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Formulation and Characterization of Antiemetic Patch Comprising Scopolamine

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ABSTRACT

Transdermal drug delivery is an effective method for controlled drug release, offering several advantages. It allows for safe and pain-free self-administration, making it suitable for poly-medicated patients and those with difficulty swallowing or constipation. Transdermal patches provide a constant, prolonged release of medication, avoiding the fluctuations associated with oral or parenteral dosing. They also enhance the therapeutic effects of drugs by bypassing issues like pre-systemic metabolism and gastrointestinal irritation. This method is particularly beneficial for short half-life drugs, reducing variability in patient response and ensuring safety in hepatocompromised patients.Additionally, transdermal systems are cost-effective and user-friendly, offering a high level of patient acceptance. They are particularly suitable for long-term treatments, such as chronic pain management and hormone replacement therapy. The ability to stop drug input by removing the patch adds to their appeal.However, transdermal drug delivery has limitations. It requires drugs with specific physicochemical properties and is not suitable for large daily doses. Careful consideration of clinical need is essential, as local irritation and skin dermatitis can occur. Skin's barrier function varies among individuals and locations, limiting the range of drugs that can be delivered this way. Highly potent, ionic, or large molecular size drugs are not suitable for transdermal delivery. The objective of this study is to formulate a transdermal patch containing scopolamine as the active ingredient for the effective prevention and treatment of nausea and vomiting, with a specific focus on motion sickness and to characterize the key physicochemical properties and in vitro release profile of the scopolamine antiemetic patch to ensure its stability and consistent drug delivery.

Keywords: Antiemetic drug,Transdermal Patch,Sustained drug delivery,Scopolamine,Preformulation

INTRODUCTION

1.1 CONTROLLED DRUG DELIVERY

Treatments of acute and chronic diseases have been accomplished by the delivery of drugs to patients using various pharmaceutical dosage forms. These dosage forms are known to provide a prompt release of the drug. But recently several technical advancements have been done and resulted in new techniques for drug delivery. These techniques are capable of controlling the rate of drug release[1]. The term-controlled release has a meaning that goes beyond the scope of sustained release. The release of drug ingredients from a controlled release drug delivery advances at a rate profile that is not only predictable kinetically but also reproducible from one unit to another.

CLASSIFICATION OF CONTROLLED DRUG DELIVERY

- Activation-modulated drug delivery systems
- Feedback-regulated drug delivery systems
- Site-targeting drug delivery systems
- Rate-preprogrammed drug delivery systems

Out of these classes, the first class contains new drug delivery systems such as transdermal delivery, intra-uterine delivery, ocular inserts, and subdermal implants. Transdermal drug delivery has the advantage to deliver medicines via skin to systemic circulation at a predetermined rate and maintain therapeutic concentration for a prolonged period.

The idea of delivering drugs through the skin is old, as the use is reported back in the 16th century B.C. The husk of castor oil plant in water was placed on an aching head[2]. Today transdermal drug delivery is well-accepted for delivering drugs to systemic circulation.

Until recently, the use of transdermal patches for pharmaceuticals has been limited because only a few drugs have proven effective delivered through the skin — typically cardiac drugs such as nitroglycerin and hormones such as estrogen. A skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. The basic components of any transdermal delivery system include the drug(s) dissolved or dispersed in a reservoir or inert polymer matrix; an outer backing film of paper, plastic, or foil; and a pressure-sensitive adhesive that anchors the patch to the skin[3]. The adhesive is covered by a release liner, which needs to be peeled off before applying the patch to the skin.

Transdermal drug delivery systems have the following benefits:[4]

- Transdermal drug delivery provides safe, useful, and pain-free self-administration for patients.
- Transdermal drug delivery may be useful in those patients who are poly-medicated.
- Transdermal drug delivery provides a constant rate of release of medicine to maintain the concentration level of drugs for a longer period to avoid peak and valley associated with oral dosing and parenteral administration.
- Transdermal patches enhanced the therapeutic effects of various drugs by avoiding specific problems associated with drugs such as pre-systemic metabolism, the formation of toxic metabolites, gastrointestinal irritation, low absorption, etc.
- Useful drugs possess short half-life to avoid the frequency of dosing administration.
- Reduced inter & interpatient variability by simplified medication regimen.
- The Greater advantage in those patients who are dysphagia (Difficulty swallowing foods or liquids), unconscious), or constipation.
- Elimination of pre-systemic metabolism results in a decrease in the amount of drug administered, resulting in the reduction of adverse effects and thus safer in hepatocompromised patients.
- Fruitful mainly when long-term treatment is required, as in chronic pain treatment example hormone replacement, etc, and smoking cessation therapy.
- The drug input can be stopped at any point in time by removing the transdermal system.
- The transdermal systems are usually low-cost and economical when compared with other treatments on a cost basis, as patches are planned to deliver drugs from one to seven days.
- The common acceptability of transdermal formulation by patients is extremely high, which is also proved by the improving market for transdermal products.
- Topical patches are easier to use and keep in mind.
- Topical patches are optional for people who cannot or prefer not to take medications or supplements orally route.
- Provide a large area of drug application in comparison with the buccal drug delivery or nasal cavity drug delivery.

Limitations

- The drug moiety must possess several physicochemical properties for penetration through the skin and if a dose of the drug is large i.e., more than 10- 25 mg/day transdermal delivery is difficult. The daily dose of the drug chosen is less than 5 mg/day.
- Clinical need is another area that must be examined carefully before a decision is made to develop a transdermal product.
- Local irritation at the place of administration such as local edema, erythema itching, and may be caused by the drug or the additive used in the formulations.
- Several patients develop contact skin irritation (dermatitis) at the location of application due to system components.
- The barrier function of the human skin changes from one site to another, from person to person, and with age.
- A high-level drug amount cannot achieve by a transdermal drug delivery system.
- Weak skin permeability limits the number of medicines that can be passed through in this manner.
- The Transdermal drug delivery system is inhibited by a potent drug.
- The transdermal drug delivery is incapable to deliver ionic drugs.
- Required significant lag time.

The large molecular size (>1000 Dalton) drug molecule cannot be formulated for transdermal delivery. Generally, use in drugs with a molecular size of 500 Dalton.

1.3 METHODS TO ENHANCE TRANSDERMAL DRUG DELIVERY

In addition to chemical means, some physical methods are being used to enhance transdermal drug delivery and penetration, such as Iontophoresis and Sonophoresis

1. 1.3.1 Iontophoresis

Iontophoretic is the delivery of charged chemical compounds across the skin membrane using an electrical field. Several drugs have been the subjects of iontophoretic studies; they include Lidocaine, Dexamethasone, amino acids, peptides, insulin, verapamil, and propranolol. There is particular interest to develop alternative routes for biologically active peptides. At present peptides are delivered by injection because of their rapid metabolism and poor absorption after oral delivery. They are poorly absorbed by the transdermal route because of their large molecular size ionic character and general impermeability of the skin. However, iontophoresis enhanced transdermal drug delivery has shown some promise as a means of peptide and protein administration.

1.3.2 Sonophoresis

It is also being studied as a means to enhance transdermal drug delivery. Among the agents examined are hydrocortisone, Lidocaine, and salicylic acid in formulations such as gels, and creams.

