

## Topical Gels: A Recent Approach for Novel Drug Delivery

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### ABSTRACT

Gel formulation provides better application property and stability in comparison to cream and ointment. Topical medication administration is a localized drug delivery system anywhere in the body by means of ophthalmic, rectal, vaginal and skin as topical routes. Skin is one of the universal and readily accessible organs of human body for topical administration and is main route of topical drug delivery system. Topical application of gels offers potential advantages of delivering the drug directly to the site of action and acting for an extended period. Topical formulations have the advantage of specific site delivery. However, drugs must overcome to the skin due to its role as a physical and chemical barrier against the penetration of chemicals and microorganisms. This barrier must be modified to allow the permeation of drugs at a suitable rate to the desired site of activity. Permeation enhancers can intercalate the skin outer layers causing structure disruption, opening favourable route for the drug to diffuse through.

**Keywords:** Topical gel; drug delivery; permeation enhancers.

### INTRODUCTION

Topical delivery is an attractive route for local and systemic treatment. The delivery of drugs onto the skin is recognized as an effective means of therapy for local dermatologic diseases. <sup>[1]</sup> It can penetrate deeper into skin and hence give fine absorption. In the formulation of topical dosage forms, efforts are being made to utilize drug carriers that ensure adequate localization or penetration of the drug within or through the skin in order to enhance the local and minimize the systemic effects, or to make sure that adequate percutaneous absorption. <sup>[2]</sup> The most frequently used approach is to include the penetration enhancers in the formulation. In addition to penetration enhancers, there are studies available in which physical methods such as

iontophoresis is used in improving the skin delivery of drugs. Topical preparation avoids the GI-irritation, avoids the metabolism of drug in the liver and increase the bioavailability of the drug. Topical preparations act directly at the site of action. <sup>[3]</sup> Topical gel preparation has remains one of the most popular and important pharmaceutical dosage forms. As a result, the therapeutics effects of the drugs are achieved effectively whereas the systemic side effects can be avoided or reduced. Topical gel formulations provide a suitable delivery system for drugs because they are less greasy and can be easily removed from the skin. <sup>[4]</sup> The release of the drug from topical preparations depends on the physicochemical of the vehicle and the drug employed. <sup>[5]</sup> Examples: Drug commonly

prepared in topical gel form includes gastrointestinal (GI) non-steroidal anti-inflammatory drugs (NSAID) and the antibacterial, antifungal, local anaesthetic and antihistaminic agents. [6] Drug delivery through skin has been a promising concept for a long time because skin is easy to approach a large surface area with vast exposure to the circulatory and lymphatic networks and the route is non-invasive. [7-9] Transdermal gel preparations are advised for superficial skin application or to some mucosal surfaces for local action or skin penetration of medicament or for their soothing or protective action. [10] Gels often provide a quick release of drug substance, independent of the water solubility of the drug, as compared to creams and ointments. [11] They are highly biocompatible with a lower risk of inflammation or adverse reactions, easily applied and do not need to be removed. [12] In this case, the active ingredient(s) stay on the skin surface or penetrate through the epidermal layers and may reach the dermis, but not absorbed into the blood circulation. This category is usually defined as topical drug delivery system. [13,14]

### Anatomy of skin

Skin is the largest organ in the body. It is composed of three layers. The outer flap is called epidermis, the middle is dermis and the inner most layer is hypodermis (Figure 1 and 2).

**Epidermis:** Consists of epithelial cells. Among these cells, both vital cells and dead cells are extant. [15] These new cells at the bottom of epidermis divide fast and push the older cells upward. The epidermis does not have any direct source of blood veins to provide nutrition for it. It takes its nutrients from the diffusion of necessary molecules from a rich vascular network in the basal dermis. Ectodermal cells are connected very strongly by desmosomes. Desmosomes are in touch with the intracellular keratin filaments. Keratin filaments generate

keratin. Keratin cells get stored and crosslink with the other keratin cells in the cytosol during their maturation. Afterward when the prior cells die, this network of keratin fibres abide and provides a tough and hard protective layer in epidermis, called custodial keratinized layer. This layer is waterproof and airtight. It baffles most substances to enter into body or leave from the body. In diseased skin, outstandingly burns, epidermis is wrecked causing potential depletion of body fluid and a rise in susceptibility to microbial infections, leading to incurable consequences untreated. [14]

