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DESIGN AND EVALUATION OF A NOVEL NANOSPONGES-BASED TOPICAL GEL OF 2-[(2,6 DICHLOROPHENYL) AMINO] BENZENEACETIC ACID DIETHYLAMINE SALT FOR ENHANCED DRUG DELIVERY

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ABSTRACT : The present work was performed with the objective of novel topical formulation development of poorly water-soluble drug Diclofenac diethylamine by loading the drug-containing nanosponge into the topical formulation. The nanosponges are polymeric nanoparticles that entrap the drug. The drug-loaded nanosponge has different absorption characteristics in comparison to the pure drug in the topical drug delivery system. The drug was first loaded in the ethylcellulose nanosponge using the emulsion solvent diffusion method. Then Diclofenac diethylamine nanosponge-loaded topical gel formulations were developed by using Carbopol 940 as a gel-forming polymer. The Diclofenac diethylamine-loaded nanosponges were evaluated for various evaluation parameters such as particle size distribution, surface morphology, drug entrapment efficiency, polydispersity index, etc. The topical gel formulations were evaluated for pH, *in vitro* drug release, viscosity, *in vivo* performance and compared with the marketed formulation. The average size of prepared nanosponge formulations was found in the range of 102.8 nm to 475.5 nm. Scanning electron microscopy photographs of developed formulations reveal the spongy and porous nature of particles along with spherical shape. The polydispersity index (PI) was found in the range of 0.756 to 0.954. It was found that formulation F3 with a drug-to-polymer ratio of 1:3 has the highest drug loading. Further nanosponges were characterized for different parameters and results revealed acceptable characteristics of B3 formulation. These prepared nanosponges were loaded in topical Carbopol gel (Formulation AB3) and evaluated for *in vitro* and *in vivo* performance. The data were fitted to different kinetic models which reveal typical zero order i*n vitro* drug diffusion with prolonged drug release. The developed formulation generated better analgesic and anti-inflammatory responses compared to the standard marketed formulation.

Key words : Nanosponge, water-insoluble drug, polymer, topical formulation.

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INTRODUCTION

The development of a novel nanosponges-based topical gel for the delivery of 2-[(2,6-Dichlorophenyl) amino] benzeneacetic acid diethylamine salt represents a significant advancement in pharmaceutical formulation, addressing the critical need for enhanced drug delivery systems (Pawar *et al*, 2019). Traditional topical formulations often face challenges such as poor skin penetration, limited bioavailability, and rapid drug degradation (Radaic *et al*, 2020). Nanosponges, as innovative drug carriers, offer a promising solution to these issues due to their unique structural properties, which include a porous network capable of encapsulating both hydrophilic and lipophilic drugs. This research focuses on the design and evaluation of such nanosponges to

improve the therapeutic efficacy of the selected drug compound (Ghai *et al*, 2022). The formulation process involves the meticulous selection of biocompatible polymers and cross-linkers to create a stable nanosponge matrix that can effectively encapsulate the active pharmaceutical ingredient (API). The resulting gel formulation is expected to provide controlled release characteristics, enhancing the drug's therapeutic window while minimizing systemic side effects (Rao *et al*, 2018). Comprehensive evaluations will be conducted to assess various parameters such as viscosity, spreadability, drug release kinetics and skin permeation capabilities (Abhishek *et al*, 2024). *In vitro* studies will further elucidate the gel's performance in mimicking physiological conditions, ensuring that the formulation can deliver the API effectively at the target site (Conte *et al*, 2014). By integrating cutting-edge nanotechnology with pharmaceutical sciences, this research aims to contribute significantly to the field of topical drug delivery systems, potentially leading to improved patient outcomes in managing conditions requiring localized treatment (Danaei *et al*, 2018). This research not only demonstrates the adaptability of nanosponges in drug delivery applications but also emphasizes their transformative potential in the formulation and administration of topical therapies, setting the stage for future advancements in pharmaceutical technology. Diclofenac is a widely recognized nonsteroidal anti-inflammatory drug (NSAID) (Altman *et al*, 2015) frequently prescribed to alleviate pain and inflammation associated with various conditions, including musculoskeletal disorders, dental pain, arthritis, dysmenorrhea and more (Dharmendra Bhati *et al,* 2024). The diethylamine salt of diclofenac is particularly favored for topical applications due to its enhanced skin permeability and limited solubility in water (Ong *et al,* 2007). The rapid advancement of nanotechnology, coupled with the need for precise and targeted drug administration, has led to the development of innovative drug delivery systems known as nanosponge formulations (Gangadharappa *et al*, 2017). These nanocarriers exhibit improved penetration capabilities in topical delivery systems and tend to accumulate passively at the desired site of action, enhancing their therapeutic effects (Vyas *et al*, 2014). Topical drug delivery systems (TDDS) can be formulated into various forms, including liquid, solid, or semisolid dosages. Their main objective is to provide an effective concentration of medication directly within the skin or mucosal layers (Ruela *et al*, 2016). One significant advantage of topical formulations over oral or injectable routes is their reduced risk of systemic side effects due to localized drug application (Benson *et al*, 2019; Sousa *et al*, 2020).

