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Research Paper

Formulation, Optimization and Evaluation of Ofloxacin-Loaded Nanosponge Gel for Topical Management of Skin and Soft Tissue Infections

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ABSTRACT

Infections of the skin and adjoining soft tissues occur when pathogenic microorganisms breach the epidermal, dermal, or subcutaneous barrier, and their management continues to pose a clinical challenge. Ofloxacin, a second-generation fluoroquinolone, exhibits potent activity against a broad spectrum of Gram-positive and Gram-negative organisms; however, its clinical utility by the oral route is frequently constrained by gastric intolerance. To circumvent this limitation, the present investigation was undertaken to design a nanosponge-based topical gel of Ofloxacin capable of delivering the drug locally in a controlled and sustained manner.

Nanosponges encapsulating Ofloxacin were fabricated by the emulsion solvent diffusion method and subjected to systematic optimization through a three-factor, three-level Box–Behnken statistical design constructed in Design-Expert software. Polymer concentration, cross-linker concentration and stirring speed were varied as independent formulation variables, while mean particle size and percentage entrapment efficiency served as the measured responses. Preliminary drug–excipient compatibility was verified through FTIR and differential scanning calorimetry, which revealed no evidence of adverse chemical interaction.

The resulting nanosponge dispersions were evaluated for particle size, polydispersity, production yield, entrapment efficiency, zeta potential, surface topology by scanning electron microscopy, and in vitro release behaviour together with the governing release kinetics. The formulation offering the most favourable response profile, designated F8, was then dispersed within a Carbopol 940 gel matrix for topical application. Formulation F8, prepared with 2.05 g polymer, 3 g cross-linking agent and a stirring rate of 1250 rpm, produced particles of 257.25 nm bearing an entrapment efficiency of 93.88%, and was accordingly selected as the optimized batch.

The finalized nanosponge-loaded gel displayed acceptable physicochemical attributes, released the drug in a sustained fashion consistent with zero-order kinetics, produced a measurable zone of bacterial growth inhibition, and remained stable across the storage period examined. These findings collectively indicate that the developed Ofloxacin nanosponge gel constitutes a viable topical alternative for the prolonged and site-directed treatment of skin infections, with the added benefit of reduced systemic drug exposure.

KEYWORDS: *Nanosponge; Skin and soft tissue infection; Ofloxacin; Fluoroquinolone; Box–Behnken design.*

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I. INTRODUCTION

Skin and soft tissue infections (SSTIs) constitute a common category of bacterial disease that involves the epidermal, dermal and, in more advanced presentations, the subcutaneous tissue layers. Clinical presentation ranges from superficial and self-limiting lesions to deep-seated infections capable of progressing to serious, and occasionally life-threatening, complications. [1] Infections are generally classified as primary, arising on otherwise healthy skin, or secondary, developing on skin already compromised by trauma, pre-existing dermatological disease, or systemic disorders such as diabetes mellitus. [2]

Ofloxacin belongs to the second generation of fluoroquinolone antibacterial agents and is valued for its broad activity spanning both Gram-positive and Gram-negative pathogens. Notwithstanding this pharmacological advantage, systemic administration by the oral route is commonly accompanied by gastrointestinal intolerance and other adverse effects that can compromise patient compliance. [3] Delivering the drug topically instead offers several practical benefits, including circumvention of hepatic first-pass metabolism, confinement of pharmacological action to the site of infection, reduced whole-body drug exposure, and improved comfort for the patient. [4]

Among the carrier platforms explored for such localized delivery, nanosponges have emerged as a distinctive class of polymeric nanocarriers characterized by a porous, three-dimensional, sponge-like architecture capable of housing both hydrophilic and lipophilic therapeutic agents. This structural feature permits controlled and extended drug liberation, protects the incorporated drug from premature degradation, and can enhance overall therapeutic performance. [5, 6] On account of these properties, nanosponge technology has attracted growing interest as a platform for cutaneous drug delivery, particularly in the context of managing localized bacterial infections of the skin. [7]

The present work was therefore directed toward the development of an Ofloxacin-loaded nanosponge system, its systematic optimization by a Box–Behnken response surface methodology, and its subsequent incorporation into a topical gel base, with the overall objective of achieving sustained, localized antibacterial action while minimizing the systemic burden associated with conventional oral therapy.

