RESEARCH PAPER

Development of Nanoemulsion-Based Topical Cream Containing 5-Fluorouracil and Piperine for Enhanced Skin Penetration in Skin Cancer Therapy

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ABSTRACT

Skin cancer represents one of the most commonly diagnosed cancers globally, with non-melanoma variants contributing to the majority of reported cases. Topical chemotherapeutic approaches provide targeted drug action at the disease site, minimizing systemic exposure while improving patient adherence. Fluorouracil (5-FU), a pyrimidine antimetabolite, is extensively employed in the topical management of actinic keratosis and superficial basal cell carcinoma. This study aims to develop and assess a topical cream formulation containing Fluorouracil (5%) incorporated with Piperine as a skin penetration enhancer. The formulation was prepared using excipients such as white petrolatum, cetyl alcohol, propylene glycol, polysorbate 60, methyl paraben, and purified water. Comprehensive pre-formulation investigations were performed to evaluate the physicochemical characteristics and excipient compatibility of Fluorouracil. The formulated cream was subjected to various evaluation tests including physicochemical assessment, stability analysis, and in-vitro drug release studies. The findings suggest that the developed cream possesses satisfactory formulation properties and demonstrates promising potential for the topical delivery of Fluorouracil in the treatment of skin cancer.

Keywords: Skin cancer, Fluorouracil, Piperine, Topical cream

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I. INTRODUCTION: -

It is increasingly being realized that skin cancer (SC) is a significant issue of global public health and is now ranked among the five most widely diagnosed cancers in the world. Its increasing popularity over the past few years has attracted much attention on the part of researchers and health care providers. (1) The projections point out in the future that cancer as a whole might soon become the principal cause of death worldwide and a significant challenge to further increase the life expectancy. International Agency on Research on Cancer (IARC) published estimates on the global incidence of cancer and found that there were about 18 million new cancer cases in 2018 with nearly 10 million deaths due to the disease. More recent statistics provided by the American Cancer Society point to the fact that melanoma is causing approximately 6 percent of newly-diagnosed malignancies in men and approximately 4 percent in women in 2023. (2) The present trends in epidemiology also indicate a gradual and alarming increase in the prevalence of skin cancer in the next two decades. All these trends help to learn about the urgency to improve awareness, intensify prevention, promote early diagnosis, and improve therapeutic interventions, which would help manage and regulate the increasing skin cancer load. (3)

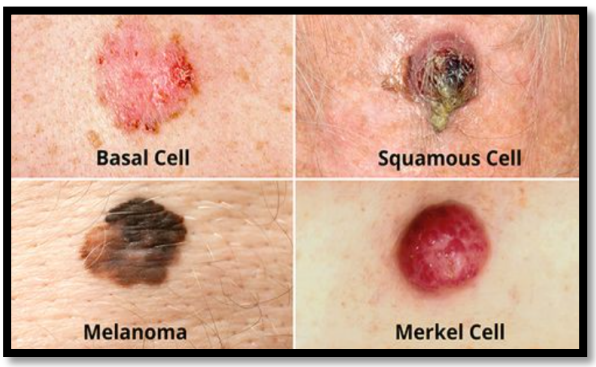


Figure 1: Types of Skin Cancer

The development of skin cancer is mainly associated with uncontrolled proliferation of skin cells resulting from unrepaired DNA damage, which arises due to genetic mutations or inherited defects. Structurally, the skin consists of two primary layers: the outer epidermis and the underlying dermis. (4) The epidermis is composed of epithelial cells along with pigment-producing melanocytes, while the dermis contains connective tissue that supports blood vessels, hair follicles, and sweat glands. Skin cancers originating from genetic alterations in melanocytes are classified as malignant melanoma. In contrast, non-melanoma skin cancer (NMSC), which arises from the epidermal layer, represents the most commonly diagnosed form of skin cancer worldwide. Depending on the specific epidermal cell type involved, NMSC is further categorized into basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). (5)

