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Research Paper

Formulation and Evaluation of a Novel High-Permeability Etoricoxib Gel for Enhanced Topical Delivery: A Review

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Abstract: *Etoricoxib is a selective COX-2 inhibitor widely used for the treatment of pain and inflammation. However, its oral administration is associated with several side effects, such as gastrointestinal irritation and cardiovascular risks. To overcome these limitations, topical drug delivery systems have gained attention as they provide localized action with reduced systemic exposure. Among these, gel-based formulations are particularly promising due to their ease of application, patient compliance, and ability to enhance drug penetration through the skin.This review focuses on the formulation and evaluation of novel high-permeability etoricoxib gels for improved topical delivery. Various formulation approaches, including the use of penetration enhancers, polymers, and advanced systems such as Nano formulations and micro emulsions, are discussed to enhance drug solubility and skin permeation. The selection of suitable excipients and optimization of formulation parameters play a critical role in achieving effective drug delivery.Key evaluation parameters such as pH, viscosity, spread ability, drug content, in vitro drug release, ex vivo permeation, and stability studies are also highlighted. Recent developments demonstrate that high-permeability gel systems can significantly improve the therapeutic efficacy of etoricoxib while minimizing adverse effects.*

Keywords: *Etoricoxib, Topical drug delivery, High-permeability gel, Transdermal Delivery, COX-2 inhibitor, Penetration enhancers.*

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I. INTRODUCTION

Etoricoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, is widely used for the treatment of osteoarthritis, rheumatoid arthritis, and other inflammatory conditions. However, its oral administration is often associated with gastrointestinal irritation, hepatic side effects, and variable bioavailability due to extensive first-pass metabolism. Topical delivery of etoricoxib offers several advantages, including targeted action at the site of inflammation, reduced systemic exposure, and improved patient compliance. [1] Yet, its low aqueous solubility and limited skin permeability restrict its therapeutic effectiveness through conventional topical formulations. To overcome these challenges, novel formulation strategies such as co-solvent systems, permeation enhancers, and gelling polymers can be employed to enhance skin permeation and sustain drug release. Therefore, this research focuses on developing a novel, high-permeability etoricoxib gelusing optimized polymeric and permeation-enhancing systems. [2]

Pain and inflammation are complex physiological responses that play a crucial role in protecting the body against injury and infection. Inflammation is characterized by redness, swelling, heat, and pain, resulting from the release of various mediators such as prostaglandins, cytokines, and leukotrienes. While acute inflammation is beneficial for healing, chronic inflammation is associated with several pathological conditions, including arthritis, musculoskeletal disorders, and autoimmune diseases. Effective management of pain and inflammation is therefore essential to improve patient quality of life and functional outcomes.

Etoricoxib provides effective analgesic and anti-inflammatory action with reduced gastrointestinal irritation compared to traditional NSAIDs. However, even with its COX-2 selectivity, long-term oral use can still lead to systemic adverse effects, including cardiovascular risks, gastric discomfort, and hepatic strain. [2, 3]Moreover, extensive first-pass metabolism reduces its bioavailability, necessitating higher doses to achieve therapeutic action.

Topical drug delivery offers an attractive alternative by directly targeting the affected area while minimizing systemic exposure. A topical gel formulation ensures convenience, ease of application, improved patient compliance, and potentially faster onset of action. Despite these advantages, the topical delivery of etoricoxib remains challenging due to its poor aqueous solubility, lipophilic nature, and limited skin permeability. These factors limit the amount of drug that can pass through the stratum corneum to exert therapeutic effects. [4]

Need for the Study

- Oral administration of etoricoxib causes gastrointestinal discomfort and first-pass metabolism.
- Topical delivery can localize the effect and minimize systemic toxicity.
- Etoricoxib's poor solubility and permeability require novel formulation approaches.
- There is a need to develop a stable, high-permeability topical gel with optimum viscosity, spread ability, and sustained drug release. [6,7]

Challenges Associated with Oral Delivery of Etoricoxib

Etoricoxib is a BCS Class II drug characterized by low aqueous solubility but high permeability. Poor water solubility restricts its dissolution in the gastrointestinal tract and contributes to variable absorption. Moreover, oral administration subjects the drug to hepatic first-pass metabolism, thereby decreasing its effective bioavailability. Long-term or high-dose oral therapy may also lead to systemic side effects such as gastric discomfort, cardiovascular risks, and hepatic stress. These limitations highlight the need to explore safer and more efficient alternative delivery routes. [8]