METHODS

Preparation of nanosponge

The synthesis of diclofenac diethylamine nanosponges was accomplished through the emulsion solvent evaporation method. For this formulation, ethylcellulose (EC) was utilized as the primary polymer (Kumar *et al*, 2021). Initially, the internal phase, containing the drug and polymer dissolved in 20 ml of dichloromethane (DCM), was gradually mixed into a 0.3% w/v solution of Poly Vinyl Alcohol in 100 ml of an aqueous external phase. This mixture was stirred continuously with a magnetic stirrer at a speed of 1000 rpm for a duration of three hours. Following this process, the resulting nanosponges were separated by filtration and subsequently air-dried in an oven set to 45ºC for 24 hours before being transferred into vials for storage.

Preparation of nanosponge loaded topical formulation

To formulate the gel containing diclofenac diethylamine-loaded nanosponges, 1 gram of carbopol 934 was incorporated into a freshly prepared suspension of the nanosponges. The pH of the mixture was adjusted to neutrality by adding triethanolamine while continuously stirring with a glass rod (Sharma and Pathak, 2011). The formulation details for the nanosponge-loaded topical gel are outlined in Table 2.

Characterization and evaluation of Nano sponges

Particle size and Polydispersity

The z-average diameter and polydispersity index of the diclofenac diethylamine-loaded nanosponge dispersion were determined using a Malvern Zeta Sizer at a temperature of 25°C (Shringirishi *et al*, 2014). This analysis provides crucial information regarding the size distribution and uniformity of the nanoparticles within the dispersion.

Morphology of Nanosponges by Scanning Electron Microscopy

The surface characteristics of the nanosponges were analyzed through scanning electron microscopy (SEM). This technique was employed to assess the particle size, shape and overall surface structure of the nanosponges. High-resolution images were captured at different magnifications using a scanning electron microscope set to an acceleration voltage of 10 kV. Prior to imaging, the samples were securely attached to the SEM sample holder using double-sided adhesive tape (Kumar Satpathy *et al*, 2022).

Drug entrapment efficiency

Nanosponges' drug entrapment effectiveness was

Table 1 : Composition of Nano sponge formulations.

Formulation Code	Drug: Polymer Ratio
B1	1:1
B2	1:2
B3	1:3
B4	1:4
B5	1:5
B6	1:6

after 1 min, the spreadability of the formulated gel was determined. The mass of the upper plate was standardized at 500g.

$$S = (m) X (l) X (t) \quad \text{Eq. 1}$$

Where, S is spreadability, m is weight or mass applied to the glass slide, l is the length of the glass slide and t is time in seconds (Ahmed *et al*, 2021).

Table 2 : Composition of Nano sponge loaded topical gel formulations.

