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Review Article

Formulation and Evaluation of Diclofenac Gel in Painkiller

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ABSTRACT

The creation of a topical gel containing diclofenac sodium for the management of localised musculoskeletal pain and inflammation is the main goal of this investigation. Because of its strong analgesic and anti-inflammatory qualities, diclofenac, a non-steroidal anti-inflammatory medication (NSAID), is used extensively. The objective was to improve the topical treatment of diclofenac using a potent gel formulation, reducing the systemic adverse effects linked to oral dosing. Different gel formulations were made with varying quantities of gelling chemicals, including Hydroxypropyl Methylcellulose (HPMC) and Carbopol 934. The physicochemical characteristics of the produced gels, such as their appearance, pH, viscosity, spreadability, drug content, and in vitro drug release, were assessed. The optimised formulation demonstrated homogeneous medication distribution, enough viscosity for topical usage, and a pH that was appropriate for skin application. The results show that a well formulated diclofenac gel can be used as a topical treatment for inflammatory diseases with better patient adherence.

INTRODUCTION

Many people frequently experience pain and swelling, particularly as a result of diseases like arthritis, injuries to the muscles, or difficulties with the joints. Among the most Diclofenac is a common drug used to treat this pain since it helps lower discomfort and inflammation. Despite its effectiveness, diclofenac pills can occasionally cause gastrointestinal issues and other negative effects, particularly when taken for extended periods of time. As a result, different ways to administer the drug have been developed, such as diclofenac gel. By applying diclofenac gel directly to the skin, the medication can target the sore spot without having an impact on the entire body. Because it lowers the possibility of adverse effects such stomach irritation that might occur with oral

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versions, this technique is advantageous. The medication is delivered precisely where it is needed by the gel's absorption through the skin and deep penetration into underlying tissues, including muscles and joints. Certain components in the gel improve this transdermal absorption by making it easier for the active substance to cross the skin barrier. After being ingested, diclofenac functions by preventing the body from producing prostaglandins, which are molecules that cause pain and inflammation. For ailments like tendinitis, sports injuries, and osteoarthritis, this targeted distribution offers efficient pain relief. The gel's localised action lowers the likelihood of systemic adverse effects by enabling high drug concentrations at the location of pain with low bloodstream levels. When the first diclofenac gel products were released in the 1990s, they immediately gained popularity among those who wished to relieve their pain without having to deal with the negative side effects of oral drugs. Improvements in pharmaceutical technology have allowed for increased skin penetration, quicker absorption, and longer-lasting effects, leading to an improvement in the formulation of these gels throughout time. Even more efficient at providing rapid and secure pain relief are more recent iterations of diclofenac gel. Knee arthritis is treated with topical diclofenac sodium gel [1] . You can apply this gel to your skin as directed; it is a member of a class of NSAIDs that lessens inflammation on the affected area of your body. It functions by lowering inflammation and is a member of the NSAID class of medications. Other conditions may also be treated with this drug. Diclofenac sodium topical gel is used to treat osteoarthritis pain in joints that may benefit from skin-based therapy. [2] In comparison to oral drug delivery systems, topical formulations are used to treat a wide range of illnesses, are simple to give, and have quick effects. Different dose forms, including gel, cream, paste, and others, are available for topical medications [3]. Topical gel formulations are a good choice for drug administration since they are less oily, simple to remove from the skin, and have physicochemical characteristics including pH, Spreadability, rheological properties, Osteoarthritis (OA) is a complicated joint disease that causes pain, stiffness, decreased mobility, and, in certain situations, disability before ultimately leading to the loss of joint function [4]. OA is characterised as a painful, inflammatory cartilage arthritis that is impacted by mechanical, immunological, genetic, and other inflammatory-related variables. Clinical evidence has demonstrated abnormalities of the subchondral bone, synovium, and synovial fluid, and inflammatory changes are frequently observed in afflicted joints, particularly with more advanced disease. OA, especially of the knee, can lead to decreased mobility, a poor quality of life, and a heavy burden of acute and chronic pain. [5]

Epidemiology:

Although OA can affect any joint, it most commonly affects the hands, foot, knees, hips, and facet joints. In 2005, estimates put the number of Americans with OA at about 26 million. However, depending on the criteria used, as well as the age, sex, and geographic location examined, the prevalence of OA varies considerably. A radiological case definition of OA is the basis for the highest reported prevalence. radiography showing the prevalence of osteoarthritis in the hands, hips, and knees [6]

Hand OA:

