Review on Transdermal Drug Delivery of Poorly Soluble Drugs

Pallavi Vadlamudi¹*, G.V Radha², Rama Rao Nadendla³

¹Department of Pharmaceutics, Chalapathi institute of pharmaceutical sciences, Lam, Guntur Andhra Pradesh India
²Department of Pharmaceutics, GITAM institute of pharmacy, Visakhapatnam Andhra Pradesh India

Abstract

Transdermal drug delivery systems (TDDS) are polymeric patches containing dissolved or dispersed drug that deliver the active pharmaceutical ingredient at a constant rate through skin. Transdermal delivery has made an important contribution to medical practice by bypassing the side effects related to oral delivery and hypodermic injections. The principle of TDDS is that they could provide controlled drug delivery over a prolonged period of time. TDDS can be designed to input drug at appropriate rate to maintain plasma-drug levels for maximum therapeutic efficacy. The success of all the transdermal systems depends on the ability of the drug to permeate skin by crossing the biological barriers in sufficient quantities to achieve its desired pharmacological action. The advantage of transdermal drug delivery system is that it is painless technique of administration of drugs and can be withdrawn whenever necessary.

Keywords: Transdermal, polymeric patches, hypodermic, therapeutic.

INTRODUCTION

Transdermal drug delivery system is one of the novel drug delivery systems which is categorized under controlled drug delivery, that aims to deliver the drug through the skin in an anticipated and controlled rate. Transdermal drug delivery systems are drug containing devices of defined surface area that deliver a calculated amount of drug to the surface of intact skin which further penetrates into the systemic circulation [1-3].

The skin as a route for systemic drug administration has become really attractive since the introduction of transdermal therapeutic systems in the form of patches. A skin patch may well be a medicated adhesive patch that’s placed on the skin to deliver a time-released dose of medication systemically for treating diseases. Transdermal therapeutic system has been accessible within the pharmaceutical market [4] since early 1980’s. The invention of transdermal drug delivery systems (TDDS) might be a quantum leap in the field of controlled drug delivery systems. The ability of TDDS to deliver drugs for general impact through intact skin while bypassing hepatic first pass metabolism has accelerated the research of transdermal drug delivery within the field of medical specialty. Since a decade of such comprehensive research activities, several transdermal patches with various classes of medication were developed and were commercialized globally.

Transdermal drug delivery system or transdermal patch is outlined as versatile, multi laminated, pharmaceutical preparation of varying size containing one or additional drug substances, to be applied to the intact skin whereby the drug enters the systemic circulation to maintain the plasma level [5]. Transdermal drug delivery can closely mimic the slow intravenous infusion, without its. Potential hazards and also offer another most significant advantage in allowing the patient to terminate the drug therapy by merely removing the patch at any desired moment if toxicity develops. On the contrary, transdermal drug delivery route is not suitable for all drugs, which may be that reason for the fact that only few drugs have been successfully designed and commercialized by different manufacturers. The fundamental reason for a slow rate of exploration of transdermal drug therapeutic system for other drugs is the highly impermeable nature of human skin. In the past twenty years, an enormous growth in the knowledge regarding skin physiology and its barrier properties, triggered interest to explore skin as a portal of entry for delivering drugs for their effects in systemic circulation.
The potential advantages of transdermal rate-controlled therapy [6, 7]

- Improved bioavailability for many drugs.
- Reliable blood levels of drug.
- Sustained therapeutic effect, allowing use of drugs with short half-lives.
- Diminished side effects.
- Improved patient compliance in long term therapy.
- Simple, non-invasive administration particularly important for patients who are unable to take medication orally.
- Reduced overall treatment costs in many instances.
- Minimizing inter and intra patient variability.
- Possibility of interrupting or terminating treatment when necessary.

Limitations of transdermal delivery [8, 9]

- The transport across the skin is also associated with numerous disadvantages, the main drawback being that not all drug molecules are suitable candidates.
- A good number of physicochemical parameters that influence the diffusion process have been identified.
- Variations in permeation rates can occur between individuals, different races and between the old and young.
- The infected skin, as well as the extent of infection can also affect permeation rates.

