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Formulation and evalution of hydrogel base transdermal patches of Flurouracil

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Abstract
To solve problems with drug administration, especially oral routes, transdermal drug delivery systems were created. Transdermal medication delivery is a technique that allows drugs to be administered either locally or systemically via the skin's surface. Transdermal patches have significantly benefited the pharmaceutical industry and medical practice by improving the way patients get both new and established medications. Various combinations of hydrogel-based transdermal patches are developed and evaluated using the solvent evaporation method. All formulations' pre-formulation results were approved. The spectral bands are examined using FTIR to determine the chemical interactions between the excipient and the API. The formulations' physicochemical characteristics, including their strength, swellability, surface pH, physical appearance, weight uniformity, folding durability, and % moisture uptake, were evaluated.
Conclusion: The best formulation was chosen after in-vitro drug penetration tests were performed on the created patches.

Keywords: Solvent casting technique, polyvinyl alcohol, hydrogel-based transdermal patches, fluorouracil and *in vitro* drug release

Introduction
Transdermal Drug Delivery System (TDDS): An alluring substitute for injection and oral administration is transdermal medication delivery. Approximately 74% of medications used orally now are discovered to be less effective than intended.

TDD is the standard term for drug administration through the skin (for systemic action). It is distinct from conventional topical medication distribution, it is often commonly referred to as "patches". Transdermal patches are dosage forms intended to transfer a therapeutically effective dosage of medication into the bloodstream from the skin's outer layers. The transdermal drug delivery system (TDDS), sometimes referred to as "patches," is a type of dosage form intended to apply a therapeutically effective quantity of medication to a patient's skin. For its systemic effects, TDDS help therapeutic amounts of medicinal substances pass through the skin and into the bloodstream. Stoughton came up with the idea of drug ingredient absorption through the skin in 1965. The FDA approved Transderm Scop (Ciba, now Novartis), the first transdermal device, in 1979 to prevent travel-related nausea and vomiting, especially when traveling by sea.

Benefits
1. Patients prefer noninvasive therapy, and TDDS, in particular, simple patches, are easy to use and non-invasive.
2. The first pass effect is avoided.
3. Extended action time.
4. Avoids environments that are too similar.
5. Simple to use, patches can lower medical expenses and improve compliance.

Drawback
1. It is not possible to provide medications that require high blood levels.
2. Not all skin types may adhere effectively to the applied adhesive.
3. Drugs or drug formulations may irritate or sensitize the skin.
4. It may be painful to wear the patches.
5. Some patients may not find this system to be cost-effective

