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Formulation And Evaluation Of Transdermal Patches Of 5-Fluorouracil For The Treatment Of Skin Cancer

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ABSTRACT

The present study focuses on the formulation and evaluation of transdermal patches of 5-fluorouracil (5-FU) intended for the topical treatment of skin cancer, aiming to enhance localized drug delivery while minimizing systemic side effects. 5-FU, a potent antimetabolite used in chemotherapy, suffers from poor skin permeability and rapid metabolism when administered conventionally. To overcome these limitations, transdermal drug delivery offers a non-invasive and controlled release system that can maintain therapeutic drug levels at the site of action.

Transdermal patches were prepared using solvent casting technique employing various polymers such as hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), and polyvinyl alcohol (PVA) either alone or in combinations, along with suitable plasticizers like glycerol or polyethylene glycol (PEG 400). The prepared patches were subjected to a series of physicochemical evaluations including thickness, weight variation, folding endurance, surface pH, drug content uniformity, moisture content, water vapor transmission rate, and in vitro drug release studies using Franz diffusion cell.

Among the different formulations, the patch containing HPMC:EC in a 2:1 ratio exhibited optimal physical properties and sustained drug release up to 24 hours, showing a cumulative drug release of over 85%, indicating a controlled release pattern. The in vitro permeation study demonstrated enhanced skin penetration, and FTIR studies confirmed no significant interaction between 5-FU and the excipients. The stability studies, conducted as per ICH guidelines, showed no significant changes in drug content and appearance over a period of three months.

In conclusion, the formulated transdermal patches of 5-fluorouracil offer a promising alternative to conventional topical or systemic therapies for skin cancer by enabling localized, sustained delivery of the drug with improved patient compliance and reduced systemic toxicity..

Keywords: *formulation, interaction, Stability, Delivery, Cancer*

1. INTRODUCTION

Transdermal drug delivery systems (TDDS) represent a progressive step in the advancement of pharmaceutical technology. These systems are designed to deliver drugs across the skin barrier in a controlled manner, directly to the targeted site or into systemic circulation. Over the past few decades, transdermal patches have gained significant attention due to their ability to bypass the gastrointestinal tract, avoid first-pass metabolism, provide sustained drug release, and improve patient compliance. These benefits are particularly important for drugs that are used for chronic conditions or for localized diseases such as skin cancer.

Skin cancer, the most common form of cancer globally, includes a wide range of malignancies that develop from different types of skin cells. The three most prevalent types are basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma. Among these, BCC and SCC are known as non-melanoma skin cancers and are often treatable with early intervention. These cancers typically appear on sun-exposed parts of the body and progress slowly. Traditional treatment methods include surgical excision, cryotherapy, radiotherapy, and topical chemotherapy. However, these treatments may be invasive, associated with cosmetic issues, or produce systemic side effects.

Topical chemotherapy is a promising approach for treating localized skin cancers. It allows direct drug application to the affected area, maximizing local concentration while minimizing systemic exposure. Among the various anticancer agents, **5-Fluorouracil (5-FU)** has been extensively used for the treatment of superficial skin cancers due to its antimetabolite action. 5-FU inhibits the enzyme **thymidylate synthase**, thereby preventing DNA synthesis and ultimately causing cell death, particularly in rapidly proliferating cancer cells. However, conventional topical formulations like creams and gels have limitations, including poor drug retention at the site, inconsistent absorption, and frequent application requirements[1-5].

To overcome these challenges, **formulating 5-FU into transdermal patches** has emerged as a novel and effective strategy. Transdermal patches offer controlled and sustained drug release, enhanced skin penetration, and better patient adherence due to reduced dosing frequency. Furthermore, the incorporation of **skin permeation enhancers** and polymeric materials into the patch design can significantly improve drug transport across the stratum corneum, the main barrier of the skin.

The formulation of a transdermal patch involves various components such as drug, polymer matrix, plasticizer, permeation enhancer, and backing membrane. The choice of polymer is critical as it determines the mechanical strength, flexibility, and drug release profile of the patch. Commonly used polymers include **hydroxypropyl methylcellulose (HPMC)**, **ethyl cellulose (EC)**, **polyvinyl alcohol (PVA)**, and **Eudragit**. Plasticizers like **glycerin**, **PEG 400**, or **dibutyl phthalate** are added to enhance flexibility and reduce brittleness. Permeation enhancers such as **oleic acid**, **dimethyl sulfoxide (DMSO)**, or **terpenes** are often used to temporarily disrupt the stratum corneum, allowing better drug penetration.

After formulation, the patches must be thoroughly evaluated for several physicochemical and performance parameters. These include:

Physical appearance and **uniformity**

Thickness and **weight variation**

Folding endurance (to assess mechanical strength)

Moisture content and **moisture uptake**

Drug content uniformity

In vitro drug release studies (usually performed using Franz diffusion cells)

Skin permeation studies

Skin irritation tests (to ensure safety and non-irritancy)

One of the major advantages of 5-FU transdermal patches is their potential to deliver the drug at a constant rate, maintaining therapeutic levels over a prolonged period. This feature is particularly useful in oncology, where stable drug concentrations can improve efficacy and reduce the development of resistance. Moreover, localized application means that systemic toxicity is significantly reduced, which is a major concern in conventional 5-FU therapy when administered intravenously or orally.[7,8]

From a patient perspective, transdermal patches are easy to use, non-invasive, and painless, contributing to better compliance, especially in elderly or long-term cancer patients. Additionally, the risk of overdosing is minimal due to the controlled release mechanism, and the patches can be easily removed if any adverse reaction occurs.

In recent years, advances in **nanotechnology** and **formulation sciences** have further enhanced the performance of transdermal patches. Techniques such as **microneedle-assisted delivery**, **nanoemulsions**, and **ethosomal formulations** are being investigated to increase the permeability of hydrophilic drugs like 5-FU, which naturally have limited ability to cross the lipophilic barrier of the skin. These approaches may eventually lead to combination products that offer even better therapeutic outcomes.

