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Formulation, Optimization, and Characterization, of Allicin-Loaded B- Cyclodextrin Nanosponges Incorporated into a Topical Gel

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ABSTRACT:

Background: Fungal infections remain a significant therapeutic challenge due to recurrence, limited treatment options, and reduced susceptibility to conventional antifungal agents. Allicin, a natural organosulfur compound, possesses promising antifungal activity but requires an appropriate delivery system for effective localized application. The present study aimed to develop an allicin-loaded nanosponge incorporated into a topical gel.

Method: Allicin-loaded nanosponges were prepared by the emulsion solvent diffusion technique using ethyl cellulose, polyvinyl alcohol (PVA), and Pluronic F68. A central composite design was employed, with PVA (600–1200 mg) and ethyl cellulose (400–600 mg) as independent variables. Particle size and entrapment efficiency were selected as responses. The optimized formulation was incorporated into 1% Carbopol 940 gel and evaluated for physicochemical properties.

Results: The prepared nanosponges showed particle sizes of 201.61–361.27 nm, zeta potentials of –11.5 to –19.3 mV, and entrapment efficiencies of 58.9–82.4%. PF7 was optimized with an entrapment efficiency of 82.4% and particle size of 273.52 ± 3.28 nm. It exhibited progressive drug release, reaching 95.57% at 12 h. The nanosponge-loaded gel was greenish-brown, clear, and thick, with pH 6.7 ± 0.09 , spreadability 12.2 ± 0.78 g·cm/s, and viscosity 4425 ± 33.64 cps.

Discussion: The nanosponge system provided nanoscale particle size, satisfactory drug entrapment, and sustained allicin release. Incorporation into Carbopol 940 produced a gel with suitable topical physicochemical characteristics, potentially supporting localized and prolonged drug delivery.

Conclusion: The developed allicin-loaded nanosponge gel demonstrated suitable characteristics for topical antifungal delivery and may provide a promising platform for localized allicin administration.

INTRODUCTION:

Fungal infections represent a significant therapeutic challenge because of their increasing prevalence, recurrence, limited availability of antifungal agents, and the emergence of reduced susceptibility to conventional antifungal therapy. Superficial fungal infections particularly affect the skin and mucosal surfaces and may cause persistent discomfort, inflammation, itching, irritation, and reduced quality of life. *Candida* species are important opportunistic fungal pathogens, while other dermatophytes and pathogenic fungi are responsible for a broad spectrum of cutaneous infections. The management of localized fungal infections generally relies on topical antifungal therapy; however, inadequate drug retention at the site of infection, poor penetration through the skin, instability of active substances, and repeated application can compromise therapeutic performance. Therefore, development of novel topical delivery systems capable of improving drug stability, localization, controlled release, and antifungal efficacy remains an important area of pharmaceutical research [1,2].

Allicin, a biologically active organosulfur compound associated with garlic (*Allium sativum* L.), has attracted considerable interest because of its broad antimicrobial and antifungal properties. It is generated from alliin through the enzymatic action of alliinase and possesses a highly reactive thiosulfinate group. Allicin can interact with thiol-containing cellular components and interfere with essential metabolic processes of microorganisms [3]. Experimental investigations have demonstrated antifungal activity of allicin against important fungal pathogens. Its activity has been associated with disruption of fungal cell membranes, alteration of membrane permeability, interaction with cellular proteins, and impairment of essential intracellular functions [3–5]. In particular, experimental evidence has shown that allicin can damage fungal membranes and organelles, supporting its potential as a natural antifungal agent [4]. However, the pharmaceutical development of allicin is challenging because of its chemical reactivity and susceptibility to degradation, which can limit its stability and effective delivery in conventional dosage forms. These limitations create a need for an appropriate carrier system capable of protecting allicin while maintaining its therapeutic activity.

Nanotechnology-based drug delivery systems have emerged as promising approaches for addressing the physicochemical and biopharmaceutical limitations of conventional formulations. Among these systems, cyclodextrin-based nanosponges (CDNS) are three-dimensional, porous, cross-linked polymeric structures derived from cyclodextrin molecules. Their interconnected network provides nanosized cavities and channels capable of accommodating various drug molecules through inclusion and non-covalent interactions [6,7]. Unlike conventional cyclodextrins, cross-linking produces an insoluble or swellable nanoporous structure with greater versatility for drug loading and controlled release. The physicochemical characteristics of CDNS can be modified by selecting appropriate cross-linkers and controlling the degree of cross-linking, thereby influencing drug loading, swelling, release, and interaction with the surrounding formulation [7,8]. Recent investigations have emphasized the importance of parameters such as particle size, surface characteristics, crystallinity, thermal behavior, molecular interactions, porosity, and cross-linking density in determining the performance of cyclodextrin nanosponges [8].

