



Topical Gels as Drug Delivery Systems: A Review

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ABSTRACT

Topical drug delivery is defined as the application of pharmaceutical dosage form to the skin for direct treatment of cutaneous disorder or the cutaneous manifestation of the general disease, with the intent of confining the pharmacological or other effect of the drug to the surface of the skin. Topical drug delivery systems include a large variety of pharmaceutical dosage form like semisolids, liquid preparation, sprays and solid powders. Most widely used semisolid preparation for topical drug delivery includes gels, creams and ointments. A gel is a cross-linked polymer network swollen in a liquid medium. Its properties depend strongly on the interaction between solid state polymer and the liquid component. Gels exhibit no steady-state flow. The interaction between polymer and the liquid dispersion medium form an interlacing three dimensional network of particles of dispersed phase. The increased viscosity caused by interlacing and consequential internal friction is responsible for the semisolid state. Topical gel formulation provides a suitable delivery system for drugs because they are less greasy and can be easily removed from the skin. Gel formulation provides better application property and stability in comparison to cream and ointments.

Keywords: Topical, drug delivery, gels, review, skin.

INTRODUCTION

Man has always been plagued with ailments and diseases of both the body and the mind. However dedicated research from scientists all over the world has made it possible to treat, prevent and eradicate many of these diseases that plague man^{1, 2}. The field of pharmaceutical science has been developing steadily over the years, and has today become invaluable in helping to keep us healthy and prevent disease. An avenue of research that has progressed a great deal in the past few decades is the treatment of diseases via biomolecules such as drugs, proteins etc. Initially these could only be administered in limited manner, due to limitations of drug delivery through harmful environments in the body^{2, 3}. Thus limited mobility reduced the effectiveness of administered drugs. Progress came with the development of carriers which could be encapsulated, or immobilized with drugs, allowing the drug to safely reach the required site without harm. These carriers allowed for the release of drug in sites which were previously inaccessible. The nature of these carriers progressed over the years from ceramics, to natural, to synthetic materials. Factors such as integrity, biocompatibility and flexibility were considered, and lead to the use of three dimensional matrices as carrier materials⁴. These are a class of materials are known as gels. These three dimensional polymer matrices are capable of imbibing large amounts of water, and biological fluids⁵. This property of gels is the reason behind its varied applications ranging from food additives to pharmaceuticals and clinical applications⁶.

TOPICAL DRUG DELIVERY SYSTEMS

Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration

into the underlying layers of skin or mucous membranes. The main advantage of topical delivery system is to bypass first pass metabolism. Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time are other advantage of topical preparations. Semi-solid formulation in all their diversity dominate the system for topical delivery, but foams, spray, medicated powders, solution, and even medicated adhesive systems are in use. The topical drug delivery system is generally used where the others system of drug administration fails or it is mainly used in pain management, contraception, and urinary incontinence. Over the last decades the treatment of illness has been accomplished by administrating drugs to human body via various routes namely oral, sublingual, rectal, parental, topical, inhalation etc. Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous manifestations of a general disease (e.g. psoriasis) with the intent of confining the pharmacological or other effect of the drug to the surface of the skin or within the skin. Topical activities may or may not require intra-cutaneous penetration or deposition^{7, 8}. Topical drug delivery systems include a large variety of pharmaceutical dosage form like semisolids, liquid preparation, sprays and solid powders. Most widely used semisolid preparation for topical drug delivery includes gels, creams and ointments⁹.

GELS AS PHARMACEUTICAL DOSAGE FORMS

The term 'Gel' was introduced in the late 1800 to name some semisolid material according to their physiological characteristics rather than molecular composition¹⁰⁻¹².



The U.S.P. defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid¹³⁻¹⁷. Gels are a substantially dilute cross-linked system, which exhibits no flow when in the steady-state¹⁸⁻²². They consist of a two component semi-solid system rich in liquid. Their one characteristic feature is the presence of continuous structure providing solid like properties²³. Gels have become a premier materials used for drug delivery formulations due to its biocompatibility, network structure, and molecular stability of the incorporated bioactive agent²⁴.

