# Development of a Topical Gel Containing 5-Fluorouracil-Loaded Microsponges for Sustained Drug Delivery

**Neha Sharma[1]*, Dr. Navjot Singh Sethi[1].**

1. IEC School of Pharmacy, IEC University, Kalujhanda, , Solan, Himachal Pradesh, India

***Corresponding author:** Neha Sharma, IEC School of Pharmacy, IEC University, Kalujhanda, Solan, H.P., India.
Email: shandlyaneha@gmail.com

**ABSTRACT:-**
This study developed and optimized a 5-fluorouracil (5-FU) loaded microsponge gel for topical treatment of skin cancer, aiming to overcome the poor drug retention and skin irritation seen with conventional 5-FU formulations. Microsponges were prepared by the quasi-emulsion solvent diffusion method and optimized using Box–Behnken statistical design. The optimized microsponges showed suitable particle size, uniformity, and stability, and were incorporated into a Carbopol gel base. Compared to a conventional 5-FU gel, the microsponge gel showed slower, more sustained drug release with good stability over three months. These results suggest that the Box–Behnken-optimized 5-FU microsponge gel offers a promising, better-tolerated alternative to conventional topical 5-FU treatment.

**Keywords:**-5-Fluorouracil; microsponge; Box–Behnken design; topical gel; sustained release; skin cancer
**How to cite this article:** Sharma N, Sethi NS. Development of a Topical Gel Containing 5-Fluorouracil-Loaded Microsponges for Sustained Drug Delivery. Int J Drug Deliv Technol. 2026;16(72s): 437-444. DOI: 10.25258/ijddt.16.72s.53

## 1. Introduction

Conventional topical dosage forms — creams, ointments, and simple gels — struggle to reconcile drug delivery with drug retention: release is typically rapid and poorly controlled, producing a high initial drug concentration at the application site followed by a need for frequent re-dosing. For potent, narrow-therapeutic-window drugs this translates directly into local toxicity and poor patient adherence, a problem that is particularly acute in the topical treatment of skin cancers and precancerous lesions, where 5-fluorouracil (5-FU) remains the most widely used chemotherapeutic agent. 5-FU is a fluorinated pyrimidine analogue that inhibits thymidylate synthase, depleting the thymidine pool needed for DNA synthesis, while its incorporation into RNA further disrupts protein synthesis in rapidly dividing cells. Despite this well-established mechanism, conventional topical 5-FU formulations are limited by a narrow therapeutic margin: the drug's hydrophilicity restricts its permeation across the lipophilic stratum corneum, while uncontrolled release and local accumulation at the application site frequently produce erythema, burning, ulceration, and inflammation severe enough to cause treatment discontinuation.

These limitations motivate carrier-based topical delivery systems designed to modulate release and improve skin retention. Among the options explored — liposomes, niosomes, solid lipid nanoparticles, and microemulsions — microsponges have emerged as a particularly well-suited platform for potent, irritant drugs.

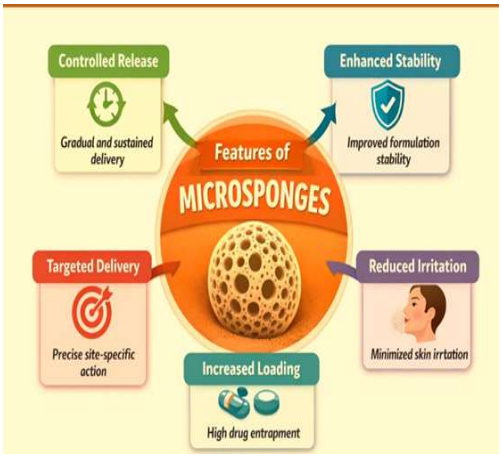


**Figure .1:- Properties of Microsponges**

Microsponges are highly porous, cross-linked polymeric microspheres, typically 5–300 µm in diameter, whose interconnected network of pores allows them to function as a drug reservoir rather than a simple carrier: the drug diffuses out gradually as it is depleted at the microsponge surface, avoiding the concentration spikes associated with conventional formulations while maintaining a therapeutic level over an extended period. Release from microsponges is governed jointly by diffusion through the pore network and partitioning at the particle surface, both of which can be tuned through polymer selection, cross-linking density, and particle size — properties that make microsponges attractive for reducing the local irritation associated with topical 5-FU.

