Recent Trends in Transdermal Drug Delivery System - A Review

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Abstract: Transdermal drug delivery systems have evolved as a successful alternative to systemic drug delivery. Despite their relatively higher costs, transdermal delivery systems have proved advantageous for delivery of selected drugs, such as estrogens, testosterone, clonidine and nitro-glycerine. Transdermal delivery provides a leading edge over injectable and oral routes by increasing patient compliance and avoiding first pass metabolism respectively. The technique is generally non-invasive well accepted by patients and can be used to provide local delivery over several days. Recently there has been an increasing awareness that the benefits of intravenous drug infusion can be closely duplicated, without its potential hazards, by continuous transdermal drug administration through Skin. For both local and systemic effects skin is the major site of application. However, to penetrate the drug through skin, stratum corneum is the main barrier.

Key words: Transdermal Drug Delivery System • Skin • Mechanism • Patents • Polymer Matrix

INTRODUCTION

The most preferred route of administration is oral route but oral route have some disadvantages like hepatic first pass metabolism, poor bioavailability and tendency to produce rapid blood level spikes and this leads to frequent dosing so to overcome these drawbacks there is a need for the development of new drug delivery system. Transdermal drug delivery provides advantages over conventional drug delivery like avoidance of first pass metabolism, predictable and extended duration of activity, utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels, minimizing undesirable side effects, inter-and intra-patient variations [1,2].

Transdermal drug delivery system [TDDS] is a new approach to provide prolonged action of the drug with low toxicity and better patient compliance and thus reduces the side effect caused by oral route [3]. Transdermal drug delivery system is the integral part of novel drug delivery system. It is defined as self-contained discrete dosage form which when applied transdermally provides systemic circulation at controlled rate [4].

Now-a-days, vesicular systems have been promoted as a mean of sustained or controlled release of drugs. Due to their specific characteristics such as biodegradation, non-toxic behaviour capacity of encapsulating both hydrophilic and lipophilic molecules, capacity of prolonging the existence of the drug in the systemic circulation by encapsulation in vesicular structures, capacity of targeting the organs and tissues, vesicles are most preferred over other formulations [5]. The primary objective of controlled drug delivery is to ensure safety and efficacy of the drugs as well as patients compliance. TDDS is one of the systems lying under the category of controlled drug delivery, in which the aim is to deliver the drug through skin in a predetermined and controlled rate [6]. For effective Transdermal drug delivery system, the drugs are easily able to penetrate the skin and easily reach the target site. TDDS increase the patient compliance and reduces the load as compared to oral route. Transdermal formulation maintain drug concentration within the therapeutic window for prolong period of time ensuring that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration [7,8].
deal Characteristics of TDDS:

- The pH of the solution should be between 5-9.
- For the therapeutic action of the drug, there is a need of optimum partition coefficient.
- Drugs with low melting point (less than 200°C) should use.
- Patch size should be less than 40 cm².
- Shelf life up to 2 yrs.

Advantages: Transdermal drug delivery systems have some advantages like [9,10]:

- Increase bioavailability.
- Reduce dosing frequency.
- It is painless and non-invasive drug delivery system.
- Avoid hepatic first pass metabolism.
- Increase patient compliance mainly in paediatric and geriatric patients.
- Maintains stable or constant and controlled blood levels for long period of time.
- They provide extended therapy with a single application.
- Self-administration medicament.

Disadvantages: Transdermal drug delivery systems have few disadvantages [11,12]:

- Small amount of drug are administered through the skin.
- Skin irritation may occur.
- It cannot achieve high drug levels in blood.
- Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.
- Higher cost.
- Should not use ionic drug.

The Skin Site for Transdermal Administration: The skin is one of the most extensive and readily accessible organs of human body covers a surface area of approx. 2 cm² (300 inch²) and receives about one third of the blood circulating through the body. Skin is the largest organ in the body account for more than 10% of body mass [13]. Skin is the complex organ and allows the passage of various chemicals into and across the skin. Skin serves as the point of administration for systemically active drugs, the drug applied topically will be absorbed, first into the systemic circulation and then transported to target tissues. The potential of using intact skin as the site of administration for dermatological preparations to elicit pharmacological action in the skin tissue has been recognized for several years.

Skin mainly consists of three layer epidermis, dermis and subcutaneous tissue as shown in Figure 1. The subcutaneous composes of outer most nonviable cell layer of epidermis and it is approximately 10 to 20 μm thick [14].

