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Formulation and Evaluation of a Natural Excipients-Based Diclofenac Sodium Topical Ointment

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Abstract

The present study reports the formulation and evaluation of a diclofenac sodium topical ointment incorporating natural excipients to improve skin compatibility and formulation sustainability. Conventional topical non-steroidal anti-inflammatory drug (NSAID) formulations frequently rely on synthetic excipients that may cause dermal irritation and pose environmental concerns. To address these limitations, a 1% w/w diclofenac sodium ointment was developed using aloe vera gel, glycerin, xanthan gum, peppermint oil, vitamin E, and isopropyl alcohol as functional excipients. The formulation was evaluated for physicochemical properties, including pH, viscosity, spreadability, homogeneity, in-vitro drug release, microbial quality, and accelerated stability. The optimized formulation exhibited a skin-compatible pH of 6.2, viscosity of 62, 000 mPa·s, and good spreadability (95.24 g·cm s^{-1}). In-vitro diffusion studies demonstrated sustained drug release, with 82.43% of diclofenac released within 6 h. Microbiological evaluation confirmed compliance with pharmacopeial limits, indicating adequate preservative efficacy. Stability studies showed that the formulation remained physically and chemically stable under ambient conditions for 30 days, with reduced stability observed at temperatures above 40 °C. These findings demonstrate that natural excipients can effectively replace synthetic components in topical diclofenac formulations without compromising performance. The developed formulation represents a promising, skin-friendly, and sustainable alternative for topical NSAID delivery, warranting further in-vivo and clinical investigations.

Keywords: Diclofenac sodium topical ointment, NSAIDs, TDDS, topical delivery, pain and inflammation

INTRODUCTION

Pain and inflammation are complex physiological responses that play a central role in a wide range of acute and chronic pathological conditions, including musculoskeletal disorders, osteoarthritis, rheumatoid arthritis, sports injuries, and post-traumatic inflammation. Although these responses are protective in nature, their persistence can significantly impair quality of life and functional mobility. Non-steroidal anti-inflammatory drugs (NSAIDs) remain the mainstay of pharmacological management due to their ability to inhibit cyclooxygenase (COX) enzymes and suppress prostaglandin-mediated inflammatory pathways. However, long-term oral administration of NSAIDs is frequently associated with systemic adverse effects such as gastrointestinal ulceration, renal dysfunction, and cardiovascular complications, which limit their clinical utility, particularly in elderly and chronic-use populations.

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To overcome these limitations, topical drug-delivery systems (TDDS) have gained considerable attention as an alternative approach for localized pain and inflammation management. Topical formulations deliver the drug directly to the site of action, enabling high local drug concentrations while minimizing systemic absorption. This route bypasses first-pass hepatic metabolism and reduces the risk of systemic toxicity, thereby improving patient safety and compliance. As a result, topical NSAIDs are widely recommended for conditions involving superficial joints and soft tissues, such as knee and hand osteoarthritis, localized muscle pain, and minor inflammatory injuries.

Diclofenac sodium is one of the most extensively studied and clinically prescribed NSAIDs for topical application owing to its strong COX inhibitory activity, favorable molecular weight, and suitable lipophilicity for transdermal penetration. Numerous commercial diclofenac-based gels, creams, and ointments are currently available and have demonstrated clinical efficacy comparable to oral NSAIDs for localized pain relief. Despite these advantages, many marketed formulations rely heavily on synthetic excipients, including carbomers, polyethylene glycols, alcohols, and parabens, to achieve desired consistency, stability, and drug-release characteristics. These synthetic components may cause skin irritation, dryness, contact dermatitis, or hypersensitivity reactions upon prolonged use. In addition, growing environmental concerns regarding the non-biodegradability and ecological persistence of synthetic excipients have prompted renewed scrutiny of conventional formulation strategies.

In recent years, there has been increasing interest in the development of topical pharmaceutical formulations incorporating natural and biodegradable excipients. Natural polymers and plant-derived materials offer several advantages, including biocompatibility, low toxicity, renewable sourcing, and inherent pharmacological benefits. Excipients such as aloe vera gel, glycerin, xanthan gum, peppermint oil, and vitamin E possess multifunctional properties, acting as bases, humectants, stabilizers, penetration enhancers, antioxidants, and soothing agents. Aloe vera gel is well known for its moisturizing, anti-inflammatory, and wound-healing properties, while glycerin enhances skin hydration and barrier function. Xanthan gum serves as an effective natural thickening and stabilizing agent, and peppermint oil provides mild analgesic and cooling effects. Vitamin E functions as an antioxidant, protecting both the formulation and the skin from oxidative damage.