Components of TDDS

- Polymer matrix/drug reservoir
- Drug
- Permeation enhancer
- Adhesive
- Backing film
- Liner
- Plasticizer

Polymer matrix/Drug Reservoir [10-12]

- It is the very important component in TDDS and control the release of drug from patch.
- The polymers used in TDDS should be stable.
- They should not produce any toxic effect either alone (or) with other excipients in TDDS formulation.
- They shouldn’t expensive one and it should be easily manufactured.
- They should have good stability and more compatibility with drugs and other components of system.
- The cross linked poly ethylene glycol, eudragit, ethyl cellulose, poly vinyl pyrolidine and hydroxyl propyl methyl cellulose are used as matrix formers in TDDS.
- The polymers like EVA, poly urethane and silicone rubber are used as rate controlling membrane.

List of polymers used in TDDS

- Natural polymers: Cellulose derivatives, gelatin, shellac, starch, waxes, gums, natural rubber, chitosan etc.
- Synthetic elastomers: Poly butadiene, hydrid rubber, poly iso butylenes, silicon rubber, nitrile, acronitrile, neoprene, butyl rubber etc.
- Synthetic polymer: PVA, poly vinyl chloride, polyethylene, PVP, poly acrylate etc.

Drug: The selection of drug is based on its properties like physiochemical as well as biological properties [13, 14].

- Drug should have higher first pass metabolism.
- Drugs having narrow therapeutic window.
- Drugs with short half life.
- Drugs with frequent dosing.
- Low molecular weight moieties (<1000 Daltons)
- Low melting point substances (<200 °C)
- Drugs having affinity with both lipophilic and hydrophilic phases.
- Drugs without any dermatological effect are suitable for formulation as transdermal patch.

Permeation enhancers

These are the substances which are reversibly changes the structure of stratum corneum and increase the permeation of drug from skin to blood stream. They are of two types:
1) **Chemical enhancers [accelerants, absorption promoters (or) permeation enhancers]:**\(^{15,16}\)

They act by:

- Increasing drug permeability by reversible damage to stratum corneum.
- To consider the stratum corneum.
- To increase partition coefficient of drug.

### List of chemical enhancers used in TDDS

<table>
<thead>
<tr>
<th>Chemical enhancers</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvents</td>
<td>Water, methanol, ethanol, propylene glycol, Dimethyl acetamide</td>
</tr>
<tr>
<td>Terpenes</td>
<td>Menthol, cardamom oil, cinnamon oil, 18-cineol, carvone</td>
</tr>
<tr>
<td>Pyrolidine</td>
<td>N-methyl 2-pyrolidine</td>
</tr>
<tr>
<td>Sulfoxides</td>
<td>DMS, Didecyl sulfoxides</td>
</tr>
<tr>
<td>Fatty Acids &amp; Esters</td>
<td>Oleic Acid, linoleic Acid, lauric Acid, capric Acid</td>
</tr>
<tr>
<td>Surfactants</td>
<td>Anionic: SLS, decodecyl methyl sulfoxide</td>
</tr>
<tr>
<td></td>
<td>Non-Ionic: Pluronic F127, Pluronic F68</td>
</tr>
<tr>
<td></td>
<td>Bile Salts: Sodium taurocholate, sodium deoxy cholate</td>
</tr>
<tr>
<td>Amides</td>
<td>Dimethyl acetamide, dimethyl formamide</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Phospholipids, amino acid derivatives, enzymes, urea</td>
</tr>
</tbody>
</table>

### Physical enhancers [17]

The following physical techniques have been used for enhancing the permeability of drug through skin.

- Iontophoresis
- Electrophoresis
- Sonophoresis
- By using micro needles
- Magnetophoresis
- By using laser radiation.

The combination of chemical enhancer and magnetophoresis have greater enhancing power which is recently detected in lidocaine hydrochloride patch.

### Adhesive [18]

- It is used to affix the patch on the skin.
- It should be adhere on the skin with light pressure applied by finger.
- It should be easily removed from the skin surface without leaving any residue.
- It should not produce any irritation.
- It should have excellent contact with the skin.
- Should compatible with other components in formulation.
- It should be allow permeating the drug freely from the patch.

