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Development and Evaluation of a Nanosponge-Based Gel for Combined Hydrocortisone and Benzocaine Delivery in Psoriasis

Dr. Nikita Gaikwad[1*], Sneha Jadhav[1], Damini shinde[1], Dr. Pravin chaudhari[1]

[1] Department of Pharmaceutics, Progressive Education Society's Modern College of Pharmacy, Nigdi, Pune-44, INDIA.

* Corresponding Author: Dr. Nikita Gaikwad, Associate Professor,
E-mail: nikigaikwad09@gmail.com

ABSTRACT:

The study aimed to develop a topical gel based on nanosponges (NS) containing a combination of benzocaine and hydrocortisone for psoriasis treatment. This project aimed to formulate topical nanosponges-based gel that includes a combination of hydrocortisone and benzocaine that can potentially be utilized for the treatment of psoriasis. The drug-loaded nanosponges were formulated using ethyl cellulose and polyvinyl alcohol as polymer and copolymer, with dichloromethane as an organic solvent. A fully randomized factorial design (3^2) examined 9 potential experimental runs. Formulation F1 was achieved after optimization, with a 195.1 nm particle size, 80.64% entrapment efficiency, 96.53% in-vitro release, 17.2 mV zeta potential, 81.69% drug loading, 50.6% percentage yield, 122% percent swelling. The gel was formulated by adjusting the concentration of polymer Guar gum and gelling agent Carbopol-934. A group of animals was used in *ex vivo* permeation and skin irritation study to check the safety & efficacy of the formulation. Hydrocortisone combined with benzocaine is more effective against psoriasis and inflammation than Hydrocortisone alone. The nanogel showed drug release through 12 hours, indicating that the combination of Benzocaine and hydrocortisone significantly increased anti-psoriatic efficacy. Therefore, the suggested Nanosponges-based hydrogel will be a more effective drug delivery method for anti-psoriatic therapy.

KEYWORDS: Nanosponges; psoriasis; hydrogel; hydrocortisone; benzocaine.

INTRODUCTION

Drug delivery systems are essential in healthcare as they provide specialized methods for administering medications with greater efficacy and fewer side effects. These devices utilize engineering, chemistry, and biology concepts to deliver medications to specific locations within the body, overcoming issues like poor solubility, quick metabolism, and off-target effects. By optimizing delivery routes, researchers and medical professionals can optimize pharmaceutical absorption, distribution, metabolism, and excretion. The application of biomaterials, nanotechnology, and biotechnology has opened up new eras in drug delivery innovation, enabling targeted medication administration to infected tissues while protecting healthy cells. This individualized approach could significantly change the way medical specialties treat patients, improving precision medicine and patient satisfaction. Combination therapy is recommended, but compatibility concerns should be considered. Topical treatments can be used continuously or sporadically, with stronger drugs administered first for short-term response and then sporadically for long-term control. This approach may help patients effectively manage their disease [1].

Psoriasis is a long-term autoimmune disease causing red, dry areas covered in silvery scales due to the skin's fast cell division. It is influenced by environmental factors like stress, infections, certain drugs, and skin injuries, as well as genetic susceptibility. Hyperkeratosis,

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epidermal proliferation, inflammation of the skin's surface, and deep skin angiogenesis are their characteristics. Approximately 125 million people worldwide suffer from this condition, which affects their quality of life, psychological distress, and even suicidal thoughts. The disease's etiology is complex, with autoimmune factors being a major contributing factor. ROS-mediated oxidative stress from exposure to UV light exacerbates psoriasis and compromises the skin's defense system. Treatment goals include symptom management, slowed skin cell development, and inflammation reduction. Lifestyle adjustments, such as avoiding triggers, moisturizing frequently, maintaining a balanced diet, and controlling stress, are crucial [2] [5] [6] [14].

Nanosponges are innovative hyper-crosslinked polymer-based colloidal structures that can encapsulate various substances, including volatile oil, proteins, peptides, antineoplastic medications, and DNA. These microscopic, mesh-like structures can be used to reorganize and shape treatment plans for various illnesses, providing reliable and precise drug administration techniques without irritants, allergies, toxicity, or mutations. Nanosponges are insoluble in water but soluble in some organic solvents, have a porous structure, and can go through body temperatures as high as 300^0C. They offer advantages such as increased entrapment efficiency, resistance to degrading molecules, and ease of integrating liquids into their three-dimensional structure. 3D printing technology can be used to develop Nanosponges with superior medication loading capacity [1] [3] [5] [9] [11].

Hydrogels are composed of hydrophilic polymers stacked in 3D networks, which enable them to retain significant amounts of water while maintaining their characteristic structure. These polymers, either natural or synthetic, expand when exposed to water and can contain vast amounts of water. The degree of cross-linking influences the hydrogel's mechanical strength and water-holding capacity. The advantages of nanosponges-based gel include enhanced penetration, targeted delivery, sustained release, and combination therapies [14].

This study aims to explore and evaluate the potential of advanced drug delivery systems, particularly focusing on nanosponges and hydrogels, in treating chronic conditions such as psoriasis. By leveraging the unique properties of these technologies such as targeted drug delivery, sustained release, and improved drug stability the research seeks to enhance the efficacy and safety of treatments. This approach aims to provide more effective management of psoriasis symptoms, reduce side effects, and improve patient quality of life. The study also examines the application of combination therapies and the integration of novel materials and techniques, like optimizing drug delivery and therapeutic outcomes.

MATERIALS AND METHODS:

Materials

Hydrocortisone and Benzocaine were purchased from Chemdyes Corporation, while ethyl cellulose was from Vishal Chem, polyvinyl alcohol from Loba Chemie, and Carbopol-934 from Research-lab fine chem. All other chemicals & reagents were of analytical grade.

Methods:

1. Preformulation Study

a) Calibration Curve by UV Spectrometer

The 10 mg of Hydrocortisone, Benzocaine, and a combination of both drugs were dissolved in 100 ml of ethanol to obtain a concentration of 100 µg/ml. Aliquots of 0.2, 0.4, 0.6, 0.8, and 1 ml were obtained from these solutions & further diluted to 10 ml to achieve concentrations of 2, 4, 6, 8, and 10 µg/ml. The resultant solution was scanned for simultaneous estimation using Jasco V-630, USA spectrometer from 400 to 800 nm & the spectrum was recorded a 241 nm & 283 nm for individual drugs & at 293 nm for combined solution respectively. Also, the calibration curve was plotted for each [8].

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b) Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR analysis was carried out on Hydrocortisone, Benzocaine, Ethylcellulose, & polyvinyl alcohol using an FTIR spectrophotometer. Potassium Bromide was added to each sample between 4000 to 600 cm^{-1}. Each sample was mixed with potassium bromide (KBr) in 1:100 ratio & examined over a range of 4000 cm^{-1} to 600 cm^{-1}. The acquired spectrum was subsequently compared with the standard reference spectrum [3] [6].

c) Differential Scanning Calorimetry (DSC)

DSC analysis was carried out to check both drug's crystallinity and melting behaviour. Samples were analyzed in a scanning range of 30-300^{0}C with a heating rate of 10^{0}C/min. DSC thermogram of drugs (Hydrocortisone & Benzocaine) was recorded [3].

