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REVIEW ARTICLE **OPEN ACCESS**

A REVIEW ON NANO PARTICULATE TRANSDERMAL PATCHES OF SIMVASTATIN

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ABSTRACT

Transdermal drug delivery system was conferred to beat the difficulties of drug delivery particularly oral route. A skin patch may be a medicated adhesive patch that's placed on the membrane to deliver a selected dose of medication through the membrane associated into the bloodstream. It promotes healing to a disabled space of the body. a plus of a trans dermic drug delivery route over alternative varieties of delivery system similar to oral, topical, IV, IM and so forth is that the patch provides a controlled unharness of the medication into the patient, sometimes through either a porous membrane covering a reservoir of medication or through body heat melting skinny layers of medication embedded within the adhesive. The most disadvantages to Trans dermic delivery systems stems from the skin may be a very effective barrier, as a result, solely medications whose molecules are little will simply penetrate the skin, and thus it is delivered by this technique. This critical review describes the introduction of transdermal patches as well as style of transdermal patches, method of preparation of transdermal patches and issue moving and so forth.

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INTRODUCTION

Oral rout is that the most known course of drug transport appliance but it'sa number of negative aspects alongside1st by skip metabolism, drug degradation so on in digestive tractowing to enzymes, hydrogen ion concentration and so on. To conquer those problems, a singular drug transport gadget changed into evolved with the help of mistreatment Chien in 1992, Banker in 1990, Guy in 1996. It turned into stratum patches or stratum transport gadget. During this gadget medicated adhesive patches are organized that provide therapeutically powerful amount of drug throughout the pores and skin while it set on pores and skin. They're to be had in one in every ofa sort sizes & having one or two of ingredient. Once they follow on unbroken pores and skin they provide energetic parts into general flow into passing through pores and skin barriers. A padcontaining excessive dose of drug internal that's preserved at the pores and skin for extended length of time, that get enters into blood glide thru diffusion process.

Drug can penetrate through skin via three pathways

- Through hair follicles.
- Through sebaceous glands.
- Through sweat duct.

Transdermal drug delivery systems are employed invaried skin disorders, conjointly with in the management of angina pectoris, pains, smoking stop &medical specialty disorders corresponding to Parkinson's unwellness (Arti Kesharwani *et al*., 2013; Sampath Sampath Kumar *et al*., 2010).

Limitation of TDDS

- Ionic medicines can't be delivered using TDDS.
- High drug levels in the blood or plasma cannot be reached with TDDS.
- It cannot grow for medications with big molecular weights.

- Cardiac drug delivery is not possible with TDDS.
- If a medication or formulation irritates the skin, TDDS cannot occur.

Popular uses

- The nicotine patch, which distributes nicotine in regulated dosages to aid in quitting smoking, is the most popular transdermal patch in the US. In Europe, the first vaping patch for quitting smoking was authorised in 2007.
- Fentanyl (sold under the brand name Duragesic) and buprenorphine are two opioid drugs that are frequently used in patch form to treat chronic pain (marketed as BuTrans).
- Menopausal symptoms and post-menopausal osteoporosis may both be treated with oestrogen patches.
- The contraceptive patch is one of the additional transdermal patches for hormone administration (marketed as Ortho Evra or Evra).
- In certain cases, nitro-glycerine patches rather than sublingual tablets are recommended for the treatment of angina.
- Under the trade name Catapres-TTS, clonidine, an antihypertensive medication, is offered as a transdermal patch.

Situations where transdermal patches are applied

When a transdermal patch is applied

- When a patient needs an alternate drug delivery mechanism because they are experiencing unbearable side effects, such as constipation, and they are unable to swallow oral medications due to dysphagia.
- Situations in which effective management might result in better pain control. Patients with cognitive impairment or those who are unable to self-medicate with their analgesics for other reasons may find this helpful.
- It may be used with other enhancement techniques to have a multiplicative impact.

Conditions when transdermal patches shouldn't be used

Transdermal patches should not be used when:

- Acute pain must be treated.
- When a quick dosage titration is necessary.
- When the dosing needed is 30 mg or less per 24 hours (Dipen Patel, 2012)

Types of TDDS

Single-layer Drug-in-Adhesive System: In this sort of patch the adhesive layer of this method contains the drug. The adhesive layer not solely serves to stick the varied layers together, at the side ofthe whole system to the skin, howeverit'sadditionallychargeable for the cathartic the drug. The adhesive layer is enclosed by a brief liner and a backing.

Reservoir System: In this System the drug reservoir is unbroken in between backing layer and a rate dominant membrane. And drug releases through micro porous rate controlled membrane. Drug may bewithin thestyle of a solution, suspension, or gel or distributedduring a solid chemical compound matrix in the reservoir compartment.