The frequency of radiographic hand OA may vary from 27 to over 80%, according to research. According to a study conducted in the Netherlands, 75% of women between the ages of 60 and 70 had distal interphalangeal (DIP) joints with OA, and 10–20% of participants between the

ages of 40 and 50 had OA radiological abnormalities.8 Data from the Framingham cohort showed that 13.2% of men and 26.2% of women aged 70 or older had at least one hand joint with symptomatic osteoarthritis. In a rural Turkish sample, every man over 65 had at least one injured hand joint [7] . Symptomatic hand OA satisfies the ACR criteria, albeit being far less common. It was shown to be 8% and 7% prevalent in the Framingham cohort and the third National Health and Nutrition Examination Survey (NHANES III) of the United States, respectively. Among senior citizens, rates increased to 13% for men and 26% for women. Teheran found that 2.2% of persons between the ages of 40 and 50 had hand OA, and by the time a person was in their sixties, that percentage had increased to 22.5%. This sample's gender disparities showed that women were more frequently affected than men, which is consistent with several studies, such as the Framingham cohort. Interestingly, data from 13 investigations including 29,621 people in China revealed that symptomatic OA of the hand was rarely present [8].

Hip OA:

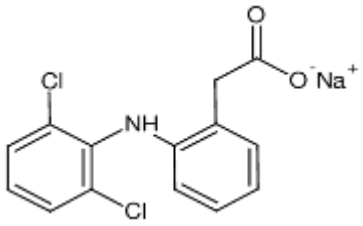
Hip OA is less common than OA in the hands or knees. The mean prevalence of primary radiographic hip OA in Asian and African studies is 1.4% and 2.8%, respectively. Compared to North America and Europe, where the mean prevalence is 7.2% and 10.1, respectively, these figures are far lower [9]. Eleven different criteria were used to assess the frequency of radiographic hip OA in women over 65 who had osteoporotic fractures. When the minimal joint gap of 2.5 mm was removed, the prevalence varied from 1.8 to 9.4%, depending on the criterion used. The frequency of symptomatic hip OA, however, varied from 5.9% in individuals aged 45 to 54 to 17% in those aged 75 and above, according to the analysis of the Johnston County sample.

Knee OA:

Knee involvement occurs less frequently than hand OA, while being more common in women (the female-to-male ratio ranges from 1.5:1 to 4:1). According to population research, knee OA prevalence rates in the USA are comparable to those in Europe. This study found that 1% of those aged 25 to 34 and over 50% of people aged 75 and older had significant radiographic abnormalities. In the Framingham Study, the prevalence of radiographic knee OA rose from 19.2% among participants over 45 to 43.7% among those over 80. According to the Dutch Institute for Public Health, 15.6% of men and 30.5% of women aged 55 and over have knee OA. Ten Knee OA symptoms were seen in just 12.1% of NHANES III participants and 16.3% of Johnston County Osteoarthritis Project participants between the ages of 55 and 64. The epidemiology of OA varies greatly by area. Research conducted in China using the same methods and criteria as the Framingham research found that the prevalence of lateral compartment disease and bilateral knee OA was two to three times higher in Chinese cohorts compared to the estimates from the Framingham OA research. According to research conducted in Asia by the Community Orientated Program for Control of Rheumatic Disorders (COPCORD), the frequency of clinically diagnosed knee OA varied from 1.4% in metropolitan Filipinos to 19.3% in rural Iranian communities. The physical and economical environment may have contributed to this disparity. The COPCORD studies conducted in Bangladesh, India, and Pakistan specifically looked at differences between rural and urban populations. In India, the crude prevalence of clinically diagnosed knee OA was higher in urban areas (5.5%) than in rural areas (3.3%). Rural areas had a higher incidence even after controlling for age and sex distribution. Additionally, men aged 60 and older from rural locations in China had

about twice as many cases of symptomatic knee OA as men from metropolitan settings [10] .

Profile of Formulation Ingredients [11]



1. Diclofenac Sodium [12]:

Role: Active Pharmaceutical Ingredient (API)

Function: the primary component in charge of the analgesic, antipyretic, and anti-inflammatory properties. It lessens discomfort, oedema, and inflammation by preventing the synthesis of prostaglandins, which mediate pain and inflammation, by the enzymes COX-1 and COX-2.

Concentration: Typically, 1% or 2% in the gel formulation, depending on the product.