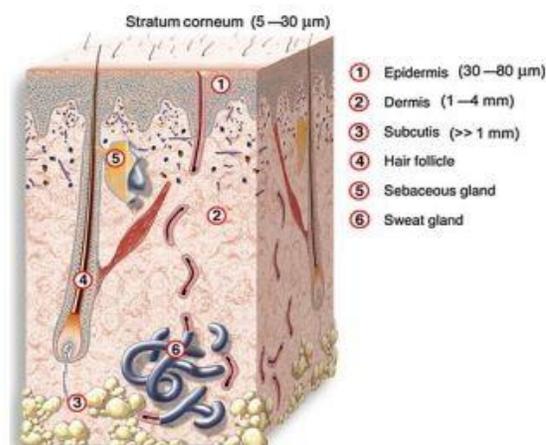


Fig. 1 Structure of human skin showing the functional layers as well as skin appendages (by courtesy of Derler S and Gerhardt LC).

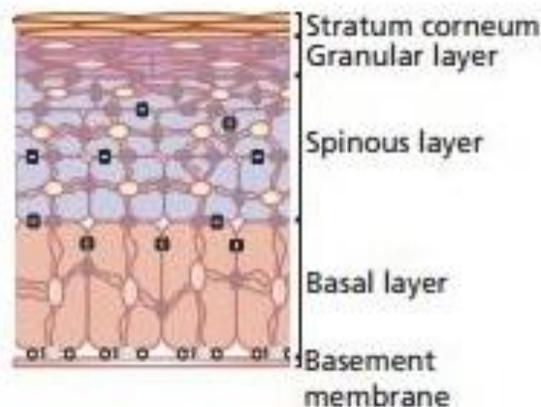


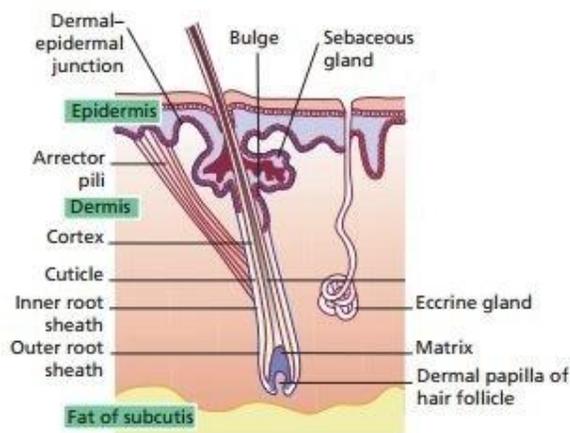
Fig 2: Layers of epidermis (by courtesy of Holbrook KA)

Cells that exist in the epidermis are:

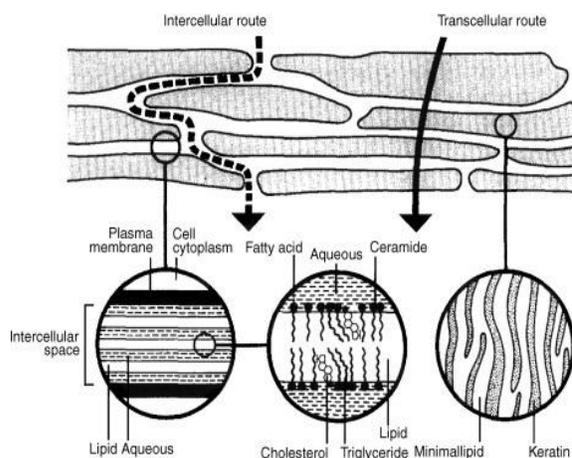
- **Keratinocytes;** these are the main cell types in epidermis (95% of cells).

- **Melanocytes**; these are the pigment artisan cells and found in the basal layers of epidermis.
- **Langerhans cells**; these cells are vital immunological cells and can be found in the mid dermis as well.
- **Merkel cells**; these cells are found in the elementary layer of epidermis and are one part of amine outrider and decarboxylation system.

