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An Introductory Way and Concise Focus on Different Generation for Transdermal Drug Delivery System

Rohit Mohan[1], Bhuwanendra Singh[2], Arshad Ahmad[3], Saurabh Agrahari[2], Anand Maurya[2], Gaurav Mishra[2]
[1]Department of Pharmacology, Aryakul College of Pharmacy and Research, Lucknow U.P.
[2]NKBR College of Pharmacy & Research Centre Phaphunda, Meerut U.P.
[3]Shri Gopichand College of Pharmacy, Bagpat U.P.

Abstract:-Transdermal drug delivery system(TDDS) is self-contained, discrete dosage form in which drug stick to the body surface and delivers the drug, across the skin at controlled rate into the blood stream. TDDS has been a great field of interest in recent times. Many drugs which can be injected directly into the blood stream via skin have been formulated by TDDS. Transdermal drug delivery system (TDDS) provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy. However, a detail study of transdermal delivery provides a lot of advantages compare to oral intake or hypodermic injection. Firstly dermal layer dermal layers provides the drug a shorter route to the bloodstream than gastrointestinal tract does. In the given review the main point of focus is to explore the commercial advantages and the strategic developed transdermal patches.

I. INTRODUCTION

Transdermal drug delivery (TDD) labels theapproach in which drugs are transported for either localor systemic effect by smearing a drug formulation ontohealthy and intact skin [1]. TDD is an beautiful meansof delivery of therapeutics for several reasons overthe conventional methods of drug delivery, including[2]Evading of gastrointestinal degradationCircumvention of significant hepatic metabolismPotential improvement of bioavailability by a non-injected route. Sustained delivery allowing maintenance of plasmaconcentrationsavoidance of pain, risk of infection andassociated compliance issues of hypodermic needleinjections.Recent indications advocate that the transdermal having energetic and accepting market, however, this only represents approximately 20 drug formulations. The limited number of products available is due to the fact thatvery scarce drugs possess the required physicochemicalproperties to permeate across the skin's excellent barrierfunction, credited by the outermost 10–15mm of tissue,the stratum corneum(SC) [3,4]. Drug substances must permitthe physiological barrier prior to entering capillaries inthe upper papillary dermis to eventually enter systemiccirculation (Fig-1). The blood capillary network may be accessedthrough three potential pathways that found in dermaltissue through hair follicles with associated sebaceousglands, via sweat ducts, or throughout SC betweenthese appendages.Approximately 0.1% of the fractional appendageal area isavailable for passage of molecules, therefore this routeoffers negligible contribution to steady state drug flux.Thus, the intact SC provides the main barrier to penetration of exogenous substances, including drug molecules [4].The SC is described by the 'bricks and mortar' model, inwhich the densely packed corneocytes are analogous to'bricks', embedded in highly organised lipid bilayerscomposed of ceramides, fatty acids, cholesterol and affiliated esters, representative of a 'mortar'. These bilayersform regions of semi-crystalline gel and liquid crystaldomains. Most molecules penetrate concluded skin via thisintercellular microroute. Enablement of drug penetrationthrough the SC may involve by-pass or reversible commotion of its elegant molecular architecture.