β -Cyclodextrin (β -CD) is particularly attractive for the development of nanosponge-based drug delivery systems because its hydrophobic cavity can accommodate suitable lipophilic molecules, whereas its hydrophilic outer surface facilitates interaction with aqueous environments. Conversion of β -CD into a cross-linked nanosponge network can provide additional cavities and channels for drug incorporation and may improve the apparent solubility, protection, and release characteristics of poorly water-soluble or unstable compounds [6–9]. Consequently, β -CD nanosponges have been investigated as carriers for different pharmaceutical actives and can be incorporated into various dosage forms, including topical preparations. Studies have specifically demonstrated the potential of β -CD nanosponges as multifunctional components of water-containing semisolid formulations intended for skin delivery [10]. This provides a rational basis for exploring β -CD nanosponges as a carrier system for topical delivery of allicin.

Topical drug delivery offers several potential advantages for localized fungal infections, including direct application to the affected site, reduction of systemic exposure, and maintenance of drug concentration at the site of infection. Nevertheless, conventional topical formulations may suffer from rapid removal from the skin surface, inadequate residence time, poor drug solubilization, and uncontrolled drug release. Incorporating a nanosponge-based system into a suitable topical gel may address some of these limitations by combining the drug-carrying and controlled-release properties of nanosponges with the convenient application and residence characteristics of a gel. Cyclodextrins have previously been explored in topical formulations to improve the solubility and physicochemical properties of active pharmaceutical ingredients, while β -CD-based nanosponges provide an additional nanoporous carrier structure [10,11].

The formulation of an allicin-loaded β -cyclodextrin nanosponge incorporated into a topical gel therefore represents a rational strategy for integrating the antifungal potential of allicin with the drug-delivery advantages of nanostructured carriers. The nanosponge may provide a protective microenvironment for allicin, facilitate its dispersion within the aqueous formulation, and modulate its release. Incorporation of the optimized nanosponge into a topical gel may further improve spreadability, residence time, application characteristics, and localized drug delivery. Such a formulation requires systematic optimization because variables associated with nanosponge preparation and gel composition can influence particle size, drug entrapment, drug loading, surface properties, rheological behavior, and release characteristics [7,8].

Accordingly, the present study focuses on the formulation, optimization, characterization, and incorporation of allicin-loaded β -cyclodextrin nanosponges into a topical gel. The nanosponge formulation is intended to be optimized using appropriate formulation variables and evaluated for physicochemical and pharmaceutical characteristics. Characterization of the optimized nanosponge may include particle size, polydispersity, surface morphology, zeta potential, drug content, entrapment efficiency, Fourier-transform infrared spectroscopy, differential scanning calorimetry, X-ray diffraction, and in-vitro drug-release studies, as appropriate. The optimized nanosponge will subsequently be incorporated into a topical gel and evaluated for parameters such as appearance, pH, viscosity, spreadability, drug content, extrudability, stability, and in-vitro release. Finally, the antifungal performance of the developed formulation can be assessed using suitable microbiological methods against selected fungal organisms.

Thus, the proposed formulation combines the natural antifungal potential of allicin, the protective and controlled-release characteristics of β -cyclodextrin nanosponges, and the patient-friendly properties of a topical gel. The development of such a delivery system may provide a scientifically relevant platform for improving the topical delivery of allicin and warrants systematic formulation and characterization studies.

MATERIAL AND METHOD

Material

Allicin was selected as the active pharmaceutical ingredient for the development of the topical nanosponge formulation. Ethyl Cellulose was used as the polymeric carrier. Polyvinyl Alcohol and Pluronic® F68 were used as stabilizing components during preparation of the nanosponges. Carbopol 940 was used as the gelling agent for the preparation of the topical gel, and Triethanolamine was used as the neutralizing agent.

