Review Article

An Overview on Transdermal Drug Delivery System

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ABSTRACT

With the advancement in technology Pharma industries have trendified all its resources. Earlier we use convectional dosage form but now we use novel drug delivery system. One of greatest innovation of novel drug delivery is transdermal patch. The advantage of transdermal drug delivery system is that it is painless technique of administration of drugs. Skin is used for the delivery of drug because skin has large surface area, there is systemic access through underlying circulatory and lymphatic networks and it is the non invasive nature of drug delivery. This route of drug delivery was invented in 1981 when Ciba Geigy marketed Transderm V which is now called as Transderm Scop to cure nausea and vomiting associated with motion sickness. The main advantage of transdermal drug delivery system is controlled release of the drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation through skin at predetermined rate with minimal inter and intra patient variation. In this paper we have covered what are transdermal patch, it's uses, limitation, factor affecting transdermal drug delivery system, component of transdermal drug delivery system, penetration enhancers methods and evaluation of transdermal drug delivery system.

Keywords: Evaluation; Microscopic needle; Polymer matrix; Patches.

INTRODUCTION

Transdermal drug delivery system is self contained, discrete dosage form[1] in which drug stick to the body surface and delivers the drug, across the skin at controlled rate in to the blood stream. Till now total 16 active ingredients and more than 35 Transdermal drug delivery products have been approved for use globally and for sale in the US market. By statistics analysis it has been found that there is an increase in transdermal market which was $ 21.5 billion in the year 2011 and will be $31.5 billion in the year 2015[4] as compare to $ 12.7 billion in year 2005. Oxybutinin drug molecule patch is largest (359 Da) and nicotine drug molecule patch is smallest (162Da)[3]. Transdermal drug delivery permits controlled release of the drug into the patient, it enables a steady blood level profile which causes reduced systemic side effects and improved efficacy over other dosage forms[5-6]. The main aim of transdermal drug delivery system is to administer drugs into systemic circulation through skin at predetermined rate with minimal inter and intrapatient variation with user friendly, convenient, painless, and is multi day dosing, it offer improved patient compliance too[1]. Patch formulation is a complex process. The rate and amount of transdermal absorption depend on factors like nature of the drug, the drug's concentration in the reservoir or matrix, area of skin covered by the patch. The formulations used are identical but the patches have different surface areas for different strengths of delivered drug when several dose strengths of a drug patch are marketed (e.g., estradiol patches). Drug is placed in large amount in the patches to keep the concentration gradient suitable for absorption because the active ingredients act at low dosage and are inexpensive, the cost of wasted excess drug is not economically significant[8-14]. New advanced technologies like chemical enhancers[11]. iontophoresis, electroporation[17], pressure waves generated by ultrasound or photoacoustic effects[18-19] have been developed to enhance transdermal drug delivery for therapeutic and diagnostic purposes[20]. The mechanisms of enhancement of these approaches are illustrated in Figure 1.

Uses of transdermal drug delivery system

The highest selling nicotine transdermal patch decrease the tobacco smoking. In Europe 2007 the first commercially available vapor patch to decrease degree of smoking was approved. Fentanyl(marketed as Duragesic) and Buprenorphine(marketed as BuTrans) are two opioid medications used for intense pain are administered in patch form. To treat menopausal symptoms as well as post-menopausal osteoporosis estrogen patches are used. Other transdermal patches for delivery of certain hormones include the contraceptive patch(marketed as Ortho Evra or Evra)and testosterone patches for both men(Androde) and women(Intrinsa). For the treatment of angina Nitroglycerin patches are sometimes prescribed instead of sublingual pills. Transdermal scopolamine is commonly used for treatment of motion sickness[21]. Anti-hypertensive drug Clonidine is available in market in form of transdermal patch[22] named as Catapres-TTS[23]. First transdermal patch used as antidepressant approved for use in the U.S. in March 2006[24] was of the MAOI (monoamine oxidase inhibitor) selegiline (brand name Emsam). A transdermal delivery patch(Daytrana) used for Attention (ADHD), drug used methylphenidate (other names Ritalin or Concerta), was approved for market sell by the FDA in April 2006[25]. Vitamin B12is also administered in the form of transdermal patch. Cyanocobalamine, stable form of vitamin B12 is used in the patch. Transdermal patch of Rivastigmin(market name Exelon) was commercially introduce in 2007 for the treatment of Alzheimer's disease[26].