Importance of Topical Drug Delivery

- Delivers anti-inflammatory agents directly to the affected area.
- Bypasses first-pass metabolism, improving drug bioavailability.
- Minimizes systemic side effects associated with oral administration.
- Allows localized and targeted therapeutic action.
- Provides more consistent and controlled drug release.
- Enhances patient compliance due to non-invasive and easy application.
- Suitable for chronic pain and inflammatory conditions requiring localized delivery.
- Topical gels are particularly effective as they spread easily and are non-greasy.
- Ensures minimal systemic drug exposure while maintaining therapeutic concentration at the site of action. [9,10]

Limitations of Topical Formulation for Etoricoxib

Despite the advantages of topical delivery, formulating etoricoxib into an effective topical product presents several challenges. Etoricoxib is lipophilic and has low water solubility, which limits its ability to permeate through the stratum corneum, the outermost barrier of the skin. Additionally, the rigid skin barrier restricts drug diffusion, resulting in inadequate therapeutic concentration reaching deeper layers. To overcome these limitations, it is essential to incorporate suitable co-solvents and permeation enhancers that can improve solubility and facilitate better skin penetration. [11]

Need for a Novel Gel Formulation

Among various topical dosage forms, gels are preferred because of their superior spread ability, non-greasy nature, and better patient acceptability. Carbopol-based gels are widely used due to their excellent rheological properties, stability, and ability to provide controlled release. Incorporating permeation enhancers such as oleic acid, propylene glycol, or Transcutol® can significantly improve the solubility and transdermal delivery of etoricoxib. [12] Developing a high-permeability novel gel formulation can help increase therapeutic effectiveness while minimizing systemic side effects, making it a promising alternative to oral etoricoxib therapy. [13]

Advantages of Gel Formulations: Gel-based formulations have gained considerable attention as effective carriers for topical drug delivery. Gels offer several advantages, including-

- Non-greasy and easily washable
- Better patient acceptance
- Good spreadability
- Cooling and soothing effect
- Controlled drug release
- Transparent and aesthetically pleasing

Rationale of the Study

Etoricoxib is an effective anti-inflammatory drug, but its oral administration is associated with poor solubility, variable absorption, and systemic side effects. A novel topical gel with enhanced permeability can address these challenges by providing localized, prolonged, and effective drug delivery. Therefore, the present study focuses on formulating and evaluating a high-permeability etoricoxib gel using optimized excipients, gelling agents, and permeation enhancers to achieve improved therapeutic outcomes and patient safety. [14]

Need of the Study

Etoricoxib is a widely used selective COX-2 inhibitor for the management of pain and inflammatory conditions. Although effective, its oral administration is associated with significant limitations, including gastrointestinal irritation, cardiovascular concerns, hepatic stress, and reduced bioavailability due to first-pass metabolism. Long-term oral therapy increases the risk of systemic side effects, making it unsuitable for patients requiring prolonged treatment. [15]

Topical drug delivery offers a safer and more targeted alternative by delivering the drug directly to the inflamed area. However, etoricoxib has poor water solubility and limited skin permeability, which restricts its therapeutic effectiveness when used in conventional topical formulations. Therefore, there is a need to develop a novel gel formulation that incorporates suitable co-solvents and permeation enhancers to improve drug solubility and facilitate deeper skin penetration. [16]

A high-permeability etoricoxib gel can provide several advantages localized action, reduced systemic toxicity, sustained drug release, ease of application, and improved patient compliance. Such a formulation may also improve therapeutic outcomes in chronic inflammatory disorders while minimizing risks associated with oral NSAID therapy. [16]

Thus, the study is justified as it aims to overcome the existing limitations of etoricoxib delivery by developing an optimized, effective, and patient-friendly novel topical gel, addressing both clinical need and formulation challenges. [17]