Approximately one-fourth of documented cases report the transformation of benign moles into malignant melanoma, a highly aggressive form of skin cancer with a strong tendency to metastasize and recur. This type of skin cancer is associated with a considerable risk of relapse even after treatment. In contrast, non-melanoma skin cancers generally show limited invasion into deeper skin layers and can be effectively managed when detected at an early stage. (6) Early diagnosis allows for relatively simple therapeutic interventions with favourable outcomes. Owing to its increasing incidence and its adverse impact on the physical, psychological, and social well-being of affected individuals, skin cancer requires substantial investment in advanced diagnostic technologies and improved treatment strategies. (7)

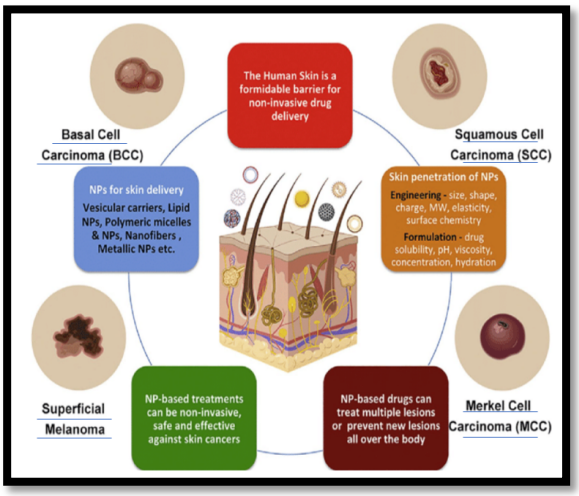


Figure 2: Types of Treatment available for treatment of Skin Cancer

Currently available treatment modalities include surgical excision, chemotherapy, and radiotherapy. However, these approaches are often associated with significant discomfort, incomplete disease control, and multiple adverse effects. Moreover, conventional therapies frequently damage healthy tissues while failing to achieve adequate selectivity toward cancer cells. In this context, emerging tumour-targeted and tissue-preserving treatment options have gained attention. (8) Phototherapy-based approaches, including photodynamic therapy (PDT) and photothermal therapy (PTT), offer promising alternatives for clinical cancer management. These techniques utilize light-activated agents to selectively destroy malignant cells, thereby minimizing collateral damage to normal tissues and reducing treatment-related side effects. (9)

II. MATERIALS AND METHOD: -

2.1 MATERIALS: -

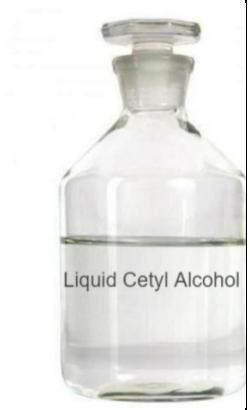
Table 1: Composition of Ingredient: -

S. No.	Ingredient	Role in Formulation	Quantity (for 50 g)
1.	Fluorouracil	Anticancer drug (API)	2.5 g (5% w/w)
2.	Piperine	Penetration enhancer	0.05 g
3.	White petrolatum	Emollient, oil phase base	10.0 g
4.	Cetyl alcohol	Stiffening agent	2.0 g
5.	Propylene glycol	Humectant, solvent	5.0 g
6.	Polysorbate 60	Emulsifying agent	1.5 g
7.	Methyl paraben	Preservative	0.1 g
8.	Purified water	Aqueous phase vehicle	q.s. to 50 g

Table 2: Drug Profile (10)

SNO.	INGREDIENTS (DRUGS)	DRUG PROFILE	PICTURE

1	Fluorouracil	Generic Name: Fluorouracil Official Name: 5-Fluorouracil Chemical Class: Antimetabolite (pyrimidine analogue) Molecular Formula: $C_4H_3FN_2O_2$ Molecular Weight: 130.08 g/mol	
2	Piperine	Chemical Name: Piperine Source: *Piper nigrum* (Black pepper) and *Piper longum* (Long pepper) Chemical Class: Alkaloid Molecular Formula: $C_{17}H_{19}NO_3$ Molecular Weight: 285.34 g/mol	
3	White Petrolatum	Official Name: White Petrolatum Synonyms: White soft paraffin, Petroleum jelly Chemical Class: Hydrocarbon mixture (semi-solid hydrocarbons) Origin: Purified fraction of petroleum	

