–polymer solutions were cast in Petri dishes, dried at controlled temperature, and peeled off to obtain uniform films.

2.4 Evaluation of Patches

- **Thickness** was measured using a micrometer screw gauge.
- **Folding endurance** was determined by repeated folding until breakage.
- **Tensile strength** was measured using a tensiometer.
- **Moisture content** was determined gravimetrically.
- **Drug content** was assessed spectrophotometrically.
- **In vitro drug release** was studied using Franz diffusion cells with phosphate buffer (pH 7.4) at 37°C.

2.5 Kinetic Modeling

Release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to identify the release mechanism.

3. RESULTS

3.1 FTIR Analysis

FTIR spectra confirmed the absence of significant drug–excipient interactions.

S. No.	Peak obtained	Reference peak	Functional group
1	3401	3400–3250	N–H stretch
2	3336	3300–2500	O–H stretch
3	1345	1320–1000	C–O stretch
4	803	1000–650	=C–H bend

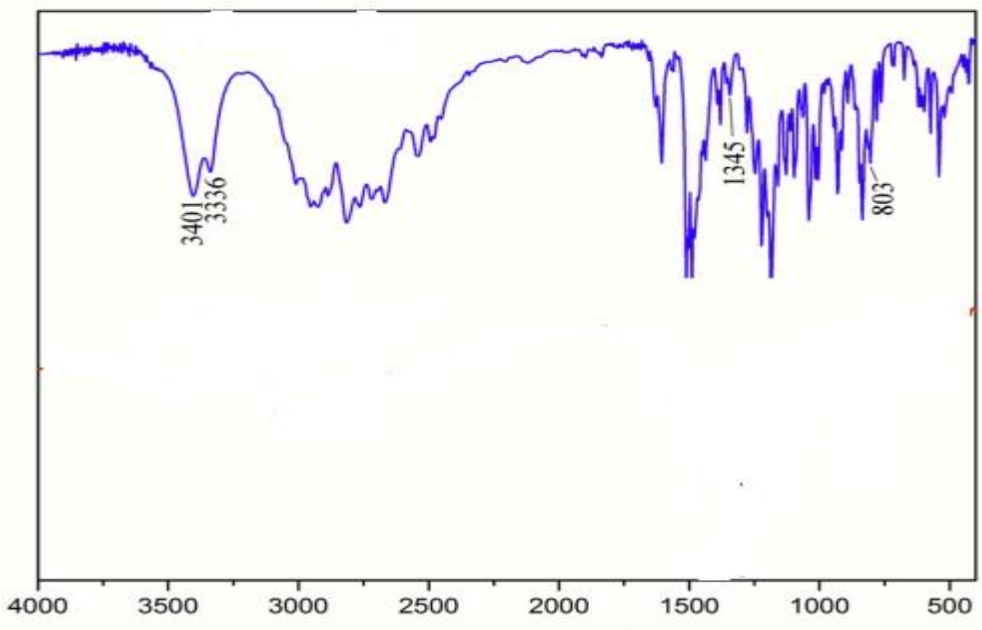

Figure 1: FTIR spectrum of paroxetine and polymer mixture.

3.2 Calibration Studies

The calibration curve of paroxetine in methanol showed linearity with a correlation coefficient close to 0.989, confirming reliability for drug estimation.

