RESEARCH PAPER

5-Fluorouracil-Loaded Microsponge-Enriched Topical Gels for the Management of Skin Cancer: A Review of Formulation Strategies and Statistical Optimization

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Abstract
Topical chemotherapy with 5-fluorouracil (5-FU) remains a widely used, non-invasive option for treating non-melanoma skin cancers and precancerous lesions such as actinic keratosis. However, conventional 5-FU creams and solutions are limited by uncontrolled drug release, poor penetration across the stratum corneum, and pronounced local toxicity — including erythema, burning, and ulceration — which frequently leads to treatment discontinuation. Microsponge delivery systems, porous polymeric microspheres capable of encapsulating high drug loads and releasing them in a controlled manner, have emerged as a promising strategy to overcome these limitations. When incorporated into a topical gel matrix, microsponges combine reservoir-type sustained release with the spreadability, transparency, and patient acceptability of a semi-solid vehicle. This review synthesizes current literature on microsponge technology, 5-FU delivery systems, and the application of statistical design-of-experiments approaches — particularly the Box–Behnken design — to optimize microsponge and microsponge-gel formulations. Evidence from studies on 5-FU microsponge gels as well as related actives (fluconazole, acyclovir, methotrexate, oxybenzone, fusidic acid, posaconazole) demonstrates consistent improvements in entrapment efficiency, sustained release, skin retention, and reduction of local irritation relative to conventional formulations. The review also considers alternative 5-FU carrier systems (nanoemulsions, transfersomes, nanostructured lipid carriers, metal–organic frameworks) for comparative context, and outlines persisting gaps around scale-up, long-term stability, and clinical translation. Collectively, the literature supports microsponge-enriched topical gels as a mechanistically sound and statistically optimizable platform for improving the therapeutic index of topical 5-FU.

Keywords : Microsponges; 5-Fluorouracil; Topical gel; Box–Behnken design; Response surface methodology; Skin cancer; Controlled drug release

How to cite this article: Neha Sharma, Amarjeet Singh. 5-Fluorouracil-Loaded Microsponge-Enriched Topical Gels for the Management of Skin Cancer: A Review of Formulation Strategies and Statistical Optimization. Int J Drug Deliv Technol. 2026;16(79s):610-614. DOI: 10.25258/ijddt.16.79s.64

.1. Introduction

Skin cancer is among the most commonly diagnosed malignancies worldwide, with non-melanoma skin cancers — basal cell carcinoma and squamous cell carcinoma — accounting for the large majority of cases, and actinic keratosis representing a common precancerous precursor lesion. Rising incidence has been linked to increased ultraviolet exposure, an ageing population, and lifestyle factors. While surgical excision remains a mainstay of treatment, it is often accompanied by cosmetic morbidity, recurrence risk, and limited suitability for elderly or immunocompromised patients. Topical chemotherapy therefore continues to occupy an important niche as a non-invasive alternative for superficial lesions.

Among topical chemotherapeutic agents, 5-fluorouracil (5-FU) is the most extensively used. As a fluorinated pyrimidine analogue, 5-FU inhibits thymidylate synthase, depleting thymidine pools and disrupting DNA synthesis; its metabolites are also incorporated into RNA, interfering with protein synthesis and reinforcing its antiproliferative action. Despite this well-characterized mechanism, the clinical utility of topical 5-FU is constrained by a narrow therapeutic window: conventional creams and solutions tend to release drug rapidly and without control, producing high local concentrations that manifest as redness, burning, ulceration, and inflammation. These adverse effects are a leading cause of poor adherence and treatment discontinuation. Compounding this, the hydrophilic character of 5-FU limits its passive diffusion across the lipophilic stratum corneum, reducing penetration efficiency and necessitating higher or more frequent dosing.

These shortcomings have motivated sustained interest in advanced topical delivery platforms capable of modulating drug release, improving cutaneous retention, and minimizing irritation while preserving therapeutic efficacy. Microsponge delivery systems, in combination with topical gel vehicles and rational, statistically driven formulation design, have been proposed as one such platform. This review consolidates the available literature on microsponge technology, 5-FU-specific delivery strategies, and statistical optimization methods — with particular attention to the Box–Behnken design — to provide an integrated

picture of the current state of the field and the gaps that remain.