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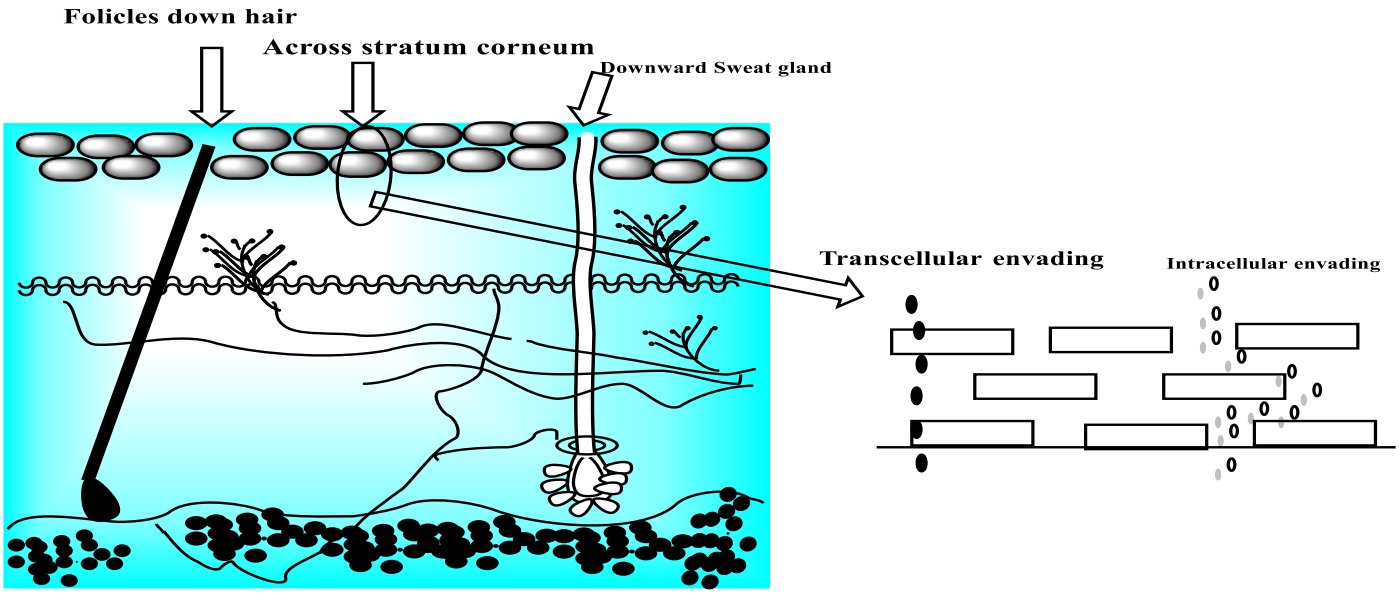

Fig-1 An Overview on Different Layers of Skin

II. ADVANCED DEVELOPMENT OF TRANSDERMAL DRUG DELIVERY SYSTEMS

The anatomical layers and appendageal structures of the skin, the epidermis and its outermost layer of stratum corneum are the most challenging barriers to transdermaldelivery [6,7]. The brick-and-mortar assembly of keratinocytes and intercellular lipids renders the epidermis impregnable to most foreign materials. Therefore, a carefully observation of transdermal delivery can regard delivery as counterintuitive strategy for delivering a drug systematically. However, a detail study of transdermal delivery provides a lot of advantages compare to oral intake or hypodermic injection. Analysed with oral delivery, transdermal delivery requires a lower dosage and has some side effects because transdermal diffusion circumvents the digestion and first-pass metabolism of the active drug in the gastrointestinal tract and liver [8]. Prior transdermal delivery is not painful, minimally invasive and convenient to patients so that the compliance with drug administration increase to a great extant. Newer design of transdermal patches to increase the skin penetration of drug have been widely investigated, and major breakthrough have been observed as the evolving generation of transdermal delivery system. Drugs for transdermal delivery are selected to have a high partition coefficient and a low molecular weight for facile diffusion through the skin barrier. The second generation research concentrated on amending the skin permeability of drugs using chemical enhances and stimulating agent through external driving forces. Chemical enhancers and nanocarriers solubilize the drugs improve their easy penetration into the skin. External actuation using heat [9], electricity [10], nanocavitational ultrasound [11] also enhance drug transportation. The third generation research focused to developed to method that cause microscopic destruction of epidermis to increases the delivery of drugs. Ultrasound [12], radiofrequency (RF) ablation [13], and lasers [14] disrupt the stratum corneum temporarily and enhance drug penetration throughthe weakened barrier. In previous generation transdermal delivery have focused on maximizing the efficiency of drug delivery, the recent growth in medicine requires a new generation of the drug delivery system aimed at controlled and feedback induced transdermal release of drugs. Wearable devices consisting of sensors and actuators are expected to meet such needs [15-17]. So, novel design and device fabrication have spurred the innovation in wearable devices for biomedical application, providing a new chance in personalized healthcare [18]. The external energy stimulates and controls state-of-the-art transdermal delivery systems. Device-assisted transdermal delivery, an ensemble of soft bioelectronics and a transdermal drug delivery system, and also controlsthe release of drugs and monitors the physiological states of the drug. All the activity provide the patients with a precise and customized medical treatment such as, The cycle of diagnosis, actuated drug release, and follow-up diagnosis constitute.