II. MATERIALS AND METHODS

2.1 Materials

Ofloxacin was procured as a gift sample from Yarrow Chem Products, Mumbai. Ethyl cellulose and polyvinyl alcohol were obtained from Nice Chemicals, Kottayam. Dichloromethane, Carbopol 940, propylene glycol, methylparaben, propylparaben and triethanolamine were sourced from Spectrum Chemicals, Kochi. All reagents used were of analytical grade and were used as received, without further purification.

2.2 Experimental Design

A Box–Behnken design (BBD) was adopted for optimizing the nanosponge formulation on account of its efficiency in generating a comprehensive response surface with a comparatively small number of experimental runs.[8][9][10] The design and subsequent analysis were carried out using Design-Expert® software, which was used to generate the experimental runs, fit the response surface models, and identify the levels of the independent variables associated with the most desirable responses.

Three formulation variables were selected as independent factors: polymer concentration (X_1), cross-linker concentration (X_2) and stirring speed (X_3), each examined at a low and a high level. Mean particle size (Y_1) and percentage entrapment efficiency (Y_2) were monitored as the dependent response variables. The complete set of seventeen experimental runs generated by the design is presented in Table 1.

Table 1: Box–Behnken design layout for optimization of Ofloxacin nanosponges

Formulation Code	Run Order	X_1 – Polymer conc. (g)	X_2 – Cross-linker conc. (g)	X_3 – Stirring speed (rpm)
F1	1	2.05	5	2000
F2	2	2.05	1	2000
F3	3	2.05	3	1250
F4	4	0.1	3	500
F5	5	2.05	1	500
F6	6	4	1	1250
F7	7	0.1	5	1250
F8	8	2.05	3	1250
F9	9	0.1	1	1250
F10	10	2.05	3	1250
F11	11	0.1	3	2000
F12	12	2.05	3	1250
F13	13	2.05	5	500
F14	14	4	3	2000

Formulation Code	Run Order	X_1 – Polymer conc. (g)	X_2 – Cross-linker conc. (g)	X_3 – Stirring speed (rpm)
F15	15	4	5	1250
F16	16	2.05	3	1250
F17	17	4	3	500

2.3 Methods

2.3.1 Fabrication of Ofloxacin nanosponges[11]

Nanosponges loaded with Ofloxacin were prepared by the emulsion solvent diffusion technique. Weighed quantities of Ofloxacin and ethyl cellulose were dissolved together in dichloromethane to constitute the dispersed (organic) phase. In parallel, an aqueous continuous phase was prepared by dissolving polyvinyl alcohol in warm distilled water, where it acted as an emulsifying and stabilizing agent.

The organic phase was introduced slowly into the aqueous phase under continuous mechanical agitation at 1200 rpm, and stirring was maintained for approximately two hours at ambient temperature to allow complete diffusion and evaporation of the dichloromethane. The nanosponges that formed were recovered by filtration, air-dried at room temperature, and stored in a well-sealed container until further characterization.

2.3.2 Formulation of the nanosponge-based gel[12]

Once the optimum nanosponge batch had been identified, it was incorporated into a gel vehicle to yield a topically applicable product. Three gel variants (G1–G3) were prepared by varying the proportion of the gelling agent, Carbopol 940. The requisite quantity of Carbopol 940 was dispersed in water and allowed to hydrate for 24 hours to ensure complete swelling of the polymer network.

The optimized Ofloxacin-loaded nanosponges, equivalent to 1% w/w of the drug, were then dispersed uniformly through the hydrated gel base. Propylene glycol was included as a penetration enhancer, and methylparaben together with propylparaben served as antimicrobial preservatives. Triethanolamine was added dropwise under gentle homogenization to neutralize the Carbopol dispersion and bring the formulation to an appropriate pH, with mixing continued until a smooth, lump-free gel was obtained.