2. Formulation of Drug loaded Nanosponges

The nanosponges were prepared using the emulsion solvent diffusion technique. Polyvinyl alcohol dissolved in an aqueous phase at 75-80^{0}C in a serological water bath. Ethylcellulose, Hydrocortisone, & Benzocaine dissolved in the organic solvent. Organic solution was slowly mixed with the aqueous solution, with the mixture stirred at 1000-2000 rpm, & the organic solvent was allowed to evaporate over 2-3 hours. Nanosponges are formed through filtration and dried in air or a vacuum oven at 40^{0}C for 24 hours.

Optimization of Formulation

The current study used Stat-Ease Design Expert (Version 13) to optimize trial batches of Nanosponges utilizing 3^2 Factorial designs. The concentration of the copolymer (PVA) was evaluated at 250 mg (-1 level), 625 mg (0 level), and 1000 mg (+1 level), while the polymer (Ethyl Cellulose) was evaluated at 250 mg (-1 level), 450 mg (0 level), and 750 mg (+1 level). The dependent variables of the Nanosponges were entrapment efficiency, drug loading, and particle size. Table 1 shows the composition of nanosponges batches [1] [4] [8] [9] [13] [15].

Table 1: Composition of Nanosponges batches

Batch No.	Drug	Polymer (Ethylcellulose) (mg)	Copolymer (PVA) (mg)	Organic Solvent (Dichloromethane) (ml)	Water(ml)
1	**1:4**	**250**	**250**	**30**	**100**
2	1:4	450	250	30	100
3	1:4	750	250	30	100
4	1:4	250	625	30	100
5	1:4	450	625	30	100
6	1:4	750	625	30	100
7	1:4	250	1000	30	100
8	1:4	450	1000	30	100
9	1:4	750	1000	30	100

Evaluation of Drug-loaded Nanosponges

a) Differential Scanning Calorimetry (DSC)

Thermal characteristics of porous nanoparticles and nanosponges employed in drug delivery have been studied using differential scanning calorimetry. This technique assesses the glass transition temperature, melting & crystallization temperatures, drug loading, encapsulation efficiency, & drug stability within the drug-loaded nanosponges [3].

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b) Scanning Electron Microscopy (SEM)

Structure, surface characteristics, & topography of drug-loaded nanosponges were examined using a NanoSEM NPEP303. The sample preparation involved spreading the powered nanosponges evenly on an aluminum stub with double-sided tape, followed by gold coating to maintain conductivity at 15 kV [8] [11].

c) Particle size

Particle size & polydispersity index of drug-loaded nanosponges were examined using a particle size analyzer (Horiba SZ100Z). All samples were examined in triplicate. For topical formulations, the optimal particle size range was identified as 100-200 nm [9] [14].

d) Entrapment Efficiency

Percentage of drugs that are effectively entrapped within the carrier system concerning total amount of drug initially delivered during formulation is known as entrapment efficiency.

The drug concentration was determined by dissolving 10 mg of drug-loaded nanosponges in ethanol and centrifuging for 15 minutes at 1000 rpm. Analyze the diluted supernatant spectrophotometrically at 293 nm using ethanol as a blank [9].

It was determined that the entrapment efficiency was:

$$\% \textbf{ Entrapment Efficiency} = \frac{\textit{Total drug} - \textit{Amount of unentrapped drug}}{\textit{Total drug}} \text{x}100$$

e) In vitro release study:

In vitro release study was evaluated using a dissolution apparatus to assess the release of drugs from drug-loaded nanosponges under conditions simulating topical skin application. A 100 mg sample of drug-loaded nanosponges was dissolved in 900 ml of phosphate buffer solution with pH 5.8. Temperature was continuously maintained at 37 ± 0.5^0C, & the solution underwent stirring at 100 rpm. To keep the conditions stable, samples were frequently removed and replaced with fresh medium. Using a UV Spectrophotometer, the amount of hydrocortisone and benzocaine released from the nanosponges was quantified [10].

f) Zeta potential

Zeta potential has been assessed for electrophoretic mobility of particles. The materials are prepared for particle size analysis and placed into transparent zeta cells. The results are then noted. The study aims to improve the stability of colloidal systems and their potential for drug release. A high zeta potential indicates strong electrostatic repulsion between particles, maintaining stability and inhibiting aggregation, while a low potential suggests aggregation may occur due to dominant attractive factors [1].

g) Determination of Percentage Yield

The Determination of the viability and efficiency of a drug-loaded carrier system requires evaluating its percentage yield. The percentage yield was assessed by calculating the weight of nanosponges and both drugs and polymers [13].

$$\textbf{Percentage yield} = \frac{\textit{Actual weight of Nanosponges}}{\textit{Theoretical weight}(\textit{Polymer}+\textit{Drug})} \text{x}100$$

h) Swelling Index

The ability of a material to swell in a certain solvent is measured by the swelling index, which is important for hydrogels. In a glass vial, 10 mg of nanosponges was submerged in 10 ml of distilled water. After being immersed in water and kept at 37°C for a full day, the nanosponges were weighed, blotted, and filtered, and the percentage swelling at equilibrium

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was determined using a formula [4] [10]:

Swelling Index (%) = $\frac{Ws-Wd}{Wd}$

3. Formulation of nanosponges-based gel

Formulation of gel base: 500 mg of Carbopol was soaked in a sufficient quantity of water for 2 hours, then stirred at 600 rpm. Dispersion is allowed to stand overnight for swelling. Triethanolamine was added to neutralize the pH of aqueous solution.

Incorporation of Drug-loaded Nanosponges in gel base: 100 mg of Guar gum and Drug-loaded Nanosponges were dissolved in 10 ml of propylene glycol, and incorporated into the Carbopol blend, and the mixing process was prolonged for 20 minutes by homogenizer. The gel was kept aside to hydrate and swell for 60 minutes. The nanosponges-based gel formulation was given 24 hours to adjust to room temperature before viscosity analysis. Table 2 shows the composition of Nanosponges-based Gel [8].

Table 2: Composition of Nanosponges-based Gel

rameter	**antities**	**es**
rbopol-934	0 mg	lling agent
ar Gum	0 mg	ickener
ethanolamine	v/v	modifier
ppylene Glycol	ml	eservative

Evaluation of Nanosponges-based Gel

a) pH measurement

The gels' pH was measured by a pH meter. Dissolve 1gm of gel in 10 ml of distilled water and add triethanolamine solution to adjust the skin's pH [13].

b) Homogeneity and clarity Examination

The Homogeneity was ensured through visual inspection of the gels after placing them in the container. The Clarity was evaluated visually using a black-and-white background, categorizing it as turbid (+), clear (++), or transparent/glassy (+++), to determine its composition, purity, and suitability for a given use [8].

c) Viscosity Determination

Viscosity of the Nanosponges-based gel was determined using a T-bar spindle in a Brookfield viscometer at room temperature. The spindle rotation speed was maintained at different rpm when the level became steady, and the readings were taken [6] [12].

d) Spreadability

A 1 mg of the formulation was distributed in a circle, and the gel formulation was sandwiched between two identical slides. A 20g weight was placed on the upper slide and left for 5 minutes, observing the gel's spreading causing the diameter to grow.