The current study aims to **formulate and evaluate 5-FU transdermal patches** using different polymeric combinations and evaluate their performance through various in vitro methods. The objective is to optimize the formulation that provides maximum drug release, effective skin permeation, good adhesion, and minimal skin irritation. Such a formulation could provide an improved therapeutic option for patients suffering from superficial forms of skin cancer.

In conclusion, the development of 5-FU transdermal patches represents an important step forward in topical chemotherapy. It combines the benefits of targeted delivery, reduced systemic toxicity, and enhanced patient compliance. With the growing incidence of skin cancer globally and the limitations of conventional therapies, such novel drug delivery systems hold significant potential in dermatological oncology. Future clinical studies and commercial translation of these formulations could offer new hope to skin cancer patients by providing a safer, more effective, and more convenient treatment option.

2. TRANSDERMAL DRUG DELIVERY SYSTEM[9-12]

The (TDDS) are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation. Transdermal drug delivery is a viable administration route

for potent, low-molecular weight therapeutic agents which cannot withstand the hostile environment of gastrointestinal tract and/or subject to considerable first-pass metabolism by the liver.

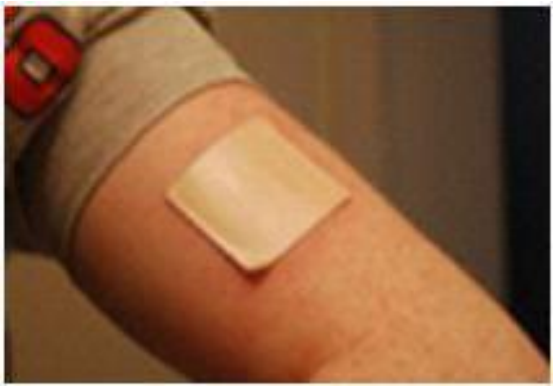

Figure : Transdermal patch

Transdermal drug delivery systems are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. These devices allow for pharmaceuticals to be delivered across the skin barrier.

Drug

For successfully developing a transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.

Physicochemical properties

The drug should have a molecular weight less than approximately 1000 Daltons

The drug should have affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin

The drug should have low melting point

Along with these properties the drug should be potent, having short half life and be non- irritating

Permeation Enhancers

These are compounds which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. These may conveniently be classified under the following main headings:[13,14]

Solvents

These compounds increase penetration possibly by swallowing the polar pathway and/or by fluidizing lipids. Examples include water alcohols – methanol and ethanol; alkyl methyl sulfoxides – dimethyl sulfoxide, alkyl homologs of methyl sulfoxide dimethyl acetamide and dimethyl formamide; pyrrolid- ones- 2 pyrrolidone, N-methyl, 2-purrolidone; laurocapram (Azone), miscellaneous solvents- propylene glycol, glycerol, silicone fluids, isopropyl palmitate.

Surfactants

These compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. The ability of a surfactant to alter penetration is a function of the polar head group and the hydrocarbon chain length.

Anionic Surfactants: e.g. Dioctylsulpho - succinate, Sodium lauryl sulphate, Decodecyl- methyl sulphoxide etc. Nonionic Surfactants: e.g. Pluronic F127, Pluronic F68, etc

Bile Salts: e.g. Sodium mstaurocholate, Sodium deoxycholate, Sodium tauroglycocholate

Binary system: These systems apparently open up the heterogeneous multilaminate pathway as well as the continuous pathways.e.g. Propylene glycol-oleic acid and 1, 4-butane diollinoleic acid.

Other Excipients

Adhesives: The fastening of all transdermal devices to the skin has so far been done by using a pressure sensitive adhesive which can be positioned on the face of the device and in the back of the device and extending peripherally.

Both adhesive systems should fulfill the following criteria

Should adhere to the skin aggressively, should be easily removed

Should not leave an un washable residue on the skin

Should not irritate or sensitize the ski

The face adhesive system should also fulfill the following criteria

Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part

Permeation of drug should not be affected

The delivery of simple or blended permeation enhancers should not be affected

Backing membrane: Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing.

It is impermeable substance that protects the product during use on the skin e.g. metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminium foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminium foil disc) etc.

Desirable features for transdermal patches

Composition relatively invariant in use

System size reasonable

Defined site for application

Application technique highly reproducible

Delivery is (typically) zero order

Delivery is efficient

Factors affecting transdermal drug delivery Skin conditions:-

The intact skin itself acts as a barrier, but many agents like acids and alkali cross the barrier cells and penetrate through the skin. Many solvents open the complex dense structure of the horny layer: solvents like methanol and chloroform remove the lipid fraction, forming artificial shunts through which drug molecules can pass easily.

Skin age

It is seen that the skin of adults and young ones is more permeable than that of the older ones. but there is no dramatic difference. Children show toxic effects because of the greater surface area per unit body weight. Thus, potent steroids, boric acid and hexachlorophene have produced severe side-effects.

Generally, when water saturates the skin, it swells tissues, softens wrinkles on the skin and its permeability increases for the drug molecules that penetrate through the skin.[14-18]

Temperature and pH of the skin

The penetration rate varies if the temperature varies and the diffusion coefficient decreases as the temperature falls however adequate clothing on the body prevents wide fluctuations in temperature and penetration rates. According to pH, only unionized molecules pass readily across the lipid membrane, and weak acids and bases dissociate to different degrees according to their pH and pKa or pKb values. Thus, the concentration of unionized drug in applied phase will determine the effective membrane gradient, which is directly related to its pH.

Because of to sunlight, the walls of blood vessels become thinner, leading to bruising, with only minor trauma in the sun-exposed areas. Also, pigmentation, the most noticeable sun-induced pigment change, is a freckle or solar lentigo.

