



Review Article

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Transdermal Drug Delivery System-A Review
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Abstract

In recent years a wide variety of newer drug delivery system like sustained/controlled release dosage forms are designed and evaluated in order to overcome the limitation of conventional therapy. These products are able to maintain steady drug plasma levels for extended periods of time as a result the variation of the drug levels in the blood are prevented and minimized drug related side effects. Controlled release drug delivery system provides a predictive control over the release pattern, and subsequent tissue or blood levels can be achieved. One of the systems which provide controlled release of drug is transdermal drug delivery systems. Depending on the therapeutic target, transdermal drug delivery systems (TDDS) are designed to provide a continuous supply of drug through the skin to allow for local or systemic drug effects. Transdermal drug delivery system (TDDS) is a novel approach for delivering drugs across the skin. Most of the drugs are administered orally and are found not to be as effective as expected. This review article describes briefly about the modes of drug administration, advantages and disadvantages of TDDS, drug penetration pathways, types of Transdermal Delivery Systems and their evaluation.

Keywords: Conventional therapy, Controlled release, Therapeutic target, Transdermal drug delivery system

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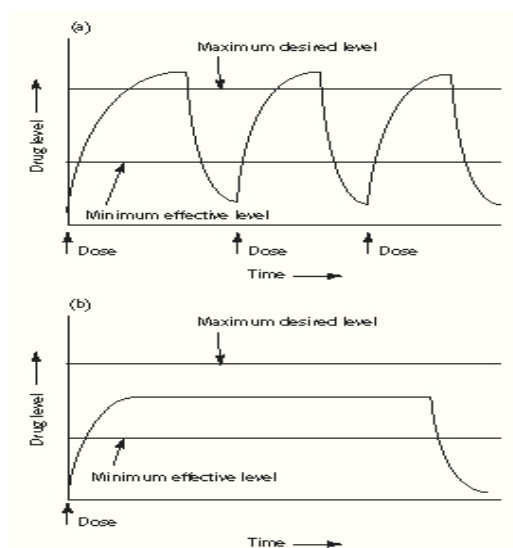

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1. Introduction

The administration of conventional oral dosage forms like tablets, capsules, liquids orals of drugs suffers a setback due to problem of gastro intestinal tract absorption, local irritation, dilution of drug strength, Liver first pass metabolism, degradation of drug by gastro intestinal tract enzymes, the protein binding of drug at an absorption surface and local toxicity. The bioavailability as well as duration of action is reduced which requires frequent administration, which in turn is associated with the problem of patients compliance to therapy and the economy of the treatment. All conventional dosage form except intravenous infusion, follow second-order kinetic.¹ Dosage form releases drug initially at faster rate, leading to quick rise in blood level of drug and then falls exponentially until a further dose is administered. This results in peak and valleys pattern of drug concentration

in blood and tissues. The time course of various modes of administration² is represented in figure.1. Drug delivery system may be a controlled release drug delivery system where there is predictive control over the release pattern, and subsequent tissue or blood levels can be achieved. From figure 1, it is observed that the equality of the rate of absorption and the rate of metabolism is only in the case of controlled drug delivery system.



1. Conventional single administration
2. Multiple administrations
3. Sustained release administration
4. Controlled drug delivery administration

Figure 1. Time course of various modes of administration

Administration of drug in conventional dosage form requires- large dose, frequent administration and lacks extended duration, with chances of toxicity. While in controlled drug delivery devices there is efficient utilization of drug, desired extended duration, with very low chances of toxicity, facilitating enhanced complication of patient, leading to better management of therapeutics. The efficacious use of drug influences cost factor and economy of therapy too.

Types of controlled release preparation

On the basis of technical sophistication, controlled drug delivery system can be categorized into 3 major classes.

A. Rate programmed controlled drug delivery system

These drug delivery system are those from which the drug release has been programmed at specific rate profiles. They are further subdivided into following subclasses.

1. Dissolution controlled drug delivery system

Slow dissolution rate of the drug

Slow dissolution rate of the reservoir membrane or matrix

2. Diffusion controlled drug delivery system

Porous matrix controlled system

Porous membrane controlled systems

3. Erosion controlled drug delivery system

Surface erosion

Bulk erosion

4. Dissolution, Diffusion and/or Erosion controlled drug delivery system

Reservoir system (membrane controlled drug delivery system)

Matrix system (monolithic drug delivery system)

Hybrid systems (membrane cum matrix drug delivery system)

B. Stimuli activated drug delivery system

1. Activation by physical process

- a. Osmotic pressure activated drug delivery system
- b. Hydrodynamic pressure activated drug delivery system
- c. Vapor pressure activated drug delivery system