2. Topical Drug Delivery: Rationale and Barriers

Topical delivery is attractive because it allows therapeutic agents to be concentrated at the site of disease while limiting systemic exposure and associated toxicity. The skin, however, is a formidable barrier: the stratum corneum's 'brick and mortar' architecture — terminally differentiated corneocytes embedded in a lipid matrix of ceramides, cholesterol, and free fatty acids — restricts the penetration of both hydrophilic and lipophilic molecules. Conventional dosage forms such as creams, ointments, and gels typically offer little control over drug release, resulting in inconsistent delivery, poor retention at the target site, and the need for frequent reapplication.

These limitations have driven the development of micro-carrier-based delivery systems — including liposomes, niosomes, solid lipid nanoparticles, microemulsions, and microsponges — each seeking to improve drug stability, control release kinetics, and enhance therapeutic outcomes. Liposomes offer enhanced penetration and biocompatibility but can present stability and cost challenges; solid lipid nanoparticles provide controlled release with improved stability but limited drug-loading capacity; microemulsions enhance solubility and control release but may cause surfactant-related irritation. Microsponges, by contrast, are notable for combining high drug-loading capacity with a porous structure that supports sustained release and reduced irritation, though they require careful optimization of polymer selection and process parameters.

3. 5-Fluorouracil: Pharmacology and the Case for Advanced Delivery

5-FU is an antimetabolite pyrimidine analogue used across multiple cancer types, including colorectal, gastric, breast, and skin malignancies. Its anticancer activity arises from inhibition of thymidylate synthase, which disrupts DNA synthesis and triggers apoptosis preferentially in rapidly dividing cells. Systemically, its clinical use is complicated by a narrow therapeutic index, myelosuppression, gastrointestinal toxicity, and a short half-life due to rapid metabolism.

Applied topically, 5-FU is commonly indicated for actinic keratosis, superficial basal cell carcinoma, Bowen's disease, and other precancerous skin changes. Conventional topical formulations, however, are associated with intense local discomfort — redness, heat, and ulceration — that undermines patient compliance. Martins (2023) reviewed the broader landscape of strategies developed to improve 5-FU's therapeutic index, including prodrugs such as capecitabine and tegafur designed for improved gastrointestinal absorption, and a range of drug delivery systems — liposomes, niosomes, transfersomes, ethosomes, microemulsions, microsponges, and microneedles — aimed at modulating its biodistribution. de Oliveira and colleagues (2021) similarly reviewed 5-FU carrier systems and concluded that microemulsions and nanocarriers meaningfully increase bioavailability and deeper skin penetration relative to conventional creams, while combination approaches such as occlusive dressings and chemowraps outperform simple cream formulations for widespread precancerous lesions.

Collectively, this body of work frames a consistent problem statement: topical 5-FU is pharmacologically effective but formulation-limited, and delivery-system innovation is the most direct route to improving its local tolerability without sacrificing efficacy.

4. Microsponge Delivery Systems: Structure, Mechanism, and Materials

4.1 Concept and Structural Features

Microsponges are highly porous, cross-linked polymeric microspheres, typically 5–300 µm in diameter, capable of encapsulating substantial quantities of active pharmaceutical ingredients within an interconnected network of pores while retaining structural integrity. Relative to conventional microspheres, they are distinguished by elevated porosity and surface area, capacity for regulated and extended drug release, reduced irritation potential, and improved formulation stability. Multiple reviews (Mandal, 2024; Biharee, 2023; Kumari and Mishra, 2016; Singhvi and Manchanda, 2019) describe microsponges as spherical, sponge-like particles that can be dispersed into gels, creams, lotions, or powders, and that have been investigated for topical, oral, colon-targeted, and even transdermal applications.

