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A Review: Effect of Permeation Enhancers on the Penetration Mechanism of Transdermal Gel

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Abstract: *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. The systems can greatly improve patient compliance through avoidance of first-past metabolism, improved bioavailability, reduction of systemic side effects and dosing schedule. In the past three decades, transdermal drug delivery has been developed to the stage where transdermal systems become a feasible way of delivering clinically effective drugs particularly those drugs with significant first-pass effect of the liver that can prematurely metabolize drugs. The advantages of this type of drug delivery include targeting specific areas of the body and decreasing the amount of drug necessary for effect as compared to drugs taken orally.*
KeyWords*: Transdermal*

I. Introduction

Transdermal delivery systems (TDS) were introduced onto the US market in the late 1970s, but transdermal delivery of drugs had been around for a very long time. There have been previous reports about the use of mustard plasters to alleviate chest congestion and belladonna plasters used as analgesics. The mustard plasters were homemade as well as available commercially where mustard seeds were ground and mixed with water to form a paste, which was in turn used to form a dispersion type of delivery system. Once applied to the skin, enzymes activated by body heat led to the formation of an active ingredient (allyl isothiocyanate). Transport of the active drug component took place by passive diffusion across the skin – the very basis of transdermal drug delivery.[1]

Since then a long path has been traversed in the field where we have seen the development of numerous transdermal patches ranging from nicotine to methylphenidate and testosterone to lidocaine. The TDSs that have been developed over the years have been classified into different generations by Prausnitz *et al*. According to the classification, the first generation dealt mostly with small, lipophilic and uncharged molecules that can be delivered in the therapeutic range by passive diffusion alone. Most of the TDS that are currently on the market belong to this generation. But with the advancement of science and engineering we have seen the use of chemical enhancers and techniques such as ultrasound and iontophoresis for the delivery of drug molecules that cannot undergo passive diffusion. These belong to the second generation of transdermal products that target reversible disruption of the skin's outer layer, the stratum corneum or use an additional driving force for drug delivery.

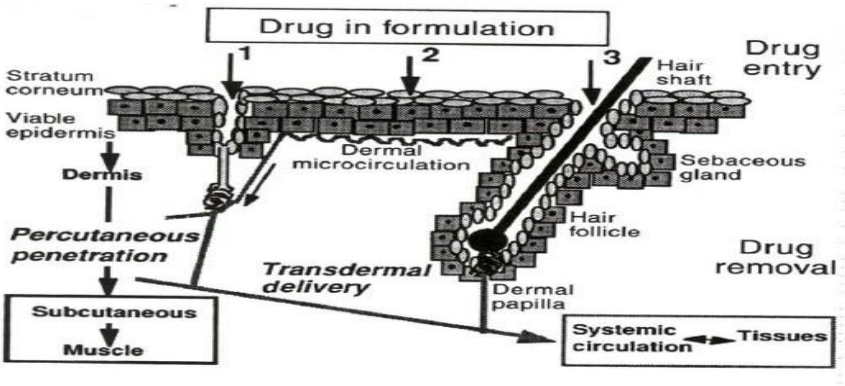


Figure1: Pathway of drug delivery through skin

Advantages Of Transdermal Drug Delivery System (Tdds)

1. Avoidance of first pass metabolism of drugs.
2. Reduced plasma concentration levels of drugs, with decreased side effects.
3. Reduction of fluctuations in plasma levels of drugs, Utilization of drug candidates with short half-life and low therapeutic index.

4. Easy elimination of drug delivery in case of toxicity.
5. Reduction of dosing frequency an enhancement of patient compliance.
6. Transdermal medications deliver a steady infusion of a drug over an extended period of time. Adverse effects or therapeutic failure frequently associated with intermittent dosing can also be avoided.
7. Transdermal delivery can increase the therapeutic value of many drugs via avoiding specific problems associated with the drug. E.g. GI irritation, lower absorption, decomposition due to 'hepatic first pass' effect.
8. Due to above advantage, it is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary, if e.g. the drug is given orally.
9. The simplified medication regimen leads to improved patient compliance and reduced inter and intra-patient variability.