Etoricoxib: Drug Profile

Property	**Description**
Chemical Name	5-chloro-6′-methyl-3-[4-(methylsulfonyl)phenyl]-2,3′-bipyridine
Molecular Formula	$C_{18}H_{15}ClN_2O_2S$
Molecular Weight	358.84 g/mol
Drug Class	Selective COX-2 inhibitor (NSAID)
Appearance	White to off-white crystalline powder
Solubility	Poorly soluble in water; soluble in organic solvents (methanol, ethanol)
pKa	4.5
Log P (Partition Coefficient)	2.8–3.0 (lipophilic)
Melting Point	134–136°C
Bioavailability	100% (oral)
Half-life (t½)	22 hours
Protein Binding	92%
Route of Administration	Oral (conventional), topical (novel formulations)
Stability	Stable under normal conditions; sensitive to extreme pH and light
BCS Classification	Class II (Low solubility, high permeability)

Mechanism of Etoricoxib: The primary mechanism of action of etoricoxib involves the selective inhibition of the COX-2 enzyme, which is responsible for the synthesis of prostaglandins at sites of inflammation. By blocking COX-2 activity, etoricoxib effectively reduces the production of inflammatory mediators, thereby alleviating pain, swelling, and inflammation without significantly affecting COX-1, which plays a protective role in the gastrointestinal tract. This selectivity contributes to its improved gastrointestinal safety profile compared to non-selective NSAIDs.

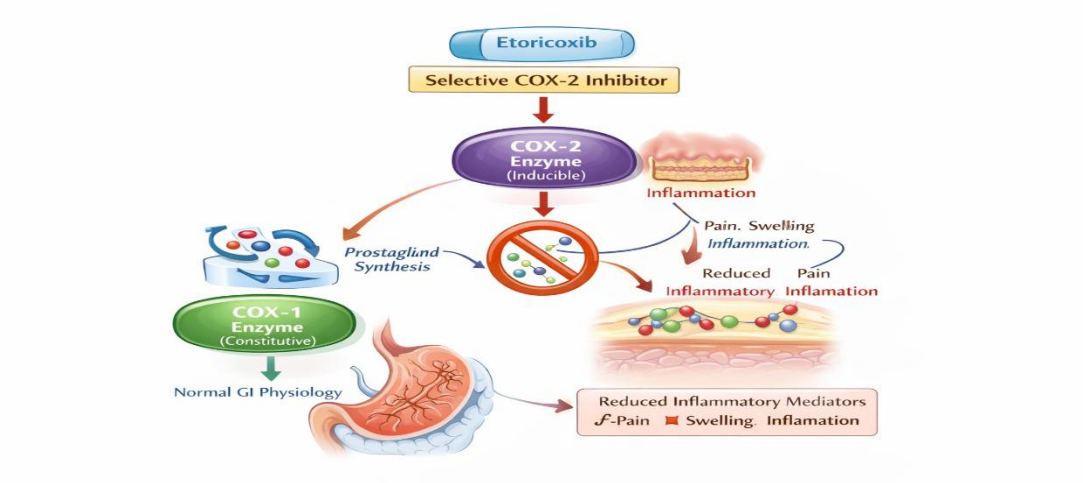

Fig: 1 Mechanism of Etoricoxib

Therapeutically, etoricoxib is indicated for the treatment of various inflammatory conditions, including osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute gouty arthritis, and postoperative pain. Its potent anti-inflammatory and analgesic effects make it an effective option for both acute and chronic conditions.

Skin as a Barrier to Drug Delivery

The skin is the largest organ of the human body and serves as a protective barrier against external environmental factors, pathogens, and chemical substances. While this barrier function is essential for maintaining homeostasis, it also poses a significant challenge for drug delivery, particularly in topical and transdermal systems. The outermost layer of the skin restricts the penetration of most therapeutic agents, making it difficult to achieve effective drug concentrations at the target site. Therefore, understanding the structure of the skin and the factors influencing drug permeation is crucial for the successful development of topical formulations.

The skin is composed of three main layers: the epidermis, dermis, and hypodermis. The epidermis is the outermost layer and serves as the primary barrier to drug penetration. It consists of multiple sublayers, among which the stratum corneum is the most critical for drug delivery. This layer is made up of dead, keratinized cells embedded in a lipid matrix, commonly described as a "brick and mortar" structure, which significantly restricts the entry of most drugs. Beneath the epidermis lies the dermis, a thicker layer composed of connective tissue, blood vessels, lymphatics, and nerve endings. Once a drug permeates through the epidermis and reaches the dermis, it can either exert a local therapeutic effect or be absorbed into systemic circulation via the blood vessels. The deepest layer, the hypodermis or subcutaneous layer, consists mainly of adipose tissue and connective tissue. It provides insulation, mechanical support, and also acts as a reservoir for drugs, contributing to prolonged drug retention and sustained release.