STRUCTURE OF GELS

A gel consists of a natural or synthetic polymer forming a three dimensional matrix throughout a dispersion medium or hydrophilic liquid. After application, the liquid evaporates leaving the drug entrapped in a thin film of the gel – forming matrix physically covering the skin²⁵. The presence of a network formed by the interlocking of particles of the gelling agent gives rise to the rigidity of a gel. The nature of the particles and the type of form that is responsible for the linkages determine the structure of the network and the property of the gel²⁶.

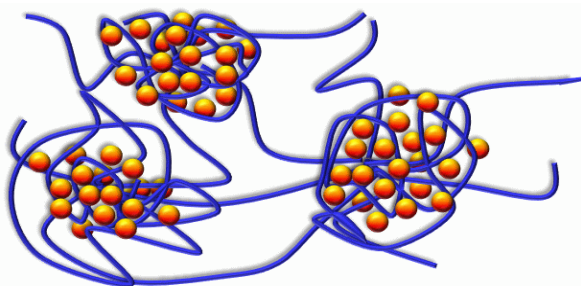


Figure 1: Structure of gels

DESIRABLE CHARACTERISTICS OF TOPICAL DRUG DELIVERY SYSTEMS²⁷⁻³¹

Topical formulations have three main functions:

- To help hydrate skin because of their emollient properties.
- To protect from external environment or heal an intact or injured area of the skin.
- To deliver medication to the skin.

ADVANTAGES OF TOPICAL DRUG ADMINISTRATION

- Avoids gastrointestinal (GI) drug absorption difficulties caused by GI pH, enzymatic activity and drug interactions with food, drink, and other orally administered drugs.
- A substitute for other routes of administration (e.g. oral administration, intravenous injection) when that route is unsuitable, as with vomiting, swallowing problems, resistant children and diarrhoea.
- Patient acceptability is better as this drug delivery system is non-invasive, avoiding the inconvenience of parenteral therapy.

- Avoids the first-pass effect, possibly avoiding the deactivation by digestive and liver enzymes.
- Reduction of doses as compare to oral dosage forms.
- Ability to dissolve a wide range of medications with different chemical properties, making combination therapy with one transdermal cream possible.
- Provides extended therapy with a single application, improving compliance.
- Drug therapy may be terminated rapidly by removal of the application from the skin surface.
- Less greasy and can be easily removed from the skin.

CLASSIFICATION OF GELS³¹

Some of the topically applied preparations are shown in Fig 2

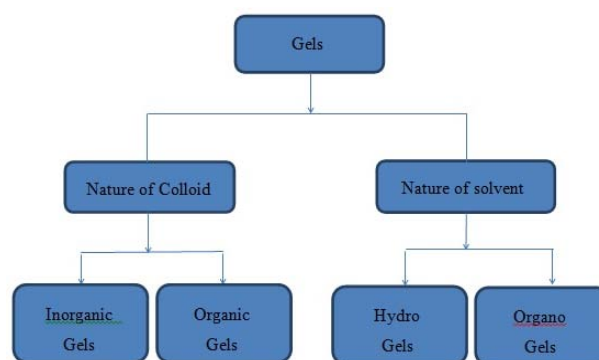


Figure 2: General Classification of Gels

Topically applied gels are classified by two schemes. The first scheme divides gels in two types of gel systems. These are called as inorganic and organic gel systems. Most inorganic hydrogels are two-phase systems, such as aluminium hydroxide gel and bentonite magma. Bentonite has also been used as an ointment base in about 10% to 25% concentrations. Most organic gels are single-phase systems and may include such gelling agents as carbomer and tragacanth and those that contain an organic liquid, such as Plastibase. The second classification scheme divides gels into hydrogels and organogels with some additional subcategories. Hydrogels include ingredients that are soluble in water; they include organic hydrogels, natural and synthetic gums, and inorganic hydrogels. Examples include hydrophilic colloids such as silica, bentonite, tragacanth, pectin, sodium alginate, methylcellulose carboxymethylcellulose sodium, and alumina, which in high concentration form semisolid gels. Sodium alginate has been used to produce gels that can be employed as ointment bases. In concentrations greater than 2.5% and in the presence of soluble calcium salts, a firm gel, stable between pH 5 and 10, is formed. Methylcellulose, hydroxy ethylcellulose, and sodium CMC are among the commercial cellulose products used in ointments. They are available in various viscosity types, usually high, medium, and low. Organogels include the hydrocarbons, animal and vegetable fats, soap base greases, and the

