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Review Article

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Short Review on Topical Diclofenac Gel

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Abstract The purpose of writing this review on pharmaceutical gel was to compile the recent literature with special focus on rational approach to topical formulation and basic components of topical drug delivery systems. Topical application of drugs offers potential advantages of delivering the drug directly to the site of action and acting for an extended period of time. Skin is one of the extensive and readily accessible organs on human body for topical administration and is main route of topical drug delivery system. Diclofenac when it is applied topically to the skin to ease muscular pains, sprains and strains.When diclofenac is applied to the skin as a gel (or a patch containing gel), instead of it having an effect on all of your body, it only works on the area that you have applied it to. Topical gels are intended for skin application or to certain mucosal surfaces for local action or percutaneous penetration of medicament or for their emollient or protective action.

Keywords

Introduction

Gels are semisolid systems in which there is interaction (either physical or covalent) between colloidal particles within a liquid vehicle. The vehicle is continuous and interacts with the colloidal particles within the three:

- Aqueous
- Hydroalcoholic
- Alcohol based or non aqueous

Gels are substantially dilute cross-linked system, which exhibits no flow when in the steady-state. By weight, gels are mostly liquid, yet they behave like solids due to a three-dimensional cross-linked network within the liquid. It is the crosslinking within the fluid that gives a gel its structure (hardness) and contributes to the adhesive stick (tack). In this way gels are a dispersion of molecules of a liquid within a solid in which the solid is the continuous phase and the liquid is the discontinuous phase.

Gel is mainly delivered into the body by topical route. Topical route is the attractive route for local and systemic treatment

Advantage of Topical Route

- It provides a largest surface area.
- It avoids first-pass effects, gastrointestinal irritation.
- It avoid metabolic degradation associated with oral administration [1].

Mechanism of Drug Absorption:

The principal mechanisms of drug absorption are:

- Passive diffusion

- Pore transport
- Facilitated diffusion
- Active transport
- Ionic or electrochemical diffusion
- Ion-pair transport Endocytosis [2]

Physiological Factors Affecting Skin Penetration

- Skin temperature
- Regional variation
- Traumatic/pathologic injury to skin
- Cutaneous drug metabolism [3]

Formulation Factors affecting Skin Penetration

- Penetration enhancer
- Occlusivity
- Drug concentration
- pH
- Solubility [4]

Advantages of Gels

- Gels are used to achieve optimal cutaneous and percutaneous drug delivery.
- They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH.
- Gels are having property to avoid enzymatic activity and drug interaction with food and drinks.
- They can substitute for oral administration of medication when the route is unsuitable.
- They can avoid the first pass effect, that is, the initial pass of drug substance through the human body.
- They avoid systemic and portal circulation following gastrointestinal absorption.
- Gels are not deactivated by liver enzymes because the liver is bypassed.
- They are non-invasive and have patient compliance.
- They are applied over skin for slow and prolonged absorption.
- Gels have also been applied in pharmacy to some viscous suspension for oral use for example Aluminium hydroxide gel.
- They have localized effect with minimum side effects [5-7].

Disadvantages of Gels

- Gels have possibility of allergenic reactions.
- Enzyme in epidermis may denature the drugs of gels.
- Drugs of larger particle size do not absorb through the skin.
- They have poor permeability of some drugs through the skin.
- Selection of area to be examined carefully during application of gels.
- Gels which are used for the introduction into body cavity or the eyes should be sterilized.
- They may cause application side reactions.
- They may cause skin allergy during application [6, 8-9].

Properties of Gels

Gels should posses the following properties

- Ideally, the gelling agent for pharmaceutical or cosmetic use should be inert, safe, and should not react with other formulation components.
- The gelling agent included in the preparation should produce a reasonable solid-like nature during storage that can be easily broken when subjected to shear forces generated by shaking the bottle, squeezing the tube, or during topical application.
- It should possess suitable anti-microbial to prevent from microbial attack.
- The topical gel should not be tacky.
- The ophthalmic gel should be sterile [10].

