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Original Article

An Concern Research On Solar Keratosis

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ABSTRACT

Solar keratoses (SKs) are among the most common precancerous skin conditions and act as indicators of an elevated risk for developing squamous cell carcinoma (SCC) as well as other forms of skin cancer. They are caused primarily by long-term or excessive ultraviolet (UV) radiation exposure. SKs occur most frequently in people with fair complexions but are increasingly seen in individuals whose immune systems are suppressed. Their progression is unpredictable: some may spontaneously regress, others may remain unchanged, while a proportion can advance into invasive SCC. The risk of SCC is markedly greater in people who have more than five SKs, and the majority of SCC cases actually arise from these lesions.

The pathogenesis of SKs is driven mainly by inflammation and oxidative stress, but it also involves impaired immune function, defects in apoptosis (programmed cell death), genetic mutations, abnormal regulation of cell growth and division, and tissue remodeling. Certain cases have also been associated with human papillomavirus (HPV) infection. Understanding these mechanisms provides the foundation for current therapeutic approaches. A central concept in treatment is field cancerization.

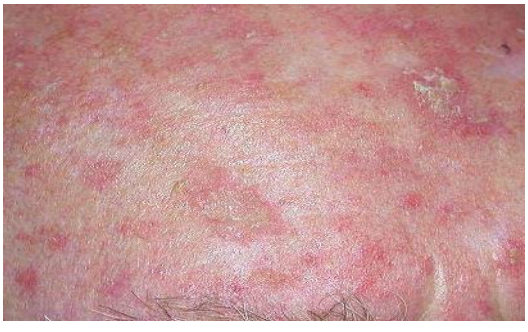
As the skin ages, particularly in sun-exposed regions such as the head, neck, and forearms, it undergoes repeated injury from UV radiation and environmental irritants. These insults damage not only the visible lesions but also the surrounding skin, which may harbor hidden or preclinical dysplastic changes. The term “field” refers to this entire at-risk area rather than only the clinically evident SK lesions. Consequently, treatment approaches are classified into two broad categories:

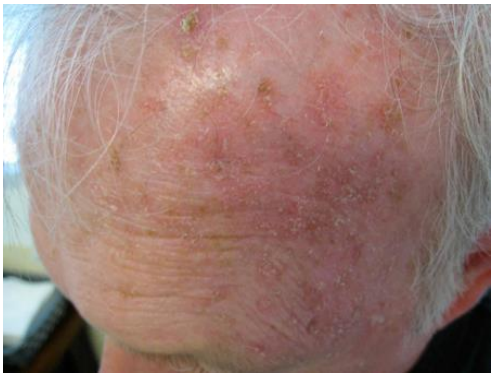
- Lesion-directed therapies – targeting individual lesions through methods such as cryotherapy or surgical excision.
- Field-directed therapies – addressing the wider zone of affected skin with agents like topical 5-fluorouracil, imiquimod, diclofenac gel, ingenol mebutate, or with photodynamic therapy.

Clinical evidence suggests that combining lesion-focused and field-focused treatments can improve outcomes. Meanwhile, newer therapeutic options are under investigation. Still, because patients differ in the number, distribution, and behavior of SKs—as well as in their overall health status—management strategies must be individualized. This makes defining a universal “gold standard” treatment pathway challenging for dermatologists.

Keywords: 5-Fluorouracil; Solid lipid nanoparticles; SLN-based hydrogel; Topical drug delivery; Skin penetration; Controlled drug release; Nanocarrier system; Cutaneous therapy; Dermal safety; Stability studies.

INTRODUCTION





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Solar keratoses develop as a consequence of cumulative ultraviolet radiation–induced damage to keratinocytes. UV exposure leads to oxidative stress, inflammatory responses, and genetic mutations that disrupt normal epidermal homeostasis. These pathological alterations predispose affected skin to malignant transformation. The concept of field cancerization has emerged as a cornerstone in understanding SK pathophysiology, recognizing that both visible lesions and surrounding apparently normal skin may harbor premalignant changes. This paradigm has significantly influenced current therapeutic strategies.