4	Cetyl Alcohol	Official Name: Cetyl Alcohol Synonyms: 1-Hexadecanol, Palmityl alcohol Chemical Class: Fatty alcohol Molecular Formula: $C_{16}H_{34}O$ Molecular Weight: 242.44 g/mol	
5	Propylene glycol	Official Name: Propylene Glycol Chemical Name: 1,2-Propanediol Chemical Class: Polyhydric alcohol Molecular Formula: $C_3H_8O_2$ Molecular Weight: 76.09 g/mol	
6	Polysorbate 60	Official Name: Polysorbate 60 Synonyms: Tween 60 Chemical Class: Non-ionic surfactant Chemical Nature: Polyoxyethylene sorbitan monostearate	
7	Methyl Paraben	Official Name: Methyl Paraben Chemical Name: Methyl p-hydroxybenzoate Chemical Class: Paraben ester (antimicrobial preservative) Molecular Formula: $C_8H_8O_3$ Molecular Weight: 152.15 g/mo	

2.3 METHOD: -

Method of Preparation of Cream

1. All required ingredients were accurately weighed according to the formulation composition.
2. The oil phase was prepared by transferring white petrolatum and cetyl alcohol into a clean beaker and heating the mixture on a water bath until completely melted.

Figure 3: Heating

3. Polysorbate 60 was added to the molten oil phase with gentle stirring to ensure uniform mixing.
4. In a separate container, the aqueous phase was prepared by dissolving methyl paraben in purified water with mild heating.

Figure 4: Separation

5. Fluorouracil was gradually incorporated into the aqueous phase under continuous stirring to obtain a clear and uniform solution.
6. Piperine was dissolved in propylene glycol, and this solution was added slowly to the aqueous phase with constant mixing.

Figure 5: Mixing

7. Both the oil and aqueous phases were maintained at the same temperature (approximately 70–75°C) to prevent phase separation.
8. The aqueous phase was slowly added to the oil phase with continuous stirring to form a homogeneous emulsion.
9. The emulsion was stirred continuously while allowing it to cool to room temperature, leading to the formation of a smooth cream.
10. The prepared cream was transferred into a suitable, well-labelled container and stored under appropriate conditions for further evaluation. (10)

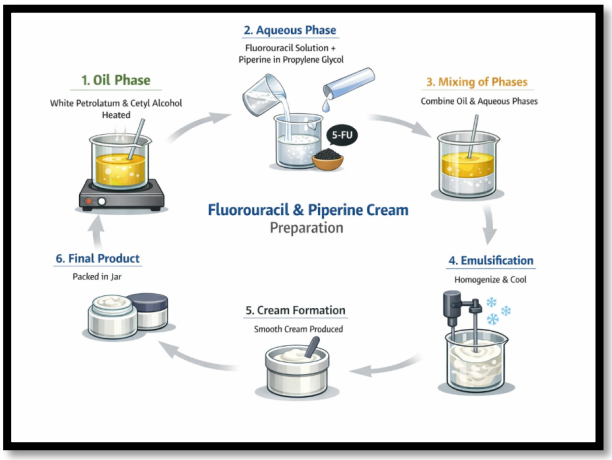


Figure 6: Method of Preparation of cream

Figure 7: Final product (Cream)

III. RESULT AND DISCUSSION: -

3.1 PRE-FORMULATION OF FLUOROURACIL: -

1. Physical Appearance: -

Fluorouracil appears as a white to off-white crystalline powder with a uniform texture and absence of visible impurities. It is odorless in nature, indicating chemical purity and stability. The crystalline form suggests good handling properties and suitability for incorporation into pharmaceutical formulations.

Table 3: Physical Appearance

Parameter	Category / Observation
Colour	White to off-white
Physical state	Solid
Nature	Crystalline powder
Odor	Odorless
Visible impurities	Absent

Figure 8: Fluorouracil Powder

2. Solubility: -

In ethanol and DMF, celecoxib has a solubility of approximately 25 mg/ml and 16.6 mg/ml, respectively.

