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DEVELOPMENT AND CHARACTERIZATION OF FLUOROURACIL-LOADED SOLID LIPID NANOPARTICLE GEL FOR ENHANCED TOPICAL DELIVERY IN SKIN CANCER

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Abstract:

Skin cancer is a major dermatological challenge, and topical chemotherapy often remains limited by inadequate skin penetration, poor retention within viable epidermis, and nonselective drug distribution. Solid lipid nanoparticles (SLNs) provide a promising platform for improving local skin targeting because they combine nanoscale size, lipid compatibility, occlusive behavior, and the potential for controlled drug deposition within epidermal and dermal layers. The present work focused on the development, characterization, and biological evaluation of fluorouracil-loaded SLNs for topical treatment of skin cancer. Fluorouracil was selected because of its established clinical role in topical management of premalignant and malignant skin lesions and because prior studies have shown its efficacy against UVB-associated skin damage and tumorigenesis (Khan et al., 2020; Narayana Pillai et al., 2020; Roy et al., 2018).

Preformulation studies included physicochemical characterization, partition coefficient estimation, Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and analytical method development for drug estimation. The study reported a highly linear calibration curve for fluorouracil at 260 nm, with R^2=0.9983, supporting reliable analytical quantification during formulation studies. Fluorouracil-loaded SLNs were then prepared and characterized for particle size, polydispersity index (PDI), zeta potential, entrapment efficiency, drug loading, morphology, crystallinity, and thermal behavior. The optimized formulation showed a mean particle size of 220 ± 0.9 nm, PDI of 0.419 ± 0.035, zeta potential of −18.5±0.3 mV, entrapment efficiency of 88.3 ± 2.3%, and drug loading of 1.9 ± 0.3%.

The optimized SLN dispersion was incorporated into a Carbopol 934 gel and evaluated for pH, viscosity, spreadability, extrudability, homogeneity, occlusive behavior, and drug content. The final gel showed a pH of 6.88 ± 0.21, drug content of

99.68 ± 0.89%, viscosity of 5.28 Pa·s, spreadability of 5.24 ± 0.24 cm, and extrudability of 53.35 g/cm2^22, indicating acceptable suitability for topical use. Dermatokinetic studies showed markedly enhanced deposition of fluorouracil from the SLN gel compared with conventional gel. In epidermis, $C_{skin\ max}$ increased from 89.7 ± 9.5 to 205.9 ± 13.8 μg/cm^2, while in dermis it increased from 96.8 ± 7.8 to 220.8 ± 8.5 μg/cm^2. Confocal laser scanning microscopy demonstrated that fluorescence from conventional gel became negligible after 45 μ\μm, whereas SLN gel fluorescence extended to about 60 μ\muμm, indicating deeper deposition.

Mechanistic studies using FTIR and DSC of treated skin suggested lipid disruption, lipid fluidization, and keratin alteration as contributors to enhanced skin permeation. Ex vivo anti-cell proliferation data showed concentration-dependent cytotoxicity of the fluorouracil SLN gel, and in vivo studies indicated absence of visible skin irritation and reduced inflammatory mediators such as IL-1α and TNF-α in tumor-bearing skin compared with placebo and conventional gel groups. Taken together, these findings indicate that fluorouracil-loaded SLN gel is a promising topical nanocarrier system for improving local drug delivery and therapeutic performance in skin cancer.

Keywords: fluorouracil; solid lipid nanoparticles; topical gel; skin cancer; Dermatokinetic; epidermal targeting

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INTRODUCTION:

Skin is the largest organ of the human body and serves as a barrier, sensory interface, and regulator of homeostasis. Because it functions as a highly organized protective structure, its outermost barrier, especially the stratum corneum, significantly limits the permeation of many therapeutic agents. This protective role is important physiologically, but it also creates a major formulation challenge when drugs must be delivered into viable epidermis or dermis to treat local pathological conditions such as psoriasis, dermatitis, actinic damage, and skin cancer.

Skin cancer remains one of the most clinically important dermatological disorders, particularly because abnormal proliferation initiated by ultraviolet exposure can progress through multiple stages of carcinogenesis and extend from superficial epidermal abnormalities to invasive dermal lesions. The study shows that skin malignancy may involve basal cells, squamous cells, or melanocytes and highlights the significance of local therapy in preserving function, limiting systemic burden, and improving patient outcomes. Conventional topical systems such as creams and gels are easy to apply, but they often provide inadequate penetration, limited localization in the target skin layers, variable release, and poor control of residence time.

Topical fluorouracil is already well recognized in dermatological practice for the management of premalignant and malignant lesions, including actinic keratosis and certain superficial non-melanoma skin cancers. Its mechanism of action is based on inhibition of thymidylate synthase and interference with both DNA and RNA synthesis, leading to selective toxicity in rapidly dividing cells. The summarized Experimental studies also support its utility in UVB-associated skin damage and skin carcinogenesis. Khan et al. (2020) linked fluorouracil's antitumor effect with downregulation of inflammatory mediators, while Narayana Pillai et al. (2020) and Roy et al. (2018) showed beneficial effects on UVB-associated cellular injury and repair pathways. Meeran et al. (2017) further demonstrated that topical fluorouracil reduced UV-induced oxidative stress by targeting infiltrating inflammatory cell populations, supporting its relevance beyond direct cytotoxicity alone.

Despite this therapeutic relevance, efficient epidermal and dermal targeting of fluorouracil remains challenging. Fluorouracil is relatively hydrophilic, and the study showed an experimental partition coefficient near 1, which helps explain why conventional formulations may not fully exploit its local therapeutic potential. Nanocarrier-based systems, especially SLNs, offer an attractive strategy to address this problem by improving deposition, modulating release, enhancing contact with skin, and altering barrier behavior through lipid interaction. SLNs are colloidal lipid carriers typically ranging from 10 to 1000 nm and are valued for biodegradability, drug protection, improved delivery efficiency, and the potential for controlled targeting. The broader value of lipid nanoparticles in dermal drug delivery, with improved penetration or retention reported for Nimesulide, methotrexate, lycopene, Idebenone, tacrolimus, and other actives (Moghaddam et al., 2016; Pinto et al., 2014; Okonogi et al., 2015; Li et al., 2012; Tosta et al., 2017).