4.2 Mechanism of Drug Loading and Release

Mechanistically, microsponges act as a drug reservoir: the permeable polymeric matrix allows gradual diffusion of the entrapped drug, sustaining therapeutic concentrations while avoiding the initial concentration spike associated with conventional formulations — the spike most often implicated in local irritation. Release rate is governed by an interacting set of parameters, including polymer type (hydrophobic polymers slow diffusion; hydrophilic polymers permit faster release), cross-linking density (higher cross-linking increases entrapment and slows release), particle size (smaller particles increase surface area and burst release), pore size (larger pores shorten the diffusion path and accelerate release), and the strength of drug–polymer interactions (stronger hydrogen bonding or van der Waals interactions slow release).

4.3 Polymers Commonly Used

Ethyl cellulose is frequently selected for its hydrophobic, film-forming character, which slows release and confers structural stability. Eudragit RS, a hydrophobic cationic polymer, provides pH-independent, sustained release through controlled swelling, while the more permeable Eudragit RL

supports faster release with moderate entrapment. Biodegradable polymers such as PLGA achieve sustained release through a combination of erosion and diffusion. The choice and ratio of polymer(s) directly determines particle morphology, entrapment efficiency, and release kinetics, and is therefore a central variable in any optimization study.

4.4 Methods of Preparation

The quasi-emulsion solvent diffusion method is the most widely reported technique for 5-FU and related microsponges: drug and polymer are dissolved in a volatile organic solvent to form an internal phase, which is emulsified into an aqueous external phase containing a stabilizer; solvent diffusion into the external phase precipitates the polymer and forms porous microspheres. Other reported methods include liquid–liquid suspension polymerization, water-in-oil-in-water (w/o/w) double emulsion solvent diffusion, oil-in-oil emulsion solvent diffusion, lyophilization, the porogen-addition method, vibrating-orifice aerosol generation, electrohydrodynamic atomization, and ultrasound-assisted preparation (Mandal, 2024; Biharee, 2023). Because microsponge attributes emerge from the interaction of several process and formulation variables — polymer concentration, drug-to-polymer ratio, stirring speed, and emulsifier concentration — conventional one-variable-at-a-time optimization is inefficient, motivating the statistical design approaches discussed in Section 8.

5. Microsponge-Based Delivery of 5-Fluorouracil: Evidence Synthesis

A cluster of studies has specifically examined microsponge-based delivery of 5-FU for dermatological and colon-targeted indications, providing the most direct evidence base for this review.

Jain and colleagues (2019) developed a 5-FU microsponge-based topical gel using ethyl cellulose and Eudragit RL 30D via quasi-emulsion solvent diffusion. Brunauer–Emmett–Teller (BET) analysis confirmed a high surface area (2.4393 m^2/g) and substantial pore volume; the optimized gel exhibited superior thixotropic and textural properties relative to a commercial cream comparator, and in-vivo local bioavailability studies demonstrated a 5.5-fold increase in skin deposition alongside significantly reduced skin irritation.

Halder and colleagues (2021, 2024) used response surface methodology (a face-centered central composite design) coupled with a scale-up strategy to develop 5-FU microsponges from ethyl cellulose and Eudragit RS 100 via a w/o/w double emulsification method. The optimized formulation (600 mg polymer, ~1198 rpm stirring speed, 2% w/v surfactant) achieved a yield of approximately 63–64%, mean particle size near 152 µm, entrapment efficiency of 75–76%, and cumulative release of roughly 74–76% over 8 hours, with FT-IR, DSC, and SEM confirming drug–polymer compatibility and porous morphology. The resulting gel displayed shear-thinning rheology consistent with dermal applicability, and the authors additionally demonstrated feasibility of scale-up via the power-law approach with fixed shape factors — a step often absent from laboratory-scale optimization studies.

Gupta (2015) extended microsponge-based 5-FU delivery to oral, colon-targeted administration, embedding 5-FU microsponges and calcium pectinate globules within enteric-coated HPMC capsules. A 3^2 factorial design was used to examine the influence of organic solvent volume and Eudragit RS 100 content on entrapment efficiency and release. In-vitro testing showed controlled release across simulated gastric, intestinal, and colonic fluid, with 97.8% cumulative release achieved in the presence of pectinase versus only 40% in its absence — illustrating how microsponge platforms can be adapted to exploit enzyme-triggered, site-specific release beyond the topical route.

