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Topical Analgesic Gels: A Promising Solution for Acute and Chronic Pain Relief

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A B S T R A C T

It is a derivative of phenyl acetic acid created as an anti-inflammatory substance. It possesses analgesic, anti-inflammatory, and antipyretic effects similar to other NSAIDs. It is advised for the long-term management of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. It is beneficial for acute bone conditions, post-surgery discomfort, and menstrual pain. Seven distinct formulations of diclofenac sodium gel were created. There are different Diclofenac gels on the market. The suggested gel contains two main ingredients, oleoresin and linseed oil, which provide an anti-inflammatory benefit. The formulations were assessed for different physical parameters, pH stability, drug release feasibility studies, and drug release mechanisms. The formulation demonstrated peak drug release after 8 hours and maximum drug concentration. Ultimately, the gel formulations prove to be cost-effective and could mitigate the issues related to the drug's absorption.

Keywords: Diclofenac sodium, Topical gel, analgesic, anti-inflammatory.

1. Introduction

Topical delivery is defined as topical application of a product containing the medicament to the skin for treatment of cutaneous conditions (e.g. an acne) or cutaneous manifestations of a systemic disease (e.g. psoriasis) with the objective of controlling the pharmacological or other action of the medicament to the skin surface or in the skin itself. Semi-solid formulations in their various forms dominate topical delivery. Issues have arisen regarding the conventional topical dosage forms of lotions, creams, ointments, and powders relative to drug release from the topical dosage form, delivery from the topical dosage form, and drug diffusion through the skin. Creams and lotions often have poor bioavailability of the medicament, in part, as a result of rapid clearance from the skin and poor release of the medicament from the base. Non-hydrophilic ointments are oleaginous, greasy, and are overall inconvenient to patients, and medicated powders for topical delivery have reduced and short residence time on skin. Gels are semisolid formulations that restrict movement of the dispersion medium through an interlacing, three-dimensional network of the dispersed phase particles or solvated macromolecules.

The semisolid phase of a gel is due to the increase in viscosity due to intertwining and resulting internal friction. A gel may also contain entwined matted strands often linked together by stronger forms of van der Waals Forces to create both crystalline and amorphous areas throughout the gel.

For topical treatment for dermatological disorders, there are several vehicle options available to clinicians and patients with a range of solids, semisolids, and liquid preparations. Within the semisolid formulations, clear gels are widely used in both cosmetics and pharmaceuticals.

Among the various semisolid dosage forms, gels have become the dosage form of choice because of their ease of application and improvement in drug absorption through the skin. The functional typical three-dimensional structure properties of gels arise from the linkages among the polymer chains. Gels can resist the physiologic stress imparted by skin flexion, blinking and mucociliary movement by taking the shape of the area to which they are applied and controlling drug delivery. The efficacy of a topical application principally depends upon its rate and extent of drug release from the base.

Gels are a good formulation for various routes of administration including oral, topical and nasal administration. A gel can be a clear formulation when all of the particles are soluble in the dispersing medium; however, this is not possible in all gels for various reasons which make some gels turbid.

Diclofenac is an FDA approved drug used to treat and manage acute and chronic pain associated with inflammatory conditions, specifically those that affect the musculoskeletal system, such as osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Topically, diclofenac is indicated for the treatment of actinic keratosis. Additionally, diclofenac is FDA approved for ophthalmic use for cataract extraction, ocular pain and photophobia. Diclofenac is a non-steroidal anti-inflammatory drug (NSAID); while it may help in managing symptoms of pain during the inflammatory processes, it does not reverse or prevent chronic joint damage associated with osteoarthritis and rheumatoid arthritis. Diclofenac was synthesized in 1973, and is the most used NSAID globally. Diclofenac has been used off-label for biliary colic, corneal abrasion, fever, gout, migraine, myalgia and post-episiotomy pain. In February 2020, diclofenac 1% gel was approved for use over-the-counter for arthritic pain management; all other products containing diclofenac are prescription only.

Some studies have proven the effectiveness of using diclofenac in the postoperative period to lessen the requirement of rescue analgesia in surgical patients.

