



Review on Gel of Diclofenac Sodium and Thiocolchicoside as a Drug

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Abstract

Topical gels or formulations have several advantages over traditional dosage modalities. Topical gels deliver medication directly to the region of action. Topical gels avoid G.I. irritation and medication metabolism, increasing drug bioavailability. Diclofenac sodium is a phenyl acetic acid derivative developed as an anti-inflammatory agent. Like other NSAIDs, it possesses analgesic, anti-inflammatory, and antipyretic properties. Long-term therapy for rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis is advised. Thiocolchicoside treats muscle spasms, cramps, and musculoskeletal and neuromuscular problems. It is available in capsules and injectable form on the market. The main issue with Thiocolchicoside is its limited bioavailability, which ranges between 25 and 30%. To reduce drug loss because of first-pass metabolism and address the difficulty associated with limited drug bioavailability, semisolid preparations in the form of gels are required. Drug interactions and Food medication interactions are also not possible with topical gels. Gels have more penetrating capability since they are composed of two phases. This review thoroughly examined the gel's manufacture, properties, and evaluation parameters.

Keywords: Topical gel, Diclofenac Sodium gel, Thiocolchicoside gel, Ideal gel characteristics, and Evaluation parameter.

Introduction

Topical gels are semisolid, homogeneous preparations to cure and treat skin disorders. Because gels are more hydrophilic, the medication or active component release rate was rapid. A gel comprises two three-dimensionally cross-connected components and contains a correspondingly high quantity of liquid medium to build an appropriate stiff network that immobilizes the continuous liquid phase.^{1,2} Inorganic particles and organic macromolecules create a gel structure network. Chemical gels are held together by permanent covalent bonding. In contrast, physical topical gels are held together by weaker and reversible secondary intermolecular forces such as hydrogen bonding, electrostatic interactions, hydrophobic interactions, and Vander Waals forces^{3,4}. The semisolid state is caused by increased viscosity induced by interlacing and the resulting internal friction. A gel may also be composed of twisted matted strands frequently held together by more potent forms of Vander Waals Forces to generate crystalline and amorphous areas throughout the system.⁵ Gels are becoming more popular among semisolid dosage forms due to their ease of administration and superior percutaneous absorption. The linkages between the polymer chains are responsible for the typical three-dimensional structures that characterize gels. Gels can withstand physiological stress from skin flexion, blinking, and mucociliary movement by conforming to the contour of the treated region and managing drug release. The pace and breadth of medication release from the base determine the effectiveness of the topical application.⁶

Structure of Gels:

The presence of a network generated by the interlinking of particles gelling agent causes the stiffness of a gel⁸. The nature of the particles and the sort of force responsible for the connections dictate the network topology and gel characteristics. Individual hydrophilic colloid particles might be spherical or isometric aggregates of tiny molecules or solitary macromolecules. Figure 1 depicts possible particle configurations in a gel network⁹. The network in linear macromolecules is made up of entangled molecules, the point of contact between which might be modest or consist of multiple molecules aligned in a crystalline arrangement, as illustrated in Figure 1 (c) and (d), respectively.

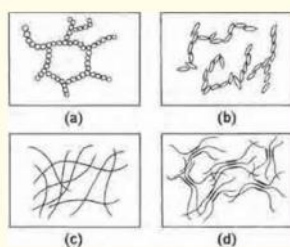


Figure 1: Representations of gel structures. (a) Flocculated particles in a two-phase gel structure. (b) Network of elongated particles or rods forming a gel structure. (c) Matted fibers as found in soap gels. (d) Crystalline and amorphous regions in a gel of carboxymethylcellulose.

Ideal Properties of Topical Gels:

- I. The gel should be clear and homogenous.
- II. The gel should be broken easily when shear or force is applied while the container is shaking.
- III. The gel should be inert.
- IV. The gel should not be sticky.
- V. The gel should never interact with other formulation components.
- VI. The gel should be stable.
- VII. It should not irritate the skin or any part where the gel is applied.
- VIII. The viscosity is optimum.
- IX. It should have antimicrobial activity¹⁰.