Electroporation

Skin electroporation has recently been shown to increase transdermal transport of small-size drugs as well as considerably larger molecules by up to 4 orders of magnitude in vitro. Nevertheless, no in vivo studies have proven that high-voltage pulses can induce therapeutic plasma levels of the drug. Thus, the study of the potential of skin electroporation in transdermal delivery of fentanyl was done in vivo[8]. The transdermal transport of timolol through the human stratum corneum was studied in three- compartment diffusion cells. The electrodes, buffer composition, and pulse conditions were optimized to study the effect of skin electroporation to achieve therapeutic fluxes

of timolol. Electroporation enhanced the transdermal transport of timolol by 1-2 orders of magnitude as compared to passive diffusion. Therapeutic fluxes of timolol (>50 mg/cm2/h) through human stratum corneum were achieved by electroporation.

1.4 IDEAL MOLECULAR PROPERTIES FOR TRANSDERMAL DELIVERY:

From the above considerations, we can conclude with some observations that can be termed ideal molecular properties for drug penetration[5].

The partition coefficient will be high if the molecular weight is less than 600 Daltons. An adequate solubility in lipids and water is necessary for better penetration of the drug. (1mg/ml)

An optimum partition coefficient is required for good therapeutic action Low melting point of the drug is desired. (<200°C) The pH of the saturated solution should be between 5 to 9.

The potent drug with a dose of 10-15 mg/day is desired.

2. MATERIAL AND METHODS

Material used in the investigation

Materials used in the present investigation are listed in Table 1

Table 1: Materials used for formulation development of transdermal patch

Sr. No.	Chemicals	Supplier
1.	Scopolamine	(Gift sample from Bioplus Life Science, Bangalore)
2.	HPMC	Ozone International, Mumbai
3.	RLPO	Evonic industries
4.	RSPO	Evonic industries
5.	PEG	Thomas beker (chemical)
6.	Disodium Hydrogen Phosphate	S. D. Fine Chem. Ltd., Mumbai
7.	Sodium Chloride	S. D. Fine Chem. Ltd., Mumbai
8.	Methanol	Qualigens Fine Chemicals, Mumbai

9.	Ethanol	Qualigens Fine Chemicals, Mumbai
10.	Chloroform	Qualigens Fine Chemicals, Mumbai

2.1 Instruments used in the investigation

The instruments used in the present investigation are listed in Table 2.

Table 2: Instruments used for the preparation and evaluation of transdermal patch

Sr. No.	Instrument / Apparatus	Supplier
1.	UV-Visible Spectrophotometer	Labindia 3000+ Mumbai
2.	Fourier Transform Infra- Red Spectroscopy	Brucker, Alpha, Germany
3.	pH Meter	Electronic India
4.	Electronic Balance	Wensor, India
5.	Melting Point Apparatus	Chemline CL-725
6.	Hot Air Oven	Electronic India
7.	Sonicator	Electronic India
8.	Dissolution Testing Apparatus	Labindia DS- 8000 Mumbai
9.	Vortex Apparatus	Ambros Lab Equipments, Ambala

2.2 Preformulation studies

In 1950 and the beginning of 1960, Preformulation investigations were developed. The first stage in the logical creation of dosage forms for a pharmacological substance is pre formulation testing. It is the examination of the physical and chemical characteristics of a drug ingredient both on its own and in combination with excipients. Reformulation testing's main goal is to produce data that the formulator can utilize to create stable, bioavailable dosage forms that can be mass manufactured. Preformulation studies are made to provide the required information, particularly on the physical, chemical, mechanical, and biological characteristics of drug ingredients, excipients, and packaging components .

2.3. Preformulation during drug discovery

Preformulation studies not only aid in formulation development but also lead to identification during the early stages of drug research. To become a therapeutic molecule, a novel chemical entity must have the best biopharmaceutical qualities. 'Drug ability' is not always implied by the mere presence of potency and selectivity. Preformulation studies aid in determining a molecule's "drug ability." Thus, preformulation may be viewed as a crucial decision-making tool both throughout the drug discovery phase and the development phase. Thorough knowledge of physicochemical characteristics and how they affect biological performance enables the choice of possible lead molecules and the detection of drug delivery difficulties.

Objectives:

- To develop elegant dosage forms (stable, effective & safe)
- It is important to have an understanding of the physical description of a drug substance before dosage form development.
- It is 1ststep in the rational development of a dosage form of a drug suit before dosage form development.

Goals:

- To establish the physicochemical parameters of the new drug substance.
- To establish the physical characteristics.
- To establish compatibility with the common excipient

2.4 Preformulation characteristics:

The following properties of active pharmaceutical ingredients (API) were investigated;

- Organoleptic properties
- Solubility Analysis
- Loss on drying

- Melting point
- UV Spectrophotometric analysis
- FTIR spectroscopy

Organoleptic properties:

The drug substance's organoleptic characteristics are crucial for creating the dosage form. The drug's testing, color, and odor are described.

Solubility Analysis:

Solubility, particularly water solubility, is a significant physical-chemical characteristic of a medicinal compound. For a medication to be therapeutically effective in the physiological pH range of 1 to 8, considerable water solubility is required.

Table 3: IP Index

Descriptive term	**Parts of solvent required for Parts of soluble**
Very soluble	Less than 1
Freely soluble	From 1to 10
Soluble	From 10 to 30
Sparingly soluble	From 30to 100
slightly soluble	From 100 to1000
Very slightly soluble	From 1000 to 10000
Practically insoluble	10000 or more

5 mg of Scopolamine was added to 10 ml of each solvent in a test tube and agitated for a few minutes at room temperature (21±1.5°C) to determine how well Scopolamine dissolved in each solvent, which included methanol, ethanol, chloroform, and distilled water, among others.

Loss on drying (%)

Loss on drying is the weight loss, given as a percentage of weight, brought on by water and any volatile material that can be driven out under certain circumstances.

IR moisture balance provided a direct measurement of loss due to drying. First, adjust the knob to calibrate the instrument. Next, take 5g of powder and fix the temperature at 100 to 105^{0}C for 15 minutes while maintaining a continuous reading. Finally, adjust the knob and verify the percentage of moisture.

$$\text{Loss on drying (\%)} = \frac{\text{initial weight of sample - weight of sample after drying x 100}}{\text{Initial weight of sample}}$$

Melting point

Scopolamine's melting point was established using the open capillary method by melting point equipment. A glass capillary tube with a sealed end was filled with the drug's fine powder. The capillary tube was fastened to the thermometer, which was then placed inside the Illies tube apparatus. The temperature of the equipment was then gradually raised, and the temperature at which the drug entirely melted was recorded. The drug's actual melting point and melting points reported in the literature were compared.

Determination of UV-visible absorption maxima of Scopolamine:

Preparation of standard solutions A standard stock solution of Scopolamine was prepared by dissolving 10 mg (accurately weighed) of the standard Scopolamine in 10 ml of methanol. This stock the solution was further diluted to get working standard solutions of 10µg/ml. Aliquots (0.05, 0.1, 0.15, 0.2, 0.25ml) of working standard solution were transferred into a series of 10 ml volumetric flasks to get the desired concentration range for calibration curve. The volumes were made up of phosphate buffer pH 7.4.

FTIR spectroscopy of Scopolamine

The purity of pure drug was determined by I.R. Approximately 10 mg of Scopolamine was triturated with 5mg of dried potassium bromide (KBr) in agate mortar. Pellet was prepared by using the KBr press pellet method [66]. Pellet was scanned between the ranges of 4000 to 400cm-1 with background correction. The spectrum was recorded and major peaks were determined.