- d. Mechanical force activated drug delivery system
- e. Magnetically activated drug delivery system
- f. Thermally activated drug delivery system
- g. Photo activated drug delivery system
- h. Photo mechanically waves (laser) activated drug delivery system
- i. Ultrasound activated drug delivery system
- j. Electrically activated (Iontophoresis) drug delivery system

2. Activation by chemical process

- a. PH activated drug delivery system
- b. Ion activated drug delivery system
- c. Hydrolysis activated drug delivery system
- d. Chelation activated drug delivery system

3. Activation by biological system

- a. Enzyme activated drug delivery system
- b. Antibody interaction drug delivery system
- c. Antigen activated drug delivery system
- d. Inflammation activated drug delivery system

C. Site targeted drug delivery system

- a. Polymeric carriers for drug targeting
- b. Albumin as carrier for drug targeting
- c. Lipoprotein as carrier for drug targeting
- d. Liposomes as carrier for drug targeting

Drug release mechanisms for controlled drug delivery system

Most of the design of controlled release dosage form employs polymers for controlling the drug release. There are three fundamental mechanisms by which polymers release drugs.¹³

Diffusion e.g.

Reservoir type systems

- a. Microcapsules
- b. Matrix/laminates

Chemical reaction

Water or enzyme causes degradation of a polymer which is used to encapsulate a drug.

- a. Erodible
- b. Degradable systems
- c. Pendant chain systems

Solvent activated

In this case drug is entrapped in the polymer until either external systems solvent swells the polymer or water imbibement creates osmotic pressure.

Other general mechanism includes

Magnetic signal:

Placement of drug into magnetic beads in matrix systems, applying an external magnetic field, the beads can be made to squeeze drug through the polymer.

Chemical signal:

This can also be utilized to create self regulated systems. In such cases an external molecule such as glucose can diffuse into a polymer membrane and react with an enzyme that is immobilized. Enzymatic reaction causes pH shifts which alters membrane permeability or drug solubility and there by changes the release rate.

2. Transdermal Drug Delivery System

Conventional systems of medication that require multi dose therapy are having many problems. The controlled drug delivery is a newer approach is to deliver drug in to systemic circulation at a predetermined rate. Our system should duplicate continuous intravenous infusion, which not only by passes hepatic 'first pass' elimination but also maintains a constant, prolonged and therapeutically effective drug level in the body. This is made possible by using intact skin as a port of drug administration to provide continuous delivery of drug in to systemic circulation. Following skin permeation, the drugs first reach the systemic circulation. The drug molecules are then transported to the target site, which could be relatively remote from the site of administration, to produce therapeutic action.

Transdermal drug delivery offers the following potential advantages

- A. Avoid the risks and inconveniences of intravenous therapy and of varied conditions of absorption and metabolism associated with the oral therapy.

- B. Continuity of drug administration in TDDS permits the use of a drug with short biological half-life.
- C. Transdermal drug delivery improves the bioavailability that reduces the total daily dose.
- D. Avoids first-pass hepatic metabolism.
- E. Less chances of over or under dosing as the result of prolonged pre programmed delivery of drug at the required therapeutic rate.
- F. Decrease gastrointestinal side effects.
- G. Elimination drug food interactions.
- H. Increased patient compliance in following manner
 - a. Provisions of simplified therapeutic regimen.
 - b. Painless delivery of drug.
 - c. Eliminates swallowing.
 - d. No chances of forgetting the dose once the device is applied on skin.
 - e. Easy to carry a patch in wallet or ladies purse.
- I. Patches offer less friability problems of wear and tear than the tablets.
- J. In a multi drug regimen TDDS avoids drug interaction in GIT.
- K. It is easy to terminate the medication simply by removing the drug delivery device from the skin surface.
- L. TDDS system can be taken without any aid, for instance, tablet and capsule need little water. Liquid oral preparation needs teaspoon and parenteral delivery needs specialized person whereas if a patient is told to apply TDDS patch, he/she can do it any where e.g. in office, in theatre, in club, in house without any aid.
- M. Problem of dose dumping is least in TDDS, because stratum corneum is more resistant than the inner membranes (i.e. mucous membrane in case of oral controlled release delivery systems) and stratum corneum itself is a rate limiting factor.
- N. Need not to be sterile obviates processing problem.