Realizing these benefits in practice, however, requires navigating a multivariable formulation space:

polymer concentration, drug-to-polymer ratio, stirring speed, and emulsifier concentration all interact to determine particle size, entrapment efficiency, and release behavior. Conventional one-variable-at-a-time optimization is slow and does not capture these interactions. Response surface methodologies, and Box–Behnken design (BBD) in particular, address this by allowing the main, interaction, and quadratic effects of several factors to be estimated from a comparatively small number of experimental runs, while avoiding extreme factor combinations that risk formulation failure. BBD has previously been applied to optimize microsponge or microsponge-gel systems for other actives — for example, fusidic acid and diclofenac microsponge gels, posaconazole microsponge hydrogels achieving high entrapment efficiency, and methotrexate-loaded microsponges with improved sustained release — but its application to 5-FU-loaded microsponges specifically remains limited in the published literature.

Related formulation strategies for topical 5-FU delivery have been explored: Ahmad et al. (2020) developed a 5-FU nanoemulsion-based gel with improved ex vivo skin permeation and reduced cytotoxicity relative to free drug, while Mashaqbeh et al. (2024) combined 5-FU with curcumin in β-cyclodextrin nanosponges for colon-specific delivery. Closest to the present work, Halder et al. (2024) prepared 5-FU-loaded microsponges by quasi-emulsion solvent diffusion and optimized the formulation using a central composite design, reporting a drug entrapment efficiency of 76% and 74.24% cumulative release over 8 h. These studies collectively support the feasibility of microsponge-based 5-FU delivery, but leave open the specific combination addressed here: a systematically Box–Behnken-optimized 5-FU microsponge system incorporated into and compared across multiple gel bases (Carbopol, HPMC, and sodium alginate), with a full characterization package spanning morphology, particle size, solid-state behavior, release kinetics, and stability.

**Table.1:- Mechanistic Influence of Microsponge Parameters on Drug Release**

| Parameter | Mechanistic Role | Effect on Drug Release |
|---|---|---|
| **Polymer Type** | Determines matrix rigidity and interaction with drug | Hydrophobic polymers slow release; hydrophilic polymers allow faster diffusion |
| **Cross-linking Density** | Governs network porosity | Higher cross-linking → slower release, increased entrapment |
| **Particle Size** | Affects surface area | Smaller particles → higher surface area → faster initial release |
| **Pore Size / Porosity** | Dictates diffusion path length | Larger pores → faster drug diffusion; smaller pores → sustained release |
| **Drug-Polymer Interaction** | Hydrogen bonding, van der Waals forces | Strong interactions → slower release; weak interactions → faster release |

The present study addresses this gap by developing 5-FU-loaded microsponges via the quasi-emulsion solvent diffusion method, using a three-factor Box–Behnken design to optimize polymer concentration, drug-to-polymer ratio, and stirring speed against particle size, entrapment efficiency, and cumulative drug release. The optimized microsponges were characterized by SEM, AFM, DLS, PXRD, FTIR, and DSC, then incorporated into Carbopol, HPMC, and sodium alginate gel bases to identify the formulation offering the best combination of rheological behavior, spreadability, and sustained, diffusion-controlled release relative to a conventional (non-microsponge) 5-FU gel. Taken together, this work aims to establish a statistically optimized, dual-controlled (microsponge + gel matrix) delivery platform that reduces the local irritation and dosing frequency associated with conventional topical 5-FU therapy.

## 2. Materials and Methods

### 2.1 Materials

5-Fluorouracil (5-FU) was received as a gift sample from a pharmaceutical manufacturer. Ethyl cellulose and Eudragit RS/RL were used as polymeric carriers for microsponge formation, and polyvinyl alcohol (PVA) served as the emulsifying agent for the external aqueous phase. Dichloromethane and ethanol (analytical grade) were used as organic solvents for the internal phase. Carbopol 934/940, hydroxypropyl methylcellulose (HPMC K4M/K15M), and sodium alginate were evaluated as gelling agents for the topical gel base, with triethanolamine as the neutralizing agent, propylene glycol/glycerin as humectants, and methylparaben/propylparaben as preservatives. All other reagents were of analytical grade and used as received; distilled water was used throughout.