Mashaqbeh and colleagues (2024) pursued a related colon-targeting strategy, combining 5-FU with curcumin-loaded β-cyclodextrin nanosponges within alginate–chitosan microbeads coated with ethyl cellulose and Eudragit S100. The coated microbeads (Coated MB5) released approximately 66% of 5-FU and 73% of curcumin over 24 hours, with in-vivo imaging confirming colonic arrival within 7–9 hours, illustrating the extensibility of porous polymeric carriers to combination chemotherapy.

Beyond microsponge-specific work, several studies have explored alternative nanocarrier strategies for topical 5-FU, offering useful comparative context. Kumar Jain and Puri (2014) optimized bioadhesive 5-FU gels using Carbopol 934, Carbopol 980, methylcellulose, and Poloxamer 188, finding Carbopol 934 (1.5% w/w) superior in viscosity, skin deposition, and bioadhesive strength, with markedly less erythema than a marketed cream on Draize testing. Kumar and Sinha (2016) formulated 5-FU water-in-oil microemulsions and demonstrated improved skin retention with lower systemic flux and no evidence of chronic irritation on 21-day rat studies. Ahmad and colleagues (2020) developed a 5-FU nanoemulsion-gel using Carbopol 934, reporting higher permeation than nanoemulsion alone across cow, goat, and rat skin models, and greater in-vitro cytotoxicity against melanoma cell lines than free drug. Khan (2015) prepared 5-FU-loaded transfersomal gel with high entrapment efficiency (~69%) and deformability, achieving 81.3% skin deposition and non-irritant behavior. Dange and colleagues (2024) developed chitosan-encapsulated 5-FU nanoparticles dispersed in a carbopol nanohydrogel, achieving 79.9% encapsulation efficiency and pH-responsive, zero-order release with improved cytotoxic potency

relative to free drug. Hasan and colleagues (2023) combined 5-FU with cannabidiol in a nanostructured lipid carrier gel, demonstrating enhanced epidermal/dermal uptake, reduced irritation on IR-camera and HET-CAM testing, and significant tumor volume reduction in an in-ovo model. Padya and Fernandes (2023) incorporated 5-FU and sonidegib into a zeolitic imidazolate framework (ZIF-8) metal–organic framework gel, showing enhanced skin retention, transfollicular penetration, and reduced Bcl-2 expression consistent with improved therapeutic effect in basal cell carcinoma models.

Taken together, these studies indicate that while several nanocarrier platforms can improve 5-FU's local pharmacokinetics, microsponge-based systems occupy a distinctive niche: they achieve comparable or superior gains in skin deposition and irritation reduction while offering simpler, more scalable manufacturing than many lipid- or framework-based nanocarriers (de Oliveira, 2021; Martins, 2023).

6. Microsponge Technology Applied to Other Actives: A Broader Evidence Base

Evidence from non-5-FU actives further substantiates the versatility and reliability of microsponge technology, and offers formulation precedents directly transferable to 5-FU systems. Parhi (2025) developed a 5-FU-adjacent emulgel platform for psoriasis using central composite design, achieving high in-vitro release (96.4% over 360 minutes) and favorable rheological and stability profiles. Prajapati (2025) applied quasi-emulsion solvent diffusion and Box–Behnken optimization to methotrexate-loaded, colon-targeted microsponges, achieving 87.2% encapsulation efficiency and pH-dependent sustained release with confirmed dose-dependent cytotoxicity in HT-29 colon cancer cells. Abdelmalak and colleagues (2012) formulated fluconazole microsponges with ethyl cellulose and Eudragit RS 100, using a 2^4 factorial design to show that polymer fraction increased both drug loading and particle size, while PVA concentration was inversely related to entrapment efficiency and particle size. Gusai and colleagues (2021) optimized acyclovir microsponge-emulgel via central composite design, achieving high ex-vivo permeation improvements over marketed formulations. Upadhye and colleagues (2021) reviewed sunscreen applications, citing microsponge-encapsulated oxybenzone formulations that achieved 96.9% release efficiency, non-irritant behavior, and an SPF of 25 versus 20 for comparable marketed products — attributed to controlled, sustained release prolonging surface retention of the active.