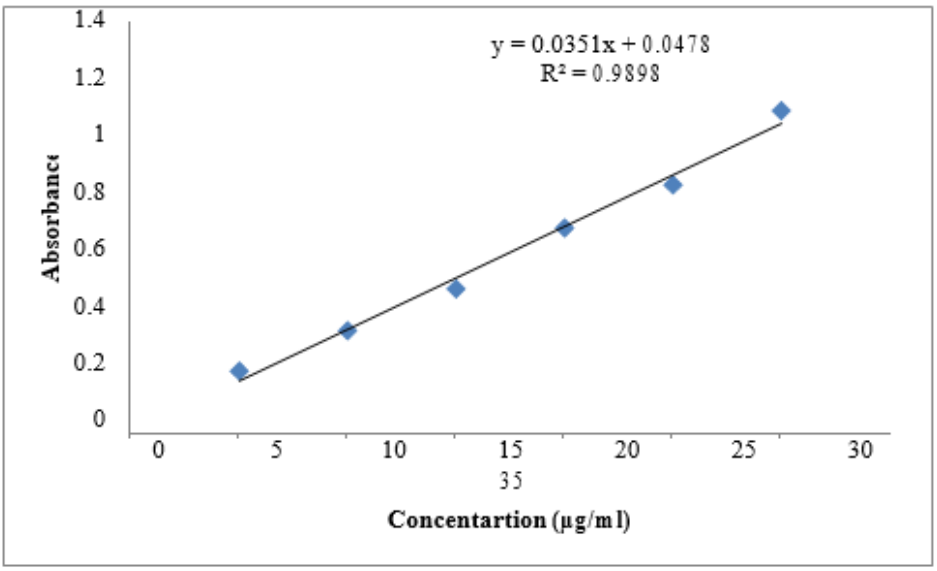

Figure 2: Calibration curve of paroxetine in methanol.

3.3 Physicochemical Evaluation

The prepared patches were evaluated for thickness, folding endurance, tensile strength, moisture content, and drug content. Results indicated uniform thickness, high folding endurance, and consistent drug loading.

Table 1: Physicochemical parameters of paroxetine patches (thickness, folding endurance, tensile strength).

S.No.	Evaluation parameters	Formulation batches					
		F1	F2	F3	F4	F5	F6
1	Folding endurance	25	48	57	85	44	52
2	Tensile strength kg/cm3	0.37	0.38	0.45	0.59	0.48	0.35
3	% elongation break test	42	35	23	25	22	41
4	Thickness (mm)	0.13	0.1.8	0.21	0.25	0.28	0.17
5	Drug content %	54.67	57.47	65.38	68.06	54.60	53.69
6	% moisture content	2.16	2.25	3.05	2.85	3.27	4.16

3.4 In Vitro Release Studies

The in vitro release profile of the optimized patch demonstrated sustained release up to 24 hours, with approximately 92% cumulative drug release.

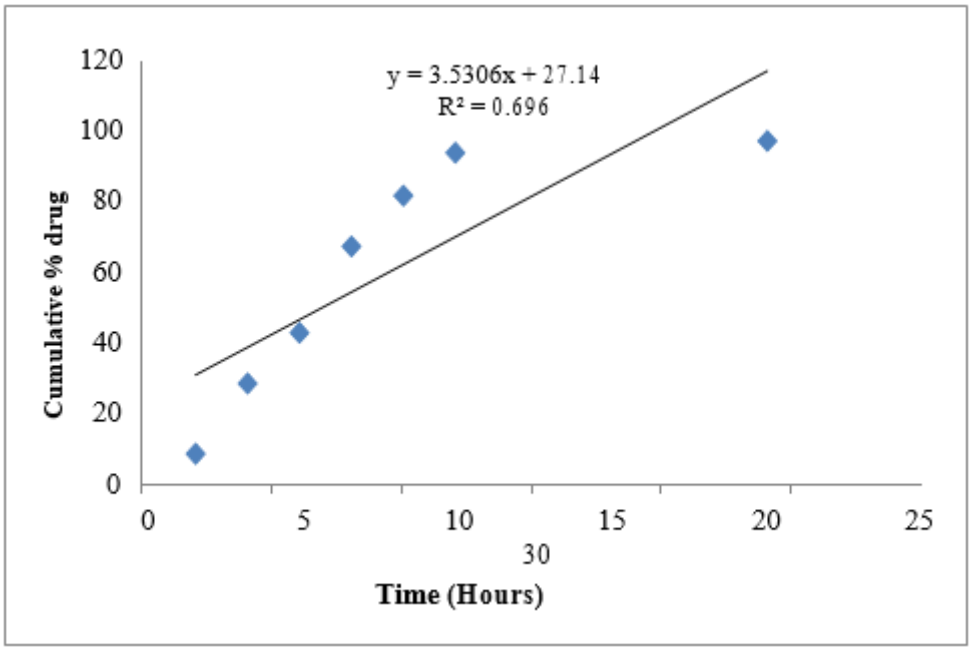

Figure 3: In vitro release profile of paroxetine patches.