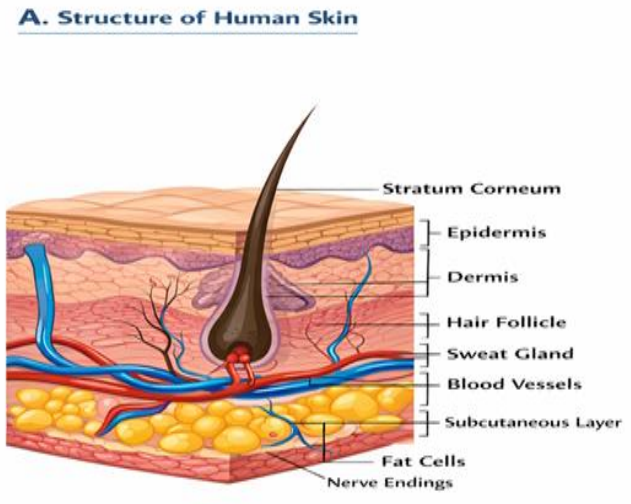

Fig: 2 Structure of Skin

The stratum corneum is the outermost layer of the epidermis and serves as the primary barrier to drug permeation through the skin. It is composed of dead, keratinized cells known as corneocytes, which are embedded within a lipid matrix consisting mainly of ceramides, cholesterol, and fatty acids. This unique arrangement is often described as a "brick and mortar" structure, where the corneocytes act as bricks and the lipid matrix functions as mortar. The stratum corneum plays a crucial role in preventing transepidermal water loss, thereby maintaining skin hydration, and protecting the body from external environmental factors such as chemicals, pathogens, and toxins. However, this barrier function also limits the penetration of most therapeutic agents, particularly hydrophilic and large molecular weight drugs.Drug permeation across the stratum corneum occurs through three main pathways.

- The transcellular route involves the passage of drugs directly through the corneocytes, requiring the drug to partition between hydrophilic and lipophilic domains, which makes this pathway less favorable due to high resistance.
- The intercellular route, which is the most common pathway, involves drug diffusion through the lipid matrix between the cells and is more suitable for lipophilic drugs.
- The appendageal route, also known as the shunt pathway, involves drug transport through hair follicles and sweat glands and plays a minor but significant role, especially for large molecules and particulate systems.

Factors affecting drug permeation

Drug permeation through the skin is influenced by a combination of physicochemical properties of the drug and biological characteristics of the skin. Among the physicochemical factors, molecular size plays a crucial role, as smaller molecules penetrate more easily than larger ones.

Lipophilicity, commonly expressed as the partition coefficient (log P), is another important factor, with moderately lipophilic drugs showing optimal permeation due to their ability to partition into both lipid and aqueous phases of the skin.

Adequate solubility in both water and lipids is essential for effective diffusion across the skin layers. The degree of ionization also affects permeation, as non-ionized forms of drugs are more permeable than ionized forms. Additionally, higher drug concentration can enhance the rate of diffusion by increasing the concentration gradient across the skin.

Biological factors also significantly impact drug permeation. Skin thickness varies across different body sites and can influence the extent of drug absorption.

Hydration of the stratum corneum enhances permeability by loosening the tightly packed lipid structure. Age is another factor, as the skin of infants and elderly individuals may exhibit different permeability characteristics.

Blood flow in the dermis affects systemic absorption by maintaining the concentration gradient. Furthermore, the condition of the skin, such as damage, disease, or inflammation, can increase permeability, while temperature elevation can enhance drug diffusion by increasing molecular movement. Overall, successful topical drug delivery depends on optimizing both drug properties and skin conditions to facilitate efficient permeation.

