

TRANSDERMAL GELS - AN ALTERNATIVE VEHICLE FOR DRUG DELIVERY

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ABSTRACT

Delivery of drugs through the skin has been an attractive as well as a challenging area for research. Compared to other conventional routes of drug delivery such as oral, injection and inhaler, transdermal delivery has a variety of advantages. Transdermal systems are non-invasive, convenient, and inexpensive and can be self-administered. They can provide sustained plasma concentration profile for long periods of time. There are many transdermal formulations like lotions, creams, ointments, patches, etc. out of these gel is preferred. Transdermal gels are becoming more popular due to ease of application and better precutaneous absorption. The term gel are semi-solid, three dimensional, polymeric matrices comprising small amounts of solid dispersed in relatively large amount of liquid, yet possessing more solid like character. These system form a three dimensional, polymeric matrix in which a high degree of physical reticulation has been compromised. Gel formulations provide better application property and stability in comparison to cream and ointments. In these study methods, advantages, gel forming substances, structure of gel, their properties, their absorption mechanism, evaluation and future perspective are discussed to improve the permeability and bioavailability of gels.

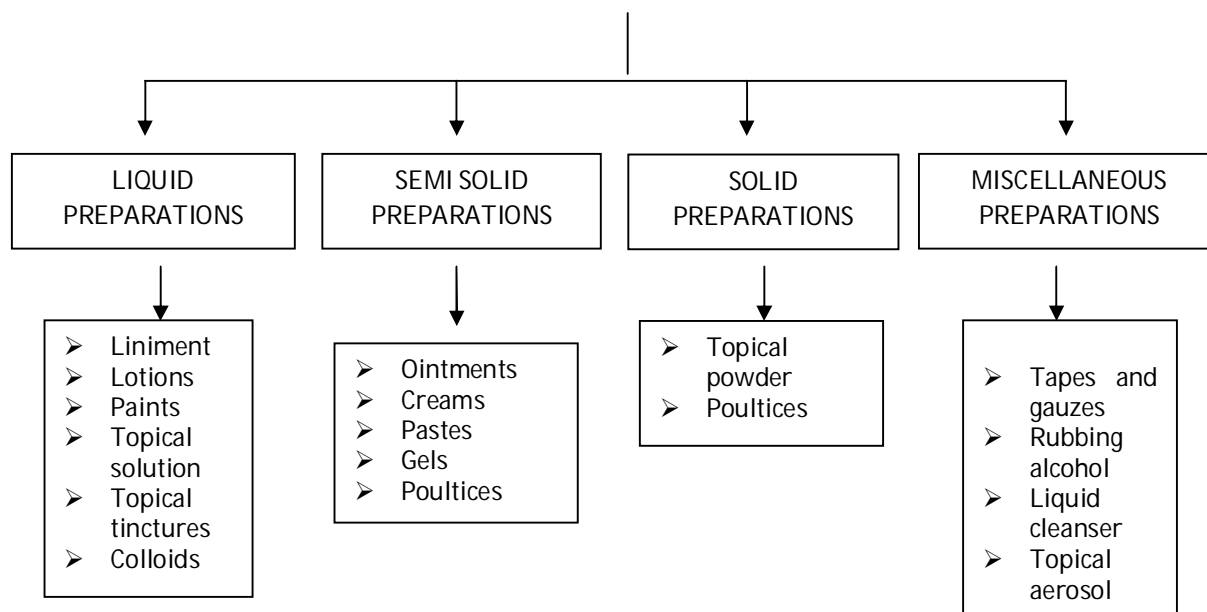
Keywords: Transdermal gel, precutaneous absorption, bioavailability, plasma concentration.

INTRODUCTION

Topical drug administration is localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes¹. Skin is one of the most readily accessible organs on human body for topical administration and is the main route of topical drug delivery system

For the topical treatment of dermatological diseases as well as skin care, a wide variety of

vehicle ranging from solids to semisolids and liquid preparation is available to clinician and patients. Within the major group of semisolid preparations, the use of transdermal gels has expanded both in cosmetics and in pharmaceutical preparations. Transdermal application of gels at pathological sites offer great advantage in a faster release of drug directly to the site of action, independent of water solubility of drug as compared to creams and ointments^{30,31}

CLASSIFICATION OF MEDICATED FORMULATION FOR THE SKIN⁸

Out of these, gel are becoming more popular due to ease of application and better precutaneous absorption

The term 'gel' was introduced in the later 1800 to name some semisolid material according to pharmacological, rather than molecular criteria.

