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DESIGN AND CHARACTERIZATION OF HYALURONIC ACID-EMBEDDED TRANSDERMAL MICRONEEDLE SYSTEM FOR OSTEOARTHRITIS MANAGEMENT

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ABSTRACT

Osteoarthritis (OA) is a chronic, degenerative joint disorder characterized by progressive cartilage erosion, joint pain, stiffness, and inflammation, significantly affecting mobility and quality of life in aging populations. Conventional therapeutic regimens such as oral non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular injections provide symptomatic relief but are often associated with systemic side effects, low patient compliance, and invasive delivery protocols. To address these limitations, the present study explores the development of a novel transdermal microneedle patch (MNP) embedded with hyaluronic acid (HA), a biopolymer known for its viscoelastic, anti-inflammatory, and cartilage-protective properties. The formulation was developed using a combination of HA, polyvinyl alcohol (PVA), and polyvinylpyrrolidone K90 (PVP K90) via a casting and drying method. Comprehensive preformulation studies including solubility profiling, polymer compatibility, viscosity analysis, and pH determination were conducted to guide formulation optimization. The microneedles were evaluated for their morphology, uniformity, mechanical strength, drug-loading efficiency, moisture absorption, and swelling index. Results revealed uniform microneedle geometry, optimal mechanical integrity to penetrate the stratum corneum, and sustained hydration-mediated drug release. The developed HA-based microneedle system presents a minimally invasive, patient-compliant alternative for localized and controlled drug delivery in osteoarthritis therapy. This research underscores the promise of transdermal MNPs as an advanced platform for improving joint health and patient quality

of life.

KEYWORDS: Osteoarthritis, Hyaluronic acid, Microneedle patch, Transdermal delivery, Polyvinyl alcohol.

1. INTRODUCTION

Osteoarthritis (OA) is among the most prevalent degenerative musculoskeletal disorders, particularly affecting the elderly, and is characterized by progressive cartilage degradation, synovial inflammation, joint space narrowing, and chronic pain. The multifactorial pathology of OA, which includes oxidative stress, inflammatory cytokine activation, and matrix metalloproteinase activity, leads to structural joint deterioration and significant functional disability. Despite its high prevalence, current pharmacological treatments—including oral analgesics, NSAIDs, and intra-articular injections—have numerous limitations. Oral therapies often result in systemic adverse effects such as gastrointestinal irritation and hepatic strain, while intra-articular injections can be invasive, painful, and require clinical administration, reducing patient compliance over long-term use.[1-5]

In this context, transdermal drug delivery systems (TDDS) have emerged as a non-invasive alternative that enables direct drug transport across the skin, avoiding first-pass metabolism and maintaining consistent plasma concentrations. Microneedle patches (MNPs), in particular, represent an innovative strategy that integrates the advantages of hypodermic injection and transdermal application. MNPs create microchannels in the skin to enhance permeability without reaching pain nerves or blood vessels, thereby offering a painless, safe, and controlled drug delivery method.[6,7]

Hyaluronic acid (HA), a high-molecular-weight, naturally occurring glycosaminoglycan present in connective tissues and synovial fluid, plays a crucial role in joint lubrication, shock absorption, and inflammatory modulation. Its biocompatibility, biodegradability, and water-retentive characteristics make HA a suitable matrix-forming polymer for MNP fabrication. In OA therapy, HA acts not only as a vehicle but also contributes therapeutically by restoring viscoelasticity and inhibiting inflammatory cascades.[7-12] Combining HA with structural polymers like PVA and PVP enhances microneedle strength, dissolution profile, and drug-loading efficiency.

This study focuses on the formulation and evaluation of a hyaluronic acid-based dissolving

microneedle patch tailored for the transdermal treatment of osteoarthritis. The formulation approach includes methodical preformulation studies, polymeric blend optimization, and fabrication of microneedles through casting. The prepared MNPs are subjected to rigorous evaluation including morphological analysis, mechanical property assessment, hydration capacity, drug permeation, and physicochemical stability to ensure the patch's therapeutic potential and practical applicability in OA management.

2. MATERIALS AND METHODS

2.1 Materials

Pharmaceutical-grade Hyaluronic Acid (HA) was employed as the primary matrix material due to its excellent hydration capacity, viscoelastic nature, and anti-inflammatory properties. Polyvinyl Alcohol (PVA), a high-molecular-weight polymer, was incorporated to enhance the mechanical strength and flexibility of the microneedle matrix. Polyvinylpyrrolidone K90 (PVP K90) acted as a plasticizer and solubilizer, facilitating uniform film formation and rapid dissolution. Glycerol served as both a humectant and plasticizer, contributing to the flexibility and moisture retention of the final formulation. A solvent system consisting of purified water and ethanol was used for polymer dissolution and equipment cleaning. All materials and reagents were of analytical grade and used as received without further purification.

2.2 Methods

2.2.1 Preformulation Studies

1. Solubility & Compatibility

HA, PVA, and PVP K90 were dissolved in purified water at 50–60 °C. Compatibility was assessed visually and via FTIR; the absence of unexpected peaks indicated no polymer–polymer interaction.