2. Water (Aqua) [13]:

Role: Solvent and base

Function: The main base and solvent in the gel is water. It facilitates the dissolution of other ingredients and gives the product its gel-like consistency. simple to use. Additionally, it facilitates diclofenac's skin absorption.

Concentration: usually between 60 and 80 percent of the composition.

3. Carbomer:

Role: Gelling Agent

Function: The polymer carbomer is what gives the gel its structure. It helps to stabilise the formulation and thickens the gel to give it the proper consistency. Additionally, carbomer makes the gel feel softer and less oily on the skin.

Concentration: Usually between 0.5% and 1%, depending on the gel consistency that is required.

4. Triethanolamine (TEA) [14]:

Role: pH Adjuster

Function: To keep the gel's pH within a range that is appropriate for the diclofenac's stability and the comfort of the skin, TEA is utilised. It neutralises the gel-forming carbomer.

Concentration: Generally low concentrations, contingent on the formulation's pH.

5. Isopropyl Alcohol:

Role: Solvent and penetration enhancer

Function: As a solvent, isopropyl alcohol aids in the dissolution of some substances and improves diclofenac's skin penetration. Additionally, it helps with rapid evaporation and drying following application.

Concentration: Depending on the formulation, between 2 and 5%.

6. Propylene Glycol [15]:

Role: Humectant and skin conditioner

Function: Propylene glycol facilitates the gel's moisture retention and improves diclofenac's skin absorption. Additionally, it can enhance the minimise discomfort and improve the gel's texture.

Concentration: Typically, around 2-10%.

7. Glycerin [16]:

Role: Humectant

Function: Glycerin draws in moisture, which keeps the skin moisturised and facilitates the gel's easy application. Additionally, it adds to the gel's feel.

Concentration: Typically, 3-5% in the formulation

Pharmacological action of Diclofenac:

Diclofenac is a phenylacetic acid derivative and non-steroidal anti-inflammatory drug (NSAID). NSAIDs inhibit cyclooxygenase (COX)-1 and-2 which are the enzyme responsible for producing prostaglandins (PGs). PGs contribute to inflammation and pain signalling. Diclofenac, like other NSAIDs, is often used as first line therapy for acute and chronic pain and inflammation from a variety of causes. Diclofenac was the product of rational drug design based on the structures of phenylbutazone, mefenamic acid, and indomethacin [17]

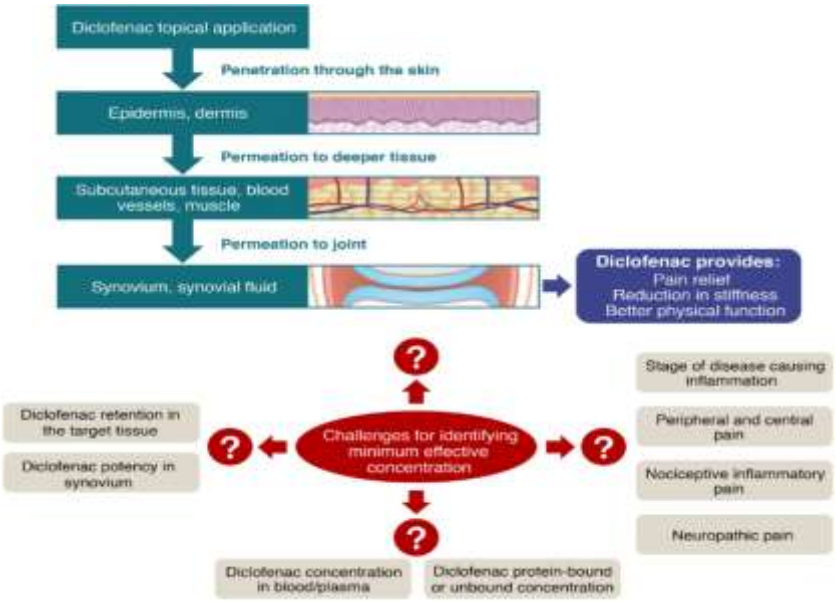
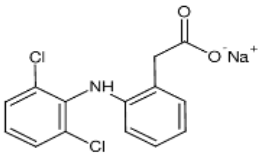


Fig.no:1- Pharmacological action of Diclofenac

The addition of two chlorine groups in the ortho position of the phenyl ring locks the ring in maximal torsion which appears to be related to increased potency. It is often used in combination with misoprostol to prevent NSAID-induced gastric ulcers. Diclofenac was first approved by the FDA in July 1988 under the trade name Voltaren, marketed by Novartis (previously Ciba-Geigy).

