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Research Article

# IN- VITRO CHARACTERIZATION OF MATRIX TYPE TRANSDERMAL DRUG DELIVERYSYSTEMS OF PAROXETINE HYDROCHLORIDE USING DIFFERENT PLASTICIZERS

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**ABSTRACT**

Transdermal drug delivery systems of Paroxetine hydrochloride have been formulated by using solvent casting method. Matrix type patches were prepared by using cellulose acetate butyrate(CAB) and ethyl cellulose (EC) polymers by incorporating polyethylene glycol 200, 400,600,DIbutyl phthalate and ethylene glycol as plasticizer, respectively Formulated transdermal patches were physically evaluated with regard to thickness, moisture content, moisture uptake, tensile strength**,** folding endurance, drug content and *In vitro* drug release study. All prepared formulations indicated good physical stability. The mercury substrate method was found to give thin uniform patches.*In-vitro* permeation studies of formulations were performed by using Franz diffusion cells. The results followed the release profile of Paroxetine hydrochloride followed mixed zero order and firstorder kinetics in different formulation. However, the release profile of the optimized formulations indicated that the permeation of the drug from the patches was governed by a diffusion mechanism. These results indicate that the formulation containing the F3 [CAB: EC (1:1) using PEG 600 as plasticizer] has shown optimum release in concentration independent manner.

**Keywords:** Transdermal film; *In-Vitro* permeation study; Paroxetine hydrochloride.

## INTRODUCTION

Transdermal delivery is one of the non-invasive methods for drug administration. Patient compliance is improved and continuous, sustained release of drug is achieved by following the application of transdermal formulation on the skin[1]. Transdermal drug delivery systems, known as patches, are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin in a predetermined time and controlled rate[2, 3].Transdermal drug delivery systems can be divided into three main groups: a) adhesive systems, in which the drug in adhesive, b) matrix type systems in which the drug in a matrix polymer and c) reservoir systems[4,5]. Although there are differences in the design of transdermal therapeutic systems, several features are common to all systems including the release liner, the pressure sensitive adhesive, and the backing layer[6].

There are four critical considerations in the selection of a transdermal drug deliverysystem: adhesion to skin, compatibility with skin, and physical or chemical stability oftotal formulation and components.The choice and design of polymers, adhesives,

penetration enhancers and plasticizers in transdermal patches are also critical because they have a strong effect on drug release, permeability, stability, elasticity, and wearing properties of transdermal drug delivery systems[7]. Formulation of polymeric patches for transdermal drug delivery system requires plasticizers. Plasticizers are added to polymeric system to modify their physical properties and to improve their film forming characteristics. Plasticizers can change the viscoelastic behaviour of polymers significantly. Plasticizers can turn a hard brittle polymer into a softer, more pliable material and possibly make it more resistant to mechanical stress[8].The plasticizer will interpose itself between the polymer chains and interact with the forces held together by extending and softening the polymer matrix[9]. The commonly used plasticizers include phthalate esters, phosphate esters, fatty acid esters and glycol derivatives[10].

Paroxetine hydrochloride is a selective serotonin reuptake inhibitor administered orally which undergoes extensive first pass metabolism. The drug produces gastrointestinal disturbances such as nausea, dry mouth, constipation, diarrhea, decreased appetite, etc. The long-term administration and fluctuation in plasma concentration of the drug causes severe side effects [11]. A transdermal delivery has been identified to overcome the difficulties of oral administration[12]. This route provides several advantages of controlled delivery, improved patient compliance, gradual dose reduction, prevention of overdose and decreased side effects. The effectiveness of transdermal delivery has been proved for some antidepressants[13,14].In the present investigation drug loaded patches of Cellulose Acetate Butyrate and Ethyl Cellulose in the ratio of 1:1 (CAB:EC)were formulated using different plasticizers viz. Polyethylene glycol 200, Polyethylene glycol 400, Polyethylene glycol 600, Dibutylphthalate and Ethylene glycol and evaluated. The effect of five different plasticizers on physicochemical properties of drug incorporated patches was also studied.