Another advantage of SLNs in topical delivery is their ability to create close contact with the skin surface and potentially increase hydration or occlusion, thereby facilitating transport across the stratum corneum. The study also shows that lipid-based nanocarriers can improve epidermal targeting, reduce fluctuations in drug delivery, and enhance therapeutic effectiveness while preserving patient convenience. At the same time, successful development depends on achieving a suitable balance of particle size,

surface charge, drug entrapment, gel properties, and stability, because all of these factors influence cutaneous delivery and formulation acceptability.

Based on this rationale, the present study aimed to formulate fluorouracil-loaded SLNs, characterize the optimized nano system, incorporate it into a topical gel, and evaluate its performance through physicochemical, permeation, Dermatokinetic, ex vivo, and in vivo studies. The study also aimed to clarify whether SLN-based topical delivery could increase fluorouracil deposition in skin layers relevant to skin carcinoma, while reducing inflammatory burden and preserving local tolerability.

1. MATERIALS AND METHODS:

1.1 Materials

Fluorouracil was procured from Unicure India Pvt. Ltd., Noida, Uttar Pradesh, India, while formulation excipients included poloxamer, sodium taurocholate, stearic acid, mannitol, glycerol monostearate, hydroxypropyl cellulose, tristearin, Carbopol, chitosan, glyceryl behenate, Tween 80, Span 20, polyethylene glycol, Compritol, and other lipid and polymeric components from various suppliers. The instrumentation included a UV spectrophotometer, FTIR spectrophotometer, particle size analyzer, zeta sizer, DSC instrument, HPLC system, X-ray diffractometer, freeze dryer, pH meter, centrifuge, and viscometer, among others.

1.2 Drug characterization and analytical method

Fluorouracil was subjected to physicochemical characterization, including organoleptic evaluation, melting point determination, solubility, and partition coefficient estimation. A UV spectrophotometric calibration curve at 260 nm across 10-80 µg/mL, with a regression equation corresponding to high linearity and R^2=0.9983 was prepared. This calibration served as the basis for subsequent estimation of fluorouracil in formulation, permeation, and related analytical studies.

FTIR studies were used to identify possible drug excipient interactions, while DSC was applied to evaluate thermal behavior and compatibility of the drug with selected excipients. The preformulation program also included development of analytical procedures for specificity, precision, accuracy, limit of detection, and limit of quantification.

1.2.1 Preparation of fluorouracil loaded SLNs

Preparation of fluorouracil-loaded SLNs using a lipid phase and surfactant-containing aqueous phase followed by homogenization and sonication, with subsequent cooling and storage under refrigerated conditions was described. The nanoparticles were freeze-dried using mannitol as cryoprotectant prior to detailed characterization.

1.3 Characterization of SLN dispersion

Particle size and PDI were measured using a Malvern Zetasizer after suitable dilution with double-distilled water, and zeta potential was measured in purified water with adjusted conductivity. Entrapment efficiency and drug loading were determined after centrifugation of diluted dispersion and analysis of supernatant drug concentration by UV spectrophotometry. TEM was used to determine morphology and size distribution of the dried formulation, while DSC and XRD were used to evaluate crystallinity and the physical state of drug within the lipid matrix.

1.4 Formulation of SLN gel

Carbopol 934 concentration was optimized by preparing gels at 1.0%, 1.5%, 2.0%, and 2.5% w/w and comparing spreadability, extrudability, consistency, and appearance. The optimized placebo gel was then loaded with fluorouracil SLN dispersion equivalent to 1 mg fluorouracil per gram of gel. The final gel was evaluated visually and by measuring viscosity, pH, homogeneity, spreadability, extrudability, drug content, and occlusion factor.

1.5 In vitro and ex vivo skin permeation

In vitro permeation was performed with Strat-M membrane in Franz diffusion cells using phosphate buffer saline pH 7.4 in the receptor compartment. Ex vivo permeation studies used excised rat abdominal skin mounted on Franz diffusion cells, with 1 g of either SLN gel or conventional gel applied to the donor compartment. Samples were withdrawn at defined time intervals and replaced with fresh buffer, and fluorouracil concentration was measured spectrophotometrically. Flux, permeability coefficient, and related permeation parameters were then calculated.

1.5.1 Skin permeation dynamics and Dermatokinetic

To explore the mechanism of permeation enhancement, treated and untreated skin samples were analyzed by FTIR and DSC after ex vivo studies. Dermatokinetic evaluation involved separating epidermis and dermis after formulation exposure, extracting fluorouracil from each layer with methanol, and plotting concentration versus time for each layer. Parameters including $T_{skin\ max}$, $C_{skin\ max}$, AUC_{0-8h}, and Ke were calculated using PK Solver software.

1.6 CLSM and biological studies

Depth of skin permeation was assessed using a rhodamine B-loaded gel and confocal laser scanning microscopy after 8 h application on skin mounted in Franz cells. The present investigation also evaluated ex vivo anti-cell proliferation activity against B16 cells, in vivo skin irritation on

mice, anti-inflammatory effects through IL-1α and TNF-α estimation in skin tumor homogenate, antitumor activity in UV-induced tumor-bearing mice, histopathology, and stability studies under different temperature and humidity conditions.

2. RESULTS:

2.1 Preformulation and analytical findings

A linear UV calibration profile for fluorouracil over the tested concentration range, with R^2=0.9983, confirming suitability of the analytical method for formulation studies was shown. The partition coefficient was reported near 1, indicating that fluorouracil does not possess strong lipophilicity and therefore may benefit from a carrier system that improves retention within skin. FTIR and DSC studies suggested compatibility of the drug with selected excipients because no destructive interaction affecting the expected formulation pathway was reported.