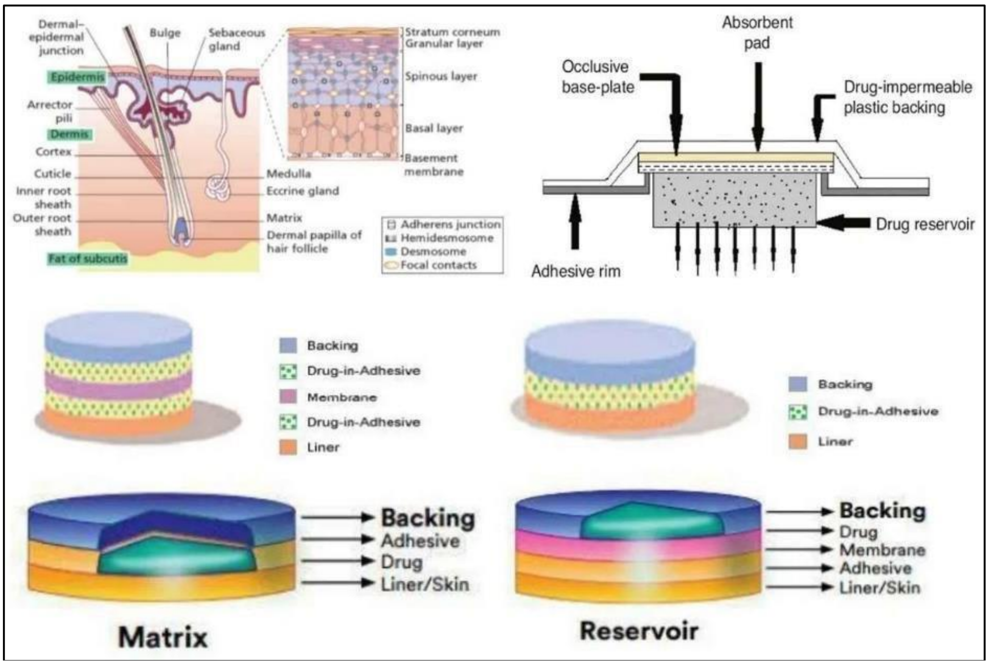

Fig 1: Transdermal drug delivery system

Various methods for preparation of TDDDS

- **Circular taflon mould method:** This method involves dissolving a solution comprising polymers in various ratios using an organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent after the prescribed dosage of medication has been dissolved in half of it. Di-N butyl phthalate is added to the drug polymer solution as a plasticizer. Before being put into a circular Teflon mold, the entire mixture is shaken for 12 hours. To control solvent vaporization, the molds are placed on a level platform and covered with an inverted funnel in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is let to evaporate for twenty-four hours. Before being evaluated, the dried films are kept in a desiccator with silica gel for a further 24 hours at 25±0.5°C to remove the effects of aging.
- **Mercury Substrate Method:** The medication is dissolved in a polymer solution containing a plasticizer in this technique. The aforementioned solution is shaken for ten to fifteen minutes, then placed over a flat surface of mercury and covered with an inverted funnel to prevent solvent evaporation and produce a homogenousdispersion.
- **IPM Membrane Method:** With the maximum permeation flux of 51.763 µg/cm²/h, isopropylmyristate (IPM) was the most effective enhancer. IPM is a commonly used nonvolatile solvent in the pharmaceutical and cosmetic industries and is a well-tolerated permeation enhancer for topical formulations. IPM is believed to alter skin permeability by upsetting the highly ordered lipid structure of the skin, which enhances penetration. Due to IPM's lipophilia. IPM is a member of the class of permeation enhancers known as aliphatic esters, which tend to increase the skin's diffusivity and partition coefficient. The drug is dissolved in a mixture of water and propylene glycol that contains the polymer carbomer 940, and it is whirled for 12 hours using a magnetic stirrer. With the addition of triethanolamine, the dispersion will be neutralized and viscous.
- **Aluminum-backed adhesive film method:** This technique is suitable when the loading dose exceeds 10-milligrams. Since the majority of medications and adhesives are soluble in chloroform, it is the preferred solvent for their manufacture. The sticky substance is introduced and dissolved in the drug solution after the drug particles have been dissolved in chloroform. The end sofa custom-made aluminum former are blanked with precisely fitting cork blocks, which are lined with aluminum foil. Blanked with precisely fitting cork blocks, which are lined with aluminum foil.
- **Free Film Method:** This approach involve casting a free cellulose acetate film over a mercury surface. A polymer solution is made with chloroform (2 percent w/w). It is recommended to use plasticizers at a 40% by weight concentration of the polymer. In a glass petridish, 5 mL of polymer solution was put into a glass ring that was positioned over the mercury surface. Placing an inverted funnel above the petridish controls the pace of solvent evaporation. The film formation is conducted when the solvent has completely evaporated and the mercury surface has been seen. The dried film is separated and kept in a desiccator between wax paper sheets until needed. By varying the amount of the polymer solution, free films of various thicknesses may be created.

Transdermal patches based on hydrogel

1. Hydrogels in Drug Delivery

Hydrogels are three-dimensional networks of water-absorbing and water-retaining polymers.

Innovative drug delivery vehicles due to their particular properties are the water content of hydrogels mimics the moisture of the skin.

- **Drug Encapsulation:** Active substances can be encapsulated in hydrogel.
- **Drug Release:** The hydrogel matrix facilitates controlled drug release.