A. First Generation: Transdermal Drug Delivery Based on Diffusion

Transdermal drug delivery is an efficient drug delivery option because it offers several advantages. Firstly dermal layer dermal layers provides the drug a shorter route to the bloodstream than gastrointestinal tract does [19] mainly, transdermal shortcuts also enhances bioavailability and reduces the dosage because the drug avoids the extensive first-pass metabolism and degradation in liver. Secondly, patients are more uses the transdermal drug administration because a drug patch is non-invasive painless and easy to use. A long-lasting patch that provides sustained drug release for up to several days is convenient for patients, and its non-invasiveness allows repeated drug application over the same part of the body. Freedom from pain, compared

particularly to needle-based injections, increases the popularity and acceptance of the transdermal delivery. The first generation of simple transdermal patches come out during the 1970s. The first approval from the U.S. Food and Drug Administration (FDA) for the use of scopolamine patch for motion sickness, approximately 19 patches including nicotine, estradiol and menthol are commercially available to date [20]. Therefore many drugs are suitable for patch formulation is severely limited because of the physiological barrier of the epidermis. The vast majority of the first generation transdermal drugs are highly lipophilic with partition coefficients greater than 10^4, small particle sizes, and molecular weights no more than 400 Da [21].

B. Second Generation: Actuation, Non-Invasive Transdermal Drug Delivery

The second-generation transdermal delivery strategies seek to maximize the permeability of the drug to the skin using chemical enhancers or external energy sources without damaging the structure of the skin. Chemical enhancers facilitate the drug to penetrate the skin by interacting with the proteins comprising the skin and by increasing the drug solubility. Presently, more benign chemical enhancers (*e.g*., fatty acids, urea,) compared to skin irritants such as dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and oxazolidinone are available to use [22]. Mostly, emulsion is a non-invasive transdermal delivery because they solubilize a wide range of both lipophilic and hydrophilic drug in a transdermal formulation [23]. The absorption profile of an emulsion is determined by the droplet size, composition, and surface charge. Particularly, reducing the size of vehicle particles to micrometer or nanometer level has been a popular strategy because smaller droplets can easily permeate the tight junctions of the skin barrier [24,25]. Recently, nanomaterials have been a potential systems for the delivery and controlled release of various drugs [26-29]. For example, drug incorporated nanoparticles (NPs) effectively overcome the epidermal barrier and deliver an encapsulated cocktail of anti-inflammatory siRNAs and capsaicin. The delivery of siRNA-capsaicin cocktail in solution form was blocked by the stratum corneum [30]. The potency of drug delivery control can be enhanced by using nano-sized vehicles responsive to physicochemical stimuli [31]. External devices, especially in the wearable forms, should be integrated with drug loaded patches. The devices help to deliver the sufficient level of energy to enhance the drug diffusion through the skin. They operate with electricity and heat are frequent drug-delivering locomotives. In another research introduced an Iontophoresis technique uses an electrical current to promote and control the penetration of charged drugs into tissue through the skin barrier [32]. The dose is easily controlled by modifying the magnitude and the duration of the stimulating current. Iontophoretic drug administration of the drug can be applied to pain relief, diagnosis of inflammation, cystic fibrosis, and cosmetic application. Recently, a cryoelectrophoresis technique was developed to increase the electrophoretic efficacy by applying a strong current to locally frozen skin to eliminate the risk of skin burns [33]. However, the non-invasive transdermal delivery does not drastically increase the efficiency of drug delivery, particularly for high molecular weight and hydrophilic drugs.

C. Third Generation: Minimally Invasive Transdermal Drug Delivery

After the studied the limitation of non-invasive transdermal delivery, alternative approach of minimally invasive transdermal delivery is rapidly adopted. Minimal invasion of the skin involves destroying the stratum corneum so that epidermal disruption is limited to clinically safe level while a large number of hydrophilic drugs and macromolecules are more effectively delivered into the inner skin [34]. High power energy and various types of microneedles are currently used to disrupt or puncture the skin and enhance drug delivery. Disturbance of the epidermis by high power energy broadens the range of drugs that can be delivered through the skin. As a significantly high level of energy is required to damage the outer layers of skin, it is necessary to carefully control the amplitude and exposure time of the applied energy to prevent unwanted damage to the inner skin layers. Laser techniques is also commonly used in cosmetics for procedures such as hair removal, skin resurfacing, and acne treatment. The laser targets a high level of energy at a designated location to penetrate the skin [35,36]. Microneedles may also incorporate a drug coated onto the surface of the solid needle substrate [37,38]. Since the coating layer decreases the physical strength and sharpness of needles, the drug load on the needle surface is limited to a small amount. Accordingly, coated microneedles are used for treatments where large amounts of drugs are not required to be delivered [39-42]. In present time increasing the variety of applicable drug candidates, microneedles represent a major breakthrough in transdermal delivery in terms of efficiency and skillfulness. Moreover, microneedles share the same limitation of transdermal patches in which the only way to control the offset of drug release is to detach the patches.