Limitation Of Tdds

The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dosage required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult if not impossible. Skin irritation or contact dermatitis due to the drug, excipients and enhancers of the drug used to increase percutaneous absorption is another limitation. Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

Criteria For Selection Of Drug

- Molecular weight of drug should be less than 500 Dalton.
- Partition coefficient should be below 2.
- Daily Dose(< 20 mg/day)
- Half- life (10 hrs or less)
- Melting Point (< 200 C)
-

Limitations For A Drug Substance To Be Incorporated Into A Transdermal Delivery System Are

- Heavy drugs molecules (>500 Da) usually difficult to penetrate the stratum cornea.
- Drugs with very low or high partition coefficient fail to reach blood circulation.
- Drugs that are highly melting can be given by this route due to their low solubility both in water and fat.
- Many approaches have been attempted to deliver medicament across skin barrier and enhance the efficacy.

The major considerations for enhancing transdermal delivery are physical enhancers (ultrasound, iontophoresis, electroporation, magnetophoresis, microneedle), vesicles, particulate systems (liposome, niosome, transfersome, microemulsion, solid lipid nanoparticle) and chemical enhancers (sulphoxides, azones, glycols, alkanols, terpenes etc.).

Percutaneous Absorption[2]

The absorption of substances from outside the skin to positions beneath the skin, including entrance into the blood stream.

Factors Affecting Percutaneous Absorption

1. Nature of the drug itself
2. Nature of the vehicle
3. The nature of the skin
4. Presence of moisture

A number of drugs may be administered by transdermal route. Transdermal drug absorption markedly alters drug kinetics and depends on a several parameters including the following-

- Medicament application site
- Thickness and integrity of the stratum cornea epidermidis.
- Size of the molecule that is to be administered.
- Permeability of the membrane for the transdermal drug delivery.
- Hydration state of skin.
- pH of the drug.
- Drug metabolism by skin fbra.
- Lipid solubility.
- Drug depot in skin.
- Blood flow alteration in the skin by additives and body temperature

The toxic effect of the drug and problem in limiting drug uptake are major considerable potential for transdermal delivery systems, especially in children because skin thickness and blood flow in the skin usually vary with age. The increased blood supply in the skin along with thinner skin has significant effects on the pharmacokinetics of transdermal delivery for children. In some situations this may be an advantageous, while in others systemic toxicity may occur. This was observed after using scopolamine patches that are used to prevent motion sickness, a eutectic mixture of local anaesthetics (EMLA) cream used to minimize the pain, corticosteroid cream applied for its local effect on skin maladies. Episodes of systemic toxic effects, including some fatalities in children have been documented with each of these, often secondary to accidental absorption through mucous membranes.[3]

Classification of Methods to Increase Skin Permeability

1. Chemical Method Or Permeation Enhancers
2. Physical Method
Permeation Enhancers
Classification of penetration enhancers[4]

- 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**.**

Chemical Permeation Enhancers

Facilitate drug permeation across the skin by increasing drug partitioning into the barrier domain of the stratum corneum, increasing drug diffusivity in the barrier domain of the stratum corneum or the combination of both. The heterogeneous stratum corneum is composed of keratin 'bricks' and intercellular continuous lipid 'mortar' organized in multilamellar strata. Depending on the nature of the drug either of these two environments may be the rate-limiting milieu (barrier domain) for the percutaneous transport. As a consequence it is anticipated that the magnitude of permeation improvement obtained with a given permeation enhancer will vary between lipophilic and hydrophilic drugs. Several mechanisms of action are known: increasing fluidity of stratum corneum lipid bilayers, extraction of intercellular lipids, increase of drug's thermodynamic activity, increase in stratum corneum hydration, alteration of proteinaceous corneocyte components and others. Permeation enhancers are conventionally divided into several groups based on their chemical structure rather than the mechanism of action. This is partially due to the difficulty determining a primary or mixed mode of action for many of them. Furthermore, compounds from the same group can exert their effect through different mechanisms. More than 300 substances have been shown to have skin permeabilization potential and this number is still growing.