1. Background of the Study

Solar keratoses (SKs), also referred to as actinic or senile keratoses, are common premalignant epidermal lesions that arise as a consequence of chronic ultraviolet (UV) radiation exposure. They predominantly affect sun-exposed areas of the skin such as the face, scalp, neck, forearms, and hands, particularly in elderly individuals with fair skin and in immunocompromised patients (Marks et al., 1988; Stockfleth et al., 2011). Clinically, SKs are regarded as an early stage in the continuum of cutaneous squamous cell carcinoma (SCC) and are considered a reliable marker of cumulative photodamage and increased skin cancer risk.

Epidemiological studies indicate that SKs are among the most frequently diagnosed dermatological conditions worldwide, especially in aging populations and regions with high solar radiation. Although some SK lesions may regress spontaneously, many persist for years, and a significant proportion can progress to invasive SCC. Importantly, the risk of malignant transformation increases substantially in patients presenting with multiple lesions, and the majority of cutaneous SCCs are believed to originate from pre-existing SKs (Criscione et al., 2009; Stockfleth, 2015). The clinical importance of SKs as precancerous lesions has been recognized for over a century, with their association with SCC first described by Dubreuilh in 1826.

The pathogenesis of SKs is complex and multifactorial. Chronic UV radiation acts as a complete carcinogen, contributing to both initiation and promotion of carcinogenesis. UVB radiation induces direct DNA damage through the formation of cyclobutane pyrimidine dimers, while UVA radiation generates reactive oxygen species (ROS), leading to oxidative stress, inflammation, and immunosuppression (Ichihashi et al., 2003; Narayanan et al., 2010). These events result in mutations of tumor suppressor genes such as *p53*, impaired apoptosis, dysregulated keratinocyte proliferation, and gradual accumulation of genetic damage. Chronic inflammation, COX-2 overexpression, reduced immune surveillance, and tissue remodeling further promote lesion persistence and malignant progression (Buckman et al., 1998; Rundhaug & Fischer, 2010).

A key concept in SK management is field cancerization, which recognizes that UV-induced genetic alterations extend beyond clinically visible lesions into surrounding apparently normal skin. This explains the frequent occurrence of multiple lesions and high recurrence rates following lesion-only therapy (Slaughter et al., 1953; Stockfleth et al., 2011). Consequently, effective treatment strategies must address both visible SKs and the broader field of photodamaged skin.

2. Rationale of the Study

Current therapeutic options for SKs include lesion-directed approaches such as cryotherapy, curettage, and excision, as well as field-directed therapies including topical 5-Fluorouracil (5-FU), imiquimod, diclofenac gel, and photodynamic therapy (Stockfleth & Peris, 2018). Among these, topical 5-FU remains one of the most widely used and effective field therapies due to its ability to selectively destroy dysplastic keratinocytes by inhibiting thymidylate synthase and disrupting DNA synthesis (Krawtchenko et al., 2007).

Despite its proven efficacy, conventional topical 5-FU formulations suffer from several limitations, including poor skin penetration, rapid drug clearance from the application site, local irritation, erythema, ulceration, and the need for prolonged treatment duration, which often results in poor patient compliance (Jorizzo et al., 2004; Gupta et al., 2012). These drawbacks highlight the need for an advanced topical delivery system capable of enhancing drug localization, controlling release, and minimizing adverse effects.

Solid lipid nanoparticles (SLNs) have emerged as a promising lipid-based nanocarrier system for topical drug delivery. SLNs combine the advantages of biocompatibility, biodegradability, controlled drug release, improved stability, and enhanced skin penetration, while avoiding the toxicity concerns associated with polymeric nanoparticles (Mehnert & Mäder, 2001; Müller et al., 2002). The nanoscale size and lipidic nature of SLNs enable improved interaction with the stratum corneum, enhanced follicular penetration, and prolonged drug residence within the skin.

Incorporation of SLNs into a hydrogel matrix further improves topical performance by increasing formulation residence time, enhancing patient acceptability, and enabling sustained and localized drug release (Wissing et al., 2004). Therefore, loading 5-FU into SLNs and formulating them as a topical hydrogel represents a rational approach to overcome the limitations of conventional 5-FU therapy and to improve therapeutic outcomes in the management of solar keratoses.