The epidermis is a stratified, squamous, keratinizing epithelium. The keratinocytes comprise the major cellular component (> 90%) and the responsible for the evolution of barrier function. Other cells present include Melanocytes, Langerhans cells and Markel cells, none of which appears to contribute to the physical aspects of the barrier. The dermis incorporates blood and lymphatic vesicles and nerve endings. The extensive microvasculature network found in the dermis represents the site of resorption for drugs absorbed across the epidermis; i.e. at this point that transdermally absorbed molecules gain entry to the systemic circulation and access to their central target. With respect drug delivery, interest in these structures has centred upon the possibility that they may provide “shunt” pathway across the skin, circumventing the need to cross the full stratum corneum. Skin is structurally complex and thick membrane. Molecules moving from the environment must penetrate the stratum corneum and any material of endogenous or exogenous origin on its surface. They must then penetrate the viable epidermis, the papillary dermis and the capillary walls into the blood stream or lymph channels, whereupon they are removed from the skin by flow of blood or lymph [15,16].

Routes of Penetration [17-19]: The following routes are observed in transportation of penetrant through skin barrier as shown in Figure 2:
Fig. 2: Possible routes of penetration

**Fig. 3: Transepidermal transport**

- Across the intact horny layer,
- Through the hair follicles with the associated sebaceous glands, or
- Via the sweat glands

Transepidermal transport means that molecules cross the intact horny layer. Two potential micro-routes of entry exist, the transcellular (or intracellular) and the intercellular pathways as shown in Figure 3.

**Factors Effecting Transdermal Permeability [20]:**
The factors controlling transdermal permeability can be broadly placed in the following cases:

**Physico-Chemical Properties of the Penetrant Molecules:**

- Penetrant concentration
- Partition coefficient
- pH conditions

**Physico-Chemical Properties of Drug Delivery Systems:**

- Release Characteristic
- Enhancement of transdermal permeation

**Physiological and Pathological Condition of Skin:**

- Reservoir effect of horny layer
- Lipid film
- Pathological injuries to the skin
- Skin temperature
- Regional variations
- Skin hydration
- Cutaneous self-metabolism

**Technologies for Development of Transdermal Drug Delivery System:**

**Polymer Membrane Permeation Controlled TDDS:**
As shown in Figure 4, In this system the drug reservoir is sandwiched between a drug-impermeable backing laminate and a rate-controlling polymeric membrane. In the drug reservoir compartment, the drug solids are dispersed homogeneously in a solid matrix, suspended in an unreachable, viscous liquid medium to form a paste like suspension, or dissolved in a releasable solvent to form a clear drug solution [21].

**Polymer Matrix Diffusion-Controlled TDDS:**
As shown in Figure 5, It is developed by dispersing drug particle in carrier matrix that is rate controlling.

In this approach the drug reservoir is formed by homogeneously dispersing the drug solid in a hydrophilic or lipophilic polymer matrix and the medicated polymer formed is then molded into medicated disks with a defined surface area and controlled thickness [22].

**Drug Reservoir Gradient-Controlled TDDS [23]:**
As shown in Figure 6, Polymer matrix drug dispersion-type TDDS can be modified to have the drug loading level
Micro Reservoir Dissolution Controlled TDD System: As shown in Figure 7, this type of drug delivery system can be considered a hybrid of the reservoir and matrix dispersion-type drug delivery system. In this approach the drug reservoir is formed by first suspending the drug solid in an aqueous solution of a water-miscible drug solubilizer, e.g. polyethylene glycol and then homogeneously dispersing the drug suspension with controlled aqueous solubility in a lipophilic polymer by high shear mechanical force, to form thousands of unleachable microscopic drug reservoirs [24].

Some Patents on Transdermal Drug Delivery System: Some important patents on transdermal drug delivery system are listed in Table 1.

Recent Advancement on Transdermal Drug Delivery System: Some advancement on transdermal drug delivery systems is discussed in Table 2:

Marketed Products [46,47]: Some marketed products of transdermal drug delivery system are as listed in Table 3.
Table 1: Patents on Transdermal drug delivery system