Development of transdermal patches

- **Preparation of blank patches:**

Preparation of blank patches previously described method. In this method. Combinations of precisely weighed polymers were dissolved in their respective solvents (chloroform and methanol in a 1:1 v/v ratio) and then added to a Petri dish with glycerin on a flat surface. After that, the film dried overnight at room temperature.

- **Preparation of rate-controlling membrane**

The creation of rate-controlling membranes involved the usage of eudragit RLPO and RSPO. Using PEG 600 as a plasticizer, polymers were dissolved in chloroform and methanol. A glass Petri dish was then filled with the solution. It took 24 hours for the solvent to evaporate at room temperature.

Preparation of matrix-type transdermal patches

Transdermal patches composed of different polymers HPMC, Ethyl Cellulose, Eudragit RLPO, and Eudragit RSPO. The polymers were dissolved in chloroform and methanol along with a plasticizer. Then the solution was poured into a glass Petri dish containing Glycerin. The solvent was allowed to evaporate at room temperature for 24 hrs. The polymers (total weight: 500 mg) and drug (20 mg) were weighed in requisite ratios and dissolved in 10 ml of chloroform and methanol and PEG 400. After the vortex then the solution was poured on glycerin placed in a glass Petri dish and dried at room temperature for 24 hrs.

Formulation code	**Scopolamine (mg)**	**HPM C (mg)**	**RLP O (mg)**	**RSP O (mg)**	**Ethyl cellulose (mg)**	**Total polymer weight (mg)**	**Plasticizer (% W/W) of total polymer PEG-6000(ml)**	**Permeation Enhancer % w/w of total polymer (Methanol, chloroform) ml**
F1	700	300	55	-	120	475	0.5	8
F2	700	350	55	--	60	465	0.5	8
F3	700	400	55	-	0	455	0.5	8
F4	700	450	-	55	120	625	0.5	8
F5	700	500	-	55	60	615	0.5	8
F6	700	550	-	55	0	605	0.5	8

Table 4: Preparation of matrix-type transdermal patches

Dose calculations

- Width of the plate = 6cm
- Length of the plate = 14cm
- No. of 3 x 3 cm^2 wafers present whole plate = 14
- Each wafers contains 50 mg of the drug.
- 14 no. of wafers contains mg of drug? = 14*50 = 700mg
- The amount of drug added in each plate was approximately equal to 700mg.

Evaluation parameters

The prepared transdermal films were evaluated for the following parameters:

Microscopic evaluation

An optical microscope (Olympus-Cover-018) with a camera attachment (Minolta) was used to observe the shape of the prepared Transdermal patch for all formulations

Thickness

The thickness of the films was measured by Vernier calipers. The thickness of the patches were measured at three different places and an average of three readings was taken with standard deviation.

Folding endurance

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

Tensile strength.

Cut the patch at the center having 2cm length and 2cm breadth. The patch was hung on the top and lower side of the instrument, then start the switch and note the reading on screen. The thickness and breadth of strips were noted at three sites and average value was taken for calculation

Were, $$Tensile\ strength\ (s) = \frac{Applied\ Force}{Cross\ section\ area}$$

S = tensile stress in 980 dynes/cm2 m = mass in grams

g = acceleration due to gravity (980 dynes/cm2) b = breadth of the strip in centimeters

t = thickness of strip in centimeters

Percentage of moisture content

The prepared patches were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs [72]. Individual films were weighed. The percentage of moisture content was calculated as the difference between final and initial weight with respect to the initial weight.

Percentage of moisture uptake

Firstly, weighed the patches and then kept in a desiccator at room temperature for 24 hrs and then it's exposed to 84% RH (A saturated solution of potassium chloride) in a desiccator. The % of moisture uptake was calculated by the difference between final and initial weight with respect to the initial weight.

Drug content analysis

The patches (n = 3) of specified area (6.16cm^2) were taken into a 10 ml volumetric flask and dissolved in methanol (10ml) with the help of a shaker. After the vortex the solution was filtered and prepared with subsequent dilutions and analyzed by UV spectrophotometer at 220 nm.

***In vitro* skin permeation study**

The *in vitro* skin permeation study was done by using a Franz diffusion cell (receptor compartment capacity: 80 ml: surface area: 3.14 cm^2. The egg membrane was separated and used for in vitro study. The receiver compartment was filled with 40 ml of phosphate buffer, pH 7.4. The Transdermal patch was firmly pressed onto the center of the egg membrane and then the membrane was mounted on the donor compartment. The donor compartment was then placed in a position such that the surface of the membrane just touches the receptor fluid surface. The whole assembly

was kept on a magnetic stirrer with suitable rpm throughout the experiment using magnetic beads. The temperature of the receptor compartment was maintained at 37± 0.5ºC.The samples were withdrawn at different time intervals of up to 10 hrs and analyzed for drug content at 220 nm. The receptor phase was replaced with an equal volume of buffer solution at each time interval.

Release Kinetics studies

Mathematically modelling of drug release/kinetic profile

Investigation for the drug release was done by studying the release data with zero-ender, first-order kinetics, and Higuchi equation. The release mechanism was understood by fitting the data to the Korsmeyer-Peppas model.

Zero Order Kinetics

When the data is plotted as cumulative "% drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K0. Zero-order release would be predicted by the following equation: -

At= A0-K0t

Where, At = Drug release at a "time", A0 = initial drug concentration,

K0 = Zero-Order rate constant (hr-1)

First-Order Kinetics

When the data is plotted as log cumulative % drug remaining versus time yields a straight line, indicating that the release follows first-order kinetics. The constant "K" can be obtained by multiplying 2.303 with the slope values. The first-order release would be predicted by the following equation: -

Log C= log C0 - Kt/2.303

Where C = Amount of drug remained at the time "t", C0 = Initial concentration of the drug,

K = first-order rate constant (hr-1)

Higuchi's model:

When the data is plotted as cumulative drug release versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to "K" Drug release from the formulation by diffusion has been described by following Higuchi's classical diffusion equation:

Q = [D ε / ε (2A-CS) CSt]1/2

Where, Q = Amount of drug released at a "time"

D = Diffusion coefficient of the drug in the matrix,

A = total amount of drug in the unit volume of a matrix, CS = Solubility of the drug in the matrix,

ε = porosity of the matrix, T = Tortuosity

Korsmeyer Equation/ Peppa's Model:

When the data is plotted as a log of drug released versus time, yield a straight line with a slope equal to "n" and the "K" can be obtained from the y-intercept. To study the mechanism of drug release, the drug release data were also fitted to the well-known exponential equation (Korsmeyer equation/Peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

Mt/Ma = Ktn

Where; Mt/Ma is the amount of drug released at time t.

K = is the release rate constant, and n is the release exponent.

n = value is used to characterize the different release mechanisms

3. RESULT AND DISCUSSION:

3.1 Preformulation study

Organoleptic properties:

Table 5: Organoleptic characteristics of Scopolamine

S. No.	Properties studied	Results
1.	Color	White
2.	Oduor	Odourless
3.	Taste	Bitter
4.	Appearance/Morphology	Fine powder

Solubility analysis:

Table 6: Solubility determination of Scopolamine in various solvents

Solvents	Results of Solubility
Methanol	Soluble
Ethanol	Soluble
Chloroform	Sparingly soluble
Distilled water	Sparingly soluble
Phosphate buffer 7.4 pH	Sparingly soluble
.1 N HCl	Sparingly soluble
0.1 N NaOH	Sparingly soluble

It was found that Scopolamine was soluble in ethanol and methanol, sparingly soluble in phosphate buffer 7.4 pH, 0.1 N HCl, distilled water, chloroform, and 0.1 N NaOH.