Classification

Classification of Gels is following:

- Controlled release gels
- Organogels
- Extended release gels
- Amphiphilic gels
- Hydrophilic gels
- Non aqueous gels
- Bioadhesive gels
- Thermosensitive sol-gel reversible hydrogels
- Complexation gels
- Hydrogel

Preparation of Gels

Gels are normally in the industrial scale prepared under room temperature. However few of polymers need special treatment before processing. Gels can be prepared by following methods.

- Thermal changes
- Flocculation
- Chemical reaction

Diclofenac

Diclofenac is a medicine called a non-steroidal anti-inflammatory drug. It is often referred to simply as 'an anti-inflammatory', or as an 'NSAID'. It works by preventing the production of some chemicals in your body which cause pain and inflammation. Diclofenac when it is applied topically to the skin to ease muscular pains, sprains and strains. When diclofenac is applied to the skin as a gel (or a patch containing gel), instead of it having an effect on all of your body, it only works on the area that you have applied it to. It is absorbed into your skin and then moves deeper into areas of your body where there is inflammation (for example, your muscle). Using a topical product means that the total amount of diclofenac in your body remains low. This in turn means that you are much less likely to have a side-effect to the medicine.

There is also a diclofenac gel called Solaraze® which is used to treat skin damage caused by sun exposure - it is not interchangeable with the gel used for pain relief. Diclofenac can also be taken by mouth in the form of tablets or capsules, and can be used in the eye as an eye drop. [13]

Preparation of Diclofenac Gel

Hydrogels were formulated by first preparing a stock solution of the nipagin and nipazol in 50 g distilled water. Separately Diclofenac sodium (1% w/w) was dissolved in preweighted amounts of glycerol. Solvent blend was transferred to conservation water and agitated by adding small amounts of HEC. The dispersion was then allowed to hydrate and swell for 60 min and then was stirred by the help of an electric mixing propeller [1,2].

Indications and Usage for Diclofenac Gel

Diclofenac sodium topical gel, 1% is indicated for the relief of the pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands.

- Diclofenac sodium topical gel, 1% has not been evaluated for use on the spine, hip, or shoulder.

Diclofenac Gel Dosage and Administration

Dosing Card

The dosing card can be found attached to the inside of the carton.

The proper amount of diclofenac sodium topical gel, 1% should be measured using the dosing card supplied in the drug product carton. The dosing card is made of clear polypropylene. The dosing card should be used for each application of drug product. The gel should be applied within the oblong area of the dosing card up to the 2 gram or 4 gram line (2 g for each elbow, wrist, or hand, and 4 g for each knee, ankle, or foot). The 2 g line is 2.25 inches long. The 4 g line is 4.5 inches long. The dosing card containing diclofenac sodium topical gel, 1% can be used to apply the gel. The hands should then be used to gently rub the gel into the skin. After using the dosing card, hold with fingertips, rinse, and dry. If treatment site is the hands, patients should wait at least one hour to wash their hands.

Lower extremities, including the knees, ankles, and feet

Apply the gel (4 g) to the affected foot or knee or ankle, 4 times daily. Diclofenac sodium topical gel, 1% should be gently massaged into the skin ensuring application to the entire affected foot or knee or ankle. Do not apply more than 16 g daily to any single joint of the lower extremities.

Upper extremities including the elbows, wrists and hands

Apply the gel (2 g) to the affected hand or elbow or wrist, 4 times daily. Diclofenac sodium topical gel, 1% should be gently massaged into the skin ensuring application to the entire affected hand or elbow or wrist. Do not apply more than 8 g daily to any single joint of the upper extremities. Total dose should not exceed 32 g per day, over all affected joint.

Special Precaution

- Showering/bathing should be avoided for at least 1 hour after the application. If diclofenac sodium topical gel, 1% is applied to the hand(s) for treatment; patient should not wash the treated hand(s) for at least 1 hour after the application.
- Diclofenac sodium topical gel, 1% should not be applied to open wounds.
- Contact of diclofenac sodium topical gel, 1% with eyes and mucous membranes should be avoided.
- External heat and/or occlusive dressings should not be applied to treated joints.
- Avoid concomitant use of diclofenac sodium topical gel, 1% on the treated skin site with other topical products, including sunscreens, cosmetics, lotions, or other topical medications.
- Concomitant use of diclofenac sodium topical gel, 1% with oral non-steroidal anti-inflammatory drugs (NSAIDs) has not been evaluated, and may increase adverse NSAIDs effects.
- Wearing of clothing or gloves should be avoided for at least 10 minutes after applying diclofenac sodium topical gel, 1%.