Although individual natural excipients have been explored in topical formulations, systematic formulation and evaluation of diclofenac sodium ointments using predominantly natural excipient systems remain limited. There is a need to establish whether such formulations can achieve comparable or superior physicochemical stability, drug-release behavior, microbial safety, and patient acceptability relative to conventional synthetic-based products.

The present study aims to formulate and evaluate a diclofenac sodium topical ointment using natural excipients as functional formulation components. The prepared formulation was systematically characterized for physicochemical properties, including pH, viscosity, spreadability, homogeneity, in-vitro drug-release performance, microbial quality, and short-term stability. By addressing both therapeutic performance and sustainability considerations, this work seeks to demonstrate the feasibility of natural-excipient-based topical NSAID formulations as a viable and eco-conscious alternative to conventional systems.

LITERATURE REVIEW: TOPICAL NSAIDS IN PAIN MANAGEMENT AND FORMULATION SCIENCE

NSAIDs in the Management of Pain and Inflammation

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed therapeutic agents for the treatment of pain, inflammation, and fever associated with musculoskeletal disorders, arthritis, and soft tissue injuries. Their primary therapeutic benefit arises from effective suppression of inflammatory mediators, leading to symptomatic relief and improved mobility. However, extensive clinical evidence indicates that long-term oral administration of NSAIDs is associated with significant systemic adverse effects, including gastrointestinal ulceration, renal toxicity, and increased

cardiovascular risk, particularly in elderly patients and those requiring chronic therapy (Derry et al., 2016; Zajdel & Wilczok, 2020). These safety concerns have driven the search for alternative drug-delivery strategies that reduce systemic exposure while maintaining therapeutic efficacy.

Mechanism of Action of Topical NSAIDs

NSAIDs exert their pharmacological action through inhibition of cyclooxygenase (COX) enzymes, namely COX-1 and COX-2, resulting in decreased synthesis of prostaglandins that mediate inflammation, pain, and edema. When administered topically, NSAIDs penetrate the stratum corneum and distribute into underlying tissues such as muscles, synovial fluid, and periarticular structures. This localized delivery enables high drug concentrations at the site of inflammation with minimal systemic absorption, thereby reducing the incidence of systemic adverse effects (Prausnitz & Langer, 2008; Zajdel & Wilczok, 2020). Pharmacokinetic studies have demonstrated that plasma concentrations following topical NSAID application are significantly lower than those observed after oral dosing, supporting their improved safety profile.

Advantages of Topical NSAID Therapy

Topical NSAID formulations offer several advantages over conventional oral dosage forms. Direct application to the affected area allows localized drug delivery, improving therapeutic effectiveness in superficial joints and soft tissues. Reduced systemic absorption minimizes gastrointestinal, renal, and cardiovascular toxicity. In addition, topical formulations are non-invasive, easy to administer, and suitable for prolonged use, thereby enhancing patient compliance. Rapid onset of action due to local absorption further supports their clinical utility in acute pain conditions (Derry et al., 2016; Kaur & Guleri, 2013). These advantages have led to strong recommendations for topical NSAIDs in clinical practice guidelines for osteoarthritis and localized musculoskeletal pain.

NSAIDs Commonly Used in Topical Formulations

Several NSAIDs have been successfully developed for topical application, including diclofenac, ibuprofen, ketoprofen, piroxicam, and flurbiprofen. Among these, diclofenac – particularly in sodium and diethylamine salt forms – has emerged as the most widely used agent due to its potent anti-inflammatory activity, favorable molecular weight, and optimal lipophilicity for transdermal penetration (Williams & Barry, 2012; Pandey & Meshali, 2018). Clinical studies have consistently demonstrated the efficacy of diclofenac-based topical formulations in managing localized pain, making diclofenac sodium a preferred candidate for formulation optimization.

Formulation Strategies for Enhanced Topical Delivery

The therapeutic performance of topical NSAID formulations is highly dependent on formulation design. Penetration enhancers such as ethanol, isopropyl alcohol, menthol, and essential oils are commonly incorporated to disrupt the lipid structure of the stratum corneum and enhance drug permeation. Functional excipients, including gelling agents, emulsifiers, and stabilizers, are essential for achieving appropriate rheological properties, uniform drug distribution, and acceptable sensory characteristics. Physicochemical parameters such as drug solubility, molecular size, partition coefficient, and formulation pH critically influence skin permeability and drug-release behavior (Rowe et al., 2009; Hadgraft & Lane, 2005). Conventional topical formulations predominantly rely on synthetic polymers such as carbomers and polyethylene glycols to meet these requirements.