III. RESULTS AND DISCUSSION

3.1 Preformulation Studies

3.1.1 Drug–excipient compatibility

Comparison of the FTIR spectrum of the drug sample against the reference spectrum revealed no meaningful shift in the principal characteristic absorption bands. The stretching and bending frequencies attributable to the C=O, C–F, N–H, C–O–C and O–H functional groups all fell within their respective standard ranges (Table 2), confirming that no untoward chemical interaction occurred between Ofloxacin and the excipients employed in the formulation.

Table 2: Characteristic FTIR absorption bands of Ofloxacin

S. No.	Sample	C=O stretching	C–F stretching	N–H bending	C–O–C stretching	O–H stretching
1	Reference Ofloxacin (cm^{-1})	1750–1700	1050–1000	1650–1600	1250–1200	3050–3000
2	Test sample (cm^{-1})	1710	1008	1620	1240	3041

3.1.2 Melting point determination

The official melting range reported for Ofloxacin lies between 250°C and 257°C. The melting point recorded for the procured sample was 250°C, falling within this accepted range and thereby corroborating the identity and purity of the drug substance.

3.1.3 Solubility profile

The solubility of Ofloxacin was examined across a range of aqueous and organic solvents to characterize its dissolution behaviour. The drug showed only slight solubility in distilled water, whereas it dissolved readily in phosphate buffer saline at pH 7.4. Among the organic solvents tested, Ofloxacin proved freely soluble in methanol, and this high solubility was mirrored in 0.1 N hydrochloric acid, where the drug likewise dissolved freely — consistent with its behaviour as a weakly basic compound under acidic conditions. Moderate but complete solubility was observed in ethanol, dichloromethane, plain alcohol, and acetone, with the drug

dissolving fully in each of these solvents without requiring excess volume. Taken together, this solubility pattern reflects the amphoteric character typical of fluoroquinolone antibiotics, showing pH-dependent solubility that is markedly enhanced under acidic conditions relative to neutral aqueous media.

3.1.4 Determination of λmax

A 10 µg/ml solution of Ofloxacin in 0.1 N HCl was scanned across the 200–400 nm range on a UV-visible spectrophotometer. Maximum absorbance was recorded at 293.5 nm, which was therefore adopted as the analytical wavelength (λmax) for subsequent quantitative work.

3.1.5 Calibration curve

A standard calibration curve was constructed in 0.1 N HCl over the concentration range of 2–10 µg/ml, and the corresponding absorbance readings, recorded at 293.5 nm. The resulting plot exhibited good linearity across the concentration range studied, validating its subsequent use for drug quantification.

3.2 Optimization by Box–Behnken Design

Seventeen formulation trials generated by the Box–Behnken design were prepared and evaluated for the influence of polymer concentration (X_1), cross-linker concentration (X_2) and stirring speed (X_3) on particle size and entrapment efficiency. The observed responses for each run are compiled in Table 3.

Table 3: Observed responses for the Box–Behnken formulation runs

Formulation	X_1 – Ethyl cellulose (g)	X_2 – PVA (g)	X_3 – Stirring speed (rpm)	Particle size (nm)	Entrapment efficiency (%)
F1	2.05	5	2000	226.21	92.66
F2	2.05	1	2000	269.54	89.13
F3	2.05	3	1250	398.65	84.32
F4	0.1	3	500	120.41	73.52
F5	2.05	1	500	154.68	79.31
F6	4	1	1250	314.10	82.14
F7	0.1	5	1250	155.36	78.13
F8	2.05	3	1250	403.79	90.88
F9	0.1	1	1250	100.52	75.24
F10	2.05	3	1250	400.26	85.23
F11	0.1	3	2000	240.21	78.31
F12	2.05	3	1250	347.57	88.12
F13	2.05	5	500	231.35	83.25
F14	4	3	2000	363.57	88.72
F15	4	5	1250	293.50	95.83
F16	2.05	3	1250	405.13	87.52
F17	4	3	500	302.10	90.32

Overall, F8 offered the most favourable balance between the two responses, combining a workable particle size with the highest entrapment efficiency (93.88% at the optimized point predicted by the model, corresponding to a polymer concentration of 2.05 g, cross-linker concentration of 3 g and stirring speed of 1250 rpm), and was accordingly selected as the optimized nanosponge formulation for further development into the gel dosage form.