Contraindications

The use of diclofenac sodium topical gel is contraindicated in patients with a known hypersensitivity to diclofenac.

Diclofenac sodium topical gel should not be administered in patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.

Diclofenac sodium topical gel is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

Warnings and Precautions

1. Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with NSAIDs, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke

2. Gastrointestinal Effects– Risk of GI Ulceration, Bleeding, and Perforation

Diclofenac can cause serious gastrointestinal (GI) events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3to 6 months, and in about 2% to 4% of patients treated for one year. . However, even short-term therapy is not without risk.NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding.Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAIDs therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population.

3. Hepatic Effects

In clinical trials, meaningful elevations of AST occurred in about 2% of approximately 5,700 patients at some time during diclofenac treatment. Elevations in transaminases were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis.Almost all meaningful elevations in transaminases were detected before patients became symptomatic. Abnormal tests occurred during the first 2 months of therapy with diclofenac in 42 of the 51 patients in all trials who developed marked transaminase elevations.Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.

If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur e.g., eosinophilia, rash, abdominal pain, diarrhea, dark urine, etc., diclofenac should be discontinued immediately. To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms ofhepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms), and the appropriate action patients should take if these signs and symptoms appear. Caution should be exercised in prescribing diclofenac sodium with concomitant drugs that are known to be potentially hepatotoxic (e.g., antibiotics, anti-epileptics).

4. Hypertension

NSAIDs, including diclofenac sodium topical gel, can lead to the onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of cardiovascular events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including diclofenac sodium topical gel should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with diclofenac sodium topical gel and throughout the course of therapy.

5. Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients treated with NSAIDs, including diclofenac sodium topical gel. Diclofenac sodium topical gel should be used with caution in patients with fluid retention or heart failure.

6. Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE-inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state..

7. Skin Reactions

NSAIDs, including diclofenac topical gel, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs and symptoms of serious skin manifestations, and the use of the drug should be discontinued at the first appearance of skin rash or any other signs of hypersensitivity. Diclofenac sodium topical gel should not be applied to open skin wounds, infections, inflammations, or exfoliative dermatitis, as it may affect absorption and tolerability of the drug.

8. Pregnancy

As with other NSAIDs, diclofenac sodium topical gel should be avoided in late pregnancy, because it may cause premature closure of the ductus arteriosus

9. Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoeisis. Patients on long-term treatment with NSAIDs, including diclofenac sodium topical gel, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients.

10. Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other non-steroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, diclofenac sodium topical gel should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Drug Interactions

1. Aspirin When diclofenac is administered with aspirin, the binding of diclofenac to protein is reduced, although the clearance of free diclofenac is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of diclofenac and aspirin is not generally recommended because of the potential of increased adverse effects.

2. Anticoagulants The effects of anticoagulants such as warfarin and NSAIDs on GI bleeding are synergistic, such thatusers of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

3. ACE-Inhibitors NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

4. Diuretics Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. The response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

5. Lithium NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs lithium clearance. The mean minimum lithium concentration

increased 15% and the, including diclofenac, and lithium are administered concurrently, patients should be observed carefully for signs of lithium toxicity.

6. Methotrexate NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs, including diclofenac, are administered concomitantly with methotrexate.

7. Cyclosporine Diclofenac, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Therefore concomitant therapy with diclofenac may increase cyclosporine's nephrotoxicity. Caution should be used when diclofenac is administered concomitantly with cyclosporine.

8. Oral Non-steroidal Anti-inflammatory Drugs The clinical trials of diclofenactopical gel prohibited concomitant use of oral NSAIDS. There is systemic exposure to diclofenac following normal use of diclofenac sodium topical gel, up to 6% of the systemic levels of a single oral dose of diclofenacsodium.Therefore, concomitant administration of diclofenac sodium topical gel with oral NSAIDs or aspirin may result in increased adverse NSAID effects.