Limitations of transdermal drug delivery systems

Transdermal delivery is not suitable for delivery of large doses of drugs. It cannot administer drugs that require high blood levels[27]. Drug which may cause irritation or sensitization are not given by this route. This route is limited when the drug is extensively metabolized in the skin and when molecular size is great enough to prevent the molecules from diffusing through the skin[28]. For a drug, which doesn't possess a favourable o/w partition coefficient this route cannot be used. From one site to another on the same person, from person to person and with age the barrier functions of the skin changes which hinders transdermal drug penetration[29].

FACTORS AFFECTING TRANSDERMAL DRUG DELIVERY SYSTEM

Table 1: is showing factors that affect TDDS30

Biological factors	Physiological factors
Skin condition	Temperature and pH
Skin age	Diffusion coefficient
Blood flow	Drug concentration
Regional skin site	Skin hydration
Species Differences	Partition coefficient
	Molecular size and shape

IDEAL PROPERTIES OF TRANSDERMAL DRUG DELIVERY SYSTEM

Table 2: is showing ideal properties of transdermal drug delivery system

S.No.	Properties	Comments
1	Shelf life	Up to 2 yrs
2	Particle size	<40cm2
3	Dose frequency	Once in a day or once in a week
4	Aesthetic appeal	Clear or white colour
5	Packaging	Easy removal of release liner and min. no. of steps required to apply
6	Skin reaction	Non irritating and non sensitizing
7	Release	Consistent pharmacokinetic and pharmacodynamic profile over time

Care taken while applying transdermal patch

The part of the skin should be properly cleaned before application of patch. Cutting the patch destroys the drug delivery system therefore patch should not be cut. It should be made sure that the old patch is removed from the site before applying a new patch[31]. Care should be taken while applying or removing the patch because anyone handling the patch can absorb the drug from the patch. The patch should be applied accurately to the site of administration.

Methods for studying transdermal drug delivery system

It is given in Table 3[32].

Table 3: Methods for studying transdermal drug delivery system

In – vitro method	In – vivo method
Excised skin	Histology, Surface loss, Micro dialysis
Artificial membrane	Analysis of blood tissue or fluid
Release methods without a rate	Observation of pharmacological or physiological response
Limiting membrane	Physical properties of skin, Bioassays

Main components of transdermal drug delivery system

Polymer matrix

Polymer act as an backbone and important component of transdermal drug delivery systems. Polymeric materials of different classes have been used to require rate controlled drug delivery. The physicochemical properties of the drug and polymer used in the manufacture of the device act as mechanism of drug release. The criteria to be satisfied for a polymer to be used in a transdermal system are molecular weight, glass transition temperature, chemical functionality or polymer must allow diffusion and release of the specific drug, the polymer should permit the incorporation of a large amount of drug, the polymer should not react physically or chemically with the drug, polymer should be easily manufactured and fabricated into the desired product and inexpensive[33].

Drug substance

The selection of drug for transdermal drug delivery depends upon various factors.
The drug should have degree of solubility greater than 1 mg/ml in both oil and water. Melting point should be less than 200 °F for the drug[34]. Concentration gradient across the membrane is directly proportional to the log solubility of drug in the lipid phase of membrane, which in turn is directly proportional to the reciprocal of melting point. The melting point should be as low as possible to obtain the best candidates for transdermal patch[37].

Drug reservoir components

It should allow drug transport at the desired rate and compatible with the drug. The drug reservoir must possess the desired viscosity attributes to ensure reliable manufacturing process if an ointment is used. It must possess the desired adhesive and cohesive properties to hold the system together. Mineral oils, polyisobutylene, colloidal silica, HPC are the examples of drug reservoir component[33].

Backing laminates

Backing laminate function is to provide support. They prevent drug from leaving the dosage form through top. They are impermeable to drugs and also to permeation enhancers. Baking laminates should chemically compatible with the drug, enhancer, adhesive and other excipients[35].