Most known enhancers fall into the following categories: alcohols (ethanol, pentanol, benzyl alcohol, lauryl alcohol, propylene glycols and glycerol), fatty acids (oleic acid, linoleic acid, valeric acid and lauric acid), amines (diethanolamine and triethanolamine), esters (isopropyl palmitate, isopropyl myristate and ethyl acetate), amides (1-dodecylazacycloheptane-2-one [Azone®], urea, dimethylacetamide, dimethylformamide and pyrrolidone derivatives), hydrocarbons (alkanes and squalene), surfactants (sodium laureate, cetyltrimethylammonium bromide, Brij®, Tween® and sodium cholate), terpenes (D-limonene, carvone and anise oil), sulfoxides (dimethyl sulfoxide) and phospholipids (lecithin). The importance of water, or hydration of the stratum corneum, is not to be underestimated.

A fully hydrated stratum corneum (under occlusion) presents lesser diffusion resistance to xenobiotics than its dehydrated counterpart. However, a common drawback of permeation enhancers is that their efficacy is often closely mimicked by skin irritation. In general, the same mechanisms that are responsible for enhanced drug transport such as disrupting ordered stratum corneum lipid bilayers or corneocyte structural organization are also responsible for skin irritation. One possibility to address this concern is to identify mixtures of permeation enhancers that exhibit synergistic effects. Karande *et al.* successfully used a screening approach to test 5000 binary mixtures of chemicals. The details are described in the next section of this article. Most of the

products on the transdermal market use the effect of occlusion, which can be classified as an enhancement technique acting through the hydration of the stratum corneum. Additionally, drugs such as nitro-glycerine (Nitro-Dur®, Nitro Disc® and Transderm-Nitro®) use fatty acid esters and lidocaine (Lidoderm®) use urea and propylene glycol as chemical enhancers. Traditionally, chemical enhancers have been used to increase the delivery of small molecules and showed only limited success in permeation enhancement of macromolecules. Overall, chemical methods, although effective, cannot compete with physical enhancement methods that provide a greater magnitude of skin permeabilization.

II. Physical Methods

The oldest and by far the most popular way of overcoming the skin barrier physically is the use of hypodermic needles. In many cases it is the only viable method of delivery for poorly absorbable and highly unstable compounds. Typically, drug solution is forced under piston pressure directly into the bloodstream or tissue (skin and muscle). Such drug administration results in quick delivery of large amounts of drug. If controlled drug delivery over longer periods of time is desired, indwelling catheters are used. However, both require mechanical perforation of skin with a needle, which causes pain and trauma. According to Hamilton, needle phobia is a medical condition that affects at least 10% of the population. This condition is a serious problem in the healthcare system in the sense that people with needle phobia tend to avoid medical care. To address these drawbacks, several alternative physical skin enhancement methods such as jet injections, dermabrasion, thermal ablation, laser, microneedles, iontophoresis, electroporation, ultrasound and combinations of the above have been investigated. These methods aim at developing more user-friendly and flexible delivery systems, and are able to produce bolus type as well as sustained drug delivery profiles.

Thermal ablation takes advantage of the external source of thermal energy, which propagates into the stratum corneum to create microchannels. Heating of the skin surface to hundreds of degrees for a very short period of time allows the thermal damage to be limited to the stratum corneum alone without further heat propagation to live epidermal layers. An interesting publication by Park *et al.* discussed the effect of heat on skin permeability. The authors pointed out skin permeability changes to a model hydrophilic compound at different temperature ranges. While an intermittent increase in the skin temperature to 100–150°C causes a moderate increase in the flux of a hydrophilic compound, 150–250°C translates into one to two orders of magnitude increase, and a temperature of over 300°C adds yet another tenfold augmentation in the transdermal flux. Different mechanisms were postulated to be responsible for such change at each temperature range. Altea Therapeutics developed a PassPort™ system that comprises a single-use disposable patch and a re-useable handheld applicator. Phase I and II clinical trials have been completed for the delivery of insulin via this enhancement system.

Classification Of Gels[5,6]

Gels are classified mainly by two methods based on

a) Nature of colloid phase

i) Inorganic gels: which have synthetic polymers
ii) Organic gels: which have natural polymers.

b) Based on nature of solvent

i) Aqueous gels: In which polymer is dissolved in water
ii) Non aqueous gels: In which polymer is dissolved in organic or inorganic solvents.