Ideal Characteristics of Gels:

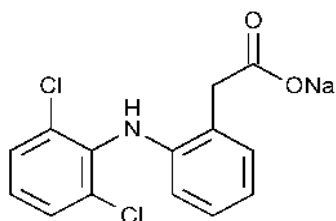
Swelling: When the gelling agent comes into contact with the liquid medium, it can expand the liquid. The swelling characteristic of the gel is determined by the gelling agent and reflects the strength and bonding of particles in the gel.

Syneresis: Most gels discharge some water or liquid when standing, and the phenomenon of releasing fluids from the gel is known as Syneresis. This indicates that the gel does not have enough gelling agents or that the concentration of gelling agents is decreasing. It also demonstrates the formulation's thermodynamic instability. The gel should be devoid of Syneresis.

Structure: Gel stiffness is determined by the gelling agent. The gelling agent used is the most critical aspect of the formulation. The gelling agent is in charge of viscosity (flow resistance), networking, and bonding between particles and the medium employed in formulation.

pH: The pH of the gel should be isotonic, and the pH variation of the gel may cause skin irritation.

Spreadability: Gel should have a high spreading power. It denotes the region of gel coverage¹¹.

Drug Profile:**Diclofenac sodium****Structure:****Figure 2: Structure of Diclofenac Sodium****Molecular Formula:** C₁₄H₁₀Cl₂NNaO₂**Molecular Weight:** 318.1**Drug Category:** A non-steroidal anti-inflammatory agent (NSAID) with antipyretic and analgesic actions.**Pharmacokinetics Profile:**

- 1) **Absorption**
- 2) **Distribution**
- 3) **Metabolism**
- 4) **Elimination**

1) Absorption:**Bioavailability:**

- First, pass metabolism occurs when a substance is well absorbed; only 50-60 per cent of the dose makes it into the bloodstream unaltered .highest plasma content typically happens in less than an hour.
- Onset: Diclofenac potassium 50 or 100mg doses work quickly to alleviate discomfort.
- Duration: Following a single 50-100mg Diclofenac sodium dosage, pain relief lasts up to 8 hours.
- Food: food slows absorption after delivery of normal, delayed-release, or extended-release tablets But does not alter the time it takes for the maximal plasma concentration to occur 12.

2) Distribution:

- Extent: concentration after direct delivery; they might be higher in joint fluid than in plasma.
- Plasma Protein Binding: >99%

3) Metabolism:

Metabolized in the liver via hydroxylation and conjugation. Some metabolites may exhibit anti-inflammatory activity.

4) Elimination:

Excreted in urine (65%) and faeces via biliary elimination (35%) as metabolites.

Half-life:

Oral preparations: 1-2 hours.

Transdermal system: approximately 12 hours.

Pharmacodynamics Profile:

- 1) **Pharmacology**
- 2) **Mechanism of Action**
- 3) **Adverse Reactions**

1) Pharmacology:

- Diclofenac has analgesic, antipyretic and anti-inflammatory activities.
- Its potency against cyclooxygenase-1 (COX-1) and COX-2s is substantially greater than other NSAIDs.

Diclofenac is used to treat pain-:

- ocular inflammation
- osteoarthritis
- rheumatoid arthritis
- spondylitis

2) Mechanism of Action:

Action by inhibition of prostaglandin synthesis by inhibition of cyclooxygenase (COX).

3) Adverse Reactions:

Topical Diclofenac could have negative consequences. If any of these signs do not go away, immediately inform your doctor: of dryness, redness, itching, swelling, pain, hardness, irritation, swelling, scaling, or numbness at the application site.

