The Pharmaceutical and Chemical Journal, 2020, 7(4):53-60

Available online www.tpcj.org

Review Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

Pros and Cons of Transdermal Drug Delivery System

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Abstract Transdermal drug delivery is having variety of benefits over traditional drug delivery systems and has increased patient compliance. Transdermal patches are easy application on skin and removal as and when required. TDDS deliver drugs for systemic effects at a predetermined and controlled rate over an extended period of time in order to enhance the therapeutic effectiveness and reduce adverse effect of the drug. TDDS helps in maintaining the concentration of drug within the therapeutic window range for extended time period ensuring that drug levels should not fall below the minimum effective concentration and it should not exceed the maximum effective concentration. The article highlights an overview of TDDS, its advantage over conventional dosage forms as well its limitations.

Keywords Transdermal drug delivery, TDDS, Transdermal/Skin patches, Polymers

Introduction

Transdermal drug delivery system is defined as topically administered self contained, distinct dosage forms used in the form of patches which deliver drugs for systemic effects at a predetermined and controlled rate over an extended period of time in order to enhance the therapeutic effectiveness and reduce adverse effect of the drug [1].

Transdermal system delivers drugs through the skin directly into the bloodstream. The transdermal route of drug delivery is very popular because large number of drugs can be delivered by this method to treat various diseases [2].

The development of TDDS is a multidisciplinary approach which comprise fundamental feasibility studies preliminary from the selection of drug entity to the demonstration of adequate drug flux in an *ex vivo* and *in vivo* model followed by production of a drug delivery system that meets all the required needs that are specific to the drug molecule (physicochemical, stability studies), the patient (comfort and cosmetic appeal), the manufacturer (scale up and manufacturability) and most essential economy [3].

Classification of Transdermal Patches [4]

There are four types of transdermal patches:

1. **Single–layer drug in–adhesive**
   In this system the drug is present in the adhesive layer which is enclosed from both sides by a temporary liner and a backing. The adhesive layer serves dual function one is to holding the various layer together, along with complete system to the skin and second is releasing of the drug.

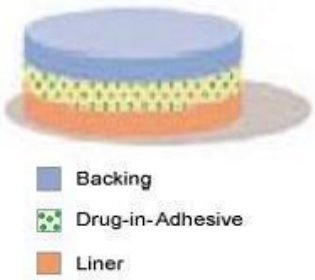

Figure 1: Single–layer drug in–adhesive

2. Multi-layer drug in adhesive

This system is similar to single–layer drug in–adhesive in which adhesive layer is responsible for adhesion and releasing of the drug. In addition to it, this system also posses another layer of drug in-adhesive, usually separated by a membrane. Temporary liner and a backing is also present in this system.

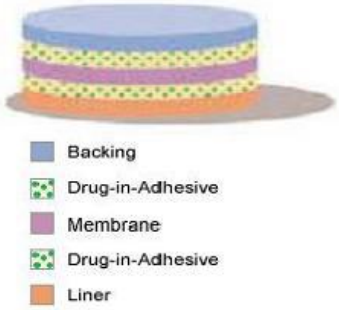

Figure 2: Multi–layer drug in–adhesive

3. Drug reservoir-in-adhesive

This system has a separate drug layer distinct from the Single-layer and Multi-layer Drug-in-adhesive systems. The drug layer present in reservoir transdermal system is a liquid compartment possessing a drug solution or suspension separated by the adhesive layer. This patch is also containing the backing layer.

Figure 3: Drug reservoir-in-adhesive

4. Drug matrix-in-adhesive

This system is containing a drug solution or suspension in the drug layer of semisolid matrix. The adhesive layer in this patch encloses the drug layer partly superimposing it.

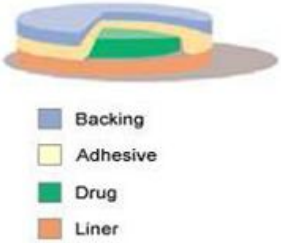

Figure 4: Drug matrix-in-adhesive

Basic Components of a Transdermal Patch [5]

