International Journal of Pharmaceutics and Drug Research
ISSN: 2347-6346
Available online at http://ijpdr.com

Original Research Article

FORMULATION AND EVALUATION OF NANOSPONGES CONTAINING HYDROGEL OF HYDROQUINONE AND ALOIN

Aastik Shankar*, Akhlesh Kumar Singhai, Steffi Thomas
School of Pharmacy, LNCT University, Bhopal (M.P.)

***Correspondence Info:**
Aastik Shankar
School of Pharmacy, LNCT University, Bhopal (M.P.)
Email:
aastikshankar610@gmail.com

***Article History:**

Received:06/04/2024
Revised: 20/04/2024
Accepted: 12/05/2024

ABSTRACT

Nanosponge loaded gels are novel drug delivery system that combines the advantages of achieving optimum concentration of drug at site of action and reduction in systemic side effects. The objective of the present study was to formulate and evaluate gel loaded with nanosponges containing Hydroquinone and aloin for topical delivery. Hydroquinone and aloin nanosponges were prepared successfully using ethyl cellulose as polymer, polyvinyl alcohol as cross-linking agent and dichloromethane as solvent by solvent evaporation technique, which undergo analysis of drug entrapment efficiency, SEM, particle size analysis and zeta potential. Among all 5 different formulations, F2 batch was considered as the best with 80.03% of drug entrapment efficiency and least particle size. From the SEM analysis it was found that nanosponges are spherical with smooth surface. The nanosponge of the best formulation F2 was loaded into the Carbopol gel which was evaluated for viscosity, spreadability, pH, drug content, in vitro drug release study and stability studies. From the study it was found that the prepared Hydroquinone and aloin nanosponge topical gel shows promised drug release and good stability.

Key words: Ethylcellulose, Hydroquinone, aloin, Nanosponges, Polyvinyl alcohol, Topical gel

INTRODUCTION

Hyperpigmentation disorders such as melasma, age spots, and post-inflammatory hyperpigmentation are common dermatological issues that significantly impact individuals' quality of life. Hydroquinone is a well-known depigmenting agent used to treat these conditions, but its topical application is often associated with skin irritation and instability. To enhance its stability and minimize side effects, hydroquinone can be incorporated into advanced drug delivery systems such as nanosponges. Nanosponges are porous, polymeric structures that provide controlled release of the drug, improving its efficacy and safety profile (Pathan and Setty, 2009). Aloin, a compound extracted from the Aloe vera plant, is known for its anti-inflammatory and antioxidant properties, making it a suitable co-ingredient in formulations aimed at skin health. The combination of hydroquinone and aloin in a nanosponges-containing hydrogel formulation offers a synergistic approach for the treatment of hyperpigmentation, potentially enhancing the therapeutic effects while reducing adverse reactions (Kumar and Garg, 2014; Peethambaran, 2015; Singh and Mishra, 2016). This study focuses on the formulation and evaluation of nanosponges containing a hydrogel of hydroquinone and aloin. The aim is to develop a stable, effective, and patient-friendly topical formulation that can deliver the active ingredients in a controlled manner,

thereby improving the treatment outcomes for hyperpigmentation disorders.

MATERIALS AND METHODS

Material

The chemicals used in the formulation of nanosponges containing hydrogel of hydroquinone and aloin include hydroquinone and aloin sourced from FDC, Mumbai, India. Methanol was obtained from Rankem, while ethanol and acetonitrile were supplied by Merck India Ltd., Mumbai. Ethyl cellulose and polyvinyl alcohol (PVA) were procured from Sigma Aldrich. Carbopol 934, a gelling agent, was sourced from Sulab. Triethanolamine, used for pH adjustment, was obtained from Loba Chemie. Additionally, propylene glycol, which serves as a humectant and penetration enhancer, and methyl paraben, a preservative, were both acquired from Merck.

