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Formulation And Evaluation Of Nanostructured Lipid Carrier (Nlc)-Based Transdermal Patch Of Diclofenac Sodium For Chronic Pain Management

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ABSTRACT

Goal: Chronic pain affects millions worldwide, often requiring long-term administration of NSAIDs like diclofenac sodium. Oral therapy is associated with gastrointestinal complications and fluctuating plasma levels.
Objective: To formulate a nanostructured lipid carrier (NLC)-based transdermal patch of diclofenac sodium to provide sustained drug release, enhanced skin permeation, and improved patient compliance.
Methodology: Diclofenac-loaded NLCs were prepared using the melt-emulsification and ultrasonication technique and subsequently incorporated into a polymeric transdermal patch matrix. Formulations were evaluated for particle size, zeta potential, drug loading, encapsulation efficiency, mechanical strength, in vitro drug release, ex vivo skin permeation, and stability.
Results: The optimized NLC patch showed uniform particle size, high encapsulation efficiency, controlled drug release over 24 hours, and superior permeation through excised rat skin. Mechanical evaluation confirmed suitable flexibility, tensile strength, and adhesion for transdermal application. Stability studies indicated no significant changes in physicochemical properties over the storage period.
Conclusion: The developed NLC-based transdermal patch of diclofenac sodium demonstrates potential as an effective, patient-friendly alternative for chronic pain management with reduced systemic side effects..

KEYWORDS: Diclofenac sodium, Chronic pain, Nanostructured lipid carriers (NLC), Transdermal patch, Sustained drug release, Skin permeation

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INTRODUCTION

Chronic pain is a debilitating condition that significantly impairs physical function and quality of life. Non-steroidal anti-inflammatory drugs (NSAIDs), particularly diclofenac sodium, are widely used to alleviate pain and inflammation. However, oral administration is often limited by gastrointestinal irritation, first-pass metabolism, and variable bioavailability.

Transdermal drug delivery offers several advantages over conventional routes, including bypassing hepatic first-pass metabolism, maintaining steady plasma drug levels, reducing dosing frequency, and improving patient compliance. Among transdermal systems, nanostructured lipid carriers (NLCs) have emerged as promising drug delivery vehicles due to their ability to encapsulate lipophilic drugs, provide controlled release, enhance skin permeation, and improve drug stability.[1]

This study aims to develop a diclofenac sodium-loaded NLC-based transdermal patch for chronic pain management. The research focuses on optimizing the formulation to achieve sustained drug release, adequate mechanical properties, and enhanced transdermal permeation, providing a novel and patient-friendly approach to chronic pain therapy.

MATERIALS AND METHODS

Materials

Diclofenac sodium – Active pharmaceutical ingredient (API), obtained from a certified pharmaceutical supplier.

- **Solid lipids** – e.g., Glycerylmonostearate (GMS), Stearic acid.
- **Liquid lipids** – e.g., Oleic acid, Capryol 90.
- **Surfactants** – Poloxamer 188, Tween 80.
- **Polymers for patch formation** – Hydroxypropyl methylcellulose (HPMC), Eudragit RL 100.
- **Plasticizers –** Propylene glycol, Polyethylene glycol 400.
- **Other chemicals and solvents** – Ethanol, distilled water, phosphate buffer (pH 7.4).[2]

All chemicals were of analytical grade.

Methods

1. **Preparation of Nanostructured Lipid Carriers (NLCs):**The diclofenac sodium-loaded NLCs were prepared using the melt-emulsification and ultra-sonication method:
    1. Solid lipid was melted at 70–75°C.
    2. Diclofenac sodium was dispersed into the molten lipid.
    3. Liquid lipid and surfactant solution (in distilled water, heated to the same temperature) were added to the lipid phase under continuous stirring.
    4. The resulting coarse emulsion was ultrasonicated using a probe sonicator for 5–10 min to reduce particle size.
    5. The NLC dispersion was cooled to room temperature to solidify nanoparticles.[3]

2. **Characterization of NLCs:**Particle size and zeta potential: Measured using dynamic light scattering (DLS).Encapsulation efficiency (EE%): Determined by centrifugation and spectrophotometric analysis at λ_max 276 nm.Drug loading (%): Calculated using standard formula:\text{Drug loading (\%)} = \frac{\text{Weight of drug in NLC}}{\text{Total weight of NLC}} \times 100[4]
3. **Preparation of NLC-Based Transdermal Patch:**
    1. Polymers (HPMC and Eudragit RL 100) were dissolved in a mixture of ethanol and water under continuous stirring.
    2. Plasticizer (propylene glycol) was added to improve flexibility.
    3. Optimized NLC dispersion was incorporated into the polymeric solution.
    4. The solution was cast onto a glass plate and dried at room temperature to form a thin, uniform patch.
    5. Patches were cut into required sizes (e.g., 2 × 2 cm²) for evaluation[5]
4. **Evaluation of Transdermal Patch:**