Modality Small Molecule	**Groups** Approved, Investigational, Vet approved **Weight** Average:296.149 Monoisotopic: 295.016684015
Structure 	**Chemical Formula** $C_{14}H_{11}Cl_2NO_2$ **Synonyms** • Diclofenac • Diclofenac acid • Diclofenaco • Diclofenacum

Ideal property of Anti-inflammatory

A perfect anti-inflammatory gel should be safe, stable, therapeutically effective, and easy to use. Important characteristics include a non-greasy, non-irritating formulation, a skin-friendly pH, and good spreadability.

Therapeutic and Safety Properties

- **Effective Anti-inflammatory Activity:** The main purpose is to drastically lessen pain and inflammation at the application site. Its effectiveness is frequently on par with or superior to that of common oral or topical drugs.
- **Minimal to No Skin Irritation:** When administered topically, the gel shouldn't result in negative side effects including erythema (redness) or oedema (swelling). The components must be inert and non-toxic, particularly the preservatives and gelling agents.
- **Appropriate pH:** To guarantee skin compatibility and the best stability/bioavailability of the active ingredients, the formulation's pH should be around the skin's normal physiological pH, which is normally between 5.0 and 7.0.
- **Good Drug Release and Permeability:** To reach the target tissues and have a localised impact, the formulation should permit a high proportion of drug release and sufficient skin penetration.

Physical and Aesthetic Properties:

Good Homogeneity and Appearance:

The gel should be free of phase separation and have a smooth, consistent, and uniform texture. The ideal viscosity is one that is both high enough to remain on the applied area and low enough to be easily dispensed from a tube for effortless application.

Outstanding Spreadability:

The gel should apply to the skin with little to no effort, which is crucial for patient comfort and adherence, particularly on skin that is injured or irritated.

Non-Sticky and Non-Greasy:

User pleasure depends on a pleasant application experience.

Washable:

With water, the gel should be simple to remove from hands and skin without leaving any residue or discolouration.

Stability and Manufacturing Properties:

Stability:

For a prolonged amount of time (e.g., several months), the formulation must be physically and

chemically stable under both standard and accelerated storage settings without experiencing appreciable alterations to its characteristics or drug content.

Good Extrudability:

It should be simple to squeeze out of its packing, such as a collapsable tube, indicating good extrudability.

Inert Gelling Agent:

The gelling agent shouldn't break down the active substances or react with other formulation elements.

Resistance to Microbial Attack:

In order to stop microbial growth, the formulation needs to be well kept.

Side effect of anti-inflammatory gel:

Topical nonsteroidal anti-inflammatory medications, often known as NSAIDs, or anti-inflammatory gels, most frequently cause modest skin reactions at the application site, including redness, itching, dryness, or irritation.

Common Local Side Effects:

- **Skin irritation**: Redness, itching, burning, or pain at the site of application.
- Dryness, scaling, or peeling skin.
- Rash.
- Increased sensitivity to sunlight (photosensitivity), which can lead to severe sunburns, blisters, and swelling if the treated area is not protected.

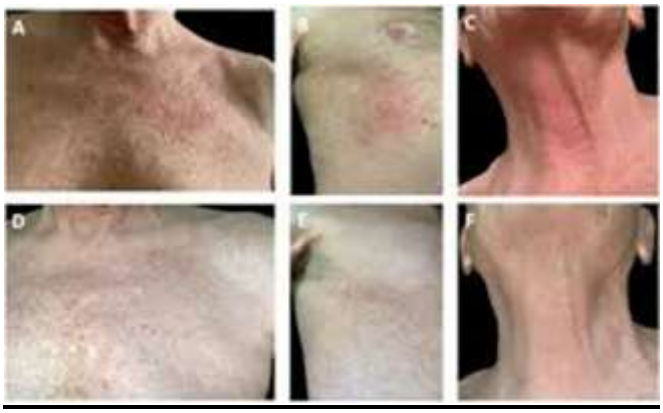


Fig.2: Local Side Effects

Serious (but Rare) Systemic Side Effects:

Because a small amount of the medication can be absorbed into the bloodstream, serious side effects associated with oral NSAIDs are possible, though rare with proper topical use.

- **Gastrointestinal issues**: Stomach pain, heartburn, nausea, and in severe cases, stomach ulcers or bleeding (indicated by black, tarry stools or vomiting blood that looks like coffee grounds).
- **Cardiovascular problems**: Increased risk of high blood pressure, fluid retention, heart failure, heart attack, or stroke.
- **Kidney or liver damage**: Symptoms may include unusual tiredness, dark-colored urine, yellowing of the skin or eyes (jaundice), or swelling of the ankles, feet, or legs.