The spreadability was determined by using the formula S=ML/T [7] [8].

e) Stability studies

The ICH guidelines mandated stability studies for 2 months during the formulation process, conducted in a stability chamber. Storage temperatures for the formulation were 25°C/60% RH, 30^0C/60% RH, and 40°C/75% RH and observed at regular intervals for variations in

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medication concentration and physical appearance.

f) In vitro diffusion study

Release of an active ingredient from gel was tested using a Franz diffusion cell apparatus with a phosphate buffer solution at pH 5.8, kept at a steady temperature of 37±0.5^{0}C. The experiment ensured no air bubbles in the membrane, used a magnetic stirrer for homogeneity, and maintained a 50 ml volume of the diffusion medium. Samples were withdrawn at hourly intervals of up to 12 hours, with each withdrawn volume analyzed using a UV spectrophotometer. To maintain conditions constant during the experiment, a fresh receptor solution was introduced. A UV spectrometer was used to determine concentration of active components in solution at 281 nm to assess the release profile of the gel formulation [8].

g) Ex vivo permeation studies

Ex vivo studies on goat skin were conducted to investigate drug release from a nanosponges-based gel, marketed cream & gel without nanosponges. Skin was divided into test and control sections, & Franz diffusion cell was kept at 37±0.5^{0}C. The gel was added to donor chamber, while receptor compartment was filled with phosphate buffer solution at pH 5.8. Samples were diluted & spectrophotometrically examined at 281 nm using a UV-visible spectrophotometer [15].

h) Skin irritation studies

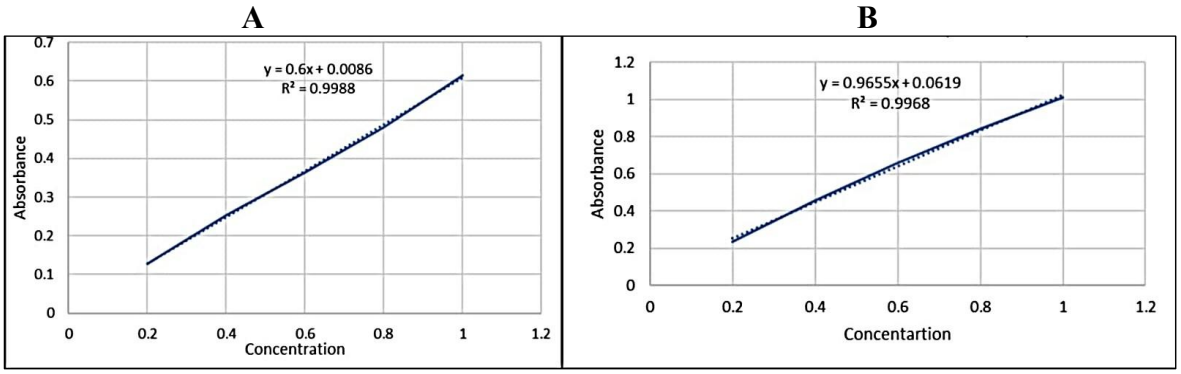
A group of Mice was assessed for skin irritation tests after shaving and gel was applied to the shaved skin. Results showed varying degrees of erythema or edema formation, ranging from no erythema to severe to moderate erythema. To enhance accuracy, readings were taken in triplicate. These studies provide valuable insights into the drug's potential for skin irritation treatment [8] [15].

RESULT AND DISCUSSION

1. Preformulation Studies

a) Calibration curve by UV spectrometer

Maximum wavelength of Hydrocortisone and Benzocaine in ethanol was recorded at 241 nm & 291 nm resp. Spectra of mixture were recorded at 283 nm. Figure 1 shows the calibration curve of Hydrocortisone, Benzocaine, & Hydrocortisone + Benzocaine in ethanol.



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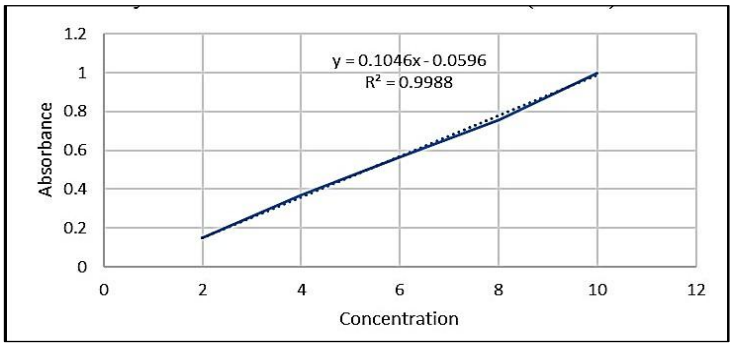

C

Figure 1: Calibration curve in ethanol (A) Hydrocortisone (B) Benzocaine (C) Hydrocortisone + Benzocaine

b) Fourier Transform Infrared Spectroscopy (FTIR):

FTIR spectra of hydrocortisone, benzocaine, ethyl cellulose, and polyvinyl alcohol were analyzed in the range of 4000 to 600 cm^{-1} to identify major functional groups such as O-H, Ar C-H, C=O, C=C, & C-C alkene, as well as C-H, which correspond to the structures of the components. The FTIR spectra for the pure drugs (hydrocortisone and benzocaine) & the polymers indicated no interaction, demonstrating compatibility between the drugs & the polymers. Figure 2 and Table 3 show the FTIR spectrum of Hydrocortisone, Benzocaine, Hydrocortisone + Benzocaine, and Drug + Polymer mixture.