## MATERIALS AND METHODS

Paroxetine hydrochloride was gifted by ZydusCadila Healthcare Ltd, Padra, India. Cellulose Acetate Butyrate (CAB) and Ethyl Cellulose (EC) were procured from Sigma Aldrich, Polyethylene glycol (PEG) 200, Polyethylene glycol (PEG) 400, Polyethylene glycol (PEG) 600, Dibutyl Phthalate and Ethylene glycol were purchased from (S. D. Fine Chem. Ltd., Mumbai),were used. Cellophane membrane was purchased from Hymedia Laboratories Pvt. Ltd, Mumbai India All other chemicals used were of analytical grade.

### Fabrication of Blank Transdermal Patches

Solutions of polymer CAB: EC blend was prepared by dissolving in Dichloro methane solvent.. The above solution (15ml) was poured into a Petri dish and kept in an oven at 40° for complete drying. Films produced were allowed to dry in oven and then stored in desiccators.

### Preparation of drug incorporated transdermal patch

In the present study, drug loaded matrix type transdermal films of Paroxetine hydrochloride were prepared by solvent evaporation method[15-18].

### Formulation of Drug Incorporated Transdermal Patches[19-20]

Accurately weighed quantities of polymer combination were dissolved in required quantity of solvents namely dichloromethane in which drug and plasticizer have been added. The solution was mixed with magnetic stirrer to get homogeneous consistency. This was casted in a Petri dish; it was covered by funnel to control evaporation of solvent and allowed to dry at room temperature over night. The films were separated and the backing membrane used was aluminum foil and the formulations were stored in desiccators. The composition of patches prepared using Paroxetine hydrochloride is given in Table 1.

### Physicochemical evaluation

The films were evaluated for the following physicochemical properties:

### Physicochemicalcompatibility of drug and polymer

The physicochemical compatibility between Paroxetine hydrochloride and polymers used in the films wasstudied by using Fourier transform-infrared (FTIR- 8300, Shimadzu Co., Kyoto, Japan) spectroscopy. The pellatization was done by theKBr pellet method. The FT-IR spectra wererecorded in the wavelength region between 4000and 400 $cm^{-1}$. The spectra obtained for Paroxetine hydrochloride and physical mixtures of Paroxetine hydrochloride with polymerswere compared.

### Thickness[21]

The thickness of patches was measured at five different places using a micrometerscrew gauze and mean values were calculated.

**Weight variation study**[22]

The patches were subjected to weight variation by individually weighing five different randomly selected patches. Such determination was carried out for each formulation.

**Folding endurance**[23]

This was determined by repeatedly folding the film at the same place until it broke. The number of times the films could be folded at the same place without breaking/cracking gave the value of folding endurance.

**Drug content uniformity**

Transdermal patches with an area of $2cm^2$ was cut into small pieces and transferred into 100ml phosphate buffer (pH 7.4) and shaken for 6h to extract the drug. A blank was prepared using a drug-free patch treated similarly. The solutions were filtered through a 0.45µm membrane, diluted suitably and absorbance was measured at 242 nm in a UV-Vis Spectrophotometer (Shimadzu, Japan).

**Moisture content**[23]

The prepared films were marked, then weighed individually and kept in desiccators containing activated silica at room temperature for 24h. The films were weighed again, until constant weight is achieved. The % moisture content wascalculated as a difference between initial and final weight with respect to final weight.

$$\%\,\text{Moisture content (MC)} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}}$$

**Percentage moisture absorption**

The films were weighed accurately and placed in the desiccators containing 100mL of saturated solution of aluminum chloride, which maintains 79.50%RH. After, three days, the films were taken out and weighed. The percentage moisture absorption was calculated using the formula[24].

$$\text{Percentage moisture absorption} = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}}$$

**Percentage moisture loss**

The films were weighed accurately and kept in a desiccators containing anhydrous calcium chloride. After three days, the films were taken out and weighed. The moisture loss was calculated using the formula[24].

