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Transdermal patches: A review

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Abstract
The transdermal drug delivery system is one of the novel drug delivery system which overcome the problems arises from conventional dosage forms. Transdermal drug delivery has a major role in increasing patient compliance and avoiding first pass metabolism. It is one of the alternative method for oral route of drug administration. This review gives valuable information about the TDDS like its advantages, disadvantages, types of TDDS, different methods for formulation, and different methods of evaluation of transdermal patches.

Keywords: transdermal drug delivery system (TDDS), vapour patch, evaluation

Introduction
Transdermal drugs are self-contained discrete dosage form that is used to deliver a drug into the systemic circulation across the skin. It provide a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy. Transdermal patches were developed in the 1970's and the first transdermal system, Transderm Scop (ciba, now Novartis) was approved by Food and Drug Administration (FDA) in 1979 for prevention of nausea and vomiting associated with travel, particularly by sea [1].

Definition
A Transdermal patch is a medicament adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream [2].

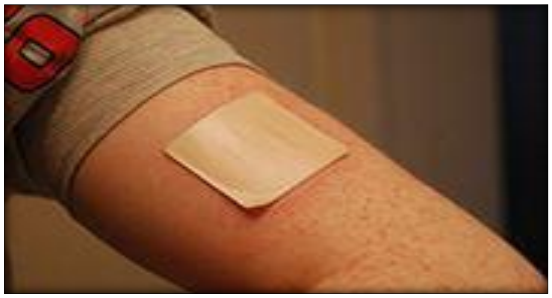

Fig 1: Transdermal patch

Advantages
1. Avoidance of first pass metabolism of drugs.
2. Reduced plasma concentration levels of drugs, with decreased side effects.
3. Reduction of fluctuations in plasma levels of drugs, Utilization of drug candidates with short half- life and low therapeutic index.
4. Reduction of dosing frequency an enhancement of patient compliance.
5. Transdermal medications deliver a steady infusion of a drug over an extended period of time.
6. It increases the therapeutic value of many drugs via avoiding specific problems associated with the drug like GI irritation, lower absorption, decomposition due to 'hepatic first pass' effect.
7. Easy elimination of drug delivery during toxicity.

Disadvantages
1. Possibility of local irritation such as erythmea, itching, and local edema at the site of application.
2. The number of drugs that can be delivered in this manner is limited because of low permeability of the skin [3].

Conditions in which the transdermal patches are not used
- The transdermal patch is not suitable when, treatment of acute pain.
- Where rapid dose irritation is required.
- Where the required dose is equal to or less than 30 mg/24 hours.

Limitations
- TDDS cannot deliver ionic drugs.
- TDDS cannot achieve high drug levels in blood/plasma.
- It cannot develop for drugs of large molecular size.
- TDDS cannot deliver drugs in a pulsatile fashion.
- TDDS cannot develop if drug or formulation causes irritation to skin [4].

Care taken while applying transdermal patch
- The part of the skin where the patch is to be applied should be properly cleaned.
- The patch should not be cut, because it destroys the drug delivery.
- The old patch should be removed before applying new patch.
- Don't touch the adhesive layer before application by hand itself or by other things it may produce changes in release rate & bioavailability.
- Then the patch is placed accurately to the site of application [5].

Uses of transdermal patches

1) It is an alternative method of drug delivery when the patient has intolerable side effects (including constipation) and who is unable to take oral medication (dysphagia).
2) Where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self-medicate with their analgesia.
3) It can be used in combination with other enhancement strategies to produce synergistic effects [6].

Types of transdermal patches

i) Single-layer Drug-in-Adhesive

The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

ii) Multi-layer Drug-in-Adhesive

It is similar to the single-layer system in that the drug is incorporated directly into the adhesive. The multi-layer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing [7].

iii) Drug Reservoir-in-Adhesive

Unlike the Single-layer and Multi-layer Drug-inadhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer.

iv) Drug Matrix-in-Adhesive

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it [8].

v) Vapour Patch

In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are new on the market and they release essential oils for up to 6 hours. The vapour patches release essential oils and are used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market [9].