Disadvantages of transdermal drug delivery system¹⁷

- a. The limitation of transdermal drug delivery is principally associated with skins barrier function, which severely constrains the absolute amount of drug that can be absorbed across reasonable area of skin during the dosing period. Thus, the major disadvantage of the method is that it is limited to potent drug molecule typically those requiring a daily dose on the order of 20 mg or less.
- b. Even if the drug is sufficiently potent, it must yet satisfy other criteria to be considered a viable candidate for transdermal drug delivery. For example its physiochemical properties must allow to be absorbed percutaneously. This mean that its molecular weight should ideally be less than 500 Daltons and it should have adequate solubility in both lipophilic and aqueous environments since, to reach dermal micro circulation and gain access to systemic circulation, the molecule must cross that stratum corneum (a lipid barrier) and then transfer through the much-more-aqueous-in-nature viable epidermis and upper dermis.
- c. The pharmacokinetic and pharmacodynamic characteristic of the drug must be such that relatively sustained and slow input provided by transdermal delivery makes sense. Tolerance inducing compounds are not intelligent choice for this mode of administration unless until an appropriate "wash out" period is programmed into the dosing regimen.
- d. Drugs that can be given once a day orally, with reproducible bioavailability and which are well tolerated by patient do not really need a patch formulation.
- e. Drugs must not be locally irritating or sensitizing.

Drug penetration pathways¹⁸⁻²²

There are critically three ways in which a drug molecule can cross the intact stratum corneum: via skin appendages (shunt routes); through the intercellular lipid domains; or by a transcellular route. A particular drug is likely to permeate by a combination of these routes, with the relative contributions of these pathways to the gross flux governed by the physicochemical properties of the molecule.

Types of Transdermal Delivery Systems

There are mainly four types of basic transdermal patches in the market²³.

1. Drug in adhesive type:

In this type drug is loaded in adhesive itself and stratum corneum acts as rate controlling barrier. This is most old type of transdermal patch design. This type of transdermal drug delivery system is best illustrated by the development and marketing of a nitro glycerin releasing system named as deponit by PharmaSchwartz/Lohmann in Europe. Basic construction includes backing membrane, adhesive loaded with drug and release liner.

2. Multi laminate type:

This is most complicated type of design for transdermal patches. Basic construction includes backing membrane, drug in adhesive, rate controlling membrane, then again adhesive (loaded with drug) on to it. This shows that there are two adhesive layers. First layer that is in contact with the release liner is actually delivering drug and second layer of adhesive (after membrane) acts as depot of drug. The example is scopolamine releasing TDDS named as Transderm-scop by Ciba and clonidine releasing TDDS named as CataPress-TTS by Boehringer Ingelheim.

3. Reservoir type:

In this type the drug is incorporated in reservoir which is lined with membrane. The adhesive is coated on to this membrane. This membrane can be rate controlling. Basic construction includes backing membrane, drug in reservoir, membrane, and adhesive and release liner. Example of this type of TDDS is nitro-glycerine releasing system named as Nitrodisc by Searle.

3. Matrix type:

In this type, the drug is incorporated in the matrix of polymer which itself releases drug in zero order. The adhesive layer is just at the periphery and little inside the periphery of the patch. Basic construction includes backing membrane, adhesive, and drug in matrix and release liner. The example of matrix type transdermal patch in nitroglycerine releasing TDDS named as Nitro-dur by Key.