Rate controlling membrane

Drug release from the dosage form is controlled by Rate controlling membranes in transdermal devices. Poly-2-hydroxyethyl methacrylate (PHEMA) membranes have been evaluated as rate controlling barriers for transdermal application which is discovered recently[38].

Adhesive layer

The main function of adhesive layer is it should not cause irritation, sensitization or imbalance in the normal skin flora during its contact with the skin and should stick to the skin aggressively[36].

Penetration enhancers

To enhance permeability of stratum corneum to achieve higher therapeutic levels of the drug penetration enhancers are used. They interact with structural components of stratum corneum which include proteins or lipids[35]. They change the protein and lipid packaging of stratum corneum, thus chemically modifying the barrier function which improved permeability.

Penetration enhancers mechanical methods

Iontophoresis

The application of a low level electric current either directly to the skin or indirectly via the dosage form enhance permeation of a topically applied drug[39-42].

Electroporation

The application of high voltage pulses to the skin that induce the formation of transient pores. High voltages of 100 V and short treatment durations of milliseconds are most implemented.

Microneedle-based Devices

The very first microneedle systems was invented in 1976. It consist of drug reservoir and plurality of projections which are microneedles of 50 to 100 mm long and they extend from reservoir which penetrate the stratum corneum and epidermis to administer the drug[43].

Skin Abrasion
The direct removal or disruption of the upper layers of the skin to enhance the permeation of topically applied drugs. It is a device based on techniques uses by dermatologists for superficial skin resurfacing like microdermabrasion which are used in the treatment of acne, scars, hyperpigmentaion and other skin blemishes[42].

Needle-less Injection
This method is based on firing the liquid or solid particles at supersonic speeds through the outer layers of the skin using a suitable energy source[43]. Compressed gas like helium is injected through the nozzle which contain drug particle too and the drug is permeated inside body through skin.

Ultrasound (sonophoresis and phonophoresis)
The use of ultrasonic energy to increase the transdermal delivery of solutes is the mechanism of this method. It uses low frequency ultrasound of 55 kHz for an average time of 15 seconds to inject drug inside body[44].

Laser Radiation
Direct and controlled exposure of a laser to the skin causing ablation of the stratum corneum without significantly destroying the underlying epidermis is the method of this process. The delivery of lipophilic and hydrophilic drugs is done by removal of the stratum corneum using this method[45].

Carriers or vehicles
Micro or nanocapsules
They contain multiple concentric bilayers of surfactant separated by a polar liquid medium, generally water in which the hydrophilic additives are added. Good skin affinity leading to cutaneous penetration and good hydration is created by their multi-lamellar structure and lipid core allows encapsulation of lipid additives[46].

Nanoemulsions or Sub-micron emulsions (SMEs) or Mini-emulsions
Nanoemulsion are oil-in-water emulsions having average droplet size ranging from 100 to 500 nm. They have very good stability and during storage they do not undergo phase separation. They give support to the barrier function of the skin by reducing transepidermal water loss which is shown in many studies[46].

In solid lipid nanoparticles (SLNs)
In solid lipid nanoparticles have sizes range from 50 to 1000 nm and are made by solid lipids[47]. Their main function is to protect active components against chemical degradation and modulate compound release.

Multiple emulsions
These are W/O/W emulsions constaining dispersion of a W/O emulsion in an aqueous phase under several conditions[48]. One can incorporate different water-soluble ingredients even if they are incompatible and also oil soluble additives.

Microemulsions
Microemulsions are highly effective for cutaneous delivery compared to other conventional vehicles[49].These systems are identified as transparent mixtures of water, oil and surfactants. Their properties include thermodynamically stable and optically isotropic. Their excellent solubilising properties is due to their good dermal and transdermal delivery properties.

Vesicular carriers
Liposomes
Liposomes are colloidal particles capable of encapsulating drugs and are formed as concentric biomolecular layers. Their delivery mechanism is governed with accumulation of the liposomes and associated drug in the stratum corneum and upper skin layers, with minimal drug penetrating to the deeper tissues and systemic circulation. Most effective liposomes are reported to be those composed of lipids similar to stratum corneum lipids[50], which are most likely to enter stratum corneum lipid lamellae and fuse with endogenous lipids.

Niosomes
Niosomes are carrier that has more permeability than liposomes for transdermal drug delivery hance consider much better than liposomes[52]. Niosomes are nonionic surfactants that are used as carriers for a number of drug and cosmetic applications and are in vesicles form.