### 2.2 Preparation of 5-FU-Loaded Microsponges

Microsponges were prepared by the quasi-emulsion solvent diffusion method. Briefly, the polymer (ethyl cellulose or Eudragit RS/RL) was dissolved in a dichloromethane–ethanol mixture to form the internal organic phase, followed by dispersion of 5-FU under continuous stirring. This organic phase was added dropwise into an aqueous phase containing PVA under constant mechanical stirring at a predetermined speed, allowing solvent diffusion and evaporation to drive formation of porous microsponges. The resulting microsponges were filtered, washed with distilled water to remove residual emulsifier, and air-dried at room temperature.

**2.3 Drug–Excipient Compatibility**

Compatibility between 5-FU and the selected polymers/excipients was assessed by Fourier-transform infrared (FTIR) spectroscopy. Spectra of the pure drug, polymers, and physical mixtures were recorded over 4000–400 $cm^{-1}$, and characteristic peak positions were compared for evidence of shifting or disappearance indicative of chemical interaction.

**2.4 Experimental Design and Optimization**

A three-factor, three-level Box–Behnken design (BBD) was used to optimize the microsponge formulation. Polymer concentration ($X_1$), drug-to-polymer ratio ($X_2$), and stirring speed ($X_3$) were selected as independent variables, each studied at low (−1), medium (0), and high (+1) levels (polymer concentration: low/medium/high; drug:polymer ratio, 1:1/1:2/1:3; stirring speed, 800/1000/1200 rpm). Particle size ($Y_1$), entrapment efficiency ($Y_2$), and cumulative drug release ($Y_3$) were evaluated as dependent responses. Experimental runs were analyzed using Design-Expert® software to generate polynomial models, contour plots, and three-dimensional response-surface plots, from which the optimized formulation was identified and subsequently confirmed experimentally.

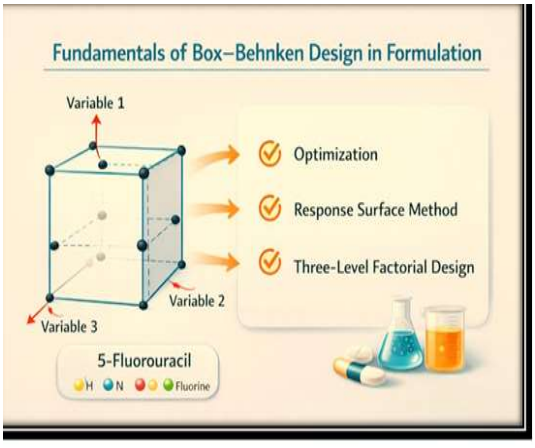


**Figure.2:- Box- Behnken Design in formulation**

**2.5 Characterization of Microsponges**

**Particle size, PDI, and zeta potential**-The optimized microsponge dispersion was analyzed by dynamic light scattering (Malvern Zetasizer). Samples were dispersed in distilled water, sonicated for 5–10 min to prevent aggregation, and diluted as needed to minimize multiple-scattering effects before measurement of mean particle size, polydispersity index (PDI), and zeta potential.

**Surface morphology**- Microsponge surface topography was examined by scanning electron microscopy (SEM). Dried samples were mounted on aluminum stubs using double-sided carbon tape, sputter-coated with gold under vacuum, and imaged at an accelerating voltage of 10–15 kV across a range of magnifications. Atomic force microscopy (AFM) in tapping mode was used as a complementary technique to obtain three-dimensional surface profiles and quantify average roughness (Ra) and root-mean-square roughness (Rq).

**Solid-state characterization**- Powder X-ray diffraction (PXRD), FTIR, and differential scanning calorimetry (DSC) were used to evaluate the crystallinity, chemical integrity, and thermal behavior of pure 5-FU as a baseline reference for comparison with the formulated microsponges.

**Percentage yield and entrapment efficiency**-Percentage yield was calculated from the ratio of practical to theoretical yield. Entrapment efficiency was determined by dissolving a known quantity of microsponges in a suitable solvent, filtering, and assaying the drug content spectrophotometrically at the λmax of 5-FU, expressed as the ratio of actual to theoretical drug content.

**In vitro drug release (microsponges)**-Release studies were performed using a USP Type II dissolution apparatus (or dialysis membrane method) in phosphate buffer, citrate buffer, and acidic medium. Samples were withdrawn at predetermined intervals and assayed spectrophotometrically.