Formulation code	Drug concentration	Carbopol 934	Distilled water (ml)	Triethanolamine (ml)	Propylene glycol (ml)
B1	1.25%	0.8%	12	1.0	0.5
B2	1.30%	0.9%	11	0.9	0.6
B3	1.20%	1.2%	10	0.7	0.5
B4	1.15%	1.1%	13	0.85	0.4
B5	1.35%	0.7%	9	1.2	0.3
B6	1.40%	1.3%	14	0.95	0.7

measured spectrophotometrically. A sample of Diclofenac diethylamine Nanosponge was combined in methanol and diluted to 100 ml with phosphate buffer (pH 6.8) before being maintained overnight. The drug content in Nanosponges was assessed and expressed as actual drug content.

Evaluation parameters of Nanosponge loaded gel

Determination of pH : The pH of formulated topical gel formulations was evaluated with the help of a digital pH meter. 0.5 gm of prepared gel was dispersed in 50 ml of distilled water. It was kept aside at 25^0 C for 3 hours. After that pH was checked by pH meter by dipping the electrode into the solution.

Drug content : The Diclofenac diethylamine content in nanosponge gel was measured by dissolving 1000 mg of gel in 10 ml solvent (methanol) by sonication. The solution was passed through the Whatman filter paper no. 42 and filtered. Absorbance was measured after suitable dilution at 284 nm in UV - 1800 spectrophotometer.

Homogeneity : It was determined by visual inspection for the appearance of gel and the presence of any aggregates.

Extrudability : Pfizer hardness tester was used to study the extrudability. 20gm of gel was filled in an aluminum tube. The plunger was set up in such a way that the tube was securely held in place. For 30 seconds, a pressure of $1kg/cm^2$ was applied. The amount of gel extruded was measured and weighed. The procedure was repeated at three equidistance places of the tube.

Spreadability : By measuring the spreading diameter of 0.5g of gel between 20 × 20 cm glass plates

Determination of viscosity : The viscosity of nanosponge-loaded gel was measured at different RPMs by using T spindle no. 1 and the heldal unit of Fungi Lab rotational viscometer.

***In-vitro* drug release studies (dialysis membrane) :** The Franze diffusion cell was selected for *in-vitro* diffusion studies by using a dialysis membrane. The diffusion cell was fabricated by a local vendor. Receptor compartment volume was made to hold 60 ml of diffusion media. The dialysis membrane was fixed between the donor and receptor chamber of the Franz diffusion cell. 0.5 gm of gel was spread homogeneously over the dialysis membrane. Dialysis membrane was tied over receptor chamber, which was filled with phosphate buffer pH 7.4. The temperature was kept at 37^0C. The media was stirred with the magnetic bead at 150 RPM. 2 ml sample was withdrawn at a periodic time interval and sink condition was maintained by replacing the same with fresh media. The sample was filtered and absorbance was taken by UV double beam spectrophotometer.

Stability studies

The topical gel was packed in aluminium collapsible tubes (5 g) and tested for 3 months at 5 °C, 25 °C/60 percent RH, 30 °C/65 percent RH, and 40 °C/75 percent RH. At 15-day intervals, samples were extracted and examined for physical appearance, pH, rheological characteristics, and drug concentration.

RESULTS AND DISCUSSION

Particle size and Polydispersity

The particle size distribution of the formulated nanosponges was analyzed using a Malvern particle size

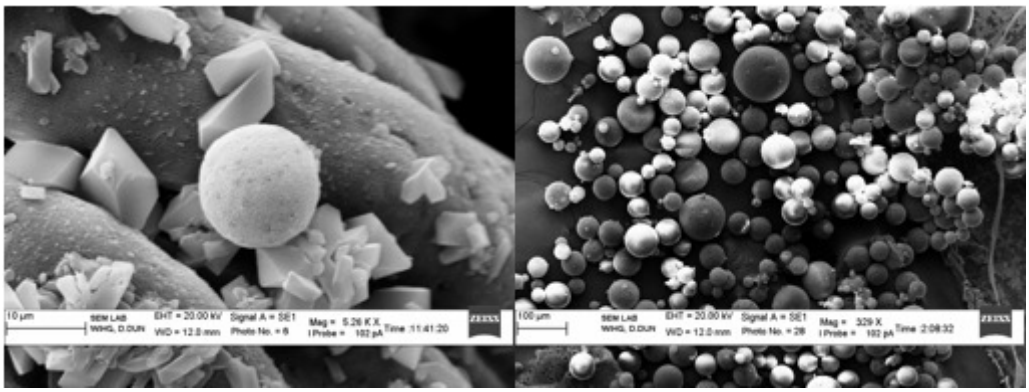

Fig. 1 : SEM images of prepared nanosponges.

