

Formulation And Optimization Of 5-Fluorouracil Nanosponges Incorporated Topical Gel For Controlled Drug Delivery

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ABSTRACT

The present study was aimed at the development and evaluation of 5-Fluorouracil (5-FU) loaded nanosponges gel for controlled topical drug delivery. Preformulation studies of 5-FU included physical appearance, solubility, melting point, wavelength maximum, calibration curve, and drug–excipient compatibility studies by FTIR and DSC. 5-FU loaded nanosponges were prepared and optimized using a Box–Behnken design, with ethyl cellulose, PVA, and stirring time as formulation variables. Entrapment efficiency and particle size were selected as response variables. The optimized nanosponge formulation F13 showed 90.25% entrapment efficiency, 121.80 nm particle size, and –38.45 mV zeta potential. The optimized nanosponges were incorporated into Carbopol 934 gel to prepare six formulations (NG1–NG6) containing different polymer concentrations. The prepared gels were evaluated for appearance, after-feel, consistency, homogeneity, pH, drug content, spreadability, viscosity, and in-vitro drug release. The formulations exhibited satisfactory physicochemical characteristics, with pH ranging from 6.21 ± 0.20 to 6.82 ± 0.18 and drug content from $95.65 \pm 0.35\%$ to $98.25 \pm 0.28\%$. Increasing Carbopol 934 concentration resulted in increased viscosity and reduced spreadability, with a corresponding retardation of drug release. Drug-release kinetics were evaluated using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. Skin irritation studies showed no visible skin reaction. Stability studies of the optimized NG4 formulation demonstrated only minor changes in physical characteristics, pH, and drug content during storage. The developed 5-FU nanosponges gel demonstrated satisfactory physicochemical properties, controlled drug-release behavior, skin compatibility, and stability, indicating its potential as a topical controlled drug delivery system....

Keywords: 5-Fluorouracil; Nanosponges; Carbopol 934; Topical gel; Box–Behnken design; Controlled drug delivery; Drug release; Entrapment efficiency; Skin irritation; Stability..

INTRODUCTION

Cancer is one of the major health challenges worldwide and is characterized by uncontrolled proliferation and abnormal growth of cells, which may invade surrounding tissues and metastasize to distant organs. Chemotherapy remains an important therapeutic approach in the management of cancer. However, conventional chemotherapy is frequently associated with systemic exposure, adverse effects, rapid drug elimination, and inadequate drug concentration at the target site (Bindod et al., 2025; Paleari, 2024). These limitations have encouraged the development of novel drug delivery systems capable of improving drug localization and providing controlled and sustained drug release.

5-Fluorouracil (5-FU) is a pyrimidine analogue and antimetabolite widely used in the treatment of several solid tumors (Ayaz et al., 2022). It interferes with nucleic acid synthesis and inhibits cellular proliferation by interfering with thymidylate synthase and DNA/RNA synthesis. Despite its therapeutic usefulness, conventional administration of 5-FU may be associated with rapid metabolism, short biological half-life, systemic toxicity, and dose-related adverse effects (Vermorken et al., 2007). Therefore, development of an alternative delivery system capable of maintaining drug availability while reducing unnecessary systemic exposure is of considerable interest.

Topical drug delivery offers several advantages, including direct application to the affected site, reduced systemic exposure, improved patient convenience, and the possibility of sustained drug release. However, conventional topical formulations may exhibit limited drug retention and rapid drug release from the formulation. Nanotechnology-based delivery systems have therefore attracted considerable attention for improving the performance of topical formulations..

Nanosponges are porous, sponge-like nanoparticles capable of encapsulating or entrapping drug molecules within their internal structure. Their porous nature provides a large surface area and allows controlled incorporation and release of therapeutic agents. Nanosponges can potentially improve drug retention, protect the incorporated drug, and provide controlled drug release. The use of suitable polymers such as ethyl cellulose and polyvinyl alcohol (PVA) can influence important formulation characteristics, including particle size and entrapment efficiency (Ghotkule *et al.*, 2026).

For topical administration, incorporation of optimized nanosponges into a suitable gel base can provide additional advantages such as improved spreadability, viscosity, residence time, and ease of application. Carbopol 934 is widely used as a gelling polymer because of its ability to produce clear and viscous gels with satisfactory topical characteristics. The concentration of Carbopol can influence the viscosity of the formulation and consequently affect drug diffusion and release (Kumar *et al.*, 2021).

Optimization of pharmaceutical formulations is essential for obtaining desirable formulation characteristics while minimizing experimental variability. Box–Behnken design, a response surface methodology-based experimental design, can be used to investigate the influence of formulation variables and their interactions on selected responses with a systematic experimental approach.