Cold season

The cold season often results in itchy and dry skin. The skin responds by increasing oil production to compensate for the weather's drying effects. A good moisturizer will help ease symptoms of dry skin. Also, drinking lots of water can keep your skin hydrated and looking radiant.

Air pollution

Air pollution can clog pores and increase bacteria on the face and the surface of skin, both of which lead to acne or spots, which affects drug delivery through the skin. Invisible chemical pollutants in the air can interfere with the skin's natural protection system, breaking down the skin's natural oils that normally Dust trap moisture in the skin and keep it supply

Types of Transdermal Patches [24]

There are four Major Transdermal Systems:

i) Single-layer Drug-in-Adhesive

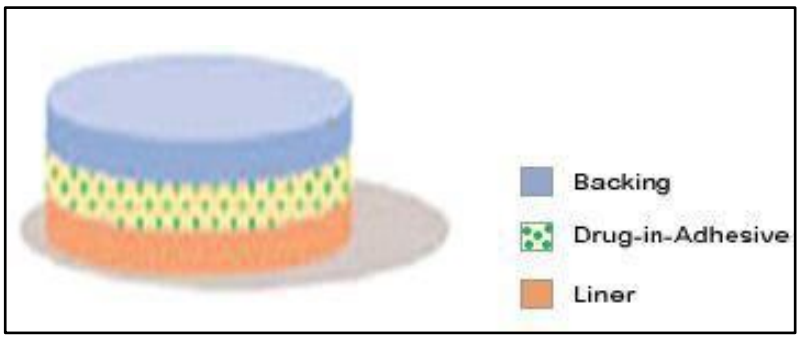

Figure 8: Single-layer Drug-in-Adhesive system.

The Single-layer Drug-in-Adhesive system is characterized by the inclusion of the drug directly within the skin-contacting adhesive. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and all the excipients under a single backing

film. The rate of diffusion of drug from this type of system is dependent on the diffusion across the skin . The intrinsic rate of drug diffusion from this type of drug delivery system is defined by

$dQ/Dt = Cr/(1/Pm+1/Pa)$

Where Cr is the drug concentration in the reservoir compartment and Pa and Pm are the permeability coefficients of the adhesive layer and the rate controlling membrane, **Multi-layer Drug-in-Adhesive**

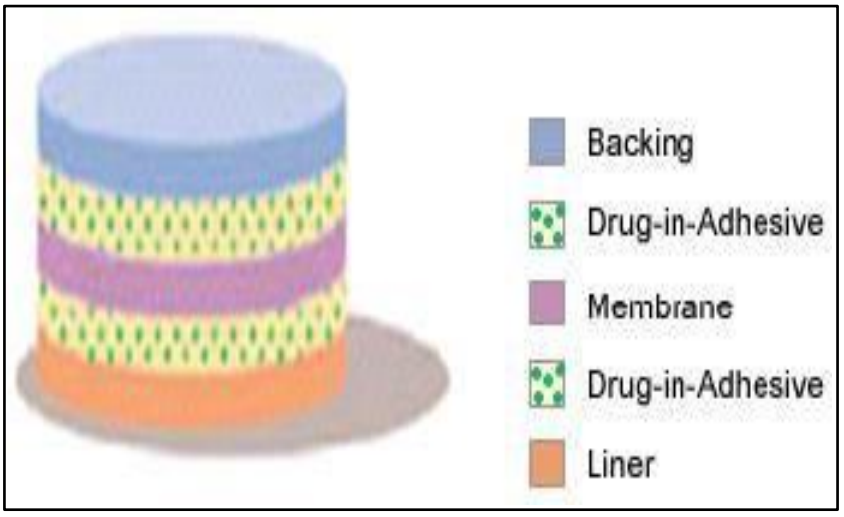

Figure : Multi-layer Drug-in-Adhesive system

The Multi-layer Drug-in-Adhesive is similar to the Single-layer Drug-in- Adhesive in that the drug is incorporated directly into the adhesive. However, the multi- layer encompasses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film.

The rate of drug diffusion in this system is defined by:

$Dq/dt = K_{a/r}.D_a$ /ha (cr)

Drug reservoir- in- adhesives

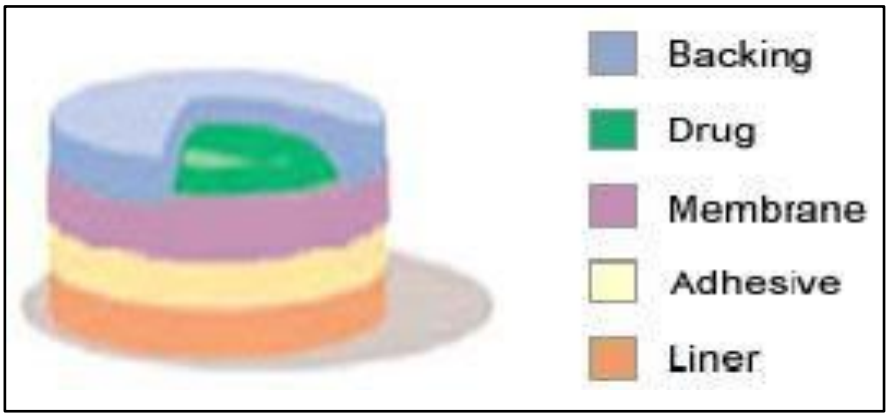

Figure : Drug Reservoir-in-Adhesive system

The Reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the diffusion liner by a semi-permeable membrane and adhesive. The adhesive component of the product responsible for skin adhesion can either be incorporated as a continuous layer between the membrane and the diffusion liner or in a concentric configuration around the membrane.

