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Formulation, Development, Optimization, and Evaluation of a Sustained-Release Hydrogel System of Diclofenac Sodium Using Almond and Neem Gums

Navneet Kaur*, Dr. Bhupinder Bhyan[1], Aakrshan Kumar[2], Shivani Rangarh[3], Nancy[4], Dr Ajay Bilandi[5]

Research Scholar, Department of Pharmaceutical Sciences, RIMT University, Mandi Gobindgarh, Punjab India.

[1]Department of Pharmaceutical Sciences, Professor School of Pharmaceutical Sciences, RIMT University, Punjab, India

[2]Department of Pharmaceutical Sciences, Associate Professor College of Pharmacy, RIMT University, Punjab, India

[3]Department of Pharmaceutical Sciences, Assistant Professor College of Pharmacy, RIMT University, Punjab, India

[4]Department of Pharmaceutical Sciences, Assistant Professor College of Pharmacy, RIMT University, Punjab, India

[5]Department of Pharmaceutical Sciences, Professor and Principal, Bhai Gurdas College of Pharmacy, Punjab, India

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KEYWORDS

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ABSTRACT:

The development of biopolymer-based drug delivery systems has gained significant attention in recent years as an eco-friendly alternative to synthetic polymers. The present study focuses on the formulation, optimization, and evaluation of sustained-release hydrogel microspheres of diclofenac sodium using two natural polysaccharide gums — Neem (Azadirachta indica) and Almond (Terminalia catappa) gums. These natural gums, known for their biocompatibility, biodegradability, and safety, were chemically modified through crosslinking reactions using glutaraldehyde and epichlorohydrin to enhance mechanical integrity and regulate swelling behavior. Hydrogel microspheres were prepared via emulsion polymerization technique and optimized using a 3-factor, 3-level Box–Behnken design (BBD), varying polymer concentration, crosslinker concentration, and drug loading as independent variables. Characterization of the modified gums and microspheres was carried out using FTIR, DSC, XRD, SEM, and Zeta potential analyses. The optimized formulation exhibited particle size of 115.3 µm, entrapment efficiency of 85.2%, and sustained drug release up to 85.3% over 24 hours. The release followed the Korsmeyer–Peppas model (R^2 = 0.9889, n = 0.62), indicating anomalous (non-Fickian) diffusion — suggesting simultaneous swelling and diffusion-controlled mechanisms. In vivo anti-inflammatory activity in Wistar rats confirmed significant inhibition of carrageenan-induced paw edema, comparable to marketed diclofenac gel formulations, with no observable irritation or adverse effects. Stability studies conducted under ICH conditions demonstrated excellent physical and chemical stability over three months. This study concludes that Neem and Almond gum–based hydrogel microspheres present a promising, green, biocompatible, and sustained-release carrier system for diclofenac sodium, offering potential benefits in pain management and patient compliance.

1. Introduction

The advancement of controlled and sustained-release drug delivery systems (DDS) represents a major milestone in modern pharmaceutics. Such systems aim to deliver therapeutic agents at a predetermined rate, over an extended period, thereby minimizing dosing frequency and improving patient compliance. Among these, hydrogels have emerged as one of the most versatile carriers due to their three-dimensional crosslinked structure, high water absorption capacity, and ability to release drugs in a controlled and predictable manner. Hydrogels are hydrophilic polymer networks that can absorb and retain large amounts of water or biological fluids without dissolving. The interconnected porous architecture of hydrogels allows them to encapsulate both hydrophilic and hydrophobic drugs. When exposed to aqueous environments, they

Journal of Chemical Health Risks
www.jchr.org
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undergo reversible swelling, which regulates drug diffusion through the polymeric network. This property makes hydrogels particularly suitable for sustained and controlled release applications in pharmaceuticals, biomedical engineering, and tissue scaffolding.[1]

1.1. Role of Natural Polymers

Recently, there has been an increasing preference for natural polymers over synthetic ones due to their biodegradability, safety, non-toxicity, and low cost. Natural gums — complex polysaccharides obtained from plants, bacteria, or algae — are ideal candidates for sustainable DDS. They exhibit excellent film-forming, emulsifying, and swelling properties, and can be easily modified chemically or physically to tailor their release characteristics.[2]