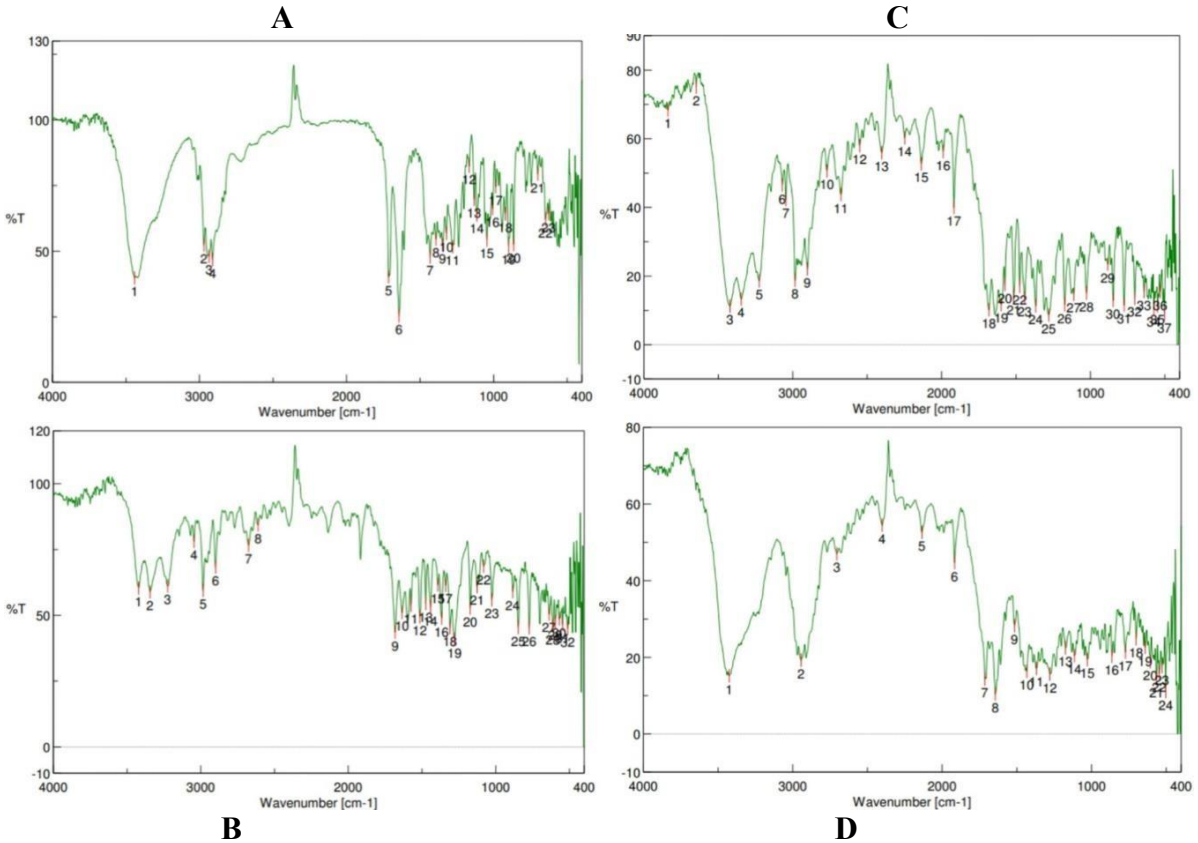

Figure 2: FTIR spectrum (A) Hydrocortisone; (B) Benzocaine; (C) Hydrocortisone + Benzocaine; (D) Drug + Polymer mixture

Table 3: FTIR spectrum ranges

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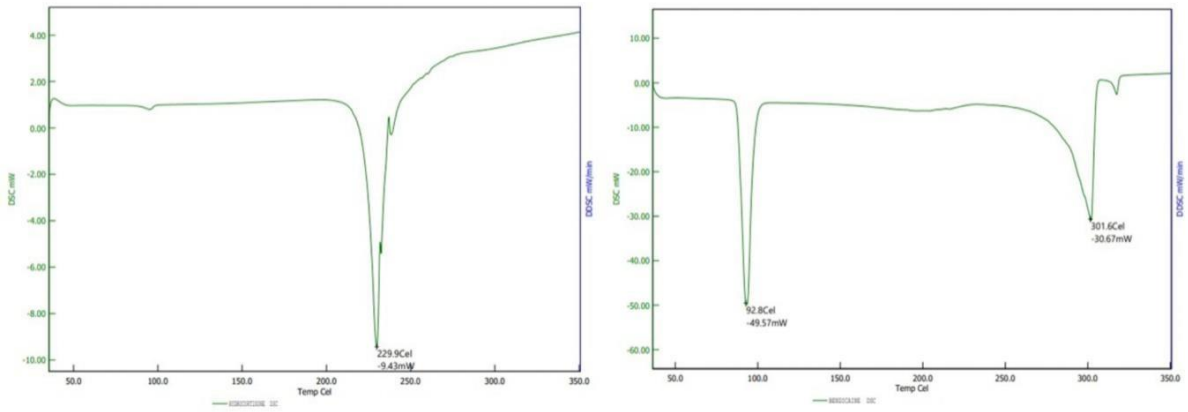
Functional group	Standard frequency range (cm^{-1})	Observed frequency range (cm^{-1})			
		Hydrocortisone	Benzocaine	Hydrocortisone+ Benzocaine	Drug+ Excipients
OH-	3690-3100	3441.35	3343.96	3422.06	3425.92
N-H	3450-3200	-	3421.1	3421.1	-
Ar C-H	3200-2800	2969.84	2984.3	2984.3	2944.77
C=O	1800-1600	1714.41	1682.59	1681.62	1644.02
C=C	1700-1500	1644.02	1636.34	1599.66	1515.78
C-C	1300-800	1279.54	1279.54	1280.5	1173.47
C-H	1200-800	863.95	846.597	847.56	863.953

c) Differential Scanning Calorimetry (DSC)

The DSC thermogram of benzocaine and hydrocortisone shows sharp melting points at 93.6 and 229.9^{0}C, indicating the crystalline nature. DSC indicates the melting point of a drug through an endothermic peak on the thermogram, which gives important details regarding the stability and physical characteristics of drugs. Figure 3 shows the DSC of Hydrocortisone and Benzocaine



A **B**

Figure 3: Differential Scanning Calorimetry (A) Hydrocortisone; (B) Benzocaine

2. Evaluation of Drug-loaded Nanosponges

The particle size, entrapment efficiency, & drug release were evaluated as dependent factors. Results for batches F1 to F9 are shown in Table 4. Among these, batch F1 showed best performance, making it optimal batch for further gel formulation.

a) Differential Scanning Calorimetry

DSC thermogram of benzocaine and hydrocortisone shows sharp melting points at 93.6 and 229.9^{0}C, indicating the crystalline nature. But compared to that in nanosponges melting point shifts to 232.5^{0}C, which indicates the drug was no longer crystalline and may be molecularly dispersed in nanosponges. Figure 4 shows the DSC overlay of Hydrocortisone, Benzocaine & Nanosponges.