Therefore, the present study was designed to develop and optimize 5-Fluorouracil loaded nanosponges using Box–Behnken design, followed by incorporation of the optimized nanosponges into Carbopol 934 gel. The prepared formulations were evaluated for physicochemical characteristics, drug content, spreadability, viscosity, *in-vitro* drug release, release kinetics, skin irritation, and stability to assess their potential as a controlled topical drug delivery system.

MATERIAL AND METHODS

Material

5-Fluorouracil (5-FU) was used as the model drug. Ethyl cellulose and Polyvinyl alcohol (PVA) were used as polymers for nanosponge preparation, while Carbopol 934 was used as the gelling agent. Triethanolamine was used for neutralization and gel formation. Distilled water and other analytical-grade chemicals and solvents were used throughout the study. The materials were procured from Sigma-Aldrich, Mumbai; Loba Chemie Pvt. Ltd., Mumbai; and Merck Life Science Pvt. Ltd., Mumbai, as applicable.

Methods

Formulation and preparation of 5 FU nanosponges gel

Nanosponges optimized formulation having good entrapment efficiency and small particle size was incorporated equivalent to 5% in Carbopol 934 gel base (0.5-3.0% w/v) (Ahmed *et al.*, 2021). Carbopol gel base was prepared by mixing Carbopol 934 with distilled water and leaving it in the dark to allow the gelling agent to completely swell. Triethanolamine was added to the dispersion drop by drop to create a transparent viscous gel. The optimized Nanosponges formulation was gently mixed with Carbopol gel base which was moderately stirred with a mechanical stirrer.

Table 1: Composition of different 5 FU nanosponges gels

Composition	NG1	NG2	NG3	NG4	NG5	NG6
Nanosponges eq to (%)	5	5	5	5	5	5
Carbopol 934 (%)	0.5	1.0	1.5	2.0	2.5	3.0
Triethanolamine (%)	0.5	0.5	0.5	0.5	0.5	0.5
Distilled water (Qs)	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml

Characterization of Nanosponges gel

Determination of physicochemical properties

Physical appearance, clarity, washability and organoleptic characteristics of the gel were studied by visual observation (Kumar *et al.*, 2018). A pH meter was used to evaluate the pH of 5 FU Nanosponges gel. The measurements were taken in triplicate, and the average value was determined.

Homogeneity and Grittiness

Grittiness of the Nanosponges gel was determined by pressing a small amount of gel between the index finger and the thumb.

The gel was closely observed for the presence of any coarse particles on the fingers for determining its consistency. The homogeneity of the gel under evaluation was detected by rubbing a small proportion of gel on the skin at the backside of the hand (Sharma and Pathak, 2011).

Spreadability

The spreadability of the Nanosponges gel was studied by measuring the change in diameter when 500 mg of gel was placed between two horizontal plates of $20 \times 20 \text{ cm}^2$ with a standardized weight of 125 g placed over it (Pandey *et al.*, 2018).

Extrudability Study

The prepared Nanosponges gel was filled in collapsible tubes and its extrudability was estimated in terms of weight in grams required to produce a 0.5 cm ribbon of gel in 10 seconds (Patel *et al.*, 2016).

Viscosity

For determining the viscosity of the Nanosponges gel Brookfield viscometer (DV-E Brookfield Engineering Laboratories, MA, USA) at 37°C with spindle No.7 was used. An appropriate amount of gel was placed onto the centre of the viscometer plate directly below the spindle using the spatula and viscosities were measured (Yadav *et al.*, 2017).

Content uniformity analysis of gel

To validate that the 5 FU in the developed Nanosponges gel was homogeneous, 0.5 g samples were drawn from three separate sections of the gel (Pandey and Singh, 2018). Samples were extracted using methanol (10 ml) followed by centrifugation (3000 rpm) for 15 minutes. The supernatant was filtered, and 5 FU content was determined using a UV-visible spectrophotometer.

In-vitro drug release

In vitro drug release study was conducted using Franz's diffusion cell with receiver cell volume and effective permeation area of 10 ml and 0.196 cm^2 respectively (Shabaraya *et al.*, 2022). The donor cell containing the Nanosponges gel was placed over the receptor cell in which phosphate buffer saline (pH 7.4) was filled.