$$\text{Percentage moisture loss} = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}}$$

***In-vitro* drug release**

Modified Chien diffusion cell was used in our studies for *In-vitro* drug release. The cell consistsof two chambers, the donor and the receptor. The effective permeation area of the diffusion celland receptor volume was 3.14 sq.cm and 50 ml respectively. The donor compartment is open atthe top and is exposed to the atmosphere. The receptor compartment is surrounded by a waterjacket for maintaining the temperature at $37^{o}\pm 2^{o}$Cand is provided with a sampling port. Thediffusion medium was phosphate buffer of pH 7.4, which was stirred with Teflon coatedmagnetic bead (operated by a magnetic stirrer). A treated cellophane membrane was placed between the two chambers. Samples (2 ml) from the receptor compartment were taken at variousintervals of time over a period of 8 hours and the concentration of the drug was determined by UV Spectrophotometric method using the standard curve at 242nm. Amount of drug diffused atvarious time intervals was calculated and plotted against time[25].

**RESULT AND DISCUSSION**

**Physicochemical compatibility of drug and polymer**

The FT-IR spectral analysis of Paroxetine hydrochloride, Paroxetine hydrochloride incorporated CAB: EC and CAB: EC alone showed that the principalpeaks were observed (Figure.1-3) that confirming thecompatibility of the drug and polymer respectively.In the FT-IR spectra of the physical mixture of Paroxetine hydrochloride,

CAB: EC andCAB: EC the major peaks of Paroxetine hydrochloride were observed at. However, some additionalpeaks were observed with the physical mixture,possibly because of the presence of polymers.

The drug loaded patches of different plasticizers were prepared by solvent casting technique employing mercury as a substrate to explore their feasibility for transdermal application. Patches without plasticizer were smooth and transparent but were very brittle, and hence addition of plasticizer was found to be essential to improve the mechanical properties of placebo patches. Plasticizer shifts the glass transition temperature to lower temperature and is an important formulation factor. PEG 200,400,600 DBP and EG at a concentration of 40 % w/w of polymer were used as a plasticizer.Plasticizers at a concentration of 40 % was found to give good

flexible patches and easily removed without any rupture. The weight of the patches varied between 0.451 g to 0.477 g. All the formulations exhibited uniform weight with low standard deviation values. The thickness of the patches varied between 0.241 mm to 0.243 mm. The drug content of formulated films was found to be in the range of 8.32 to 9.73 mg per 3.14 $cm^2$ strip. CAB: EC polymer combination with DBP as plasticizer has maximum folding endurance while CAB: EC with PEG 200 showed least folding endurance. The tensile strength of the patches was found to vary with the nature of polymer and plasticizer. A soft and weak polymer is characterized by low tensile strength and low elongation, a hard and brittle polymer is defined by a moderate tensile strength and low elongation, and a soft and tough polymer is characterized by moderate tensile strength and high elongation, whereas a hard and tough polymer is characterized by high tensile strength and high elongation. Polymer combination CAB: EC plasticized with DBP possessed high tensile strength while polymers plasticized with PEG 600 possessed low tensile strength. Among the plasticizers the tensile strength of the patches decreased in the following order DBP>EG>PEG200>PEG400>PEG600.

Physical studies conducted on different polymeric patches favored the combination of these polymers with different plasticizers for the preparation of transdermal patches.The results of physicochemical parameters are showed in Table 2 & 3.The *In vitro* permeation data across treated cellophane membrane showed anomalous diffusion transport and its release mechanism can be said to followsfirst order kinetics (figures 4-8)The cumulative amount of Paroxetine hydrochloride released from different polymeric films was found to be between 7.061 to 8..98 mg in 24hrs using treated cellophane membrane. The formulation no.F3 (CAB: EC PEG 600) have showed optimum release (98.42 %) in 24hrs using treated cellophane membrane. All he formulations showed an optimum release of about 98 % drug mg in 24 hrs. However the release profile of formulation F3 showed the release of the drug in a controlled manner.