Results of loss on drying:

Results: Results of loss on drying of Scopolamine was found 0.125±0.006%

Melting point:

Results: The melting point of Scopolamine was found to be 58-60°C.

Determination of UV-visible absorption maxima of Scopolamine:

Absorption maxima (λmax) of SCOP were found to be at 220 nm in Methanol as shown in Figure 5. The measurements of the stock solution were taken by using a UV-visible spectrophotometer (Carry win-60, UV-Visible Spectrophotometer, Agilent, U.S.A).

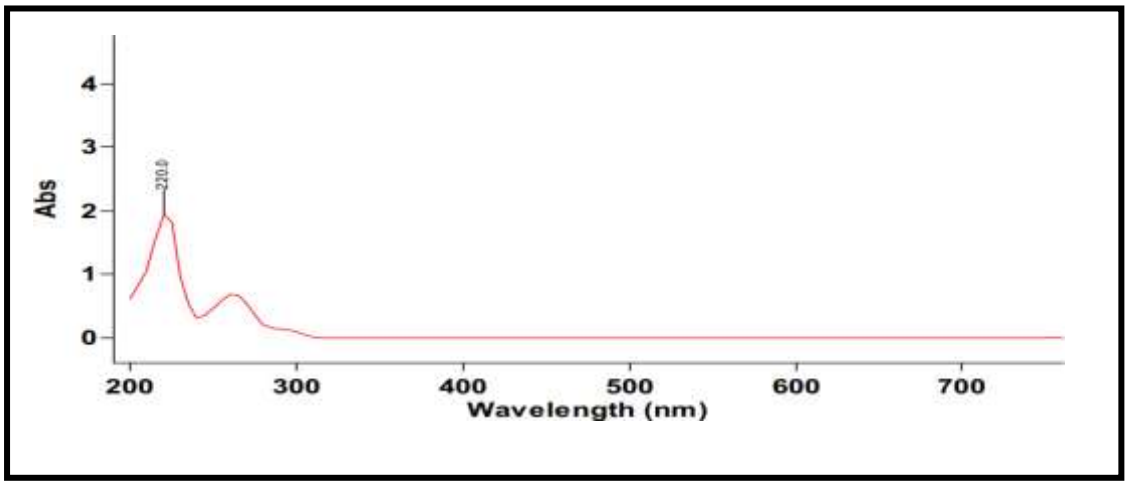


Figure 1. **Showing absorption maxima of Scopolamine**

Preparation Standard calibration curve of SCOP in Methanol

The calibration curve of SCOP in methanol was carried out by using a UV-Visible spectrophotometer (Cary-win60 UV-Visible Spectrophotometer Agilent, USA). The calibration curve of SCOP was plotted between absorbance vs concentration as shown in Table 8 and Figure 7. The R^2 value was found to be 0.9981 as reported by nalluri et. al (51).

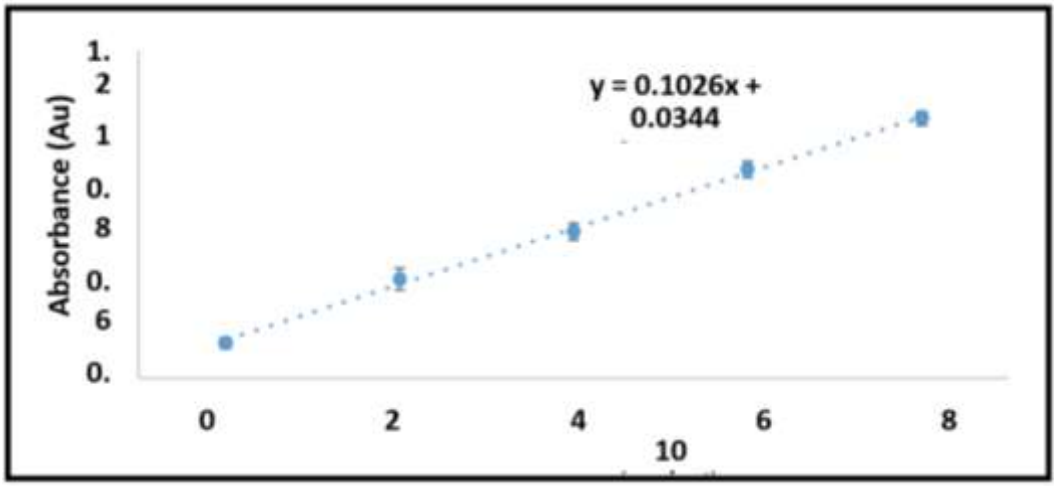


Figure 2.Showing Standard Calibration Curve Scopolamine

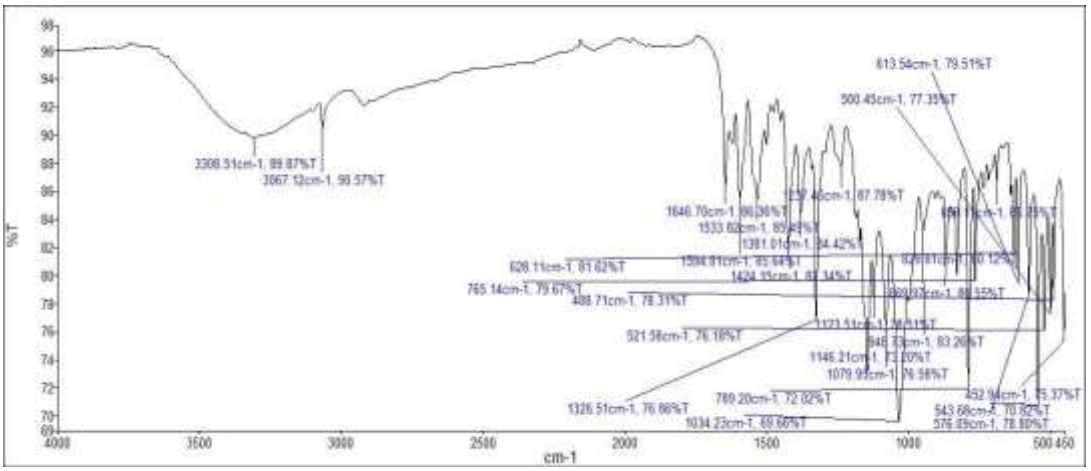
Table 7: Showing Concentration (µg/mL) vs absorbance of SCOP in methanol

Sr. No.	Concentration (µg/mL)	Absorbance (A.U.) (Mean ± SD)
1	1	0.1263±0.0208
2	3	0.3611±0.0401
3	5	0.5355±0.0306
4	7	0.7634±0.0295
5	9	0.9854±0.0259

FTIR spectroscopy of Scopolamine

FTIR spectrum of the drug was obtained by KBr using (FT-IR Alpha, BRUKER,). The principal peaks of the drug were identified and matched with the standard FTIR of the drug confirming the identity and purity of the drug. In the FTIR spectra of SCOP, there are many peaks at 3308.51 cm^{-1} N-H stretching, 1646.70 cm^{-1} C=O stretching, 1237.46cm^{-1} C-N stretching, 1424 cm^{-1} C-H bending, 1381 cm^{-1} O-H phenol bending, 1276 cm^{-1} C-O Stretching Alkyl aryl ether, 1146.21 cm^{-1} C-O Stretching primary Alcohol, 689 cm^{-1} C=C Bending Alkene, 660 cm^{-1} C- Cl Stretching halo compound and 3067 cm^{-1} C=C stretching. The presence of all of these groups in FTIR spectra confirmed the chemical structure of SCOP.