Epidermis composed of five layers, from inside to outside; stratum germinativum (basal layer), stratum spinosum, stratum granulosum, stratum lucidum and stratum corneum (**Figure 3**). Stratum corneum is the outer most layer of epidermis and has a girth of 10-20  $\mu\text{m}$  when it is dry and 40  $\mu\text{m}$  when it is hydrated and becomes swollen. [16] Stratum corneum has a structure of “bricks and mortar” arrangement (Figure 4). In this model the keratin rich corneocytes (bricks) are sitting in the intracellular lipid rich matrix (mortar), Corneocytes (the bricks) contains 85 % of stratum corneum and intracellular lipids (15%) are arranged in 15-20 layers. Stratum corneum consists of 70% proteins, 15% lipids and only 15% water. Molecules can permeate through skin by two altered pathways. The first pathway is called the transappendageal route. In this route, the molecules should steep through skin by permeation through sweat glands and across the hair follicles. The number of molecules, which can penetrate through this pathway, is very limited. The second pathway of penetration through skin is the Trans epidermal pathway. In this pathway, molecules should pass through stratum corneum as multi-layered barrier. This pathway has two micro pathways; the intracellular micro pathway and the Trans late micro pathway.



**Fig3:** A diagrammatical representation of a cross-section through human skin showing the different cell layers and appendages. (by courtesy of Holbrook KA)



**Fig 4:** Structure of stratum corneum and penetration pathways (by courtesy of Roberts M and Cross S)

**Dermis:** Dermis is positioned under epidermis and is characterized by many of elastin fibres that provide the stretching ability as well as lots of collagen that provides the strength to the skin. Blood vessels found in dermis provide nutrients for both dermis and epidermis. Dermis also plays a major role in temperature regulation. Nerves present there are responsible for pressure and pain sensations. [14] Dermis has a thickness of 3-5 mm. In addition to elastin fibres, blood vessels and nerves, an interfibrillar gel of glycosaminoglycan, salt, water, lymphatic cells and sweat glands are parts of dermis. [17]

Cell types found in dermis are:

- Fibroblasts: collagen producing cells

- Macrophages: scavenger cells
- Mast cells: responsible for immunological reactions and interactions with eosinophils.

Dermis plays an important role as connection to other skin layers also. Modification in the metabolism in dermis can influence growth integrity of the epidermis, hair follicles and skin glands.

**Hypodermis:** Hypodermis is the inner layer of skin. It is the junction layer between skin and the veiled tissues in body such as muscles and bone. Skin exocrine glands and hair follicles: Sweat glands, sebaceous glands and hair follicles enfold in epidermis but they stem from dermis. Sweat glands produce a dilute salt solution into the surface of skin. The dehydration of this solution makes skin cool and this is important for temperature regulation of both body and skin. Sweet glands are present all over the body. The amount of dilutions (sweat) that is produced depends on environmental temperature, the amount of heat inducing skeletal muscle activity and various emotional factors. The sebaceous glands produce sebum. Sebum is an oily liquid released into hair follicles and from thereunto the skin surface. Sebum protects both hair, skin from drying out, and provides water proof layer. <sup>[18]</sup>

### **STRUCTURE OF GELS <sup>[3]</sup>**

The rigidity of a gel arises from the presence of a network formed by the interlinking of particles gelling agent. The type of the particles and the type of force that is responsible for the linkages, which tells about the structure of the network and the properties of gel. The single particles of hydrophilic colloid may consist of either spherical or an isometric aggregates of small molecules, or single macromolecules. Possible arrangements of such particles in a gel network. In linear macromolecules the network is composed of entangled molecules, the point of contact between which may be either relatively small or

consist of several molecules aligned in a crystalline order. The force of attraction responsible for the linkage between gelling agent particles may range from strong primary valences, as in silicic acid gels, to delicate hydrogen bonds and van der waals forces. The infirm nature of these latter forces is indicated by the fact that a slight increase in temperature often causes liquefaction of gel.

### **ADVANTAGES OF TOPICAL DELIVERY**

- 1) They can avert gastro intestinal drug absorption difficulties caused by gastrointestinal pH and enzymatic activity and drug interaction with food and drinks.
- 2) Alternative route for oral administration of medication when that route is unsuitable.
- 3) To bypass the first pass effect, that is, the initial pass of drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding.
- 4) The deactivation by digestive and liver enzyme.
- 5) They are non-invasive and have patient compliance <sup>[19]</sup>
- 6) They are less greasy and can be easily removed from the skin.
- 7) Cost effective.
- 8) Less dose as compare to oral dosage forms.
- 9) Local action with minimum side effects.
- 10) Avoidance of risks and inconveniences of intravenous drug delivery
- 11) Easily abort the medications, when desired
- 12) Avoids fluctuation in drug plasma levels, inter and inpatient variations.
- 12) Delivers drug more selectively to a specific site.
- 13) Improving physiological and pharmacological response.

