SKIN BARRIERS: CHALLENGE FOR TRANSDERMAL DRUG DELIVERY

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ABSTRACT
Transdermal system is a self contained and discrete dosage form, for systemic action of various drugs. Skin is the main barrier to be overcome for this delivery system. Three mechanisms are involved in skin permeation kinetics such as sorption by stratum, penetration of drug through viable epidermis and uptake of the drug by capillary network in dermal papillary layer. Polymer matrix, drug, permeation enhancers and excipients are main components of transdermal drug delivery systems. Various permeation enhancers are used to overcome these barriers. Recent advances in this system include the formulation of emulgel which contains properties of both emulsion as well as gel.

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INTRODUCTION

The skin is the largest organ of the body, accounting for more than 10% of body mass, and the one that enables the body to interact most intimately with its environment[1]. Figure 1 shows a diagrammatic illustration of the skin[2]. The skin consists of four layers: the stratum corneum (nonviable epidermis), the remaining layers of the epidermis (viable epidermis), dermis, and subcutaneous tissues. There are also several associated appendages: hair follicles, sweat ducts, apocrine glands, and nails. Many of the functions of the skin can be classified as essential to survival of the body bulk of mammals and humans in a relatively hostile environment[2]. In a general context, these functions may be classified as protective, maintaining homeostasis, or sensing. The importance of the protective and homeostatic role of the skin is illustrated in one context by its barrier property.

SKIN DISEASES[3]

1. Psoriasis:-
Psoriasis is a chronic inflammatory skin disease of unknown etiology that affects between 1 and 3% of the population. There is increased proliferation of the epidermis with infiltration of inflammatory cells within the dermis and epidermis, coupled with dilation of the upper dermal capillaries.

2. Atopic Eczema:-
Patients have increased levels of serum IgE and some have precipitating antibodies to environmental allergens, including foods and inhaled materials. Many patients will have a positive response to intracutaneous challenge with pollen, house dust mite, cat fur, and fish antigens. However, the significance of these positive reactions is unclear. Patients with atopic eczema have reduced numbers of circulating T-suppressor cells which are responsible for modulating immunoglobulin-producing B lymphocytes.

3. Acne:-
Acne is one of the most common and distressing of skin diseases commonly present during adolescence and usually (but not always) resolves in early adult life. Several variants of acne are recognized, including infantile acne, which occurs on the face during the first few months and usually settles spontaneously, and occupational acne, resulting from exposure to oil, coal tar, chlorinated hydrocarbons, or insecticides. Acne may be precipitated or exacerbated by certain combined oral contraceptive pills or by androgenic hormones. Acne vulgaris commonly affects the face, chest, and upper back, and usually presents during puberty. The clinical features include an increased rate of sebum secretion, comedones, papules, and pustules.

4. Rosacea:-
Rosacea is a chronic inflammatory skin disorder, affecting the face, which causes persistent erythema associated with telangiectasia and papules. The patients may also complain of flushing in response to trivial stimuli. The rash may resemble that seen in acne, but rosacea usually affects an older-aged group and is not characterized by comedones. Persistent inflammation of the nose may result in rhinophyma (an irregular bulbous enlargement of the nose characterized by prominent hair follicles). Over 30% of patients with rosacea may also suffer with conjunctivitis and blepharitis.

5. Lichen Planus:-
Lichen planus is an inflammatory skin disorder, of unknown etiology, characterized by the presence of pruritic violaceous papules. Common sites are the flexural aspect of the wrists and forearms, but the rash may also affect the trunk and limbs. Lichen planus may be associated with other autoimmune diseases, including vitiligo and myasthenia gravis. The etiology is unknown but the deposition of IgM at the dermoepidermal junction, coupled with a dense inflammation in the upper dermis, suggest an autoimmune
process. Lichen planus-like rashes may be precipitated by various drugs, including thiazide diuretics, gold, tetracyclines, and paraaminosalicylic acid (PAS). The disease is usually self-limiting, but topical corticosteroids may be helpful.