Table 1 Calibration curve of Fluorouracil

Concentration µg/ml	Absorbance* at 260 nm
10	0.264
20	0.34
30	0.41
40	0.48
50	0.55
60	0.62
70	0.71
80	0.792

Source: *Researcher's Data Analysis, 2022.*

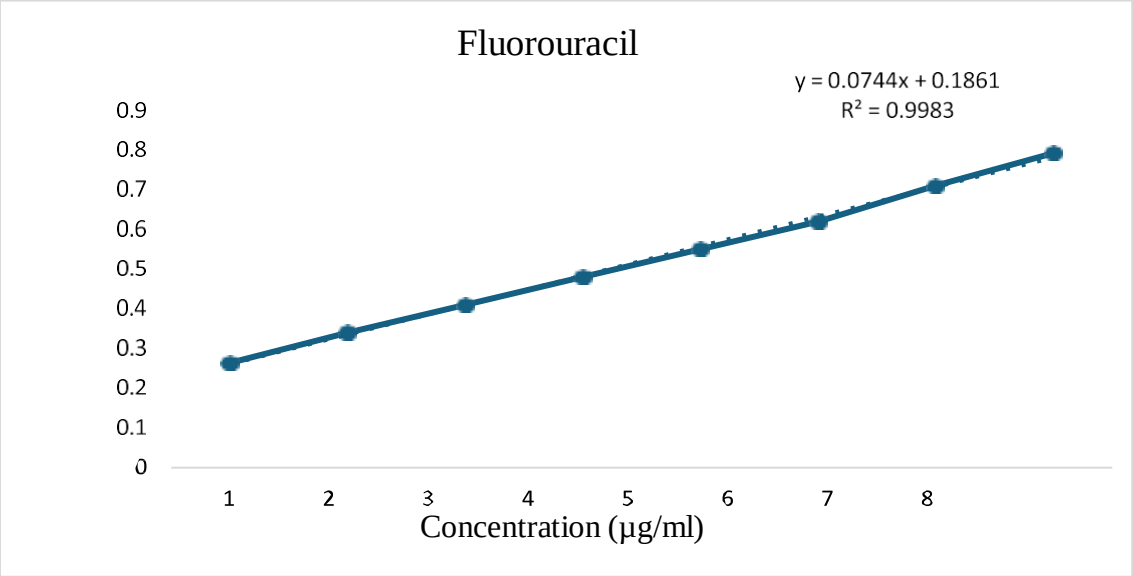

Figure 1. Calibration curve of fluorouracil

Source: Researcher's Data Analysis, 2022.

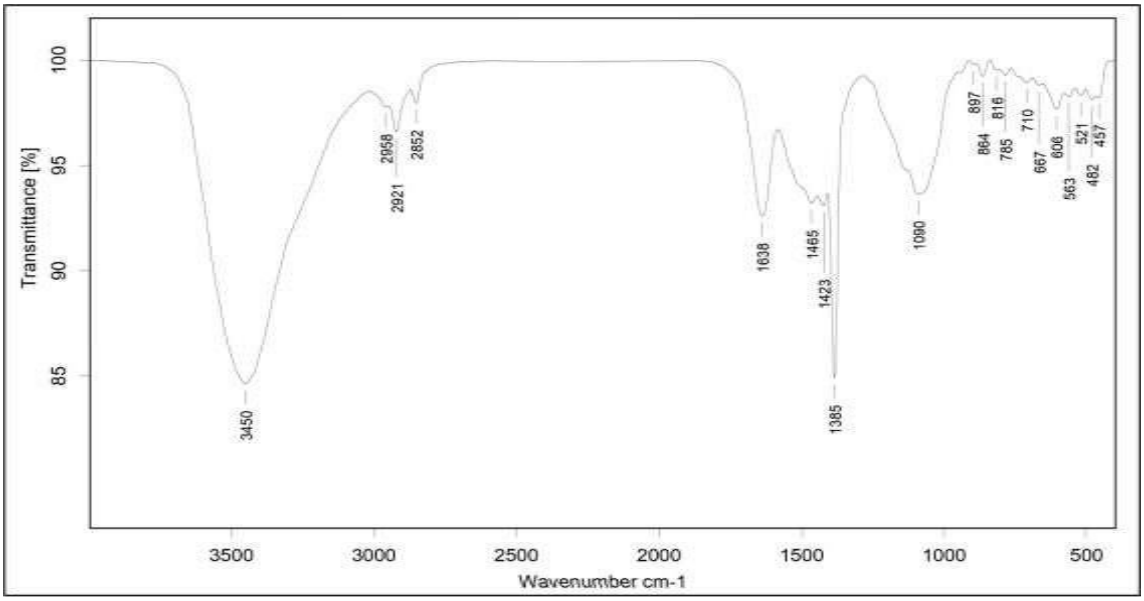

Figure 2. Fluorouracil FTIR
Source: Researcher's Data Analysis, 2022.

Table 2. FTIR spectra data of fluorouracil

Wave Number	Characteristic
3450	N-H
2852	CH-Strech
1385	C=O
1090	C=C
667	CH-bend
475	C-O alcohol

Source: Researcher's Data Analysis, 2022.

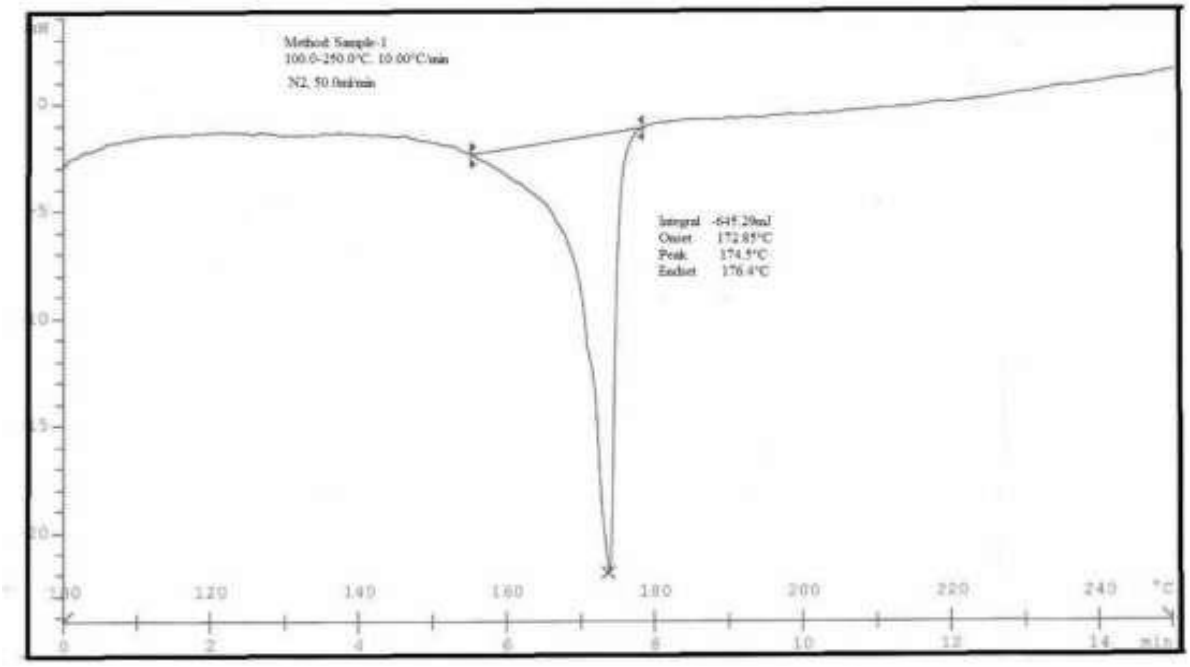

Figure 3 DSC of Fluorouracil

Source: Researcher's Data Analysis, 2022.