- **Severe allergic reactions**: Symptoms such as difficulty breathing, wheezing, hives, or swelling of the face, lips, tongue, or throat require immediate medical attention.

Important Precautions:

- Do not apply to damaged, broken, infected, or inflamed skin.
- Avoid covering the treated area with a bandage or applying external heat (like a heating pad).
- Consult a healthcare provider before use if you have a history of heart disease, high blood pressure, kidney or liver problems, stomach ulcers, or bleeding disorders.
- Seek emergency help if you experience symptoms of a heart attack, stroke, stomach bleeding, or a severe allergic reaction.

Fig.3: Precautions

Drug Profile of Diclofenac Sodium

1. Drug Name

- Generic name: Diclofenac Sodium
- Brand names: Dicloflex, Dynapar, Diclowin(varies by country)

2. Chemical Information

- Chemical name: Sodium 2-[(2,6-dichlorophenyl) amino]phenylacetate
- Molecular formula: $C_{14}H_{10}Cl_2NNaO_2$
- Molecular weight: 318.13 g/mol
- Drug class: Non-Steroidal Anti-Inflammatory Drug (NSAID)
- BCS class: Class II (low solubility, high permeability)

3. Pharmacological Category

- Anti-inflammatory
- Analgesic
- Antipyretic

4. Mechanism of Action

Diclofenac sodium inhibits cyclooxygenase enzymes (COX-1 and COX-2), leading to reduced synthesis of prostaglandins. Prostaglandins are mediators responsible for pain, inflammation, swelling, and fever. Diclofenac has a relatively higher COX-2 selectivity, which contributes to its strong anti-inflammatory action, particularly in osteoarthritis.

5. Indications

- Osteoarthritis
- Rheumatoid arthritis
- Ankylosing spondylitis

- Acute musculoskeletal pain
- Post-operative pain
- Dysmenorrhea
- Migraine attacks

6. Dosage Forms and Strengths

- Oral tablets/capsules: 25 mg, 50 mg, 75 mg (immediate/extended release)
- Topical gel: 1%, 2%, 3%
- Injection: 75 mg/3 ml (IM/IV)
- Transdermal patch
- Suppositories: 50 mg, 100 mg

7. Dose

- Adults: 75–150 mg per day in divided doses
- Osteoarthritis: Usually 100–150 mg/day
- Topical use: Apply 2–4 times daily
- Maximum dose: 150 mg/day (oral)

8. Pharmacokinetics

Absorption:

- Well absorbed orally; bioavailability ~50–60% due to first-pass metabolism

Distribution:

- Highly protein bound
- Widely distributed to synovial fluid

Metabolism:

- Extensively metabolized in the liver

Elimination:

- Excreted via urine (~65%) and bile (~35%)

Half-life:

- 1–2 hours

9. Adverse Effects

- Gastrointestinal irritation, ulcer, bleeding
- Nausea, vomiting, abdominal pain
- Cardiovascular risk (hypertension, thrombotic events)
- Renal impairment
- Hepatotoxicity (rare)
- Skin reactions (topical use)

10. Contraindications

- Hypersensitivity to diclofenac or other NSAIDs
- Active peptic ulcer disease
- Severe heart failure
- Severe hepatic or renal impairment
- Third trimester of pregnancy

11. Special Precautions

- Use lowest effective dose for shortest duration
- Caution in elderly patients
- Monitor liver and kidney function during long-term therapy

12. Storage

- Store below 25°C
- Protect from moisture and light

13. Therapeutic Importance in Osteoarthritis

Diclofenac sodium is one of the most effective NSAIDs for pain and inflammation relief in osteoarthritis. Its availability in topical formulations provides targeted action with fewer systemic side effects, making it suitable for long-term OA management.

CONCLUSION:

All of the essential pharmaceutical requirements for a topical analgesic were satisfied by the formulated Diclofenac Sodium gel (1%). It had an excellent pH and consistency. It is a viable and efficient substitute for oral NSAIDs due to its

compatibility, spreadability, and stability. The gel lowers the risk of renal and gastrointestinal adverse effects by reducing systemic exposure. With room for improvement through better formulations and clinical testing, this study validates topical Diclofenac's promise as a safe and efficient treatment for localised pain and inflammation.

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