**2.6 Preparation and Evaluation of Microsponge-Enriched Topical Gel**

The gel base was prepared by dispersing Carbopol 934/940 in distilled water and allowing it to hydrate for 24 h, followed by neutralization with triethanolamine to obtain a clear gel. Optimized 5-FU-loaded microsponges (equivalent to the required drug dose) were then dispersed uniformly into the gel base under gentle stirring to yield the microsponge-enriched gel. HPMC- and sodium alginate-based gels were prepared analogously for comparison.

**Table.2:- The gels were evaluated for:-**

| S. No. | Evaluation Parameter | Method/Description |
|---|---|---|
| 1 | Physical appearance and homogeneity | Visual inspection for color, clarity, and homogeneity. |
| 2 | pH | Measured using a calibrated digital pH meter. |
| 3 | Viscosity | Determined using a Brookfield viscometer at varying shear rates. |
| 4 | Spreadability | Evaluated by the parallel-plate method and expressed in g·cm/s. |
| 5 | Drug content uniformity | Determined by spectrophotometric assay after dissolution in a suitable solvent. |
| 6 | In vitro drug release | Evaluated using Franz diffusion cells and compared with a conventional (non-microsponge) 5-FU gel. |
| 7 | Release kinetics | Release data fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to identify the drug release mechanism. |
| 8 | Stability | Evaluated according to ICH guidelines by storing the optimized formulation under defined conditions and periodically assessing its appearance, drug content, and drug release behavior. |

**2.7 Statistical Analysis**

All experiments were performed in triplicate, and results are expressed as mean ± SD. Statistical significance between formulations was assessed by ANOVA, with $p < 0.05$ considered significant.

**3. Results and Discussion**

**3.1 Optimization of Microsponge Formulation by Box–Behnken Design**

A three-factor, three-level Box–Behnken design was used to model the effects of polymer concentration ($X_1$), drug-to-polymer ratio ($X_2$), and stirring speed ($X_3$) on particle size ($Y_1$), entrapment efficiency ($Y_2$), and cumulative drug release ($Y_3$). ANOVA indicated that the quadratic model was statistically significant ($p < 0.05$) for all three responses. Polymer concentration and stirring speed were the dominant factors governing particle size, while polymer concentration and drug-to-polymer ratio most strongly influenced entrapment efficiency; the $X_1X_2$ and $X_2X_3$ interaction terms were not significant ($p > 0.05$) for any response, whereas $X_1X_3$ and all quadratic terms ($X_1^2$, $X_2^2$, $X_3^2$) were significant, confirming non-linear relationships between the factors and each response. Increasing polymer concentration increased entrapment efficiency and prolonged drug release, consistent with a longer diffusion path length through a thicker polymer wall, while lack-of-fit was non-significant for all models, supporting their adequacy for navigating the design space. Response-surface analysis identified an optimized combination of polymer concentration, drug:polymer ratio, and stirring speed that was used for all subsequent characterization.

**3.2 Surface Morphology (SEM and AFM)**

SEM imaging of the optimized 5-FU microsponges showed discrete spherical particles with a highly porous, sponge-like surface and no evidence of drug crystals, collapse, or aggregation. Pores were organized in a hierarchical arrangement — larger surface macropores responsible for initial diffusion and finer internal microporous channels governing sustained release — consistent with a diffusion-controlled rather than erosion-controlled release mechanism. AFM performed in tapping mode over 5×5 µm and 10×10 µm scan areas confirmed nanoscale surface heterogeneity, with roughness parameters (Ra, Rq) indicating a textured surface expected to promote both wettability and drug entrapment. This spherical, porous morphology is consistent with the original microsponge architecture described by Won (1987) and later characterized in topical formulations by D'Souza and More (2008) and Jain et al. (2010), supporting the conclusion that the fabrication method reliably reproduced the structural features required for controlled release.