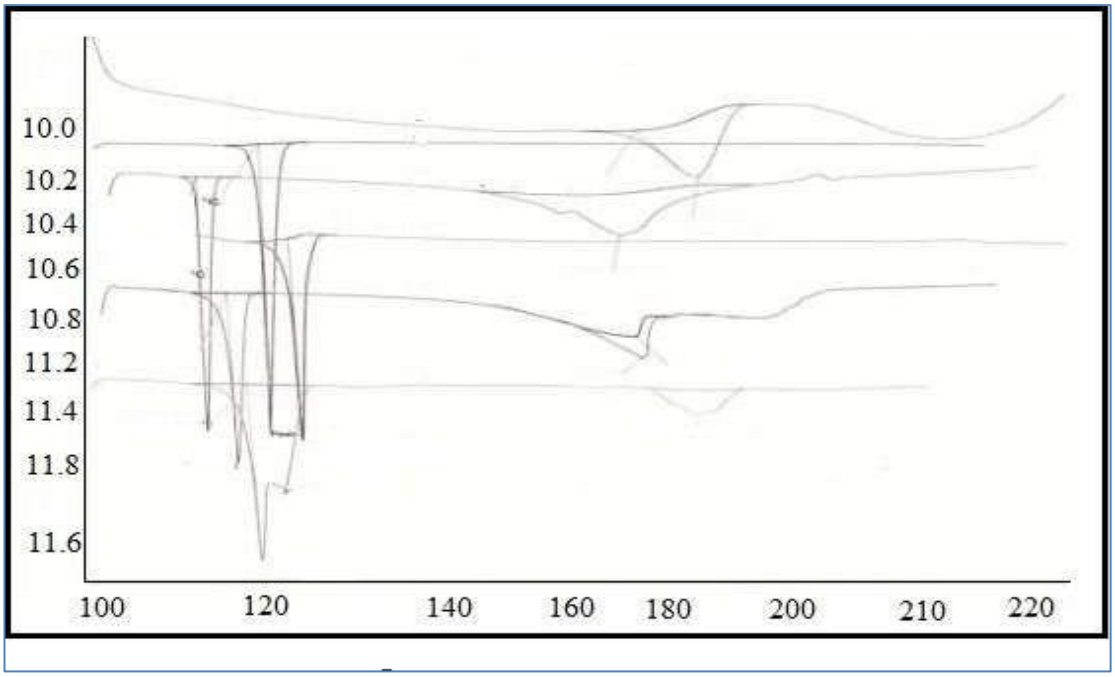

Figure 4 Thermogram of fluorouracil, stearic acid, Compritol, fluorouracil +stearic acid, fluorouracil + Compritol, fluorouracil +stearic acid+compritol

Source: Researcher's Data Analysis, 2022.

Table 3. DSC studies of pure drugs and lipids

S.no	DSC studies of pure compounds/physical mixtures	Experimental Melting point
1	Fluorouracil	174^{0}C
2	stearic acid	68.5^{0}C
3	Compritol	70^{0}C
4	fluorouracil +stearic acid	190^{0}C
5	fluorouracil + Compritol	68.7^{0}C
6	fluorouracil +stearic acid+compritol	150.6^{0}C

Source: *Researcher's Data*

Table 4. Calibration curve data of fluorouracil by HPLC method

Conc. (µg/ml)	**Mean area ± SD (n=3)**
55	5478452± 489.15
65	5789747±478.16
75	6879412±589.36
85	9856745±365.17
95	854796±419.78
105	12565475±125.47
115	13654778±754.28
125	15358748±356.74
135	16478514±236.78
145	17898456±425.87

Source: *Researcher's Data*

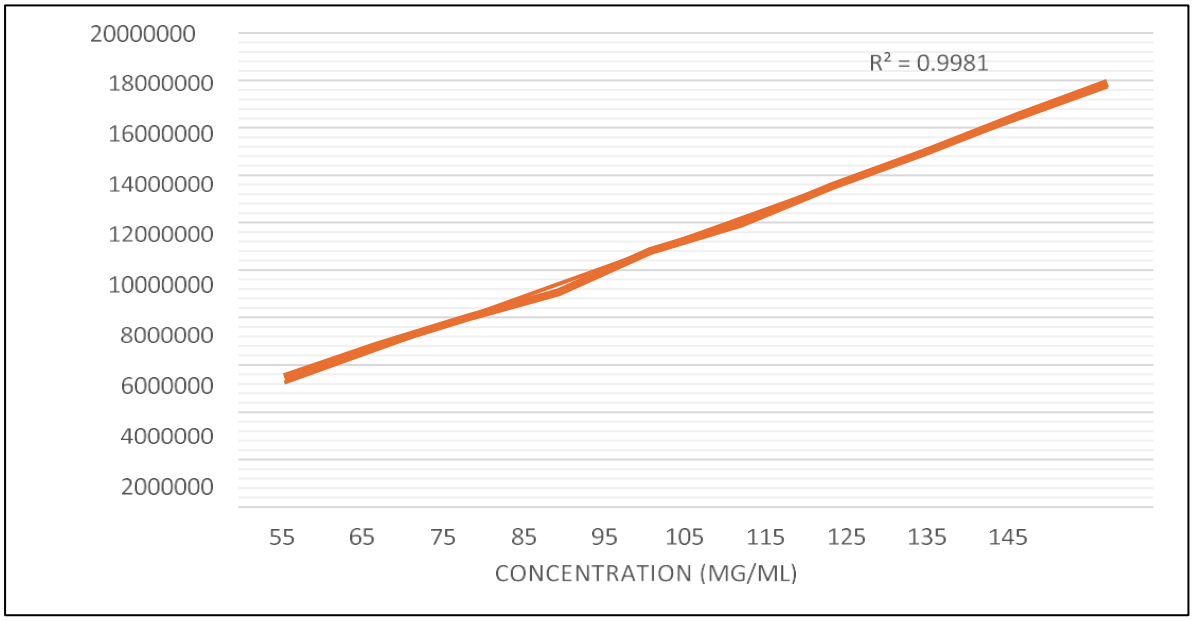

Figure 5: Calibration curve data of fluorouracil by HPLC method *Source: Source:* *Researcher's Data Analysis, 2022.*

2.2 Optimized SLN characteristics

The optimized fluorouracil-loaded SLN formulation had a mean particle size of 220 ± 0.9 nm and a PDI of 0.419 ± 0.035. This size range is appropriate for topical delivery because it permits high surface contact with skin while remaining within the nanoscale range associated with improved localization. The zeta potential of the optimized system was -18.5±0.3 mV, suggesting moderate electrostatic stabilization of the colloidal dispersion.