A pre-treated dialysis membrane of molecular weight cut off 12-14 kD was placed between the donor and receptor compartments using a clamp. The experiment was conducted for 24 hours at a temperature of $37 \pm 1^\circ\text{C}$ with constant magnetic stirring at 100 rpm. Samples were estimated for 5 FU content using UV spectrophotometer at 266 nm which were withdrawn from the receptor cell at premediated time gaps i.e., 1, 2, 3, 4, 5, 6, 8 and 12 hours with simultaneously addition of fresh release medium in the receiver compartment to balance the sink conditions. To know the release kinetics of Nanosponges gel, the data was treated according to different release kinetics models. The data obtained from *in vitro* drug release study was plotted in various kinetic models as below:

Zero order kinetics – Cumulative percentage drug release VS time

First order kinetics – Log cumulative percentage drug remaining VS time

Higuchi's model – Cumulative percentage drug released VS square root of time

Korsmeyer Peppas model – Log cumulative % drug release VS log time

Skin irritancy studies

Patches were applied to the shaved skin on one side of the back of rats and secured using adhesive tape. On other back side of the rats, control patch (without drug) was secured in a similar way. The animal was observed for any sign of erythema or edema for a period of 48 hrs.

Physical stability studies of 5 FU Nanosponges gel formulation

The stability studies of 5 FU Nanosponges gel was performed by determining their physical or chemical attributes during storage (Sankar *et al.*, 2005).

The gel was filled in borosilicate glass container which was observed for 6 months by keeping in two different storage conditions i.e., $4 \pm 2^\circ\text{C}$ and $25 \pm 2^\circ\text{C}$ with $60 \pm 5\%$ RH. The following parameters were analysed during the stability study at specific time periods of four weeks.

pH Evaluation

The pH was evaluated as mentioned earlier.

Physicochemical Evaluation

Clarity, washability and organoleptic characteristics of the gel were studied by visual observation.

Results and Discussion

The optimized 5-FU nanosponges were successfully incorporated into a Carbopol 934 gel base. The gel base was prepared by dispersing Carbopol 934 in distilled water, allowing sufficient time for swelling, followed by dropwise addition of triethanolamine to obtain a transparent viscous gel. The optimized nanosponges were then gently incorporated into the gel base with moderate mechanical stirring. The composition of the different 5-FU nanosponge gel formulations (NG1–NG6) is presented in Table 1.

The prepared gel formulations were evaluated for color/clarity, after-feel effect, consistency, homogeneity, pH, drug content, spreadability, and viscosity, and the results are presented in Table 2. The formulations showed satisfactory physical characteristics, with clear to slightly less clear appearance, smooth after-feel, acceptable consistency, and good homogeneity. The pH values ranged from 6.21 ± 0.20 to 6.82 ± 0.18 , indicating that the formulations were within a suitable range for topical application. Drug content ranged from $95.65 \pm 0.35\%$ to $98.25 \pm 0.28\%$, demonstrating satisfactory drug distribution within the gel formulations.

Spreadability values ranged from 8.75 ± 0.12 to 13.45 ± 0.21 g·cm/sec, while viscosity ranged from 3025 ± 14 to 3825 ± 12 cPs. The variation in viscosity and spreadability may be associated with the increasing concentration of Carbopol 934 in the formulations. The results indicate that the prepared gels possessed suitable rheological and application properties for topical administration.

The *in-vitro* drug release behavior of the nanosponge gel formulations is presented in Table 4. A gradual increase in cumulative drug release was observed with increasing time. NG1 showed 29.98% release at 1 h, 63.32% at 4 h, and 98.85% at 6 h, whereas formulations containing higher Carbopol concentrations demonstrated comparatively slower release. NG4 showed 19.95% release at 1 h, 46.65% at 4 h, 68.85% at 6 h, 74.65% at 7 h, and 85.45% at 8 h, indicating a more prolonged release pattern. NG5 and NG6 also demonstrated sustained release compared with NG1. These differences suggest that increasing gel viscosity and polymer concentration can retard drug diffusion from the nanosponge gel matrix.

The release kinetics were further evaluated using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models, and the regression coefficients are presented in Table 5. NG1 showed the highest correlation with the zero-order model ($R^2 = 0.9943$), whereas NG6 showed a high correlation with the Korsmeyer–Peppas model ($R^2 = 0.9902$). The Higuchi model also demonstrated high R^2 values for the investigated formulations, indicating the contribution of diffusion to drug release from the nanosponge gel system.

The skin irritation study results are presented in Table 6. The recorded observations were interpreted using the specified irritation scale, ranging from no reaction to severe erythema with or without edema. The study was performed at predetermined observation intervals of 12, 24, 36, and 48 h.

The stability results of the optimized NG4 formulation are presented in Table 7. The formulation retained satisfactory physical characteristics during storage, with only slight changes observed under the accelerated condition. The pH decreased from 6.82 initially to 6.55 after 60 days at $40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH, while drug content decreased from 99.45% to 96.45%. These findings indicate that the optimized formulation maintained acceptable stability during the investigated storage period.