Transfersomes
Transfersomes are vesicles comtaining phospholipids as their main ingredient with 10-25% surfactant like sodium cholate and 3-10% ethanol. The surfactant molecules act as "edge activators", causing ultradeformability on the transfersomes, which reportedly allows them to squeeze through channels in the stratum corneum that are less than one-tenth the diameter of the transfersome[53].

Ethosomes
Ethosomes are liposomes containing high alcohol content enhancing penetration to deep tissues and the systemic circulation[51-54]. Alcohol fluidizes the ethosomal lipids and stratum corneum bilayer lipids thus allowing the soft, malleable ethosomes to penetrate.

MISCELLANEOUS TECHNIQUES

Prodrugs and Ion-Pairs
To enhance dermal and transdermal delivery of drugs with unfavourable partition coefficients the prodrug approach is used[55]. This technique involves addition of a pro-moiety to increase partition coefficient and solubility which increase the transport of the drug in the stratum corneum. By hydrolysis esterases release the active drug thereby optimising concentration in the epidermis viable epidermis.

Vehicle – Saturated and Supersaturated Solutions
When a drug is at its highest thermodynamic activity like supersaturated solution maximum skin penetration rate is obtained. Due to evaporation of solvent or by mixing of cosolvents supersaturated solutions can occur[56].

Eutectic Systems
Solubility and hence skin penetration is influenced by melting point of a drug. According to solution theory, lower the melting point, greater the solubility of a material in a given solvent, including skin lipids. The melting point of a drug delivery system can be lowered by formation of a eutectic mixture, which is a binary system. At a constant ratio, the components inhibit the crystallization process of each other, such that the melting point of the two components in the mixture is less than that of each component alone[56].

Complexes
Cyclodextrins are large molecules, with molecular weights greater than 1000 Da, therefore it would be expected that they would not readily permeate the skin. To enhance aqueous solubility and drug stability complexation of drugs with cyclodextrins is used. Cyclodextrins contain 6, 7 or 8 dextrose molecules bound in a 1,4- configuration to form rings of various diameters. Complexation with cyclodextrins are used to increase and decrease skin penetration of drugs[56-57].

Evaluation of transdermal patch
Interaction studies
Excipients are essential constituent of all pharmaceutical formulations. Compatibility of the drug with the excipients is the factor which control the stability of a formulation. The drug and the excipients must be compatible with one another to produce a product that is stable. It is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug[58-59].

Thickness of the patch
The thickness of the drug loaded patch is measured by using a digital micrometer which also determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch[60].

Drug content
A specified area of patch is dissolved in a suitable solvent in specific volume, the solution is filtered through a filter medium and the drug content is analyzed with the suitable method like UV or HPLC technique[59].

Polariscope examination
It involve examine drug crystals from patch by polariscope. A specific surface area of patch is kept on the object slide and we have to observe whether the drug is present in crystalline or amorphous form[60].

Thumb tack test
This test is for tack property determination of adhesives. The thumb is simply pressed on the adhesive and the relative tack property is detected[60].

Percentage Elongation break test
By noting the length just before the reak point the percentage elongation break is determined. The mathematical formulae used for this method is Elongation percentage = L1-L2 ×100 L2 .Where, L1is the final length of each strip and L2 is the initial length of each strip[62].

In vitro drug release studies
The release of the drug from the prepared patches is done by the paddle over disc method or USP apparatus V. Dry films of known thickness is cut into definite shape, weight and fixed over a glass plate with an adhesive. The glass plate is placed in a 500-mL of the dissolution medium or phosphate buffer pH 7.4. The apparatus was equilibrated to 32± 0.5°C. The paddle is then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. 5- mL aliquots

sample are withdrawn at 24 hrs time interval and UV spectrophotometer or HPLC is used to analyse the sample[63].

In vitro skin permeation studies

In vitro permeation study is done in diffusion cell. Full thickness abdominal skin of male Wistar rats of weights 200 to 250g is taken. By using a electric clipper hair from the abdominal region is removed and dermal side of the skin is cleaned with distilled water to remove tissues and blood vessels. It is equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment. Then we place it on magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. By using a thermostatically controlled heater the temperature of the cell is maintained at 32 ± 0.5°C. The isolated rat skin piece is mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is replaced. Samples are filtered through filtering medium and checked in HPLC[63].