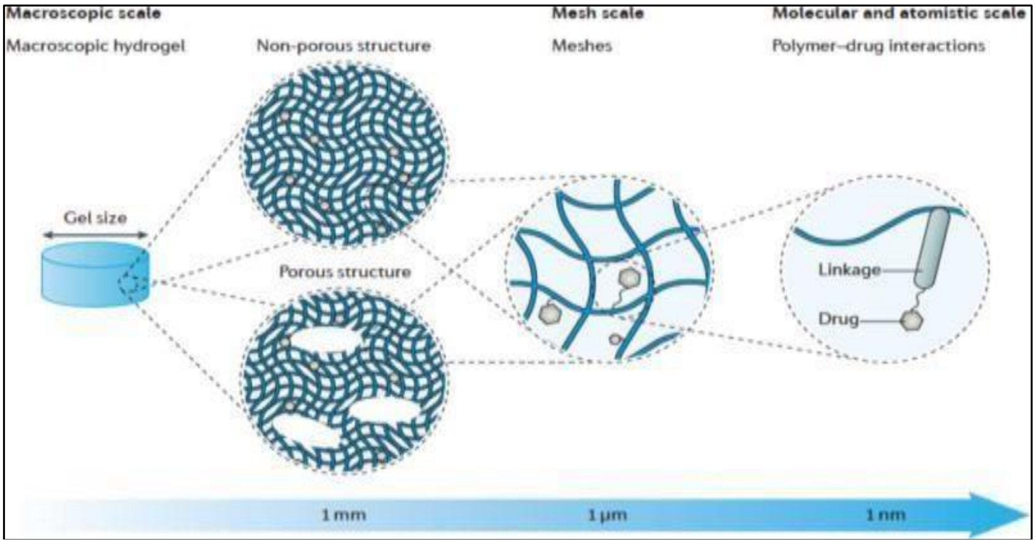

Fig 2: Hydrogels in drug delivery

2. Hydrogel strategies for drug release

- **Swelling/Deswelling Mechanism:** Hydrogels swell in the presence of water, allowing drug molecules to diffuse out. Deswelling occurs when the environment changes (e.g., pH, temperature).
- **Diffusion Mechanism:** Drug molecules diffuse through the hydrogel matrix based on concentration gradients.
- **Chemical Mechanism:** Some hydrogels undergo chemical reactions (e.g., hydrolysis) to release drugs over time.

3. Materials used for hydrogel

- **Natural Polymers:** Examples include chitosan, alginate, cyclodextrin and collagen.
- **Synthetic Polymers:** Examples include N-isopropyl acrylamide (NIPAM), acrylamide, polyvinyl alcohol (PVA), and polyethylene glycol (PEG).

Materials and Methods

- **Solvent Evaporation Method:** Solvent evaporation technique is a flexible method of particle preparation, in which various macromolecules and drugs may be employed. Parameters of emulsion obtained as first step of particle preparation are crucial in terms of particle size, drug loading, and morphology.