Method

Preformulation Studies

Preformulation studies were conducted to evaluate the physicochemical and analytical properties of Allicin before formulation development. Organoleptic evaluation showed that Allicin was a pale-yellow oily liquid. The UV-Visible spectrum was recorded over 200–800 nm, and the maximum absorbance (λ_{max}) was observed at 241 nm.

A calibration curve was prepared using Allicin concentrations of 1–6 µg/mL in ethanol, with absorbance measured at 241 nm. The solubility of Allicin was qualitatively assessed in water, ethanol, methanol, and chloroform. The melting point was determined using the capillary method with a Veego melting-point apparatus. FTIR analysis was performed for pure Allicin and its physical mixture with selected excipients using the KBr pellet method over 4000–400 cm⁻¹. The characteristic functional-group peaks were compared to assess possible drug–excipient interactions. These preformulation findings provided essential information for subsequent formulation and optimization of Allicin-loaded β-cyclodextrin nanosponges.

Experimental Design

A central composite design (CCD) was employed to optimize the formulation of Allicin-loaded nanosponges. Nine experimental formulations were designed using two independent numerical variables: X₁, representing the concentration of polyvinyl alcohol (PVA), and X₂, representing the concentration of ethyl cellulose (EC).

The selected dependent variables (responses) were R₁, representing entrapment efficiency (%), and R₂, representing particle size (nm). The experimental design was used to investigate the influence of the selected independent variables on the formulation characteristics and to identify the optimized formulation. [13].

Table 1: Layout of Two-Factor Three-Level Experimental Design

Independent Variable	Factor	Coded Value	Actual Value (mg)
Polyvinyl alcohol	X ₁	–1	600
Polyvinyl alcohol	X ₁	+1	1200
Ethyl cellulose	X ₂	–1	400
Ethyl cellulose	X ₂	+1	600

Dependent Variables (Responses)

R₁: Entrapment efficiency (%)

R₂: Particle size (nm)

Table 2: Composition of Allicin-Loaded Nanosponges

Composition	PF1	PF2	PF3	PF4	PF5	PF6	PF7	PF8	PF9
Allicin (mg)	24.32	24.32	24.32	24.32	24.32	24.32	24.32	24.32	24.32
Polyvinyl alcohol (mg)	600	900	1324.26	1200	1200	475.73	900	900	600
Ethyl cellulose (mg)	400	641.42	500	400	600	500	500	358.57	600
Pluronic F68 (mg)	200	200	200	200	200	200	200	200	200
Dichloromethane (mL)	30	30	30	30	30	30	30	30	30
Distilled water	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL

Preparation of Allicin-Loaded Nanosponges

Allicin-loaded nanosponges were prepared by the emulsion solvent diffusion technique using different concentrations of ethyl cellulose, polyvinyl alcohol (PVA), and Pluronic F68. Allicin (24.32 mg) and the required quantity of ethyl cellulose were dissolved in 30 mL dichloromethane to form the organic phase. This phase was slowly added to 100 mL of aqueous PVA containing Pluronic F68 with continuous stirring at 1000 rpm for 2 h. The formed nanosponges were collected by vacuum filtration and dried in an oven at 40 °C for 24 h.

Evaluation of Allicin-Loaded Nanosponges

Particle Size: The particle size of Allicin-loaded nanosponges was determined by dynamic light scattering using a Malvern Zetasizer Nano ZS. Samples were appropriately diluted with distilled water and analyzed in triplicate (n = 3).

ZetaPotential:

The zeta potential was measured using a Malvern Zetasizer Nano ZS based on laser Doppler microelectrophoresis. The analysis was performed after suitable dilution of the nanosponge dispersion to evaluate surface charge and dispersion stability.

Entrapment Efficiency:

Entrapment efficiency was determined by UV–Visible spectrophotometry. Accurately weighed nanosponges were extracted with methanolic HCl, centrifuged, filtered, and appropriately diluted. Allicin content was estimated at 241 nm using the previously established calibration curve. Entrapment efficiency was calculated as:

$$\text{Entrapment efficiency (\%)} = (\text{Actual drug content} / \text{Theoretical drug content}) \times 100$$

Preparation of Nanosponge-Loaded Gel

The optimized Allicin-loaded nanosponges, equivalent to 24.32 mg Allicin, were incorporated into 1% w/v Carbopol 940 gel. Carbopol 940 was gradually dispersed into the nanosponge dispersion with continuous stirring at 400 rpm. The dispersion was allowed to hydrate and was neutralized with triethanolamine to approximately pH 7.0, producing a homogeneous nanosponge-loaded topical gel.