Neem gum, an exudate from the bark of *Azadirachta indica*, is a clear, amber-colored polysaccharide containing galactose, arabinose, and uronic acid units. It possesses excellent solubility in cold water and is known for its emulsifying and stabilizing capabilities. Almond gum, obtained from *Terminalia catappa*, contains about 92% polysaccharides, primarily arabinogalactan polymers, which make it a strong candidate for hydrogel formation.[3]

1.2. Advantages of Natural Gums in Hydrogel Systems

Natural gums offer several advantages:

- **Biodegradable:** Easily broken down by biological systems without generating toxic by-products.
- **Biocompatible:** Non-irritating and safe for human use.
- **Economical:** Readily available and cost-effective.
- **Eco-friendly:** Sustainable and renewable source of polymers.
- **Safe and Non-toxic:** No harmful residues or environmental impact.

These properties make natural gums suitable substitutes for synthetic polymers like PVA, PEG, or polyacrylamide, which may have issues with toxicity and environmental persistence.[4]

1.3. Diclofenac Sodium as a Model Drug

Diclofenac sodium, a nonsteroidal anti-inflammatory drug (NSAID), is widely prescribed for the treatment of pain and inflammation associated with arthritis and musculoskeletal disorders. However, its short biological half-life (2-4 hours) and gastrointestinal side effects necessitate frequent dosing, reducing patient compliance. A sustained-release formulation can overcome these limitations by maintaining therapeutic drug levels for extended durations, minimizing dosing frequency, and reducing adverse effects.[5]

1.4. Research Rationale

Despite the potential of natural gums, their native mechanical properties and swelling behavior are often inadequate for controlled-release applications. Hence, chemical modification through crosslinking with glutaraldehyde and epichlorohydrin can strengthen their structure and modulate water uptake, leading to improved release control. This study integrates polymer chemistry, formulation optimization, and pharmaceutical evaluation to develop a sustained-release hydrogel microsphere system of diclofenac sodium using Neem and Almond gums. The study employs a Box-Behnken statistical design for systematic optimization, correlating formulation variables with key responses such as particle size and entrapment efficiency.

1.5. Objectives of the Study

1. To modify Neem and Almond gums chemically using glutaraldehyde and epichlorohydrin.
2. To develop hydrogel microspheres of diclofenac sodium using the modified natural gums.
3. To optimize the formulation parameters (polymer concentration, crosslinker concentration, and drug loading) using Box–Behnken Design (BBD).
4. To characterize the prepared microspheres using FTIR, DSC, XRD, SEM, and Zeta potential analysis.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 544-552 | ISSN:2251-6727

5. To evaluate in vitro drug release kinetics, in vivo anti-inflammatory efficacy, and stability of the optimized formulation.

2. Materials and Methods

2.1 Materials

Drug and Natural Polymers:

Diclofenac sodium was used as the model drug. Almond gum (Terminalia catappa) and Neem gum (Azadirachta indica) were procured.[6]

Crosslinking Agents and Reagents:

Analytical-grade glutaraldehyde (25%) and epichlorohydrin (Loba Chemie, India) were used for chemical modification of gums. Other chemicals included sodium hydroxide (NaOH), dimethyl sulfoxide (DMSO), phosphate buffer saline (PBS, pH 7.4), n-octanol, and ethanol were used.[7]

Instruments and Equipment:

- **FTIR Spectrophotometer:** Perkin Elmer Spectrum RX-1
- **DSC Analyzer:** SETLINE DSC+
- **XRD System:** PANalytical X'Pert PRO
- **SEM:** ZEISS EVO LS10
- **Zetasizer Nano ZS:** Malvern Instruments
- **UV–Visible Spectrophotometer:** Shimadzu UV-1800
- **Brookfield Viscometer:** DV-II+ Pro
- **Dissolution Apparatus (USP II):** Electrolab TDT-08L
- **Design-Expert® Software:** Version 13 (Stat-Ease, USA) for statistical optimization.

2.2. Natural Gums

2.2.1. Neem Gum

Neem gum was procured and authenticated from NISCAIR.

2.2.2. Almond Gum

Almond gum was procured and authenticated from NISCAIR.

2.3. Chemical Modification of Natural Gums

To improve mechanical properties and control swelling, the natural gums were chemically crosslinked using glutaraldehyde and epichlorohydrin.

Procedure:

1. **Preparation of Gum Solution:**

   A 2% w/v aqueous solution of each gum was prepared under continuous stirring.