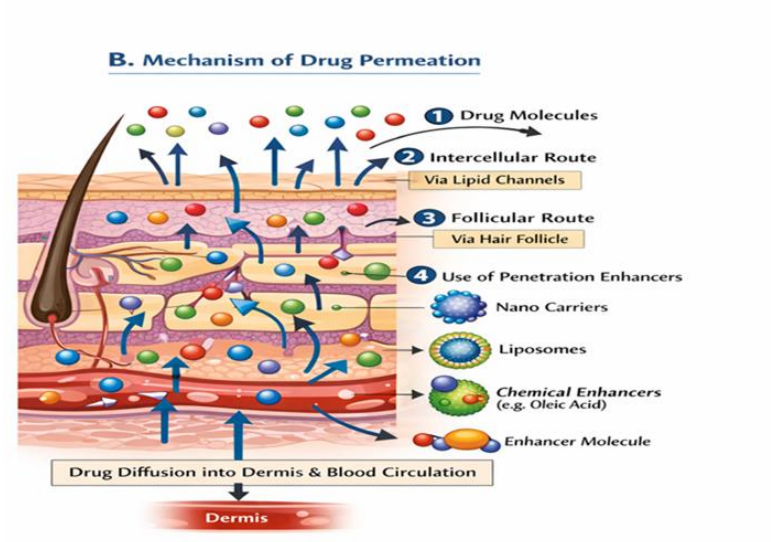

Fig: 3, Mechanism of Drug permeation

Need for Enhanced Permeation

The effectiveness of topical drug delivery is largely limited by the barrier function of the stratum corneum, which restricts the penetration of many therapeutic agents, especially those with poor aqueous solubility like Etoricoxib. Therefore, enhancing drug permeation is essential to achieve sufficient drug concentration at the site of action. High-permeability gel formulations are designed to overcome this limitation by incorporating penetration enhancers, optimizing drug solubility, and utilizing advanced delivery systems such as nanoemulsions and liposomes. These strategies help in improving drug diffusion across the skin and ensure better therapeutic efficacy.

High-permeability gel formulations enable targeted drug delivery by delivering the drug directly to the affected site, thereby minimizing systemic exposure and reducing adverse effects. This localized action is particularly beneficial in the treatment of inflammatory conditions such as arthritis, where the drug is required at a specific site. Furthermore, the ease of application, non-invasive nature, and reduced dosing frequency associated with gel formulations contribute to improved patient compliance. Overall, high-permeability gels represent an effective and patient-friendly approach for enhancing the therapeutic outcomes of topical drug delivery systems.

Formulation Strategies for High-Permeability Etoricoxib Gel

Selection of Polymers

The choice of polymer plays a crucial role in determining the consistency, stability, and drug release behaviour of gel formulations. Polymers such as Carbopol, hydroxypropyl methylcellulose (HPMC), and Poloxamer are widely used in topical gel systems. Carbopol is a synthetic high-molecular-weight polymer known for its excellent gelling properties, high viscosity, and ability to provide controlled drug release. HPMC is a semi-synthetic polymer that offers good film-forming ability, biocompatibility, and sustained drug release characteristics. Poloxamer, a thermoreversible polymer, forms gels at body temperature and enhances drug permeation due to its surfactant properties. The selection and concentration of these polymers significantly influence the rheological properties and permeability of the gel.

Penetration Enhancers

Penetration enhancers are incorporated into gel formulations to improve drug permeation across the stratum corneum. Chemical enhancers such as ethanol, propylene glycol, and oleic acid are commonly used. Ethanol enhances permeation by extracting lipids from the skin and increasing drug solubility, while propylene glycol acts as both a solvent and a humectant, improving drug partitioning into the skin. Oleic acid disrupts the lipid structure of the stratum corneum, thereby facilitating drug diffusion. In addition to synthetic agents, natural penetration enhancers such as essential oils and terpenes are gaining attention due to their safety, biocompatibility, and minimal irritation potential. The appropriate selection of penetration enhancers is essential to achieve optimal drug delivery without causing skin damage.

Novel Drug Delivery Approaches

Advanced drug delivery systems are increasingly employed to enhance the permeability and bioavailability of poorly soluble drugs like Etoricoxib. Nanoemulsions and micro emulsions improve drug solubility and provide a large surface area for absorption, thereby enhancing skin permeation. Liposomes and niosomes are vesicular carriers that encapsulate the drug and facilitate its transport through the skin by merging with biological membranes. Nanostructured lipid carriers (NLCs) are another promising approach, offering improved drug loading capacity, controlled release, and enhanced stability. These novel systems help in overcoming the barrier properties of the skin and significantly improve therapeutic efficacy.