Evaluation of Nanosponge-Loaded Gel

Colour and Appearance:

The prepared gel was visually examined for colour, homogeneity, clarity, consistency, and overall appearance.

Odour:

The odour of the prepared gel was evaluated organoleptically.

pH:

The pH was determined using a digital pH meter. The gel was dispersed in distilled water and equilibrated before measurement. Measurements were performed in triplicate, and the mean pH was recorded [51,52].

Spreadability:

Spreadability was determined by the modified glass-slide method. A measured quantity of gel was placed between two glass slides, and the time required to separate the slides under a specified load was recorded. Spreadability was calculated using $S = M \times L/T$, where S is spreadability, M is the applied weight, L is the slide length, and T is the time required for separation.

Viscosity:

The viscosity of the gel was measured using a Brookfield viscometer with spindle No. 04 at 2.5 rpm after equilibration. The viscosity was recorded in triplicate where applicable.

RESULT AND DISCUSSION

Preformulation Study

The preformulation studies established the basic physicochemical and analytical characteristics of Allicin. UV–Visible spectral scanning showed a λ_{max} of 241 nm, which was selected for quantitative estimation. The calibration curve showed good linearity over 1–5 $\mu\text{g/mL}$, with a correlation coefficient ($R^2 = 0.9976$), indicating suitability for spectrophotometric analysis. Allicin exhibited slight solubility in water ($5.89 \pm 0.77 \mu\text{g/mL}$), while higher solubility was observed in ethanol ($9.83 \pm 0.67 \text{ mg/mL}$), chloroform ($8.43 \pm 0.68 \text{ mg/mL}$), and phosphate buffer pH 6.8 ($7.54 \pm 0.54 \text{ mg/mL}$). The observed melting point ($25\text{--}28^\circ\text{C}$) was comparable to the standard range ($24\text{--}27^\circ\text{C}$). DSC analysis showed a characteristic thermal peak at 61.57°C for pure Allicin and 69.88°C for the Allicin–excipient mixture. The absence of new significant thermal events indicated satisfactory drug–excipient compatibility. FTIR analysis showed characteristic peaks of Allicin with only minor shifts in the Allicin–excipient spectrum. The principal peaks were retained, suggesting no significant chemical interaction between Allicin and the selected excipients. Overall, the preformulation results supported the suitability of Allicin for further nanosponge formulation development.

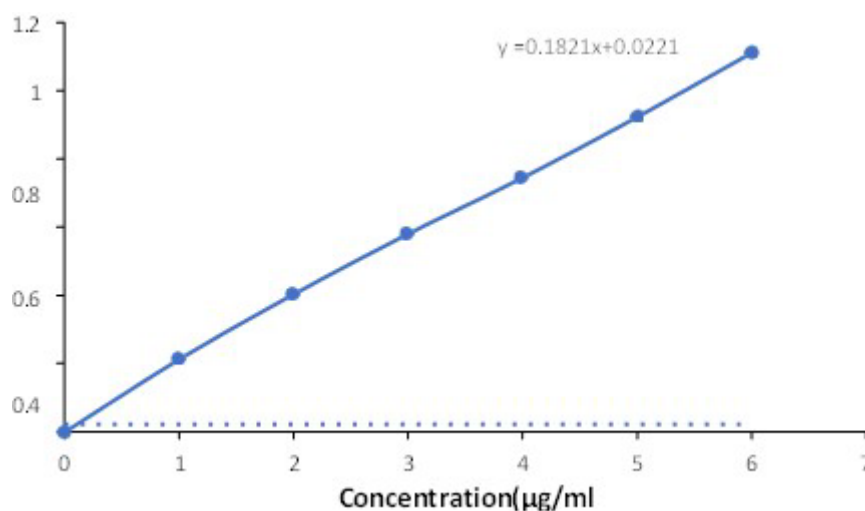


Figure 1: Calibration curve of Allicin in ethanol

Preparation of Allicin-Loaded Nanosponges

Allicin-loaded nanosponges were successfully prepared using the emulsion solvent diffusion technique. The selected formulation variables, including the concentrations of ethyl cellulose, PVA, and Pluronic F68, resulted in the formation of discrete and free-flowing nanosponge particles. The prepared formulations exhibited satisfactory physical appearance and were obtained as dry, easily collectable particles after filtration and drying. The use of ethyl cellulose as the polymeric matrix and PVA/Pluronic F68 as stabilizing agents facilitated the formation and stabilization of the nanosponge system. The prepared allicin-loaded nanosponges were subsequently subjected to further evaluation for particle size, polydispersity index, zeta potential, drug entrapment efficiency and drug loading.