Formulation of nanosponges

Hydroquinone and aloin loaded NS (PNS) were prepared by the emulsion solvent evaporation technique (ESE-Tech) using the drug 100 mg (1:1 ratio) and polyvinyl alcohol (PVA) 0.3%, w/v, compositions of formulations were tabulated in Table 5. Briefly, organic phase was prepared by dissolving ethyl cellulose (EC) (100–300 mg) and Hydroquinone and aloin in 20 mL dichloromethane (DCM). Separately, an aqueous phase was prepared composed of (0.3%, w/v) PVA in 100 mL of deionized water. Thereafter, the organic phase was emulsified drop wise into the aqueous phase by ultrasonication for 3 to 5 min (Ahmed *et al.,* 2021). the generated NS was stabilized using PVA, which prevented particle aggregation. The dispersion was then held on a thermostatically controlled magnetic stirrer "(Remi)" with continuous stirring at atmospheric pressure and room temperature for 3 to 4 hours. After the organic solvent had completely evaporated, the tretinoin and aloin nanosponges were washed three times with ultra-purified water to remove the adsorbed PVA. The NSs were then recovered via ultracentrifugation and freeze dried (Kumar *et al.,* 2018).

Evaluation parameter of nanosponges

Particle size

The particle size analysis of Hydroquinone and aloin loaded NS was performed by using ‘‘Malvern Zetasizer Nano ZS Malvern Instruments. The sample being investigated was diluted with distilled water (1:200) and placed in a disposable plastic cuvette. The particle size was measured using the dynamic light scattering (DLS) hypothesis (Penjuri *et al.,* 2016).

Zeta potential

The zeta potential was measured to determine the particle movement velocity in an electric field as well as the particle charge. In this study, the nanosponges were diluted tenfold with pure water and evaluated using Zetasizer Malvern equipment. All samples were sonicated for 5-10 minutes before zeta potential measurements (Solunke *et al.,* 2019; Anwer *et al.,* 2019).

Entrapment efficiency

To calculate the entrapment efficiency, an accurately weighed quantity of nanosponges (10 mg) was mixed with 5 ml of methanol in a volumetric flask and agitated for 1 minute with a vortex mixer. The volume was increased to 10 ml. Then the solution was filtered and diluted and the concentration of entrapped Hydroquinone and aloin was

determined spectrophotometrically (Abbas *et al.,* 2019).

%EE = Initial amount of drug added - Drug amount in supernatant / Initial amount of drug added * 100

Scanning Electron Microscopic (SEM)

The morphological features of the Hydroquinone and aloin loaded nanosponges were obtained using an electron beam from a scanning electron microscope. The nanosponges were coated with a thin layer (2-20 nm) of metal(s) such as gold, palladium, or platinum using a sputter coater in vacuum. The pretreated specimen was then bombarded with an electron beam and the interaction resulted in the formation of secondary electrons called auger electrons. From this interaction between the electron beam and the specimen's atoms, only the electrons scattered at 90° were selected and further processed based on Rutherford and Kramer's Law for acquiring the images of surface topography (Silpa *et al.,* 2021).

Formulation of Nanosponges loaded gel

Initially, carbopol-934 was immersed in 50 mL of warm water (A) for 2 hours and homogeneously distributed using a magnetic stirrer at 600 rpm. In a separate container, carboxymethyl cellulose and methyl paraben were mixed with 50 ml of warm water (B) and agitated continuously to form a hard gel. Both the mixtures A and B were mixed with the continuous stirring. Then tri-ethanol amine (Drop wise) was added to neutralize the pH and nanosponges of optimized formulation were incorporated into the dispersion to obtained Gel. At this stage, permeation enhancer (Propylene glycol) was added. The final dispersion was agitated until smooth gel was formed without lumps (Eswaraiah *et al.,* 2020; McGlynn, 2003).

Characterization of nanosponges loaded Gel

Physical appearance

The prepared Gel formulation was evaluated for appearance, Color, Odor, and homogeneity by visual observation (Monica and Gautami, 2014).

pH

The meter was allowed to stabilize as needed before being calibrated. Rinse the probe with de-ionized or distilled water and blot it dry with lint-free tissue paper. Immerse the sensor tip of the probe in the sample and record the pH reading. Rinse the probe, blot it dry, and repeat step 2 with a fresh sample. The two readings should accord within the meter's accuracy limitations. The samples were examined in triplicate. If tiny differences in pH were noticed, it was corrected to skin pH by adding tri-ethanolamine solution drop by drop (Sandeep, 2020).