2. **pH Adjustment:**

   The pH was adjusted to **8.0** using **1N NaOH**, creating favorable conditions for crosslinking.

3. **Addition of Crosslinker:**

   To the alkaline gum solution, glutaraldehyde (25%) was added dropwise while stirring.

4. **Crosslinking Reaction:**

   The reaction mixture was maintained at 50°C for 3 hours under constant stirring.

5. **Neutralization and Washing:**

   After the reaction, the solution was cooled, neutralized, and filtered. The residue was washed repeatedly with distilled water to remove unreacted reagents.

6. **Drying:**

   The modified gum was dried in a hot air oven at **50°C** until constant weight and stored in a desiccator.

Chemical Mechanism:

The aldehyde groups of glutaraldehyde form acetal bridges with hydroxyl groups on the gum polysaccharides, resulting in increased crosslink density and mechanical strength. This modification converts the naturally water-soluble gum into a hydrogel-forming polymer suitable for sustained drug release.[8]

Journal of Chemical Health Risks
www.jchr.org
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2.4. Characterization of Natural and Modified Gums

2.4.1. Fourier Transform Infrared (FTIR) Spectroscopy

FTIR analysis (4000–400 cm^{-1}) was performed using the KBr pellet method. The spectra of natural and modified gums were compared to confirm chemical modification.

- **Characteristic bands observed:**

  - Broad –OH stretching: 3200–3600 cm^{-1}
  - C–H stretching: 2900 cm^{-1}
  - New C=O and C=N peaks (post-modification): 1719–1601 cm^{-1}
    These shifts confirmed successful crosslinking reactions between glutaraldehyde and hydroxyl groups of the gums.

2.4.2. Differential Scanning Calorimetry (DSC)

Thermal behavior was analyzed using 5 mg of sample, heated at 10°C/min from 30°C to 300°C under nitrogen purge (50 mL/min). The modified gums exhibited higher thermal stability with broadened endothermic peaks, indicating stronger molecular interactions and reduced crystallinity.

2.4.3. X-Ray Diffraction (XRD)

XRD was carried out at 2θ = 5°–80°, using Cu Kα radiation (λ = 1.5406 Å).
The natural gums displayed sharp crystalline peaks, while the modified gums showed diffused peaks, confirming partial amorphization — an indicator of enhanced swelling and drug entrapment capacity.

2.4.4. Viscosity Measurement

The viscosity of 1% w/v gum solution was measured using a Brookfield viscometer at 25°C ± 0.5°C, spindle no. 2, varying shear rates (rpm). Results indicated a non-Newtonian pseudoplastic flow, ideal for controlled-release formulation.

2.4.5. Swelling Index

The swelling index was determined gravimetrically by immersing 100 mg of the dried gum in phosphate buffer (pH 7.4) at 37°C. The samples were weighed at predetermined time intervals (0.5–24 h).

2.5. Formulation of Diclofenac Sodium Hydrogel Microspheres

Hydrogel microspheres were prepared by the emulsion polymerization method, as it allows fine control over particle size and encapsulation efficiency.

Procedure:

1. The modified gum (5% w/v) was dissolved in distilled water under stirring.
2. Diclofenac sodium was dissolved separately in DMSO and added to the polymer solution.
3. The mixture was emulsified at 15,000 rpm using a high-speed homogenizer for 4 hours.
4. Microspheres formed were collected by filtration, washed with water to remove unbound drug, and dried at 50°C.
5. Dried microspheres were stored in airtight vials for further testing.

2.6. Optimization of Formulation Variables

A Box–Behnken Design (BBD) with three factors and three levels was employed to optimize formulation variables using Design-Expert® software.

Variable	Symbol	Levels (Low, Medium, High)
Polymer concentration (% w/v)	A	1, 3, 5
Crosslinker concentration (% v/v)	B	0.5, 1.0, 1.5
Drug loading (% w/w)	C	10, 15, 20

Dependent responses measured:

- **Y_1:** Particle size (µm)
- **Y_2:** Entrapment efficiency (%)

A total of 15 experimental runs were generated. The polynomial equation obtained was analyzed for significance using ANOVA, and 3D response surface

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 544-552 | ISSN:2251-6727

plots were generated to visualize interactions between factors.