Evaluation of Nanosponge Formulations

The prepared nanosponge formulations (F1–F9) were evaluated for particle size, zeta potential, and entrapment efficiency. The particle size ranged from 201.61 ± 2.35 to $361.27 \pm 2.34 \text{ nm}$, with F8 showing the smallest and F3 the largest particle size. Zeta potential values ranged from -11.5 to -19.3 mV , with F4 showing the highest magnitude, indicating comparatively better colloidal stability. Entrapment efficiency ranged from $58.9 \pm 2.32\%$ to

82.4 ± 5.38%, with F7 showing the highest drug entrapment. Overall, the formulations demonstrated satisfactory physicochemical characteristics, with F7 showing the highest entrapment efficiency and F8 the smallest particle size.

Table 3: Physicochemical parameters of prepared nanosponge formulations

Formulation n	Particle size (nm)	Zeta potential (mV)	Entrapment efficiency (%)
F1	222.76 ± 2.87	−13.3	65.3 ± 2.65
F2	277.44 ± 1.54	−15.5	61.6 ± 3.54
F3	361.27 ± 2.34	−18.4	69.4 ± 4.76
F4	277.64 ± 2.52	−19.3	67.8 ± 5.44
F5	331.49 ± 2.28	−11.5	68.3 ± 3.63
F6	341.46 ± 3.93	−16.8	63.3 ± 4.43
F7	273.52 ± 3.28	−15.3	82.4 ± 5.38
F8	201.61 ± 2.35	−12.8	58.9 ± 2.32
F9	332.42 ± 1.82	−17.4	62.4 ± 3.23

Optimization of Allicin-Loaded Nanosponges Using Central Composite Design

A Central Composite Design (CCD) was employed to optimize the formulation of Allicin-loaded nanosponges using A Central Composite Design (CCD) was employed to optimize the formulation of Allicin-loaded nanosponges using PVA concentration (X_1) and ethyl cellulose concentration (X_2) as independent variables. Nine experimental formulations (PF1–PF9) were generated, and entrapment efficiency (R_1 , %) and particle size (R_2 , nm) were selected as dependent responses. The experimental formulations were prepared using a constant amount of allicin (24.32 mg), Pluronic F68 (200 mg), dichloromethane (30 mL), and aqueous phase volume of 100 mL, while PVA and EC concentrations were varied according to the design. The entrapment efficiency results were analyzed using a quadratic model. The model was statistically significant ($F = 11.36$, $p = 0.0365$) with an R^2 of 0.9498 and adjusted R^2 of 0.8662, indicating that the model explained 94.98% of the observed variability. The linear effects of PVA and EC and their interaction were not statistically significant ($p > 0.05$). However, the quadratic effects of PVA ($p = 0.0154$) and EC ($p = 0.0058$) were significant, indicating a nonlinear influence of the formulation variables on entrapment efficiency. The coefficient of variation was 3.77%, and the Adequate Precision value was 10.2880, demonstrating an adequate signal for prediction within the experimental design space.

Particle size was also successfully modeled using a quadratic model. The model was significant ($F = 27.38$, $p = 0.0105$) with a high R^2 of 0.9786 and adjusted R^2 of 0.9428. The linear effect of EC concentration was significant ($F = 53.07$, $p = 0.0053$), indicating that EC was the most influential linear formulation variable affecting particle size. The linear effect of PVA ($p = 0.1146$) and the PVA–EC interaction ($p = 0.1238$) were not significant. The quadratic effect of PVA was significant ($p = 0.0162$), whereas the quadratic effect of EC was not significant ($p = 0.1005$). The model showed a standard deviation of 13.14 nm, coefficient of variation of 4.51%, and Adequate Precision of 16.2354. The contour and three-dimensional response surface plots demonstrated the influence of PVA and EC concentrations on both responses. The predicted-versus-actual plots showed close agreement between experimental and predicted values, supporting the adequacy of the developed models. Numerical optimization using Design-Expert software identified PF7 as the optimized formulation. The predicted entrapment efficiency of PF7 was 82.4%, which was identical to the experimental value (82.4%), with a difference of 0%. For particle size, the

predicted value was 281.3 nm, while the experimentally observed value was 273.5 nm, giving a difference of 7.8 nm. The close agreement between predicted and experimental results confirmed the suitability of the optimized formulation.