Viscosity

The viscosity of the gel formulations was measured using a Brookfield viscometer with spindle number 61 at 100 rpm and a temperature of 25ºC (Sandeep, 2020).

Spreadability

An ideal topical gel should have a high spreading coefficient when applied or rubbed over the skin's surface. This was assessed by placing approximately 1g of formulation on a glass slide. Another glass slide of the same length was placed above it, and a 50 mg mass was placed on it, sandwiching the gel between the two glass slides and spreading at a specific distance. The time taken for the gel to travel the distance from the place of its position was

noted down. Spreadability was determined by the following formula

S= M*L/T

Where, S-Spreadability, g.cm/s M-Weight placed on the upper glass L-Length of glass slide T is the time it takes to distribute gel in seconds.

***In- vitro* drug release study**

The *in-vitro* drug release study of Hydroquinone and aloin loaded nanosponges formulation was studied by dialysis bag diffusion method. Hydroquinone and aloin loaded nanosponges were dispersed into dialysis bag and the dialysis bag was then kept in a beaker containing 100 ml of pH 7.4 phosphate buffer. The beaker was placed over a magnetic stirrer and the temperature of the assembly was maintained at 37 ± 2 °C throughout the experiment. During the experiment rpm was maintained at 100 rpm. Samples (2 ml) were withdrawn at a definite time intervals and replaced with equal amounts of fresh pH 7.4 phosphate buffers. After suitable dilutions the samples were analyzed using UV–Visible spectrophotometer.

RESULTS AND DISCUSSION

The particle size of nanosponges formulations F1 to F5 varied, with formulation F2 having the smallest particle size of 481.4 nm, indicating a potentially higher surface area and improved drug encapsulation. Formulation F1 exhibited the largest particle size at 671.1 nm. The particle size results are presented in Table 3.

Zeta potential measurements (Table 4) indicated that all formulations had negative values, with F1 showing the least negative potential at -0.1 mV and F5 the most negative at -3.0 mV. These values suggest moderate stability of the nanosponge formulations in suspension, with higher negative values generally indicating better colloidal stability.

The nanosponges loaded gel was observed to have a yellowish color, odorless nature, brown appearance, and homogeneous texture, as summarized in Table 5. The physical appearance is crucial as it influences patient acceptance and compliance.

The viscosity of the nanosponges loaded gel was found to be 6835±0.32 cps, indicating a moderately thick consistency suitable for topical application. The pH was measured at 6.6, close to the skin's natural pH, reducing the likelihood of irritation upon application. The spreadability value was 13.09 g.cm/s, reflecting good spreadability essential for ease of application over a wound or skin surface (Table 6).

The release kinetics study of the optimized nanosponge formulation F2 revealed a cumulative drug release of 96.13% at 16 hours, indicating a sustained release profile. The kinetics of drug release was further analyzed using various models. The correlation coefficients (R^2 values) for the zero order, first order, Higuchi, and Korsmeyer-Peppas models were determined. The Higuchi model showed the highest R^2 value (0.9961), indicating that the drug release followed a diffusion-controlled mechanism (Table 7-8).

Table 1: Composition of Nanosponges formulation

Ingredients	F1	F2	F3	F4	F5
Hydroquinone and aloin (mg)	100	100	100	100	100
Ethyl cellulose (EC) (mg)	100	150	200	250	300
Poly vinyl alcohol (PVA) (%)	0.3	0.3	0.3	0.3	0.3
Dichlomethane (DCM) (ml)	20	20	20	20	20
Distilled water (ml)	100	100	100	100	100

Table 2: Composition of gel formulation

S. No	Excipients	Quantity
1.	Carbopol 934	1.00 gm
2.	Carboxymethyl cellulose	1.00 gm
3.	Propylene glycol	0.5 ml
4.	Methyl paraben	0.2 ml
5.	Nanosponges	1.0 gm
6.	Tri-ethanolamine	q.s
7.	Water	100 ml