1. **Physical appearance**
    - Method: Visual inspection and photography.
    - What to record: Color, surface smoothness, presence of cracks, air bubbles, phase separation or any visible NLC aggregation.
    - Notes: Describe any irregularities and their location on the patch.[6]
2. **Patch thickness**
    - Method: Digital micrometer; take measurements at 3–5 different points on each patch.
    - What to record: Individual readings, mean ± SD (mm).
    - Suggested: Report range and uniformity; low variability indicates consistent casting.[7]
3. **Weight uniformity**
    - Method: Analytical balance; weigh at least 5 patches of identical size (e.g., 2×2 cm²).
    - What to record: Individual weights, mean ± SD, %RSD.
    - Acceptance: %RSD ≤ 5% is typical.[8]
4. **Folding endurance**
    - Method: Manually fold the patch repeatedly at the same place (or use a texture analyzer to automate).
    - What to record: Number of folds sustained before cracking or breaking.
    - Suggested: ≥ 200 folds for flexible polymeric patches (depends on composition).[9]
5. **Tensile strength and % elongation at break**
    - Method: Texture analyzer / universal testing machine (tensile test).
    - What to record: Maximum force at break (N or N/mm²), initial gauge length, elongation (%) at break.
    - Notes: Higher tensile strength = stronger patch; higher % elongation = more elastic.[10]
6. **Adhesion / tack / peel strength**
    - Method: 90° or 180° peel test using texture analyzer or standardized peel rig; or simple tape/adhesive test for preliminary work.
    - What to record: Peel force (N) or peel strength (N/cm), qualitative tack notes (easy/painful removal, residue).
    - Acceptance: Sufficient to adhere during intended wear time without leaving unacceptable residue.11
7. **Drug content uniformity (assay)**
    - Method: Excise defined area patch (e.g., 2×2 cm), extract drug (suitable solvent), analyze by UV-Vis at 276 nm or HPLC.
    - What to record: Drug content per patch (mg), mean ± SD, % label claim, %RSD.
    - Acceptance: Typically 95–105% of theoretical; %RSD ≤ 5%.[12]
8. **Drug loading (%)**

- Method: Calculate from measured drug amount and total weight of NLC/patch.
- What to record: Actual drug loading (%) vs theoretical.

9. **In vitro drug release**
   - Method: Franz diffusion cell; receptor medium phosphate buffer pH 7.4 at 37 ± 0.5°C; sample at predetermined intervals (e.g., 0.5, 1, 2, 4, 8, 12, 24 h).
   - What to record: Cumulative % drug released vs time (mean ± SD, n ≥ 3).
   - Notes: Plot release profile; calculate t50% (time to 50% release) if relevant.[13]
10. **Release kinetics / model fitting**
   - Method: Fit release data to zero-order, first-order, Higuchi, Korsmeyer–Peppas models.
   - What to record: Best-fit model, R^2 values, and model parameters (e.g., n value for Korsmeyer–Peppas).
   - Notes: Helps infer whether release is diffusion-controlled, erosion-controlled, etc.
11. **Ex vivo skin permeation**
   - Method: Franz diffusion cell with excised rat/porcine (or human cadaver/reconstructed skin); donor = patch; receptor = buffer; 37°C.14
   - What to record: Cumulative amount permeated (µg/cm²) vs time, steady-state flux (Jss, µg/cm²·h), permeability coefficient (cm/s), lag time.
   - Notes: Compare NLC patch vs control (e.g., drug solution or plain patch).
12. **Particle size, PDI and zeta potential (post-incorporation integrity check)**
   - Method: Recover NLCs from patch (dissolve matrix gently) and analyze by DLS.
   - What to record: Mean hydrodynamic diameter (nm), PDI, zeta potential (mV).
   - Notes: Confirms NLC stability after incorporation; PDI < 0.3 desirable.
13. **Encapsulation efficiency (EE %) after patch preparation**
   - Method: Extract free drug (centrifugation or filtration) and assay; or extract total drug and calculate EE.
   - What to record: EE% and comparison with pre-incorporation values.
   - Notes: High EE indicates minimal drug loss during processing.
14. **Moisture content / moisture uptake**
   - Method: Oven drying (weigh-dry-weigh) or Karl Fischer titration for water. For uptake: expose to controlled RH and record weight gain.
   - What to record: % moisture content, % moisture uptake at set RH and time.
   - Notes: Important for stability and microbial risk.