General reviews of microsponge technology (Kumar, 2025; Mandal, 2024; Biharee, 2023; Rahman, 2022; Mahant et al., 2020; Kumari and Mishra, 2016; Singhvi and Manchanda, 2019; Kshatriya and Shinde, 2020) consistently emphasize the platform's applicability across acne, fungal infection, inflammation, and oncology indications, its compatibility with a wide pH range, low genotoxicity and immunogenicity, and its extension beyond topical use into oral, parenteral, pulmonary, and colon-targeted delivery. Mahant and colleagues (2020) additionally catalogued marketed microsponge-based dermatological products, underscoring that the technology has already achieved commercial and regulatory precedent — a relevant consideration for translational feasibility of 5-FU microsponge systems.

7. Topical Gel as the Delivery Vehicle for Microsponges

Topical gels are favored vehicles because of their oil-free character, ease of application, patient acceptability, and capacity to uniformly disperse particulate carriers such as microsponges. When microsponges are embedded in a gel matrix, drug release becomes governed by two sequential barriers: diffusion out of the microsponge pores, and secondary diffusion through the hydrated gel network. This two-stage process further dampens burst release and stabilizes delivery kinetics, while polymer relaxation, gel hydration, and drug solubility within the gel modulate the overall release profile. Drug–polymer interactions (hydrogen bonding, electrostatic interactions) can further slow or modulate release and enhance entrapment, and external factors such as pH, temperature, and skin hydration influence both diffusion rate and cutaneous permeation. Kinetic models such as Higuchi, Korsmeyer–Peppas, and zero-order are commonly applied to characterize and predict release from these composite systems. Across the reviewed literature, incorporation of microsponges into gels — rather than delivering microsponge powder directly — is consistently associated with improved spreadability, prolonged retention time, and more consistent release, properties particularly relevant to indications requiring repeated, self-administered application such as dermato-oncology.

8. Statistical Optimization: Box–Behnken Design and Response Surface Methodology

Because microsponge and gel performance depend on the simultaneous interaction of multiple formulation and process variables — polymer concentration, drug-to-polymer ratio, stirring speed, emulsifier concentration, and others — conventional trial-and-error formulation is inefficient, resource-intensive, and prone to missing interaction effects. Response surface methodology (RSM), and the Box–Behnken design (BBD) in particular, addresses this by allowing simultaneous evaluation of main, interaction, and quadratic effects with fewer experimental runs than a full factorial design, while systematically avoiding extreme factor combinations that risk formulation failure.

Direct precedent for BBD application to microsponge systems includes work on fusidic acid–

diclofenac microsponge gels, where BBD optimization improved both controlled-release behavior and particle properties, and posaconazole microsponge hydrogels, where BBD-optimized formulations achieved high entrapment efficiency (approximately 98.5%) and prolonged release relative to conventional gels. Prajapati's (2025) BBD-optimized methotrexate microsponges, discussed above, similarly demonstrated the design's capacity to simultaneously balance particle size, entrapment efficiency, and controlled release. Outside the microsponge literature strictly, Gannu and colleagues (2010) applied a three-factor, three-level Box–Behnken design to optimize a microemulsion-based transdermal system, generating validated regression models for permeation flux and lag time and achieving a 3.5-fold bioavailability improvement over oral administration — illustrating the design's broader reliability for skin-delivery optimization tasks structurally similar to microsponge-gel development.

Although 5-FU-specific BBD studies remain limited in the published literature, the consistency of outcomes across chemically diverse actives (fusidic acid, diclofenac, posaconazole, methotrexate, lacidipine) — improved entrapment efficiency, more predictable release kinetics, and reduced formulation failure — provides strong indirect support for applying BBD to 5-FU microsponge-gel systems specifically. The principal translational advantages of BBD in this context are a reduced number of experimental runs (lowering material and time costs), explicit modeling of interaction and quadratic effects among formulation variables, avoidance of extreme, failure-prone factor combinations, and generation of predictive mathematical models that allow response estimation for untested parameter combinations.