Table 4: Solubility of Drug

S.no.	Solvent	Observation	Standard*
1.	Ethanol	++++	++++
2.	DMSO	+++	+++
3.	DMF	++	++

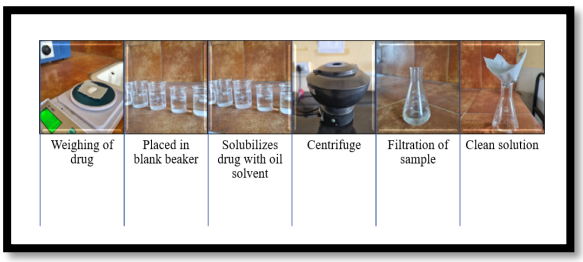


Figure 9: Solubility of drug

3. Melting Point: -

The melting point is the temperature at which a solid substance turns into a liquid at atmospheric pressure. At this specific temperature, the solid and liquid phases of the substance are in equilibrium.

Table 5: melting point of Fluorouracil

S.no	Observed Melting Point	Average Melting Point	Reference Melting Point
1	149°C	161°C	159°C - 165°C
2	154°C		
3	161°C		

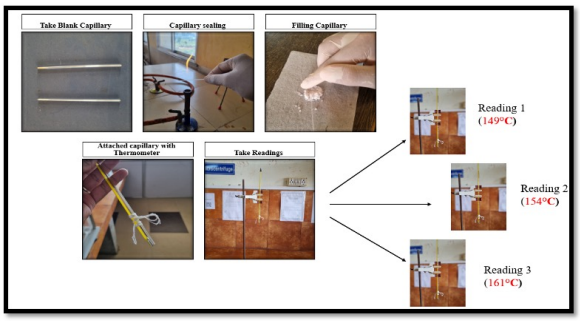


Figure 10: Melting point

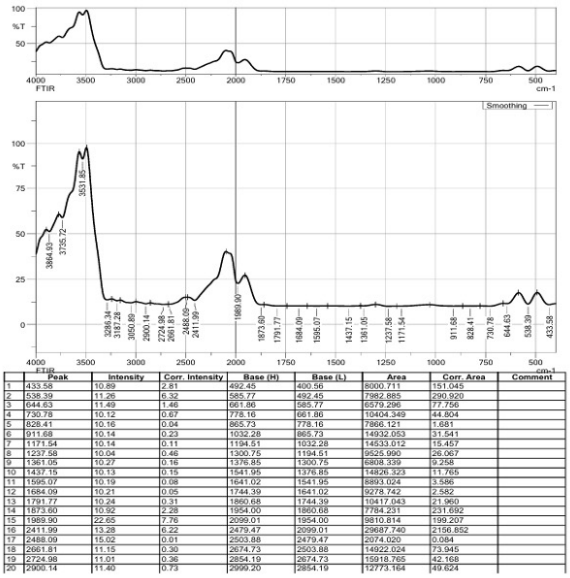
4.Fourier transform infrared spectrometry (FTIR): -

Fourier Transform Infrared Spectroscopy (FTIR) is a powerful analytical technique used to obtain the infrared spectrum of absorption or emission of a solid, liquid, or gas. It is widely used in various fields, including chemistry, biology, materials science, and pharmaceuticals, to identify and characterize chemical compounds.

Principle of FTIR:

FTIR works on the principle that molecules absorb specific frequencies of infrared light, which causes molecular vibrations. When infrared radiation passes through a sample, certain wavelengths are absorbed by the sample, while others are transmitted. The resulting spectrum represents the molecular fingerprint of the sample, allowing for the identification of functional groups and molecular structures. (11)

Here, is the FTIR of Fluorouracil Drug



	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area	Comment
1	433.58	10.89	2.81	492.45	400.56	8000.711	151.045	
2	538.39	11.26	6.32	585.77	492.45	7982.885	290.920	
3	644.63	11.49	1.46	661.86	585.77	6579.296	77.756	
4	730.78	10.12	0.67	778.16	661.86	10404.349	44.804	
5	826.41	10.16	0.04	865.73	778.16	7866.121	1.681	
6	911.68	10.14	0.23	1032.28	865.73	14932.053	31.541	
7	1171.54	10.14	0.11	1194.51	1032.28	14533.012	15.457	
8	1237.58	10.04	0.46	1300.75	1194.51	9525.990	26.067	
9	1361.05	10.27	0.16	1376.85	1300.75	6808.339	9.258	
10	1437.15	10.13	0.15	1541.95	1376.85	14826.323	11.765	
11	1595.07	10.19	0.08	1641.02	1541.95	8893.024	3.586	
12	1684.09	10.21	0.05	1744.39	1641.02	9278.742	2.582	
13	1791.77	10.24	0.31	1860.68	1744.39	10417.043	21.960	
14	1873.60	10.92	2.28	1954.00	1860.68	7784.231	231.692	
15	1989.90	22.65	7.76	2099.01	1954.00	9810.814	199.207	
16	2411.99	13.28	6.22	2479.47	2099.01	29687.740	2156.852	
17	2488.09	15.02	0.01	2503.88	2479.47	2074.020	0.084	
18	2661.81	11.15	0.30	2674.73	2503.88	14922.024	73.945	
19	2724.98	11.01	0.36	2854.19	2674.73	15918.765	42.168	
20	2900.14	11.40	0.73	2999.20	2854.19	12773.164	49.624	