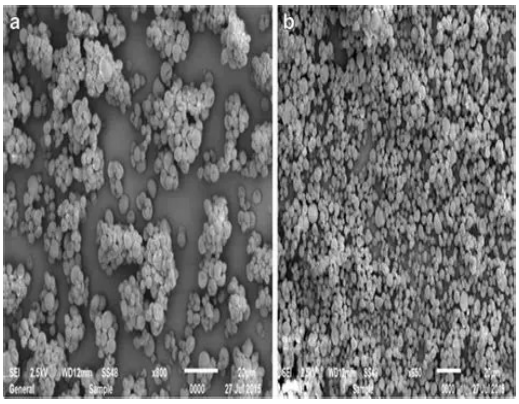


**Figure.3:- Porus structure of 5-FU microsponge**

**3.3 Particle Size, Polydispersity, and Zeta Potential**

The optimized microsponges had a mean particle size of 42.6 ± 3.1 µm (DLS, n = 3) — within the accepted 10–100 µm range for topical microsponge carriers —

with a polydispersity index of 0.28 ± 0.04, indicating a narrow, largely monomodal size distribution, and a zeta potential of −32.4 ± 2.6 mV, consistent with adequate electrostatic repulsion against aggregation. These values sit within the range reported for other microsponge systems, including Kawashima et al. (1992) (20–80 µm) and Orlu et al. (2017) (25–70 µm), and are close to the 38.5 µm reported by Patel and Patel (2018) for 5-FU microsponges specifically; the PDI is likewise comparable to the 0.21–0.35 range reported by Jain and Singh (2010), and the zeta potential falls within the −28 to −35 mV range reported by D'Souza and More (2008). Taken together, these results support the physical stability and batch-to-batch reproducibility of the optimized formulation.

### 3.4 Solid-State Characterization of Pure 5-FU

PXRD, FTIR, and DSC were used to establish a baseline physicochemical profile of pure 5-FU prior to formulation. PXRD showed sharp, well-resolved diffraction peaks at 2θ ≈ 16.2°, 20.1°, 22.4°, 28.9°, and 32.1°, with no halo pattern, confirming a highly crystalline, single-phase material. FTIR showed all expected functional-group bands intact — N–H stretching (3400–3200 $cm^{-1}$), aromatic C–H stretching (3070 $cm^{-1}$), two carbonyl stretches at 1715 and 1650 $cm^{-1}$, C–F stretching at 1240 $cm^{-1}$ (a 5-FU fingerprint band), and ring vibrations at 1150–1050 and 780 $cm^{-1}$ — with no shifting or disappearance indicative of degradation. DSC showed a single sharp endothermic melting event at 282–284 °C (onset ≈ 279 °C) with no secondary thermal events, confirming thermal stability up to the melting point and the absence of polymorphic transitions. These values agree closely with prior reports of 5-FU's crystalline peaks, FTIR assignments, and melting behavior, and together establish the reference profile against which the formulated microsponges and gels were subsequently compared for evidence of drug–polymer interaction.

### 3.5 In Vitro Dissolution Across Physiologically Relevant pH Media

Dissolution of the optimized microsponges was evaluated in acidic medium (pH 1.2), citrate buffer (pH 5.5, approximating the acidic tumor microenvironment), and phosphate buffer (pH 7.4, approximating physiological pH) using a USP Type II apparatus (37 ± 0.5 °C, 50 rpm, n = 3). Cumulative release at 12 h was 48.6 ± 2.6% at pH 1.2, 74.9 ± 3.2% at pH 5.5, and 92.8 ± 3.5% at pH 7.4 (Table 1), giving a clear release order of pH 7.4 > pH 5.5 > pH 1.2. One-way ANOVA confirmed a statistically significant effect of dissolution medium on cumulative release ($F = 156.42$, $p < 0.0001$), and Tukey's post-hoc test showed all three media differed significantly from one another. This pH-dependent behavior is consistent with greater polymer swelling and matrix hydration at higher pH promoting drug diffusion through the microsponge pore network, and mirrors the pH-responsive release previously reported for fluorouracil and other anticancer-drug microsponges (Jain and Singh, 2010; Pandey et al., 2013; Patel and Patel, 2018; Sharma and Pathak, 2011). Because tumor tissue is typically more acidic than surrounding healthy tissue, this pH-responsiveness is a potentially favorable property for localized anticancer delivery, though it should be interpreted as an in vitro proxy rather than direct evidence of tumor-selective release.