Drug Matrix-in-Adhesives

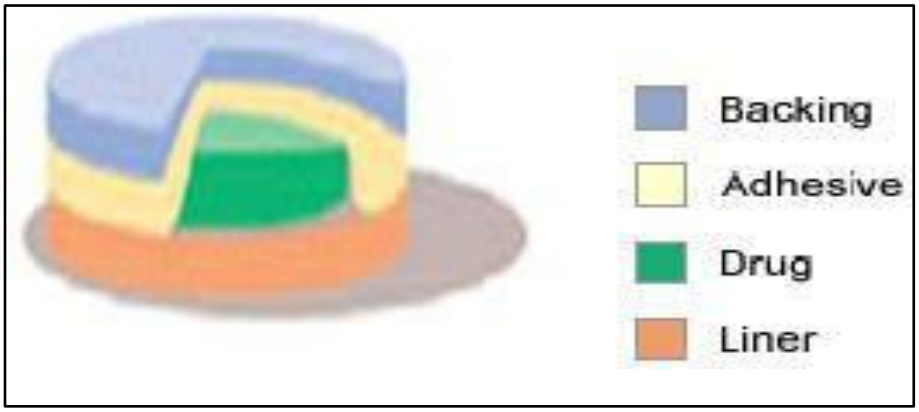

Figure : Drug Matrix-in-Adhesive system

The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the diffusion liner. The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix.

Various Methods of Preparing TDDS[19-20]

a. Solvent Casting Method

Drug and polymer are dissolved in a suitable volatile solvent (e.g., ethanol, chloroform).

The homogeneous mixture is poured into a mold or petri dish.

Solvent is evaporated, leaving behind a uniform drug-loaded film.

b. Film Spreading Method

Drug-polymer solution is spread over a flat surface.

After evaporation of solvent, a film is formed.

c. Hot-Melt Extrusion

Polymer and drug are melted together at high temperatures.

The molten mass is then extruded and rolled into thin films.

No solvent is used, making it solvent-free and eco-friendly.

d. Matrix Dispersion Method

Drug is dispersed uniformly in a melted polymer or in a polymeric matrix solution.

The dispersion is spread and dried or solidified.

e. Roller Spinning Technique

A polymer solution containing the drug is applied onto a rotating drum.

Uniform thin films are formed due to centrifugal forces and solvent evaporation.

f. Direct Compression or Pressing

Drug and excipients are compressed into thin films using a hydraulic press.

Selection of Solvent Casting Method (With Reason)

Why choose Solvent Casting Method for 5-FU TDDS?

Low melting point of HPMC polymer: Hot-melt extrusion might degrade drug/polymer.

Better uniformity of drug dispersion in polymer matrix.

Smooth, transparent films with uniform thickness are achievable.

Ease of adjusting film thickness by controlling volume and solvent evaporation.

No high temperature needed – 5-FU is heat-sensitive.

Cost-effective and simple for laboratory-scale preparations.

Step-by-Step Procedure for Solvent Casting Method for 5-FU TDDS

Materials:

5-Fluorouracil

HPMC (polymer)

Polyethylene glycol 400 (plasticizer)

Ethanol (solvent)

DMSO (permeation enhancer)

Glycerin

Distilled water

Petri dishes / glass molds

Magnetic stirrer

Beakers, measuring cylinders, pipettes

Procedure:

1. **Polymer Gel Preparation:**

Weigh 300 mg of HPMC and slowly disperse it in 10 mL of distilled water with continuous stirring (avoid lumps).

Let it hydrate fully (~1 hour) to form a clear viscous gel.

2. **Drug Solution Preparation:**

Dissolve 20 mg of 5-FU in a small volume of ethanol (~2 mL).

Stir until a clear solution is obtained.

3. **Plasticizer and Enhancer Addition:**

Add polyethylene glycol 400 (150 mg) and glycerin (100 mg) to the drug-ethanol solution.

Add DMSO (5% v/v) as a permeation enhancer.

Mix well.

4. **Combining the Solutions:**

Slowly add the drug-plasticizer solution to the hydrated HPMC gel under constant stirring.

Continue stirring until a homogeneous solution is formed.

5. **Deaeration:**

Allow the mixture to stand for 30 minutes to remove any air bubbles.

6. **Casting the Film:**

Pour the final solution into a clean, leveled petri dish (or glass mold).

Spread uniformly by tilting the petri dish to achieve even thickness.

7. **Drying:**

Allow the cast solution to dry at room temperature for 24–48 hours in a dust-free environment.

Avoid direct heat or sunlight to prevent degradation.

8. **Peeling the Patch:**

After drying, carefully peel off the formed transdermal patch using a spatula or blunt knife.

9. **Storage:**

Store the patch in a desiccator or airtight container to prevent moisture absorption.

FORMULATION TABLE

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**
5-Fluorouracil (mg)	20	20	20	20	20
HPMC (mg)	300	300	300	300	300
Polyethylene glycol 400 (mg)	100	150	100	150	150
Ethanol (% v/v)	5	5	10	10	10
Glycerin (mg)	50	50	50	75	100
DMSO (% v/v)	1	2	2	3	5
Water (q.s.) (mL)	10	10	10	10	10