<table>
<thead>
<tr>
<th>Patent No.</th>
<th>Invento Work</th>
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<tbody>
<tr>
<td>20060135911</td>
<td>Mittur et al Prepared a device which is known as a trans-body-surface drug delivery device or the administration of at least one drug to an individual at a therapeutically effective rate. The device including a reservoir having at least one drug and a thermo effector having a first surface[25].</td>
</tr>
<tr>
<td>6011022</td>
<td>ElKhoury, George F The invention relates to the pharmaceutical compositions for the topical administration. The model drug used is Neostigmine [26].</td>
</tr>
<tr>
<td>5866143</td>
<td>ElKhoury, George F Provides topical application of an opioid analgesic drug to an area of skin irritation of a patient in which quantity of an opioid analgesic drug and mixing the opioid analgesic drug with a non-transdermal carrying agent is used [27].</td>
</tr>
<tr>
<td>4626539</td>
<td>Aungst et al Provides effective transdermal delivery of a therapeutic dose of the opioid to the systemic circulation of a mammal. Propylene glycol is used as a suitable pharmaceutical carrier [28].</td>
</tr>
<tr>
<td>20050186262</td>
<td>Osborne et al Prepared a transdermal delivery device for treatment of hypertension with the drug delivery of dihydropyridine-type calcium antagonist through the skin [29].</td>
</tr>
<tr>
<td>20070224253</td>
<td>Franklin, Richard The invention relates to the delivery of meptazinol precursor which increases the bioavailability of meptanizol by an effective amount to provide analgesic relief is disclosed [30].</td>
</tr>
<tr>
<td>20120277695</td>
<td>Cottrell et al The invention relates to the composition of suitable transdermal patch for administration of an opioid the composition comprising a phosphate compound of tocopherol and a polymer carrier [31].</td>
</tr>
<tr>
<td>5736154</td>
<td>Fuisz, Richard C Prepared drug delivery system that is useful in treatment of maladies, noduloulcerative carcinomas and individuals having certain skin infections using the present invention drug delivery system including topical and/or subcutaneous administration of one or more drugs to the individual in a controlled, sustained release manner [32].</td>
</tr>
<tr>
<td>8252319</td>
<td>Yum et al The invention relates to the transdermal delivery of Sufentanil which provides sufficient amount of sufentanil to induce and maintain analgesia for extended periods when applied to a subject [33].</td>
</tr>
<tr>
<td>5817332</td>
<td>Urtti et al Prepared transdermal system for the delivery of at least one therapeutic agent which compromises mainly the ionized form of the therapeutic agent, a pH adjusting agent and a cyclized polysaccharide selected from a group consisting of cyclodextrin. The system allows the release of a therapeutic agent which may be a weak acid or base in a manner which shows less variation between patients than previous systems [34].</td>
</tr>
<tr>
<td>4956171</td>
<td>Chang, Yunik Describes transdermal drug delivery system with dual permeation enhancers and has a basal surface that contacts an area of skin and transmits the drug and the dual permeation enhancer to the area for absorption. The dual permeation enhancers used are sucrose cocoate&amp; methyl laurate [35].</td>
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Table 2: Some Recent advancements

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Recent Advances Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Formulation, development and evaluation of transdermal drug delivery system of Glimepiride Prepared a novel matrix controlled transdermal system using glimepiride as a novel drug and chitosan as a polymer for the extended and controlled delivery of the drug for the treatment of diabetes mellitus. Optimization of the system was done using in vitro drug permeation studies through rat skin. Skin irritation tests and pharmacokinetic evaluations were carried out in healthy rats [36].</td>
</tr>
<tr>
<td>2.</td>
<td>Design and evaluation of pectin based metrics for transdermal patches of meloxicam Prepared transdermal patch using Meloxicam as a novel drug and pectin as a polymer. In-vitro release studies were carried out with modified Franz diffusion cell using pH 7.4 phosphate buffers as receptor medium and it showed controlled release of drug [37].</td>
</tr>
<tr>
<td>3.</td>
<td>Design and Development of Transdermal Drug Delivery for Anti-Hypertensive Drug Using Different Polymeric System Developed matrix type transdermal drug delivery using different polymeric system for treatment of hypertension. Atenolol is used as a model drug. Di butyl phthalate is used as a plasticizer which prolongs the therapeutic effect. The different polymers used are: Cellulose Acetate Butyrate (CAB), Cellulose Acetate Phthalate (CAP), Poly Methyl Methacrylate (PMMA) and their combinations [38].</td>
</tr>
<tr>
<td>4.</td>
<td>Development and characterization of transdermal patches of metoprolol tartrate Prepared matrix type transdermal patch by solvent casting technique using metoprolol as a model drug. Employing a mercury substrate by using the combinations of EC-PVP and Eudragit RL100-PVP in different proportions. The permeability of Metoprolol tartrate was increased with increase in PVP content. It can be reasonably concluded that Eudragit RL100-PVP polymers are better suited than EC-PVP polymers for the development of transdermal patches of Metoprolol tartrate [39].</td>
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Table 2: Continue