Clinical Applications of Topical NSAIDs

Topical NSAIDs are widely used in the management of osteoarthritis, particularly in superficial joints such as the knees and hands, as well as in muscle strains, sports injuries, back and neck pain, and postoperative inflammation. Evidence from systematic reviews and meta-analyses indicates that topical NSAIDs provide pain relief comparable to oral NSAIDs for localized conditions, with a significantly lower risk of systemic adverse effects (Derry et al., 2016). These findings support their growing acceptance in both primary and specialist care settings.

Limitations of Marketed Diclofenac Formulations

Despite their clinical effectiveness, many commercially available diclofenac topical formulations contain synthetic excipients such as carbomers, parabens, menthol, and methyl salicylate. Prolonged exposure to these components may result in skin irritation, dryness, burning sensation, and allergic contact dermatitis (Zajdel & Wilczok, 2020). Additional formulation-related challenges include phase instability, limited residence time on the skin, and variability in drug-release performance. Furthermore, increasing environmental concerns regarding the non-biodegradable nature of synthetic excipients have raised questions about the sustainability of conventional topical pharmaceutical products (Mahapatra et al., 2015).

Role of Natural Excipients in Topical Drug Delivery

Growing emphasis on biocompatibility and environmental sustainability has led to increased interest in the use of natural excipients in topical formulations. Natural polymers and plant-derived materials such as aloe vera gel, xanthan gum, glycerin, essential oils, and vitamin E offer several advantages, including biodegradability, low toxicity, and renewable sourcing. Aloe vera exhibits moisturizing, anti-inflammatory, and wound-healing properties, while glycerin improves skin hydration and barrier function. Xanthan gum serves as a natural thickening and stabilizing agent, peppermint oil provides mild analgesic and counterirritant effects, and vitamin E acts as an antioxidant, protecting both the formulation and skin lipids from oxidative damage (Mahapatra et al., 2015; Thakur & Jain, 2020).

Ointment Bases and Formulation Considerations

The choice of ointment base plays a crucial role in determining drug-release behavior, formulation stability, and patient acceptability. Ointment bases are broadly classified into hydrocarbon, absorption, emulsion, and water-soluble bases, each exhibiting distinct occlusive properties and cosmetic characteristics. Natural-excipient-based emulsion and hydrogel systems have gained prominence due to their non-greasy texture, ease of application, and improved patient compliance. Compatibility between the drug, base, and excipients is essential to ensure formulation stability and consistent therapeutic performance (Rowe et al., 2009; Allen et al., 2013).

Microbial Stability and Preservation Challenges

Formulations containing natural excipients are inherently susceptible to microbial contamination and physicochemical instability due to the presence of water and organic constituents. Common challenges include microbial growth, viscosity changes, phase separation, and oxidative degradation. Strategies to mitigate these issues include the incorporation of suitable preservatives, optimization of formulation pH, use of appropriate packaging, and adherence to stability testing protocols in accordance with ICH guidelines (ICH Q1A(R2); USP <1111>). Comprehensive microbial evaluation is critical to ensure product safety and regulatory compliance.

Regulatory and Quality Considerations

Topical pharmaceutical products must comply with regulatory requirements established by authorities such as the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and Central Drugs Standard Control Organization (CDSCO, India). These regulations mandate adherence to Good Manufacturing Practices (GMP), comprehensive physicochemical and microbiological testing, stability studies under ICH conditions, and appropriate labeling and documentation (EMA, 2019; ICH Q1A–Q1E). Increasing regulatory focus on patient safety and sustainability further highlights the need for well-characterized natural-excipient-based formulations.

Research Gap and Rationale

Although extensive literature exists on topical NSAIDs and individual natural excipients, systematic formulation and evaluation studies of diclofenac sodium topical ointments based predominantly on natural excipient systems remain limited. There is a clear need to assess whether such formulations can achieve physicochemical stability, sustained drug release, microbial safety, and patient acceptability comparable to or superior to conventional synthetic-based products. Addressing this gap forms the basis of the present investigation.

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FORMULATION AND METHODOLOGY

Formulation Design

The topical gel was designed to deliver diclofenac sodium, a non-steroidal anti-inflammatory drug (NSAID), through a biocompatible and stable dermal delivery system. The formulation strategy focused on the use of predominantly natural excipients to enhance skin compatibility, percutaneous absorption, and physicochemical stability while minimizing irritation associated with synthetic carriers. Aloe vera gel was selected as the primary vehicle owing to its moisturizing, soothing, and anti-inflammatory properties, while glycerine and xanthan gum were incorporated to improve hydration and rheological stability, respectively. Peppermint oil and vitamin E were included to provide mild analgesic and antioxidant effects, and isopropyl alcohol was employed as a co-solvent and penetration enhancer. Phenoxyethanol was used as a preservative to ensure microbiological stability.