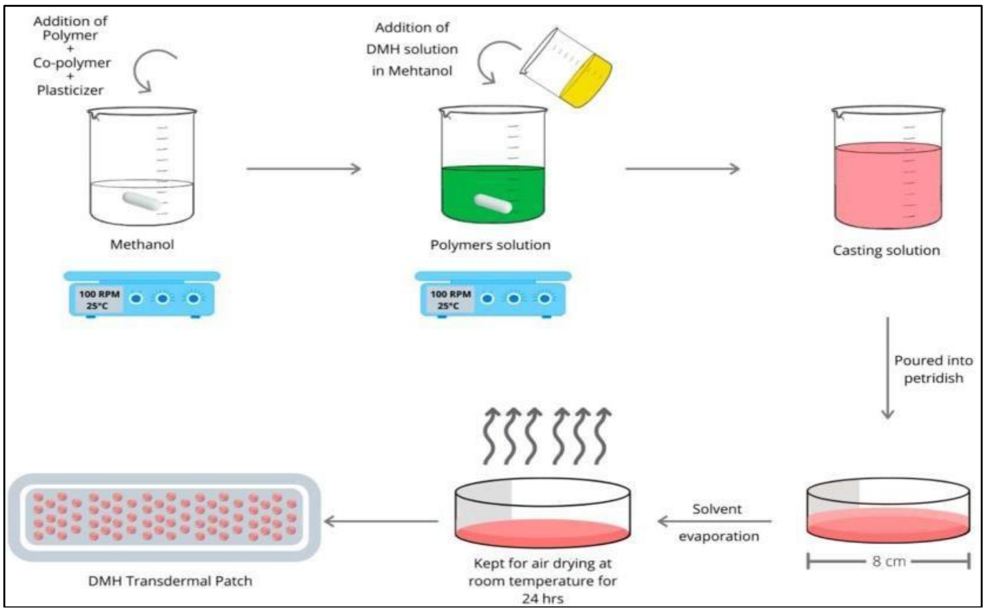

Fig 3: Solvent Evaporation Method

- **Mechanism of action:** The precise mechanism of action has not been fully determined, but the main mechanism of fluorouracil is thought to be the binding of the deoxyribonucleotide of the drug (FdUMP) and the folate cofactor, N5-10-methylenetetrahydrofolate, to thymidylate synthase (TS) to form a covalently bound ternary complex. This results in the inhibit ion of the formation of thymidylate from uracil, which leads to the inhibit ion of DNA and RNA synthesis and cell death. Fluorouracil can also be incorporated into RNA in place of uridinetri phosphate (UTP), producing a fraudulent RNA and interfering with RNA processing and protein synthesis.
- **Metabolism:** The catabolic metabolism of fluorouracil result in degradation products (e.g., CO2, urea and α-fluoro-ß-alanine) which are inactive.

Pharmacokinetics
- **Interpatient variability:** Variations in dihydropyrimidine dehydrogenase (DPD) activity result in differences in toxicity
- **Oral Absorption:** Erratic; 28-100%
- **Distribution:** Approximately 22% of total body water; penetrates extracellular fluid and third space fluids(e.g., malignant effusions and ascitic fluid) cross blood-brain barrier, the volume of distribution is 6 8-11 L/m2 plasma protein binding is 7-10%.
- **Metabolism:** activated in target cells; 80% degraded in liver by DPD6 active metabolite(s) FdUMP, FUTP and FdUTP inactive metabolite(s) dihydrofluorouracil.
- **Excretion:** 60-80% excrete dasrespiratory CO_2, 2-3% by biliary system urine.

Materials

Table 1: Drug & excipient used in formulation

Sr. No.	API Name	Category
1	Fluorouracil	Anticancer
Sr. No.	**Excipient Name**	**Category**
1	PVA	Water soluble Polymer
2	Gelatin	Hydrogel base
3	PEG	Plasticizers
4	Pthalic anhydride	Organic compound

Methods
Solvent evaporation was applied to create nine different formulations of transdermal patches, each with different quantities of PVA, chitosan, PEG & drug. 10 ml of hot water was used to dissolve PVA after it was accurately weighed. Everything was thoroughly mixed. Drop by drop, Pthalicic anhydride solution was added. The mixture was then thoroughly stirred for 30 minutes. Polyethylene glycol was utilized as a plasticizer. Pour the solution into Petriplates. Cover the Petri plate with an inverted funnel to avoid evaporation. Dry the patches for 24 hrs and dry patches stored in desiccators.