6. Pityriasis Rosea:-

Pityriasis rosea is an erythematous scaling rash, of unknown etiology, thought to be secondary to infection with an, as yet unidentified, virus. Patients develop a solitary erythematous scaling patch some 2–3 cm in diameter. After a few days, other smaller plaques develop on the trunk. The individual lesions tend to be oval and their longitudinal axis run parallel to the lines of the ribs. The rash may be associated with mild pruritus and can last for several weeks before resolving spontaneously. Topical steroids may be of benefit.

7. Solar Keratosis:-

Solar (actinic) keratoses present as scaling hyper keratotic plaques or papules on skin exposed to light. They are most commonly seen on elderly subjects with fair skin who have had high levels of ultraviolet exposure over many years. They may be associated with other signs of photodamage such as yellowing, coarsening, and wrinkling of the skin. Individuals with large numbers of solar keratoses are at increased risk of developing nonmelanoma skin cancer. Histologically, the lesions show epidermal thickening, with abnormal epidermal differentiation and scaling. Solar keratoseare common, and up to 20% of individuals over the age of 60 are affected. Some solar keratoses may resolve spontaneously, but a small proportion may develop into squamous cell carcinoma. Solar keratoses may respond to topical 5% 5-fluorouracil cream (Efudix) an antimetabolite that inhibits DNA synthesis.

8. Ulcers:-

Ulcers may be seen at any body site, but are most commonly seen on the legs, probably caused by a combination of trauma and impaired circulation. The venous return of blood from the legs depends on efficient working of the calf muscles to act as a pump coupled with the action of valves in the deep veins preventing the reflux of blood. Damage to the valves of the deep veins following deep vein thrombosis may be associated with pregnancy. Injury or immobilization may also lead to valvular incompetence. The most common types of ulcer are venous ulcers caused by leaking valves in the deep veins, resulting in venous hypertension, and edema of the subcutaneous tissue. An extravascular accumulation of fibrinous material leaked from dermal blood vessels results in a fibrous cuff around the capillaries that prevents diffusion of oxygen and other nutrients through the blood vessel wall as well as causing fibrosis, and sclerosis of the dermal capillaries.

CATEGORY OF DRUGS FOR TREATMENT OF SKIN DISEASES[4]
1. Antibacterial:- Mupicrocin, Anthralin etc.
2. Antifungal:- Clotrimazole, Ketoconazole etc.
3. Antibiotics:- Erythromycin, Ciproflocacin etc.
4. Antifungal:- Ketoconazole, Miconazole etc.
5. Antiviral:- Acyclovir, Arbidol etc.

BARRIERS IN SKIN

Stratum corneum & Epidermis

The Stratum corneum consists of multiple layers of horny dead cells, which are compacted, flattened, dehydrated and keratinized. The horny cells are stacked in highly interdigitated columns with 15-25 cells in the stack over most of the body. It has a density of 1.55g/cc. The stratum corneum has a water content of only 20% as compared to 70% present in physiologically active stratum germinativum. It exhibits regional differences over most of the body and is approximately 10-15μm in thickness. However, the thickness may be several hundred micrometers (300-400μm) on friction surfaces such as the palms of the hand and soles of the feet[4]. Keratin present in the cells of the SC is a fibrous protein, which is poor in sulphur and forms a filamentous network to assure cohesion, flexibility and recovery. The unique properties of stability, insolubility and resistance observed in the SC are due to the thick cell membrane and cell matrix, which consists of amorphous proteins rich in sulphur content and lipids with many disulphide linkages[5].

Dermis

The site of systemic absorption. The dermis is 0.2-0.3 cm thick and is made of a fibrous protein matrix, mainly collagen, elastin and reticulum embedded in an amorphous colloidal ground substance. It is divided into two distinct zones: a superficial finely structured thin papillary layer adjacent to the epidermis and a deeper coarse reticular layer (the main structural layer of skin). The dermis is also the locus of the blood vessels, sensory nerves, segments of the sweat glands and sebaceous units. The blood vessels supply blood to the hair[6].

Subcutaneous fatty tissue

It acts as a heat insulator and a shock absorber. It essentially has no effect on the percutaneous absorption of drugs because it lies below the vascular system[7].
Transdermal Permeation\cite{8}

Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration. Skin is the most intensive and really accessible organ of the body as only a fraction of millimeter of tissue separates its surface from the underlying capillary network. The various steps involved in transport of drug from patch to systemic circulation are as follows.