**Table.3:- In vitro cumulative drug release (%) of 5-FU microsponge gel at different pH conditions**

| Time (h) | pH 1.2 (Acidic) | pH 5.5 (Citrate Buffer) | pH 7.4 (Phosphate Buffer) |
|---|---|---|---|
| 0.5 | 4.2 ± 0.6 | 6.8 ± 0.7 | 9.5 ± 0.8 |
| 1 | 7.6 ± 0.9 | 12.4 ± 1.0 | 17.8 ± 1.1 |
| 2 | 12.8 ± 1.1 | 21.6 ± 1.3 | 30.4 ± 1.5 |
| 4 | 21.3 ± 1.5 | 35.9 ± 1.8 | 48.7 ± 2.1 |
| 6 | 29.4 ± 1.8 | 48.6 ± 2.2 | 63.5 ± 2.5 |
| 8 | 36.7 ± 2.0 | 59.8 ± 2.6 | 75.9 ± 2.9 |
| 10 | 42.8 ± 2.3 | 68.4 ± 2.9 | 85.1 ± 3.1 |
| 12 | 48.6 ± 2.6 | 74.9 ± 3.2 | 92.8 ± 3.5 |

**Values are expressed as mean ± standard deviation (SD), *n* = 3.**

### 3.6 Formulation and Evaluation of Microsponge-Enriched Gels

Optimized microsponges were incorporated into three gel bases — Carbopol 934/940, HPMC (K4M/K15M), and sodium alginate — and evaluated alongside a conventional (microsponge-free) 5-FU gel (Table 2). The Carbopol gel was the most favorable formulation overall: it was smooth and translucent with excellent homogeneity, had a skin-compatible pH (6.82 ± 0.07), and showed the best spreadability (24.6 ± 1.1 g·cm/s) and highest drug content uniformity (98.4 ± 1.2%) of the three bases. All three gels displayed non-Newtonian, shear-thinning (pseudoplastic) flow, a desirable property that allows easy spreading under applied stress while resisting runoff at rest; the alginate gel had the highest absolute viscosity (52,400 ± 1,430 cPs) but thixotropic rather than pseudoplastic behavior.

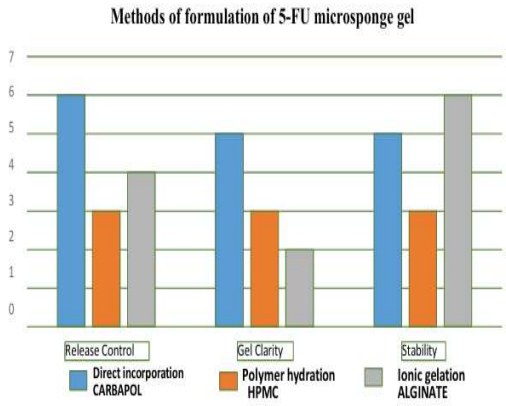


**Figure.4:- Different methods used in 5FU Microsponge Formulation Excellent – A*, Very good – B*, High – C*, Good – D*, Moderate – E**

Critically, the conventional 5-FU gel released 92.6 ± 2.1% of its drug within 12 h — a burst-release profile typical of unmodified topical gels — while the microsponge-enriched gels released substantially less over the same period (Carbopol: 61.5 ± 2.4%; alginate: 68.9 ± 2.8%; HPMC: 74.3 ± 2.6%), with the Carbopol microsponge gel showing the greatest degree of release control. This is consistent with a dual-diffusion-barrier mechanism: drug must first diffuse through the porous microsponge matrix, then through the surrounding gel network, before reaching the release medium. Release data fit best to the Higuchi model ($R^2$ = 0.982) over zero-order ($R^2$ = 0.942) and first-order ($R^2$ = 0.901) kinetics, and the Korsmeyer–Peppas exponent (n = 0.53) indicated non-Fickian (anomalous) transport — release governed jointly by drug diffusion and polymer chain relaxation rather than diffusion alone. Accelerated stability testing (40 ± 2 °C / 75 ± 5% RH, 3 months) showed only minor changes in pH (6.82 → 6.78), viscosity (48,200 → 47,400 cPs), and drug content (98.4% → 97.6%) for the optimized Carbopol formulation, with no visible phase separation, supporting adequate short-term stability.