### **PROPERTIES OF TOPICAL GELS**

1. Ideally, the gelling agent for pharmaceutical or cosmetic use should be

inactive, secure, and should not react with other formulation components. [20]

2. 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 squeezing the tube or during topical application.

3. The topical gel should not be tacky.

4. Drug highly acidic or alkaline

5. The ophthalmic gel should be sterile. In solution is not suitable for topical delivery.

## **CHARACTERISTICS OF TOPICAL GELS**

### **A) Swelling**

When a gelling agent is kept in contact with liquid that solvates it, then an appreciable amount of liquid is taken up by the agent and the volume raises. [21] This process is known as swelling. This process occurs as the solvent get into the matrix. Gel-gel interactions are changed by gel solvent interactions. The degree of swelling depends on the number of linkages between individual molecules of gelling agent and on the strength of these linkages. [22, 23]

### **B) Ageing**

Colloidal systems usually exhibit slow spontaneous aggregation. This phenomenon is referred to as ageing. In gels, ageing results in progressive formation of a denser network of the gelling agent. [24]

### **C) Syneresis**

Many gels often contract spontaneously on standing and exude some fluid medium. This process is known as syneresis. The extent to which syneresis occurs, increases as the concentration of gelling agent decreases. The occurrence of syneresis indicates that the original gel was thermodynamically unstable. [24]

### **D) Structure**

The rigidity of a gel arises from the latency of a network formed by the inter linking of particles of the gelling agents.

### **E) Rheology**

Solutions of the gelling agents and dispersions of flocculated solid are pseudo plastic i.e. showing non-Newtonian flow behaviour, represented by a decrease in viscosity with increase in shear rate. [24]

## **CLASSIFICATION OF GELS**

Gels can be classified based on colloidal phases, nature of solvent used, physical nature and Rheological properties. [25, 26]

### **1. Based on colloidal phases**

They are classified into inorganic (two-phase system) type of force that is responsible for the linkages determine the structure of the network and the properties of the gel.

**A) Two phase system:** If particle size of the dispersed phase are relatively large and form the three-dimensional structure throughout gel, such a system consists of floccules of small particles rather than larger molecules and gel structure, in this system is not always stable. They must be thixotropic forming semisolids on standing become liquid on agitation.

**B) Single phase system:** These consist of large organic molecules existed on the twisted synthetic polymers are referred as gel formers, they tend to entangle with each other their random motion or bound together by Vander Waals forces.

### **2. Based on nature of solvent**

**A) Hydro gels (water based):** they contain water as their continuous liquid phase.

Examples: Mennonite magma, gelatin, cellulose derivatives, poloxamer gel.

**B) Organic gels (with a non-aqueous solvent):** These contain a non-aqueous solvent on their continuous phase.

Examples: Plasti base (low molecular weight polyethylene dissolved in mineral oil and short and Cooled) olag (aerosol) gel and dispersion of metallic stearate in oils.

**C) Xero gels:** Solid gels with low solvent concentration are known as xerogels. These are produced by evaporation of solvent or freeze drying, leaving the gel framework

behind on contact with fresh fluid, they swells and can be reconstituted.

Examples: Tragacanth ribbons, acacia, dry cellulose.

### 3) Based on rheological properties

In general gels exhibit non-Newtonian flow properties. They are classified into,

**A) Plastic gels:** Bingham bodies, flocculated suspensions of aluminium hydroxide exhibit plastic flow and the plot of rheogram gives yield value of the gels above which the elastic gel distorts and begins to flow.

**B) Pseudo plastic gels:** Examples, liquid dispersion of tragacanth sodium alginate, sodium CMC etc. exhibits pseudo plastic flow. The viscosity of these gels decreases with increasing rate of shear.

**C) Thixotropic gels:** The bonds between particles in these gels are very weak and can be broken down by shaking. The resulting solution will revert to gel due to the particles [25] colliding and linking together again. (The reversible isothermal gel-sol-gel transformation)

Examples: Kaolin, bentonite and agar. [26]

### 4) Based on physical nature

**a) Elastic gels:** Gels agar, pectin, guar gum and alginates exhibit an elastic behaviour. The fibrous molecules being linked at the point of junction by relatively weak bonds such as hydrogen bonds and dipole attraction. If the molecule possesses free -COOH group then additional bonding takes place by salt bridge of type -COO-X-COO- between two adjacent strand networks.