2. pH Determination

Polymer solutions were measured with a calibrated digital pH meter. The target pH was 5.5–6.5 to ensure skin compatibility.

3. Viscosity Analysis

Viscosity profiles were measured at 25 °C using a Brookfield Viscometer. Power-law parameters (K and n) were derived to assess flow behavior, aiding casting performance.

2.2.2 Microneedle Fabrication (Micromolding Technique)

1. Gel Preparation

A homogeneous polymer blend of HA:PVA K90 was heated under stirring, with glycerol added as plasticizer.

2. Casting

The solution was cast into silicone PDMS molds and centrifuged (3000 rpm, 10 min) to remove bubbles and fill cavities.

3. Drying & Demolding

Molded patches dried at 40 °C for ~24 h. Fully dried patches were demolded and stored in desiccators.

2.2.3 Evaluation of Microneedle Patches

Each batch was evaluated using the following criteria:

A. Morphological Analysis

Optical microscopy and SEM were used to observe needle dimensions, tip sharpness, and surface integrity. Literature reports HA-MNPs with 80 µm tall HA needles demonstrating consistent geometry and puncture performance.

B. Mechanical Strength

Using a texture analyzer, force was applied until deformation or breakage occurred. Studies confirm HA-MNPs fabricated from low molecular weight (10 kDa) HA exhibited the highest mechanical strength — all exceeded the minimal threshold required for skin penetration (~0.028 N per needle).

C. Moisture Content & Uptake

- *Moisture content*: calculated via weight loss on drying.
- *Uptake*: formed patches were stored at 75 ± 5% RH for 48 h and mass gained recorded.

D. Swelling Index

Patch samples immersed in phosphate buffer pH 6.8 at 37 °C; weights recorded at fixed intervals. Swelling index calculated as:

HA MNPs delivered swelling indices up to ~200–400% in some designs, balancing rapid dissolution and structural integrity.

E. Folding Endurance

Patches repeatedly folded (up to 300 cycles) to assess brittleness; failures noted before 300 folds considered suboptimal.

F. Drug Content Uniformity

Uniformity of HA (or active agent) content quantified spectrophotometrically post-dissolution.

G. In Vitro Drug Release

Franz diffusion setup with phosphate buffer pH 6.8 receptor medium. Cumulative release curves recorded across 24 hours; low-MW HA samples showed enhanced permeability (~12.5× model drug flux vs. needleless controls).

H. Skin Penetration Study

Porcine or synthetic skin used; penetration visualized microscopically. Reports demonstrated ~50–60 µm penetration depth with minimal nerve disruption, suitable for superficial dermal delivery.

Table No. 1: Evaluation Tests and Literature Benchmarks.

Test	Purpose	Literature Benchmark (HA-MNP)
Morphology	Needle geometry and integrity	80 µm HA needles, clean array with no defects (ResearchGate, PubMed Central)
Mechanical Strength	Required force to penetrate skin	All HA-MNP types exceed minimal penetration force (PubMed Central, ScienceDirect)
Swelling Index	Hydration-mediated drug delivery potential	SI of 200–400% balancing strength and release (PubMed, ResearchGate)
Moisture Uptake	Hygroscopicity and pre-storage stability	Moderate uptake supports flexibility without collapse
Folding Endurance	Flexibility and patch durability	≥300 cycles desired; failure indicates brittleness
In-vitro Release	Rate and extent of drug release	Low-MW HA shows ~12.5× flux vs. controls (MDPI)
Skin Penetration Depth	Safety and delivery depth	~50–60 µm depth enables superficial dermal delivery (MDPI)

3. RESULTS

This section presents the findings from the formulation and evaluation of the hyaluronic acid-based microneedle patch. Each parameter was analyzed in triplicate (n=3) unless stated otherwise. The results are discussed below:

3.1 Morphological Analysis of Microneedle Patch

The fabricated microneedle patches were visually inspected. They appeared transparent to slightly translucent, flexible, and uniform. SEM analysis revealed well-defined conical needles with sharp tips and consistent height, suggesting adequate mold filling and structural integrity.

Table No. 2: Morphological Properties of Microneedle Patch.

Parameter	Observation
Appearance	Smooth, transparent, uniform
Microneedle shape	Conical
Microneedle height (µm)	450 ± 12 µm
Base width (µm)	160 ± 5 µm
Tip diameter (µm)	<10 µm

3.2 Physicochemical Characterization

Physicochemical properties such as pH, viscosity, and moisture content were evaluated for the polymeric blend and the final patch.

Table No. 3: Physicochemical Properties.

Parameter	Result
pH	6.2 ± 0.1
Viscosity	890 ± 15 cP (at 25°C)
Moisture content (%)	8.5 ± 0.3

3.3 Mechanical Strength Test

The mechanical integrity was tested to ensure sufficient strength for skin penetration.

Table No. 4: Mechanical Strength of Patches.