1.1 Mechanism of action of Diclofenac sodium

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) in the phenylacetic families and reduces inflammation like other NSAIDs. It has analgesic and antipyretic effects like other NSAIDs. Diclofenac exerts its effects by inhibiting cyclooxyge- nase-1 (COX-1) and cyclooxygenase-2 (COX-2) by suppressing the synthesis of proteinoid inflammatory elements, such as prostaglandin-E2 (PGE2), prostacyclins, and thromboxane, that are key components of inflammation and the nocice- ptive response. Diclofenac competitively inhibits arachidonic acid to bind to COX-1 and COX-2. Diclofenac inhibits COX-1 and COX-2 in roughly equal amounts but some evidence suggests that diclofenac selectively inhibits COX-2 roughly four times more than COX-1 in vitro experiments. However, this value is significantly different than reported selectivity of 20 times with reported selective COX-2 inhibitors of forecoxa. This way diclofenac can be better understood by similarity to celecoxib. Diclofenac and other NSAIDs also posses the ability to inhibit thromboxane's, primarily thromboxane-b2 (TXB2). Diclofenac is widely regarded is one of the more potent inhibitors of PGE2 production, the primary proteinoid elevation during inflammatory re- action.

COX-1 is an enzyme that is always functionally active and is expressed nearly everywhere in the body, with seemingly stable levels and activity. COX-1 is involved in normal platelet activity and blood flow to the renal tissues and helps protect the gastric mucosa from harmful acid, among other functions. COX-2 is an inducible enzyme that is greatly overexpressed in the setting of tissue damage or inflammatory mediators that are also nociceptive and induce pain in the surrounding area. These mediators include thromboxane's, leukotrienes, and prostaglandins. The effects of Diclofenac's COX-2 inhibition are believed to primarily occur in the target tissues, such as synovial fluid and the joint capsules. The inhibition of COX in other tissues, such as the stomach, may lead to the depletion of many protective substances and may ultimately lead to gastric irritation, for example. Many of these proposed mechanisms of action are considered tentative by the clinical community.

The analgesic effects of diclofenac on the periphery can be attributed to its ability to reduce the availability of sensitized peripheral pain receptors, via downregulation, stimulated by the L-arginine nitric oxide cGMP pathway through ATP-sensitive potassium channels. There is also some evidence that diclofenac has an effect on reducing elevated levels of substance P, which is a well-established pro-inflammatory neuropeptide that has nociceptive effects, in the synovial fluid of patients with rheumatoid arthritis.

The mechanism of action of diclofenac by inhibiting the formation of downstream metabolite biotransformation of arachidonic acid may provide a rationale for use in actinic keratosis and the prevention of more malignant conditions. In this mechanism, topical diclofenac can inhibit the production of epithelial growth factor that would frighten angiogenesis and inhibit apoptosis in proliferating tissues. However, this mechanism is still undergoing investigation and discussion.

1.2 Linseed Oil (Linum usitatissimum)

The Latin name for the flax plant, the source from which the oil is derived, means most useful. The usefulness of the plant, oil, and seeds are documented throughout history. There are two familiar names for the products of the same plant, linseed oil and flaxseed oil. Linseed oil is more commonly used and is produced commercially by extracting oils from the seeds using either heat or by compressing the seeds under steam and high pressure. This is the oil that is widely used in producing paints, wood preservatives, varnishes, stains, linoleum, and putty. Flaxseed oil is produced by cold pressing the seed. The oil produced from cold pressing is not filtered, deodorized or refined. Linsegu and the oils have been used internally for digestive disorders, including stomach disorders, and a laxative. Linseed oil has been shown to be a valuable ingredient in cosmetic formulations including emollients, soaps, and shaving creams. Linseed is also thought to be a valuable ingredient of skin poultices for treating burns and scalds. Chemically, it is viewed as high in omega-3 fatty acids compared to common fish oils. A typical fatty-acid composition would include linolenic (57%), oleic (19%), linoleic (15%), palmitic (6%) and stearic (3.5%). Flaxseed oil contains vitamin A and beta carotene (a precursor of vitamin A).

The oils oxidize rapidly; therefore, it is necessary to avoid storage in a refrigerated airtight bottle. The study of topical linseed oil's anti-inflammatory activity showed that clinical evidence of inflammation was decreased and the oil tested showed radical scavenging capacity. The anti-inflammatory activity of linseed oil is due to its antioxidant capacity and bioactive ingredients (Barra et al., 2020). Flaxseed oil (rich in ω-3 PUFAs) with the probiotic L. plantarum has anti-inflammatory properties, supports Th1-mediated cell-mediated immunity and phagocytosis, and appears to moderate the inflammatory response (Chytilová et al., 2013). A double blind, randomized clinical trial participant, conducted on pre-diabetic subjects, was undertaken to study the effects of flazxseed oil supplementation on some inflammatory indices. Subjects took two 1000 mg capsules of flaxseed oil per day, for 14 weeks. The authors of the trial said flaxseed oil supplementation had a beneficial effect on inflammatory indices in prediabetic patients. Thus, this study indicated that flaxseed oil supplementation may be a beneficial method of improving inflammatory markers in pre-diabetic patients.