3.5 Release Kinetics

Drug release data were fitted to various models. The optimized formulation showed the highest correlation with the Higuchi model, suggesting a diffusion-controlled release mechanism.

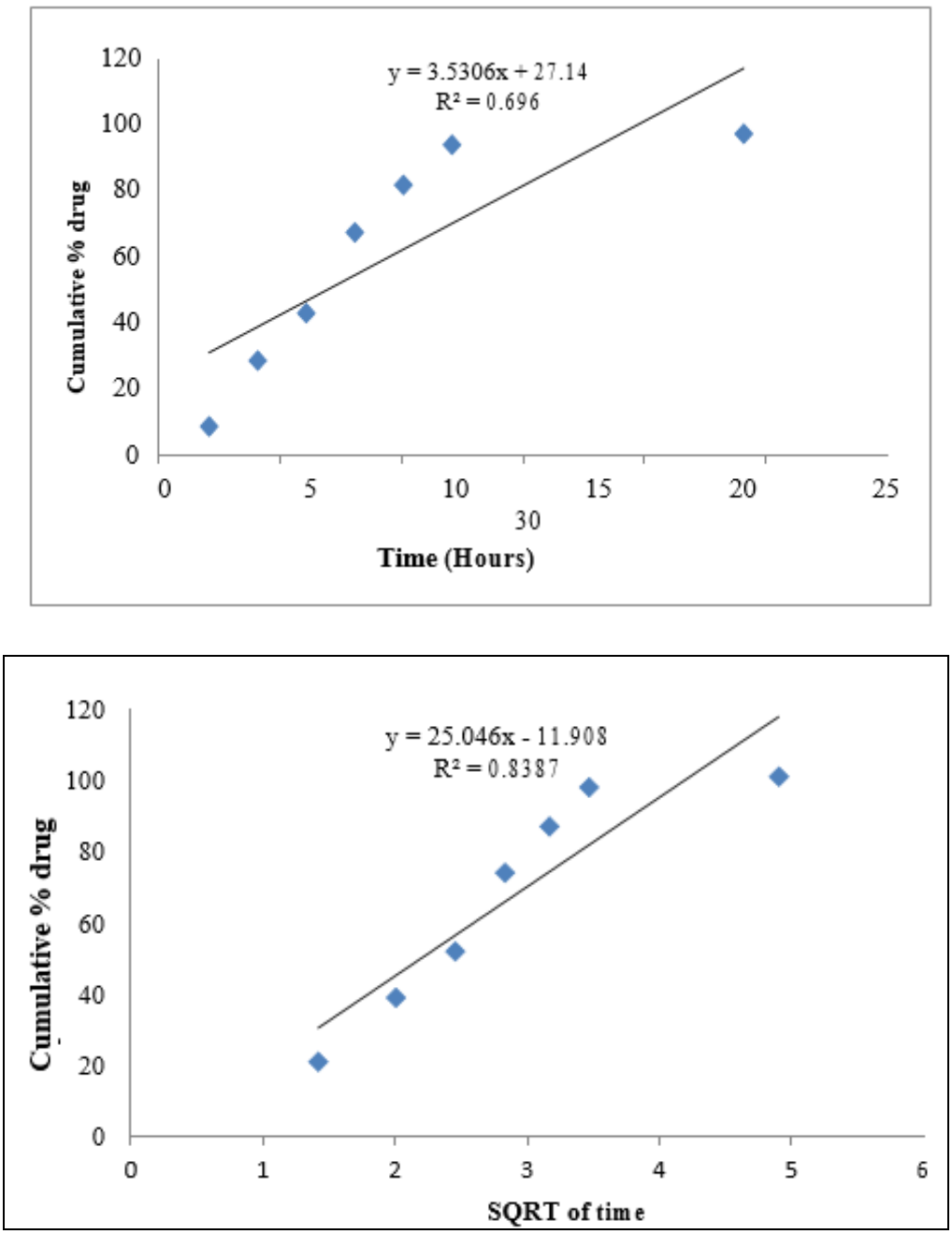

Figure 4: Higuchi plot for optimized paroxetine patch.