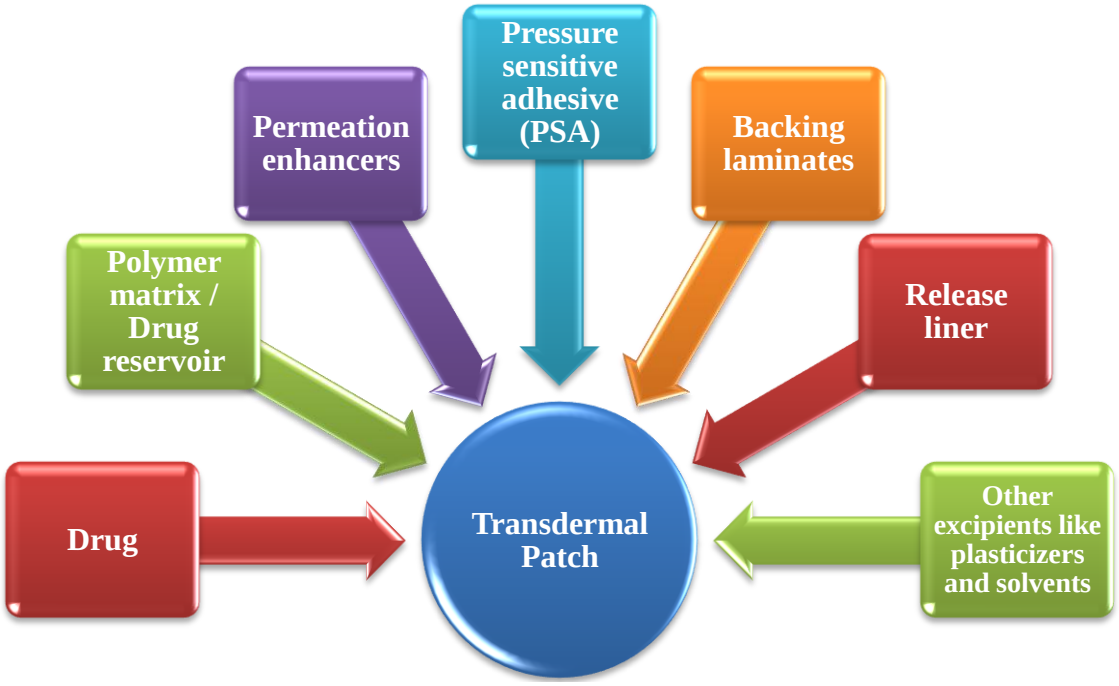

Figure 5: Basic components of transdermal patch

- **Drug**

  For effectively developing a transdermal drug delivery system, the drug should be selected with enormous care.

Ideal characteristics of drug for transdermal drug delivery [6]

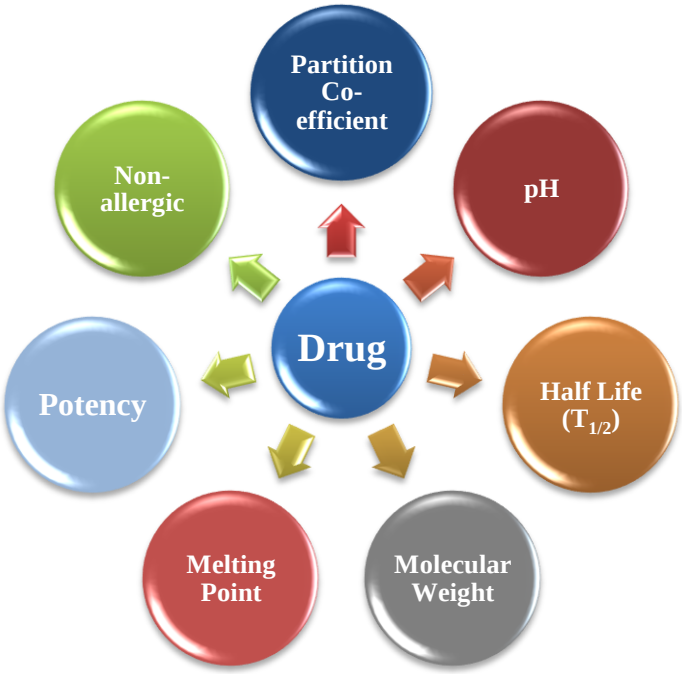

Figure 6: Ideal Properties of drug

- **Partition Coefficient**
  The drug should have an adequate solubility in lipid and water as it is necessary for better penetration of drug. It is required for good therapeutic action.
- **pH**
  The rates of absorption of acidic and basic drugs are mainly dependent on pH. Many drugs may be significantly absorbed by transdermal route at significant pH values but the unionized form of the drug determines the drug concentration in skin.
- **Half Life ($T_{1/2}$)**
  The biological half life of the drug should be short i.e., less than 10 hours.
- **Molecular Weight**
  Absorption of drug is inversely proportional to the molecular weight, small molecules penetrate faster than large molecules. The molecular weight should not be more than 1000 Daltons.
- **Melting Point**
  The drug should have low melting point. It should not be more than 200°C.
- **Potency**
  Drug should be potent enough so that it should be effective in daily dose of few mg/day. Therapeutic index of the drug should be low.
- **Non- allergic**
  The drug should not give rise to any immune response or any kind of hypersensitivity. It should be non-irritant and non-allergic to human skin.