The composition of the optimized topical gel formulation and the functional role of each component are summarized in (Table 1).

Table 1. Composition of the optimized diclofenac sodium topical gel formulation.

S. N.	Ingredient	Functional role
1	Diclofenac sodium	Active pharmaceutical ingredient (NSAID).
2	Aloe vera gel	Base; moisturizing and anti-inflammatory.
3	Glycerine	Humectant; enhances skin hydration.
4	Xanthan gum	Thickener and stabilizer.
5	Vitamin E (tocopherol)	Antioxidant.
6	Peppermint oil	Mild analgesic and counterirritant.
7	Isopropyl alcohol	Co-solvent and penetration enhancer.
8	Phenoxyethanol	Preservative.
9	Purified water	Solvent.

Materials and Methods

Extraction of Aloe Vera Gel

Fresh Aloe barbadensis leaves were collected and washed thoroughly with purified water to remove surface contaminants. The leaves were longitudinally filleted, and the inner gel was carefully separated using sterile tools. The extracted gel was homogenized using a laboratory blender and filtered through muslin cloth to remove fibrous material. The processed gel was stored in sterile, airtight containers at 4 ± 1 °C until further use.

Preparation of Diclofenac Sodium Topical Gel

Preparation of Gel Base

Seventy-five grams of aloe vera gel was transferred into a sterile beaker and stirred using a mechanical stirrer. Xanthan gum (1 g) was added gradually with continuous stirring to avoid agglomeration. The dispersion was allowed to hydrate for 30 min to obtain a uniform gel base.

Incorporation of Humectant

Glycerine (5 g) was added to the hydrated gel base and mixed thoroughly to ensure uniform distribution.

Solubilization of Active Ingredient

Diclofenac sodium (1 g) was dissolved in a 50% w/w isopropyl alcohol–water mixture (5 g IPA and 5 g water) under continuous stirring. The clear solution was added slowly to the gel base with gentle mixing to achieve homogeneity.

Addition of Functional Excipients

Vitamin E (0.5 g) and phenoxyethanol (0.5 g) were incorporated sequentially under low-speed stirring to minimize air entrapment. Peppermint oil (1 g) was added at the final stage, and the formulation was mixed gently to preserve its volatile components.

Final Adjustment

Purified water was added quantity sufficient to obtain a total formulation weight of 100 g. The gel was stirred until a smooth, bubble-free, and homogeneous product was obtained.

Sterilization Procedures

To ensure microbiological safety, a combination of sterilization techniques was employed. The diclofenac sodium–isopropyl alcohol solution was sterilized by membrane filtration using a 0.22 µm filter prior to incorporation into the gel. Excipients and containers were exposed to UV-C radiation (254 nm) for 30 min. Glassware and metallic instruments were sterilized using dry heat at 160–170 °C for 2 h.

Hazard and Operability (HAZOP) Analysis

A hazard and operability (HAZOP) study was conducted to identify potential deviations during formulation and processing steps. Critical variables such as weighing accuracy, dispersion of thickening agents, incorporation of volatile components, and final mixing were evaluated. Preventive control measures, including calibrated equipment, controlled mixing speeds, and appropriate packaging, were implemented to minimize formulation risks. A summary of the HAZOP analysis is presented in (Table 2).

Table 2. HAZOP analysis of critical formulation steps.

Process step	Deviation	Cause	Consequence	Control measure
API weighing	Over/under dosing	Human error	Sub-therapeutic or toxic dose	Double-check weighing; calibrated balance.
Xanthan gum dispersion	Lumping	Rapid addition	Inhomogeneous gel	Gradual addition with continuous stirring.
Peppermint oil addition	Volatilization	Excessive mixing or heat	Reduced efficacy	Low-speed mixing at ambient temperature.
Final mixing	Air entrapment	High shear	Foam formation, instability	Gentle mixing and deaeration.
Storage	Light/heat exposure	Improper packaging	Drug degradation	Light-resistant, airtight containers.

Formulation Batch Composition

The optimized batch (Batch No. MJD-2503) was prepared as a 100 g laboratory-scale formulation. The quantitative composition is presented in (Table 3).

Table 3. Composition of optimized diclofenac sodium topical gel (Batch MJD-2503).