The U.S.P. defines Gels²⁹ as a semisolid system consisting of dispersion made up of either small inorganic particles or large organic molecules enclosing and interpenetrated by liquid. The inorganic particle forms a three -dimensional "house of card" structure. Gels consists of two phase system in which inorganic particles are not dissolved but merely dispersed throughout the continuous phase and large organic particles are dissolved in the continuous phase, randomly coiled in the flexible chains.

Within the major group of semisolid preparations, the use of transdermal gels has expanded both in cosmetics and in pharmaceutical preparations². A gel is colloid that is typically 99% weight liquid, which is immobilized by surface tension between it and a macromolecular network of fibers built from small amount of a gelating substances present³. Topical drug administration a localised drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Skin is one of the most accessible organs of human body for topical administration and main route for topical drug delivery system.

Numbers of medicated products are applied to skin or mucous membrane that either enhance or

restore a fundamental function of a skin or pharmacologically alter an action in the underlined tissues. Such products are referred to as topical or dermatological products⁴. Hydroxy propyl methyl cellulose (HPMC), Carbopol 934P, sodium alginate has been used as hydrophilic polymers topically in gel drug delivery system^{5,6}. A series of grades based on molecular fractions of these polymers are used at a concentration between 1 to 5% in topical gel formulation. Due to their non greasy properties, they can easily provide a washable film on the skin^{5,7}. HPMC, Carbopol 934P, sodium alginate polymers of high molecular weight do not penetrate the skin and are non toxic in nature.

Drug Permeation through Skin⁹

Skin acts as a major barrier for permeation of any substance into the body and this is mainly due to the stratum corneum, which is its outer layer. In most of its areas, there are 10-30 layers of stacked corneocytes with palms and soles having the most. Each corneocyte is surrounded by a protein envelope and is filled with water-retaining keratin proteins. The cellular shape and orientation of the keratin proteins add strength to the stratum corneum (Figure 1).

When a formulation is applied onto the skin, several gradients are established across it, and drugs, to a certain extent, are able to pass through the stratum corneum. It is also reported that one important factor for drugs to permeate stratum

corneum is the water gradient, which can be altered by application of several formulations onto the skin. Hence for effective drug delivery through the skin, an external water gradient could be established.

Drugs, when applied onto the skin, can penetrate it via three major routes *viz.*, through sweat glands, stratum corneum or hair follicles (Fig 1)

There has been a continuous effort for understanding the structural barrier and properties of stratum corneum. The permeation of drugs through hair follicles compared to the stratum corneum is also widely being discussed²⁰. Further, it is reported that the follicular route is more favorable for permeation of polar molecules, as their influx through the stratum corneum is difficult²⁵. There are specific factors which determine efficiency of drug permeation through the skin. The physicochemical nature of drug, site and condition of skin, the formulations, and their influence on the properties of stratum corneum are also important²⁶.

Classification of Gels

Gels are classified mainly by two methods based on^{8,33}:

- a) Nature of colloid phase
 - i) Inorganic gels
 - ii) Organic gels
- b) Based on nature of solvent
 - i) Aqueous gels
 - ii) Non aqueous gels

Pharmaceutical gels may be loosely categorized based upon their network microstructure according to the following scheme suggested by Faucci²¹

- A. Covalently bonded polymer network with completely disordered structure.
- B. Physically bounded polymer network predominantly discovered but containing ordered loci.
- C. Well ordered lamellar, including gel mesophases formed by inorganic clays.

1) Covalently Bonded Structure

Covalently cross-lined gel networks are irreversible systems. They are typically prepared from synthetic hydrophilic polymer in one of two ways.