## CONCLUSION

In the present investigation an attempt has been made to design and develop the formulation of Paroxetine hydrochloride patches using different types of plasticizers by solvent evaporation technique and mercury substrate method. Paroxetine hydrochloride was successfully formulated as controlled release transdermal patches, which prevents the frequency of administration and gives good patient compliance.From the experimental results obtained, F-3formulation can be selected as the best formulation among all the other formulations. The *in-vitro* drug diffusion study from the formulation was found to be controlled release. All the evaluation parameters obtained from the best formulation were found to be satisfactory.The data obtained from the *in-vitro* release studies were fitted to zero order kinetic models, from the kinetic data it was found that drug release follows zero order release by diffusion technique from the polymer. Based on the observations, it can be concluded that the attempt of formulation and evaluation of theParoxetine hydrochloride patches was found to be successful in the release of the drug for an extended period of 24 hrs.Further, *in vivo*studies have to be performed to correlate with *invitro* release data for the development of suitablecontrolled release patches for Paroxetine hydrochloride.

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**Table 1: Composition of different formulations containing Paroxetine Hydrochloride**

| Formulation code | Paroxetine HCL(mg) | Polymer (1:1) | Plasticizer 30% (w/w) | Solvent |
|---|---|---|---|---|
| F1 | 150 | CAB:EC | PEG-200 | Dichloromethane |
| F2 | 150 | CAB:EC | PEG-400 | Dichloromethane |
| F3 | 150 | CAB:EC | PEG-600 | Dichloromethane |
| F4 | 150 | CAB:EC | DBP | Dichloromethane |
| F5 | 150 | CAB:EC | EG | Dichloromethane |

**Table 2: Results of Thickness (mm), Weight uniformity (g), Folding endurance, % Moisture absorption, %Moisture loss,**

| Formulation code | Thickness (mm) | Weight (gm) | Folding endurance | Moisture absorption (%) | Moisture loss (%) |
|---|---|---|---|---|---|
| F1 | 0.242±0.012 | 0.469±0.016 | 310±2.0 | 4.78±0.15 | 5.97±0.15 |
| F2 | 0..243±0.010 | 0.456±0.022 | 337±3.0 | 4.17±0.15 | 5.62±0.15 |
| F3 | 0.242±0.010 | 0.477±0.003 | 362±3.0 | 7.12±0.28 | 6.58±0.15 |
| F4 | 0.242±0.012 | 0.461±0.012 | 328±4.0 | 3.48.±0.15 | 5.75±0.15 |
| F5 | 0.241±0.010 | 0.451±0.005 | 318±2.0 | 5.23±0.15 | 6.09±0.15 |

All values are given in (mean ± SD) for n = 3.

**Table 3: Results of tensile strength, drug content and *in vitro* drug release**

| Formulation code | Tensile strength (kg/mm$^2$) | Drug content (%) | % Drug released |
|---|---|---|---|
| F1 | 2.42±0.016 | 96.41±0.30 | 98.157(up to 24 hrs) |
| F2 | 2.89±0.024 | 96.16±0.25 | 95.651(up to 24 hrs) |
| F3 | 2.04±0.036 | 94.67±0.17 | 96.317(up to 24 hrs) |
| F4 | 2.55±0.014 | 95.94±0.37 | 91.866(up to 24 hrs) |
| F5 | 2.76±0.013 | 94.22±0.30 | 94.546(up to 24 hrs) |