E.g. Polyacrylates, poly isobutylenes, silicone derivatives.

### Backing laminate [19, 20]

It is used to protect the patch from outer environment.

- They must be chemically resistant.
- They will not allow the permeation of components into the patches.
- They have optimal elasticity, flexibility and tensile strength.
- If a drug incorporated into a liquid (or) gel in the formulation, the backing material should be heat stable to allow fluid tight packing of drug reservoir (form-fill seal process).

E.g. Vinyl, poly ethylene and poly ester film.

### Transdermal drug delivery system designs

Transdermal delivery of drugs may be achieved via active or passive process depending on whether external energy is utilized to assist the transport of the drug through the skin. The active systems use heat, electric current (iontophoresis), sound waves (sonophoresis), or transient high-voltage electrical pulses (electroporation) to bolster the delivery of medication into the systemic circulation. The drug diffuses from a region of high concentration to a region of low concentration i.e. through the skin into the systemic circulation in passive diffusion. The concentration gradient of
the drug across the skin and the difference in solubility between the adhesive and the skin is the driving force for delivery to the surface of the skin. Chemical permeation enhancers (pharmaceutical excipients) are required for passive delivery of the drug from a patch of a reasonable size (surface area of \( \leq 40 \, \text{cm}^2 \)).

**Polymer membrane permeation controlled TDDS**

![Cross section view of polymer membrane permeation controlled TDDS](image)

In this transdermal delivery system the reservoir of drug is sandwiched between a rate-controlling polymeric membrane and a drug-impermeable backing laminate. The polymeric membrane which controls the release rate prolongs the release of drug molecules. In the drug reservoir compartment, the solid drug is dispersed homogeneously in a solid polymer matrix (e.g., poly isobutylene), suspended in an unleachable, viscous liquid medium (e.g., silicone fluid) to form a fine dispersion with the consistency of a paste, or dissolved in a solvent (alkyl alcohol) from which it is easily released to form a clear drug solution. On the external surface of the polymeric membrane a thin layer of drug-compatible, non-allergenic pressure-sensitive adhesive polymer, (e.g., silicone adhesive) may be applied to provide intimate contact of the TDDS with the skin surface. The release rate of drug from polymer membrane permeation controlled TDDS is defined by

\[
\frac{dQ}{dt} = \frac{K_{m/r} \cdot K_{a/m} \cdot D_m \cdot D_a}{K_{m/r} \cdot D_m \cdot h_a + K_{a/m} \cdot D_a \cdot h_m} \cdot C_R
\]

………………Eq 1.1

Where,

- \( C_R \) - Drug concentration in the reservoir compartment.
- \( K_{m/r} \) & \( K_{a/m} \) - Partition coefficients for the surface partitioning of drug from the reservoir to the membrane and from the polymeric membrane to the adhesive.
- \( D_m \) & \( D_a \) - Diffusion coefficients in the polymer membrane and in the adhesive layer.
- \( h_m \) & \( h_a \) - Thickness of the polymer membrane and the adhesive layer.

**Polymer matrix diffusion -controlled TDDS**

![Cross section view of polymer matrix diffusion-controlled TDDS](image)
In this design the drug is homogeneously distributed in a hydrophilic or hydrophobic polymer matrix and the medicated polymer obtained is then molded into medicated discs with a controlled thickness and a definite surface area. This disc of polymer embedded with drug reservoir is then ascended onto an occlusive base plate in a compartment fabricated from a drug-impermeable plastic backing. In this approach, the circumference of the patch is coated with the adhesive polymer to create a strip of adhesive rim encompassing the medicated disc. The rate of drug release from this polymer matrix drug dispersion type TDDS is given by:

\[
\frac{dQ}{dt} = \left( \frac{L_d C_p D_b}{2t} \right)^{1/2}
\]

Where,
- \( L_d \) — loading dose of drug initially dispersed in the polymer matrix.
- \( C_p \) and \( D_p \) — Solubility and diffusivity of the drug in the polymer matrix.
- \( T \) — Time