In first method of preparation, infinite gel network arises from the non-linear co-polymerization of two or more monomer species with the one being at least trifunctional. Both direction and position by

which each polymer chain grows during the reaction is random, resulting in final microstructure of this gel being completely disordered. The gel point for co-polymerization between equimolar concentrations of two monomer species can be predicted, using modified *Carothers equation*:

$$X_n = 2/2 - P f_{av}$$

Where,

X_n = the number average degree of polymerization

P = the fractional conversion and

f_{av} = the average functionality of monomers involved

The gel point reaches when $X_n \rightarrow \infty$ {indicating that critical conversion for gelation (PG) is equal to $2/f_{av}$ }

2) Physically bonded structure

Physically bonded gel networks are reversible systems. Factors such as temperature and ion additions can induce a transition between the sol and gel phases. These gels are formed primarily by natural organic polymers (proteins and polysaccharides) and semi synthetic derivatives. The particular organization of polymer chains in a junction zone depends on a chemical structure of the repeating unit. For example, sulfated polysaccharides (e.g. agar and carrageenans) that contain assortment sulfated galactose residues from double helices, two or more of which aggregate into multi-helices functional zone. However, presence of few concomitant residues produces links that effectively block helix formation in large section of chains indicating that steric fit is critical to get formation.

Other zone junction requires the presence of multivalent ions to form a bridge between polymer chains. An egg box model was proposed by Pawel et al. for the formation of calcium alginate gels, in which calcium cations are cooperatively bound between ionized carboxy groups located on the polyguluronate sequence of alginic acid. Locations are coordinated in the interstices of ordered segments of the polysaccharides chains.

3) Well Ordered Gel Structure

Under suitable conditions, certain silica, alumina and clay soils form rigid gels or lyogels. When clay belongs to smectite class,

such as bentonite, hectorite and loponite, come into contact with water, they undergo interlayer swelling spontaneously followed by osmotic swelling to produce a gel. The plate like clay particles associates into a "cubic cardhouse" ordered structure, which is stabilized by repulsive forces, caused by interacting electrical double layer. Highly ordered lamellar gel microstructures are formed by certain mixture of surfactant and long chain fatty alcohols in water using small angle X-ray scattering (SAXS), an ordered lamellar stack lattice model was proposed for the gel formed by 10% w/w cetosteryl alcohol containing 0.5% cetrimide surfactant. In contrast, the microstructure of Brij 96 gel depends on the surfactants concentrations. A hexagonal liquide-crystalline gel structure was detected by SAXS at concentration of 40-60% w/w in water, whereas extended lamellar structure was detected at higher concentration (70-80% w/w).

GEL FORMING SUBSTANCES⁸

Polymers are used to give the structural network, which is essential for the preparation of gels. Gel forming polymers are classified as follows:

1. NATURAL POLYMERS
 - Proteins – Collagen, Gelatin
 - Polysaccharides – Agar, Alginate acid, Sodium or Potassium carageenan, Tragacanth, Pectin, Guar Gum, Cassia tora, Xanthan, Gellum Gum
2. SEMISYNTHETIC POLYMERS CELLULOSE DERIVATIVES
 - Carboxymethyl cellulose, Methylcellulose, Hydroxypropyl cellulose, Hydroxy propyl (methyl cellulose), Hydroxyethyl cellulose
3. SYNTHETIC POLYMERS
 - Carbomer – Carbopol 940, Carbopol 934
 - Poloxamer
 - Polyacrylamide
 - Polyvinyl alcohol
 - Polyethylene and its co-polymers
4. INORGANIC SUBSTANCES
 - Aluminium hydroxide
 - Bentonite
5. SURFACTANTS
 - Cebrostearyl alcohol
 - Brij – 96

Advantages^{10,23,24}

The topical administration of drug in order to achieve optimal cutaneous and percutaneous drug

delivery has recently gain an importance because of various advantages:

- They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH and enzymatic activity and drug interaction with food and drinks.
- They can substitute for oral administration of medication when that route is unsuitable.
- To avoid the first pass effect, that is, the initial pass of drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzyme.
- They are non-invasive and have patient compliance.
- They are less greasy and can be easily removed from the skin.
- Cost effective.
- Reduction of doses as compare to oral dosage forms.
- Localized effect with minimum side effects.
- Improving drug bioavailability, reducing dose frequency.
- Stabilizing drug delivery profiles.