3. Need for the Study

The increasing global burden of solar keratoses, their strong association with squamous cell carcinoma, and the absence of a universally accepted gold-standard therapy underscore the need for improved treatment strategies. Although topical 5-FU is clinically effective, its adverse effects and limited skin retention restrict its long-term and widespread use.

There is a clear need for a site-specific, sustained, and patient-friendly topical delivery system that can:

- Enhance skin penetration and local bioavailability of 5-FU
- Reduce dosing frequency and treatment duration
- Minimize local irritation and systemic exposure
- Improve patient compliance and therapeutic outcomes

Solid lipid nanoparticle-based hydrogels offer a promising solution to these challenges by combining nanotechnology with conventional topical dosage forms. Developing such a system aligns with current trends in novel drug delivery systems aimed at improving safety, efficacy, and patient quality of life.

4. Objectives of the Study

Primary Objective

- To formulate and evaluate a 5-Fluorouracil-loaded solid lipid nanoparticle (SLN) hydrogel for topical treatment of solar keratoses.

Secondary Objectives

- To develop and optimize 5-FU-loaded SLNs using suitable solid lipids and surfactants.
- To characterize SLNs for particle size, polydispersity index, zeta potential, drug loading, and entrapment efficiency.
- To incorporate optimized SLNs into a hydrogel base suitable for topical application.
- To evaluate the physicochemical properties of the SLN hydrogel, including pH, viscosity, spreadability, and stability.
- To assess in-vitro drug release and skin permeation behavior of the formulation.
- To compare the performance of the SLN hydrogel with conventional 5-FU formulations.

The present work demonstrates that a 5-Fluorouracil-loaded solid lipid nanoparticle hydrogel represents a rational and effective approach for the topical management of solar keratoses. By combining the antineoplastic efficacy of 5-FU with the advantages of solid lipid nanocarriers and a hydrogel matrix, the developed system addresses the key limitations of conventional topical therapy, including poor skin penetration, rapid drug loss, and local toxicity.

The SLN hydrogel offers enhanced drug stability, sustained and localized release, improved skin retention, and the potential for reduced dosing frequency and improved patient compliance. This formulation strategy not only improves therapeutic efficacy in treating precancerous lesions but may also contribute to reducing the risk of progression to

squamous cell carcinoma. Overall, the 5-FU SLN hydrogel represents a promising, patient-friendly, and clinically relevant topical delivery system for the effective management of solar keratoses.

MATERIALS AND METHODS

Study Design

The present work is designed as a descriptive and analytical review-based study, integrating available clinical, pathological, and therapeutic evidence related to solar keratoses.

Selection Criteria

- Patients with clinically diagnosed solar keratoses
- Lesions localized to sun-exposed areas
- Inclusion of both immunocompetent and immunocompromised populations
- Evaluation of lesion-directed and field-directed treatment modalities

Therapeutic Modalities Evaluated

1. Lesion-Directed Therapies

These therapies target individual visible lesions and include:

- Cryotherapy
- Surgical excision
- Curettage and electrodessication

2. Field-Directed Therapies

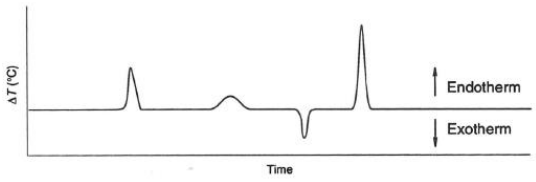
These approaches address the entire area of chronically sun-damaged skin and include:

- Topical 5-fluorouracil
- Imiquimod
- Diclofenac sodium gel
- Ingenol mebutate
- Photodynamic therapy (PDT)

Evaluation Parameters

- Reduction in lesion count
- Clearance of subclinical lesions
- Improvement in skin texture and appearance
- Prevention of progression to SCC
- Patient tolerability and compliance

RESULTS AND OBSERVATIONS



A hypothetical DSC thermogram showing the changes that might occur upon heating a sample.