**Drug reservoir gradient-controlled TDD system**

This is a modification of the polymer matrix drug dispersion type TDD system which have the varied drug loading level in an incremental manner, forming a gradient of drug reservoir along the diffusional path across the multi laminated adhesive layers. The rate of drug release from this drug reservoir gradient-controlled TDD system can be expressed by:

\[
\frac{dQ}{dt} = \frac{K_a D_a}{h_a(t)} L_d (h_a)
\]

**Fig-3: Cross section view of drug reservoir gradient-controlled TDDS**

The thickness of diffusional path through which drug molecules diffuse increases with time, i.e., \( h_a(t) \) in this system. To compensate this time-dependent increase in diffusional path as a result of drug depletion due to release, the drug loading level in the multi laminate adhesive layers is designed to increase proportionally, i.e. \( (h_a) \) which yields a more constant drug release profile.

**Micro reservoir dissolution controlled TDD system**
This drug delivery system might be considered as a hybrid of the reservoir and matrix dispersion type drug delivery systems. In this approach the drug reservoir is formulated by suspending the solid drug in an aqueous solution of a water-miscible solubilizer, e.g., polyethylene glycol and then the suspended drug with optimum aqueous solubility is homogeneously dispersed in a lipophilic polymer by high shear mechanical homogenizer to create a number of unleachable microscopic drug reservoirs. This thermodynamically unstable dispersion is immediately stabilized by cross-linking the polymer chains \textit{in situ}, which produces a medicated polymer disc with a constant surface area and a fixed thickness. The rate of drug release from a micro reservoir drug delivery system is defined by:

\[
\frac{dQ}{dt} = \frac{D_p D_j A K_p}{D_p h_d + D_j h_p A K_p} \left[ BS_p - \frac{D_p S_0 (1 - B)}{h_p} \left( \frac{1}{K_i} + \frac{1}{K_p} \right) \right] \quad \ldots \ldots \text{Eq. 1.4}
\]

Where,

- \( A = a/b \), \( a \) is the ratio of the drug concentration in the bulk of elution solution over the drug solubility in the same medium, and \( b \) is the ratio of the drug concentration at the outer edge of the polymer coating membrane over the drug solubility in the same polymer composition.

- \( B \) — Ratio of the concentration of drug at the inner edge of the interfacial barrier over the solubility of drug in the polymer matrix.

- \( K_i, K_m \& K_p \) — Partition coefficients for the interfacial partitioning of drug from the liquid compartment to the polymer matrix, from the polymer matrix to the polymer coating membrane, and from the coating membrane constituted of polymer to the elution solution.

- \( D_p, D_j \& D_s \) — Diffusivities of the drug in the liquid compartment, polymer coating membrane and elution solution (or skin).

- \( S_l \& S_p \) — Solubility of the drug in the liquid compartment and in the polymer matrix.

- \( h_l, h_p \& h_d \) — Thickness of the liquid layer surrounding the drug particles, the polymer coating membrane around the polymer matrix, and the hydrodynamic diffusion layer surrounding the polymer coating membrane.

### Ideal properties of the drug candidate for transdermal delivery [21]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility</td>
<td>High</td>
</tr>
<tr>
<td>Dose</td>
<td>Should be below 20 mg/day</td>
</tr>
<tr>
<td>Half-life in hrs</td>
<td>10 or less</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>&lt;400 Daltons</td>
</tr>
<tr>
<td>Partition co-efficient</td>
<td>Log p (octanol-water) between 1-4</td>
</tr>
<tr>
<td>Skin permeability co-efficient</td>
<td>&gt;0.5×10^{-3} cm/hr</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>Non-irritating and non-sensitizing</td>
</tr>
<tr>
<td>Oral bioavailability</td>
<td>Low</td>
</tr>
<tr>
<td>Therapeutic index</td>
<td>Low</td>
</tr>
</tbody>
</table>

The solubility of poorly soluble drugs can be enhanced by formulating them as solid dispersions. The formulated solid dispersions of the poorly soluble drugs can be incorporated into transdermal patches in order to improve the dissolution and bioavailability.