Limitations¹⁰

- The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dose required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult.
- Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin's impermeability.
- Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.
- The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

MECHANISM OF DRUG ABSORPTION²²

The rate of permeation across various layers of skin tissues in the course of topical application can be expressed mathematically as

$$dQ / dt = Ps (Cd - Cr)$$

where

dQ / dt = rate of permeation across various layers.

Cd = concentration of drug in the donar phase.

Cr = concentration of drug in the receptor phase.

Ps = permeability coefficient of the skin tissues.

The concentration in the systemic circulation which is penetrating in the form of pharmacological active form such as:

$$Ps = KcDs / hs$$

where

Kc = partition coefficient of the penetrant molecules.

hs = overall thickness of the skin tissues.

Ds = apparent diffusivity for the steady state diffusion of penetrate moles.

If $Cd \gg Cr$ than the equation is written

$$dq / dt = PsCd$$

PHYSIOLOGICAL FACTORS IN PERCUTANEOUS ABSORPTION⁸

1. Skin integrity
2. Hydration
3. Temperature
4. Anatomic location
5. Age
6. Disease

FORMULATION FACTORS IN PERCUTANEOUS ABSORPTION⁸

1. Occlusivity
2. Drug concentration
3. pH
5. Surfactant
4. Solubility
6. Penetration enhancer

Permeation Enhancer¹¹

The skin is a barrier to topically administered drugs. Although the outer layer also provides resistance to the global permeation process, *in-vitro* experiments have shown that the stratum corneum, with 10 – 15 micrometer thickness is the principal barrier. Penetration enhancement technology is a challenging development that would increase significantly the number of drugs available for topical administration. The permeation of drugs through skin can be enhanced by physical methods such as mechanical disruption, electrical disruption, chemical modification and by chemical penetration enhancers e.g. sulphoxides (dimethyl sulphoxides), pyrrolidone, alcohols, glycols,

surfactants and terpenes. These compounds increase skin permeability by increasing the partition coefficient of the drug into the skin and by increasing the thermodynamic activity of the drug in the vehicle.

Classification of penetration enhancers

➤ Terpenes (essential oils)

E.g. Nerodilol, menthol, 1 8 cineol, limonene, carvone etc.

➤ Pyrrolidones

E.g. N-methyl-2-pyrrolidone(NMP), azone etc.

➤ Fatty acids and esters

E.g. Oleic acid, linoleic acid, lauric acid, capric acid etc.

➤ Sulfoxides and similar compounds

E.g. Dimethyl sulfoxide(DMSO), N,Ndimethyl formamide

➤ Alcohols, Glycols, and Glycerides

E.g. Ethanol, Propylene glycol, Octyl alcohol etc.

➤ Micellaneous enhancers

E.g. Phospholipids, Cyclodextrins, Amino acid derivatives, Enzymes etc.

Methods of Preparation^{21, 33}

- **DISPERSION METHOD:** In this method polymer is dispersed over water for 2 hours till all the polymer is soaked with water after that other chemical ingredients are mixed and stirred well until a homogenous mass is obtained
- **COLD METHOD:** In this method all the ingredients are mixed together to form a homogenous mass, under low temperature at about 5°C. In this polymer is mixed with permeation enhancer to form solution A, drug is mixed with solvent to form solution B. After that solution B is poured into solution A slowly with complete stirring.
- **CHEMICAL REACTION:** In the preparation of sols by precipitation from solution, e.g., Aluminum hydroxide sol precipitated by interaction in aqueous solution of an aluminum salt and sodium carbonate, increased concentration off reactants will produce a gel structure. Silica gel is another example and is produced by interaction of sodium silicate and acids in aqueous solution.
- **TEMPERATURE EFFECT:** As lower the temperature the solubility of most lyophilic

colloids, e.g., gelatin, agar, sodium-oleate, is reduced, so that, if cooling a concentrated hot sol will often produce a gel. Similarly to hydrogen bonding with water. Increasing the temperature of these sols will break the hydrogen bonding and the reduced solubility will produce gelatin.