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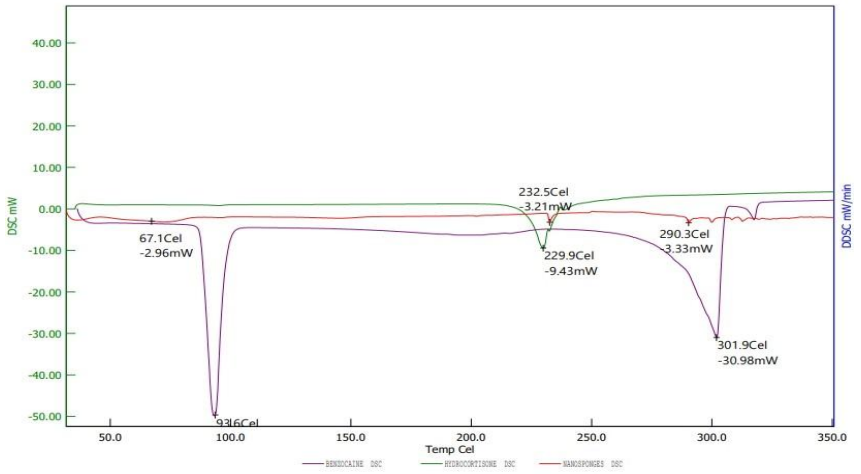


Figure 4: DSC overlay (Hydrocortisone, Benzocaine & Nanosponges)

b) Scanning Electron Microscopy (SEM)

SEM analysis was carried out to assess the hydrocortisone & benzocaine nanosponge's surface shape. SEM images demonstrated the smooth surface morphology and porous, spherical form of the nanosponge. These illustrations show the porous and spongy nature of the nanosponges. Sizes of drug-loaded nanosponges vary from 142.9 to 215.8 nm which is ideal for topical formulation. Figure 5 shows SEM images of Nanosponges

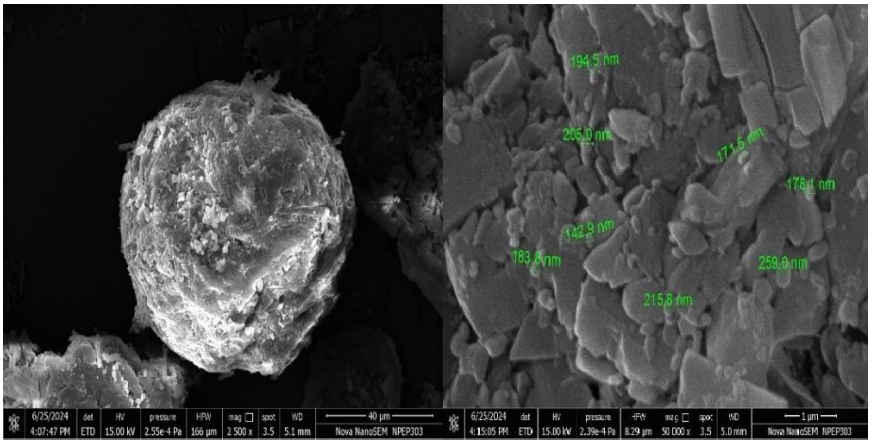


Figure 5: SEM images of Nanosponges

c) Particle Size Determination

Batch F1, with a particle size of 194.92±2.37 nm, was identified as an optimized formulation and identified as most suitable for topical formulation. This determination was based on its significantly smaller particle size than other formulations with different polymer ratios, making F1 the preferred choice for enhanced topical application. Figure 7 shows 3D plots for particle size.

d) Entrapment Efficiency

Study assessed the entrapment efficiency of Drug-loaded Nanosponges for drug incorporation in batches F1 through F9. The entrapment efficiency ranged from 56.89-81.27%, with variations due to polymer concentration and cross-linking degree. F1 had the highest entrapment efficiency of 81.27%, due to its higher medication per unit polymer. The formulation with the highest entrapment effectiveness and smallest particle size was used to create hydrogel. Figure 7 shows 3D plots for entrapment efficiency.

e) Invitro Drug Release

The study demonstrates the drug release of batches F1 through F9 for up to 12 hours, with benzocaine and hydrocortisone being released at the 12th hour. The study found that a higher polymer ratio reduced medication release, while a 1:1 polymer-to-co-polymer ratio increased hydrocortisone and benzocaine release. F1 Nanosponges formulation showed the largest hydrocortisone and benzocaine release during the 12th hour. The optimal formulation F1 showed significant improvement in dependent optimization and drug release profile. Figure 6 shows the cumulative drug release and Figure 8 shows 3D plots for Invitro release.