Component	Function	% w/w	Amount (g)
Diclofenac sodium	API	1.00	1.0
Aloe vera gel	Base	75.00	75.0
Glycerine	Humectant	5.00	5.0
Xanthan gum	Stabilizer	1.00	1.0
Vitamin E	Antioxidant	0.50	0.5
Peppermint oil	Essential oil	1.00	1.0
Isopropyl alcohol	Co-solvent	5.00	5.0
Phenoxyethanol	Preservative	0.50	0.5
Purified water	Solvent (q.s.)	—	11.0
Total		100	100 g

Apparatus and Equipment

Standard laboratory equipment was used for formulation and evaluation, including analytical balances, magnetic and mechanical stirrers, glassware, pH meters, filtration assemblies, and micropipettes to ensure accuracy and reproducibility.

Preliminary Physical Evaluation

The prepared gel was subjected to visual and physical evaluation to assess appearance, consistency, odor, homogeneity, and skin feel. The formulation exhibited a smooth, translucent appearance with mild peppermint odor, non-greasy consistency, good washability, and uniform spread on the skin, indicating acceptable cosmetic and application properties for topical use.

METHODOLOGY

Extraction of Aloe vera Gel

Fresh leaves of Aloe barbadensis were collected and washed thoroughly with purified water to remove surface contaminants. The leaves were longitudinally sliced, and the inner mucilaginous gel was carefully separated using sterile instruments. The extracted gel was homogenized using a laboratory blender to obtain a uniform consistency and subsequently filtered through muslin cloth to remove fibrous residues. The processed gel was transferred into sterile containers and stored at 4 ± 1 °C until further use.

Preparation of Diclofenac Sodium Topical Gel

Preparation of Gel Base

A measured quantity (75 g) of aloe vera gel was transferred into a sterile beaker and stirred using a mechanical stirrer. Xanthan gum (1 g) was gradually dispersed into the gel under continuous stirring to prevent agglomeration. The dispersion was allowed to hydrate for 30 min to form a uniform and stable gel base.

Incorporation of Humectant

Glycerine (5 g) was added to the hydrated gel base and mixed thoroughly to ensure uniform distribution throughout the formulation.

Solubilization and Incorporation of Active Pharmaceutical Ingredient

Diclofenac sodium (1 g) was dissolved in a 50% w/w isopropyl alcohol–water mixture (5 g isopropyl alcohol and 5 g purified water) under constant stirring until a clear solution was obtained. This solution was added slowly to the gel base with continuous gentle stirring to achieve homogeneity.

Addition of Functional Excipients

Vitamin E (0.5 g) and phenoxyethanol (0.5 g) were incorporated sequentially into the formulation with gentle mixing to minimize air entrapment. Peppermint oil (1 g) was added as the final component, and the mixture was stirred at low speed to preserve its volatile constituents.

Final Adjustment

Purified water was added quantity sufficient to obtain a total formulation weight of 100 g. The formulation was mixed until a smooth, uniform, and bubble-free gel was obtained.

Sterilization Procedures

To ensure microbiological safety and product integrity, multiple sterilization techniques were employed. The diclofenac sodium–isopropyl alcohol solution was sterilized by membrane filtration using a 0.22 µm filter prior to incorporation. Excipients and packaging materials were exposed to UV-C irradiation (254 nm) for 30 min. Glassware and metallic instruments were sterilized by dry heat at 160–170 °C for 2 h.

Hazard and Operability (HAZOP) Assessment

A hazard and operability (HAZOP) analysis was conducted to identify and evaluate potential risks associated with critical formulation and processing steps. Possible deviations, including inaccurate weighing, incomplete dispersion of thickening agents, volatilization of essential oils, and air incorporation during mixing, were systematically assessed. Preventive control measures such as standardized weighing procedures, controlled mixing conditions, and the use of calibrated instruments were implemented to minimize operational risks. A summary of the HAZOP analysis is presented in (Table 4).

Table 4. HAZOP analysis of critical formulation steps.

Process step	Deviation	Cause	Consequence	Control measure
API weighing	Over/under dosing	Human error	Ineffective or toxic formulation	Weight verification; balance calibration.
Xanthan gum dispersion	Lumping	Rapid addition	Inhomogeneous gel	Gradual addition; controlled stirring.
Peppermint oil addition	Volatilization	Excessive mixing or heat	Reduced therapeutic efficacy	Low-speed mixing at ambient temperature.
Final mixing	Air entrapment	High shear	Foam formation, instability	Gentle mixing; deaeration.
Storage	Light or heat exposure	Inadequate packaging	Drug degradation	Light-resistant, airtight containers.