- **FLOCCULATION WITH SALTS AND NON-SOLVENTS:** Gelatin is a popular collagen derivative primarily used in food, pharmaceutical, photographic and technical products. In foods, gelatin provides a melts-in-the-mouth function and to achieve a thermo-reversible gel property. Gelatin is produced by adding just sufficient precipitant to produce the gel structure state but in sufficient to bring about complete precipitation. It is necessary to ensure rapid mixing to avoid local high concentration of precipitants. Solutions of ethyl cellulose, polystyrene, etc, in benzene can be gelled by rapid mixing with suitable amount of a nonsolvent such as petroleum ether. The addition of salts to moderately sols such as aluminum hydroxide, ferric hydroxide and bentonite, produces gels.

1.14 Evaluation¹²⁻¹⁷

- pH
- Drug content
- Viscosity
- Spreadability
- Extrudability study
- Skin irritation studies
- *In vitro* release
- *In vivo* study
- Stability
- Consistency

1. Measurement of pH

The pH of various gel formulations is determined by using digital pH meter. One gram of gel is dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation is done in triplicate and average values are calculated.

2. Drug content

1 g of the prepared gel is mixed with 100ml of suitable solvent. Aliquots of different concentration are prepared by suitable dilutions after filtering the stock solution and absorbance is measured. Drug content is calculated using the

equation, which is obtained by linear regression analysis of calibration curve.

3. Viscosity study

The measurement of viscosity of the prepared gel is done with a Brookfield Viscometer. The gels are rotated at 0.3, 0.6 and 1.5 rotations per minute. At each speed, the corresponding dial reading is noted. The viscosity of the gel is obtained by multiplication of the dial reading with factor given in the Brookfield Viscometer catalogues.

4. Spreadability

One of the criteria for a gel to meet the ideal quantities is that it should possess good spreadability. It is the term expressed to denote the extent of area to which gel readily spreads on application to skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreading value.

Spreadability is expressed in terms of time in seconds taken by two slides to slip off from gel and placed in between the slides under the direction of certain load. Lesser the time taken for separation of two slides, better the spreadability. It is calculated by using the formula:

$$S = M \cdot L / T$$

Where M = wt. tied to upper slide
L = length of glass slides
T = time taken to separate the slides

5. Extrudability study

The formulations are filled in the collapsible tubes after the gels are set in the container. The extrudability of the formulation is determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of gel in 10 second.

6. Skin irritation study

Guinea pigs (400-500 g) of either sex are used for testing of skin irritation. The animals are maintained on standard animal feed and had free access to water. The animals are kept under standard conditions. Hair is shaved from back of guinea pigs and area of 4 cm² is marked on both the sides, one side served as control while the other side is test. Gel is applied (500 mg / guinea pig) twice a day for 7 days and the site is observed for any sensitivity and the reaction if any, is graded as 0, 1, 2, 3 for no reaction, slight patchy erythema, slight but confluent or moderate but patchy erythema and severe erythema with or without edema, respectively.

7. *In vitro* Diffusion studies

The diffusion studies of the prepared gels can be carry out in Franz diffusion cell for studying the dissolution release of gels through a cellophane membrane. Gel sample (0.5g) is taken in cellophane membrane and the diffusion studies are carried out at $37 \pm 1^\circ$ using 250 ml of phosphate buffer (pH 7.4) as the dissolution medium. Five milliliters of each sample is withdrawn periodically at 1, 2, 3, 4, 5, 6, 7 and 8 h and each sample is replaced with equal volume of fresh dissolution medium. Then the samples are analyzed for the drug content by using phosphate buffer as blank.

8. Stability

The stability studies are carried out for all the gel formulation by freeze - thaw cycling. In this syneresis is observed by subjecting the product to a temperature of 4°C for 1 month, then at 25°C for 1 month, then at 40°C for 1 month. After this gel is exposed to ambient room temperature and liquid exudates separating is noted.

9. Consistency³²

The measurement of consistency of the prepared gels is 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 penetration by the cone is measured from the surface of the gel to the tip of the cone inside the gel. The distance traveled by cone is noted down after 10sec.