Skin Irritation study

Healthy rabbits of average weight 1.2 to 1.5 kg are taken and skin irritation and sensitization testing is performed. The dorsal surface 50cm2 area of the rabbit is cleaned, hairs are removed from the clean dorsal surface by shaving and cleaning the surface by rectified spirit and the representative formulations is applied over the skin. The patch is removed after 24 hr and the skin is observed and classified into 5 grades on the basis of the severity of skin injury[60].

Stability studies

According to the ICH guidelines, stability studies are conducted in which samples are stored at 40±0.5°c and 75±5% RH for 6 months. The samples are taken at 0,30,60,90,180 days and drug content is analyzed[60].

Future of transdermal therapy

Ten years ago, the nicotine patch had revolutionized smoking cessation; patients were being treated with nitroglycerin for angina, clonidine for hypertension, scopolamine for motion sickness and estradiol for estrogen deficiency, all through patches. At that time, biotech medicinal was still being developed. During the past decade, the number of drugs formulated in the patches has hardly increased, and there has been little change in the composition of the patch systems. Modifications have been mostly limited to refinements of the materials used. The reason is the only a limited number of drugs fit the molecular weight, and potency requirements for transdermal absorption. The total approved transdermal patches are shown in Figure 2.

worldwide market growth of transdermal patches

It is given in Figure 3.

CONCLUSION

Since 1981, transdermal drug delivery systems have been used as safe and effective drug delivery devices. Their potential role in controlled release is being globally exploited by the scientists with high rate of attainment. If a drug has right mix of physical chemistry and pharmacology, transdermal delivery is a remarkable effective route of administration. Due to large advantages of the TDDS, many new researches are going on in the present day to incorporate newer drugs via the system. A transdermal patch has several basic components like drug reservoirs, liners, adherents, permeation enhancers, backing laminates, plasticizers and solvents, which play a vital role in the release of drug via skin. After preparation of transdermal patches, they are evaluated for physicochemical studies, in vitro permeation studies, skin irritation studies, animal studies, human studies and stability studies. But all prepared and evaluated transdermal patches must receive approval from FDA before sale. Future developments of TDDSs will likely focus on the increased control of therapeutic regimens and the continuing expansion of drugs available for use. Transdermal dosage forms may provide clinicians an opportunity to offer more therapeutic options to their patients to optimize their care.