Table 3: Particle size of nanosponges formulation F1 to F5

S. No	Formulation code	Particle size (nm)
1.	Nanosponges F1	671.1nm
2.	**Nanosponges F2**	**481.4 nm**
3.	Nanosponges F3	546.9 nm
4.	Nanosponges F4	637.2 nm
5.	Nanosponges F5	712.2 nm

Table 4: Zeta potential of nanosponges formulation F1 to F5

S. No	Formulation Code	Zeta potential
1.	Nanosponges F1	-0.1 mV
2.	**Nanosponges F2**	**-1.2 mV**
3.	Nanosponges F3	-2.1 mV
4.	Nanosponges F4	-2.5 mV
5.	Nanosponges F5	-3.0 mV

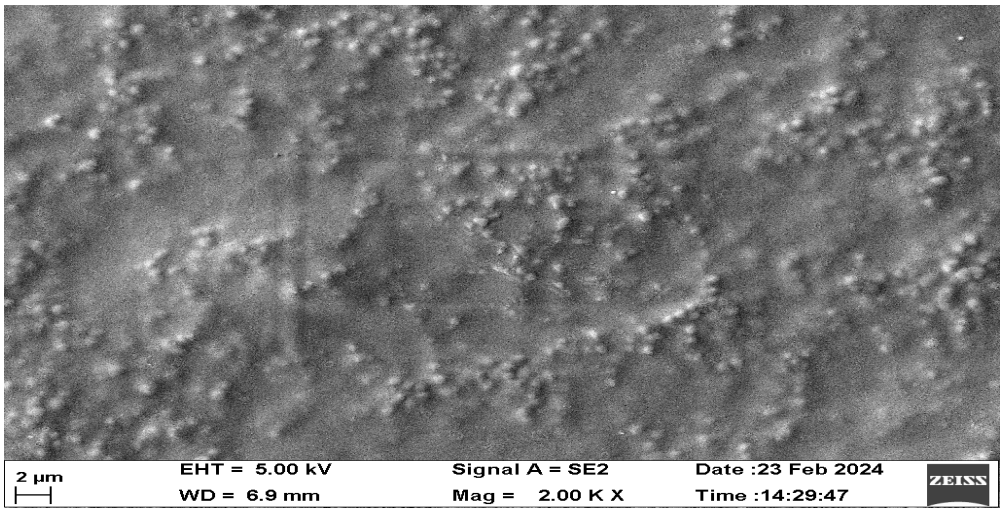

Figure 1: Scanning electron microscope of Optimized nanosponges formulation F2

Table 5: Physical appearance of nanosponges loaded gel

S. No	Parameter	Result
1.	Colour	Yellowish
2.	Odour	Odourless
3.	Appearance	Brown colour
4.	Homogeneity	Homogeneous

Table 6: Viscosity, pH and Spreadability of nanosponges loaded gel

S. No	Formulation	Viscosity (cps)	pH	Spreadability (g.cm/s)
1.	Gel	6835±0.32	6.6	13.09

Table 7: Release kinetics study of nanosponges loaded gel

Time (Hr)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	log time	log Cumu % drug released
0	0	100	0.000	2.000	0.000	0.000
1	23.18	76.82	1.000	1.885	0.000	1.365
2	36.09	63.91	1.414	1.806	0.301	1.557
4	43.63	56.37	2.000	1.751	0.602	1.640
6	57.6	42.4	2.449	1.627	0.778	1.760
8	66.13	33.87	2.828	1.530	0.903	1.820
10	77.56	22.44	3.162	1.351	1.000	1.890
12	82.45	17.55	3.464	1.244	1.079	1.916
16	96.13	3.87	4.000	0.588	1.204	1.983

Table 8: Correlation value (R^2 value)

Formulation	Model	Kinetic parameter values
Gel	Zero Order	$R^2 = 0.9253$
	First Order	$R^2 = 0.8512$
	Higuchi	$R^2 = 0.9961$
	Korsmeyerpeppas	$R^2 = 0.6015$