hydrophilic organogels. Fig 2 shows the general classification for gels.

CHARACTERISTICS OF GELS^{32, 33}

Gels should possess 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 activity against microbial attack.
- The topical gel should not be tacky.
- The gels intended for ophthalmic use should be sterile.

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 increases. This process is referred to as swelling. This phenomenon occurs as the solvent penetrates the matrix. Gel-gel interactions are replaced 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.

B. Syneresis

Many gels often contract spontaneously on standing and exude some fluid medium. This effect is known as syneresis. The degree to which syneresis occurs, increases as the concentration of gelling agent decreases. The occurrence of syneresis indicates that the original gel was thermodynamically unstable. The mechanism of contraction has been related to the relaxation of elastic stress developed during the setting of the gels. As these stresses are relieved, the interstitial space available for the solvent is reduced, forcing the liquid out.

C. Ageing

Colloidal systems usually exhibit slow spontaneous aggregation. This process is referred to as ageing. In gels, ageing results in gradual formation of a denser network of the gelling agent. In gels, ageing results in gradual formation of a denser network of the gelling agent. Theimer suggests that this process is similar to the original gelling process and continues after the initial gelation, since fluid medium is lost from the newly formed gel.

D. Structure

The rigidity of a gel arises from the presence of a network formed by the interlinking of particles gelling agent. The nature of the particles and the type of force that is

responsible for the linkages, which determines the structure of the network and the properties of gel. The individual particles of hydrophilic colloid may consist of either spherical or an isometric aggregates of small molecules, or single macromolecules.

E. Rheology

Solutions of the gelling agents and dispersion of flocculated solid are pseudo plastic i.e. exhibiting Non-Newtonian flow behaviour, characterized by a decrease in viscosity with increase in shear rate. The tenuous structure of inorganic particles dispersed in water is disrupted by n gels, ageing results in gradual formation of a denser network of the gelling agent.

ANATOMY AND PHYSIOLOGY OF SKIN

The human body has two systems that protect it from the harmful organisms existing in the environment. The internal defence system destroys microorganisms and bacteria that have already attacked the body. The external defence system prevents microbial microorganisms to enter the body. Skin is biggest external defence system. Skin covers the outside of the body but has other functions beside the defence mechanism. It serves as a mechanical barrier between the inner part of the body and the external world³⁴. Temperature of skin varies in a range of 30 to 40 °C degree depending on the environmental conditions.³⁵

Anatomy of skin

Skin is the largest organ in the body. It consists of three layers. The outer layer is called epidermis, the middle layer is dermis and the inner most layer is hypodermis.

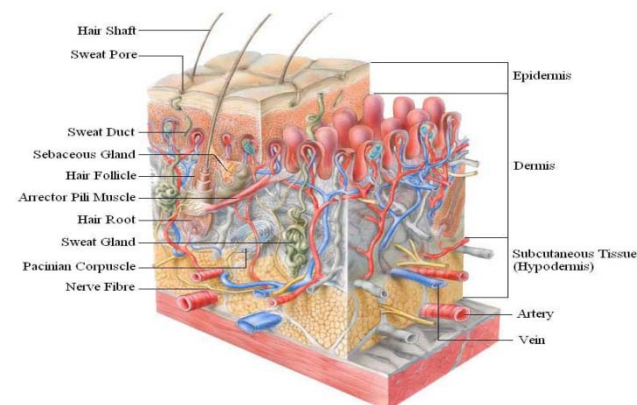


Figure 4: Longitudinal section of skin

Epidermis: Consists of epithelial cells. Among these cells, both living cells and dead cells can be found. 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. It takes its nutrients from the diffusion of necessary molecules from a rich vascular network in the underlying dermis. Epidermal cells are connected very strongly by desmosomes. Desmosomes are in contact with the intracellular keratin filaments. Keratin filaments produce keratin. Keratin cells accumulate and crosslink with the