Table 8: Showing Wavenumber(cm^{-1}) Observed value of Scopolamine functional group



So. No.	Functional group	Wavenumber(cm^{-1}) Observed value for Scopolamine
1	N-H Stretching	3308.51
2	C=O Stretching	1646.70
3	C-N bending	1237.46
4	C-H Bending Alkene	1424
5	O-H Phenol Bending	1381
6	C-O Stretching Alkyl aryl ether	1276
7	C-O Stretching primary Alcohol	1146.21
8	C=C Bending Alkyne	689
9	C-Cl Stretching Halo compound	660
10	C=C Stretching	3067

Evaluation of Formulated Patch

Thickness:

The thickness of the films varied from 92±8 to 105±6 mm. The values obtained for all the formulations are given in the table.

Folding Endurance:

The folding endurance was measured in triplicate, according to the procedure given in table 5.5 and the folding endurance was found to be in the range. The thickness was approximately close to every formulation. It depends on the polymer ratio. All the patches showed satisfactory folding endurance properties. Folding endurance values of all formulations, more than 170 indicate good elasticity and strength.

Table 9: Showing thickness and folding endurance

S. No.	Formulation Code	Thickness* (µm)	Folding Endurance* (Times)
1.	**F1**	97±5	187±5
2.	**F2**	99±7	171±7
3.	**F3**	101±9	208±6
4.	**F4**	92±8	183±8
5.	**F5**	98±4	175±4
6.	**F6**	105±6	181±3

Average of Three determinations (n=3, Mean ± S.D.)

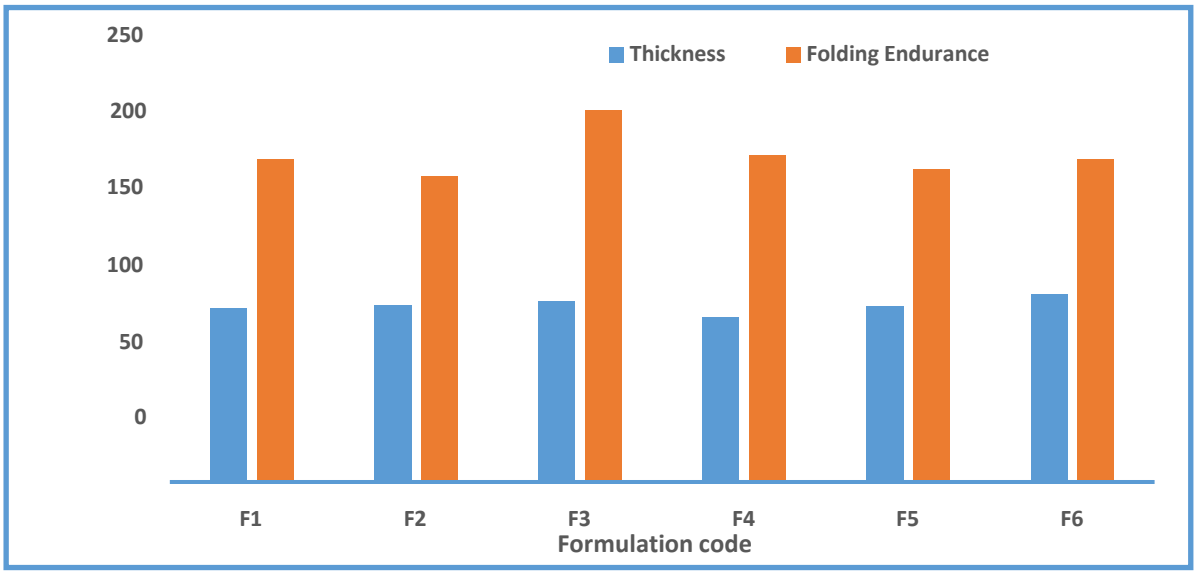


Figure 3. Graph of thickness and folding endurance

Moisture Content:

The moisture content was determined by keeping patches in a desiccator containing activated silica. The percentage moisture uptake was calculated as the difference between initial and final weight with respect to final weight. The results of the moisture content studies for different formulations are shown in Table 7.5 and Fig. 7.5.

Moisture Uptake:

The percentage moisture uptake was calculated as the difference between the final and initial weight with respect to the initial weight. The results of moisture uptake studies for different formulations are shown in Table 7.5.

The formulation F3 shows the lowest moisture content and moisture uptake than other formulation. This is due to because of polymer ratio (like Ethyl Cellulose). If lower moisture content in the transdermal patch it be good to prevent brittleness with 100% dryness and also maintain the stability of the formulation. If formulation content higher moisture can lead the microbial contamination during the storage of patches

Table 9: % Moisture content and moisture uptake of different formulations

S. No.	Formulation Code	% Moisture content*	% Moisture uptake*
1.	F1	6.88±0.14	3.47±0.21
2.	F2	6.02±0.35	3.65±0.65
3.	F3	5.78±0.24	2.45±0.33
4.	F4	7.30±0.15	3.25±0.14
5.	F5	6.30±0.32	3.49±0.25
6.	F6	5.4±0.25	1.95±0.25

*Average of Three determinations (n=3, Mean ± S.D.)

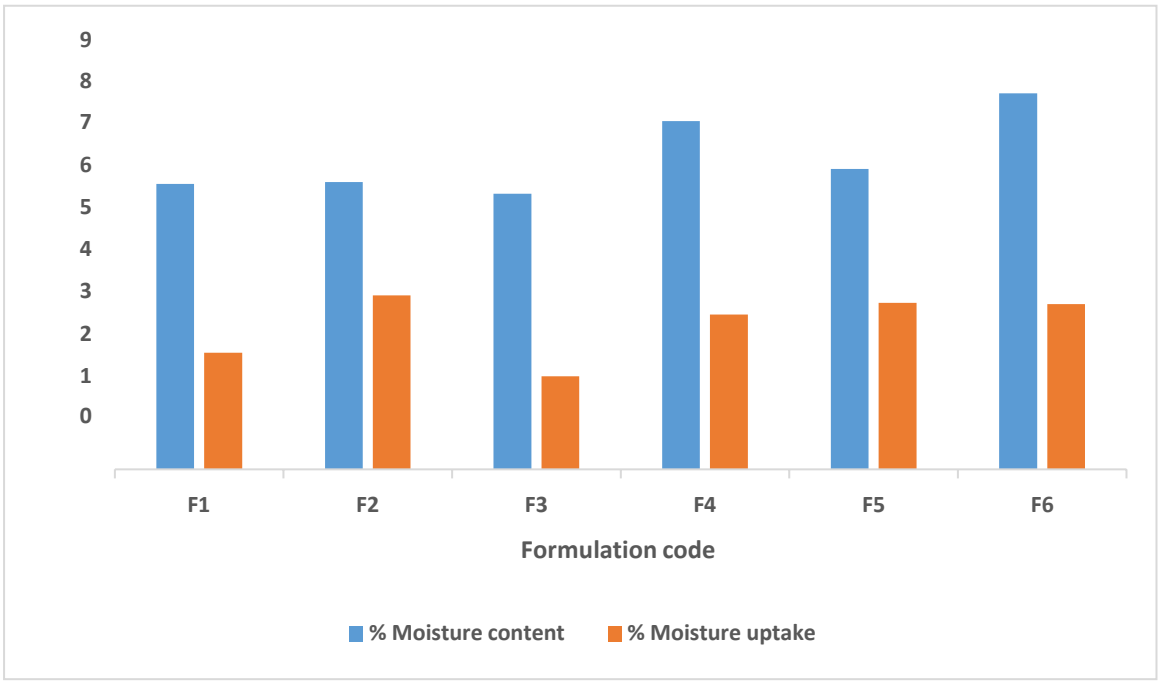


Figure 4. Showing % Moisture content and moisture uptake of different formulations