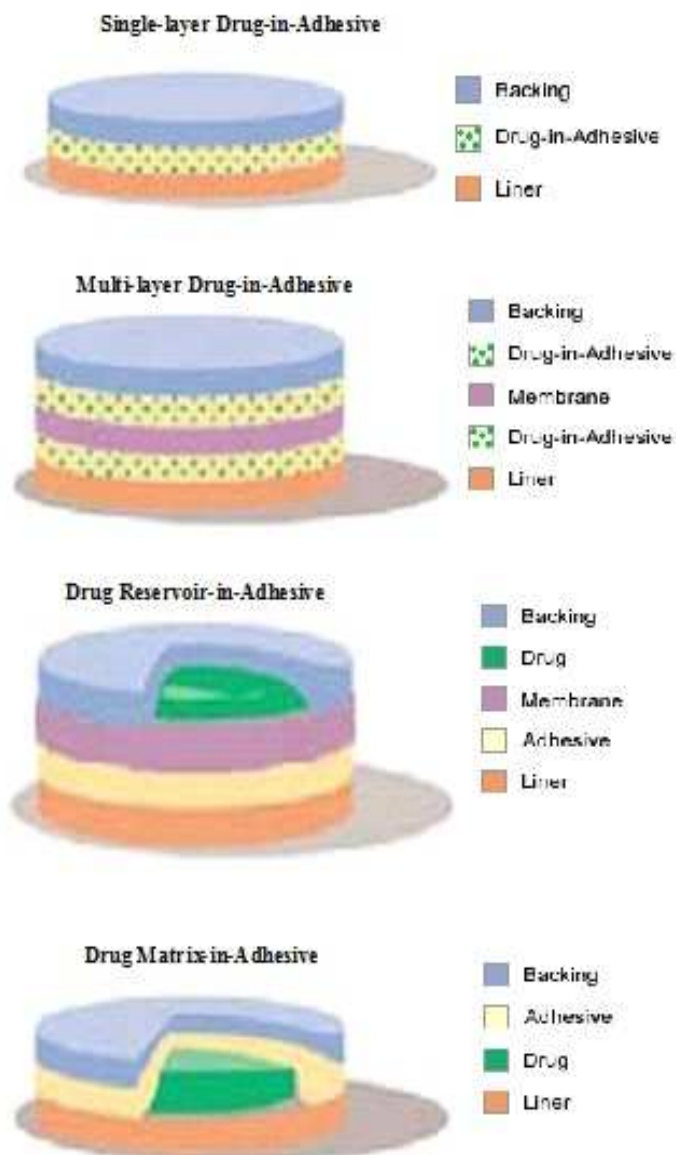


Figure 2. Basic patch construction

Evaluation of Transdermal Drug Delivery Device

Table 1. Testing of transdermal drug delivery system^{24,25}

Type of Test on Final Product	Tests
Chemical test	<ul style="list-style-type: none"> • Content • Content uniformity • Purity • Residual Solvent
Physical test	<p>Release testing</p> <ul style="list-style-type: none"> • USP apparatus 5 (Paddle over disk) • USP apparatus 6 (Cylinder) • USP apparatus 7 (Reciprocating disk) <p>Test for Adhesion</p> <ul style="list-style-type: none"> • Peel property • Tack property <ul style="list-style-type: none"> Thumbtack test Rolling ball tack test Quick stick test Probe tack test • Shear strength
Cutaneous toxicity	<ul style="list-style-type: none"> • Contact dermatitis • Growth of microorganisms • Cytotoxicity • Sensitization study
Percutaneous absorption model	<ul style="list-style-type: none"> • <i>In vitro</i> testing • <i>In vivo</i> testing

Proper skin preparation and appropriate cell design gives good *in vivo* results. Skin preparation includes selection of proper skin. One can choose human skin or can also go for animal or artificial membrane like Nylon, Cellulose acetate etc. Skin separation includes the treatments needed for separation of required part of skin from other unwanted parts. Then separated skin we mount on the diffusion cell which can be one chambered (one donor compartment) or two chambered (two donor compartments).

Selection of membrane for in vitro study of transdermal drug delivery system:

Various skin models have been used by various researchers. Though there is no rule regarding to selection of the skin model. But generally researchers starts with artificial membrane, then *in vitro* animal skin, then *in vitro* human skin (cadaver skin), then *in vivo* animal skin, then finally *in vivo* human skin.

Franz diffusion cell

It is one chambered (vertical) type cell. Most widely used for in-vitro testing of TDDS. Many modifications have been made in the Franz diffusion cell design according to the requirement. Here skin is mounted on the plate above O ring. 20-70 ml phosphate buffer of pH 7.4 is filled in reservoir compartment. Transdermal patch is applied on upper layer of skin. Diffusion medium in reservoir is stirred at particular rpm. Sampling is done at particular interval from reservoir compartment i.e. specified volume of fluid is withdrawn and is replaced by equivalent amount of the same fluid.

3. In vitro drug release profile modeling

In-vitro drug release has been recognized as an important tool in drug development and as an important parameter in quality control. Under certain conditions, it can be used as a surrogate for the assessment of bio equivalence or prediction of bioequivalence.²⁷ A good understanding of the release mechanism of the dosage form as well as the physical chemical properties of the drug will enable development of accurate Dissolution tests.²⁸ An appropriate drug release test is required to characterize the drug product and ensure batch-to-batch reproducibility and consistent pharmacological/biological activity and to evaluate scale up and post approval changes such as manufacturing site changes, component and composition changes. The release of drug from a sustained release formulation is controlled by various factors through different mechanisms such as diffusion, erosion or

osmosis. Several mathematical models are proposed by many researchers to describe the drug release profiles from various systems^{29,30}. In order to characterize the kinetics of drug release from dosage forms several model dependent methods are reported by various researchers.^{31,32} The model dependent methods all rely upon a curve fitting procedure. Different mathematical functions have been used to model the observed data. Both the linear and non-linear models are being used in practice for dissolution modeling. Linear models include Zero order, Higuchi, Hixson-Crowell, quadratic and Polynomials, where as the nonlinear models include First order, Weibull, Korsmeyer-Peppas, Logistic etc.³³

4. Conclusion

Transdermal drug delivery system represents a beneficial innovation for the delivery of drugs, particularly in patients who cannot swallow or remember to take their medications. Despite some disadvantages, transdermal drug delivery offers many advantages capable of improving patient health and quality of life. Their potential role in controlled release is being globally exploited by the scientists with high rate of attainment. Due to the recent advances in technology and incorporation of the drug to the site of action without rupturing the skin membrane, transdermal route is becoming the most widely accepted route of drug administration. It promises to eliminate needles for administration of a wide variety of drugs in the future.

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