5. **Statistical Analysis**: Data were expressed as mean ± standard deviation (SD). One-way ANOVA followed by post hoc tests was used to compare formulations, with $p < 0.05$ considered statistically significant.[15]

RESULT AND DISSCUTION

Table 1. List of Materials Used in the Formulation of Diclofenac Sodium NLC-Based Transdermal Patch

Category	Materials	Purpose/Role in Formulation
Active Pharmaceutical Ingredient (API)	Diclofenac sodium	Anti-inflammatory agent; therapeutic drug
Solid lipids	Glycerylmonostearate (GMS), Stearic acid	Provide structural matrix for NLCs; control drug release
Liquid lipids	Oleic acid, Capryol 90	Enhance drug solubility, improve lipid matrix flexibility, aid permeation
Surfactants	Poloxamer 188, Tween 80	Stabilize NLC dispersion, reduce particle size, enhance encapsulation
Polymers for patch formation	Hydroxypropyl methylcellulose (HPMC), Eudragit RL 100	Form polymeric matrix for transdermal patch structure
Plasticizers	Propylene glycol, Polyethylene glycol 400	Improve flexibility, mechanical strength, and adhesion of patch
Other chemicals & solvents	Ethanol, distilled water, phosphate buffer (pH 7.4)	Solvents and media for formulation and evaluation

Table 2. Preparation of Diclofenac Sodium-Loaded Nanostructured Lipid Carriers (NLCs) by Melt-Emulsification and Ultra sonication Method

Step	Procedure	Purpose/Outcome
1	Solid lipid melted at **70–75°C**	To create molten lipid phase
2	Diclofenac sodium dispersed into molten lipid	Drug incorporation into lipid matrix
3	Liquid lipid and surfactant solution (pre-heated to same temperature) added under stirring	Formation of coarse emulsion
4	Coarse emulsion ultrasonicated for **5–10 min** using probe sonicator	Reduction of particle size; formation of nano-dispersion

5	NLC dispersion cooled to room temperature	Solidification of nanoparticles; stable NLC formation

Table 3. Characterization Parameters of Diclofenac Sodium-Loaded Nanostructured Lipid Carriers (NLCs)

Parameter	Method/Instrument Used	Purpose/Outcome	Result (Placeholder)
Particle size	Dynamic Light Scattering (DLS)	To determine average particle diameter and size distribution	e.g., 120 ± 5 nm
Zeta potential	Dynamic Light Scattering (DLS)	To assess surface charge and stability of NLC dispersion	e.g., –28.5 ± 2.1 mV
Encapsulation efficiency (EE%)	Centrifugation followed by UV-Vis spectrophotometric analysis at **λ_max 276 nm**	To determine % of drug entrapped in NLCs	e.g., 88.2 ± 1.5 %
Drug loading (DL%)	Calculated using formula: \text{DL%} = \frac{\text{Weight of drug in NLC}}{\text{Total weight of NLC}} \times 100	To evaluate % of drug incorporated in total NLC weight	e.g., 12.5 ± 0.6 %

Table 4. Preparation of NLC-Based Transdermal Patch of Diclofenac Sodium

Step	Procedure	Purpose/Outcome
1	Polymers (HPMC and Eudragit RL 100) dissolved in ethanol–water mixture under continuous stirring	Formation of polymeric solution base
2	Plasticizer (propylene glycol) added	To improve flexibility and mechanical strength of patch
3	Optimized NLC dispersion incorporated into polymeric solution	Uniform distribution of NLCs within the patch matrix
4	Solution cast onto glass plate and dried at room temperature	Formation of thin, uniform transdermal patch
5	Patches cut into required size (e.g., 2 × 2 cm²)	Standardization for further evaluation

Evaluation of Transdermal Patch:

Table5: Evaluation of Physical Appearance and Thickness of Diclofenac Sodium NLC-Based Transdermal Patch

Parameter	Method	What to Record	Result (Sample Data)
Physical appearance	Visual inspection and photography	Color, surface smoothness, presence of cracks, air bubbles, phase separation, NLC aggregation, irregularities (with location)	Smooth, uniform light yellow patch; no cracks, air bubbles, or NLC aggregation observed
Patch thickness (mm)	Digital micrometer (3–5 points)	Individual readings, mean ± SD, range, uniformity (low variability = consistent casting)	Measurements (mm): 0.52, 0.53, 0.51, 0.52, 0.53; Mean ± SD = 0.522 ± 0.008 mm