III. VARIANTS OF TRANSDERMAL PATCHES

A. Single layer Drug in Adhesive

The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together (Fig-2), along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing [43].

B. Multi-layer Drug-in-Adhesive

The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug(Fig-2). The multi-layer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing.

C. Reservoir

Unlike the Single-layer and Multi-layer Drug-in-adhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer (Fig-2). This patch is also backed by the backing layer. They generally followed the zero order release kinetics.

D. Vapour Patch

In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are new on the market and they releaseessential oils for up to 6 hours. The vapours patches release essential oils and are used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep(Fig-2). Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market.

E. Matrix

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it (Fig-2). The adhesive matrix layer of the tape is attached with the active ingredients with the help of heat and pressure and it also may be assisted and having diffusion process by the help of matrix layer.

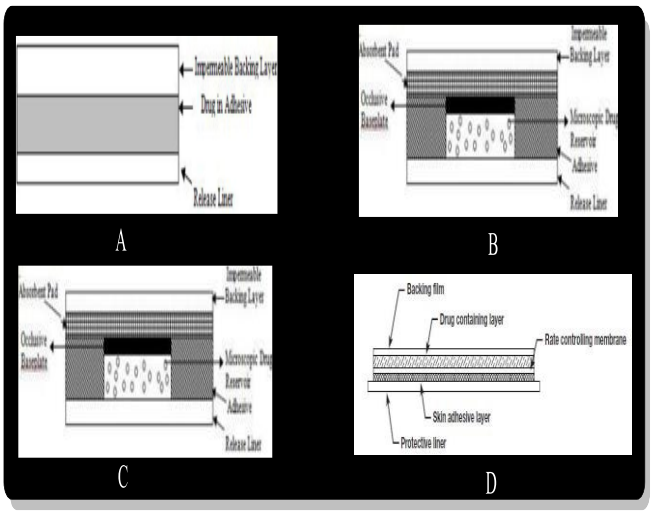

Fig-2 Different Types of TDDS

IV. EXAMPLES OF COMMERCIALLY AVAILABLE TRANSDERMAL PATCHES

There are different transdermal patches which are used rapidly and having very wide acceptance because it is giving good response on the human many of the companies are involved in the development of such a patch useful for human health (Table-1).

Drug/product name	**Utilization**	**Year of FDA approval**	**Company**
Capsaicin	Neuropathic pain	2009	NeurogesX
Rivastigmine	Dementia	2007	Novartis Pharmaceuticals
Rotigotine	Parkinson’s disease	2007	Schwarz BioSciences
Selegiline	Major depressive disorder	2006	Somerset Pharmaceuticals
Methylphenidate/Daytrana	Attention deficit hyperactivity disorder	2006	Noven Pharmaceuticals
Oxybutynin/Oxytrol	Overactive bladder	2003	Watson Laboratories
Ethinyl estradiol with norelgestromin	Contraception	2001	R.W. Johnson Pharmaceutical Research Institute
Lidocaine with epinephrine	Local dermal analgesia	1995	IOMED

Table 1 Examples of Commercially Available Transdermal Patches

V. CONCLUSION

The current review emphasised on the transdermal drug delivery system and its impact on the human beings and it also concluded the novel factor i.e. the device assisted transdermal drug delivery system which is having a great importance and potential and acting as a strategic therapy towards the above category of drug delivery system. In the current review mechanistic approach is also discussed which is having high threshold in TDDS. Therefore different stages showed the transformation and upliftment in TDDS and also marketed formulation brings a way to the researchers for bringing a front in this category. Overall we can say that the above review is an umbrella under which all the discussed points can be fined with solid potentials and also more information can be abstracted.

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