Examples: Alginate and carbapol.

**b) Rigid gels:** This can be formed from macromolecule in which the framework linked by primary valence bond.

Examples: In silica gel, [27] silic acid molecules are held by SI-O-SI-O bond to give a polymer structure possessing a network of pores.

### GEL FORMING SUBSTANCES [28, 29]

Polymers are used to give the structural network, which is essential for the preparation of Gels

Gel forming polymers are classified as follows [30]

1) Natural polymer

a) Proteins

Examples: Gelatin, collagen

b) Polysaccharides [31]

Examples: Alginic acid, agar, tragacanth, pectin, xanthin, guar gum

2) Semi synthetic polymers

a) Cellulose derivatives [32]

Examples: Hydroxy ethyl cellulose, methyl cellulose, carboxy methyl cellulose

3) Synthetic polymers

a) Carbomer

Examples: carbopol-941, carbopol-940

b) Poloxamer

Examples: poly vinyl alcohol, poly acrylamide

4) Inorganic substances

Examples: Bentonite, aluminium hydroxide

5) Surfactants

Examples: Brij-96, cetostearyl alcohol

### METHODS OF PREPARATION OF GELS [33]

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

1) Thermal changes

2) Flocculation

3) Chemical reaction

**1) Thermal changes:** Solvated polymers (lipophilic colloids) when subjected to thermal changes causes gelatin. Many hydrogen formers are more soluble in hot than cold water. If the temperature is decreasing, the degree of hydration is reduced and gelatin occurs (cooling of a concentrated hot solution will produce a gel) [29]

Examples: Gelatin, agar sodium oleate, guar gum and cellulose derivatives etc. In contrast to this, some materials like cellulose, ether have water solubility to hydrogen bonding with the water raising the temperature of these solutions will disrupt

the hydrogen bonding and reduced solubility, which cause gelation.

**2) Flocculation:** Here gelation is produced by adding just sufficient quantity of salt to precipitate to produce gel state but insufficient to bring about complete precipitation. It is needed to ensure rapid mixing to avoid local high concentration of precipitant.

Examples: Solution of ethyl cellulose, polystyrene with benzene can be gelled by rapid mixing with suitable amounts of a non-solvent such as petroleum ether. The gels formed by flocculation method are thixotropic in behaviour [34-36]

**3) Chemical reaction:** In this method, gel is produced by chemical interaction between the solute and solvent.

Examples: Aluminium hydroxide gel can be developed by interaction in aqueous solution of an aluminium salt and sodium carbonate, an increased concentration of reactants will produce a gel structure. [24]

## EVALUATION PARAMETERS OF THE FORMULATED GELS: [37, 29, 38]

### 1) Measurement of $p^H$ [22]

The pH of various gel formulations was determined by using digital  $p^H$  meter. [39]

One gram of gel was dissolved in 100ml distilled water and reserved for 2 hours. The measurement of  $p^H$  of each formulation was done in triplicate and average values are calculated [39, 40]

### 2) Drug content

1 gm of the prepared gel was mixed with 100ml of desolved solvent. Aliquots of different concentration were prepared by suitable dilutions after filtering the stock solution and absorbance was measured. [41-43]

### 3) Spreadability

It indicates the extent of area to which gel readily spreads on application to skin or affected part. The therapeutic efficiency of a formulation also depends upon its spreading value [44, 45] Spreadability is considered in terms of time in seconds taken by 2 slides to

slip off from gel which is placed in between the slides under the direction of certain load, [46] if the time taken for the separation of two slides is lesser, then spreadability will be better. It is calculated by using the formula [42, 47]

$$S=M.L/T$$

M= weight tied to upper slide

L= length of glass slide

T= time taken to separate the slides

### 4) Viscosity study

The measurement of viscosity of the prepared gel was done with a brook field viscometer. The gels were rotated at 0.3, 0.6 and 1.5 rotations per minute. At separate speed, the coinciding dial reading was noted. The viscosity of the gel was calculated by multiplication of the dial reading with factor given in the brook field viscometer catalogues. [42, 48]

### 5) Extrudability study

The formulations were filled in the collapsible tubes after the gels were set in the container. The extrudability of the formulation was determined in terms of weight in grams required to expel a 0.5 cm ribbon of gel in 10 seconds. [49, 26]