Figure 11: FTIR of Drug

5. Calibration and absorption of Fluorouracil:

The lambda max of the Fluorouracil was found to be 266 nm. After the determination of lambda max the calibration curve and absorption are to be evaluated by the UV spectroscopy. The results of the absorption and concentration were given below in the Table 7.(12-18)

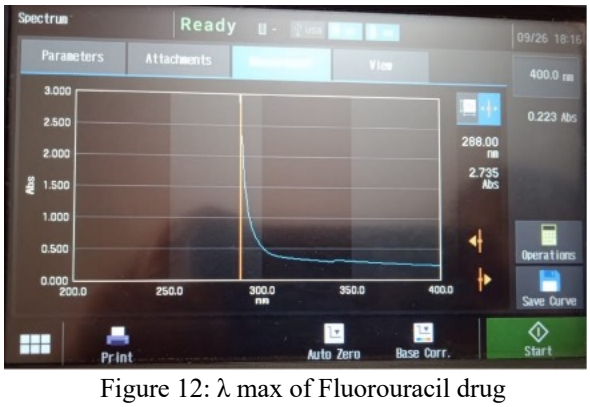


Figure 12: λ max of Fluorouracil drug

Table 7: Concentration and absorption of Fluorouracil.

S.no	Concentration (ug/ml)	Absorption
1	**2**	**1.662**
2	**4**	**1.835**
3	**6**	**1.990**
4	**8**	**2.020**
5	**10**	**2.257**
6	**12**	**2.998**

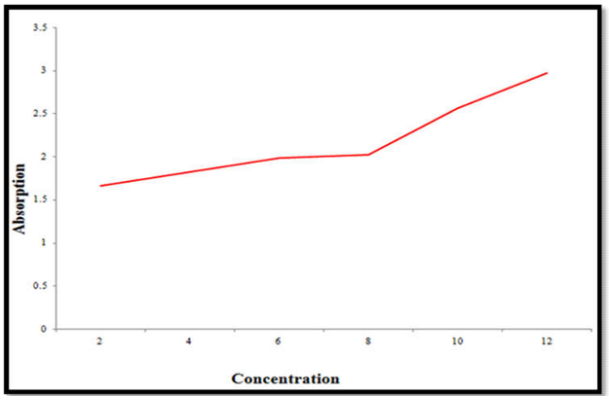


Figure 13: Graph showing Absorption vs. concentration of Fluorouracil

IV. CONCLUSION: -

The present study was aimed at formulating and evaluating a topical cream containing Fluorouracil (5%) with Piperine as a penetration enhancer for the treatment of skin cancer. Pre-formulation studies confirmed that Fluorouracil possesses suitable physicochemical properties for topical application, although its hydrophilic nature limits skin penetration. The incorporation of Piperine was therefore justified to improve permeation across the stratum corneum. The cream was prepared using appropriate excipients to obtain acceptable consistency, stability, and patient-friendly characteristics. Evaluation of the formulated cream showed satisfactory physical appearance, pH, spreadability, viscosity, and uniform drug content. In-vitro drug release studies indicated a controlled release pattern, supporting prolonged local drug availability. Stability studies demonstrated that the formulation remained stable under prescribed conditions. Overall, the developed Fluorouracil–Piperine cream exhibited promising potential as an effective topical delivery system for skin cancer management. Further in-vivo and clinical investigations are recommended to establish its therapeutic efficacy and safety.

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