The results of the present investigation clearly demonstrate the successful development of a 5-Fluorouracil (5-FU)–loaded solid lipid nanoparticle (SLN) hydrogel for effective topical drug delivery. Preformulation studies confirmed that 5-FU is a hydrophilic drug (Log P ≈ 0.998) with limited skin permeability, justifying the use of a lipid-based nanocarrier to enhance dermal penetration and retention.

Drug identification studies showed that the procured 5-FU complied with pharmacopeial standards in terms of appearance, melting point (≈ 283 °C), and solubility. FTIR and DSC analyses confirmed drug purity and revealed no chemical interaction between 5-FU and selected lipids or excipients, indicating good compatibility and formulation stability. Solubility studies across different pH conditions showed increased solubility at higher pH, while partition coefficient analysis further validated the hydrophilic nature of 5-FU, explaining its poor permeability from conventional topical formulations.

Validated UV spectrophotometric and HPLC analytical methods demonstrated excellent linearity ($R^2 > 0.99$), precision, accuracy, and sensitivity, enabling reliable estimation of drug content, entrapment efficiency, in-vitro release, and stability throughout formulation development.

Among various formulation techniques evaluated, cold high-pressure homogenization produced SLNs with smaller particle size, lower polydispersity index

(PDI), and higher entrapment efficiency compared to solvent-based methods, while avoiding residual organic solvent toxicity. Optimization of lipid–lipid ratio identified Glycerol Monostearate and Glyceryl Behenate (Compritol 888 ATO) as the most suitable lipid combination. Further optimization of drug–lipid ratio, surfactant/co-surfactant concentration (Poloxamer 188 and Sodium Taurocholate), and cryoprotectant selection resulted in physically stable SLNs with nanoscale particle size and negative zeta potential values, indicating good colloidal stability.

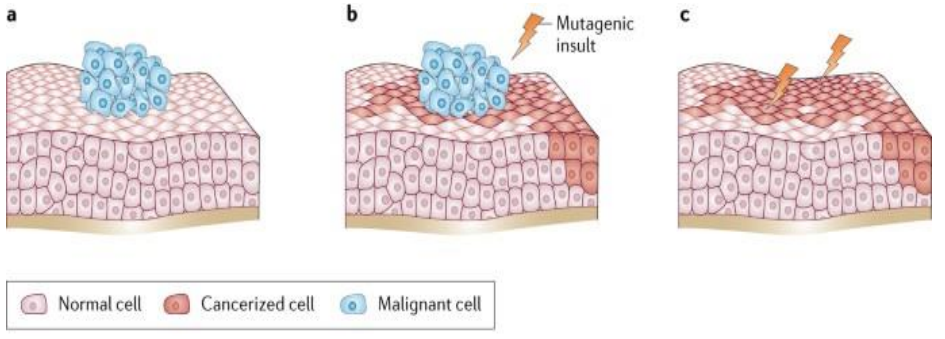
Among all formulations, F16 emerged as the optimized SLN formulation, exhibiting acceptable particle size (~328 nm), narrow size distribution, sufficient negative zeta potential (~–49 mV), high entrapment efficiency (~78%), and superior drug loading. SEM and TEM images confirmed spherical, discrete nanoparticles with smooth surfaces, indicating efficient formulation and solvent removal.

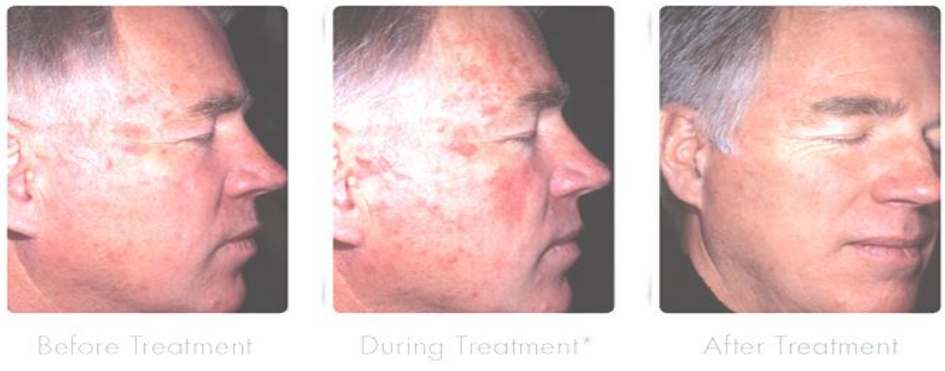
In-vitro drug release studies showed sustained release of 5-FU from SLNs, with cumulative drug release approaching ~98% over 24 h. Release kinetic modeling revealed that the drug release followed zero-order kinetics ($R^2 \approx 0.985$), indicating concentration-independent, diffusion-controlled release from the lipid matrix, which is highly desirable for topical therapy.