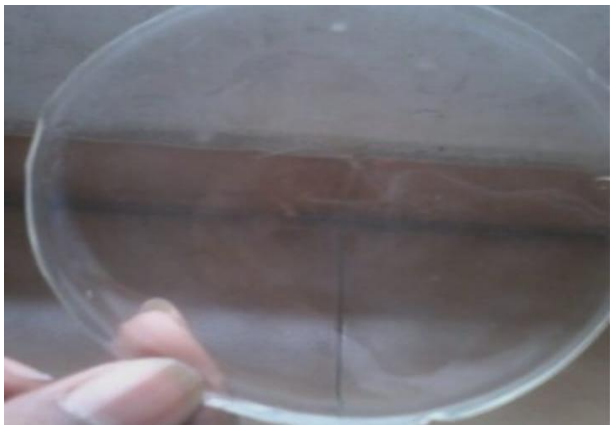

Figure- patch

3. RESULT DISCUSSION-

1 PRE FORMULATION DATA:

Table: FORMULATION TABLE

S. No.	Parameter	Method / Observation	Result
1	**Organoleptic Properties**	Visual and sensory inspection	Appearance: White crystalline powder ODOUR: odorless TASTE: tasteless
2	**Solubility**	Solubility in water, ethanol, chloroform, acetone, methanol	Freely soluble in water slightly soluble in ethanol practically insoluble in chloroform and acetone
3	**Melting Point**	Capillary method	282–286°C
4	**Thin Layer Chromatography (TLC)**	Silica gel 60 F254, methanol: water (70:30) as mobile phase; UV detection	Single spot Rf value: 0.54
5	**pH (1% w/v aqueous solution)**	pH meter	4.8
6	**Partition Coefficient (octanol/water)**	Shake-flask method	0.15 (log P = -0.82)
7	**FTIR**	FTIR spectrophotometer; KBr disc method	Characteristic peaks at: 3120 cm^{-1} (N-H stretch), 1670 cm^{-1} (C=O stretch), 1245 cm^{-1} (C-F stretch)
8	**UV-Visible Spectroscopy**	UV-Vis spectrophotometer; 265 nm in distilled water	λmax = 265 nm

4. EVALUATION PARAMETERS:

1. Physical Appearance

Method:

Visually inspect the patch for color, transparency, smoothness, uniformity, and flexibility.

Procedure:

Place the patch on a clean white background in natural or bright light.

Look for air bubbles, cracks, or surface imperfections.

Record observations about appearance, flexibility, and uniformity.

Table: Physical Appearance

Formulation	Color	Transparency	Surface Texture	Flexibility	Air Bubbles / Cracks	Remarks
F1	Off-white	Slightly opaque	Rough with uneven spots	Moderate	Few small air bubbles	Needs improvement in uniformity
F2	Pale white	Semi-transparent	Slightly coarse	Moderate	Occasional small cracks	Fair appearance
F3	White	Semi-transparent	Mostly smooth	Good	No visible air bubbles	Good, but slight unevenness
F4	White	Transparent	Smooth	Good	No air bubbles	Very good
F5	Pure white	Transparent	Very smooth and uniform	Excellent	No air bubbles or cracks	Best appearance and flexibility

2. Thickness

Method:

Use a digital micrometer (accuracy: 0.01 mm) or vernier caliper.

Table: Thickness

Formulation	Thickness at Point 1 (mm)	Thickness at Point 2 (mm)	Thickness at Point 3 (mm)	Thickness at Point 4 (mm)	Thickness at Point 5 (mm)	Average Thickness (mm)	Standard Deviation (SD)	Remarks
F1	0.18	0.21	0.19	0.22	0.20	0.20	0.015	Uneven thickness, variable results
F2	0.22	0.23	0.21	0.20	0.22	0.216	0.011	Moderate uniformity
F3	0.19	0.20	0.21	0.21	0.20	0.202	0.008	Good thickness uniformity
F4	0.20	0.20	0.21	0.20	0.21	0.204	0.006	Very uniform thickness

F5	0.20	0.20	0.20	0.21	0.20	0.202	0.005	Optimal, highly uniform thickness

3. Weight Uniformity

Method:

Weigh multiple patches of identical area using a digital balance.

Procedure:

Cut 5–10 patches (e.g., 2×2 cm).

Weigh each patch individually and record weights.

Calculate mean weight, standard deviation, and % weight variation.

Table no : Weight Uniformity

Formulation	Patch 1 Weight (mg)	Patch 2 Weight (mg)	Patch 3 Weight (mg)	Patch 4 Weight (mg)	Patch 5 Weight (mg)	Average Weight (mg)	Standard Deviation (SD)	Remarks
F1	55.2	57.0	54.5	56.8	55.9	55.88	1.03	Slight variation in weight
F2	58.1	57.5	58.4	59.0	58.3	58.26	0.57	Moderate uniformity
F3	56.4	56.8	57.1	56.9	56.7	56.78	0.27	Good uniformity
F4	55.9	56.0	56.1	55.8	56.0	55.96	0.11	Very uniform weights
F5	56.2	56.1	56.3	56.2	56.2	56.20	0.07	Highly uniform, optimal weight

4. Folding Endurance

Method:

Manually fold the patch repeatedly at the same point until it breaks.

Procedure:

Hold the patch with both hands.

Fold at one point and straighten repeatedly.

Count the number of folds until it cracks or breaks.

Record the average folding endurance for 3 patches.

Table : Folding Endurance

Formulation	Folding Endurance Trial 1	Folding Endurance Trial 2	Folding Endurance Trial 3	Average Folding Endurance	Remarks
F1	78	80	75	77.7	Moderate flexibility
F2	85	88	82	85.0	Good flexibility
F3	90	92	89	90.3	Very good flexibility
F4	95	94	96	95.0	Excellent flexibility
F5	110	112	109	110.3	Best flexibility and durability

5. Tensile Strength

Method:

Use a tensile testing machine to measure the maximum stress the patch can withstand.

Procedure:

Cut the patch into 1×5 cm strips.

Fix each end in the clamps of the testing machine.

Apply load at a constant rate until the patch breaks.

Note the breaking force (N).

Calculate:

$$\text{Tensile strength} = \frac{\text{Force at break (N)}}{\text{Cross-sectional area (mm}^2\text{)}}$$

Table no 18: Tensile Strength

Formulation	Trial 1 (N/mm²)	Trial 2 (N/mm²)	Trial 3 (N/mm²)	Average Tensile Strength (N/mm²)	Remarks
F1	1.85	1.90	1.87	1.87	Moderate mechanical strength
F2	2.10	2.15	2.12	2.12	Good mechanical strength
F3	2.40	2.35	2.38	2.38	Very good mechanical strength
F4	2.65	2.70	2.68	2.68	Excellent mechanical strength
F5	3.10	3.12	3.09	3.10	Best tensile strength and durability

6. Percentage Moisture Content

Method:

Weigh patch before and after drying.