CONCLUSION

The nanosponge formulations of hydroquinone and aloin demonstrated suitable particle sizes and zeta potentials for effective drug delivery. The physical characteristics of the gel, including viscosity, pH, and spreadability, were favorable for topical application. The drug release study indicated a sustained release profile, particularly well-fitted to the Higuchi model, suggesting a diffusion-controlled release mechanism. These findings support the potential of the formulated nanosponge gels as effective vehicles for the topical delivery of hydroquinone and aloin, offering controlled release and improved therapeutic efficacy for wound healing applications.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

REFERENCES

- 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, 215–222.
- Ahmed, M.M., Fatima, F., Anwer, M.K., Ibnouf, E.O., Kalam, M.A., Alshamsan, A., Aldawsari, M.F., Alalaiwe, A. & Ansari, M.J. (2021) Formulation and in vitro evaluation of topical nanosponge-based gel containing butenafine for the treatment of fungal skin infection. *Saudi Pharmaceutical Journal*, 29, 467–477.
- Anwer, M.K., Mohammad, M., Ezzeldin, E., Fatima, F., Alalaiwe, A. & Iqbal, M. (2019) Preparation of sustained release apremilast-loaded PLGA nanoparticles: In vitro characterization and in vivo pharmacokinetic study in rats. *International Journal of Nanomedicine*, 14, 1587–1595.
- Eswaraiah, S., Kumar, K.N., Kim, Y.H., Chalapathi, G.V., Lee, W., Jiang, G., Yan, C., Yang, G., Ratnam, M.V., Prasanth, P.V., Rao, S.V.B. & Thyagarajan, K. (2020) Low-latitude mesospheric signatures observed during the 2017 sudden stratospheric warming using the fuke meteor radar and ERA-5. *Journal of Atmospheric and Solar-Terrestrial Physics*, 207, 105352.
- Monica, A.S., & Gautami, J. (2014). Design and evaluation of topical hydrogel formulation of diclofenac sodium for improved therapy. *International Journal of Pharmaceutical Sciences and Research*, 5, 1973.

- Kumar, S. & Garg, S.K. (2014) Nanosponges: A novel and emerging drug delivery system. *World Journal of Pharmacy and Pharmaceutical Sciences*, 3, 458–473.
- Kumar, S., Pooja, Trotta, F. & Rao, R. (2018) Encapsulation of babchi oil in cyclodextrin-based nanosponges: Physicochemical characterization, photodegradation, and in vitro cytotoxicity studies. *Pharmaceutics*, 10, 169.
- McGlynn, W. (2003). *Choosing and Using a pH Meter for Food Products*. Oklahoma Cooperative Extension Service.
- Pathan, I. & Setty, C. (2009) Chemical penetration enhancers for transdermal drug delivery systems. *Tropical Journal of Pharmaceutical Research*, 8, 173–179.
- Peethambaran, K.N. (2015) Formulation and evaluation of hydroquinone loaded nanosponges. *International Journal of Pharmaceutical Sciences Review and Research*, 35, 34–39.
- 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, 304–310.
- Sandeep, D.S. (2020) Development, characterization, and in vitro evaluation of aceclofenac emulgel. *Asian Journal of Pharmaceutics (AJP)*, 14.
- Silpa, G.S., Mathan, S. & Dharan, S.S. (2021) Formulation and evaluation of nanosponges loaded hydrogel using different polymers containing selected antifungal drug. *Journal of Pharmaceutical Sciences and Research*, 13, 101–111.
- Singh, A.K. & Mishra, J. (2016) Aloin: A valuable therapeutic agent in the treatment of skin disorders. *Journal of Dermatological Treatment*, 27, 587–597.
- Solunke, R.S., Borge, U.R., Murthy, K., Deshmukh, M.T. & Shete, R.V. (2019) Formulation and evaluation of gliclazide nanosponges. *International Journal of Applied Pharmaceutics*, 11, 181–189.