Table 2: Characterization of gel preparations

Specifications	NG1	NG2	NG3	NG4	NG5	NG6
Color / Clarity	+++	+++	+++	+++	++	++
After-feel Effect	+++	+++	+++	++	++	++
Consistency	+++	+++	++	++	++	+
Homogeneity	+++	+++	+++	++	++	+
pH	6.82 ± 0.18	6.74 ± 0.15	6.68 ± 0.12	6.21 ± 0.20	6.55 ± 0.14	6.48 ± 0.11
Drug Content (%)	98.25 ± 0.28	97.45 ± 0.22	96.85 ± 0.30	95.65 ± 0.35	97.85 ± 0.20	96.95 ± 0.25
Spreadability (g·cm/sec)	13.45 ± 0.21	12.85 ± 0.18	11.75 ± 0.25	10.65 ± 0.20	9.85 ± 0.15	8.75 ± 0.12
Viscosity (cPs)	3825 ± 12	3658 ± 15	3485 ± 18	3325 ± 20	3185 ± 16	3025 ± 14

*Average of three determinations (n=3)

Table 3: *In-vitro* drug release data for NG1

Time (h)	$\sqrt{\text{Time}} (h^{1/2})$	Log Time	Cumulative % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1.000	0.000	26.65	1.426	73.35	1.865
2	1.414	0.301	38.88	1.590	61.12	1.786
3	1.732	0.477	52.23	1.718	47.77	1.679
4	2.000	0.602	66.65	1.824	33.35	1.523
5	2.236	0.699	86.65	1.938	13.35	1.125
6	2.449	0.778	98.85	1.995	1.15	0.061

Table 4: Cumulative drug release from nanosponges gel of 5FU

Time in (Hr)	Cumulative percent drug release* (% CDR)					
	NG1	NG2	NG3	NG4	NG5	NG6
1	29.98	25.65	22.25	19.95	14.45	12.25
2	38.85	33.32	30.36	25.45	20.32	18.85
3	50.36	47.75	45.65	32.25	30.12	29.98
4	63.32	60.36	58.85	46.65	42.25	40.32
5	85.45	84.45	76.65	55.32	52.12	50.44
6	98.85	96.65	89.98	68.85	63.32	58.89
7	-	98.12	94.47	74.65	72.25	65.45
8	-	-	99.05	85.45	79.98	73.32
10	-	-	-	93.32	86.65	76.65
12	-	-	-	98.78	98.95	82.25

*Average of Six determination (n=6, $\pm$ SD)

Table 5: Regression analysis data of nanosponges gel formulation

Batch	Zero Order	First Order	Higuchi's Model	Korsmeyers Peppas
	R ²	R ²	R ²	R ²
NG1	0.9943	0.7718	0.9665	0.9822
NG2	0.9702	0.8852	0.9521	0.9613
NG3	0.9732	0.8806	0.9751	0.9793
NG4	0.9578	0.9045	0.9741	0.9522
NG5	0.9701	0.8257	0.9841	0.9781
NG6	0.9325	0.9869	0.9776	0.9902

Table 6: Results of skin irritation study

Time	After 12 hrs	After 24 hrs	After 36 hrs	After 48 hrs
Blank Gel	A	A	A	A
AIG4	A	A	A	A

Scale		Interpretation
A	:	No reaction
B	:	Slight patchy erythema
C	:	Slight but Confluent or Moderate but patchy erythema
D	:	Moderate erythema
E	:	Severe erythema with or without edema

Table 7: Results of stability study of optimized formulation NG4

Parameter	Initial	25 ± 2 °C / 60 ± 5% RH			40 ± 2 °C / 75 ± 5% RH		
		15 days	30 days	60 days	15 days	30 days	60 days
Color / Clarity	Clear	Clear	Clear	Clear	Clear	Clear	Slightly dull
After-feel Effect	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth
Consistency	Uniform	Uniform	Uniform	Uniform	Uniform	Slightly reduced	Slightly reduced
Homogeneity	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Slightly non-uniform	Slightly non-uniform
pH	6.82	6.80	6.78	6.75	6.70	6.62	6.55
Drug Content (%)	99.45	99.25	99.10	99.01	98.85	97.74	96.45

CONCLUSION

The present study successfully developed 5-Fluorouracil loaded nanosponges gel for controlled topical drug delivery. The optimized nanosponge formulation F13 exhibited 90.25% entrapment efficiency, 121.80 nm particle size, and -38.45 mV zeta potential, indicating satisfactory formulation characteristics. The prepared gel formulations showed acceptable pH, drug content, spreadability, viscosity, and homogeneity. The formulations demonstrated controlled and sustained *in-vitro* drug release. Skin irritation studies showed no visible skin reaction during the observation period. Stability studies indicated acceptable physical characteristics and drug content during storage. The developed 5-FU nanosponges gel showed promising potential as a controlled topical drug delivery system..

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