2.7. Evaluation of Hydrogel Microspheres

2.7.1. Particle Size Analysis

Particle size distribution was determined using Malvern Mastersizer 3000 (laser diffraction). Mean diameter (D50) was recorded for each batch.

2.7.2. Surface Morphology

Surface structure was analyzed using SEM. Microspheres were gold-coated and observed at magnifications of 500× and 1000×. Smooth and spherical morphology indicated optimal crosslinking and stability.

2.7.3. Zeta Potential

Zeta potential was measured at 25°C using Zetasizer Nano ZS to assess colloidal stability. A value of −35 mV confirmed good electrostatic repulsion, preventing aggregation.

2.7.4. Entrapment Efficiency

100 mg microspheres were dissolved in ethanol: phosphate buffer (70:30 v/v), sonicated, filtered, and analyzed at λmax = 223 nm by UV spectrophotometry. The optimized batch showed ~85% entrapment efficiency.

2.7.5. Swelling Index and Water Uptake

Swelling behavior was tested in PBS (pH 7.4) at 37°C for 24 hours to assess hydration capacity, a key factor for sustained release.

2.8. In Vitro Drug Release Study

Drug release was studied using USP II dissolution apparatus in phosphate buffer (pH 7.4) at 37 ± 0.5°C and 50 rpm. Samples (5 mL) were withdrawn at fixed intervals (0.5–24 h), replaced with fresh buffer, and analyzed at 223 nm.

Release data were fitted to Zero-order, Higuchi, and Korsmeyer–Peppas models.
The best-fit model was Korsmeyer–Peppas ($R^2 = 0.9889$, $n = 0.62$), indicating anomalous non-Fickian transport.

2.9. In Vivo Anti-Inflammatory Study

Animal Model: Wistar rats (8–12 weeks, 150–200 g) were divided into six groups (n = 6 per group).

Group	Treatment
G1	Normal Control
G2	Carrageenan Control
G3	Marketed Diclofenac Gel
G4	Diclofenac–Neem Gel
G5	Diclofenac–Almond Gel
G6	Optimized Hydrogel Formulation

Inflammation was induced using 0.1 mL carrageenan (1.2% w/v) in the hind paw. Test formulations were applied topically immediately after injection. Paw edema was measured using a Vernier caliper at regular intervals up to 24 hours. Ethical approval was obtained from the Institutional Animal Ethics Committee (IAEC), and procedures followed CPCSEA guidelines.

2.10. Stability Studies

Stability testing was conducted per ICH Q1A (R2) at two storage conditions for 3 months:

Condition	Temperature / RH	Duration
Accelerated	40°C ± 2°C / 75% ± 5% RH	3 months
Ambient	25°C ± 2°C / 60% ± 5% RH	3 months

Parameters monitored:

- Physical appearance
- Entrapment efficiency (%)
- Drug content (%)
- In vitro release profile

The optimized formulation retained >96% drug content and >81% entrapment efficiency at 3 months, indicating strong physical and chemical stability.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 544-552 | ISSN:2251-6727

3. Results and Discussion

3.1. Characterization of Natural and Modified Gums

3.1.1. Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of both Neem and Almond gums (before and after modification) provided strong evidence of successful crosslinking with glutaraldehyde and epichlorohydrin.

- Native gums displayed characteristic absorption peaks at 3340 cm^{-1} (O–H stretching), 2910 cm^{-1} (C–H stretching) — confirming their polysaccharide nature.
- Modified gums exhibited new absorption peaks around 1730 cm^{-1} (C=O stretching of aldehyde) and 1619 cm^{-1} (C=N stretching). The emergence of these bands confirmed the formation of acetal and imine linkages, resulting from interactions between the aldehyde groups of glutaraldehyde and hydroxyl groups of the gums.

This chemical modification improved polymer rigidity and reduced solubility, creating a matrix capable of sustaining drug release.

Inference: FTIR confirmed the successful chemical modification and crosslinking of both natural gums, essential for forming stable hydrogel microspheres.

3.1.2. Differential Scanning Calorimetry (DSC)

The thermal behavior of natural and modified gums was analyzed to evaluate changes in crystallinity and stability.

- **Natural Almond gum** showed a sharp endothermic peak at ~110°C, corresponding to moisture loss and crystalline melting.
- **Modified Almond gum** exhibited a broader endothermic peak at ~145°C with reduced intensity, suggesting increased amorphousness and thermal stability due to crosslinking.
- **Neem gum** showed a similar pattern, with the modified sample demonstrating higher glass transition temperature (Tg) compared to the native form.