Formulation Batches

A topical diclofenac sodium gel was prepared using natural and biocompatible excipients to ensure optimal therapeutic efficacy, dermal compatibility, and physicochemical stability. The formulation was developed at laboratory scale, and the optimized batch (Batch No. MJD-2503) was selected for further evaluation based on preliminary physicochemical assessment.

Composition of Optimized Batch

The quantitative composition of the optimized formulation is presented in (Table 5).

Tables 5. Composition of optimized batch.

Component	Function	% w/w	Amount (g)
Diclofenac sodium	Active pharmaceutical ingredient	1.00	1.0
Aloe vera gel	Base/vehicle	75.00	75.0
Glycerine	Humectant	5.00	5.0
Xanthan gum	Stabilizer and gelling agent	1.00	1.0
Vitamin E (tocopherol)	Antioxidant	0.50	0.5
Peppermint oil	Essential oil (analgesic)	1.00	1.0
Isopropyl alcohol	Co-solvent and penetration enhancer	5.00	5.0
Phenoxyethanol	Preservative	0.50	0.5
Purified water	Solvent (q.s.)	—	11.0
Total		**100**	**100 g**

Preliminary Visual and Physical Evaluation

The optimized gel formulation was subjected to preliminary visual and physical evaluation to assess its suitability for topical application. Parameters including appearance, odor, consistency, homogeneity, pH, spreadability, viscosity, skin sensation, and washability were evaluated. The observations are summarized in (Table 6).

Table 6. Visual and physical evaluation of optimized formulation.

Parameter	Observation	Expected performance
Appearance	Smooth, translucent gel	Uniform and aesthetically acceptable.
Odor	Mild peppermint aroma	Pleasant and characteristic.
Consistency	Semi-solid, non-greasy	Suitable for topical application.
pH	6.2	Skin-compatible (6.2 ± 0.2).
Spreadability	Excellent	Uniform coverage with minimal effort.
Viscosity	Moderately high and stable	Adequate retention on skin.
Homogeneity	No lumps or phase separation	Uniform drug distribution.
Skin sensation	Cooling, soothing, non-irritant	Improved patient acceptability.
Washability	Easily washable	No greasy residue.

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EVALUATION OF DICLOFENAC SODIUM TOPICAL GEL

Spreadability

Method

Spreadability of the optimized formulation (Batch MJD-2503) was determined using the slip–drag method. Approximately 1 g of gel was placed between two glass slides (20 × 20 cm). A 100 g weight was applied to the upper slide for 5 min to ensure uniform spreading. The time required for the upper slide to move a fixed distance of 10 cm was recorded. Spreadability was calculated using the following equation:

- S=M×LTS = frac{M \times L}{T}S=TM×L.

Where M is the applied mass (100 g), L is the distance moved (10 cm), and T is the time in seconds.

Results

The formulation exhibited an average spreadability of 95.24 $g \cdot cm \cdot s^{-1}$, indicating easy application and uniform distribution on the skin.

Discussion

The high spreadability value suggests favorable rheological behavior, attributed to the combined effects of aloe vera gel and glycerine, which impart smooth texture and reduce interfacial resistance during application. The observed value exceeds the minimum acceptable limit (≥ 90 $g \cdot cm \cdot s^{-1}$) for topical gels, confirming suitability for dermal use.

Viscosity

Method

Viscosity was measured using a Brookfield RV viscometer equipped with spindle #6 at 10 rpm and 25 ± 1 °C. Measurements were taken after allowing the sample to equilibrate thermally.

Results

The viscosity of the formulation was 62, 000 mPa·s, within the acceptable range of 30, 000–100, 000 mPa·s for topical gels.

Discussion

The measured viscosity indicates an optimal balance between spreadability and retention at the application site. Xanthan gum contributed to structural stability, while aloe vera gel ensured a non-greasy, semi-solid consistency appropriate for topical administration.

In-Vitro Drug Release

Method

In-vitro drug release was evaluated using a Franz diffusion cell fitted with a dialysis membrane. The receptor compartment was filled with phosphate buffer (pH 7.4) and maintained at 37 ± 0.5 °C with continuous stirring. One gram of formulation was placed in the donor compartment. Samples were withdrawn at predetermined intervals up to 6 h and analyzed spectrophotometrically at 276 nm.

Results

The cumulative percentage of diclofenac sodium released reached 82.43% within 6 h.

Discussion

The release profile demonstrated sustained drug diffusion, likely governed by the gel matrix formed by xanthan gum and aloe vera. The presence of glycerine and isopropyl alcohol facilitated drug solubilization and membrane permeation, supporting prolonged therapeutic action.