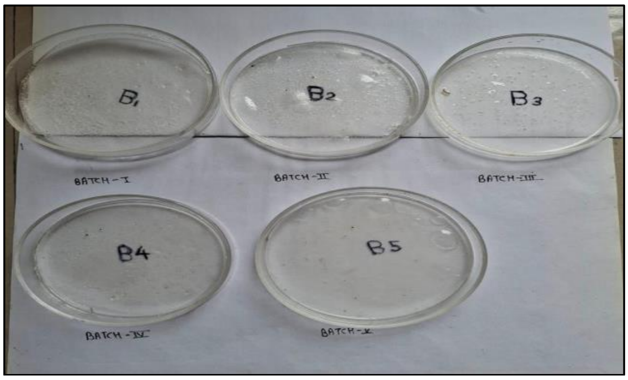

Fig 4: Formulated Patches

Evalution
- **Physical appearance:** The prepared rasagiline tarterate patches were evaluated visually for physical appearance like Colour, clarity, smoothness, and flexibility.
- **Thickness:** The thickness of the prepared patches was measured using verniercaliper with a least count 0.01mmat different spot of the patch. The thickness was measured at the least spot of the patches and average was taken and final thickness is note down.
- **Weight uniformity:** Weight variation study is carried out by selection of randomly 10 patches, with a size of 4cm². Weight an individual patch in digital balance and calculate the average weight. The individual weight of the patches should not deviate significally from the average weight.
- **Folding endurance:** The folding endurance also called as the number of folds. (Number of the folds given to the patch at the same time) for the break the preparation or create the visible crack. This test is performed for TO check the stability of the formulation. Folding endurance performed by repetitively folding a small strip of patch (2 x 2 cm) at the same place till it broken or make visible crack. The number of time patches fold at the same place gave the value of folding endurance and it was note down.
- **Moisture uptake:** In this study, initially weighed patches were placed in the desiccators for 24 hrs. Which contain saturated solution of potassium chloride to maintained humidity inside at 80% Relative Humidity (RH) after completion of study, the patches were take-out side and once again weighed. The percentage moisture absorption of the patches calculated by the following equation.
- **Swell ability:** The 2.5 cm2 patches were weighed, placed in a Petri dish with 10 ml of double-distilled water, and allowed to absorb. The patch's weight was increased at predetermined intervals until a steady weight was noticed.
- **Surface pH:** The patches were placed in glass tube sand allowed to swell for one hour by using contact with 0.5 ml of double-distilled water. After that, the surface pH was measured by placing a combination glass electrode close to the patch's surface and letting it a minute to acclimate.

Result and Discussion
Evalution of transdermal patch

Table 2: Physical appearance

Batches	Color	Clarity	Appearance
B1	Colorless	Transparent	Thin, Smooth
B2	Colorless	Transparent	Thin, Smooth
B3	Colorless	Transparent	Thin, Rough
B4	Colorless	Transparent	Smooth
B5	Colorless	Transparent	Rough

Table 3: Physicochemical Properties

Batches	Thickness (mm)	Weight uniformity (mg)	Folding endurance
B1	0.23±.018	100± 8.84	98±3.249
B2	0.27±.016	115± 3.49	114±6.741
B3	0.30±.034	125± 6.32	126±2.684
B4	0.31±.014	149± 7.14	154±0.356
B5	0.34±.004	150± 7.34	186±7.027

Table 4: Surface PH and swell ability

Batches	Surface PH	Swell ability (%)
B1	7.0±.091	12.456+.252
B2	7.1±.012	19. 433+ .084
B3	7.2±.034	19.452+.094
B4	7.2 ±.074	20.133+.317
B5	7.3±.121	22.727+.125

Conclusion

In contrast to oral drug delivery, the hydrogel-based transdermal patch of fluorouracil formulations that were prepared and optimized using polymers such as PVA, Gelatin, and PVG plasticizer permeation enhancers showed their ability to provide prolonged release due to the drug's excellent release and penetration and influence better TDDS bioavailability data. These formulations produced a favorable result. These studies can help the industrial sector scale up for commercial production. These improving their capacity to treat them. Results may potentially give physicians other therapeutic options for their patients with skin cancer, Formulation number F8 exhibits the optimal formulation compared to the others due to the following factors: drug content (93%), moisture uptake (8.12%), thickness (0.35±0.016mm²), folding endurance (236), and *in vitro* drug penetration investigations were conducted on the developed patches.

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