Available dosage form:

- Tablets
- Solutions
- Injections
- Gels

Thiocolchicoside

Structure:

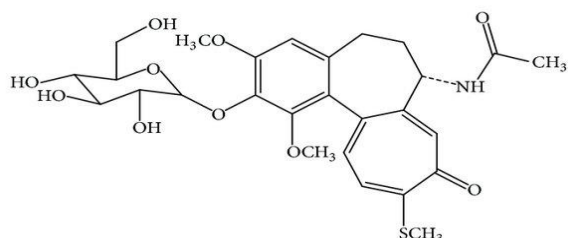


Figure 3: Structure of Thiocolchicoside

Molecular Formula: C₂₇H₃₃NO₁₀S

Molecular Weight: 563.6

Drug Category:

Colchicine is a naturally occurring anti-inflammatory glycoside that is derived from the flower seeds of the plant *Superba gloriosa*. Thiocolchicoside is a semi-synthetic derivative of colchicine, and it is a muscle relaxant with analgesic and anti-inflammatory properties.

Pharmacokinetics Profile:

1. The body converts Thiocolchicoside to a metabolite called 3-demethylthiocolchicin that could damage dividing cells, inducing toxicity in the embryo, neoplastic changes and fertility reduction in males.
2. After oral treatment, Thiocolchicoside is quickly absorbed and transformed into three primary metabolites¹⁸. Thiocolchicoside is not eliminated unchanged but rather as one of three metabolites found in either faeces (~79 %) or in urine 20%.
3. Thiocolchicoside apparent dispersion volume is approximated at around 42.7 L after an I.M. administration of 8 mg.
4. Biotransformation After oral administration, Thiocolchicoside is first metabolized in the aglycon 3-demethylthiocolchicine or SL59. 0955. This step mainly occurs by intestinal metabolism explaining the lack of circulating unchanged Thiocolchicoside by this route of administration.
5. After I.M. administration, the apparent t_{1/2} of Thiocolchicoside is 1.5h, and the plasma clearance is 19.2 L/h. - After oral administration, total radioactivity is mainly excreted in faeces (79%), while urinary excretion represents only 20%. No unchanged Thiocolchicoside is excreted either in urine or faeces.

Commented [H1]:

Pharmacodynamics Profile:

- 1) Pharmacology
- 2) Mechanism of Action
- 3) Adverse Reactions

1) Pharmacology:

Thiocolchicoside is used as a muscle relaxant to treat painful muscular conditions. It is thought to act on receptors in the nervous system that regulate muscle function.

2) Mechanism of Action:

Thiocolchicoside is used clinically for its muscle relaxant, anti-inflammatory, and analgesic properties. It has been shown to interact with gamma-amino butyric acid (GABA) type A receptors (GABAARs) and strychnine-sensitive glycine receptors in the rat's central nervous system.

3) Adverse Reaction:

Some of the Thiocolchicoside most common side effects include drowsiness, abdominal pain, gas, nausea, and diarrhea. If severe symptoms such as itching, rashes, dry mouth, yellowing of eyes, a sudden drop in blood pressure, or a racing heart are seen, then one must immediately contact a doctor.

Available dosage form:

- 1) Tablets
- 2) Capsules
- 3) Injections
- 4) Ointments
- 5) Gels

The formulation for Pharmaceutical Gels:**Gelling Agents:**

Gelling agents are the polymers that are used to structural network or provide texture to the gels. Gelling agents are classified as follows:-

Natural: E.g., Gelatin, Xanthine, Cassia Tora, collagen, pectin, Guar gum etc.

Synthetic: E.g., Carbopol 934, Carbopol 940, Polaxamers and Polyvinyl Alcohol etc.

Semi-synthetic: E.g., Hydroxypropyl methylcellulose, Carboxyl methyl Cellulose and Hydroxyethyl Cellulose¹³.

The Choice of Vehicle:

Solvents are often made of purified water. Co-solvents may be employed to improve the therapeutic agent's solubility in the dosage form and/or to improve the drug's penetration through the skin.

E.g., Alcohol, PG, etc.