Excipients and Their Role

Excipients play a vital role in ensuring the stability, efficacy, and acceptability of gel formulations. Solvents such as ethanol and water are used to dissolve the drug and other components, while co-solvents help improve drug solubility. Stabilizers are added to maintain the physical and chemical stability of the formulation, preventing phase separation and degradation. Preservatives are essential to inhibit microbial growth and extend the shelf life of the product. Other excipients, such as humectants and buffering agents, help maintain moisture and pH, ensuring compatibility with the skin. The careful selection and optimization of excipients are critical for developing an effective and stable high-permeability gel formulation.

Methods of Preparation of Gel

Conventional Gel Preparation

The preparation of topical gels generally begins with the dispersion of a suitable gelling agent in an appropriate solvent system, usually purified water. Polymers such as Carbopol or HPMC are slowly added with continuous stirring to avoid lump formation and allowed to hydrate completely. In some cases, the dispersion is

kept aside for a specific period to ensure proper swelling of the polymer. The hydrated polymer forms the base of the gel, which determines its viscosity and consistency. Temperature control and gentle stirring are essential during this step to maintain uniformity and prevent air entrapment.

Incorporation of Drug and Excipients

The drug, such as Etoricoxib, is first dissolved in a suitable solvent or co-solvent system (e.g., ethanol or propylene glycol) to enhance its solubility. This drug solution is then gradually incorporated into the hydrated gel base with continuous stirring to ensure uniform distribution. Other excipients, including penetration enhancers, preservatives, stabilizers, and humectants, are added sequentially depending on their compatibility and function. Care is taken to maintain homogeneity and avoid phase separation. The order of addition and mixing speed play a critical role in achieving a stable formulation.

Neutralization and Homogenization Techniques

For gels prepared using polymers like Carbopol, neutralization is a crucial step to achieve proper gel formation. Neutralizing agents such as triethanolamine or sodium hydroxide are added gradually to adjust the pH, leading to swelling of the polymer and conversion of the dispersion into a clear gel. The pH is carefully adjusted to match the skin's physiological range to avoid irritation. Homogenization is then carried out using mechanical stirrers or homogenizers to ensure uniform consistency, smooth texture, and even distribution of all components. This step also helps in reducing particle size and eliminating air bubbles, resulting in a stable and aesthetically acceptable gel formulation.

Evaluation of Etoricoxib Gel

Physical Evaluation

The prepared gel formulations are first evaluated for their physical characteristics, including appearance, colour, clarity, and homogeneity. The gel should be visually inspected for the presence of any lumps, phase separation, or particulate matter. A good formulation should be smooth, transparent or uniformly opaque, and free from grittiness. Homogeneity is assessed by applying a small quantity of gel on the skin to check for uniform consistency and absence of aggregates, which ensures proper distribution of the drug within the gel base.

pH Determination

The pH of the gel is measured using a digital pH meter by immersing the electrode directly into the gel formulation. The pH should ideally be in the range of skin pH (approximately 5–7) to avoid irritation and ensure compatibility with the skin. Maintaining an appropriate pH is also important for drug stability and permeability, as extreme pH values may lead to skin irritation or degradation of the formulation.

Viscosity

Viscosity is a critical parameter that influences the consistency, spreadability, and drug release behaviour of the gel. It is commonly measured using a Brookfield viscometer at different rotational speeds. The viscosity should be optimized to ensure that the gel is neither too thick nor too fluid, allowing easy application and adequate retention on the skin. Viscosity also affects drug diffusion, although its exact relationship with drug release may vary depending on the formulation.

Spreadability

Spreadability determines the ease with which the gel can be applied to the skin. It is measured by placing a known quantity of gel between two glass slides and applying a specific weight, then calculating the time required for the gel to spread. A shorter spreading time indicates better spreadability. Good spreadability ensures uniform application, enhances patient compliance, and improves therapeutic effectiveness.

Drug Content Uniformity

Drug content uniformity is evaluated to ensure that the active ingredient is evenly distributed throughout the gel. A known quantity of gel is dissolved in a suitable solvent, filtered, and analyzed using UV-visible spectrophotometry. Samples are usually taken from different portions (top, middle, and bottom) of the formulation to confirm uniform distribution. Consistent drug content is essential for accurate dosing and therapeutic efficacy.