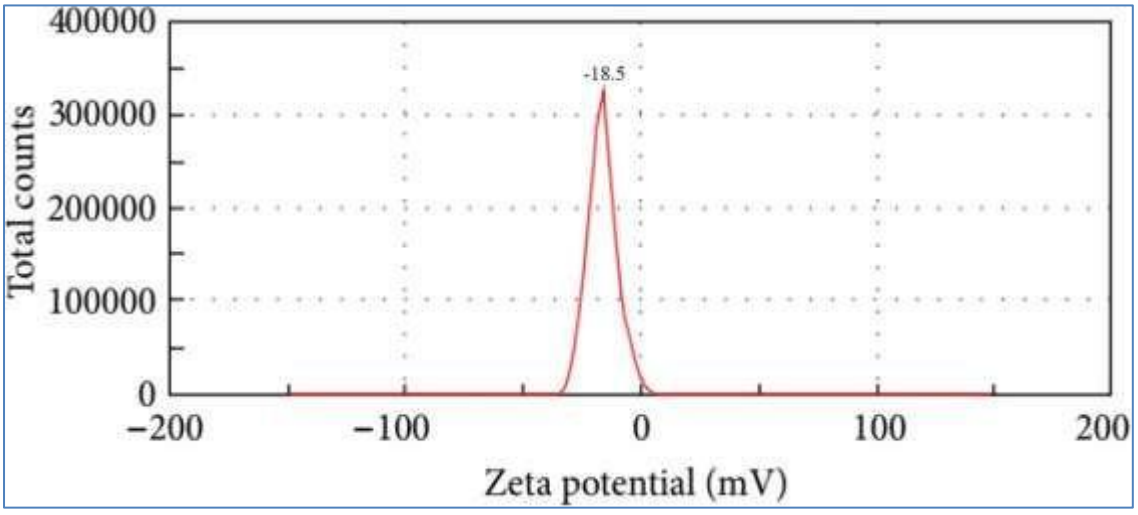

Figure 6. Zeta potential distribution of optimized fluorouracil loaded SLN dispersion

Source: Source: *Researcher's Data Analysis, 2022.*

Entrapment efficiency and drug loading were 88.3 ± 2.3% and 1.9 ± 0.3%, respectively. These values indicate that the lipid matrix effectively retained most of the incorporated fluorouracil despite the drug's modest partitioning behavior. TEM showed nearly spherical nanoparticles, supporting successful nanosystem formation and consistency with the measured particle size distribution.

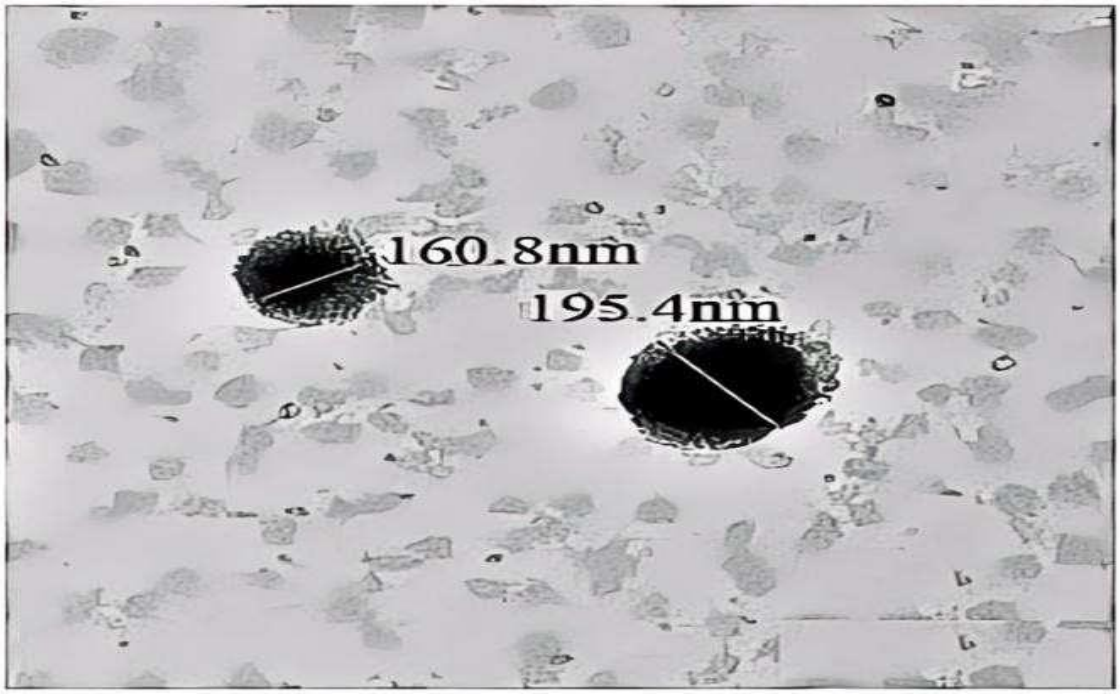

Figure 7. TEM image of fluorouracil loaded SLN dispersion

Source: *Researcher's Data*

Thermal and diffraction analysis further supported successful formulation. DSC showed altered thermal behavior in the optimized system relative to bulk components, and the study interpreted these changes as evidence that fluorouracil was molecularly dispersed or less crystalline within the lipid matrix. XRD likewise showed reduction or disappearance of characteristic crystalline signals of the pure drug within the final formulation, further supporting amorphization or reduced crystallinity after encapsulation.