Inference: Crosslinking enhanced the thermal stability and structural rigidity of both gums, indicating the formation of a stable, amorphous polymeric matrix suitable for controlled drug delivery.

3.1.3. X-Ray Diffraction (XRD) Analysis

The XRD diffractograms of natural gums exhibited **distinct crystalline peaks** between 2θ = 15°–30°, reflecting semi-crystalline nature. After modification, these peaks became broad and diffused, confirming a transition from crystalline to amorphous structure.

Amorphous matrices facilitate enhanced swelling and diffusion-controlled release, making them ideal for sustained drug delivery.

Inference: The reduction in crystallinity supports improved hydration and diffusion capacity of modified gums in aqueous environments.

3.1.4. Viscosity and Swelling Index

The viscosity of natural and modified gums was measured using a Brookfield viscometer. Modified gums showed slightly higher viscosity due to crosslinking, contributing to slower erosion and more sustained release.

Swelling index studies revealed that the modified gums absorbed 2.3–2.8 times their dry weight in water over 24 hours, compared to ~1.5 times for native gums. This increased swelling confirmed that crosslinking improved network formation without compromising hydration ability.

Inference: Balanced swelling and viscosity indicate that the modified gums have ideal viscoelastic properties for hydrogel formation.

3.2. Optimization of Formulation Variables

A **Box–Behnken Design (BBD)** was used to optimize formulation parameters influencing particle size and entrapment efficiency. The design generated 15 experimental runs with polymer concentration (A), crosslinker concentration (B), and drug loading (C) as independent variables.

Journal of Chemical Health Risks
www.jchr.org
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3.2.1. Statistical Model and Fit Summary

ANOVA results showed the model was highly significant ($p < 0.05$) with $R^2 = 0.987$ for particle size and $R^2 = 0.981$ for entrapment efficiency. The lack-of-fit was non-significant, confirming that the model fit the experimental data well.

3.2.2. Effect of Variables

- **Polymer concentration (A):** Directly proportional to both particle size and entrapment efficiency — higher gum concentration increased matrix density and encapsulation.
- **Crosslinker concentration (B):** Increased crosslinking improved stability but excessively high levels reduced drug loading due to matrix tightening.
- **Drug loading (C):** At moderate levels, entrapment improved, but beyond saturation, drug loss occurred during emulsification.

3.2.3. 3D Response Surface Analysis

- The 3D surface and contour plots clearly depicted a "sweet spot" region — an optimal balance where both particle size (~115 µm) and entrapment efficiency (~85%) were maximized.
- Increasing polymer concentration beyond 5% and crosslinker beyond 1.5% led to reduced encapsulation, emphasizing the need for optimization balance.

Inference: The Box–Behnken design effectively identified critical variable interactions, resulting in a statistically validated optimized formulation.

3.3. Evaluation of Optimized Hydrogel Microspheres

3.3.1. Particle Size and Morphology

The optimized microspheres exhibited a mean particle size of 115.3 ± 2.8 µm with a narrow size distribution (PDI = 0.21), confirming uniformity. SEM images showed smooth, spherical, and porous microspheres, indicating controlled crosslinking and good polymer distribution. Porous surfaces promote water diffusion and swelling — crucial for controlled release behavior.

3.3.2. Zeta Potential

The optimized batch displayed a zeta potential of −35.2 mV, suggesting strong electrostatic repulsion and high colloidal stability. Negative potential was attributed to free hydroxyl and carboxyl groups present in the polysaccharide backbone.

Inference: The formulation is electrostatically stable and resistant to aggregation during storage.

3.3.3. Entrapment Efficiency

Entrapment efficiency of the optimized formulation was 85.2 ± 1.5%, which demonstrates minimal drug loss during processing. Higher polymer concentration led to increased encapsulation, as the viscous matrix reduced drug diffusion into the continuous phase during emulsification.

3.4. In Vitro Drug Release Study

The cumulative drug release from the optimized hydrogel microspheres was ~85.3% at 24 hours, exhibiting a sustained-release pattern with an initial moderate burst followed by steady diffusion.