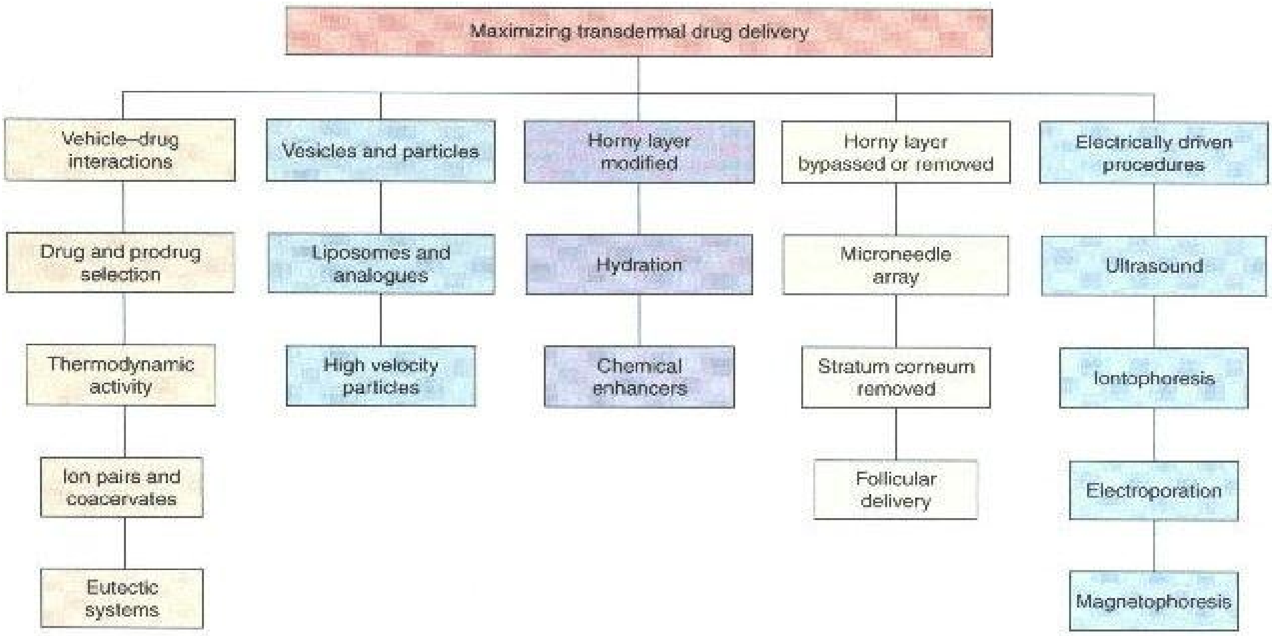

Fig. 1: Mechanisms of enhancement of transdermal delivery system

Currently Approved TDDS

Year	Generic (Brand) Names	Indication
1979	Scopolamine (Transderm Scop®)	Motion sickness
1984	Clonidine (Catapress TTS®)	Hypertension
1986	Estradiol (Estraderm®)	Menopausal symptoms
1990	Fentanyl (Duragesic®)	Chronic pain
1991	Nicotine (Nicoderm®, Habitrol®, Prostep®)	Smoking cessation
1993	Testosterone (Androderm®)	Testosterone deficiency
1995	*Lidocaine/epinephrine (Iontocaine®)*	Local dermal analgesia
1998	Estradiol/norethindrone (Combipatch®)	Menopausal symptoms
1999	Lidocaine (Lidoderm®)	Post-herpetic neuralgia pain
2001	Ethinyl estradiol/norelgestromin (OrthoEvra®)	Contraception
2003	Estradiol/levonorgestrel (Climara Pro®)	Menopause
2003	Oxybutynin (Oxytrol®)	Overactive bladder
2004	*Lidocaine/ultrasound (SonoPrep®)*	Local dermal anesthesia
2005	Lidocaine/tetracaine (Synera®)	Local dermal analgesia
2006	*Fentanyl/iontophoresis (Ionsys®)***	Acute postoperative pain
2006	Methylphenidate (Daytrana®)	ADHD
2006	Selegiline (Emsam®)	Depression
2007	Rotigotine (Neupro®)**	Parkinson's disease
2007	Rivastigmine (Exelon®)	Dementia
2008	Granisetron (Sancuso®)	Chemo-induced emesis
2009	*Oxybutynin (Gelnique®)*	Overactive bladder
2010	Buprenorphine (Butrans®)	Chronic pain

Fig. 2: Transdermal drugs with their uses

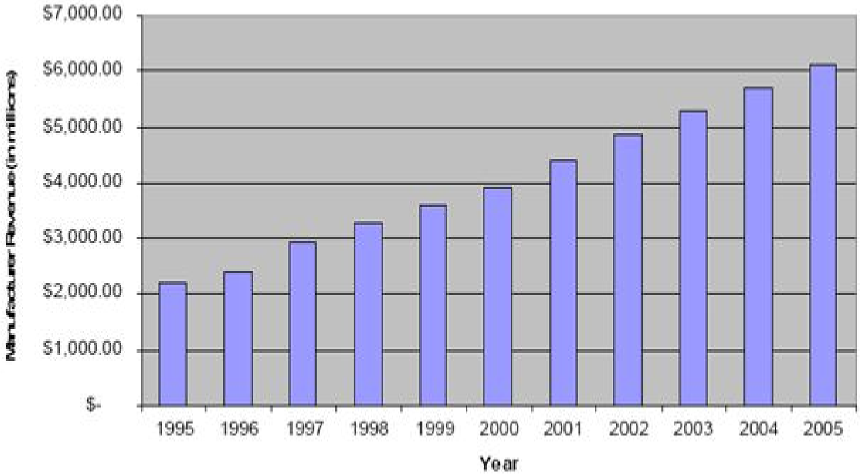

Fig. 3: Worldwide market growth of transdermal patches

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