other keratin cells in the cytosol during their maturation. Afterward when the older cells die, this network of keratin fibres remains and provides a tough and hard protective layer in epidermis, called protective keratinized layer. This layer is waterproof and airtight. It prevents most substances to enter the body or leave from the body. In diseased skin, particularly burns, epidermis is destroyed causing potential loss of body fluid and an increase in susceptibility to microbial infections, leading to fatal consequences untreated

Cell types that exist in the epidermis are:

- Keratinocytes; these are the main cell types in epidermis (95% of cells).
- Melanocytes; these are the pigment producer cells and found in the basal layers of epidermis
- Langerhans cells; these cells are important immunological cells and can be found in the mid dermis as well Merkel cells; these cells are found in the basal layer of epidermis and are one part of amine precursor and decarboxylation system^{36,37}.
- Epidermis consists of five layers, namely from inside to outside;
- stratum germinativum (basal layer)
- stratum spinosum
- stratum granulosum
- stratum lucidum
- and stratum corneum
- Stratum corneum is the outer most layer of epidermis and has a thickness of 10-20 μm when it is dry and 40 μm when it is hydrated and becomes swollen³⁷.

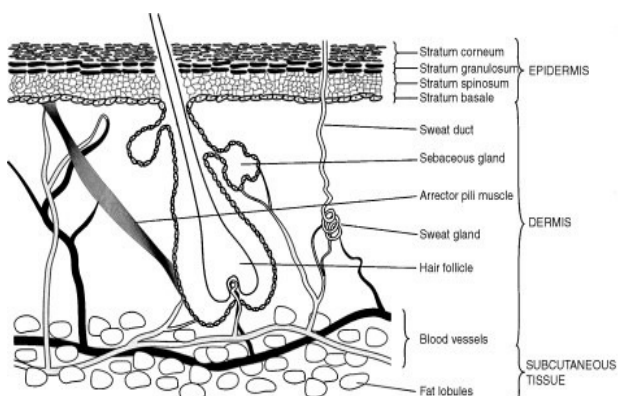


Figure 5: Epidermal and skin layers³⁷

Stratum corneum has a structure of “bricks and mortar” arrangement. In this model the keratin rich corneocytes (bricks) are sitting in the intracellular lipid rich matrix (mortar)³⁷.

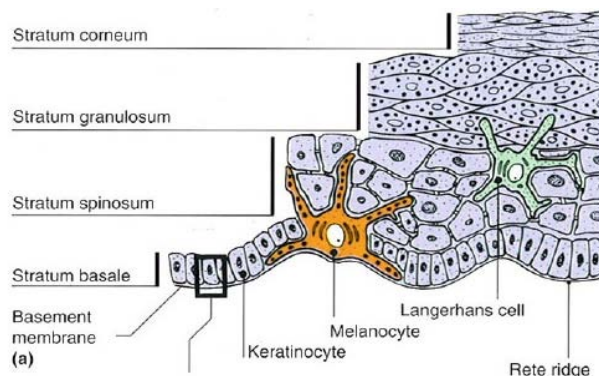


Figure 6: Layers of epidermis³⁹

Corneocytes (the bricks) create 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% water³⁸.