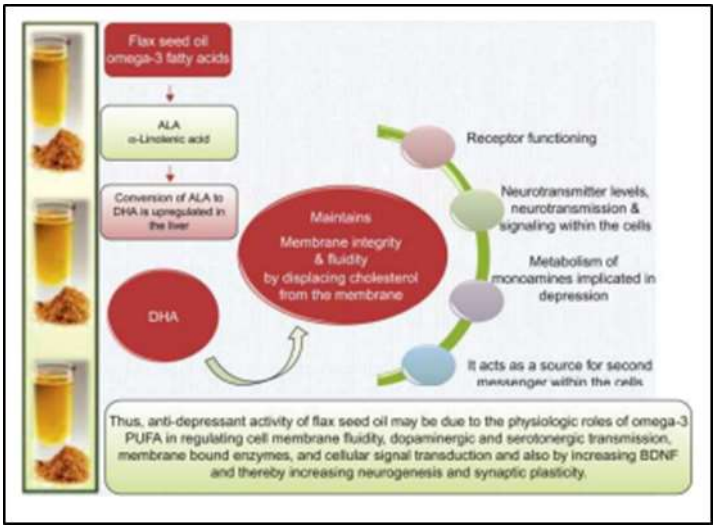

Fig. 1: Properties of linseed oil

Fig. 2: Diclofenac linseed oil topical analgesic gel

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3. Background

3.1 Materials and Methods

Material: Diclofenac sodium, Methyl paraben, Propyl paraben, Alcohol isopropyl, Menthol, Propylene glycol, and Carbopol 940P.

Procedure:

1. Carbopol was added in a ratio of 100ml of purified water and left for 8 hours.
2. Added Triethanolamine to neutralize the citric acid and the Carbopol base for proper PH Adjustment.
3. Diclofenac was added in propylene glycol before adding heat at a temperature of 65 degrees Celsius.
4. Then add methyl paraben + Add the solution of Propylene glycol.
5. Cool down to stop during room temperature.
6. Add Linseed oil as Base.
7. The resultant mixture was there added to Carbopol Base with help of a Mechanical Stirrer by Rotating At 600 RPM.

3.2 Method of Preparation

Preparation of gel: Carbopol 934 gels were initially created by preparing a stock solution of the Carbopol in distilled water and propylene glycol. Separately Diclofenac sodium (1w/w) was dissolved in reweighed amounts of propylene glycol. The solvent mix was then transferred to the Carbopol beaker and stirred for an additional 20 minutes. The dispersion was also allowed to hydrate and swell for an hour, later neutralized to pH with sodium hydroxide solution while stirring. The samples were also allowed to equilibrate for at minimum 24 hours at room temperature before carrying out rheological measurements.

Preparation of diclofenac gel: For the preparations F1, F2, F3, 0.2g of diclofenac sodium was accurately weighed and dissolved in 3ml of propylene glycol with the assistance of gentle heating (SOLUTION A). The weighed amount of Carbopol was then added to the 16ml of distilled water which was stirred until it was completely dissolved (SOLUTION B). Solutions A and B were then mixed thoroughly, and the total weight was set to 20g. For preparations F4, F5, F6, 0.2g of diclofenac sodium was weighed, and again dissolved in 3ml of propylene glycol with a gentle heating (SOLUTION A). The weighed amount of Carbopol 940P was then added to the 20 ml of distilled water and stirred to dissolve. Then the solution was neutralized by 10% NaOH (SOLUTION B). Solutions A and B were mixed thoroughly and was then adjusted up to 20g. In some batches (F1, F3, F4, F6) of the polymer-based gel that contained Diclofenac sodium, precipitation was observed, which may be due to an incompatibility within the system. Therefore, these batches were discarded and the remaining batches (F2, F5) were considered for subsequent studies.

3.3 Therapeutic indications

(Diclofenac Diethylamine, Linseed Oil, Methyl Salicylate, and Menthol Gel) is used to treat sprains, strains, bruises, and soft tissue rheumatism. Diclofenac Sodium, Linseed Oil, Methyl Salicylate, and Menthol Gel is a non-staining warming gel indicated for quick relief in the aches and pains of joints and muscles associated with arthritis, backaches, rheumatism, fibrositis, lumbago, sciatica, stiff neck, as a home treatment for a stiff nose, aching feet, tennis elbow, rheumatic pain, bruised, chilblains.