Tensile Strength:

The tensile strength was found to be in the range of 0.74±0.02 to 0.87±0.03. The formulation Scopolamine F3 showed the best tensile strength. The values for all the patches are tabulated in the table

Table 10 Showing Tensile of different formulation

S. No.	Formulation code	Tensile strength (kg/cm2)
1	F1	0.85±0.05
2	F7	0.78±0.02
3	F3	0.75±0.04
4	F4	0.82±0.05
5	F5	0.87±0.03
6	F6	0.74±0.02

Figure :. Graph of Tensile strength of different formulations

Drug Content Analysis

The drug content analysis of different formulations was done. The drug content ranged between 96.12±0.36 and 99.44±0.25. The percentage drug content of all formulations are shown in Table

Table 11: Showing Percentage drug content of all the formulations

S. No	Formulation Code	% Drug content
1	**F1**	98.78±0.45
2	**F2**	97.85±0.25
3	**F3**	96.12±0.36
4	**F4**	97.68±0.21
5	**F5**	98.55±0.18
6	**F6**	99.47±0.25

***Average of Three determinations (n=3, Mean ± S.D.**

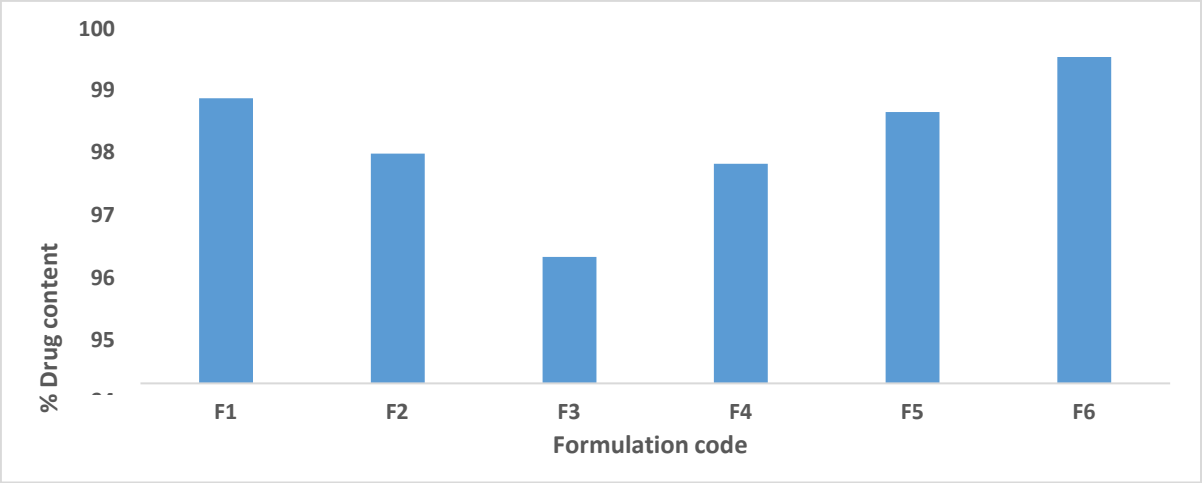


Figure 5: Graph of percentage drug content of formulation F1 to F6

This test is essential to check the uniformity of drug content in different patches from a single batch. The drug content analysis of the patch show that the process employed to prepare the patch was capable of giving uniformity drug content and minimum batch variability. F6 is an optimized formulation that shows a good result.

***In vitro* skin permeation study**

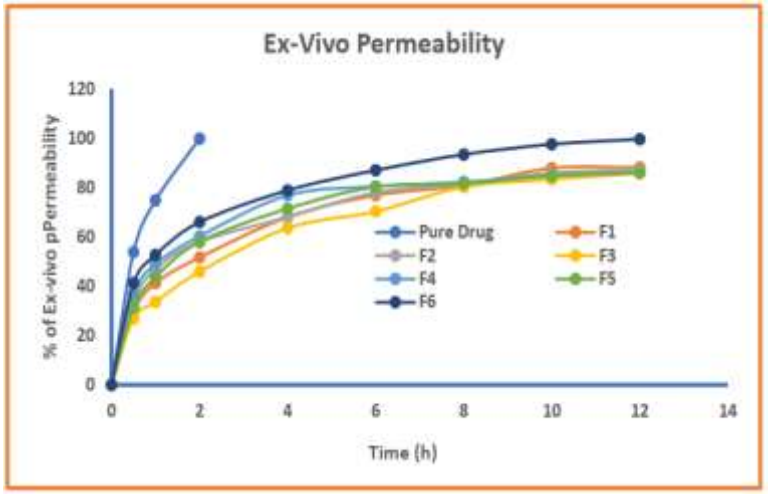
The *in vitro* permeation studies are predictions of *in vivo* performance of a drug. These studies were performed for different formulations across egg membranes using phosphate buffer, pH 7.4 as an *in vitro* study fluid in the receptor compartment of Franz diffusion cell. The results of these studies are given in Tables 7.8-7.10 and Fig. 7.8-7.10. F6 formulation is more permeated i,e 99.62 across egg membrane than the other formulation.

Table 12: % Ex-Vivo Permeability profile of Scopolamine-loaded-Patches formulation F1-F6.

Time	**% *Ex-Vivo* Permeability**						
hrs	**Pure Drug**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
0	**0**	**0**	0	0	0	0	0
0.5	53.85	29.25	33.65	26.85	36.85	31.45	41.25
1	74.85	41.25	46.85	33.65	48.98	43.65	52.65
2	99.78	51.65	57.98	45.89	60.23	57.98	65.98
4	-	67.98	67.98	63.56	76.85	71.45	78.85
6	-	76.85	77.98	70.32	80.45	80.23	86.98
8	-	80.85	81.32	80.23	82.23	81.65	93.4
10	-	87.85	85.85	83.36	84.85	84.78	97.55
12	-	88.17	87.12	85.75	86.07	86.14	99.62

Figure 6; % Ex-Vivo Permeability profile of Scopolamine-loaded-Patches formulation F1-F6.

In-Vitro drug released study



In-vitro % CDR of pure scopolamine was found to be 99.78% within 2 hours. In vitro % CDR of F6 formulation was found to be 99.82% within 12 hours. We can say after incorporation of scopolamine inside the patches to show control release of drug from the patches. Formulation F6 showing the maximum drug release in comparison to other formulations.

Table 13: % In- vitro drug release profile of Scopolamine-loaded-Patches formulation F1-F6

Time	**% Cumulative Drug Release**						
hrs	**Pure Drug**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
0	**0**	**0**	0	0	0	0	0
0.5	53.85	29.25	33.65	26.85	36.85	31.45	41.25
1	74.85	41.25	46.85	33.65	48.98	43.65	52.65
2	99.78	51.65	57.98	45.89	60.23	57.98	65.98
4	-	67.98	67.98	63.56	76.85	71.45	78.85
6	-	76.85	77.98	70.32	83.45	80.23	86.98
8	-	85.85	91.32	80.23	90.23	91.65	99.4
10	-	96.85	96.85	91.36	95.85	95.78	99.55
12	-	92.17	94.12	94.75	94.07	93.14	99.82

Figure 7: % In- vitro drug release profile of Scopolamine-loaded-Patches formulation F1-F6.