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<thead>
<tr>
<th>S.No.</th>
<th>Recent Advances Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.</td>
<td>Design and evaluation of Valsartan transdermal patch Prepared the transdermal patch by solvent casting technique using Valsartan as a model drug. The membrane of ethylcellulose and Eudragit RS 100 and Eudragit RL 100 along with HPMC combination was used to achieve controlled release of the drug [40].</td>
</tr>
<tr>
<td>6.</td>
<td>Formulation and evaluation of transdermal patches of Atenolol Prepared a matrix type transdermal patch using Atenolol as a model drug with different ratios of HPMC and EC. The technique used is solvent casting technique. Propylene glycol was used as plasticizer. Formulated transdermal patches were evaluated with regard to physicochemical characteristics, in-vitro permeation studies and stability studies [41].</td>
</tr>
<tr>
<td>7.</td>
<td>Design and development of a proniosomal transdermal drug delivery system for captopril Developed a proniosomal carrier system for captopril for the treatment of hypertension using Captopril as a model drug. Proniosomes were characterised by transmission electron microscopy. In vitro studies showed prolonged release of entrapped captopril [42].</td>
</tr>
<tr>
<td>8.</td>
<td>Formulation and evaluation of matrix type transdermal patch of Glibenclamide. Prepared matrix type transdermal patches using solvent evaporation technique. Glibenclamide is used as a model drug. Three different polymers were used for the formulation. PEG 400 and DMSO were used as a plasticizer and penetration enhancers respectively [43].</td>
</tr>
<tr>
<td>9.</td>
<td>Lercanidipine Hydrochloride matrix type transdermal drug delivery systems: In Vitro characterization. Developed matrix type transdermal therapeutic system containing Lercanidipine hydrochloride. The formulation using Eudragit RL and Ethyl Cellulose with Oleic acid as permeation enhancer and PEG 4000 as plasticizer showed the maximum release[44].</td>
</tr>
<tr>
<td>10.</td>
<td>Formulation and evaluation of transdermal drug delivery system of clopidogrelbisulfate Prepared transdermal drug delivery system using Clopidogrel bisulfate as a drug. Various polymers were used such as HPMC, PVP and Ethyl Cellulose. The technique used is solvent casting technique. The prepared formulations were evaluated for different physicochemical characteristics like thickness, folding endurance, drug content, percentage moisture absorption, percentage moisture loss and weight uniformity[45].</td>
</tr>
</tbody>
</table>

Table 3: Marketed preparations

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Manufacturer Name</th>
<th>API</th>
</tr>
</thead>
<tbody>
<tr>
<td>SonoDerm</td>
<td>Imarx</td>
<td>Insulin</td>
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<tr>
<td>Sono prep</td>
<td>Sontra Medical corporation</td>
<td>Peptides</td>
</tr>
<tr>
<td>Chadd</td>
<td>Zarsloc</td>
<td>S-caine</td>
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<tr>
<td>Powderjet</td>
<td>Powderjet Pharmaceuticals</td>
<td>Insulin</td>
</tr>
<tr>
<td>Macroflux</td>
<td>Alza Corporation</td>
<td>Vaccines &amp; Therapeutic proteins</td>
</tr>
<tr>
<td>Intraject</td>
<td>Weston medical</td>
<td>Vaccines</td>
</tr>
<tr>
<td>E-Trans</td>
<td>Alza Corporation</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>Testoderm</td>
<td>Alza corporation</td>
<td>Testosterone</td>
</tr>
<tr>
<td>Nicoderm</td>
<td>GlaxoSmithKline</td>
<td>Nicotine</td>
</tr>
<tr>
<td>Transderm nitro</td>
<td>Novartis</td>
<td>Nifedipine</td>
</tr>
<tr>
<td>Estraderm</td>
<td>Novartis</td>
<td>Estradiol</td>
</tr>
<tr>
<td>Oxyntol</td>
<td>Watson Pharma</td>
<td>Oxycodone</td>
</tr>
<tr>
<td>Son3Prep</td>
<td>Echo Therapeutics</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>Habitrail</td>
<td>Novartis</td>
<td>Nicotine</td>
</tr>
<tr>
<td>ClimaPrep</td>
<td>Ethical Holdings/Wyeth-Ayerst</td>
<td>Estradiol</td>
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**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. Transdermal drug delivery system may be ideal for many injected as well as orally given drugs, but many drugs cannot penetrate the skin membrane effectively because of low permeability of skin barrier.

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Conflict of Interest: Authors have no conflict of interest

**REFERENCES**