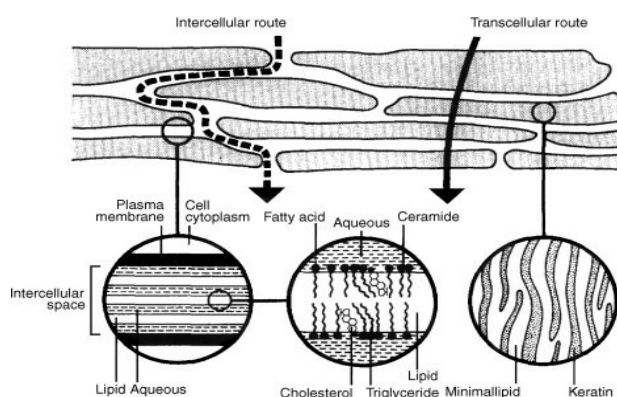


Figure 7: Structure of stratum corneum and penetration pathways³⁷

Molecules can basically permeate through skin by two different pathways. The first pathway is called the transappendegeal route. In this route the molecules should permeate 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 transepidermal 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 transcellular micro pathway³⁷.

Dermis: Dermis is positioned under epidermis and is characterized by lots 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 sensations³⁴. 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 dermis³⁷. Cell types found in dermis are:

- Fibroblasts: collagen producing cells

- Macrophages: scavenger cells
- Mast cells: responsible for immunological reactions and interactions with eosinophils³⁶

Dermis plays an important role as connection to other skin layers also. Changes in the metabolism in dermis can influence growth integrity of the epidermis, hair follicles and skin glands³⁵.

Hypodermis: Hypodermis is the inner layer of skin. It is the contact layer between skin and the underlying tissues in body such as muscles and bone³⁴. Sweat glands, sebaceous glands and hair follicles enfold in epidermis but they stem from dermis. Sweat glands release a dilute salt solution into the surface of skin. The evaporation 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 (sweet) that gets produced depends on environmental temperature, the amount of heat generating skeletal muscle activity and various emotional factors³⁴. The sebaceous glands produce sebum. Sebum is an oily liquid released into hair follicles and from there onto the skin surface. Sebum protects both hair and skin from drying out and provides waterproof layer³⁴.

PERCUTANEOUS ABSORPTION AND KINETICS OF DRUG PERMEATION⁴⁰⁻⁴²

Knowledge of skin permeation kinetics is vital to the successful development of topical systems. Topical permeation of a drug involves the following steps:

- Sorption by stratum corneum
- Penetration of drug through viable epidermis
- Uptake of the drug by the capillary network in the dermal papillary layer

This permeation can be possible if the drug possesses certain physico-chemical properties. The rate of permeation across the skin (dQ/dt) is given by:

$dQ / dt = Ps (Cd - Cr)$ Eq. 1

Where,

C_d = Concentration of skin penetrant in the donar compartment (e.g., on the surface of stratum corneum)

C_r = Concentration in the receptor compartment (e.g., body) respectively

Ps = Overall permeability constant of the skin tissue to the penetrant

$Ps = (KsDss) / hs$ Eq. 2

Where,

Ks is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium

Dss is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues hs is the overall thickness of skin tissues.

As Ks , Dss and hs are constant under given conditions, the permeability coefficient (Ps) for a skin penetrant can be considered to be constant.

From Eq.1 it is clear that a constant rate of drug permeation can be obtained only when $C_d \gg C_r$ i.e., the drug concentration at the surface of the stratum corneum (C_d) is consistently and substantially greater than the drug concentration in the body (C_r), then Eq. 1 becomes:

$dQ / dt = PsC_s$ Eq. 3

Permeability coefficient = $(KsDss) / hs = 1 / \text{resistance}$

FORMULATION DESIGN

Topical gel may include the following components:

- A) Gel forming agent or polymer
- B) Drug Substance
- C) Penetration Enhancers

A) Gel forming agent or Polymer⁴¹⁻⁵²

Different classes of polymeric materials have been used to achieve rate controlled drug delivery. The mechanism of drug release depends upon the physicochemical properties of the drug and polymer.

