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A Review article: Topical Drug Delivery System (Skin)

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Abstract In general; many approaches found to delivered the drug to the site of action, one of these approaches used the skin barrier as a rout to reach the drug to the local or systemic targeting; Both local and transdermal drug product are intended for external use (applied on the skin). It was localized action on one or more layers of the skin, or may reach to the systemic circulation to get systemic effect. So, in this review authors aimed to highlight on the anatomy of the skin layers epidermis, dermis and hypodermis (to know the way of the drug transport), drug application, drug penetration through the skin, factors affecting on the skin drug absorption, advantage of this rout and limitation of the drug delivery system; in addition to mention to many examples of this dosage forms are used in drug delivery system. Finally, this approach of drug delivery system is widely used and preferred from the patient at any life stages because of its improved the patient compliance and decreased the side effects of drugs in addition to easy rout of admiration and avoid pain and suitable to patient with swallowed problem.

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Keywords: *Topical drug delivery system, localized therapeutics, transdermal, skin layers, drug penetration and patients' compliance.*

1. INTRODUCTION

Skin anatomy

The skin is the largest organ in the body of human which has many functions example act as a barrier protection from external environment. It consists from three layers as shown in the Figure (1); *Epidermis* is the outer most layer, contain keratinocyte with thickness about 0.2 mm and no vein or capillaries in this layer, *Dermis* is the second layer of the skin beneath the epidermis, contain capillaries and nerve fiber with thickness about 1-4 mm, and the third layer is *Subcutaneous* which elastic layer located beneath the dermis layer (hypodermis), contain a large amount of fat cells with thickness about 4-9 mm [(1,2)].

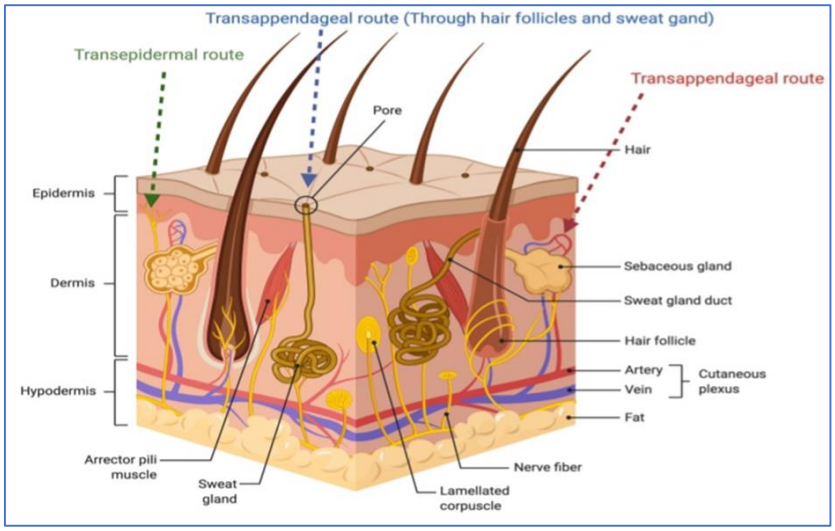

Figure (1): *The structure of the skin with pointed pathways of the drugs transport through it (3)*

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Drug application on the skin

Topical and transdermal pharmaceutical products are intended for external use. The uses of topical pharmaceutical products can divide into 3 types depended on which layer that's product will action on it, localized action which act on the outer layer of the skin (ex. keratinolytic agent) or penetrate to more layers of skin (ex. anti-inflammatory agents), also; some of drugs from these topical products reach to the systemic circulation and can used this action in the systemic drug delivery system (nicotine transdermal) [4,5].

Drug penetration

Topical and transdermal need to overcome the stratum corneum (is the first layer of the epidermis which consist of dead cells from keratinocyte). So; The stratum corneum is the rate limiting barrier for penetration of drug into the skin. Ther are three pathways for transdermal permeation of drugs (Figure -1) [3, 6]:

1. Through intercellular lipid and stratum corneum (paracellular) and this pathway for most unchurched particles.
2. Through the skin appendages (pores of hair follicles, sweat gland and sebaceous gland) and this pathway for electrolyte and large molecules.
3. Through intracellular pathway (transcellular which have hydrophilic corneocytes and lipophilic lipid layers) and this pathway needs both partitioning and diffusion to transport the drug to the systemic circulation.

Generally, passive diffusion is the mechanism of drug absorption into the skin, since the rate of drug transport across the stratum corneum was follow Fick's law diffusion as shown in the equation below; and that's explain that's drug absorption depend on others factors which mentions in this equation in addition to the solubility of the drug [7,8].

$$\frac{dm}{dt} = D.A.K.C/h$$

Where: *dm/dt* is the study state of flux across stratum corneum, *D* is the diffusion coefficient, *A* is the surface area, *K* is the partition coefficient of the drug between skin and formulation medium, *C* is the concentration of the drug across the stratum corneum and *h* is the thickness of the stratum corneum [7,8].

Factors affecting of the drug absorption

Thers are many factors that's effect on the absorption of drug through the skin; and if that's factors related to the skin; these factors will call "*physiological factors*", while if these factors related to the drugs; these factors will call "*physicochemical factors*" as shown below.

Physiological factors

There are many physiological factors are affecting on the absorption of the drug through the skin as shown in the Table (1) and that's explain the individual variation of response for same dosage form [9, 10].