Kinetic model fitting showed:

Model	R^2 Value	Mechanism
Zero-order	0.943	Constant drug release
Higuchi	0.975	Diffusion-controlled
Korsmeyer–Peppas	**0.9889**	Anomalous (non-Fickian) diffusion

An n-value of 0.62 in the Korsmeyer–Peppas model indicated anomalous transport, meaning both polymer relaxation (swelling) and diffusion governed the release process.

Inference: The optimized hydrogel microspheres effectively achieved controlled drug diffusion over 24 hours, confirming suitability for sustained-release applications.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 544-552 | ISSN:2251-6727

3.5. In Vivo Anti-Inflammatory Evaluation

In vivo studies on Wistar rats revealed that the hydrogel microsphere gel exhibited significant anti-inflammatory activity.

- At 3 hours, paw edema inhibition was 46.8%, increasing to 73.2% at 24 hours, comparable to the marketed diclofenac gel (74.5%).
- The sustained effect demonstrated prolonged drug retention at the site of application, reducing inflammation effectively.

No erythema, irritation, or allergic response was observed in any treatment group, confirming the biocompatibility of the natural gum-based system.

Inference: The hydrogel microsphere formulation provided a comparable anti-inflammatory effect to commercial gel while maintaining longer therapeutic action.

3.6. Stability Studies

The optimized batch retained **>96% drug content** and **>81% entrapment efficiency** after 3 months under accelerated and ambient conditions. Physical appearance remained unchanged except slight color darkening at 40°C due to Maillard-type interactions between polysaccharides and trace impurities. Drug release profiles remained consistent with <3% variation, confirming excellent physicochemical and kinetic stability.

Inference: The hydrogel microsphere formulation is robust, thermally stable, and storage-stable under ICH conditions.

3.7. Mechanistic Insight

The sustained-release mechanism can be attributed to:

1. **Crosslinked polymer matrix:** Reduced erosion and maintained integrity.
2. **Controlled swelling:** Regulated water penetration and drug diffusion.
3. **Dual transport mechanism:** Combined polymer relaxation and Fickian diffusion ensured smooth, extended release without burst effect.

4. Conclusion

The present investigation successfully demonstrated the formulation, development, optimization, and evaluation of sustained-release hydrogel microspheres of diclofenac sodium utilizing Almond and Neem gums as natural polymeric carriers. Through systematic chemical modification and crosslinking using glutaraldehyde and epichlorohydrin, both gums were transformed into robust hydrogel matrices capable of regulating water uptake and modulating drug diffusion. The FTIR, DSC, and XRD analyses confirmed successful structural modification and crosslinking, enhancing thermal stability and reducing crystallinity — essential for controlled release. The Box–Behnken Design (BBD) provided a scientific framework to optimize formulation parameters, yielding a statistically significant model ($R^2 > 0.98$). The optimized batch exhibited a particle size of ~115 µm, entrapment efficiency of ~85%, and an in vitro sustained release (~85.3% over 24 h) following Korsmeyer–Peppas kinetics ($R^2 = 0.9889$, $n = 0.62$). The in vivo anti-inflammatory study in Wistar rats revealed that the hydrogel system achieved a therapeutic effect comparable to the marketed diclofenac gel, while providing prolonged anti-inflammatory action and improved bioavailability. Furthermore, stability studies confirmed excellent physicochemical stability under ICH conditions, establishing the long-term integrity of the optimized system. Thus, the developed Neem–Almond gum hydrogel microsphere system can be regarded as a promising, eco-friendly, biocompatible, and cost-effective platform for sustained delivery of NSAIDs like diclofenac sodium. This formulation offers potential benefits in reducing dosing frequency, improving patient compliance, and minimizing side effects, aligning with the principles of green pharmacy and sustainable therapeutics.

5. Future Scope

1. **Scale-up and industrial feasibility:** Further studies should focus on pilot-scale manufacturing and evaluating reproducibility under GMP conditions.
2. **Bioavailability studies:** Pharmacokinetic profiling and bioavailability comparison with conventional diclofenac formulations will provide quantitative insights into absorption enhancement.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(1), 544-552 | ISSN:2251-6727

3. **Alternative drug encapsulation:** The same hydrogel system can be adapted for other drugs requiring sustained release, such as ibuprofen, naproxen, or ketoprofen.
4. **Molecular modeling and crosslinking kinetics:** Computational studies could further elucidate the mechanism of crosslinking and drug–polymer interactions.

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