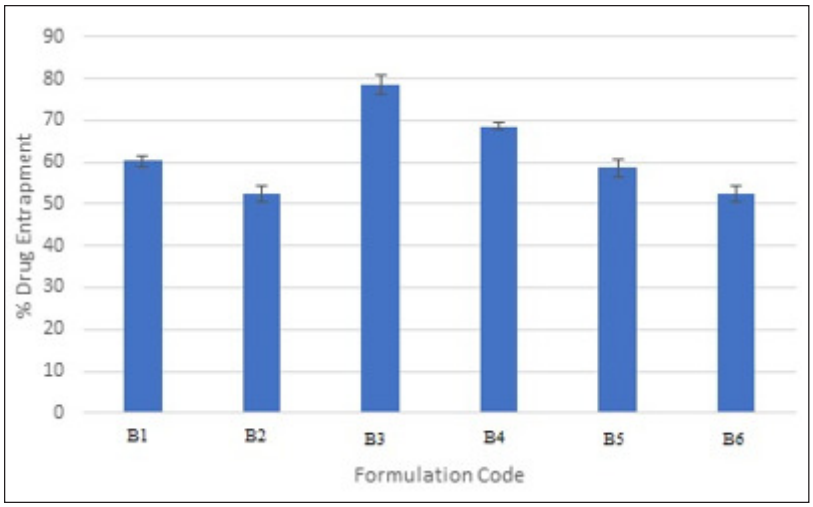

Fig. 2 : Percentage drug entrapment of different formulations.

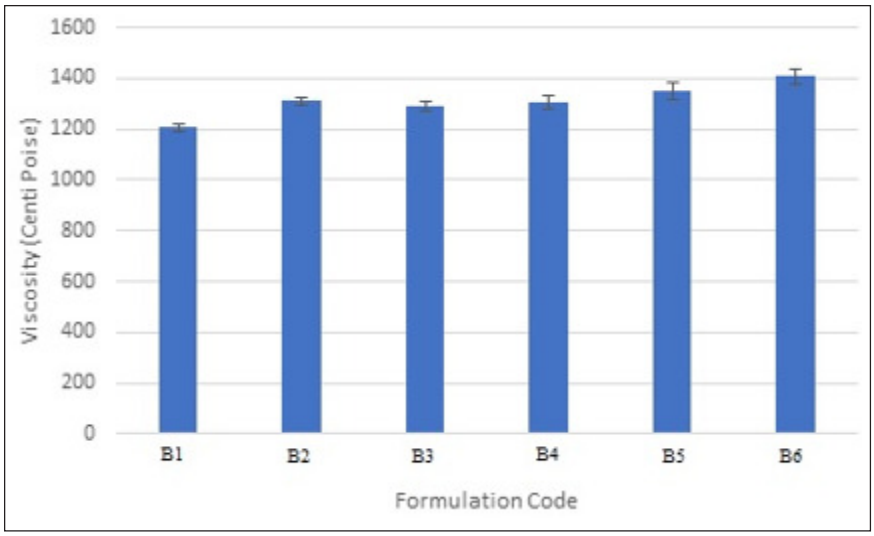

Fig. 3 : Viscosity of different formulations.

analyzer. The results indicated that the average particle size of the nanosponges varied between 102.8 nm and 475.5 nm. Detailed measurements of the particle sizes for each formulation are presented in Table 3. Additionally, the polydispersity index (PI) for these formulations ranged from 0.756 to 0.954, reflecting the degree of size variation within the particle population. The polydispersity index serves as an important indicator of the uniformity of particle sizes in a sample. According to guidelines set by the International Standards Organization (ISO), a PI value below 0.05 indicates a monodisperse sample, while values exceeding 0.7 suggest a polydisperse sample with a wide range of particle sizes.