Polymers matrix/Drug reservoir [7]

Polymers used in transdermal drug delivery system

Polymers are the principal part of transdermal drug delivery system as it offers steady and effective delivery of a medicament all through the product's intended shelf life. Polymer matrix is prepared by dispersing the drug molecule in liquid or solid state synthetic polymer base. System for transdermal delivery are formulated as multifaceted polymeric laminates in which a drug polymer matrix is sandwiched between two polymeric layers, an external impermeable backing layer which prevents the loss of drug through the backing surface and an internal polymeric layer which functions as an adhesive, or rate controlling membrane.

Classification of polymers used in TDDS [8]

1. **Natural Polymers:**
   These are naturally obtained substances or extracted from nature for example cellulose derivatives, gelatin, zein, shellac, waxes, gums, natural rubber and chitosan etc.
2. **Synthetic Elastomers:**
   These polymers are having viscosity and elasticity in them e.g. polybutadiene, polyisobutylene, silicon rubber, nitrile, acrylonitrile, neoprene, butylrubber, silicon, nitrile etc.
3. **Synthetic Polymers:**
   These polymers are not naturally occurring and are manmade macromolecules which are made up of repeated chemical units.
   Examples include polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc.
   The polymers like cross linked polyethylene glycol, eudragits, ethyl cellulose, polyvinylpyrrolidone and hydroxypropylmethylcellulose are used as matrix formers for TDDS.
   Other polymers like EVA, silicon rubber and polyurethane are used as rate controlling membrane.

Ideal properties of polymer to be used in a transdermal system [9]

1. The polymer should be inexpensive.
2. The polymer must be an inert drug carrier and should be chemically non-reactive.
3. It should be stable and must not decompose on storage or during its shelf life.
4. Molecular weight, physical and chemical functionality of the polymer must allow the diffusion and release of the specific drug substance at controlled rate.
5. The polymer and its decomposed product should be nontoxic. It should be biocompatible with skin as well as non-antagonistic to the host.
6. It should be easy to manufacture and fabricate into desired product. It should also permit inclusion of large amounts of active agent.

- **Permeation enhancers** [8]

Permeation enhancers are chemical compounds which are used to increase permeability of stratum corneum in order to attain higher therapeutic levels of the drug molecule. They help in improving the permeability of the drug by interacting with structural components of stratum corneum i.e., proteins or lipids.

Ideal properties of permeation enhancers to be used in a transdermal system

- Permeation enhancers should be non-irritating, non toxic & non-allergic.
- They must be chemically and physically compatible with drug and other pharmaceutical excipients used in the system.
- Pharmacological inertness is must and they should not bind to receptor site which does not show any pharmacological activity.
- They should be odorless, colorless, economical and cosmetically acceptable with an appropriate skin feel.
- They must posses controlled and reversible enhancing action.
- They should not cause any loss of body fluids, electrolytes or other endogenous materials.

Classification of penetration enhancers [7]

- **Terpenes (essential oils):** E.g. Nerodilol, menthol, 1 8-cineol, limonene, carvone etc.
- **Pyrrolidones:** E.g. N-methyl-2-pyrrolidone (NMP), azone etc.
- **Fatty acids and esters:** E.g. Oleic acid, linoleic acid, lauric acid, capric acid etc.
- **Sulfoxides and similar compounds**: E.g. Dimethyl sulfoxide (DMSO), N,N-dimethyl formamide Alcohols, Glycols, and Glycerides : E.g. Ethanol, Propylene glycol, Octyl alcohol etc.
- **Micellaneous enhancers**: E.g. Phospholipids, Cyclodextrins, Amino acid derivatives, Enzymes etc.

- **Pressure sensitive adhesive (PSA)** [10]

  - The selection of an adhesive is based the design of the patch and drug formulation. Pressure sensitive adhesive assists in adhering transdermal system to the skin surface.
  - It should easily remove from the surface of the skin without leaving a residue on it.
  - It should stick on the stick with the pressure applied by the finger and should not need any strong holding force.
  - PSA should be compatible physically, chemically as well as biologically and should not modify drug release.
  - It can be placed on the face or in the backside of the device.
  - For e.g.: polyacrylamates, polyacrylates, polyisobutylene, silicone based adhesive.