2.3 Gel optimization and characterization

Carbopol 934 concentration strongly influenced practical gel properties. At 1.0%, spreadability was 6.29 ± 0.25 cm and extrudability was 38.21 g/cm^2, whereas 1.5% and 2.0% gave improved handling profiles with good flowability. The 2.5% gel showed poor flowability and very high extrudability demand of 221.75 g/cm^2, making it less acceptable for topical use. Based on these comparative findings, 2.0% Carbopol is the optimized gel base.

The optimized fluorouracil-loaded SLN gel appeared as a yellowish translucent semisolid with gel-like consistency and no gritty particles. Its drug content was 99.68 ± 0.89%, indicating uniform distribution of the nanoparticle dispersion within the gel matrix. The pH of 6.88 ± 0.21 was considered suitable for topical application, and the viscosity of 5.28 Pa·s supported practical semisolid behavior. Spreadability was 5.24 ± 0.24 cm, extrudability was 53.35 g/cm^2, and the occlusion factor was 29.78, indicating that the system provided both acceptable handling and a degree of occlusive interaction with skin.

Table 5. Different concentration of carbopol 934

Carbopol (%w/w)	Spreadability (cm)Mean ± S.D	Extrudability (g/cm2) Mean ± S.D	Consistency	Appearance
1	6.29 ± 0.25	38.21	Good flowability	Smooth
1.5	6.59 ± 0.31	56.94	Good flowability	Smooth
2	7.27 ± 0.21	74.85	Good flowability	Smooth
2.5	6.94 ± 0.20	221.75	Poor flowability	Smooth

Source: *Researcher's Data*

Table 6 Drug permeation study of fluorouracil loaded conventional gel through rat skin

Time (h)	Cumulative amount of drug permeated (µg/mL)	Cumulative drug permeated acceptor cell (µg)	Cumulative drug permeated per cm^2 (µg/cm^2)	Flux (µg/ cm^2/h)	Permeability coefficient (cm/h)
0.5	1.51 ± 0.09	25.89±1.56	33.85 ± 3.41	7.25	0.78×10^{-2}
1	3.15±0.2	42.19±1.28	65.28±2.18		
1.5	6.78±0.19	83.91±3.58	131.28±4.15		
2	7.25±0.16	103.74±3.18	162.28±4.28		
4	8.49±0.35	118.59±4.28	191.28±5.69		
6	9.24±0.25	130.28±3.28	198.75±3.85		
8	9.25±0.75	141.29±3.25	215.25±4.25		

Source: *Researcher's Data*

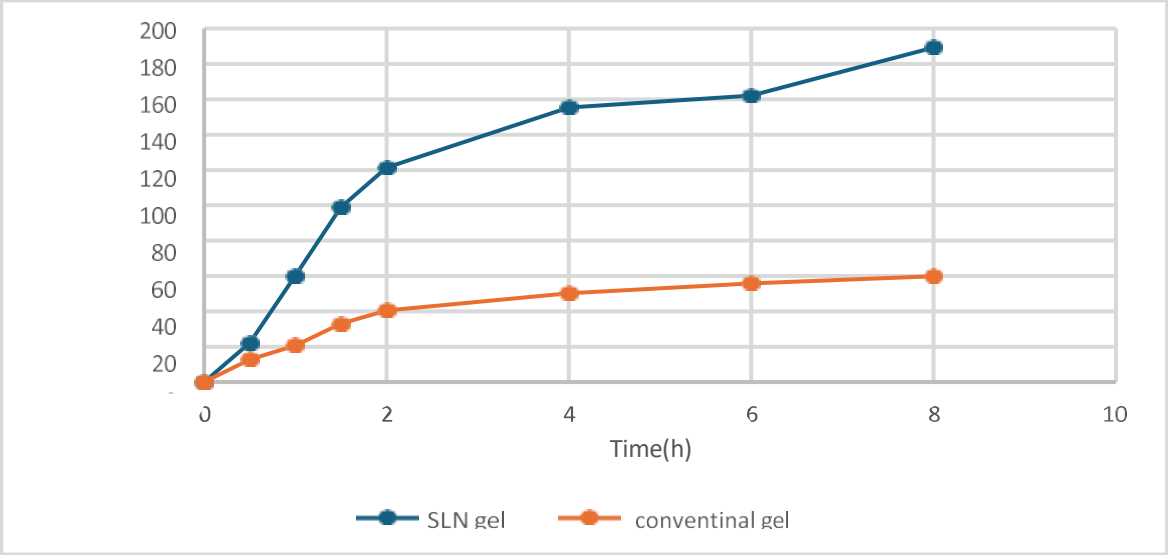

Figure 8. Comparative permeation of fluorouracil through rat skin

Source: *Researcher's Data*

2.4 Dermatokinetic performance

The Dermatokinetic data provide some of the strongest evidence for the superiority of the SLN gel over conventional gel. In epidermis, the SLN gel achieved $T_{skin\ max}$=0.9±0.2 h, $C_{skin\ max}$=205.9±13.8µg/cm^2, AUC_{0-8h}=652.2±23.6µg·cm^{-2}, and K_e=0.12±0.03 h^{-1}. The conventional gel showed slower and weaker epidermal exposure, with $T_{skin\ max}$ =2.1±0.3h, $C_{skin\ max}$=89.7±9.5µg/cm^2, and AUC_{0-8h}=378.8±15.7µg·cm^{-2}.

In dermis, the advantage remained pronounced. The SLN gel reached $T_{skin\ max}$=1.8±0.4h, $C_{skin\ max}$=220.8±8.5µg/cm^2, and AUC_{0-8h}=1138.7±25.4µg·cm^{-2} h, whereas the conventional gel gave $T_{skin\ max}$=3.7±1.5h, $C_{skin\ max}$=96.8±7.8µg/cm^2, and AUC_{0-8h}=522.8±15.7µg·cm^{-2} h. These differences indicate both faster delivery and stronger retention in target skin layers with the SLN system.

A simple enhancement analysis makes this improvement easier to interpret. The epidermal $C_{skin\ max}$ enhancement ratio of SLN gel versus conventional gel is approximately 205.9/89.7=2.29205.9/89.7 = 2.29205.9/89.7=2.29, while the dermal ratio is 220.8/96.8=2.28220.8/96.8 = 2.28220.8/96.8=2.28. The epidermal AUC enhancement is approximately 652.2/378.8=1.72652.2/378.8 = 1.72652.2/378.8=1.72, and the dermal AUC enhancement is 1138.7/522.8=2.181138.7/522.8 = 2.181138.7/522.8=2.18. These values suggest that the nanoparticle gel provides not merely a marginal improvement, but a major increase in localized skin exposure.