Morphology of Nano sponges by Scanning Electron Microscopy

The surface morphology of developed nanosponge formulations was studied by using scanning electron microscopy (SEM). The representative scanning electron microscopy photographs of the nanosponge formulation were shown in Fig. 1. Scanning electron microscopy photographs of developed formulations reveal the spongy and porous nature of particles along with spherical shape.

Drug entrapment efficiency

Drug entrapment efficiency was measured for all developed formulations. The entrapment efficiency was maximum in the B3 formulation having a 1:3 Drug: Polymer ratio. Random % of drug entrapment was found when polymer concentration was increased. No correlation can be established between polymer concentration and drug entrapment.

Estimated parameter of nanosponge based topical gels

The nanosponge-loaded gel was evaluated for various parameters like pH, homogeneity, spreadability, % drug content, and extrudability. The results were reported in Table 5. Prepared gel formulations revealed a pH range between 6.5 to 6.9. All gel formulations showed good

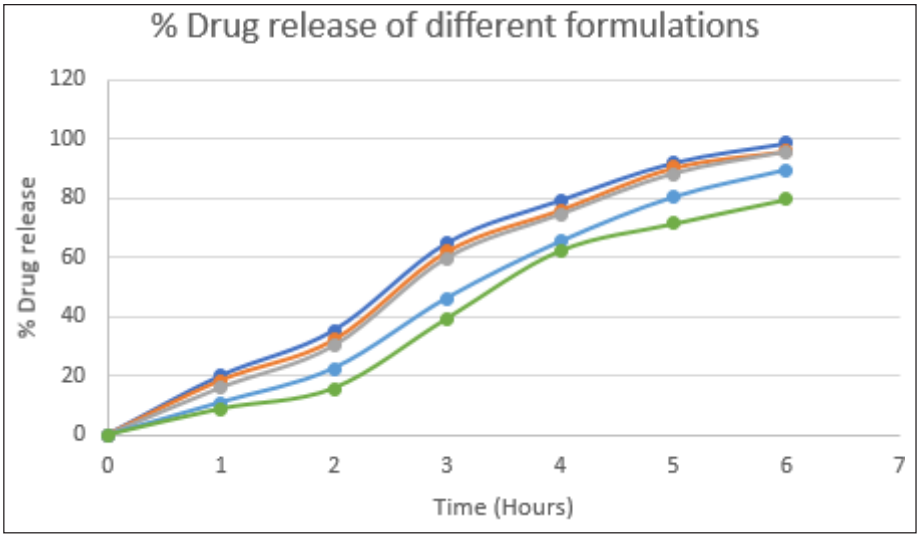

Fig. 4 : % Drug Release of different gel formulations loaded with Diclofenac diethylamine nanosponge.

Table 3 : Particle size distribution study of Nano sponge formulations.

Formulation Code	Particle Size (nm)	Polydispersity Index
B1	450.7	0.767
B2	475.5	0.954
B3	102.8	0.856
B4	201.2	0.867
B5	350.9	0.756
B6	405.5	0.856

Table 4 : Drug entrapment efficiency of different Nano sponge formulations.

Formulation code	% Drug entrapment
B1	60.34±1.20%
B2	52.40±1.82%
B3	78.50±2.50%
B4	68.60±1.50%
B5	58.60±2.20%
B6	52.50±1.80%

Table 5 : Characterization of Nano sponge loaded topical gel formulations.

Formulation Code	pH Data	Homogeneity	Spreadability (gm-cm/sec)	% Drug Content	Extrudability
B1	6.4	Good	28.15±0.75	92.3±1.2	
B2	7.1	Good	21.50±1.10	87.8±1.0	
B3	6.3	Good	24.75±1.25	95.0±0.90	
B4	6.8	Good	19.80±0.45	95.5±1.3	
B5	6.9	Good	23.60±0.95	91.7±1.4	
B6	6.7	Good	27.30±1.05	89.5±1.1	

Symbol: () Acceptable, () Good, () Excellent.

homogeneity. % Assay of gel formulations was found in the range of 85.6±1.4% to 94.6±0.86%. Extrudability was found in an acceptable range. Spreadability was found in the range of 18.24 to 26.06 gm-cm/sec.