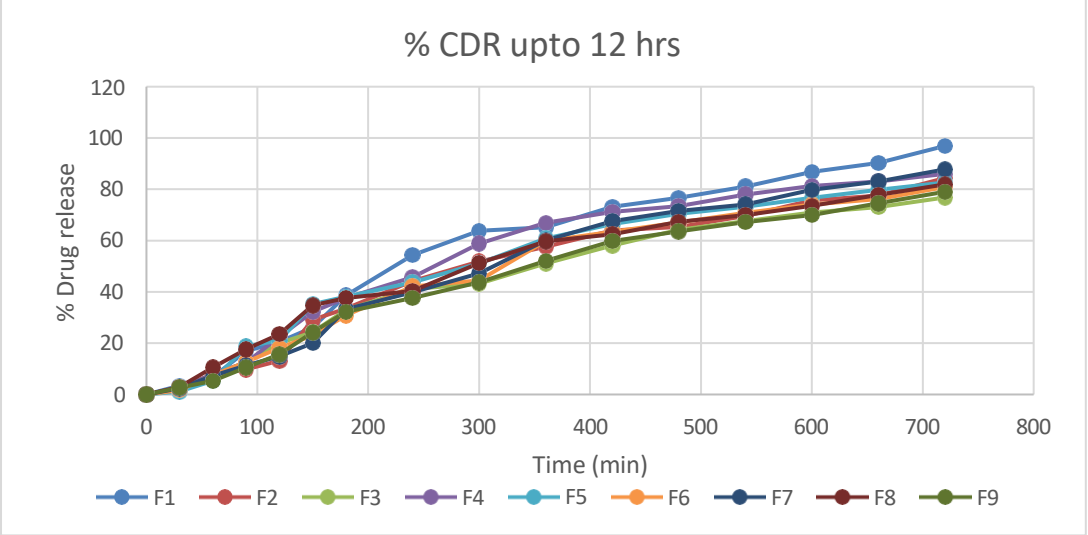


Figure 6: % CDR up to 12 hours

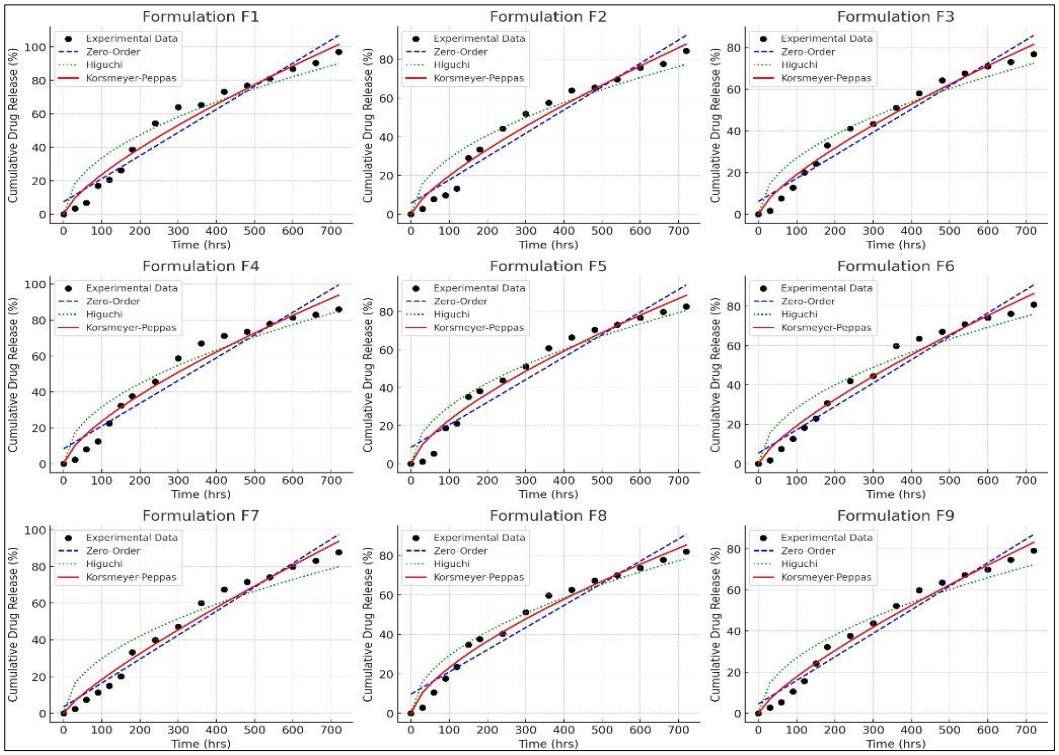
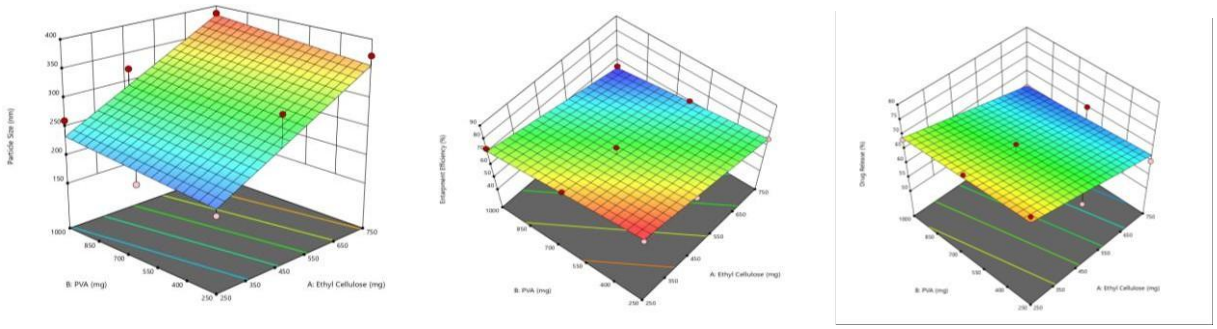


Figure 7: Drug Release kinetic models (A) Black dots: Experimental data (B) Blue dashed line: Zero-order model (C) Green dotted line: Higuchi model (D) Red solid line: Korsmeyer-Peppas model

The Korsmeyer-Peppas model provides the best overall fit ($R^2 \approx 0.96–0.98$) for all

formulations (F1–F9), indicating an anomalous (non-Fickian) drug release mechanism. This suggests that drug release is governed by a combination of diffusion and polymer matrix erosion, with contributions from polymer swelling and degradation.



A **B** **C**

Figure 8: 3D Response Surface Plot (A) Particle size (B) Entrapment Efficiency (C) Invitro release

f) Zeta Potential

Study assessed the zeta potential of various formulations using a Horiba SZ1002 analyzer, evaluating their long-term physical stability. The highest zeta potential values were found in batch F4 and formulation F6, with F1 showing enhanced stability. The zeta potential values between -30mV and 30mV showed good physical stability, with the optimized F1 batch showing -17mV. The negative ions at the -CH2 group in the polymer ethylene's structure are primarily responsible for the negative charge.

g) Percentage yield of drug-loaded nanosponges

The weight of the drug and polymer, along with the actual weight of the drug-loaded nanosponges, impacts the % yield of all nanosponges batches varied from 47.3±1.52 to 81±1, with increased polymer quantity causing foaming and aggregation.

h) Percent Swelling

The swelling range of nanosponges in the hydrogel was assessed using percent equilibrium swelling in distilled water. The swelling ratio ranged from 109.25±2.14 to 135.46±2, with a rise in swelling ratio with polymer concentration. Increasing the stirring speed also decreased the swelling ratio in testing batches.

Optimization of Formulation

Table 4: Evaluation of formulated NS batches F1-F9

Batches	Parameters					
	Particle Size (nm)	**Zeta Potential (mV)**	**Entrapment Efficiency (%)**	**Drug Release**	**Percentage Yield**	**Percent Swelling**
F1	**194.92±2.37**	**-17.2 ±0.6**	**81.27 ±1.25**	**96.53±1.39**	**50.6±1.52**	**122±1**
F2	320± 1.81	-24.8 ±1.23	85.33 ±1.21	85.33±1.21	81±1	113.6±1.52

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F3	373.87±1.61	-8.66 ±0.58	75.99±1.63	75.99±1.63	50.3±2.08	129.3±1.51
F4	195.9±1.91	-1.23 ±1	86.85±1.31	86.85±1.31	70.6±1.52	109.25±2.1
F5	206.3±1.75	-36.1 ±1.2	`83.07±1.03	83.07±1.03	53±2.64	112.4±2
F6	345.53±3.36	-40.5 ±1.34	81.21±1.39	81.21±1.39	50.6±2	135.46±2.4
F7	261.1±1.64	-3.3 ±0.5	87.18±1.57	87.18±1.57	47.3±1.52	126.3±0.6
F8	324.07±2.73	-2.29 ±1	81.49±0.63	81.49±0.63	54.3±1.52	109.6±1.52
F9	385.8±2	-25.4 ±1.6	80.04±1	80.04±1	51.3±1.52	121.3±1.58

Table 4 represents measurements from nine batches (F1 to F9) of nanoparticle formulations, detailing particle size, zeta potential, entrapment efficiency, invitro release, percentage yield, & percent swelling. Particle sizes range from about 194.9 to 385.5 nm, with zeta potential values indicating varying stability levels from -40.5 mV (F6) to -1.23 mV (F4). Entrapment efficiency peaks at 81.27% (F1) to 55.81% (F9), while drug release correlates with particle sizes. Percentage yield varies, with F2 being the highest at 81%. Percent swelling ranges from 109.25% (F4) to 135.46% (F6), indicating different water absorption capacities among the batches. These variations illustrate the diverse characteristics & potential performance impacts of each formulation.

3) Evaluation of Nanosponges-based Gel

a) pH measurement

The pH of the hydrogel was found to be 5.8, which is comparable to the pH of the skin. The study indicated a suitable pH range for topical application, which ruled out any possibility of skin irritation brought on by pH variations.

b) Homogeneity and clarity examination

The formed gel was found to be homogenous and free of lumps, particles, and air entrapment upon visual inspection. When the gel's clarity was examined visually, it was discovered to be translucent and clear (+++).

c) Viscosity determination

The standard viscosity of gels for pharmaceutical use typically ranges from 1,000 to 100,000 centipoise (cps), depending on the specific application and formulation requirements. Table 5 shows the viscosity of NS-based gel.