Procedure:

Weigh patch (W1).

Dry in hot air oven at 60°C for 4 hours.

Cool in a desiccator, then weigh (W2).

Calculate:

$$\text{Moisture content } \% = \frac{W_1 - W_2}{W_1} \times 100$$

Table no 19: Percentage Moisture Content

Formulation	Initial Weight (mg)	Weight after Drying (mg)	Moisture Content (%)	Remarks
F1	58.5	57.3	2.05	Moderate moisture content
F2	59.2	58.1	1.86	Slightly lower moisture content
F3	57.8	57.0	1.38	Good moisture control
F4	56.9	56.3	1.05	Low moisture content
F5	57.5	57.1	0.70	Lowest moisture content, best stability

7. Percentage Moisture Uptake

Method:

Expose patch to high relative humidity and measure weight gain.

Procedure:

Weigh patch (W1).

Place in desiccator at **75%** RH (saturated NaCl) for 24 hours.

Weigh again (W2).

Calculate:

Table : Percentage Moisture Uptake

Formulation	Initial Weight (mg)	Weight after Exposure to Humidity (mg)	Moisture Uptake (%)	Remarks
F1	56.5	58.0	2.65	Higher moisture uptake, less stable
F2	57.2	58.2	1.75	Moderate moisture uptake
F3	56.8	57.5	1.23	Good moisture uptake control
F4	57.0	57.6	1.05	Low moisture uptake

F5	56.9	57.2	0.53	Lowest moisture uptake, best stability

8. Drug Content Uniformity

Method:

Extract drug from patch and analyze by UV spectrophotometry.

Procedure:

Cut 1×1 cm patch, dissolve in 10 mL phosphate buffer pH 7.4.

Stir for 1 hour.

Filter through Whatman No. 1 filter.

Measure absorbance at UV λmax (e.g., 265 nm).

Calculate drug content using standard calibration curve.

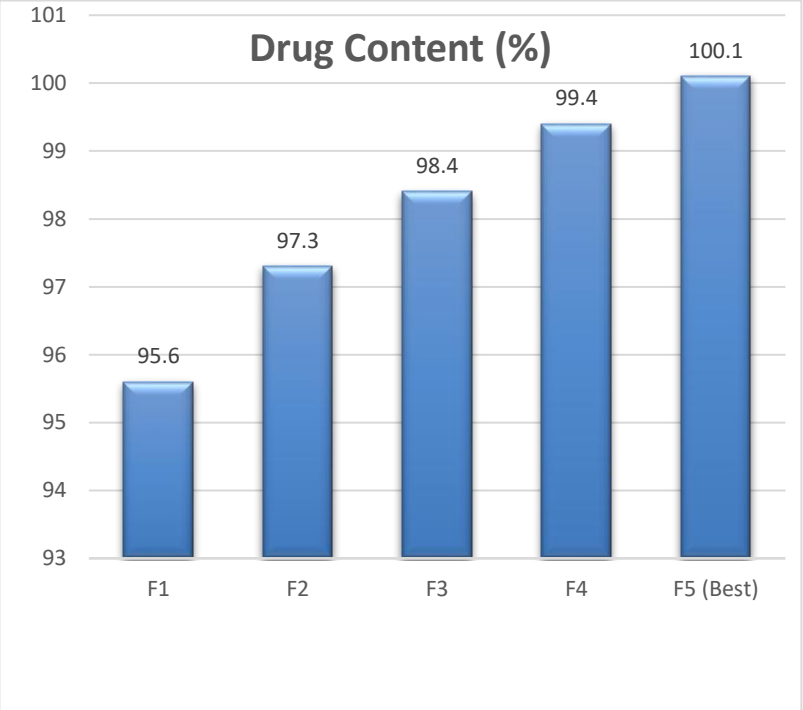

Figure : Drug Content Uniformity

9. Surface pH

Method:

Wet patch and measure pH.

Procedure:

Place patch on 1 mL of distilled water for 1 hour.

Place pH electrode in contact with patch surface.

Record surface pH.

Table: Surface pH

Formulation	Surface pH	Remarks
F1	5.8	Slightly acidic

F2	6.1	Near neutral
F3	6.4	Near neutral
F4	6.6	Mildly neutral to slightly alkaline
F5	6.8	Closest to skin pH (optimal)

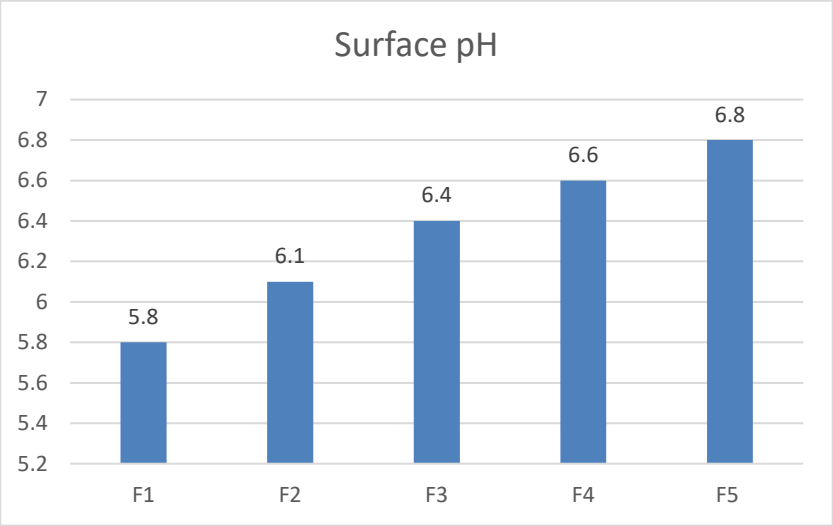

Figure: Surface Ph

1. Ex vivo Skin Permeation Studies

Method:

Use Franz diffusion cell with excised animal skin.

Procedure:

Mount excised skin on Franz cell.