- **Backing laminates** [11]

  - Backing laminates are supportive layer and it must be impermeable to drug and permeation enhancers.
  - It helps in holding the entire transdermal system together.
  - It also helps in protecting the drug reservoir from exposure to the environment, which could result in the leakage or loss of the drug by the process of volatilization.

- It should be chemically compatible with the drug, penetration enhancer, adhesive and other excipients of the system.
- Examples are vinyl, polyethylene and polyester films.

- **Release liner** [12]
  - Release liner is the primary packaging material that helps in preventing the loss of drug which has transferred into the adhesive layer. It is removed when the patch is applied to the skin.
  - It should be chemically inert and permeable to drug, penetration enhancers & water.
  - As it is in intimate contact with the delivery system, it also helps protect patch from contamination.
  - Release liner is composed up of base layer which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and a release coating layer made up of silicon or Teflon.

- **Other excipients** [13]

  Various solvents like chloroform, methanol, acetone, isopropanol and dichloromethane are used in preparing drug reservoir. In addition plasticizers such as dibutylpthalate, triethylcitrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.

Advantages of Transdermal Delivery [14-19]

The positive features of transdermal drug delivery across the skin to achieve systemic effects are:

- **No interaction with gastrointestinal fluids**

  They can circumvent gastrointestinal drug absorption complexity caused due to gastrointestinal pH, enzymatic activity, and drug interactions with food, drink, and other orally administered drugs.
- **Alternative route**

  They can be the best substitute for oral administration of medication when that route is incompatible because of vomiting and diarrhea.

  Dose delivery is unaffected by vomiting or diarrhea.
- **Self administration**

  TDDS provide suitability for self administration and the daily dose of the drug required is lower than that with conventional therapies.
- **Avoid the first-pass metabolism**

  They help avoid the first-pass effect, that is, the initial passage of drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzymes.
- **Comfortable & Suitable**

  They are noninvasive, avoiding the inconvenience of parenteral therapy.

  These patches are easier to use and remember.
- **Flexibility of Termination**

  Drug therapy can be terminated rapidly by removal of the applied patch from the surface of the skin.
- **Patient compliance**

  They provide extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration.
- **Reduced side-effects**

  The lack of peaks in plasma concentration can reduce the risk of side effects, thus drugs that require relatively consistent plasma levels are very good candidate for transdermal drug delivery.
- **Steady state plasma concentration**

  The patch also permit constant dosing rather than the peaks and valley in medication level associated with orally administered medication. Thus helps avoiding in drug fluctuation drug levels.

- **Others**
  - → They are easily and rapidly identified in emergencies (e.g., unresponsive, unconscious, or comatose patient) because of their physical presence, features, and identifying markings.
  - → Improving physiological and pharmacological response.
  - → Provides utilization of drugs with short biological half lives, narrow therapeutic window.
  - → Inter and intra patient variation.

Drawbacks of Transdermal Delivery [20- 25]

Transdermal drug delivery has few disadvantages listed below that are limiting the use transdermal delivery:

- **High cost**
  The use of transdermal delivery may be uneconomical.
- **Molecular size restriction**
  TDDS cannot be developed for drugs having large molecular size.
- **Local irritation / uncomfortability**
  These systems may cause allergic reactions to few patients.
  Some patients may develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
- **Low permeability limits**
  Transdermal delivery is neither practical nor affordable when required to deliver large doses of drugs through skin.
- **No ionic drug delivery**
  TDDS does not allow delivery of ionic drugs.
  It is not suitable for a drug, which doesn't possess a favorable o/w partition coefficient.
  Only relatively potent lipophilic drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin's impermeability.
- **Low drug levels in blood/plasma**
  This delivery system cannot be used for drugs requiring high blood levels.
- **No rapid / pulsatile drug release**
  TDDS cannot deliver drugs in a pulsatile fashion. Long time adherence is difficult.
- **Variation in barrier function**
  The barrier function of the skin changes from one site to another on the same person, from person to person and with age for better understanding of transdermal drug delivery, the structure of skin should be briefly discussed along with penetration through skin and permeation pathways.

Conclusion

This article provides valuable information regarding the pros and cons of the transdermal drug delivery system. Transdermal drug delivery systems correspond to a beneficial innovation for drug delivery, predominantly in patients who cannot swallow or remember to take their medications. Topical administration of therapeutic agents provides many advantages over conventional oral and invasive methods of drug delivery systems. However, due to certain disadvantages like large drug molecules cannot be delivered, large dose cannot be given, the rate of absorption of the drug is less, skin irritation; etc., the use of TDDS has been restricted. But with continuous regular invention of new devices and new drugs that can be administered via this system, the use of TDDS is increasing rapidly in the present time.

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