### SOLID DISPERSIONS

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage to achieve an increased dissolution or sustained release of drug, altered solid state properties and improved stability. There are various reasons for the improvement of solubility of poor water soluble drug using solid dispersion technology [22].

### Advantages of solid dispersions [23]

Generally, solid dispersions are mainly used

- To reduce the size of particles.
- To improve wettability.
- To improve the porosity of drug.
• To convert the crystalline drug into amorphous form.
• To improve the solubility in water of a poorly water soluble drug in a pharmaceutical formulation.
• To mask the taste of the drug substance.
• To improve disintegration rate of oral dosage forms.
• To acquire a homogeneous distribution of small amount of drugs at solid state.
• To stabilize unstable drugs.
• To dispense liquid or gaseous compounds as solids.
• To formulate an immediate release prim inch dosage form into a sustained release product.

To formulate prolonged release dosage forms of soluble drugs using insoluble or poorly soluble carriers.

Methods of preparation of solid dispersion

Fusion method [24]

The fusion method otherwise known as melting method, involves the preparation of physical mixture of a drug and a water soluble carrier which is further heated directly until it melted. The molten mixture is solidified rapidly in an ice-bath under vigorous stirring. The solid dispersion obtained is crushed, pulverized and sieved. The dispersion obtained has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and solidified by flowing water or air from the other side of the plate. In addition, a super saturation of a drug or solute in a system will typically be obtained by ending the softening rapidly from a high temperature. Beneath such conditions, the solute molecule is in remission within the solvent matrix by the instantaneous solidification process. The quenching technique provides a far finer dispersion of crystallites when used for simple eutectic mixtures.

Solvent method [25]

In this approach, the physical mixture of drug and carrier is dissolved in a common solvent, which is then evaporated until a transparent, solvent free film is obtained. The film formed is dried to constant weight. The preliminary step in this method is the preparation of a homogeneous solution containing both drug and polymer material. The next step involves the removal of solvent(s) resulting in optimal dissolution properties.

The main advantage of this method is the use of relatively low temperatures for the evaporation of organic solvents which prevents the thermal decomposition of drugs or carriers.

Limitations with this method are

• The preparation is expensive.
• The complete removal of liquid solvent may be difficult.
• The traces of the solvent may adversely affect the chemical stability.
• The tedious process of selection of a common volatile solvent.
• The reproduction of crystal form may not be easy.

Melting solvent method (melt evaporation)[26]

This approach involves preparation of solid dispersion by solubilising the drug in an appropriate solvent and then incorporating the solution into the melt of polyethylene glycol directly, which is then evaporated until a transparent film is obtained. The film is dried further to constant weight. 5-10% (w/w) of liquid components can be incorporated into high molecular weight polyethylene glycol without any significant loss of its solid property. The chosen solvent or dissolved drug may not be miscible with the melt of polyethylene glycol. Additionally the solvent used could have an effect on the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses distinct advantages of both the fusion and solvent evaporation strategies. From a sensible standpoint, this method is only restricted to drugs with a dose below 50mg.

Melt extrusion method [27]

The mixture of drug and carrier is processed with a twin-screw extruder. The mixture of drug and carrier is simultaneously melted, homogenized and then extruded and shaped as granules, pellets, sheets, sticks, tablets or powder. The intermediates can be further processed into conventional tablets. An added advantage is that the drug and carrier mix is subjected to an elevated temperature for about 1 min, which enables the processing of thermolabile drugs.

Lyophilisation technique [28]

Lyophilization or freeze drying involves transfer of heat and mass to and from the product under preparation. This technique alternative to solvent evaporation. Lyophilization is a molecular mixing technique in which the drug and carrier are co-dissolved in a common solvent, frozen and sublimed to obtain a lyophilised dispersion. The advantage of
the technique is that the drug is subjected to minimal thermal stress during the formation of solid dispersion. Moreover, a crucial advantage of lyophilisation is that the risk of phase separation is reduced as soon as the solution is vitrified.