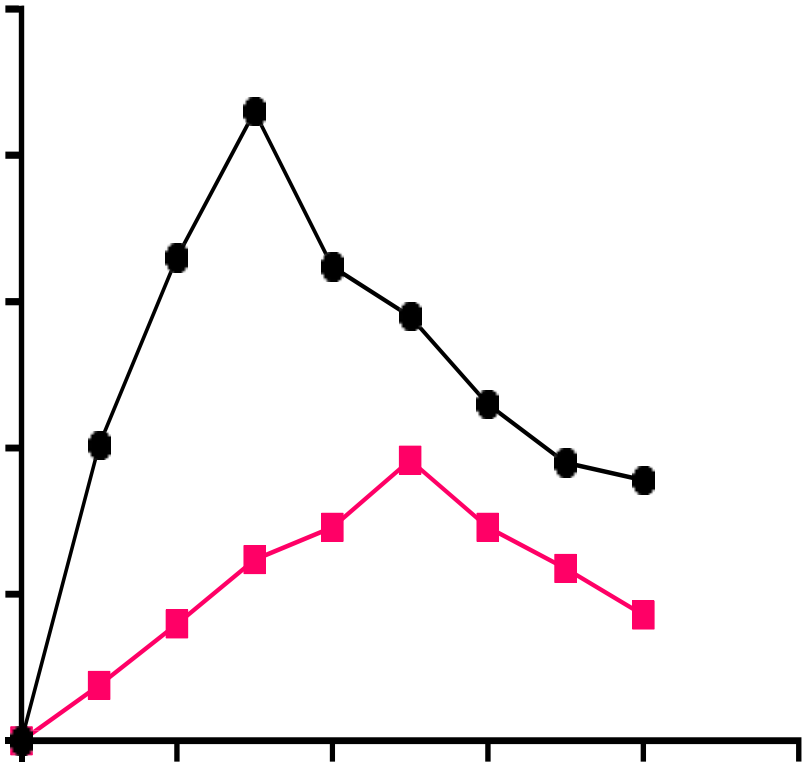

Figure 9. Epidermal Fluorouracil concentration profile

Source: *Researcher's Data*

Table 7. Dermatokinetic parameters of SLN gel and conventional gel

Dermatokinetic Parameters	SLN Gel		Gel	
	Epidermis	Dermis	Epidermis	Dermis
TSkin max (h)	0.9 ± 0.2	1.8 ± 0.4	2.1 ± 0.3	3.7± 1.5
CSkin max (µg/cm2)	205.9± 13.8	220.8 ± 8.5	89.7 ± 9.5	96.8± 7.8
AUC0-8h ($\mu g cm^{-2} h$)	652.2± 23.6	1138.7 ± 25.4	378.8 ± 15.7	522.8± 15.7
Ke(h^{-1})	0.12 ± 0.03	0.004 ± 0.002	0.04 ± 0.02	0.0035 ± 0.0005

Source: *Researcher's Data*

2.5 CLSM and permeation-depth findings

Confocal laser scanning microscopy confirmed deeper penetration of the SLN formulation. The conventional gel showed maximum fluorescence intensity at 15.0 µ\muµm, after which the intensity declined and became negligible after 45.0 µ\muµm. In contrast, the SLN gel showed maximum fluorescence at 30.0 µ\muµm and remained detectable up to about 60.0 µ\muµm. The study interprets this result in light of average rat stratum corneum and epidermal thicknesses of about 18.0 and 32.0 µ\muµm, respectively, indicating that the SLN system deposited fluorouracil near the viable epidermis–dermis interface, which is highly relevant for treatment of epidermis-originating carcinoma.

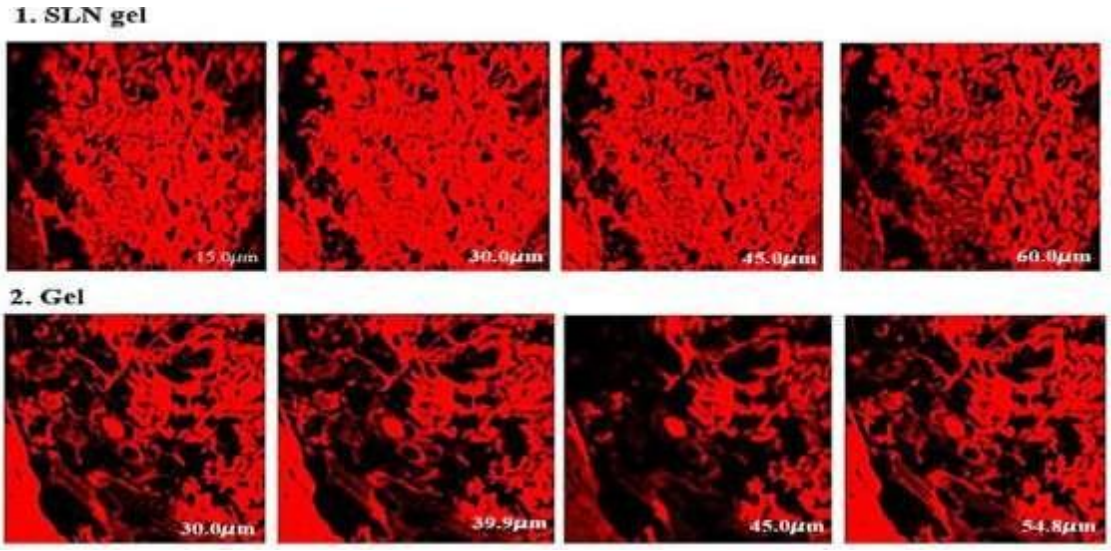

Figure 10. Confocal image of skin treated with SLN gel

Source: *Researcher's Data*

2.6 Anti-cell proliferation and skin safety

Ex vivo anti-cell proliferation studies on B16 cells showed concentration-dependent cytotoxicity of the SLN gel. Cell viability was 71 ± 8.25% at 50 µg/mL, 65 ± 5.19% at 100 µg/mL, and 55 ± 5.2% at 200 µg/mL after 24 h exposure. The study interpreted these findings to mean that about 100 µg/mL fluorouracil was required to inhibit cell viability by roughly 50%, and the dermatokinetic data indicated that the SLN gel could deposit fluorouracil in the skin at levels adequate to approach this effect locally.