Table 1: Required properties of pharmaceutical gels¹⁸

Pharmaceutical gel application	Favorable properties
DENTAL	Highly thixotropic, optimal viscosity for filling fissure, adherent to enamel surface, optically clear, water soluble, oral digestible.
DERMATOLOGICAL	Thixotropic, good spreadability, greasless, easily removable, emollient, demulcent, non-staining, compatible with number of excipients (water soluble or miscible).
NASAL	Adherent, odourless, non-irritant, water-soluble.
OPHTHALMIC	Optically clear, sterile, mucomimetic, lubricating or non-sensitizing, water soluble or miscible.
SURGICAL AND MEDICAL PROCEDURES	Lubricating, adherent to instrument surfaces, maximal contact with mucus.
VAGINAL	Acid stable, adherent, does not liquefy at body temperature; slow dissolving, lubricating, greasless and non-tacky, non-irritating.

Table 2: General classification and description of gels¹⁸

Class	Description	Examples
Inorganic	Usually two-phase systems	Aluminium hydroxide gel, bentonite magma
Organic	Usually single-phase systems	Carbopol®, tragacanth
Hydrogels	Contains water	Silica, bentonite, pectin, sodium alginate, methylcellulose, alumina
Organogels	Hydrocarbon type Animal/vegetable fats Soap-base greases Hydrophilic organogels	Petrolatum, mineral oil/polyethylene gel, Plastibase Lard, cocoa butter Aluminium stearate with heavy mineral-oil gel Carbowax bases (PEG ointment)
Hydrogels	Organic hydrogels Natural and synthetic gums Inorganic hydrogels	Pectin paste, tragacanth jelly Methylcellulose, sodium carboxymethylcellulose, Pluronic® F-127 Bentonite gel (10% to 25%), Veegum®

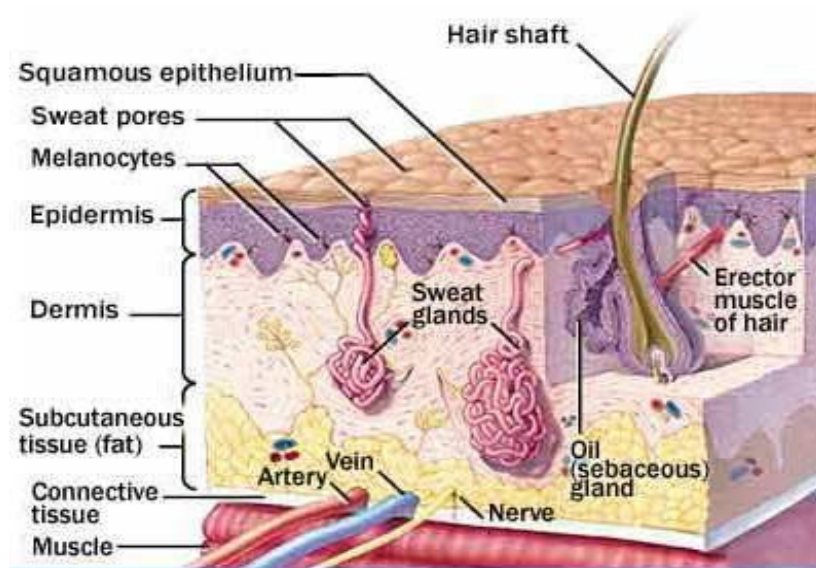


Figure 1: Structure of skin(19)

CONCLUSION

Transdermal drug delivery system is useful for topical and local action of the drug. The drugs which shows hepatic first pass effect and unstable in GI conditions are the suitable candidate for TDDS through gel.

FUTURE PROSPECTIVE

Expanding the use of novel permeation enhancement techniques with macromolecules and other conventional molecules for a wider range of indications is highly desirable for the transdermal industry. Physical enhancement methods afford substantial improvement in the rate of delivery of therapeutic agents across skin. Currently, a variety of them are undergoing extensive investigation and new device-based TDS can be expected in the near future. One can also expect the first transdermal prodrug product to emerge on the market in the near future. Novel prodrugs would not only help to reach the therapeutic levels for some drugs, but may also help alleviate skin irritation.

The incidence and significance of skin irritation reactions will decrease with the increasing

availability of physical permeation enhancement methods and new breakthroughs in topical drug formulations, such as liposomes, microemulsions, nanoparticles and evaporating gels. Breakthroughs in chemical permeation enhancer analogs showing significant improvements in limiting cutaneous irritation show promise for the development of safe chemical enhancers and should be further examined in the future

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