Table 5: Viscosity of NS-based gel

Sr. No.	RPM	Viscosity (cps)
1	50	3248

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2	100	1624
3	150	1083
4	200	812

The gel's viscosity was measured at various rpm and 81.2% torque. Viscosity is inversely proportional to rpm. The results showed that viscosity decreases as rpm increases. This inverse relationship between viscosity and rpm indicates shear-thinning behavior, where the gel becomes less viscous under higher shear rates, which is typical for non-Newtonian fluids.

d) Spreadability

A key characteristic of ideal gels is their spreadability, which has been demonstrated to be excellent in nanosponges-based gel formulations. These gels spread easily even in small quantities. However, as the concentrations of guar gum and Carbopol-934 increase, spreadability decreases, which is inversely related to the gel's viscosity. This indicates that optimal gel performance relies heavily on maintaining good spreadability.

e) Stability Studies

The Stability test was carried out on nanosponges-based gel formulation for 2 months under the ICH Guidelines, with different storage temperatures of 25°C/60% RH, 30^0C/60% RH, & 40°C/75% RH. Studies showed no significant changes in the formulation's appearance or pharmacological content over 2 months under different storage conditions.

f) In vitro Diffusion

The in vitro diffusion investigation demonstrates drug release controllability of gel. Drugs are adsorbed on the surface of the nanosponges-based gel, causing an initial burst release, and drug diffusion from the porous nature of the nanosponges-based gel causes a controlled release phase. The release of the nanosponges-based formulation is 95.27 % displaying drug release for a maximum of 12 hours. The drug is shown to be released from a gel at the 12th hour of invitro release. Franz diffusion cell was used to carry out a study of the diffusion of gel. A considerable maintained-release characteristic was seen in the gel loaded with nanosponges. The therapeutic advantages of the medications may last longer due to the maintained concentration made available by controlled release. Figure 8 shows the Invitro Diffusion of nanosponges-based gel.

Table 6: Invitro Diffusion of Gel

Time(hrs)	% Drug Release	Time(hrs)	% Drug Release
0	0	7	59.8
1	4.2	8	66.84
2	8.84	9	72.34
3	17.7	10	80.09
4	28.5	11	88.45
5	39.16	12	95.27
6	46.63		

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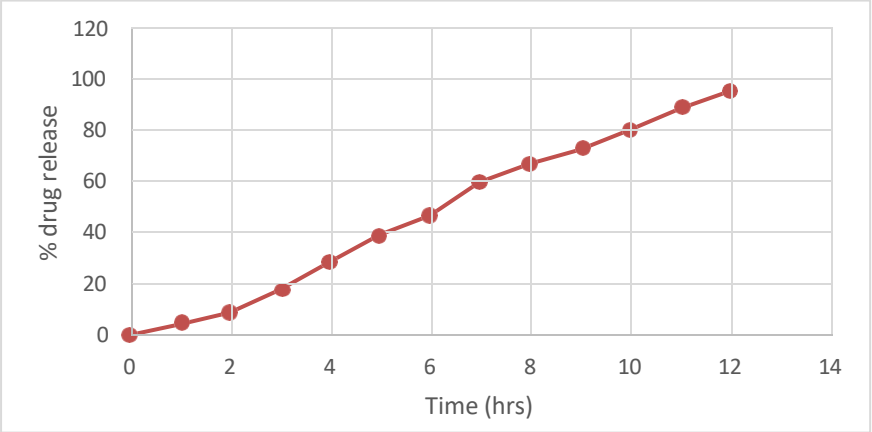

Figure 9: Invitro Diffusion of nanosponges-based gel

g) Ex vivo studies

Table 7 & Figure 10 illustrates *ex vivo* gel permeation over time for three different formulations: Test formulation, Marketed formulation, and Gel formulation. The test formulation gradually releases the drug, reaching 95% after 12 hours. The marketed formulation shows a release of up to 64% after 7 hours and the gel formulation contains only drugs without nanosponges achieves 60% in 6 hours and then levels off. This shows that the test formulation offers the most extended release as compared to the other two formulations.

Table 7: Ex vivo permeation of Gel

Time(hrs)	% Drug Release (Test Formulation)	% Drug Release (Marketed Formulation)	% Drug Release (Gel formulation)
0	0	0	0
1	3.42	5.68	9.25
2	9.84	10.82	23.05
3	19.87	24.77	31.23
4	25.53	33.2	42.95
5	30.16	47.07	54.72
6	42.63	56.49	61.23
7	51.28	63.26	
8	59.84		
9	65.23		
10	73.18		
11	87.08		
12	94.78		

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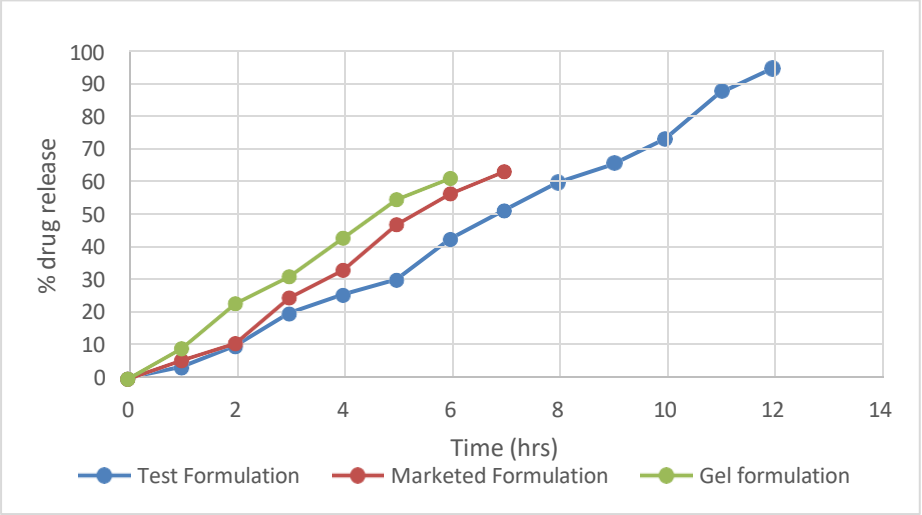

Figure 10: Ex vivo permeation of Gel

h) Skin irritation studies

The edema and erythema responses of three mice were monitored at 1, 24, 48, and 72 hours after treatment. Initially, all 3 mice showed no erythema. This lack of erythema persisted through the 24-hour and 48-hour checks. However, at 72 hours, while 2 mice continued to exhibit no erythema, one mouse displayed slight erythema, indicating a mild irritation response at this later time point. The results of this study have demonstrated the optimized NS-based gel's compatibility and non-irritating properties. Table 8 and Figure 11 show observations of skin irritation study.