9. Topical Treatments Concomitant use of diclofenac sodium topical gel with other topical products, including topical medications, sunscreens, lotions, moisturizers, and cosmetics, on the same skin site has not been tested and should be avoided because of the potential to alter local tolerability and absorption.

Use in Specific Populations

Pregnancy The safety of diclofenac sodium topical gel has not been established during pregnancy. There are no well-controlled studies of diclofenac in pregnant women. Human and animal studies indicate that diclofenac crosses the placenta. In late pregnancy, as with other NSAIDs, diclofenac sodium topical gel should be avoided because it may cause premature closure of the ductusarteriosus.

Teratogenic Effects Pregnancy Category C: Studies in mice, rats, and rabbits in which diclofenac was administered orally throughout gestation revealed no evidence of teratogenicity despite the induction of maternal toxicity and fetal toxicity corresponding to a human equivalent dose approximately 4.5-, 2-, and 9-fold (mouse, rat, rabbit, respectively) of the maximum human topical dose of diclofenac sodium topical gel (based on bioavailability and body surface area comparison).

Nonteratogenic Effects The use of diclofenac, as with other NSAIDs, is associated with the adverse fetal cardiovascular effect of premature closure of the ductusarteriosus.

Labor and Delivery In rat studies with oral NSAIDs, including diclofenac, as with other drugs known to inhibit prostaglandin synthesis, there is an increased incidence of dystocia and delayed parturition corresponding to a human equivalent dose approximately similar to the maximum recommended clinical dose (based on bioavailability and body surface area comparison). The effects of diclofenac sodium topical gel on labor and delivery in pregnant women are unknown.

Nursing Mothers It is not known whether diclofenac is excreted in human milk; however, studies in animals detected diclofenac in the milk after oral administration. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from diclofenac sodium topical gel a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use Safety and effectiveness in pediatric patients have not been established.

Geriatric Use Of the total number of subjects treated with diclofenac topical gel in clinical studies, 498 were 65 years of age and over. Diclofenac, as with any NSAID, is known to be substantially excreted by the kidney, and the risk of toxic reactions to diclofenac sodium topical gel may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken when using diclofenac sodium topical gel in the elderly, and it may be useful to monitor renal function.

Over-dosage

No events of accidental ingestion have been reported with diclofenac sodium topical gel. Symptoms following acute oral NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure,

respiratory depression, and coma may occur. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur after an overdose.

Clinical Pharmacology

Mechanism of Action

The mechanism of action of diclofenac is similar to that of other non-steroidal anti-inflammatory drugs. Diclofenac inhibits the enzyme, cyclooxygenase (COX), an early component of the arachidonic acid cascade, resulting in the reduced formation of prostaglandins, thromboxanes and prostacylin. It is not completely understood how reduced synthesis of these compounds results in therapeutic efficacy.

Pharmacodynamics

Diclofenac, the active component of diclofenac sodium topical gel has anti-inflammatory, anti-nociception, and anti-pyretic effects.

Pharmacokinetics

The pharmacokinetics of diclofenac sodium topical gel were assessed in healthy volunteers following repeated applications during 7 days of diclofenac sodium topical gel to 1 knee (4 x 4 g per day) or to 2 knees and 2 hands (4 x 12 g per day) versus the recommended oral dose of diclofenac sodium for the treatment of osteoarthritis (3 x 50 mg per day).

Systemic exposure (area under the concentration-time curve) and maximum plasma concentrations of diclofenac are significantly lower with diclofenac sodium topical gel than with comparable oral treatment of diclofenac sodium.

Systemic exposure with recommended use of diclofenac sodium topical gel (4 x 4 g per day applied to 1 knee) is on average 17 times lower than with oral treatment. (Basis: treatment with diclofenac sodium topical gel of 1 knee, 4 times a day versus 50 mg, 3 times a day of oral diclofenac tablets.) The amount of diclofenac sodium that is systemically absorbed from diclofenac sodium topical gel is on average 6% of the systemic exposure from an oral form of diclofenac sodium. The average peak plasma concentration with recommended use of diclofenac sodium topical gel (4 x 4 g per day applied to 1 knee) is 158 times lower than with the oral treatment.

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