Table (1): *The Physiological Factors are Affecting on the Absorption of the Drug Through the Skin.*

Physiological factors of the skin	Drug absorption
↑ thickness	↓
↑ Lipid content	↑
↑Density of sweat gland (↑ skin hydration)	↑
Change in pH	Change (ionization of drug)
↑ blood flow	↑
Disease (dermatitis or psoriasis)	↓
↑ Temperature	↑

Physicochemical factors

Some of the Physicochemical properties of the drugs that's effects on the absorption of the drug through the skin are listed in the Table (2) [9,11].

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Table (2): *The Physicochemical Factors are Affecting on the Absorption of the Drug Through the Skin.*

physicochemical factors of the drug	Drug absorption
↑ Molecular weight > 400 Dalton	↓
↑ Partition coefficient	↑
↑ Degree of ionization	↓
↑ contact time of drug with skin	↑
↑ affinity to its vehicle	↓
↑ particle size	↓

Advantage of skin delivery system [12, 13]

1. Painless and ease of administration by patients and that's improved patient's compliance.
2. A voidness of first pass metabolism and that's mean increase in the bioavailability and efficacy of drug.
3. Avidness gastrointestinal degradation and a voidness drug- drug interaction by oral administration.
4. Suitable for children, elderly and patients have difficult in the swallowing, nausea, vomiting and unconsciousness.
5. Can prepare extended release of drug and that decreased of dose frequency.
6. Reduced side effect.

Limitation of skin delivery system [14]

1. Restriction skin permeability
2. Restricted to potent drug
3. Can not use for large molecule (> 400 Daltone) due to difficult penetrate it through stratum corneum.
4. Some drug may degradation in the skin tissue.
5. Variation in absorption efficacy at different sits of skin.
6. May cause skin allergy.

Physical enhancement drug penetration through skin

In addition to different dosage form that's permit the drug penetrate the skin layer, these is other approaches that's improved the drug penetration and can classified to two approaches: direct and in direct approaches as showed in the Table (3).

Table (3): *Physical enhancement drug penetration through the skin* [14, 15]

Method	Comments
Indirect physical method	
Electroporation	Put a known voltage (50- 1500 V) electric pulses for short time to form a pore in the lipid bilayer in stratum corneum and allow more diffusion of drug through the skin
Iontophoresis	Applies a mild electric current to increase electromigration or enhanced passive diffusion
Laser assisted delivery	This photomechanical wave cause disrupt the lipid arrangement in the stratum corneum intracellular space.
Direct physical method	
Microdermabrasion	Local disruption of stratum corneum and superficial of epidermis
Thermal ablation	Applied extreme heat at skin surface for microsecond without reach to the epidermis or deeper tissue
Biolistic injector	injectors apply high pressure to emit through a small nozzle, at velocity (100-200 m/s) to get deep penetration of drug
Microneedle	Microneedle patch used to pass stratum corneum layer

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Types of topical preparation

Many topical preparations were applied on the skin; locally and transdermal delivery system, can be found as (Figure- 2): *solid* like dusting powder (antifungal powder), *semisolid* like: ointment (lidocaine®), cream (Fucidin®), gel (Reparile®), lotion (Calamina®) and *liquid* (Canstine® solution) in addition to spray (Angiovage®), foam (vaginal wash foam), transdermal and microneedle patch [16].

Jassim and Al- khedairy formulated silymarin as topical gel for wound healing which easily applied and removed from the skin [17], Alkiro A R and Gareeb formulated ironoxicam as dissolving microneedle patch to replace parenteral administration and used Tween® 80 to increase penetration of drug through skin layers [18], Muhammed K *et al* are formulated extract of fenugreek seeds as topical cream w/o act as antioxidant and skin soothing [19]. Haifa T and *et al* study effect of verapamil combined with zinc oxide cream as a treatment option for topical anal fissures [20]. Neamah A J and *et al* study the effect of ionic liquid to increased permeability for topical and transdermal drug delivery system [21], Thomas L and *et al* studies the effect of nanotechnology on topical drug delivery for dandruff and Seborrheic Dermatitis [22]. Kadhum W R and *et al* used nanotechnological method for enhancing the topical drug delivery by newly developed liquid crystal formulations [23], Abdullah T M and Al-Kinani K K used nano-emulsion to enhance topical delivery for propranolol hydrochloride to reduce the adverse effect of this drug [24], Ghareeb M M and Mohammed M S formulated isoconazole nitrate as topical nano-emulsion gel [25], Abbas M M and Rajab N A formulated a etodalac as a topical nano-spong hydrogel [26]. Alwan L A and 1 Al-Akkam E J formulated meloxicam as dissolved microneedle patch to increase local effect and decrease side effect of the anti- inflammatory drug and improve patient compliance [27]. Banerjee D et al formulated a group of natural herbs like alovera, lemon, turmeric, red of sandal wood as a lotion for a cosmetic soothing to trat a dry skin in addition to easily applied to the skin [28], Khullar R *et al* prepared a mefenamic acid as emulgel for topical application to treatment of local inflammatory action and used a carbapol 940 as a gelling agent and mentha oil and clove oil as penetration enhancer [29, 30]. Dawooda B Yand Kassab H J formulated naproxen as pH sensitive in-situgel for ocular as topical delivery to increase ocular residence time and increase drug effectiveness [31].

Figure (2): *Types of topical preparations*

Conclusion

Topical drug delivery through skin is one of the important routs of admiration which provide topical, local and transdermal drug delivery and that's improved patients' compliance by easy rout of admiration, avoid painless, decreased side effect, preferred by pediatric, geriatric and patient with swallowing. Many preparations of topical dermal dosage forms like: ointment, cream, gel, lotion, solution and patch transdermal.

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