Table 8: Observation of skin irritation study

Sr. No.	Time (hrs)	Edema/ Erythema (Mice 1)	Edema/ Erythema (Mice 2)	Edema/ Erythema (Mice 3)
1	1	0 – No erythema	0 – No erythema	0 – No erythema
2	24	0 – No erythema	0 – No erythema	0 – No erythema
3	48	0 – No erythema	0 – No erythema	0 – No erythema
4	72	0 – No erythema	1- Slight erythema	0 – No erythema

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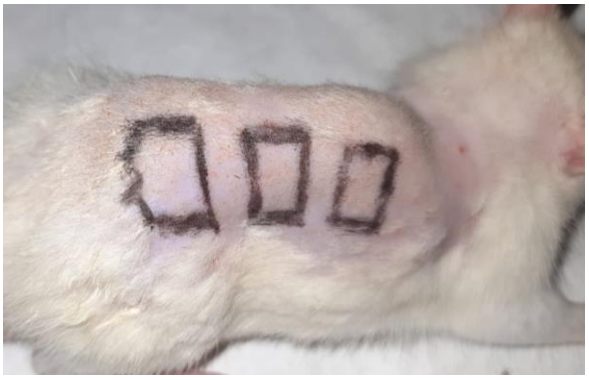

Figure 11: Skin irritation

CONCLUSION

The study explores using Hydrocortisone & benzocaine-loaded nanosponges (NS) in a gel formulation. The gel exhibited excellent consistency, homogeneity, & pH levels. The drug-loaded nanosponges exhibited desirable properties including particle size, zeta potential, high entrapment efficiency, & controlled release of drug. Invitro drug release study confirmed sustained drug release. Polymer composition & concentration variations affected the particle size, zeta potential, entrapment efficiency, and drug release. Batch F1 was chosen as the optimal formulation due to its minimal particle size, increased drug entrapment, and improved drug release form. The nanosponges-loaded gel maintained good consistency, homogeneity, and white color, caused no skin irritation, and enhanced skin permeation. The incorporation of Hydrocortisone and benzocaine-loaded nanosponges in topical gel offered superior therapeutic effects for psoriasis compared to standard marketed formulation.

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ABBREVIATION:
REFERENCES:

1. Uday B. Bolmal, F V Manvi, Kotha Rajkumar, Sai Sowjanya Palla, and Korivi Ramamohan Reddy, Recent Advances in Nanosponges as Drug Delivery System, International Journal of Pharmaceutical Sciences and Nanotechnology, Volume 6, April- June 2013 https://doi.org/10.37285/ijpsn.2013.6.1.3
2. Kim WB, Jerome D, Yeung J. Diagnosis and management of psoriasis. Can Fam Physician. 2017 Apr;63(4):278-285. PMID: 28404701; PMCID: PMC5389757.
3. Moin, Afrasim, et al. "Design and Formulation of Polymeric Nanosponge Tablets with Enhanced Solubility for Combination Therapy." RSC Advances, vol. 10, no. 57, 2020, pp. 34869–34884, pubs.rsc.org/en/content/articlehtml/2020/ra/d0ra06611g, https://doi.org/10.1039/D0RA06611G.
4. Kartik Tiwari[1], Sankha Bhattacharya[1] The ascension of nanosponges as a drug delivery carrier: preparation, characterization, and applications. *J Mater Sci: Mater Med* **33**, 28 (2022). https://doi.org/10.1007/s10856-022-06652-9
5. Raina, N., Rani, R., Vijay Kumar Thakur, & Gupta, M. (2023). New Insights in Topical Drug Delivery for Skin Disorders: From a Nanotechnological Perspective.

Research Paper © 2012 IJFANS. All Rights Reserved

https://doi.org/10.1021/acsomega.2c08016
6. Sunil Kumar[a], Minakshi Prasad[b], Rekha Rao[a,*] Topical delivery of clobetasol propionate loaded nanosponge hydrogel for effective treatment of psoriasis: Formulation, physicochemical characterization, antipsoriatic potential, and biochemical estimation, Materials Science & Engineering C 119 (2021) 111605, https://doi.org/10.1016/j.msec.2020.111605
7. Roop K. Khar, S. P. Vyas, Farhan J. Ahmad, Lachman/Lieberman's the Theory and Practice of Industrial Pharmacy, Edition 4, revised, CBS Publishers & Distributors, 2017, Page no. 712-722.
8. Padmini Iriventi1 & N. Vishal Gupta1 & Riyaz Ali M. Osmani[2] & V. Balamuralidhara1, Design & Development of nanosponge loaded topical gel of curcumin and caffeine mixture for augmented treatment of psoriasis, DARU Journal of Pharmaceutical Sciences https://doi.org/10.1007/s40199-020-00352-x

9. PENJURI, S. C. B., RAVOURU, N., DAMINENI, S., BNS, S., & POREDDY, S. R. (2016). Formulation and Evaluation of Lansoprazole Loaded Nanosponges. *Turkish Journal of Pharmaceutical Sciences*, *13*(3), 304–310. https://doi.org/10.4274/tjps.2016.04

10. Sarfraz, M.; Iqbal, R.; Khan, K.U.; Minhas, M.U. Carbopol Based Hydrogels for ITOPRIDE Hydrochloride Delivery; Synthesis, Characterization and Comparative Assessment with Various Monomers. J. Funct. Biomater. 2022, 13, 295. https://doi.org/10.3390/jfb13040295

11. Hamid Saeed Shah, Sumera Zaib, Khan, I., Sliem, M. A., Alharbi, O., Al-Ghorbani, M., Jawad, Z., Kiran Shahzadi, & Awan, S. (2023). Preparation and investigation of a novel combination of Solanum nigrum-loaded, arabinoxylan-cross-linked β-cyclodextrin nanosponges for the treatment of cancer: in vitro, in vivo, and in silico evaluation. Frontiers in Pharmacology, 14. https://doi.org/10.3389/fphar.2023.1325498

12. Sunil, Kumar, et al. "A New Perspective for Psoriasis: Dithranol Nanosponge Loaded Hydrogels." Applied Surface Science Advances, vol. 12, 1 Dec. 2022, pp. 100347–100347, https://doi.org/10.1016/j.apsadv.2022.100347

13. Abbas, N., Parveen, K., Hussain, A., Latif, S., Uz Zaman, S., Shah, P. A., & Ahsan, M. (2019). Nanosponge-based hydrogel preparation of fluconazole for improved topical delivery. Tropical Journal of Pharmaceutical Research, 18(2), 215. https://doi.org/10.4314/tjpr.v18i2.1

14. Jamatia, T., Das, S. & Das, M.K. Topical Delivery of Methoxsalen Co-loaded Curcumin Using Hybrid Nanocarrier-Based Polymeric Hydrogel for Synergistic Therapy in the Treatment of Psoriasis. J Pharm Innov 18, 2305–2324 (2023). https://doi.org/10.1007/s12247- 023-09794-7

15. Sivadasan, D., Venkatesan, K., Mohamed, J.M.M. et al. Application of 3^2 factorial design for loratadine-loaded nanosponge in topical gel formulation: comprehensive in-vitro and ex vivo evaluations. Sci Rep 14, 6361 (2024). https://doi.org/10.1038/s41598-024-55953-2