4. DISCUSSION

The paroxetine transdermal patches demonstrated desirable mechanical properties, with uniform thickness, good folding endurance, and adequate tensile strength. Drug content analysis confirmed uniform distribution of paroxetine across the patches, while moisture content remained within acceptable limits, ensuring stability.

FTIR spectra indicated no significant drug–excipient interactions, confirming the compatibility of paroxetine with the chosen polymers and plasticizers. The calibration curve demonstrated linearity and reliability for drug estimation, providing a strong analytical basis for further evaluation.

In vitro release studies revealed sustained drug release over a 24-hour period, with the optimized patch achieving approximately 92% cumulative release. Release kinetics analysis indicated that the data best fitted the Higuchi model ($R^2 > 0.95$), suggesting a diffusion-controlled mechanism of release. This aligns with findings reported for other polymeric matrix-based TDDS in the literature.

The ability to sustain drug release over 24 hours has significant clinical relevance for the management of depression and anxiety disorders, as it may reduce dosing frequency and improve adherence. Compared with oral administration, transdermal delivery of paroxetine could minimize gastrointestinal side effects, bypass first-pass

metabolism, and provide more stable plasma drug concentrations. Transdermal patches are patches that adhere to the skin as a way to deliver drugs. They provide a specific, predetermined dose of medication which is absorbed through the skin and into the bloodstream.

The transdermal patches of Paroxetine were prepared by solvent casting method using a combination of excipient like HPMC, Polyethylene glycol and propylene glycol as plastisizer and permeation enhancer.

Preformulation studies of the drug were performed first and the solubility of the drug was found to be it is freely soluble in ethanol and soluble in ethanol and distilled water.

The melting point and partition coefficient were determined by open capillary method and phase separation method. The melting point and partition coefficient of the drug were found to be 140ºC and 0.95.

The UV absorbance's of Paroxetine standard solution in the range of 5-30 µg/ml of drug in distilled water showed linearity at λ max 296 nm. The linearity was plotted for absorbance against concentration with R2 value 0.989 and with the slope equation y= 0.0351x + 0.0478.

The compatibility between the drug and other Excipient was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug- excipient mixture, which confirmed the absence of any chemical interaction between the drug, and other chemicals.

Paroxetine transdermal patches were prepared in six batches with varying the excipient and its amount and evaluated for different evaluating parameters.

The folding endurance values of all the batches of patches were performed and it is found satisfactory which indicates that the patches prepared using Polyethylene glycol in a concentration of 30% w/w of polymer were having optimum flexibility and were not brittle.

The % elongation of all the batches of formulation was performed and found to be in the range of 22 to 42%.

The drug content of all the prepared batches were performed and found in the range of 53.69 to 68.38%. All the formulations were acceptable with Paroxetine content. Among all the formulations F4 showed maximum drug content of 68%. The moisture content of all the formulations were evaluated and it is found in the ranged of 2.16 to 4.16%. The moisture content in the formulations was found to be increased by increase in the concentration of PVP and also with increasing the concentration of HPMC.

From all the evaluating parameters performed it is concluded that the formulation F4 was found to be the best formulation and it was chosen for drug release analysis and release kinetics studies.

5. CONCLUSION

Sustained-release paroxetine patches were successfully formulated and optimized using solvent casting. The patches exhibited desirable mechanical strength, uniform drug content, and extended release over 24 h, following Higuchi kinetics. These findings support the feasibility of transdermal delivery as an effective and patient-friendly alternative to oral paroxetine therapy.

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