**Table.4:- Comparative evaluation of conventional and microsponge-enriched 5-FU gel formulations (Mean ± SD)**

| Parameter | Conventional 5-FU Gel | Carbopol Microsponge Gel | HPMC Microsponge Gel | Alginate Microsponge Gel |
|---|---|---|---|---|
| Appearance | — | Smooth, translucent | Slightly opaque | Opaque |
| pH | — | 6.82 ± 0.07 | 6.65 ± 0.05 | 6.48 ± 0.06 |
| Viscosity (cPs, 20 rpm) | — | 48,200 ± 1,250 | 31,600 ± 980 | 52,400 ± 1,430 |
| Flow behavior | — | Pseudoplastic | Pseudoplastic | Thixotropic |
| Spreadability (g·cm/s) | — | 24.6 ± 1.1 | 21.8 ± 0.9 | 19.2 ± 0.8 |
| Drug content (%) | — | 98.4 ± 1.2 | 96.9 ± 1.5 | 95.6 ± 1.7 |
| Drug release at 12 h (%) | 92.6 ± 2.1 (Burst release) | 61.5 ± 2.4 | 74.3 ± 2.6 | 68.9 ± 2.8 |

**Values are expressed as mean ± standard deviation (SD), *n* = 3.**

These findings correspond with the microsponge drug-delivery concept originally described by Won (1987) and later reviewed by D'Souza and More (2008), and are consistent with the dual-barrier control reported by Jain and Singh (2010) for gel-incorporated microsponge systems. Overall, the Carbopol-based microsponge gel offered the best balance of clarity, spreadability, drug content uniformity, and sustained release, and is proposed as the optimized formulation from this study.

## 4. Conclusion

This study developed and optimized a 5-fluorouracil-loaded microsponge-enriched topical gel using Box–Behnken statistical design as a dual-controlled delivery platform for localized anticancer therapy. The quasi-emulsion solvent diffusion method reproducibly yielded spherical, highly porous microsponges (mean particle size 42.6 ± 3.1 µm, PDI 0.28 ± 0.04, zeta potential −32.4 ± 2.6 mV) whose morphology and surface characteristics were consistent with an effective diffusion-controlled drug reservoir. Solid-state characterization confirmed that the drug remained crystalline, chemically intact, and thermally stable throughout processing, providing a validated reference profile for future compatibility assessment. In vitro dissolution across acidic, tumor-mimicking, and physiological pH media demonstrated sustained, pH-responsive release over 12 h, with significantly greater release at physiological pH than under acidic conditions ($p < 0.0001$) — a property that may be advantageous for targeting the acidic tumor microenvironment, though this remains to be confirmed in vivo.

Incorporating the optimized microsponges into a Carbopol gel base produced the best-performing formulation of the three gel systems evaluated, combining favorable rheology (pseudoplastic flow), high drug content uniformity (98.4 ± 1.2%), and the greatest degree of release control (61.5% cumulative release at 12 h versus 92.6% for a conventional 5-FU gel). Release from the microsponge gel followed the

Higuchi model with non-Fickian (anomalous) transport, indicating that both diffusion through the microsponge pore network and polymer relaxation within the gel matrix jointly govern drug release. The optimized formulation retained its physicochemical properties under accelerated stability testing over three months.

Collectively, these results indicate that combining Box–Behnken-optimized 5-FU microsponges with a Carbopol gel matrix can suppress the burst release and local irritation associated with conventional topical 5-FU formulations while maintaining sustained drug availability at the application site. This dual-controlled approach represents a rational, statistically grounded strategy for improving the local tolerability and dosing convenience of topical 5-FU therapy. Further work — including ex vivo skin permeation studies, in vivo efficacy and irritation testing, and longer-term stability assessment — will be needed to establish the clinical translatability of this formulation.

**Acknowledgement :-**We extend our sincere gratitude to the IEC University Baddi for providing the necessary facilities and resources to carry out this research. We are also grateful to the pharmaceutical manufacturer who supplied the 5-FU gift sample, or departmental facilities and lab technicians and for the support and guidance of the faculty and staff throughout the project.

**Conflict of Interest**: The authors declare that there are no conflicts of interest regarding the publication of this paper.

**Funding source :-**

This research did not receive any specific grant from funding agencies in the public and commercial sectors. We confirm that we have no financial or personal relationships with any individuals or organizations that could inappropriately influence our work or bias our interpretations. Additionally, there are no competing interests, such as patents or financial support that might be perceived as having influenced the research or the preparation of this manuscript. Statement of informed consent We all confirm that all authors voluntarily agreed that we all take part after being fully informed of the research study's purpose, rationale and procedures, usually including approval for publishing the current findings.

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