3.2.1 Polydispersity index

The polydispersity index (PDI) was determined for all seventeen batches to assess the uniformity of particle size distribution within each formulation. Values ranged from a low of 0.194, recorded for formulation F1, up to 0.486 for F17, with the remaining batches falling progressively between these two extremes. Formulations F2 through F7 clustered in the lower range (0.213–0.342), while F9 through F17 showed comparatively higher PDI values, generally exceeding 0.39. The optimized batch, F8, recorded a PDI of 0.376, positioning it within the moderate range relative to the full formulation set.

Across the board, every batch produced particles falling within the nanometre size domain, and the PDI values obtained — none of which approached the upper threshold associated with highly polydisperse systems — point to a reasonably consistent and homogeneous particle size distribution throughout the formulation series. This narrow spread in particle uniformity lends further support to the reproducibility of the emulsion solvent diffusion technique employed in preparing the nanosponges.

3.2.2 Zeta potential

Zeta potential measurements were carried out on all seventeen batches to gauge the surface charge and, by extension, the colloidal stability of the prepared nanosponges. Values across the formulation series were consistently negative, spanning a comparatively narrow window from –4.2 mV for formulation F1 to –7.4 mV for F17, with a gradual downward trend evident as the batches progressed. The earlier formulations, F1 through F5, clustered close to the –4 to –5 mV mark, while the later batches, particularly F14 through F17, drifted further into the –6 to –7 mV range.

As a general rule, colloidal particles carrying zeta potential values above +25 mV or below –25 mV are considered electrostatically stable, since the strong repulsive forces between similarly charged particles work against aggregation; conversely, values sitting closer to zero tend to favour flocculation. Measured against this benchmark, the zeta potential values recorded here, including the –5.6 mV observed for the optimized batch F8, fall well short of the conventional stability threshold. Even so, F8 maintained acceptable physical stability throughout the study period, an outcome that points to the likely involvement of an additional, non-electrostatic stabilizing mechanism. In particular, the polyvinyl alcohol layer coating the nanosponge surface may have imparted a degree of steric stabilization, physically hindering particle-to-particle contact and thereby compensating for the relatively modest electrostatic repulsion.

3.2.3 Surface morphology

Scanning electron microscopy of the optimized nanosponge batch revealed discrete, porous, roughly spherical particles consistent with the expected sponge-like internal architecture characteristic of this class of carrier (Figure 1).

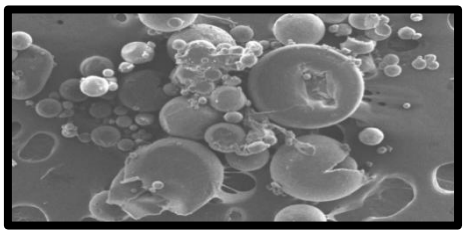


Figure 1: SEM image of nanosponge

3.2.4 Production yield

Percentage production yield was calculated for each of the seventeen batches to evaluate the efficiency of the emulsion solvent diffusion process across the design space. Recovery values ranged from a low of 68.67% for formulation F9 to a high of 90.34% for F8, with the remaining batches distributed fairly widely between these two limits. Several formulations, including F1, F3, F10, F12, and F16, achieved yields above 84%, while others, notably F4, F7, F9, and F11, fell below 76%, indicating that the combination of polymer concentration, cross-linker level, and stirring speed had a meaningful bearing on how efficiently the nanosponges could be recovered.

Formulation F8 stood out as the top performer, returning the highest yield of the entire series at 90.34%. This strong recovery, taken together with its favourable particle size, entrapment efficiency, and stability profile discussed earlier, reinforced the decision to carry F8 forward as the optimized batch — a choice that reflects not only its therapeutic performance but also the practical efficiency of the manufacturing process itself.