The viscosity of optimized formulations (F3)

The viscosity of nanosponge-loaded gel was measured at different RPMs by using T spindle no. 1 and the heldal unit of Fungi Lab rotational viscometer. The viscosity reading was tabulated in table 6 and graphically represented in Fig. 3.

In-vitro diffusion studies

In-vitro diffusion study was performed by using Franz diffusion cell. *In-vitro* diffusion data were tabulated in Table 7 and graphically represented in Fig. 4. *In-vitro* diffusion data revealed that % drug release was decreased as the concentration of polymer increased in initial hours.

In-vitro diffusion studies

In-vitro diffusion study was performed by using Franz

Table 6 : Viscosity of Nano sponge loaded topical gel formulations.

Formulation code	Viscosity (Centipoise)
B1	1205.5±15.75
B2	1310.8±14.25
B3	1291.6±20.52
B4	1308.5±25.20
B5	1350.95±30.5
B6	1408±28.5

Table 7 : *In Vitro* Drug Release profile of Nanosponge Formulations over time.

Time (Hours)	% Drug release of formulation B1	% Drug release of formulation B2	% Drug release of formulation B3	% Drug release of of formulation B4	% Drug release of formulation B5	% Drug release of formulation B6
0	0±0	0±0	0±0	0±0	0±0	0±0
1	22.15±0.45	19.75±1.2	17.85±1.15	14.30±0.35	12.10±2.1	9.95±1.25
2	37.50±1.10	34.00±1.5	31.40±0.90	28.15±1.80	24.30±2.5	16.40±2.3
3	68.25±1.40	64.50±1.7	61.75±1.10	58.20±0.60	48.90±1.70	42.10±2.00
4	82.10±1.60	78.25±1.30	75.80±1.20	72.15±1.40	67.30±1.10	63.85±1.20
5	95.50±2.20	92.00±0.80	89.20±0.75	86.50±1.00	81.70±2.00	73.40±1.50
6	99.20±0.30	97.00±0.80	96.10±0.85	95.00±0.70	90.25±2.10	80.50±1.20

diffusion cell. *In-vitro* diffusion data were tabulated in Table 7 and graphically represented in Fig. 4. *In-vitro* diffusion data revealed that % drug release was decreased as the concentration of polymer increased in initial hours.

Stability study

After 3 months of storage, all of the generated nanosponge-loaded gel formulations were determined to be stable, with no changes in their physical appearance, pH, rheological properties, or drug concentration.

CONCLUSION

The formulation of nanosponge carriers for the poorly water-soluble drug diclofenac diethylamine was successfully accomplished using ethyl cellulose as the polymer matrix. Various drug-to-polymer ratios were explored to optimize drug loading efficiency, and it was determined that formulation B3, with a ratio of 1:3, achieved the highest loading capacity. Subsequent characterization of the nanosponges revealed that formulation B3 exhibited favorable properties across multiple evaluation parameters. These nanosponges were then incorporated into a topical Carbopol gel and subjected to in vitro release studies. The release data were analyzed using different kinetic models, indicating a zero-order release pattern, which suggests a sustained drug diffusion profile. This characteristic makes the formulation particularly suitable for pain management applications. The nanosponge-based topical gel is particularly advantageous for effective pain relief and anti-inflammatory treatment, as the nanocarrier system facilitates deeper penetration of the drug into the skin layers, surpassing the limitations of conventional topical semisolid formulations. The gels containing diclofenac diethylamine loaded in nanosponges demonstrated uniformity and homogeneity. The pH of the formulations was measured to be close to neutral at approximately 7. Additionally, all formulated topical gels exhibited excellent spreadability and satisfactory extrudability properties.

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