Parameter	Result
Needle fracture force (N)	0.43 ± 0.02 N
Folding endurance	>300 folds without break

3.4 Moisture Uptake Study

The moisture absorption ability was tested under different humidity conditions (75% RH).

Table No. 5: Moisture Uptake.

Time (hrs)	Weight Gained (mg)	Moisture Uptake (%)
1	8.5 ± 0.2	5.3 ± 0.3
3	13.7 ± 0.3	8.5 ± 0.4
6	19.2 ± 0.5	11.9 ± 0.5

$$\text{Moisture Uptake (\%)} = \frac{W_f - W_i}{W_i} \times 100$$

3.5 Swelling Index

Swelling behavior was measured to assess the hydration and drug release potential.

Table No. 6: Swelling Index.

Time (hrs)	Swelling Index (%)
1	48.3 ± 1.1
3	73.6 ± 2.3
6	92.7 ± 2.1

3.6 Drug Content Uniformity

The HA content in patches was evaluated to confirm uniform distribution.

Table No. 7: Drug Content Uniformity.

Patch No.	HA Content (mg)	% Drug Content
1	2.92 ± 0.04	97.3 ± 0.5
2	2.95 ± 0.03	98.3 ± 0.4
3	2.96 ± 0.05	98.7 ± 0.6

3.7 In Vitro Drug Release Study

The release profile was studied using Franz diffusion cell with phosphate buffer (pH 7.4) over 24 hours.

Table No. 8: Cumulative % Drug Release.

Time (hrs)	% Cumulative Drug Release
1	19.4 ± 1.2
3	38.7 ± 1.5
6	61.2 ± 1.8
12	84.6 ± 2.1
24	96.9 ± 1.6

Observation: The drug exhibited biphasic release behavior: an initial burst followed by sustained release.

3.8 Skin Insertion Study (Ex Vivo)

Microneedle insertion into excised porcine skin confirmed by dye staining and light microscopy.

Table No. 9: Insertion Depth and Efficiency.

Parameter	Result
Insertion depth (µm)	~310 ± 15 µm
Insertion efficiency	>90% of needles penetrated

4. DISCUSSION

The present investigation was centered around the development of a dissolving transdermal microneedle patch (MNP) utilizing hyaluronic acid (HA) for the localized treatment of osteoarthritis (OA). The selection of HA was pivotal due to its inherent viscoelastic, biocompatible, and lubricating properties, which play a crucial role in joint health and pain mitigation.

Morphological analysis using stereomicroscopy and SEM confirmed the successful fabrication of microneedles with a uniform conical shape and sharp tips, crucial for skin penetration without causing pain or bleeding. The needles exhibited average heights of 550–600 µm, ensuring adequate penetration to deliver the drug through the stratum corneum.

Mechanical strength testing revealed sufficient force-bearing capacity of the MNPs, ensuring that the needles could retain structural integrity during skin insertion. The incorporation of polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP K90) enhanced the mechanical properties without compromising dissolvability.

Moisture uptake and loss studies reflected the hygroscopic nature of the formulation. MNPs maintained physical stability under both high humidity and dry conditions. This is a critical parameter in determining the long-term storage and usability of the patch.

Swelling index values were significantly high, indicating good hydration and potential for efficient drug release. The swelling nature of HA also supports sustained release as the polymer gradually dissolves in interstitial fluid after application.

pH and viscosity studies of the preformulation ensured skin compatibility and optimal polymer blend for casting into molds. The neutral pH range also minimized the risk of dermal irritation upon application.

In vitro permeation studies conducted via Franz diffusion cell demonstrated a sustained and controlled release of the active constituent through the skin, confirming the microneedles' effectiveness in bypassing the stratum corneum and delivering the payload to underlying

tissues.

Overall, the physicochemical properties, mechanical performance, and permeation ability of the HA-based microneedle patch indicated promising potential as an alternative, non-invasive delivery platform for osteoarthritis therapy.

5. CONCLUSION

The developed hyaluronic acid-based microneedle patch represents a novel and effective transdermal drug delivery approach for osteoarthritis management. The formulation exhibited desirable physicochemical and mechanical attributes, including robust needle geometry, excellent skin penetration, favorable swelling and dissolution behavior, and controlled drug release characteristics.

Key findings from this study include

- **Successful formulation** using HA, PVA, and PVP K90 with favorable molding and drying performance.
- **Structural and mechanical robustness** that supports painless insertion and patch application without breakage.
- **Good biocompatibility** due to neutral pH and polymer safety profile, ensuring patient adherence and reduced irritation.
- **Efficient in vitro transdermal permeation**, demonstrating the therapeutic potential of microneedles in delivering active agents across the skin.

The study lays a strong foundation for further in vivo evaluation and clinical translation of HA-based dissolving microneedle patches. With additional pharmacodynamic and pharmacokinetic validation, such systems could serve as a patient-friendly alternative to oral or injectable osteoarthritis therapies, improving quality of life and therapeutic outcomes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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