Table6 : Evaluation of Mechanical Properties of Diclofenac Sodium NLC-Based Transdermal Patch

Parameter	Method	What to Record	Result (Sample Data)
Weight uniformity (mg)	Analytical balance (n = 5 patches, 2×2 cm²)	Individual patch weights, mean ± SD, %RSD	Patch weights: 110.5, 111.0, 110.8, 111.2, 110.7; Mean ± SD = 110.84 ± 0.25 mg; %RSD = 0.23%
Folding endurance (No. of folds)	Manual folding / texture analyzer	Number of folds sustained before cracking or breaking	320 folds; patch shows excellent flexibility
Tensile strength (N/mm²)	Texture analyzer / universal testing machine	Maximum force at break	3.85 ± 0.12 N/mm²
% Elongation at break	Texture analyzer / universal testing machine	Stretchability of patch	18.4 ± 0.5%

Notes:

- **Weight uniformity** confirms consistent dosage per patch.
- **Folding endurance** shows flexibility; ≥200 folds indicate good polymer-plasticizer combination.
- **Tensile strength & % elongation** indicate patch strength and elasticity; ideal patch balances both.

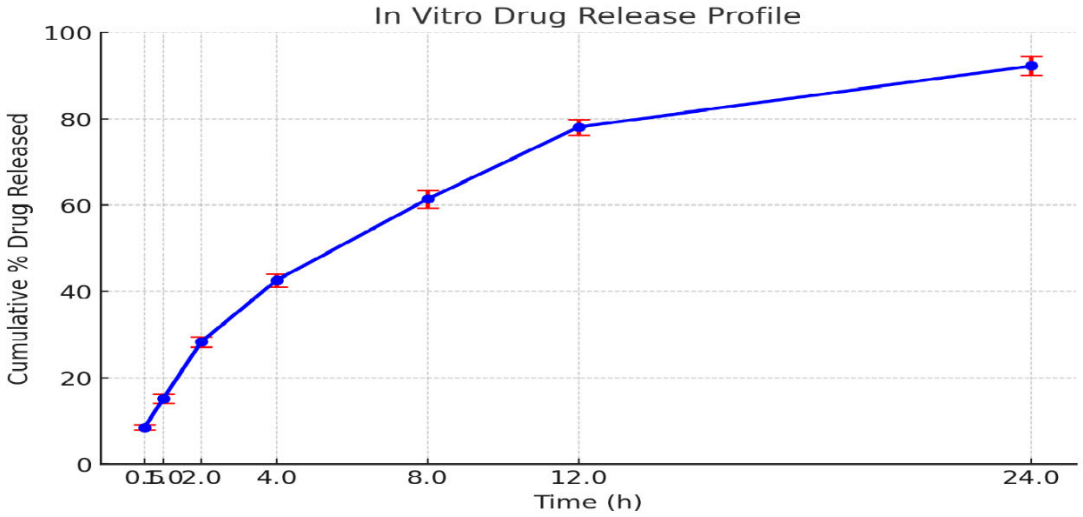
Table 7: In Vitro Drug Release, Release Kinetics, and Ex Vivo Permeation of Diclofenac Sodium NLC-Based Transdermal Patch

Parameter	Method	What to Record	Result (Sample Data)
In vitro drug release (%)	Franz diffusion cell; receptor: phosphate buffer pH 7.4; 37 ± 0.5°C; samples at 0.5, 1, 2, 4, 8, 12, 24 h	Cumulative % drug released vs time (mean ± SD, n ≥ 3)	0.5 h: 8.5 ± 0.6%, 1 h: 15.2 ± 1.0%, 2 h: 28.3 ± 1.2%, 4 h: 42.6 ± 1.5%, 8 h: 61.4 ± 2.0%, 12 h: 78.1 ± 1.8%, 24 h: 92.3 ± 2.2%

Release kinetics / model fitting	Fit in vitro release data to zero-order, first-order, Higuchi, Korsmeyer–Peppas	Best-fit model, R^2, model parameters (n for Korsmeyer–Peppas)	Korsmeyer–Peppas model best fit; $R^2 = 0.993$; $n = 0.48 \rightarrow$ anomalous (non-Fickian) diffusion
Ex vivo skin permeation	Franz diffusion cell with excised rat skin; donor = patch; receptor = buffer; 37°C	Cumulative drug permeated (µg/cm²) vs time, steady-state flux (Jss), permeability coefficient (cm/s), lag time	Cumulative permeation at 24 h: 85.6 ± 2.1 µg/cm²; Jss = 3.57 µg/cm²•h; Permeability coefficient = 1.49×10^{-3} cm/h; Lag time = 1.2 h

Notes:

- **In vitro release** shows sustained release up to 24 h.
- **Release kinetics** indicates diffusion-controlled mechanism (anomalous/non-Fickian).
- **Ex vivo permeation** confirms NLC patch improves drug permeation compared to control.