Gel Forming Substances

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**: (Used as viscosifying agent and used as a vehicle for drug delivery)
   - 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: (used as gelling agent)
- Aluminium hydroxide
- Besitonite

5. Surfactants: (Used as emulsifying agent, solubilising agent)
- Cebrotearyl alcohol
- Brij – 96

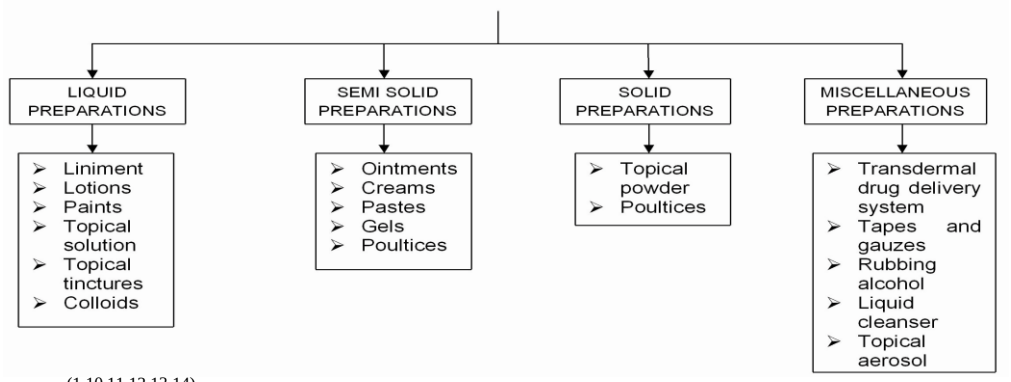
Advantages[7,8,9]

The topical administration of drug in order to achieve optimal cutaneous and percutaneous drug delivery has recently gained 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.

III. Methods Of Preparation

- **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, no heat is applied to solublize the ingredients. 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.Aluminium hydroxide sol precipitated by interaction in aqueous solution of an aluminium 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 produce 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 aluminium hydroxide, ferric hydroxide and bentonite, produces gels.

Classification Of Medicated Transdermal Formulation For The Skin[5]



13 Evaluation [1,10,11,12,13,14]

- pH
- Drug content
- Viscosity
- Spreadability
- Extrudability study
- Skin irritation studies
- Invitro release
- Invivo study
- Stability

Measurement Of Ph

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

1. Drug Content

1 g of the prepared gel was mixed with 100ml of suitable solvent. Aliquots of different concentration were prepared by suitable dilutions after filtering the stock solution and absorbance was measured. Drug content was calculated using the equation, which was obtained by linear regression analysis of calibration curve.

2. Viscosity Study

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

3. 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:

$$S = M. L / T$$

Where, M = wt. tied to upper slide

L = length of glass slides

T = time taken to separate the slides

4. 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 extrude a 0.5 cm. ribbon of gel in 10 second.

5. Skin Irritation Study

Guinea pigs (400-500 g) of either sex were used for testing of skin irritation. The animals were maintained on standard animal feed and had free access to water. The animals were kept under standard conditions. Hair was shaved from back of guinea pigs and area of 4 cm^2 was marked on both the sides, one side served as control while the 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 cofluent or moderate but patchy erythema and severe erythema with or without edema, respectively.

6. In Vitro Dissolution Studies

Dissolution study was carried out across egg membranes by using USP apparatus-II, paddle type for 8 hr. The stirring rate was 50 rpm. Phosphate buffer pH 7.4 was used as medium (900 ml) and was maintained at 37 ± 0.5^0 C. Samples (5ml) were collected periodically at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hr and assayed for dissolution spectroscopically at 350 nm. Each sample was replaced with equal volume of fresh dissolution medium, and dissolution rate test was repeated thrice and average values were reported.

7. Ex Vivo Diffusion Studies

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

8. 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° 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.

IV. Conclusion

There are various routes for delivering the drugs . Among which oral delivery route is very important. But the drug delivery through skin provides several advantages over oral drug delivery. Mainly transdermal drug delivery system is used for their local action. Drug delivery through transdermal route provide less chance of an overdose or underdose and permits both local and systemic effects. It provides the system which maintain the constant drug profile in the blood. This system has less systemic side effects than oral and intravenous delivery system.

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