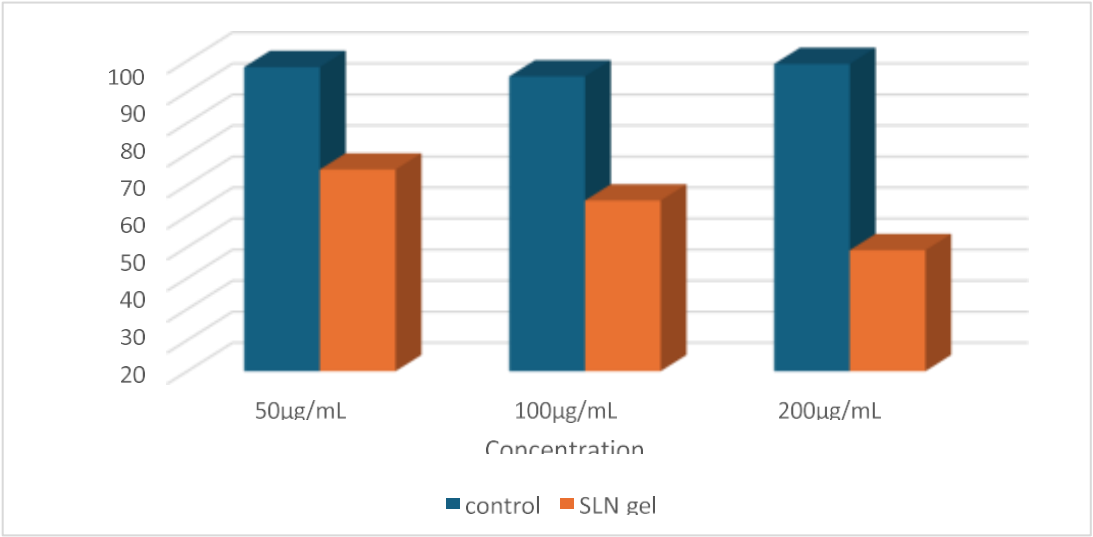

Figure 11. Percent cellular viability in B16 treated with SLN gel of fluorouracil

Source: *Researcher's Data*

Skin irritation testing in mice showed a zero erythema score for both conventional gel and SLN gel after seven days of topical use. This absence of visible irritation is important because it suggests that the enhancement in drug delivery was not achieved at the cost of overt local toxicity under the tested conditions.

2.7 Anti-inflammatory outcome

The anti-inflammatory study focused on proinflammatory cytokines in skin tumor homogenate. For IL-1α\alphaα, the levels were significantly higher in placebo-treated animals than in fluorouracil-treated groups and significantly lower in SLN gel-treated animals than in conventional gel-treated animals. A similar pattern was reported for TNF-α\alphaα, indicating that fluorouracil reduced inflammatory burden and that this effect was more pronounced when delivered through the SLN gel. These findings align with prior reports that fluorouracil can suppress inflammatory and oxidative pathways involved in skin damage and tumor progression (Khan et al., 2020; Meeran et al., 2017).

DISCUSSION:

The results indicate that SLN-mediated topical delivery substantially improved the skin-targeting profile of fluorouracil. The optimized nanoparticles were in a favorable nanosize range and exhibited high entrapment efficiency, which suggests efficient loading of fluorouracil into the lipid matrix despite the drug's limited lipophilicity. These features are important because small lipid nanoparticles can increase interfacial contact with skin, facilitate close adherence to the stratum corneum, and promote localized deposition rather than simple surface loss. The findings agree broadly with prior literature describing the utility of SLNs and related NLCs for improving topical delivery of dermally active compounds (Moghddam et al., 2016; Pinto et al., 2014; Okonogi et al., 2015).

The dermatokinetic profile is especially persuasive. A roughly 2.3-fold increase in both epidermal and dermal Cskin maxC_{\text{skin max}}Cskin max, together with enhanced AUC, indicates that the SLN gel not only accelerated the arrival of drug into the skin but also increased total localized exposure. This is highly relevant because skin carcinoma originates in the epidermis and then invades toward the dermis, making drug distribution at this interface particularly important. CLSM findings reinforce this interpretation, since fluorescence from the SLN gel reached deeper levels and remained visible at larger penetration depths than fluorescence from the conventional gel.

FTIR and DSC analyses of treated skin indicated lipid disruption, lipid fluidization, and keratin structural changes, all of which would be expected to reduce barrier rigidity and allow more efficient penetration of the drug-bearing nanosystem. This interpretation is plausible because lipid-based nanocarriers often interact with skin lipids and temporarily alter the organization of the stratum corneum, especially when surfactants and occlusive effects are also present.

The biological readouts strengthen the pharmaceutical findings. The concentration-dependent anti-cell proliferation result suggests that the delivered drug remained pharmacologically active after formulation into SLNs. Meanwhile, the in vivo cytokine data indicate that the SLN gel produced stronger anti-inflammatory effects than conventional gel, which is important because skin tumor progression and UV-associated damage are linked not only to abnormal proliferation but also to inflammatory signaling (Khan et al., 2020; Meeran et al., 2017). The absence of visible irritation after repeated topical exposure further supports the practical feasibility of the delivery system.

One limitation is that the investigation contains some internal inconsistencies in a few method and discussion passages, including occasional mixing of fluorouracil with silymarin terminology. However, the main quantitative dataset, title, objectives, formulation results, dermatokinetic table, CLSM findings, and cytokine studies consistently support a fluorouracil-loaded SLN gel interpretation. For publication, these inconsistencies should be editorially standardized, but they do not negate the overall direction of the experimental evidence.

CONCLUSION:

Fluorouracil-loaded SLNs were successfully developed and incorporated into a Carbopol gel with suitable physicochemical and topical application properties. The optimized nanosystem showed favorable particle size, high entrapment efficiency, acceptable gel characteristics, and markedly improved epidermal and dermal deposition relative to conventional gel. CLSM confirmed deeper skin localization, mechanistic studies supported barrier modification as a permeation-enhancing pathway, and biological studies showed concentration-dependent anti-cell proliferation together with reduced IL-1α\alphaα and TNF-α\alphaα levels and no visible irritation. Overall, the SLN gel represents a promising topical

nanomedicine approach for improving local fluorouracil delivery in skin cancer.

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