Stability Studies

Method

Stability studies were conducted by storing samples at 15, 25, 30, 35, 40, and 50 °C. Samples were evaluated at 0, 15, 30, and 60 days for appearance, pH, spreadability, and drug content.

Results and Discussion

The formulation remained physically and chemically stable up to 35 °C, with only minor softening and negligible pH variation. At 40 °C, early signs of phase separation and reduced drug content were observed, while 50 °C resulted in clear instability and significant drug degradation.

Conclusion

The formulation is stable under ambient and moderately elevated temperatures. Storage below 30 °C is recommended to ensure long-term product integrity.

Microbiological Evaluation

Method

Microbial load testing was performed over 7 days at 25 ± 2 °C. Total aerobic microbial count (TAMC), total yeast and mold count (TYMC), and specific pathogens were evaluated according to pharmacopeial methods.

Results

Final microbial counts were 30 CFU/g (TAMC) and 38 CFU/g (TYMC), with no detection of E. Coli, S. Aureus, P. Aeruginosa, or Salmonella spp.

Discussion

All values were well within pharmacopeial limits. The preservative system (phenoxyethanol) in combination with 50% isopropyl alcohol provided effective microbial control.

Summary of Evaluation

All evaluated parameters – including pH (6.2), spreadability, viscosity, drug release, stability, and microbial quality – met predefined acceptance criteria, confirming the formulation's suitability for topical application.

SCALE-UP PROCESS HYPOTHESIS (PILOT-SCALE)

A pilot-scale manufacturing hypothesis was developed for a 10 kg batch based on the optimized laboratory formulation.

Material Balance

The scaled formulation maintained identical percentage composition, ensuring process consistency.

Energy Requirement

Total estimated energy consumption was approximately 3 kWh per batch, dominated by mixing and sterilization processes.

Equipment Selection

Stainless-steel mixing vessels, overhead stirrers, membrane filtration units, UV sterilization chambers, and aseptic filling systems were identified as suitable for pilot-scale production.

Discussion

The formulation is amenable to scale-up using standard pharmaceutical equipment without significant modification. Mild processing conditions and low energy requirements support economic feasibility and sustainability.

OVERALL CONCLUSION

The diclofenac sodium topical gel formulated with natural excipients demonstrated excellent physicochemical performance, sustained drug release, microbiological safety, and acceptable stability. The proposed pilot-scale process indicates strong potential for industrial translation following regulatory validation.

Pilot-Scale Manufacturing Considerations

Sterilization Protocol

A comprehensive sterilization protocol was implemented to ensure microbiological integrity during pilot-scale manufacturing. Stainless steel (SS) vessels and agitators were sterilized using dry heat at 160 °C for 1 h to eliminate microbial contaminants. The diclofenac sodium–isopropyl alcohol solution was sterilized by membrane filtration through a 0.22 µm filter prior to incorporation into the formulation. Aloe vera gel and other excipients were subjected to surface decontamination using UV irradiation at 254 nm for 30 min. Final packaging operations were performed under controlled cleanroom conditions, with containers exposed to UV sterilization to minimize the risk of contamination during filling (Figure 1).