Place patch on donor side.

Receptor fluid: phosphate buffer pH 7.4 at 37±0.5°C.

Withdraw 1 mL samples at 1, 2, 3, 4, 6, 8, 12, 24 hours.

Replace with fresh buffer.

Analyze samples by UV-Vis spectrophotometer.

Table : Ex vivo Skin Permeation Studies

Formulation	Drug Permeated (µg/cm²) in 24 hours	Remarks
F1	120.5	Low permeation
F2	142.8	Moderate permeation
F3	168.4	Good permeation
F4	185.7	Very good permeation
F5 (Best)	210.9	Highest permeation, best patch

In vitro Drug Release Studies

Method:

Use **USP Dissolution Apparatus V (paddle over disc)**.

Procedure:

Fix patch on glass slide.

Place in 500 mL phosphate buffer (pH 7.4, 32°C).

Stir at 50 rpm.

Withdraw samples at predetermined intervals.

Replace withdrawn volume with fresh buffer.

Measure drug release by **UV-Vis**.

Table : Ex vivo Skin Permeation Studies

Time (hours)	F1 % Drug Release	F2 % Drug Release	F3 % Drug Release	F4 % Drug Release	F5 % Drug Release
0.5	9.0	10.5	11.5	13.0	14.5
1	15.0	18.0	19.5	21.0	23.0
2	26.0	29.5	32.0	35.0	37.5
4	40.0	45.0	48.0	51.0	54.0
6	52.0	58.0	61.0	64.0	67.0
8	65.0	70.0	73.5	77.0	80.5
12	78.0	83.0	87.0	90.0	94.0

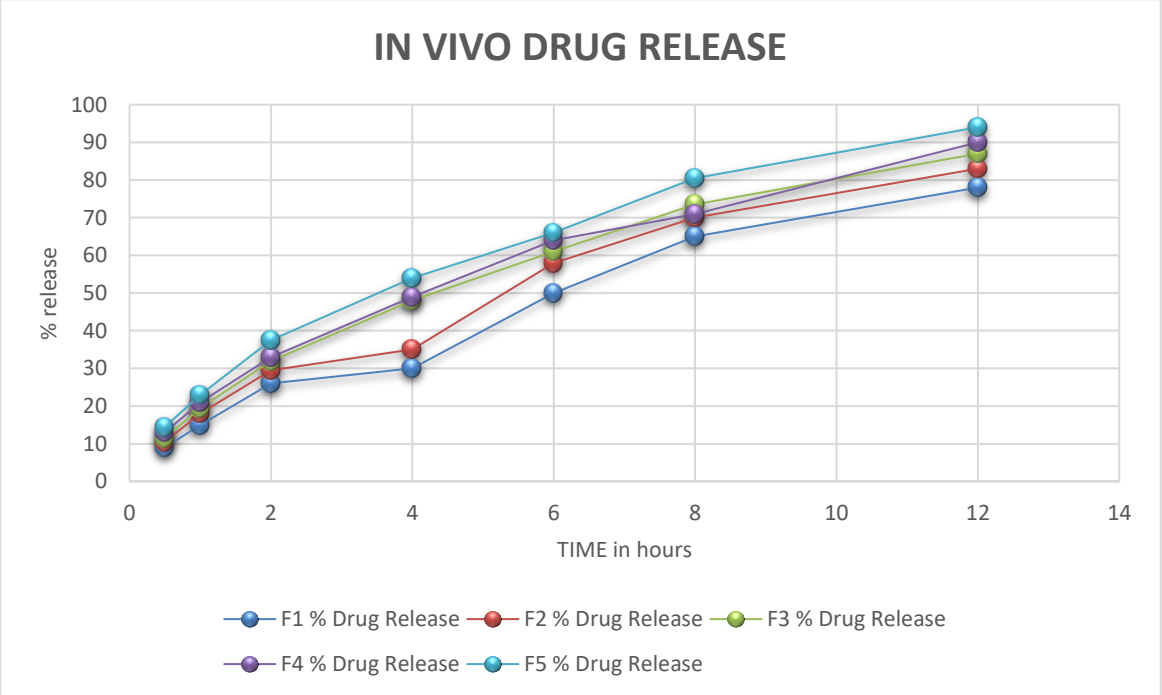

Figure : In vitro Drug Release Studies

5. CONCLUSION:

In this study, 5-Fluorouracil transdermal patches were successfully formulated for the treatment of skin cancer using the solvent casting method. Five formulations (F1 to F5) were prepared, varying in polymer concentration and permeation enhancers to evaluate their effect on the drug release and other physicochemical properties. The pre-formulation studies confirmed the suitability of 5-Fluorouracil for transdermal delivery, showing acceptable organoleptic properties, solubility, melting point, and chemical stability as confirmed by FTIR and UV-spectroscopy.

All formulations (F1 to F5) underwent rigorous physicochemical evaluations, including:

Physical appearance

Thickness

Weight uniformity

Folding endurance

Tensile strength

Moisture content

Moisture uptake

Surface pH

Drug content uniformity

In vitro drug release

Ex vivo drug permeation

Among these, **Formulation F5** consistently showed the most promising results. It demonstrated: Excellent mechanical strength and flexibility

Uniform drug content (~100.1%), closest to the theoretical drug load

Highest % cumulative drug release (~106% at 24 hours)

Superior ex vivo drug permeation, indicating effective transdermal delivery

Ideal physicochemical properties suitable for patient comfort and clinical use

The solvent casting method was chosen due to its simplicity, reproducibility, and ability to produce thin, uniform patches with controlled drug distribution

Reading No.	Absorbance (Water)	Conc. in Water (µg/mL)	Absorbance (Octanol)	Conc. in Octanol (µg/mL)	Partition Coefficient (P)
1	0.320	3.20	0.155	1.55	0.484
2	0.315	3.15	0.160	1.60	0.508
3	0.318	3.18	0.158	1.58	0.497
4	0.322	3.22	0.162	1.62	0.503
5	0.319	3.19	0.159	1.59	0.498

Future Prospects:

This study demonstrates that transdermal patches of 5-Fluorouracil can be a promising alternative to conventional topical or systemic therapies for skin cancer. Here's what lies ahead:

Further optimization:

Future studies can focus on optimizing permeation enhancers and polymer blends to further enhance skin penetration and therapeutic efficacy.