All values are given in (mean ± SD) for n = 3

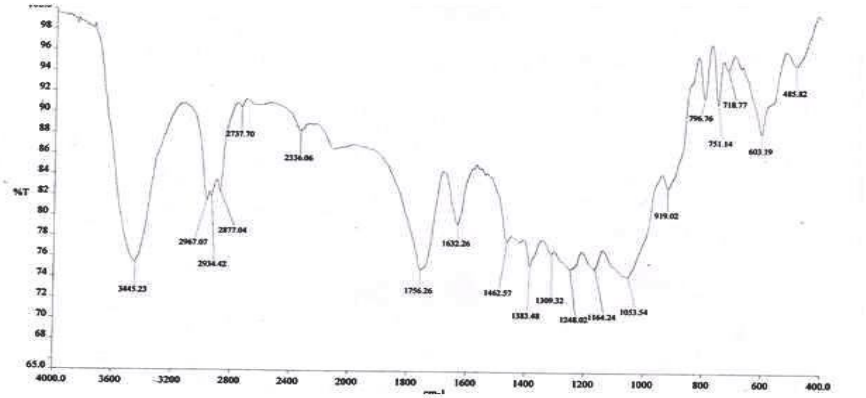


**Fig. 1: FT-IR Spectra of Polymer**

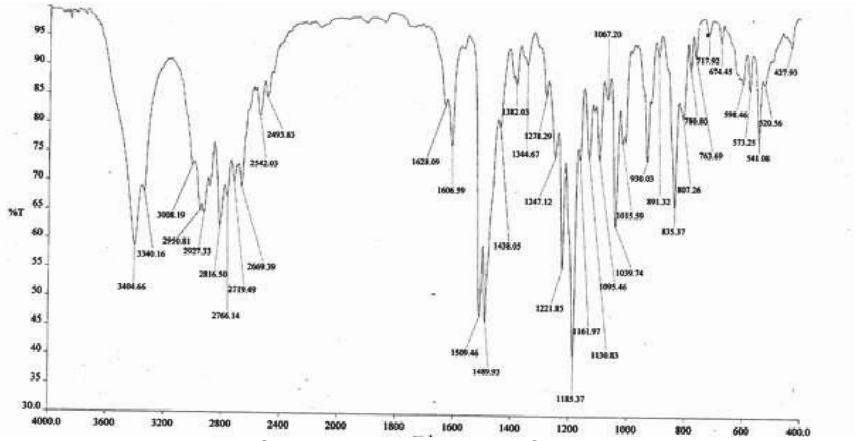


**Fig. 2: FT-IR Spectra of Drug**

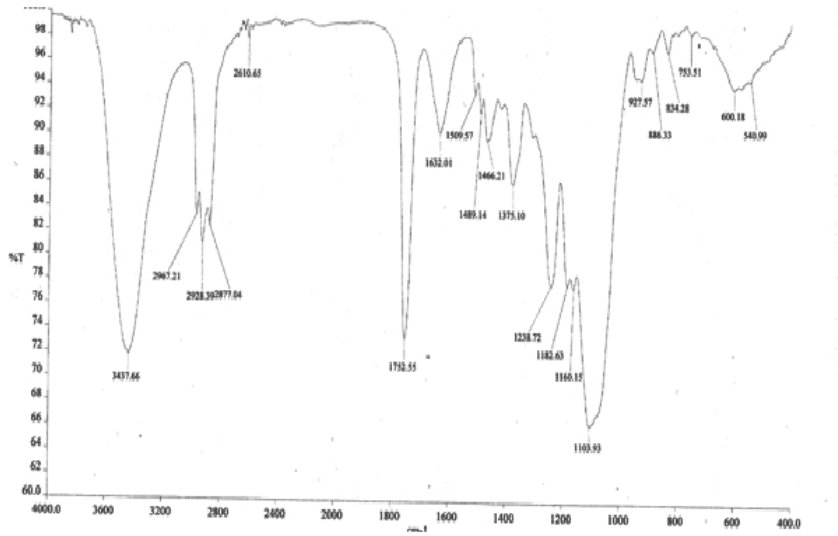


**Fig. 3: FT-IR Spectra of drug and polymer**

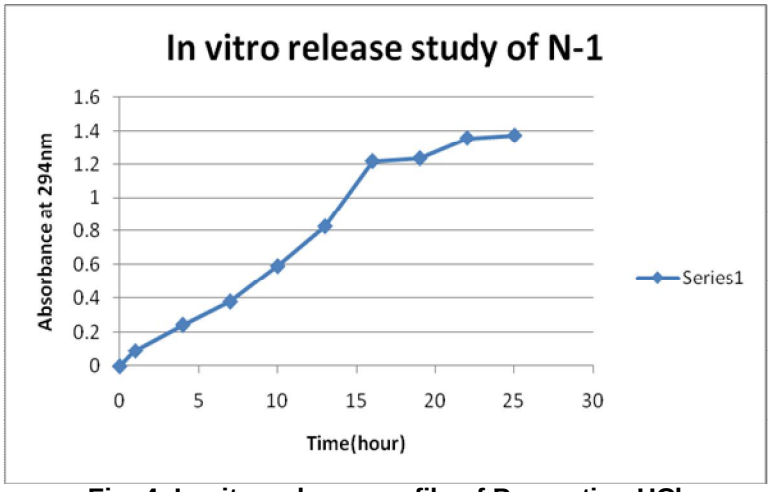