The following criteria should be satisfied for a polymer to be used in a topical system:

- Molecular weight, chemical functionality of polymer must allow diffusion and release of the specific drug.
- The polymer should permit the incorporation of a large amount of drug.
- The polymer should not react, physically or chemically with the drug.
- The polymer should be easily manufactured and fabricated into the desired product and inexpensive.
- The polymer must be stable and must not decompose in the presence of drug and other excipients used in the formulation, at high humidity conditions, or at body temperature.
- Polymers and its degradation products must be non-toxic.

No single material may have all these attributes, certain excipients may be incorporated to alter some properties for example Co-solvents such as ethanol, propylene glycol, PEG 400 could be added to increase drug solubility. Gel forming polymers are classified as below.

- a) Natural Polymers:
 - i. Proteins – E.g. Collagen, Gelatin, Xanthin, Gellum Gum



ii. Polysaccharides – E.g. Agar, Alginic acid, Sodium or potassium carrageenan, Tragacanth, Pectin, Guar Gum, Cassia tora

b) Semisynthetic Polymers

i. Cellulose Derivatives – E.g. Carboxymethyl cellulose Methylcellulose, Hydroxypropyl cellulose, Hydroxypropyl methylcellulose, Hydroxyethyl cellulose

c) Synthetic Polymers

- i. Carbomer – E.g. Carbopol -940, Carbopol -934, Carbopol -941
- ii. Poloxamer
- iii. Polyacrylamide
- iv. Polyvinyl Alcohol
- v. Polyethylene and its copolymers

d) Inorganic Substances – E.g. Aluminium Hydroxide, bentonite

e) Surfactants – E.g. Cetosteryl alcohol, Brij-96

B) Drug Substance⁴¹⁻⁵²

Drug Substance plays a very important role in the successful development of a topical product. The important drug properties that effect its diffusion through gels as well as through skin are as follows.

1. Physicochemical properties

- Drug should have a molecular weight of less than 500 Daltons.
- Drugs highly acidic or alkaline in solution are not suitable for topical delivery.
- Drug must have adequate lipophilicity.
- A saturated aqueous solution of the drug should have a pH value between 5 and 9.

2. Biological properties

- The drug should not be directly irritated to the skin.
- Drugs, which degrade in gastrointestinal tract or are inactivated by hepatic first pass effect, are suitable for topical delivery.
- Tolerance to the drug must not develop under the near zero order release profile of topical delivery.
- The drug should not stimulate an immune reaction in the skin.
- Drugs which have to be administered for a long time or which cause adverse effects to non-target tissue can also be formulated for topical delivery.

C) Penetration Enhancer⁵³⁻⁶⁵

Penetration enhancers (also called accelerants or sorption promoters) are defined as substances that are capable of

promoting penetration of drugs into skin, or their permeation through skin, by reversibly reducing the skin barrier resistance. Percutaneous absorption involves the passage of the drug molecule from the skin surface into the stratum corneum under the influence of a concentration gradient and its subsequent diffusion through the stratum corneum and underlying epidermis, through the dermis, and into the blood circulation. The skin behaves as a passive barrier to the penetrant molecule. The stratum corneum provides the greatest resistance to penetration, and it is the rate-limiting step in percutaneous absorption.

A penetration enhancer acts by altering the skin as a barrier to the flux of a desired penetrant and are considered as an integral part of most topical formulations. To achieve and maintain therapeutic concentration of drug in the blood, the resistance of skin (stratum corneum) to diffusion of drugs has to be reduced in order to allow drug molecules to cross skin and to maintain therapeutic levels in blood. They can modify the skin's barrier to penetration either by interacting with the formulation that applied or with the skin itself. Ideally, these materials should be pharmacologically inert, non-toxic, non-irritating, non-allergenic, and compatible with the drug and excipients, odourless, tasteless, colourless, and in-expensive and have good solvent properties. The enhancer should not lead to the loss of body fluids, electrolytes, and other endogenous materials, and skin should immediately regain its barrier properties on its removal.