Release kinetics of Scopolamine Transdermal patches

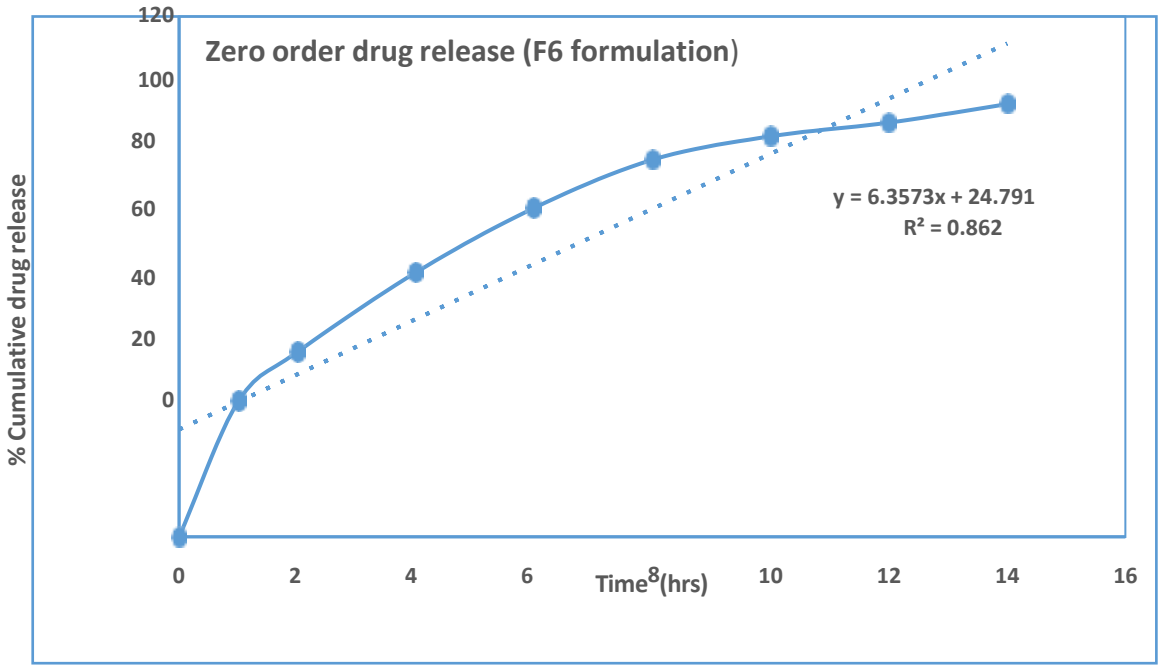


Figure8:. Zero Order Release Kinetic Model of F6 optimized formulation

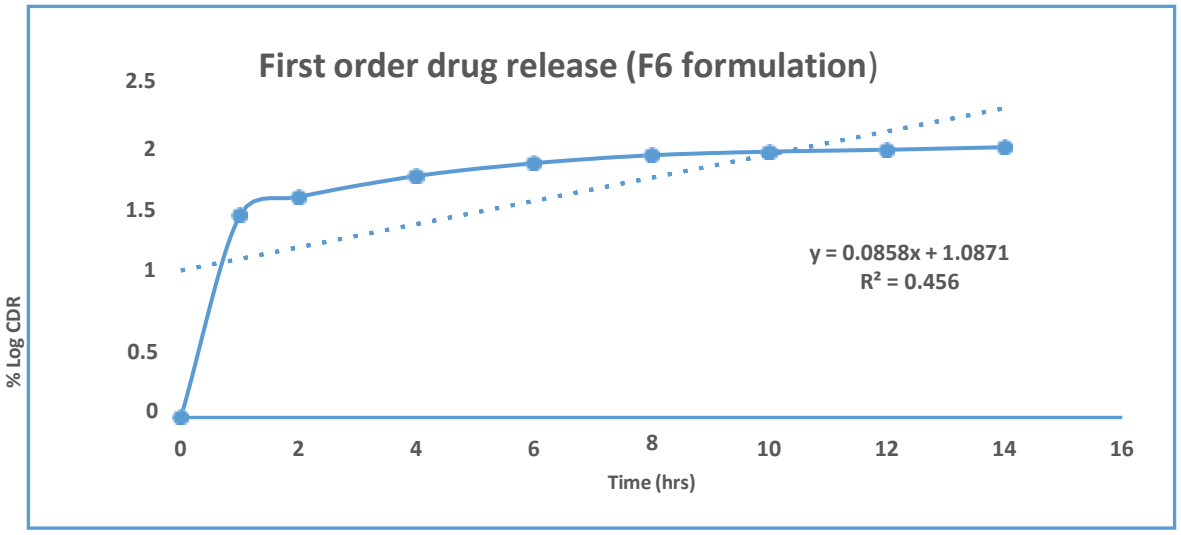


Figure 9: First Order Release Kinetic Model of F6 optimized formulation

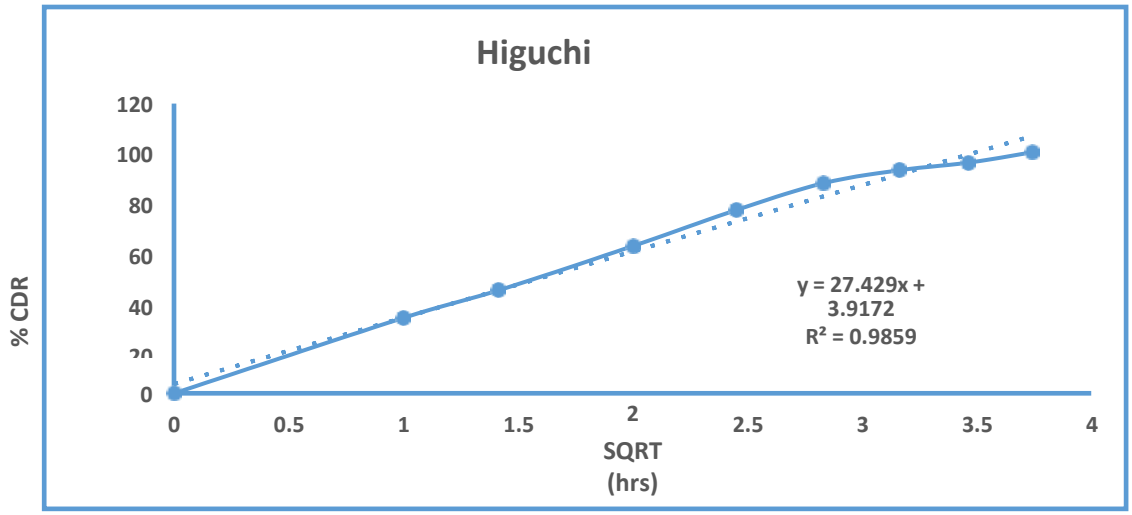


Figure 10 : Higuchi model Release Kinetic Model of F6 optimized formulation

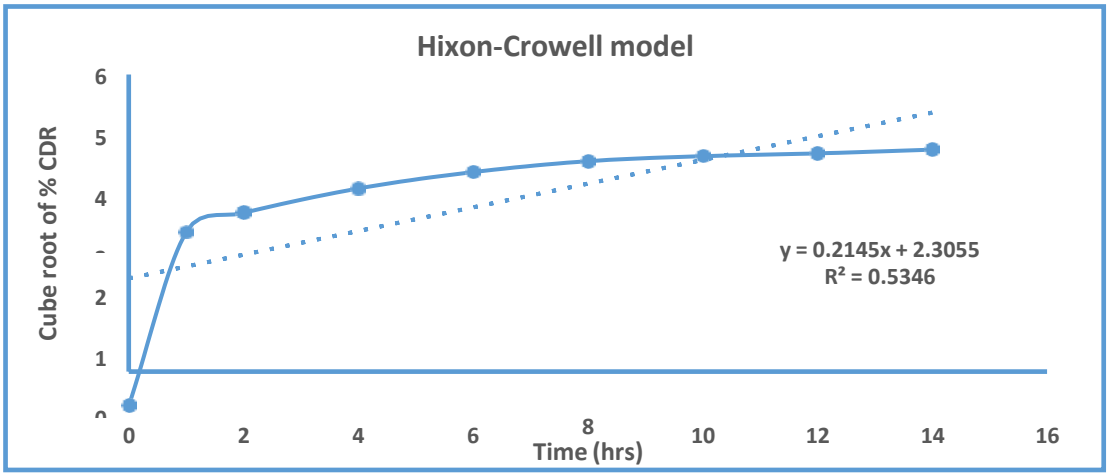


Figure 11. Hixon-Crowell model Release Kinetic Model of F6 optimized formulation

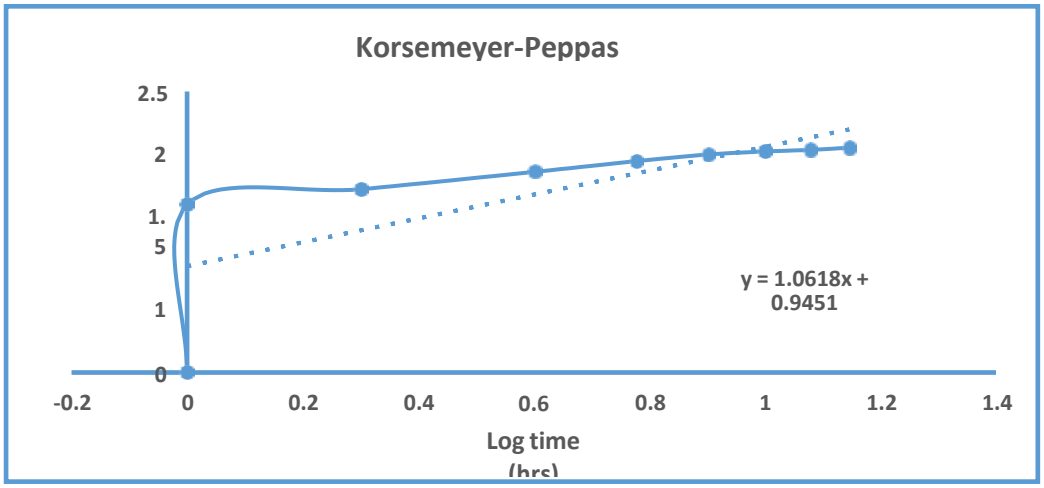


Figure 12 . Korsemeyer-Peppas model Release Kinetic Model of F6 optimized formulation

Table 13: R^2 Values as per Different Release Kinetic Models.

Release Model	**Zero- order**	**First order**	**Higuchi model**	**Hixon Crowell model**	**Korsemeyer Peppas mode**
$_R2$	0.862	0.456	0.9859	0.5346	0.5594

F6 formulation was fitted into various release kinetic models and the correlation coefficient (R^2) value was found to be highest in the case of the Higuchi Model, i.e., 0.9859 shown in Fig.7,11, and table 7.9 indicating that the drug is released and Scopolamine was released from the patches following a controlled release pattern

4. SUMMARY AND CONCLUSION

The transdermal approach has garnered appreciation for its benefits over conventional methods, including avoiding first-pass metabolism and reducing gastrointestinal discomfort linked to oral delivery. Other benefits include simple cessation of medication, which makes it possible to maintain a steady plasma level profile and reduce adverse effects. Topical preparations' physicochemical characteristics and the kind of gels used to determine how quickly medicines are released from them. The benefits of thixotropic, emollient, greaseless, readily spreadable, and easily removable gels for dermatological treatment are numerous. When gelling agents are combined with the right solvent, a three-dimensional colloidal network is created that traps and immobilizes the solvent molecules, restricting fluid movement. The network structure of gels' resistance to deformation and the resulting viscoelastic characteristics are further benefits.

In the current study, transdermal patches containing scopolamine were to be developed and evaluated utilizing HPMC, RLPO, RSPO, EC, and PEG. Clarity, viscosity, drug content, and in vitro permeation tests were performed on the produced gels.

The thickness of the films varied from 97±5 to 105±6mm. The thickness was approximately close to every formulation. It depends on the polymer ratio. All the patches showed satisfactory folding endurance properties. Folding endurance values of all formulations more than 181±3 indicating good elasticity and strength. the moisture content of the patches was calculated by keeping the all patches in an active silica desiccator. The difference between the beginning and final weights relative to the final weight was used to compute the % moisture absorption. The moisture content was found to be 5.98±0.25 to 6.88±0.14.