An even more excellent drying technique is spray-freeze drying in which the solvent is sprayed into cold dry air or liquid nitrogen and the frozen droplets are subsequently lyophilised. Direct contact with the freezing agent and the enormous surface area results in quick vitrification, thereby decreasing the risk for phase separation. Spray freeze drying offers the potential to customize the size of the particles to make them suitable for the design of pulmonary or nasal drug delivery systems.

Melt agglomeration process [29]
This approach of preparing solid dispersions uses binder as a carrier. In addition to these solid dispersions are prepared either by melt-in procedure which involves heating drug, excipients and binder to a temperature above the melting point of the binder or by spray-on procedure which involves spraying a dispersion of active ingredient in molten binder on the heated excipient by using a high shear homogenizer. A rotary processor may be preferred over high melt agglomeration because it may be convenient to control the temperature and also high content of binder can be incorporated during agglomeration. The effect of binder used, the manufacturing procedure and particle size are critical parameters in preparation of SD(s) by melt agglomeration, since these parameters result in variation in dissolution rate and mechanism of agglomeration. The melt in procedure generally gives an increased rate of dissolution than the spray-on procedure with poloxamer 188, PEG 3000 and gelucire 50/13 which is attributed to immersion mechanism of agglomerates while fine particles cause adherence of the mass to the bowl after melting, which is further attributed to distribution of the finer particles.

The use of surfactant [30]
The utility of the surfactant systems in solubilisation is thoroughly understood. Adsorption of surfactant onto the solid surface can modify their hydrophobicity, charge on the surface, and other crucial properties that control the interfacial processes such as flocculation or dispersion, wetting, floatation, solubilisation, detergency, enhanced oil recovery and inhibition of corrosion. It is reported that surfactants can cause solvation or plasticization, which manifests in the reduction of melting point of the active ingredients and the combined glass transition temperature of solid dispersions. Surfactants have gained importance for preparation of solid dispersion because of the above unique properties.

Electrospinning [31]
Electro spinning is a technique in which solid fibres are produced from a melt delivered through a millimetre-scale nozzle or polymeric fluid stream solution. This technique involves the application of a strong electrostatic field over a conductive capillary attached to a reservoir containing a melt or solution of a polymer and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charged species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape (Taylor’s cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the cone (relieving the charge built-up on the surface of the pendant drop). The ejected charged jet is then moved to the collecting screen via the static force. The Coulombic repulsion force is liable for dilution of the charged jet throughout its trajectory to the collecting screen. The thinning down of the charged jet is limited by the increase in viscosity, as the charged jet is dried. This technique has a tremendous potential for the preparation of nano fibres and controlling the release of biomedicine, as it is simple and cheapest technique which can be utilized for the preparation of solid dispersion in the near future.

Super critical fluid (SCF) technology [32]
Supercritical fluid technique utilizes carbon dioxide (CO₂), as a solvent for drug and matrix or as an anti-solvent. When supercritical CO₂ is used as solvent, matrix and drug dissolved are sprayed through an orifice, into an expansion vessel with low pressure where the particles are subsequently formed. The rapid cooling of the mixture is a result of the adiabatic expansion. This technique does not require organic solvents and as carbon dioxide is considered eco-friendly, it is referred to as ‘solvent free’. This method is also known as rapid expansion of supercritical solution (RESS). This technique has limited applications owing to poor solubility (<0.01 w %) of most pharmaceutical compounds in carbon dioxide which further decreases with increasing polarity. Therefore, scale up might be impractical.

Co-precipitation method [33]
In this method accurately weighed quantity of drug is dissolved in organic solvent and carrier is dissolved in water. After complete dissolution the aqueous solution of carrier is transferred in to the organic solution of the drug. The solvents are then evaporated. The obtained dispersion is pulverized with pestle in mortar, sieved and dried until free from traces of solvent.
CONCLUSION

This article briefs the improvement of solubility of poorly soluble drugs by solid dispersion technique. These drugs can be formulated into various designs of the transdermal patches by thorough understanding of the structure and barrier properties of the skin. The properties of the drug, characteristics of the device, status of patient skin are all important for safe and effective administration. TDSS have proven to be remarkable, safe and effective route of drug administration.

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