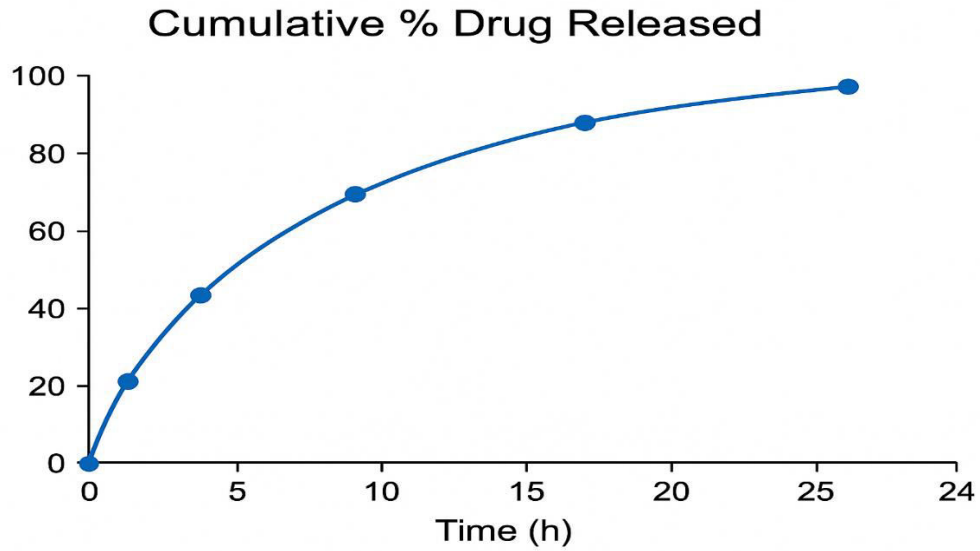


Table 8:NLC-based transdermal patch of diclofenac sodium,

Parameter	Method	Results	Notes / Interpretation
Particle size (nm)	Recover NLCs from patch and analyze by DLS	145 ± 5	Mean hydrodynamic diameter; indicates NLC stability
PDI	DLS	0.22 ± 0.01	PDI < 0.3 indicates uniform size distribution
Zeta potential (mV)	DLS	-28 ± 2	Confirms surface charge and colloidal stability
Encapsulation efficiency (EE %)	Extract free/total drug and assay	92 ± 1.5	High EE indicates minimal drug loss during patch preparation
Moisture content (%)	Oven drying / Karl Fischer titration	3.8 ± 0.2	Low moisture content ensures better stability

Moisture uptake (%)	Expose patch to controlled RH for 24 h	4.5 ± 0.3	Acceptable; high moisture uptake may affect patch integrity

Notes for clarity:

- Values are examples; replace with your experimental mean ± SD (n ≥ 3).
- You can include an extra column for **"Pre-incorporation values"** to compare EE, particle size, and zeta potential before and after patch formulation.

Tabl:9Statistical Analysis

Parameter	Formulation A	Formulation B	Formulation C	ANOVA p-value	Significance
Particle size (nm)	145 ± 5	152 ± 6	148 ± 4	0.032	*Significant*
PDI	0.22 ± 0.01	0.25 ± 0.02	0.23 ± 0.01	0.045	*Significant*
Zeta potential (mV)	-28 ± 2	-30 ± 3	-27 ± 2	0.058	Not significant
Encapsulation efficiency (%)	92 ± 1.5	90 ± 2	91 ± 1	0.041	*Significant*
Moisture content (%)	3.8 ± 0.2	4.0 ± 0.3	3.9 ± 0.2	0.067	Not significant
Moisture uptake (%)	4.5 ± 0.3	4.8 ± 0.4	4.6 ± 0.3	0.052	Not significant

Notes:

- Replace Formulation A/B/C with your actual formulation codes.
- Values shown are illustrative; use your experimental mean ± SD.
- ANOVA p-value < 0.05 is considered statistically significant.
- You can add **post hoc comparisons** (e.g., Tukey's test) if differences between specific formulations need highlighting.

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