An ideal penetration enhancer should have the following properties:

- It should be pharmacologically and chemically inert, and chemically stable.
- It should be non-toxic, non-irritant, non-comedogenic and non-allergenic.
- It should have a rapid onset of action, predictable duration of activity, as well as a reproducible and reversible effect.
- It should be chemically and physically compatible with the formulation ingredients.
- After it is removed from the skin, the stratum corneum should rapidly and fully recover its normal barrier property.
- It should be odourless, tasteless, colourless, and inexpensive.
- It should be pharmaceutically and cosmetically acceptable.
- It should have a solubility parameter similar to that of skin.

In spite of the fact that a variety of compounds have been proposed as skin penetration enhancers, to date, no substance has been found to possess all the aforementioned ideal properties. Nevertheless, many



known and newly developed compounds have been assessed for their enhancing abilities and some have shown more promising characteristics.

Classification of permeation enhancers

A large number of compounds have been reported to increase the penetration of drugs through the skin, and therefore a simple, relevant system for classification of compounds is essential. Several classification systems have been used in the literature. Most penetration enhancers are divided into three classes, namely simple fatty acids and alcohols, weak surfactants containing a moderately sized polar group (e.g. Azone) and those enhancers that function mainly as solvents and hydrogen bond acceptors (e.g. dimethylsulfoxide, dimethylacetamide, and dimethylformamide). Another classification divides penetration enhancers into three distinct areas, Area I, Area II, and Area III, according to a conceptual diagram. The construction of this diagram was based on the "organic" and "inorganic" characters of compounds, with the organic character depending on carbon atoms and the inorganic character depending on substituted groups. With respect to this diagram, Area I consists of solvent-type enhancers such as dimethylsulfoxide, ethanol, propylene glycol, and N-methyl pyrrolidone. Area II comprises enhancers for hydrophilic drugs such as Azone, oleic acid, lauryl alcohols and ketone terpenes. Area III is composed of enhancers for lipophilic drugs including hydrocarbon terpenes. Penetration enhancers are also classified as either polar or nonpolar based on the Hildebrand solubility parameter. A chemical classification divides penetration enhancers into 10 classes according to their chemical structures; sulfoxides, alcohols, polyols, fatty acids, fatty acid esters, amides, surfactants, terpenes, alkanols and organic acids. Chemical enhancers may be placed into several groups depending on their activity. Classification of chemical enhancers based on their chemical structures can be considered as the most promising system in comparison with the other categorizations. Overall, it is the simplest and easiest system that allows rapid identification. In this classification, penetration enhancers are classified by functional groups and chemical structures and include Water, Sulfoxides and similar compounds, Pyrrolidones, Alcohols, Glycols, Urea and Derivatives, Azone and derivatives, Enzymes, Iminosulfuranes, Cyclodextrins, Fatty acid esters, Fatty acids, Surfactants, Terpenes, Polymers, Monoolein and Oxalidinones.

APPLICATION OF GELS^{7, 33, 67}

Application of gels in Pharmaceutical and cosmetic industry:

- Gels are applied directly to the skin, mucus membrane or the eye to provide local action.
- They act as long acting forms of drug injected intramuscularly or implanted into the body
- Gelling agents are useful binders in tablet granulation, protective colloids in suspensions, thickeners in oral liquid, and suppository bases.
- Cosmetically gels have been employed in wide variety of products, including shampoos, fragrance products, dentifrices, skin and hair care preparations.
- Gel products containing anti-inflammatory steroids are used to treat inflammations of scalp because this is an area of the body where creams and ointments are too greasy for patient acceptance.
- Gels have better potential as a vehicle to administer drug topically in comparison to ointment, because they are nonsticky, require low energy during formulation, are stable and have aesthetic value.

CONCLUSION

Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. The main advantage of topical delivery system is to bypass first pass metabolism. Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time are other advantages of topical preparations. Moreover, patient acceptability is better than other drug delivery systems owing to its non-invasiveness. The topical drug delivery system is generally used where the other system of drug administration fails. Gels have become a premier material used for drug delivery formulations due to its biocompatibility, network structure, and molecular stability of the incorporated bioactive agent. There is a great need for optimizing gel formulations as they have the potential to enhance efficacy and tolerability, improve patient compliance.

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