Formulation F6 shows the lowest moisture content and moisture uptake than other formulations. This is due to because of polymer ratio (like Ethyl Cellulose). If lower moisture content in the transdermal patch it be good to prevent brittleness with 100% dryness and also maintain the stability of the formulation. If formulation content higher moisture can lead the microbial contamination during the storage of patches. The tensile strength was found to be in the range of 0.85±0.05 to 0.74±0.02. The formulation scopolamine F6 showed the best tensile strength.

The prepared patch showed good tensile strength and there was no cracking sign in patch. There was an increase in tensile strength with an increase in Eudragit RLPO in polymers ratio. The drug content ranged between 97.78±0.45 and 99.47±0.25. This test is necessary to determine whether the medication content in several patches from the same batch is consistent. The patch's drug content analysis demonstrates that the preparation method used was capable of producing a patch with consistent drug content and minimal batch variability.

F6 is a well-performing formulation that has been optimized. In order to improve the formulation for the in-vitro study, the in-vitro permeation study was carried out to observe the effect of polymers through the Franz diffusion cell from patch having Eudragit RLPO, RSPO, HPMC, and EC in varied conc. to understand the diffusion process and pattern, every formulation was examined, and all data was fitted on a zero- order, first-order basis.

The % cumulative drug release was calculated over the study time range of 0-12 hrs. Data analysis for order of release kinetics the formulation followed zero order release kinetics. From the in-vitro permeation study, it was confirmed that the release of formulation, F6 was to be found higher as compared to other formulations (F1, F2, F3, F4, F5).

5. CONCLUSION

In the current study, an attempt was made to administer scopolamine, an anti- emetic drug, via the transdermal route using transdermal patches.

Transdermal matrix patches were created, and it was determined that the matrix kind of patches were suitable. The optimum formulation of the various matrix types (F1 to F6) was decided to be F6, which contains HPMC and Eudragit RLPO. It was also discovered that the drug permeation profile followed zero-order kinetics. The patches were translucent, thin, and flexible. The current study has shown that scopolamine matrix transdermal patches performed better in vitro than pure medication.

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