In Vitro Drug Release Studies

In vitro drug release studies are performed to determine the rate and extent of drug release from the gel formulation. These studies are typically carried out using a Franz diffusion cell with a suitable membrane (e.g., cellophane membrane). The gel is placed in the donor compartment, and the receptor compartment contains a suitable dissolution medium maintained at physiological conditions. Samples are withdrawn at predetermined intervals and analyzed spectrophotometrically. These studies help in understanding the release kinetics and performance of the formulation.

Ex Vivo Skin Permeation Studies

Ex vivo permeation studies are conducted using animal or human skin (e.g., rat or goat skin) mounted on a Franz diffusion cell. The gel is applied to the donor compartment, and the receptor compartment contains a buffer solution maintained at 37°C. Samples are collected over time to determine the amount of drug permeated through the skin. Parameters such as flux, permeability coefficient, and enhancement ratio are calculated to evaluate the effectiveness of the formulation in delivering the drug across the skin barrier.

Skin Irritation Studies

Skin irritation studies are performed to evaluate the safety of the gel formulation. These studies are usually carried out on animal models or human volunteers by applying the gel to a specific area of skin and observing for signs of irritation such as redness, itching, or swelling over a defined period. A non-irritant formulation is essential for patient safety and acceptability.

Stability Studies

Stability studies are conducted to assess the physical, chemical, and microbiological stability of the gel over time. The formulation is stored under different conditions of temperature and humidity (e.g., 25°C, 40°C) as per ICH guidelines. Parameters such as appearance, pH, viscosity, and drug content are evaluated at regular intervals. Stability studies help in determining the shelf life and storage conditions of the formulation.

Future Perspectives

Need for Clinical Trials

Although preclinical and in vitro studies have demonstrated promising results for high-permeability etoricoxib gel formulations, there is a significant need for well-designed clinical trials to establish their safety, efficacy, and therapeutic equivalence or superiority over conventional oral formulations. Clinical studies are essential to evaluate parameters such as bioavailability, onset of action, patient outcomes, and long-term safety. Additionally, regulatory approval for topical formulations requires robust clinical evidence, making clinical trials a critical step toward successful translation from laboratory research to clinical application.

Personalized Topical Therapies

Advancements in pharmaceutical sciences and precision medicine are paving the way for personalized topical therapies. Individual variations in skin type, age, disease condition, and genetic factors can significantly influence drug absorption and response. Future formulations may be tailored to meet patient-specific needs by adjusting drug concentration, formulation type, or permeation enhancers. The integration of nanotechnology and smart delivery systems may further enable controlled and targeted drug release, improving therapeutic outcomes and minimizing side effects.

Industrial and Commercial Potential

High-permeability etoricoxib gel formulations hold substantial industrial and commercial potential due to their advantages over conventional oral dosage forms. The growing demand for non-invasive and patient-friendly drug delivery systems has increased interest in topical formulations within the pharmaceutical market. These gels offer opportunities for product differentiation, improved patient compliance, and reduced systemic side effects, making them attractive for commercialization. However, successful scale-up, cost-effectiveness, regulatory compliance, and long-term stability are key factors that must be addressed for industrial production. With continued research and technological advancements, etoricoxib gel formulations are likely to emerge as viable and competitive therapeutic products in the global pharmaceutical market.

II. Conclusion

In summary, the development of high-permeability gel formulations of Etoricoxib represents a promising approach for effective topical drug delivery. These formulations address the limitations associated with oral administration, such as gastrointestinal and cardiovascular side effects, by providing localized drug action with reduced systemic exposure. Various formulation strategies, including the use of suitable polymers, penetration enhancers, and novel drug delivery systems, play a crucial role in improving drug permeation across the skin barrier.

High-permeability gels are particularly important as they enhance drug absorption through the stratum corneum, ensuring adequate therapeutic concentration at the site of action. Their non-greasy nature, ease of application, and improved patient compliance further support their use as an alternative to conventional dosage forms.

Despite these advantages, further research is required to optimize formulation parameters, ensure long-term stability, and validate clinical efficacy through human studies. Future advancements in nanotechnology and personalized medicine may further improve the performance of topical gel systems, making them a valuable option in the management of inflammatory conditions.

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