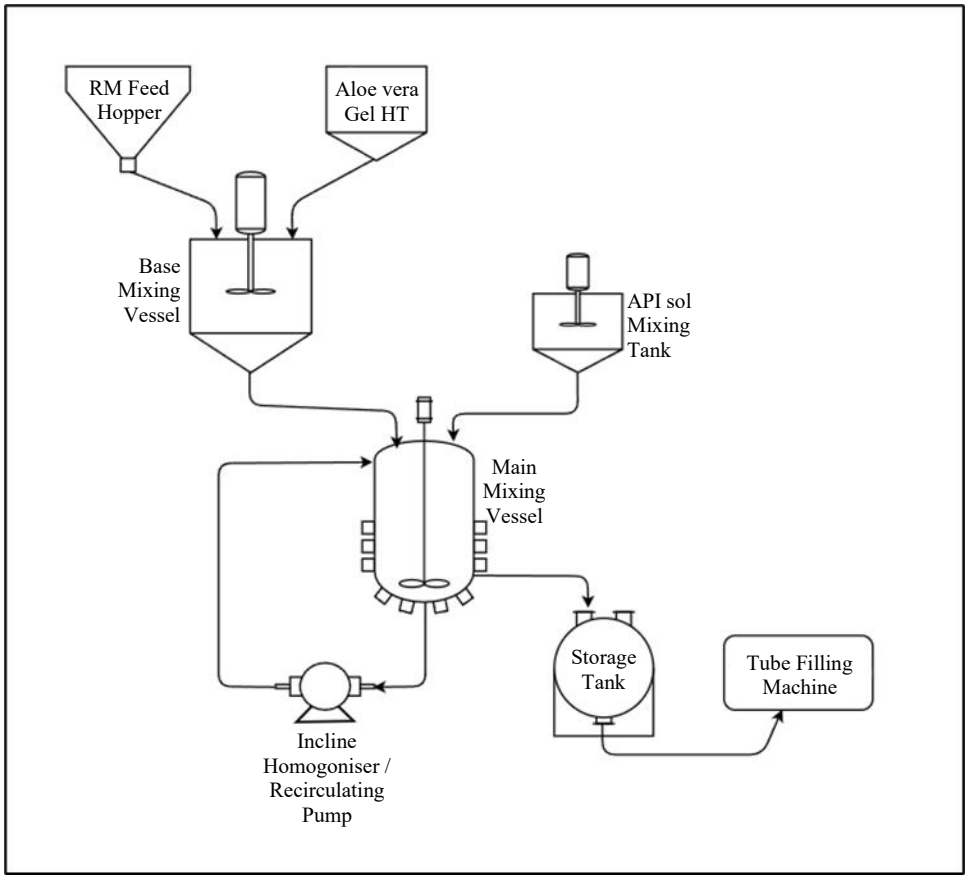

Figure 1. Equipment assembly.

Pilot-Scale Manufacturing Process

Pilot-scale manufacturing was designed for a 10 kg batch using standard pharmaceutical processing equipment. Aloe vera gel (7.5 kg) was charged into a stainless steel mixing tank, followed by gradual addition of xanthan gum (100 g) under controlled high-shear mixing. The dispersion was allowed to hydrate for 30–45 min to form a uniform gel base. Glycerine (500 g) was subsequently incorporated with gentle mixing to improve hydration and texture.

Diclofenac sodium (100 g) was dissolved in a pre-filtered 50% w/w isopropyl alcohol solution (500 g) and slowly added to the main vessel under continuous stirring. Functional excipients – vitamin E (50 g), phenoxyethanol (50 g), and peppermint oil (100 g) – were added sequentially at low stirring speed to prevent volatilization and foam formation. Purified water (1.1 kg) was added to achieve the final batch weight. In-process pH and viscosity were monitored and adjusted if necessary. The finished gel was transferred using a peristaltic pump and aseptically filled into pre-sterilized aluminum tubes or HDPE containers under laminar airflow conditions.

Cost Analysis

A preliminary cost analysis was performed for laboratory-scale production to assess economic feasibility.

Variable Costs

The raw material cost for a 100 g batch was estimated at ₹35.22, with diclofenac sodium representing the major cost contributor. Packaging materials, including laminated tubes and secondary cartons, contributed an additional ₹12 per batch.

Manufacturing and Quality Costs

Direct manufacturing costs – including labor, utilities, quality control, sterilization, and equipment depreciation – were estimated at ₹40 per batch.

Total Cost and Unit Price

The total batch cost for 100 g was calculated as ₹87.22. Based on an output of three 30 g tubes, the estimated production cost per unit was approximately ₹29.07. These findings suggest that the formulation is economically competitive with commercially available topical NSAID products.

RESULTS AND DISCUSSION

The formulated diclofenac sodium gel exhibited a smooth, uniform appearance without grittiness or phase separation, indicating effective dispersion of excipients and API. The measured pH (6.2) fell within the skin-compatible range, minimizing the risk of irritation and supporting drug stability.

Spreadability testing yielded a value of 95.24 $g \cdot cm \cdot s^{-1}$, exceeding the minimum acceptable limit for topical gels and confirming ease of application. Viscosity measurements (62, 000 mPa·s at 25 °C) demonstrated an optimal balance between retention and spreadability, attributable to the structured gel network formed by xanthan gum and aloe vera gel.

In-vitro drug release studies showed sustained diffusion, with 82.43% of diclofenac sodium released within 6 h. This release profile is consistent with prolonged therapeutic action and improved patient compliance. Stability studies indicated that the formulation remained stable under ambient and moderately elevated temperatures (≤ 35 °C), while higher temperatures led to phase separation and drug degradation.

Microbiological evaluation confirmed compliance with pharmacopeial limits, with low microbial counts and absence of pathogenic organisms. The preservative system, combined with isopropyl alcohol, provided effective antimicrobial protection.

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