Various methods for preparation of TDDS

i) Circular teflon mould method (Baker and Heller 1989)

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. To this solution plasticizer is added. The total contents are to be stirred and then poured into a circular teflon mould. And rate of solvent vaporization controlled with placing inverted glass funnel on teflon mould. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored in a desiccators [10].

ii) Asymmetric TPX membrane method (Berner and John 1994)

A prototype patch can be fabricated by a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive21 [11].

iii) Mercury substrate method

In this method required amount of drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for some time to produce a homogenous dispersion and it is keep aside until air bobbles removed completely and then poured in to a glass ring which is placed over the mercury surface in a glass petri dish covered with inverted funnel to control solvent evaporation. The dried films are to be stored in a desiccators [12].

iv) "IPM membranes" method

In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymers and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. If the drug solubility in aqueous solution is very poor, Buffer pH 7.4 can be used in order to obtain solution gel. The formed gel will be incorporated in the IPM membrane [13].

v) "EVAC membranes" method

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol; carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device [14].

vi) Aluminium backed adhesive film method

If the loading dose is greater than 10 mg transdermal drug delivery system may produce unstable matrices. Aluminium backed adhesive film method is a suitable one. For it's preparation, chloroform is used as the choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custom made aluminum former is lined with aluminum foil and the ends blanked off with tightly fitting cork blocks.

vii) Glass Substrate Method

The polymeric solutions are kept a side for swelling then required quantity of plasticizer and drug solution are added and stirred for 10 min. Further, it is set-a side for some time to exclude any entrapped air and is then poured in a clean and dry anumbra petriplate. The rate of solvent evaporation is controlled by inverting a glass funnel over the petriplate. After overnight, the dried films are taken out and stored in a desiccators [15].

Evaluation of transdermal patches

Physicochemical evaluation

Thickness: The thickness of transdermal film is determined by travelling microscope, dial gauge, screw gauge or micrometer at different points of the film.

Uniformity of weight

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight [16].

Drug content determination

It can be determined by completely dissolving a small area (1 cm 2) of polymeric film in suitable solvent of definite volume. The solvent is selected in which the drug is freely soluble. The selected area is weighed before dissolving in the solvent. The whole content is shaken continuously for 24 h in a shaker incubator followed by sonication and filtration. The drug in solution is assessed by appropriate analytical method [17].

Content uniformity test

The test is carried out by performing assay to find out the content of drug material contained in polymeric film of the patch. If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity [18].

Moisture content

The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight [19]. The percent moisture content is calculated using following formula,

$$\% \text{ moisture content} = \frac{(\text{Initial weight} - \text{final weight}) * 100}{\text{Final weight}}$$

Flatness

A transdermal patch should possess a smooth surface and should not constrict with time.For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness [20].

Folding Endurance

It involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking gives the folding endurance value [21].

***In-vitro* drug release studies**

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches

***In-vitro* skin permeation studies**

An *In vitro* permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male wistar rats weighing 200 to 250 g. Hair from the abdominal region is to be removed carefully by using an electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in diffusion medium or phosphate buffer pH 7.4 before starting the experiment pared patches [22, 23].

***In-vivo* studies**

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 and Human volunteers [24].

Table 1: Transdermal patches available in the market currently

Brand name	Drug	Indication
Alora	Estradiol	Postmenstrual syndrome
Androderm	Testosterone	Hypogonadism in males
Catapress	Clonidine	Hypertension
Habitraol	Nicotine	Smoking cessation
Minitran	Nitroglycerine	Angina pectoris
Nicoderm	Nicotine	Smoking cessation
Testoderm	Testosterone	Hypogonadism in males

Conclusion

The transdermal drug delivery system has been used as safe and effective drug delivery devices since 1981.It has been designed as an alternative, safest, and easy route for systemic drug delivery. It promises to eliminate needles for administration of a wide variety of drugs in the future. This article gives valuable information about the formulation and evaluation of transdermal patches. We can overcome the challenges associated with current popular drug delivery by formulating the drug as transdermal patches. Some advanced techniques are also developed in TDDS, so TDDS is the next generation of drug delivery system.

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