9. Skin Barrier Considerations Relevant to Formulation Design

Optimizing a microsponge-gel system in isolation from skin physiology risks producing a formulation that performs well in vitro but underdelivers in vivo. The stratum corneum, composed of terminally differentiated keratinocytes within a ceramide-, cholesterol-, and fatty-acid-rich lipid matrix, remains the principal diffusional barrier; microsponges are understood to act as a surface reservoir that prolongs release against this barrier rather than actively overcoming it. The viable epidermis presents a comparatively minor diffusional barrier and primarily supports gradual absorption and retention, while the dermis, with its vascular supply, represents the site of systemic absorption — one microsponge systems are specifically designed to limit, in favor of local retention. Skin appendages, particularly hair follicles, constitute a shunt pathway for penetration; because microsponges below approximately 300 µm can deposit within follicular openings, particle size control has a direct bearing on both retention and the balance between local and follicular drug deposition. Formulation variables that influence stratum corneum hydration, pH compatibility, and temperature-dependent gel rheology should therefore be considered jointly with microsponge-specific parameters during optimization, rather than as separate design problems.

10. Current Challenges and Research Gaps

Despite consistently encouraging in-vitro and small-animal results, several gaps constrain clinical translation of 5-FU microsponge-gel systems. Manufacturing scale-up remains under-addressed; only a minority of studies (notably Halder et al., 2021, 2024) report validated scale-up methodology, and reproducibility of porous microsponge morphology across production scales is not yet well characterized. Long-term physical and chemical stability data, particularly under real-world storage conditions, are limited relative to the volume of short-term optimization studies. Residual organic solvent from quasi-emulsion solvent diffusion methods warrants more systematic toxicological evaluation given the sensitive, often compromised skin of the intended patient population. Comparative in-vivo and clinical data remain sparse: most entrapment-efficiency and release-kinetics claims rest on in-vitro or ex-vivo permeation studies, with relatively few controlled comparisons of therapeutic outcomes (lesion clearance, recurrence, patient-reported tolerability) against marketed 5-FU creams. Finally, while Box–Behnken and related RSM designs are well validated for microsponge systems generally, dedicated, published BBD optimization studies specific to 5-FU microsponge-gel formulations remain scarce, representing a clear and addressable gap in the literature.

11. Future Directions

Priority areas for future work include: (i) systematic, validated scale-up protocols for microsponge manufacturing that preserve porosity and particle-size distribution; (ii) long-term real-time and accelerated stability studies extending beyond the typical short-term windows reported in current literature; (iii) head-to-head in-vivo and, where feasible, early clinical comparisons of microsponge-gel formulations against marketed 5-FU creams, assessing both efficacy and tolerability endpoints; (iv) dedicated Box–Behnken or other RSM-based optimization studies specific to 5-FU microsponge-gel systems, building on the design precedents established for structurally analogous actives; and (v) closer mechanistic integration of skin-barrier science (follicular deposition, hydration-dependent permeation) with formulation-variable optimization, rather than treating these as separate stages of development.

12. Conclusion

The literature reviewed here consistently supports microsponge-enriched topical gels as a mechanistically well-grounded strategy for improving the local delivery of 5-fluorouracil. Across studies spanning 5-FU and structurally diverse comparator actives, microsponge incorporation reliably improves controlled and sustained drug release, enhances skin deposition and retention, and reduces local irritation relative to conventional creams and solutions. Statistical design-of-experiments approaches, and the Box–Behnken design in particular, offer an efficient, interaction-aware route to optimizing the multiple formulation and process variables that govern microsponge and gel performance, with demonstrated success across several structurally analogous systems even though 5-FU-specific Box–Behnken studies remain limited. Realizing the clinical potential of this platform will depend on closing existing gaps around scale-up, long-term stability, and controlled in-vivo and clinical evaluation — but the convergent evidence base assembled in this review provides a strong rationale for continued development of 5-FU microsponge-gel systems as a patient-friendly alternative to conventional topical chemotherapy.

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