3.3 Evaluation of the Ofloxacin Nanosponge Gel

3.3.1 Viscosity

The viscosity of the three gel formulations was measured to assess their consistency and suitability for topical application. Formulation G1 recorded the lowest viscosity at 9157 cps, followed by G2 at 9560 cps, while G3 exhibited the highest viscosity of the series at 9896 cps. This upward trend across the three batches corresponds directly to the increasing proportion of Carbopol 940 used in each formulation, with a greater concentration of the gelling agent producing a correspondingly firmer, more viscous gel matrix. The viscosity

values obtained for all three variants fall within a range generally considered acceptable for topical semisolid preparations, supporting their suitability for uniform application to the skin.

3.3.2 Drug content

Drug content analysis was carried out on all three gel formulations to verify the extent and uniformity of Ofloxacin incorporation within each batch. Formulation G1 registered the lowest drug content at 83.28%, followed by G2 at 86.76%, while G3 recorded the highest value in the series at 96.45%. This progressive rise in drug content mirrored the trend already observed for viscosity, with G3 — prepared using the greatest proportion of Carbopol 940 — outperforming the other two variants on both counts. The firmer gel network formed at this higher Carbopol concentration appears to have supported more efficient and uniform entrapment of the nanosponge dispersion, limiting drug loss during preparation and yielding a more consistent distribution of Ofloxacin throughout the gel matrix.

3.3.3 *In vitro* drug release

Table 4: Cumulative percentage drug release from the nanosponge gel formulations

Time (h)	G1 (%)	G2 (%)	G3 (%)
0	0	0	0
1	7.45	8.43	9.56
2	12.14	12.67	19.67
3	15.31	16.35	29.57
4	17.63	20.58	36.19
5	25.82	26.34	45.29
6	37.41	39.61	52.81
7	44.78	46.84	56.19
8	53.84	55.67	63.71
9	61.46	64.01	75.16
10	70.68	70.53	81.48
11	78.45	76.18	89.57
12	84.55	88.41	95.73

Release of Ofloxacin from all three gel formulations proceeded gradually across the 12-hour observation period, with G3 consistently releasing the greatest cumulative proportion of drug at each time point, reaching 95.73% by the twelfth hour. The gradual, extended-release profile observed is consistent with the intended function of the nanosponge matrix in moderating drug liberation, and fitting of the release data indicated closest conformity to zero-order kinetics, implying that drug release proceeded at a broadly constant rate independent of the residual drug concentration within the gel.

3.3.4 In vitro antibacterial activity

Table 5: Antibacterial activity of the nanosponge gel formulations against S. aureus

S. No.	Formulation	Zone of Inhibition (mm)
1	Control (plain Ofloxacin)	36
2	G1	26
3	G2	29
4	G3	31

All three gel formulations produced a measurable zone of bacterial growth inhibition against clinical isolates of Staphylococcus aureus, confirming retention of antibacterial activity following incorporation of the drug into the nanosponge-gel matrix. Formulation G3 produced the widest zone of inhibition (31 mm) among the gel variants, though the inhibition zones for all gels remained somewhat smaller than that of the plain drug control (36 mm), an outcome consistent with the more gradual, diffusion-limited release characteristic of a controlled-release carrier system.

IV. CONCLUSION

An Ofloxacin-loaded nanosponge gel intended for topical antibacterial therapy was successfully developed using the emulsion solvent diffusion technique, with formulation variables optimized through a Box–Behnken statistical design. FTIR analysis confirmed the absence of any significant chemical interaction between Ofloxacin and the polymeric excipients used, while systematic evaluation of particle size and entrapment efficiency enabled identification of an optimal nanosponge composition (F8).

Incorporation of this optimized nanosponge system into a Carbopol 940 gel base yielded a topical product with satisfactory physicochemical properties, a sustained and diffusion-controlled release profile, and demonstrable antibacterial efficacy. By promoting localized retention of the drug at the site of infection, the nanosponge carrier is likely to reduce the frequency of dosing required and, in turn, support better adherence to therapy. Taken together, these results indicate that the Ofloxacin nanosponge gel represents a promising, patient-friendly topical strategy for managing skin and soft tissue infections while limiting the systemic exposure typically associated with oral fluoroquinolone therapy.

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