**Fig. 4: In-vitro release profile of Paroxetine HCl transdermal patches (N1)**

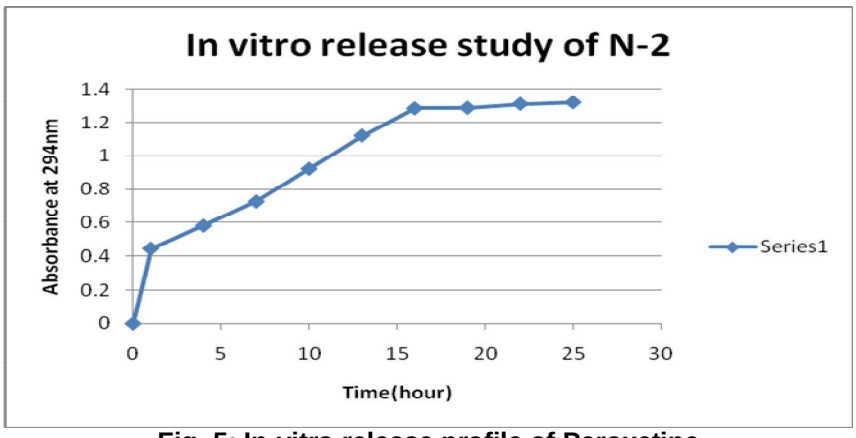


**Fig. 5: In-vitro release profile of Paroxetine HCl transdermal patches (N2)**

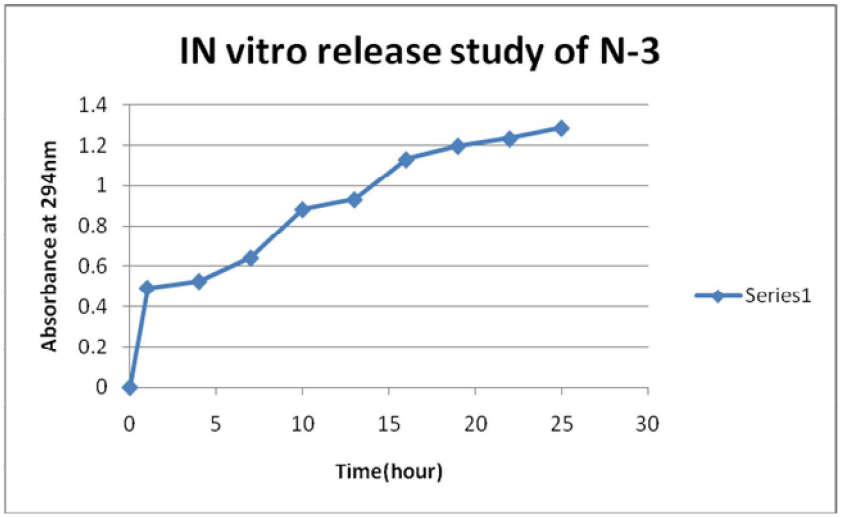


**Fig. 6: In-vitro release profile of Paroxetine HCl transdermal patches (N3)**

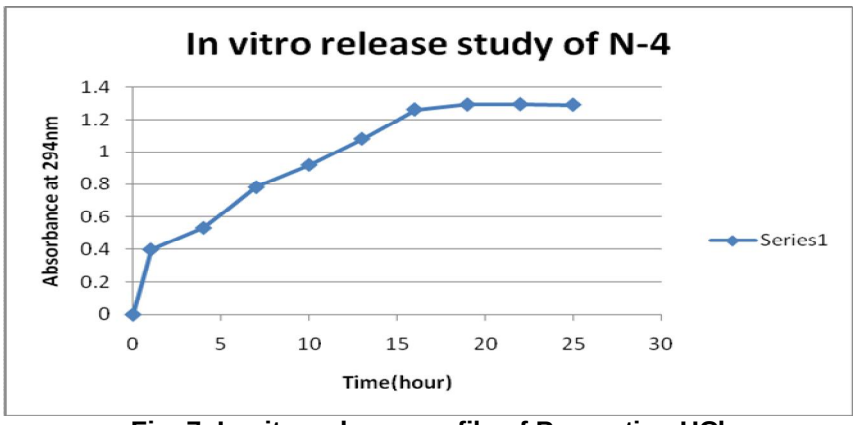