3.4 Posology and Method of Administration Direction

A one-inch ribbon of KRISHAT RELIEF GEL (Diclofenac Diethylamine, Linseed Oil, Salicylic Acid and Menthol Gel) should be applied to the site of injury 3—4 times daily by rubbing until the film disappears. Route: For external application only.

Dosage: Gently rub a small amount of gel onto intact skin over the area of pain or swelling until it disappears. Usually, a dollop approximately 3 cm will be enough, but the amount can change depending on the size of the affected area. Do not cover the area of application with a bandage or similar product. Apply 3-4 times daily or as directed by your physician. Do not apply the gel to cuts, open wounds, or diseased skin. Do not apply the gel to or around the eyes, nose, mouth, genital, or anal area. If the gel comes into contact with any of these areas, rinse thoroughly with a lot of clean water. Obtain your physician's consent before using this gel if you are pregnant or breastfeeding.

3.5 Contraindications

DICLOFENAC RELIEF GEL (Diclofenac Diethylamino, Linseed Oil, Methyl Salicylate & Menthol Gel) is not recommended for patients who have shown hypersensitivity to any of the constituents included in the gel formulation. Do not use Diclofenac Sodium, Linseed Oil, Methyl Salicylate & Menthol Gel to treat patients with a history of asthma, acute rhinitis or urticaria, or an allergic-type reaction to aspirin or other NSAIDs. Patients have reported severe, rarely fatal, anaphylactic-like reactions to NSAIDs. KRISHAT RELIEF GEL (Diclofenac Diethylamino, Linseed Oil, Methyl Salicylate & Menthol Gel) is not recommended for use during the third trimester of pregnancy.

3.6 Special warnings and precautions

Patients should refrain from taking a hot bath or shower around the time of gel application as this may exacerbate the burning sensation. This drug should not reach the eyes or mucous membranes. Tight dressings should not be placed on the gel. The hands should be cleansed immediately after applying the gel unless treating hands and fingers. As with other NSAIDs, anaphylactoid reactions may happen in patients without previous exposure to diclofenac. Diclofenac sodium should be used with caution in the aspirin triad. This triad may occur primarily in an asthmatic patient with rhinitis (with or without nasal polyps) or having severe, even deadly, bronchospasm after ingestion of aspirin or other NSAIDs. The diclofenac product should be avoided on open skin wounds, infected lesions, or exfoliative dermatitis conditions. The product should be used carefully in the presence of a history of active gastrointestinal ulceration or bleeding or reduced heart, liver, or renal function because isolated cases of systemic adverse reactions including renal toxicity have been reported with topical anti-inflammatory agents. NSAIDs are known to affect platelet function. Even if the chance of systemic side effects is very low, caution needs to be taken in patients with an intracranial hemorrhage or bleeding diathesis. While being treated it is advised to avoid direct sunlight including solarium. If skin reactions of sensitivity occur, discontinue use.

Fertility, pregnancy and breastfeeding. There is no or insufficient evidence for human safety in pregnancy or while breastfeeding. As a precaution, KRISHAT RELIEF GEL (Diclofenac dimethylamine, Linseed Oil, Methyl Salicylate & Menthol Gel) should be prescribed for use in pregnancy or while breastfeeding only if there is no other safer alternative.

Effect on driving and using machinery Not applicable. Undesirable effects Localized cutaneous side effects such as rash, itching and redness are infrequently noted, In clinical studies in patients treated with GEL (Diclofenac dimethylamine, Linseed Oil, Methyl Salicylate & Menthol Gel), localized terminal side effects including dermatitis, exfoliation, dry skin and rash, were noted at a higher incidence than in subjects taking placebo. If severe dermal reactions occur, treatment with GEL (Diclofenac dimethylamine, Linseed Oil, Methyl Salicylate & Menthol Gel) may be stopped until the severe event is resolved.

3.7 Overdose Signs and symptoms

Because topical Diclofenac is minimally absorbed systemically, overdose is very unlikely. If a significant systemic side effect occurs after ingestion caused by accidental use, the typical therapeutic measures for poisoning with a nonsteroidal anti-inflammatory drug would be appropriate.