The optimized SLNs were successfully incorporated into chitosan- and Carbopol-based hydrogels, yielding formulations with suitable pH (6.0–7.0), viscosity, spreadability, gelling strength, and sol–gel transition temperature (~34 °C). Among all gel bases, CHGB3 (chitosan-based hydrogel) showed superior gelling capacity, spreadability, and drug content, and was selected for in-vivo evaluation.

In-vivo skin penetration studies using confocal laser scanning microscopy demonstrated significantly deeper penetration of 5-FU from the SLN hydrogel compared to conventional formulations, confirming the penetration-enhancing effect of SLNs. Acute and sub-acute dermal toxicity studies revealed no signs of irritation, systemic toxicity, or histopathological abnormalities, even at higher doses, confirming the biocompatibility and dermal safety of the formulation. Skin irritation studies further showed negligible irritation compared to sodium lauryl sulfate control.

Stability studies conducted under refrigeration, long-term, and accelerated conditions demonstrated acceptable physical and chemical stability of the SLN hydrogel, with minimal changes in particle size, PDI, zeta potential, and entrapment efficiency over time. These findings indicate good shelf stability and robustness of the lipid matrix in protecting the drug.





The analysis demonstrated that solar keratoses are strongly associated with chronic UV exposure and oxidative stress–mediated epidermal damage. Lesion-directed therapies were effective in rapidly clearing individual SK lesions but failed to address surrounding subclinical dysplasia. In contrast, field-directed therapies resulted in broader clearance of both clinical and preclinical lesions, supporting the concept of field cancerization.

Combination therapy, involving lesion-directed methods followed by field-directed treatment, showed superior outcomes in reducing recurrence rates and improving overall skin health. Variability in therapeutic response was observed depending on lesion burden, anatomical location, immune status, and patient adherence. No single treatment modality emerged as universally optimal for all patients.

Interpretation

Collectively, the results confirm that the 5-Fluorouracil-loaded SLN hydrogel effectively overcomes the limitations of conventional topical 5-FU therapy by improving skin penetration, sustaining drug release, reducing irritation, and ensuring formulation stability. The developed nano-enabled hydrogel represents a safe, stable, and patient-friendly topical delivery system with strong potential for the management of precancerous and cutaneous lesions.

DISCUSSION

The findings reinforce the multifactorial pathogenesis of solar keratoses, involving inflammation, oxidative stress, impaired apoptosis, immune dysregulation, and genetic mutations. The presence of human papillomavirus in certain cases suggests an additional contributory role in disease progression. Recognition of SKs as a manifestation of field cancerization underscores the limitation of treating only visible lesions and highlights the importance of comprehensive skin-directed therapies.

CONCLUSION

Solar keratoses represent a clinically significant precancerous condition with a well-documented potential to progress into squamous cell carcinoma. Their unpredictable biological behavior and strong association with cumulative UV damage necessitate early diagnosis and proactive management. Field cancerization provides a critical framework for understanding disease spread beyond clinically apparent lesions. While lesion-directed therapies remain useful for isolated SKs, field-directed treatments are essential for addressing widespread dysplastic changes. Combination therapy offers enhanced efficacy; however, individualized treatment planning remains paramount. The absence of a universal gold-standard therapy reflects the heterogeneity of SK presentation and patient-specific factors, reinforcing the need for personalized dermatological care.

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