**Fig. 7: In-vitro release profile of Paroxetine HCl transdermal patches (N4)**

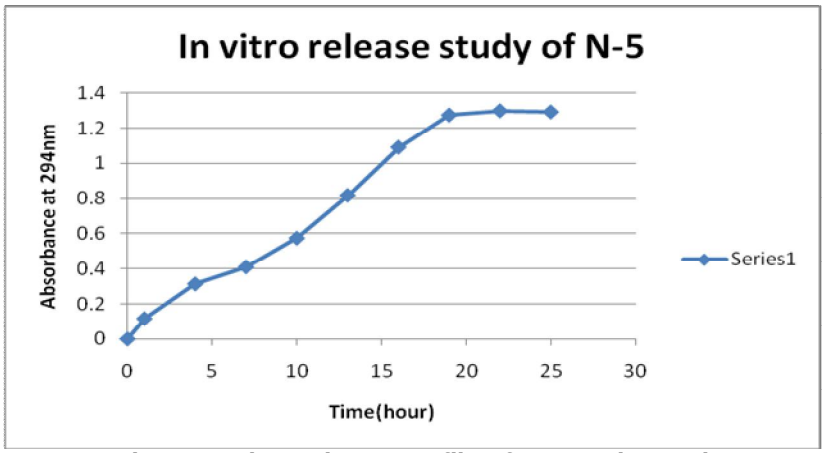


**Fig. 8: In-vitro release profile of Paroxetine HCl transdermal patches (N5)**

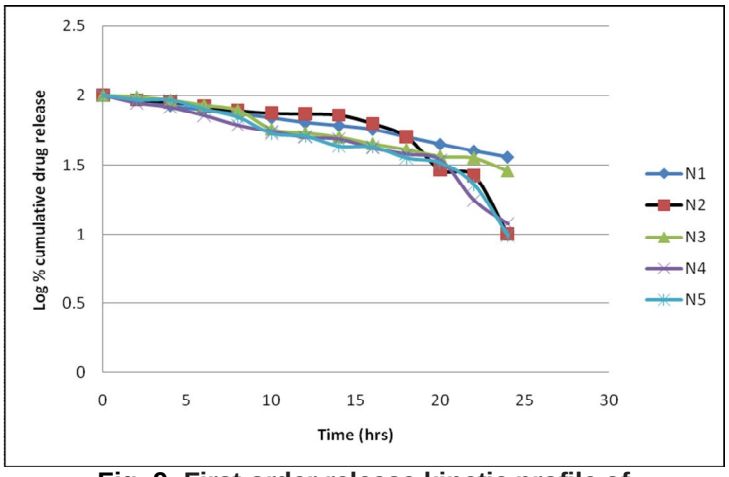


**Fig. 9: First order release kinetic profile of Paroxetine HClTDDS**

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