1. Diffusion of drug from drug reservoir to the ratecontrolling membrane.
2. Diffusion of drug from rate limiting membrane to stratum corneum.
3. Sorption by stratum corneum and penetration through viable epidermis.
4. Uptake of drug by capillary network in the dermal papillary later.

TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS)

In transdermal drug delivery system the drug is mainly delivered through the skin with the aid of transdermal patch or transdermal gel\cite{9}. A Transdermal patch is a medicament adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream\cite{10}. A drug is applied in a relatively high dose to the inside of a patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration in the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow\cite{10}.

Emulgel

Emulgel is biphasic drug delivery system. Emulgel is the combination of gels and emulsions. Gel formulations generally provide faster drug release as compared with ointments and creams. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation emulgels are prepared\cite{11}.

EXPERIMENTAL METHODS\cite{12-15}

a) Aqueous material and oils:

This forms the aqueous phase of the emulsion. Commonly used agents are water and alcohols.

b) Emulsifiers:

Emulsifying agents are used to promote the emulsification and to promote the stability of drug. Span 80 and Tween 80 is used as emulsifier in formation of emulgel.

c) Polymers:

Carbopol and Hydroxypropylmethyl cellulose K1000M and E5LV (HPMC) are the polymers used in preparation of topical Emulgel. These are used to increase the consistency of dosage form.

d) Penetration Enhancers:

Oleic acid, Tween and Isopropyl Alcohol are used as penetration enhancers. These are the agents which cause an increase in the skin permeability.

e) Preservatives:

Methyl paraben and propyl paraben are added in aqueous phase. These are used as preservatives.

ADVANTAGES\cite{14-15}

a) The Transdermal drug delivery system (TDDS) can be defined as a delivery device, which upon application on a suitable skin surface will be able to deliver the drug into the systemic circulation at sufficient concentration to ensure therapeutic efficacy, an additional limitation to oral drug delivery, can be avoided with transdermal administration.

b) Steady permeation of drug across the skin, allowing consistent serum drug level, often a goal of therapy.

c) Similar to intravenous infusion, it also achieves consistent plasma levels, but noninvasive in nature.

d) In addition, if toxicity develops from a drug administered transdermally, the effects could be moderated by removing the patch.

DISADVANTAGES\cite{16}

a) Many drugs especially drugs with hydrophilic structures permeate the skin too slowly may not achieve therapeutic level.

b) The drug, the adhesive or other excipients in the patch formulation can cause erythema, itching, and local edema.

APPLICATIONS\cite{17}

Transdermal drug delivery system has emerged as a potential novel drug delivery system in the last 30 years to improve the therapeutic efficacy and safety, maintain steady state plasma level of drugs and overcome significant drawbacks of the conventional oral dosage forms and parenteral preparations. TDDS is ideally suited for diseases that demand chronic treatment with frequent dosing. This review deals with a brief insight on the formulation aspects, the physical and chemical enhancers being explored to
enhance the transdermal delivery of drugs across the stratum corneum, the evaluation parameters (physicochemical, in vitro, in vivo studies) and therapeutic applications of TDDS.

**CRITERIA FOR IDEAL DRUG CANDIDATE FOR TRANSDERMAL GELS**[18]

a) Stratum corneum.
b) Skin permeation assessment.
c) Melting points.
d) o/w partition coefficient

**FACTORS AFFECTING TRANSDERMAL BIOAVAILABILITY**[19-20]

Two major factors affect the bioavailability of the drug through transdermal routes:

1. Physiological factors
2. Formulation factors

**Physiological factors**

a) Stratum corneum layer of the skin
b) Anatomic site of application on the body
c) Skin condition and disease
d) Skin metabolism
e) Skin irritation and sensitization

**Formulation factors**

a) Penetration enhancers used
b) Vehicles and membrane used
c) Physical chemistry of transport
d) Method of application
e) Device used

**CONCLUSION**

Transdermal drug therapy will revolutionize the concept of dose to be administered. No longer dose consideration will be overcome by rate. Transdermal drug delivery system has advantages over oral dosage form. It is used when there is a first pass effect metabolism of liver that can metabolize drug. Transdermal system is self administered drug delivery system.

**REFERENCES**