The in-vitro release study showed progressive drug release from all formulations over 12 h. At 2 h, PF6 exhibited the highest release (15.89%), whereas PF1 showed the lowest release (8.02%). After 12 h, PF7 showed 95.57% release, compared with 80.25% for PF1 and 81.39% for PF8, demonstrating sustained release behavior of the optimized nanosponge formulation. and ethyl cellulose concentration (X_2) as independent variables. Nine experimental formulations (PF1–PF9) were generated, and entrapment efficiency (R_1 , %) and particle size (R_2 , nm) were selected as dependent responses. The experimental formulations were prepared using a constant amount of allicin (24.32 mg), Pluronic F68 (200 mg), dichloromethane (30 mL), and aqueous phase volume of 100 mL, while PVA and EC concentrations were varied according to the design.

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Table 4 : The Predicted and Experimental Values of Response Variables and Percentage Error

F. Code	Composition	Response	Predicted Value	Experimental Value	Error Difference
PF7	Ethyl Cellulose	Entrapment Efficiency	82.4	82.4	0
PF7	Pluronic F68	Particle Size	281.3	273.5	7.8

In-Vitro Drug Release Studies of Nanosponge (NS) Formulations

The in-vitro drug release study of PF1–PF9 showed a formulation-dependent and progressive release pattern over 12 h. At 2 h, drug release ranged from 8.02% (PF1) to 15.89% (PF6). At 12 h, the release increased substantially, with PF7 showing the highest release (95.57%), whereas PF1 and PF8 showed 80.25% and 81.39%, respectively. The differences in release profiles may be attributed to variations in polymer concentration, matrix structure, particle size, and drug entrapment. PF7 was selected as the optimized formulation based on its desirable release profile.

Characterization of Nanosponge-Loaded Gel (Optimized Batch–PF7)

Table 5 : Results of the Characterization of the NS-Loaded Gel Formulation of Allicin

Batch	Color	Appearance	Odor	pH	Spreadability (gm. cm/sec)	Viscosity (cps)
GF	Greenish Brown	Clear, Thick	Odourless	6.7 ± 0.09	12.2 ± 0.78	4425 ± 33.64

The optimized nanosponge-loaded gel (GF) showed satisfactory physicochemical characteristics. It was greenish-brown, clear and thick, and odourless. The pH was 6.7 ± 0.09 , indicating suitability for topical application. The spreadability was 12.2 ± 0.78 g·cm/s, suggesting good ease of application, while the viscosity of 4425 ± 33.64 cps indicated adequate consistency and retention at the application site. Overall, the optimized gel demonstrated acceptable physical properties for topical delivery of allicin-loaded nanosponges.

CONCLUSION:

The present study successfully demonstrated the formulation and optimization of allicin-loaded nanosponges and their incorporation into a topical gel. The emulsion solvent diffusion technique produced nanosponge formulations with satisfactory particle size, surface charge, and drug entrapment characteristics. Application of the central composite design enabled systematic evaluation of PVA and ethyl cellulose concentrations and identified PF7 as the optimized formulation, with 82.4% entrapment efficiency and a particle size of 273.52 ± 3.28 nm. The optimized nanosponge exhibited progressive drug release over 12 h, indicating its potential for sustained topical delivery. Incorporation of PF7 into 1% Carbopol 940 produced a homogeneous gel with suitable pH, spreadability, and viscosity for topical application. Overall, the developed nanosponge-loaded gel combines the drug-delivery advantages of nanosponge systems with the practical characteristics of a topical gel and may provide a promising platform for localized delivery of allicin. Further studies, including comprehensive stability, skin permeation, and in-vitro/in-vivo antifungal evaluation, are warranted to establish its therapeutic potential.

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