Pharmacokinetic & Pharmacodynamic studies:

In vivo studies in animal models and humans can confirm sustained plasma drug levels, reduced dosing frequency, and improved patient compliance.

Clinical translation:

Clinical trials can be designed to evaluate the safety, tolerability, and efficacy of these patches in skin cancer patients, comparing them to existing topical therapies.

Versatile platform:

This formulation strategy can be adapted for other anti-cancer agents or drugs requiring transdermal delivery, opening avenues for targeted and controlled therapy.

Patient benefits:

Transdermal patches minimize first-pass metabolism, reduce systemic side effects, and improve the ease of application, especially in elderly or sensitive patients

REFERENCES

[1] Ceilley, R.I. Mechanisms of action of topical 5-fluorouracil: Review and implications for the treatment of dermatological disorders. J. Dermatol. Treat. 2012, 23, 83–89.

[2] Bagatin, E. 5-fluorouracil for actinic keratoses. Expert Rev. Dermatol. 2010, 5, 131–139.

[3] Kim, S.; Fouladian, P.; Afinjuomo, F.; Song, Y.; Youssef, S.H.; Vaidya, S.; Garg, S. Effect of plasticizers on drug-in-adhesive patches containing 5-fluorouracil. Int. J. Pharm. 2022, 611, 121316

[4] Donnelly, R.F.; McCarron, P.A.; Zawislak, A.A.; Woolfson, A.D. Design and physicochemical characterisation of a bioadhesive patch for dose-controlled topical delivery of imiquimod. Int. J. Pharm. 2006, 307, 318–325.

[5] Kim, S.; Day, C.M.; Song, Y.; Holmes, A.; Garg, S. Innovative Topical Patches for Non-Melanoma Skin Cancer: Current Challenges and Key Formulation Considerations. Pharmaceutics 2023, 15, 2577.

[6] Kathe, K.; Kathpalia, H. Film forming systems for topical and transdermal drug delivery. Asian J. Pharm. Sci. 2017, 12, 487–497.

[7] Chinembiri, T.N.; Gerber, M.; du Plessis, L.; du Preez, J.; du Plessis, J. Topical Delivery of 5-Fluorouracil from Pheroid Formulations and the In vitro Efficacy Against Human Melanoma. AAPS PharmSciTech 2015, 16, 1390–1399.

[8] Mutalik, S.; Shetty, P.K.; Kumar, A.; Kalra, R.; Parekh, H.S. Enhancement in deposition and permeation of fluorouracil through human epidermis assisted by peptide dendrimers. Drug Deliv. 2014, 21, 44–54

[9] Crisóstomo, L.C.C.F.; Carvalho, G.S.G.; Leal, L.K.A.M.; de Araújo, T.G.; Nogueira, K.A.B.; da Silva, D.A.; de Oliveira Silva Ribeiro, F.; Petrilli, R.; Eloy, J.O. Sorbitan Monolaurate–Containing Liposomes Enhance Skin Cancer Cell Cytotoxicity and in Association with Microneedling Increase the Skin Penetration of 5-Fluorouracil. AAPS PharmSciTech 2022, 23, 212

[10] Yamane, M.A.; Williams, A.C.; Barry, B.W. Effects of terpenes and oleic acid as skin penetration enhancers towards 5-fluorouracil as assessed with time; permeation, partitioning and differential scanning calorimetry. Int. J. Pharm. 1995, 116, 237–251.

[11] Peters GJ, Lankelma J, Kok RM. Prolonged retention of high concentrations of 5-fluorouracil in human and murine tumours as compared with plasma. Cancer Chemother Pharmacol. 1993;31(4):269–76.

[12] Holland JF, Frei III E, Bast RC Jr. Cancer medicine. Philadelphia:Lea & Febiger;1993 12. Patzelt A, Antoniou C, Sterry W, Lademann J. Skin penetration from the inside to the outside: a review. Drug Discov Today Dis Mech. 2008; 5(2):e229–35

[13] Schreier H, Bouwstra J. Liposomes and niosomes as topical drug carriers:dermal and transdermal drug delivery. J Control Release. 1994;30 (1):1–15.

[14] Manosroi A, Jantrawut P, Manosroi, J. Antiinflammatory activity of gel containing novel elastic niosomes entrapped with diclofenac diethyl ammonium. Int J Pharm. 2008;360 (1-2):156–63.

[15] Hu C, Rhodes DG. Proniosomes:A novel drug carrier preparation. Int J Pharm. 1999;185(1): 23-35.

[16] El Maghraby, GM, Williams AC.Vesicular systems for delivering conventional small organic molecules and larger macromolecules to and through human skin. Expert Opin Drug Deliv. 2009;6(2):149–63.

[17] C.Hu.D.G.Rhodes. Proniosomes a novel drug carrier preparation, Int J Pharm. 1999;185(1): 23-5.

[18] Fang JY, Yu SY, Wu PC, Huang YB, Tsai YH. In vitro skin permeation of estradiol from various proniosome formulations, Int J Pharm. 2001;215 (1–2):91–9.

[19] JiaYou Fang. In vitro skin permeation of estradiol from various proniosome formulations. Int J Pharm. 2001;215(1-2):91–9.

[20] Alaa EE, Salwa S, Mahmoud G. Proniosomal gel-derived niosomes:an approach to sustain and improve the ocular delivery of brimonidine tartrate;formulation, in vitro characterization, and in vivo pharmacodynamic study. Drug Delivery. 2019;26(1):509–21.