Penetration Enhancers:

Penetration enhancers, sometimes called sorption promoters or accelerants, are well-known methods for enhancing transdermal medication delivery. The skin decreases the barrier resistance reversibly.

E.g., Linseed oil, Eucalyptus oil, etc.

Inclusion of Buffers:

Buffers may be used to adjust the pH of aqueous and hydro alcoholic-based gel formulations. Buffer salt solubility is lowered in hydro-alcoholic-based vehicles.

E.g., Phosphate, citrate, etc.

Preservatives:

Certain preservatives interact with the hydrophilic polymers used to make gels, lowering the product's concentration of free (antimicrobial active) preservatives. To compensate, the initial concentration of these preservatives should be increased.

E.g., Parabens, Phenolic, etc¹⁴.

Evaluation Parameters of Gel:

- a) Measurement of pH
- b) Drug content
- c) Viscosity study
- d) Spreadability
- e) Extrudability study
- f) Skin irritation study
- g) In-vitro dissolution studies
- h) Stability
- i) Homogeneity
- j) Grittiness

a) Measurement of pH

pH can be determined by using a digital P.H. meter.

Example: 1g of gel mixed in 100 ml distilled water and stored for 2 hrs. Measurement of P.H. in triplicate and an average value is calculated.

b) Drug content:

1 g of the gel has been dissolved in 100 ml of suitable solvent stock solution. The absorbance of produced aliquots of various concentrations is measured using appropriate dilution. The drug content is calculated using a linear regression analysis of the calibration curve.

c) Viscosity study:

Using a Brookfield viscometer, the gels are rotated at 0.3, 0.6, and 1.5 RPM. At each speed, the resulting dial reading is recorded. The dial reading X factor defined in the Brookfield viscometer catalogues was used to calculate viscosity^{15,16}.

d) Spreadability:

It depicts the coverage of the region to which gel quickly spreads when applied to the damaged section or skin. The curative efficacy is dependent on the propagation of value. The duration in seconds two slides need to fall off from the gel retained between the slides towards the course of a specific lead is stated as spreadability¹⁷. It can be designed using the formula.

$$\text{Spreadability [s]} = M \times L/T$$

Where,

M= Weight tied to upper slide.

L= Length of glass slides.

T= Time taken to detach the slides.

e) Extrudability studies:

Formulations are packaged in collapsible tubes before being placed into the container. This is determined in terms of mass in gms, and it is required to extrude a 0.5cm ribbon at gel in 10 seconds¹⁸.

f) Skin irritation study:

The primary skin irritancy test was evaluated according to the Draize test to determine the irritant effect or any chance of erythema using Transdermal gels. Transdermal gels were applied to the dorsal skin of albino rats, which were shaved the previous day of the study. The rats were divided into three groups (six animals in each group). The gels are to be removed after 24 hrs, and the skin was observed and classified into five grades

(0 to 4) based on the severity of skin injury. The scores were given for erythema from 0 to 4 depending on the degree of erythema as follows:

0= No erythema,

1- Slight erythema (barely perceptible-light pink),

2= Moderate erythema (dark pink),

3= Moderate to severe erythema (light red),

4= Severe erythema (extreme redness)^{19, 20}.

g) In-Vitro diffusion studies:

It is accomplished using a Franz diffusion cell to learn the gel's dissolution discharge across a cellophane membrane. 0.5 of the gel sample was filled by the cellophane membrane. Diffusion experiments were carried out at $37 \pm 1^\circ\text{C}$ using a dissolving medium of 250ml P.H. buffer (PH 7.4).

h) Stability:

It is accomplished by freeze-thaw cycles. The goods were held at 4°C for one month, then at 25°C for one month, and finally at 40°C for one month, and Syneresis was discovered. The gels are stored at room temperature and separate the liquid exudates.

i) Homogeneity:

After placing the gel in the container, it was visually inspected for homogeneity. They were examined for the existence of aggregates and their appearance.

j) Grittiness:

The formulations were examined under a light microscope for the presence of visible particulate particles.

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