An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

TRANSDERMAL DRUG DELIVERY: AN OVERVIEW

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ARTICLE INFO

Key Words

Transdermal,
Drug kinetics,
Skin,
Drug delivery system,
stratum corneum

ABSTRACT

Much attention has been given in recent years with regard to the transdermal delivery devices. Broadly this system can be considered as single layer and multilayer. Ficks' first law of diffusion is the principle of drug kinetics. As a substitute for the oral route transdermal drug delivery enables the avoidance of gastrointestinal absorption, with its associated pit falls of enzymatic and pH associated deactivation. Transdermal delivery has many advantages over conventional modes of drug administrations, it thus avoids hepatic first pass metabolism and improves patient compliance. Its main advantages includes controlled drug release with minimum side effects, improved bioavailability, bypass first pass metabolism and many more. There are factors such as physiochemical as well as biological which affect the bioavailability of transdermal medicament. During the past decade, number of drugs formulated in the patches is hardly increased; there has been little change in the composition of the patch system. Modifications have been mostly limited to refinements of the materials used. The present review article explores the overall study on transdermal drug delivery system (TDDS) which leads to novel drug delivery system (NDDS).

INTRODUCTION:

During the past few years, interest in the development of novel drug delivery systems for existing drug molecules has been renewed. The development of a novel delivery system for existing drug molecules not only improves the drug's performance in terms of efficacy and safety but also improves patient compliance and overall therapeutic benefit to a significant extent. [1] Transdermal Drug Delivery System (TDDS) are defined as self contained, discrete dosage forms which are also known as "patches" [2, 3] when patches are applied to the intact skin, deliver the drug through the skin at a controlled rate to the systemic circulation. [4] TDDS are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin.[5] The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation into the skin through skin at predetermined rate with minimal inter and intra patient variation. [3] Currently transdermal delivery is one of the most promising methods for drug application. [6] It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliances and minimizes harmful side effects of a drug

caused from temporary over dose and is convenience in transdermal delivered drugs that require only once weakly application.[7] That will improves bioavailability, more uniform plasma levels, longer duration of action resulting in a reduction in dosing frequency, reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms.[8] Transdermal delivery not only provides controlled, constant administration of drugs, but also allows continuous input of drugs with short biological half lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects.[3] Several important advantages of transdermal drug delivery are limitations of hepatic first pass metabolism, enhancement of therapeutic efficacy and maintenance of steady plasma level of drug.[1] The developments of TDDS is a multidisciplinary activity that encompasses fundamental feasibility studies starting from the selection of drug molecule to the demonstration of sufficient drug flux in an *ex vivo* and *in vivo* model followed by fabrication of a drug delivery system that meets all the stringent needs that are specific to the drug molecule (physicochemical, stability factors), the patient (comfort and cosmetic appeal), the manufacturer (scale up and manufacturability) and most important economy.[7] The first transdermal system, Transderm SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with travel. Most transdermal patches are designed to release the active ingredient at a zero order rate for a period of several hours to days following application to the skin. This is especially advantageous for prophylactic therapy in chronic conditions. [9] The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and its metabolites in the urine and through the clinical response of the patient to the administered drug therapy.[10]

Transdermal route and drug delivery prospects

Skin: The skin is the largest organ of the human body which covers a surface area of approximately 2 sq.m. and receives about one third of the blood circulation through the body. [5] It serves as a permeability barrier against the transdermal absorption of various chemical and biological agents. It is one of the most readily available organs of the body with a thickness of few millimeters **(**2.97 0.28 mm**)** which,

- Separates the underlying blood circulation network from the outside environment.
- Serves as a barrier against physical, chemical and microbiological attacks.
- Acts as a thermostat in maintaining body temperature.
- Plays role in the regulation of blood pressure.
- Protects against the penetration of UV rays.
- Skin is a major factor in determining the various drug delivery aspects like permeation and absorption of drug across the dermis. The diffusional resistance of the skin is greatly dependent on its anatomy and ultrastructure.[11,12]

Advantages of transdermal drug delivery system

- First pass metabolisms of drug get avoided.
- Gastrointestinal incompatibilities get avoided.
- Self medication is possible.
- Duration of action gets extended & predictable.
- Unwanted side effects get minimized.

- Drug plasma concentration gets maintained.
- Number of doses get reduces which improve patient compliance.
- Therapeutic value of many drugs get increased by avoiding problems associated with drug like lower absorption, GI irritation, decomposition due to hepatic first pass metabolism.(3,4)

Disadvantages of Transdermal drug delivery

- System Chances of allergic reactions at the site of application like itching,rashes,local edema etc.
- Larger molecular size of drug (above 1000) creates difficulty in absorption.
- Barrier function of skin varies from site to site on the same or different person.
- Drug with hydrophilic character is less suitable as compare to drug with lipophilic character because of their low permeability.

Formulation of transdermal drug delivery system:

Various components of a transdermal drug delivery system are shown in Fig. 1.

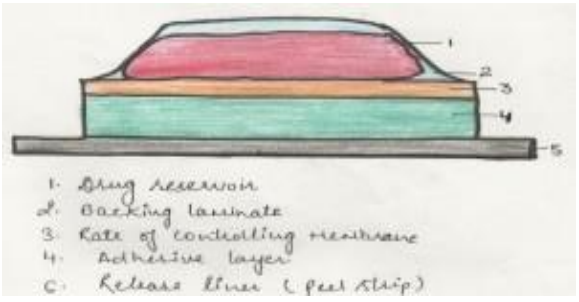

Fig. 1: Schematic representation of components of TDDS

Drug substance: For successfully developing a transdermal drug delivery system, the drug should be choosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.[28]

***In vitro* release studies:** Transdermal patches can be *in vitro* evaluated in terms of Franz diffusion cell the cell is composed of two compartments: donor and receptor. The receptor compartment has a volume of 5-12ml and effective surface area of 1-5 cm 2cm. The diffusion buffer is continuously stirred at 600 rpm by a magnetic bar. The temperature in the bulk of the solution is maintained by circulating thermostated water through a water jacket that surrounds th**e** receptor compartment. The drug content is analyzed using suitable method; maintenance of sink condition is essential.[13]

***In vivo* Studies:** Transdermal patches can be *In vivo* evaluated in terms of *In vivo* evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during *in vitro* studies can be fully explored during *in vivo* studies. *In vivo* evaluation of TDDS can be carried out using animal models human volunteers.[14]

Animal models: Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. The most common animal species used for evaluating transdermal drug delivery system are mouse, hairless rat, hairless dog, hairless rhesus monkey, rabbit, guinea pig etc. Various experiments conducted leads to a conclusion that hairless animals are preferred over hairy animals in both *in vitro* and *in vivo* experiments. Rhesus monkey is one of the most reliable models for *in vivo* evaluation of transdermal drug delivery in man.[15]

Human model: The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers.[39] Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase-I clinical trials are conducted to

determine mainly safety in volunteers and phase-II clinical trials determine short term safety and mainly effectiveness in patients. Phase-III trials indicate the safety and effectiveness in large number of patient population and phase-IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Though human studies require considerable resources best to assess the performance of the drug.[15]

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