3.8 Treatment

Treatment of overdose with NSAIDs is generally supportive and symptom based. There is not a typical clinical presentation of diclofenac overdose. Supportive and symptomatic treatment should be given in cases of complications like hypotension, renal failure, convulsions, gastrointestinal irritation, and respiratory depression; specific measures like forced diuresis, dialysis, or hemoperfusions may be needed.

3.9 Treatment

Pharmacodynamic properties Pharmacotherapeutic group: Topical antirheumatics and analgesics. ATC Code: MA01AB55 Mechanism of Action: Diclofenac acts by inhibiting the effect of the cyclo-oxygenase (COX) enzymes. The cyclo-oxygenase enzymes help to generate prostaglandins, which are the chemicals that are produced at sites of injury or damage causing pain and inflammation. By inhibiting the effect of the COX enzymes, the number of prostaglandins is decreased, which ultimately reduces pain and inflammation. The linseed oil assists with penetration of diclofenac through the skin. Methyl salicylate also functions as an analgesic, and menthol provides relief from its cooling effects. Pharmacokinetic properties When known, and or applied topically, diclofenac sodium, methyl salicylate, linseed oil and menthol readily distribute and penetrate into subcutaneous tissue, muscle tissue and in or around the joint. Preclinical safety data Not relevant.

Table 1: Formulation chart od's diclofenac linseed oil gel,

DRUG	Diclofenac[%]	2gm	2gm	2gm	2gm
EXCIPIENT	Propylene Glycol[%]	10ml	10ml	10ml	10ml
	Methyl paraben[%]	0.15gm	0.15gm	0.15gm	0.15gm
	Propyl Paraben[%]	0.005gm	0.05gm	0.05gm	0.05gm
	Carbopol[%]	1.5gm	1.5gm	0.05gm	0.05gm
	Triethanolamine[%]	2ml	2ml	1.5	2ml
VEHICLE	Ethanol[%]	0	16.86ml	30ml	67.4ml
	Purified water[%]	20ml	20ml	20ml	10ml
	Oleoresin	1.0gm	1.4gm	1.4gm	1.4gm
	Linseed oil	8.5ml	8.5ml	8.5ml	8.5ml

Table 1

Table 2. Composition of gel formulation

INGREDIENTS	F1(gm)	F2(gm)	F3(gm)	F4(gm)	F5(gm)
Clove oil(ml)	0.75	0.75	0.75	0.75	0.75
Carbopol(gm)	0.3	0.4	0.5	0.6	1
Polyethylene glycol(ml)	15	15	15	1.5	15
Glycerin(ml)	5	5	5	5	5
Methyl Paraben(gm)	0.18	0.18	0.18	0.18	0.18
Propyl paraben(gm)	0.02	0.02	0.02	0.02	0.02
Aspartame(gm)	0.4	0.4	0.4	0.4	0.4
Distilled water(ml)	q. s	q. s	q. s	q. s	q. s

Table 2

4. Conclusion

Diclofenac sodium is an NSAID (non-steroidal anti-inflammatory drug) with anti-inflammatory, analgesic and antipyretic properties. To avoid the adverse effects seen with oral administration of diclofenac sodium while retaining the benefits of topical effectiveness, it was necessary to formulate topical gels in and for this study. Within the study it was shown that F2 gel was produced with good consistency, homogeneity, and spread capability. As the polymer is water soluble, it formed a water-washable gel and has broader options for topical dosage forms. Protein denaturation is the process whereby a protein loses its tertiary structure and secondary structure by the action or influence of some external stressor such as a strong acid, organic solvent or heat. The majority of biological proteins lose whatever biological activity they may have had when they denature, as denaturation is a verified mechanism causing inflammation in biological systems. In the interest of studying the mechanism of action for the anti-inflammatory properties of diclofenac sodium, the ability of diclofenac sodium to inhibit protein denaturation was studied, which has been demonstrated by other anti-inflammatory drugs when induced by thermal conditions, to be dose-dependent in its thermal denaturation property. Denaturation of protein is a well-documented cause of inflammation. Part of the study on the mechanism of anti-inflammatory action, the effect of diclofenac sodium on protein denaturation was investigated. Other anti-inflammatory drugs have been shown to inhibit thermally induced protein denaturation in a dose-dependent manner. Linseed Oil is a highly versatile product. It has a wide range of uses, from health food supplements, linoleum flooring, to many other applications. Linseed oil has a high tri- and di-unsaturated ester content, and it readily reacts with air. Since products of linseed oil can quickly dry from exposure, it is important to store it sealed in an airtight container.

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