### 6) Skin irritation study

Guinea pigs (400-500 gm) of either sex were used for testing of skin irritation. The animals were used for testing of skin irritation. The animals were retained on standard animal feed and had free access to water. The animals were kept under standard conditions. Hair was rimed from back of guinea pigs and area of  $4\text{cm}^2$  was mark done both the sides, one side served as control while other side was test. Gel was applied (500 mg/guinea pig) twice a day for 7 days and the site was observed for any sensitivity and the reaction if any, was graded as 0, 1, 2, 3 for no reaction, slight patchy erythema, slight but confluent or moderate but patchy erythema and severe erythema without or with edema, respectively. [49]

### 7) Homogeneity

After the gels have been set in the container, all prepared gels were tested for homogeneity by visual inspection. [27] They were examined for their appearance and presence of any aggregates. [5,47]

### 8) Grittiness

All the formulations were evaluated microscopically for the presence of any appreciable particulate matter which was seen under light microscope. Hence, obviously the gel preparations fulfil the requirement of freedom from particular matter and from grittiness as desired for any topical preparation. [48]

### 9) Consistency

The quantification of consistency of the prepared gels was done by dropping a cone attached to a holding rod from a fix distance of 10cm in such way that it should fall on the centre of the glass cup filled with the gel. The stabbing by the cone was measured from the surface of the gel to the tip of the cone inside the gel. The extent travelled by cone was noted after 10sec. [47]

### 10) In vitro diffusion studies

The diffusion studies of the prepared gels can be carrying out in Franz diffusion cell [36] for studying the dissolution release of gels through a cellophane membrane and the diffusion studies were carried out at  $37 \pm 1^\circ$  using 250ml of phosphate buffer (pH 7.4) as dissolution medium. 5ml of each sample was withdrawn periodically at 1, 2, 3, 4, 5,

6, 7 and 8hrs and each samples was replaced with equal volume of fresh dissolution medium. Then the samples were interpreted for the drug content by using phosphate buffer as blank. [37]

### 11) Stability

The stability studies were carried out for all the gel formulation by freeze- thaw cycling. In this syneresis was observed by subjecting the product to a temperature of  $4^\circ\text{C}$  for 1 month, then at  $25^\circ\text{C}$  for 1 month, then at  $40^\circ\text{C}$  for 1 month. After this gel is exposed to ambient room temperature and liquid exudates, separating is noted. [7,30]

### THERAPEUTIC APPLICATIONS OF TOPICAL GELS [50]

- 1) As delivery systems for orally administered drugs.
- 2) To convey topical drug directly to the skin, mucous membrane or the eye.
- 3) As long acting forms of drug injected intramuscularly.
- 4) As binders in granulation, protective colloids in suspensions, thickeners in oral liquid.
- 5) Topical oral gels for dental use to control dental bleeding
- 6) Enhancement of wound healing by topical gels with epidermal growth factor.
- 7) In cosmetics like shampoos, fragrance products, dentifrices, skin and hair care preparations. [51,52]

Table.1: Different type of topical gel dosage forms.

Topical gel Products	Indications	Adverse effects	References
Diclofenac sodium 1% gel	Acute musculoskeletal pain	ulcerative colitis, Crohn's disease	[21]
Menthol 5% gel	Neuralgia	Hypersensitivity reaction	[51,52]
Sufentanil gel	Chronic pain	Difficulty in breathing, tightness in the chest, swelling of the mouth, seizures	[22,53]
Benzoyl peroxide gel 2.5%	Acne	Painful irritation of skin, including burning, blisterin, itching, severe redness, swelling	[54]
Lidocaine 2% gel	Anesthetic	noisy breathing, swelling of the eyelids, face, lips, hands, or feet, troubled breathing or swallowing	[55]

### CONCLUSION

Gels are more stable and can provide controlled release than other semisolid

preparations. Gels have good homogeneity, appearances and drug release. Gel has wider prospects to be used as a topical drug

delivery dosage form. Topical formulations include creams, ointments, pastes, gels etc. Out of which gels are getting more popular now a days because they are more stable and also can provide controlled release than other semisolid preparations. The gel formulation can Topical gels are one of the promising drug delivery systems, gels are getting more popular now a provide better absorption characteristics and hence the bioavailability of drug. It also provides the better information regarding to the formulation and evaluation parameters of the gel and to provide the better therapeutic effects to patient compliance.

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