Matrix System

Drug-in-Adhesive System: For the formation of drug reservoir, the drug distributed in Associate in nursing adhesive compoundthen spreading the medicated polymer adhesive by solvent casting or by melting the adhesive (in the case of hot-melt adhesives) on to an resistant backing layer.

Matrix-Dispersion System: In this system the drug is spread homogeneously Associate in Nursingexceedingly in a very hydrophilic or lipotropiccompound matrix. And this containing polymer in conjunction with drug is fastened onto an occlusive base plate in a compartment fictional from a drug- impervious backing layer. During this system the adhesive is spread on the circumference rather than applying on the face of drug reservoir to create a strip of adhesive rim (Saurabh Pandey *et al*., 2013).

Micro-Reservoir System: This system may be a combination of reservoir and matrix- dispersion systems. Within which drug is suspended during ansolution of solublechemical compoundand so dispersing the answer homogeneously in a oleophilic polymer to make thousands of unreachable, microscopic spheres of drug reservoirs (Gaur, 2009).

Ideal Product Requirements

- Up to two years of shelf life.
- Small patch (less than 40 cm2) and practical dosage frequency (i.e., once a day to once a week).
- Appearance-wise acceptable (i.e., clear, white color).
- Simple packaging (i.e., fewer stages and pouches needed to apply the solution)
- simple release liner removal (i.e., for children and elderly patients)
- No residue (i.e., "cold flow" around the border of the patch in storage or after application to skin or under the patch after removal) Adequate skin adhesion (i.e., no slip off during the dosing interval and simple removal without skin harm)
- No leftover material, i.e., "cold flow" around the patch's edge during storage, after application to the skin, or underneath the patch following removal.
- No dermal responses that are unsatisfactory (i.e., contact dermatitis, skin sensitization, photo toxicity, photosensitization, erythema, itching, stinging, burning, etc.).
- Consistent biopharmaceutical performance, or the ability to precisely predict the requisite pharmacokinetic and pharmacodynamic response in the same subjects throughout time and among people (Gaur, 2009)

Components of TDDS

- Polymer matrix/ Drug reservoir
- Drug
- Permeation enhancers.
- Pressure sensitive adhesive (PSA).
- Backing laminate.
- Release liner.
- Other excipients like plasticizers and solvents (Vandana Yadav, 2012).

Polymer Matrix/ Drug Reservoir: It is prepared by dispersing the drug in liquid or solid state artificialchemical compound base. It should have biocompatibility and chemical compatibility with the drug and differentparts of the system like penetration enhancers. In addition, they mustgive consistent and effective delivery of a drug throughout the product's meanttime periodand may be of safe status.

Polymers utilized instratum drug delivery systems are classified as

- **Natural Polymers:** e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.
- **Synthetic Elastomers:** e.g. polybutadiene, hydrin rubber, silicon rubber, polyisobutylene, acrylonitrile, neoprene, butyl rubber etc.
- **Synthetic Polymers**: e.g. polyvinylalcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate etc. (Nikhil Sharma, 2012; Saurabh Pandey).

Drugs: Some of ideal properties of drug & some factors to be contemplatethroughout preparation of transdermal patches are as follows:

Permeation Enhancers: The chemical compounds that enhance the permeableness of horny layerthuson attain therapeutic levels of the drug candidate. They improve the permeability by interacting with Stratum corneum. a) Ideal Properties of Permeation Enhancers

- They should be non-irritating, non-toxic & non- allergic.
- They should not bind to receptor site i.e. not showing any pharmacological activity.
- They should be cosmetically acceptable with an appropriate skin feel (Kamal Gandhi, 2011)

Pressure Sensitive Adhesive (PSA): It helps to increase the adherence of transdermal patch to the skin surface. It can easily remove from the smooth surface without leaving a residue on it.

- Polyacrylates
- Polyisobutylene
- Silicon based adhesives

Methods of Preparation of TDDS

- Asymmetric TPX membrane method. b) Circular Teflon mould method.
- Mercury substrate method.
- By using "IPM membranes" method.
- By using "EVAC membranes" method.
- Preparation of TDDS by using Pro-liposomes.
- By using free film method.

Asymmetric TPX Membrane Method: This technique was discovered by Berner Associate in Nursing John in 1994. By this method model patch will beready by victimization heat sealable polyester film (type 1009, 3m) with a dished of 1cm diameter because the backing membrane. Drug distributed on concave membrane, coated by a TPX (poly (4-methyl-1- pentene)) uneven membrane, and sealed by an adhesive.

Preparation: These are made by using a method called dry or wet inversion. In this, TPX is converted to a polymer solution by dissolving it at 60 °C in a mixture of solvent (cyclohexane) and non-solvent additives.

SR/NO.	PARAMETERS	PROPERTIES
1	Dose	Should be low in weight
2	Half life	10/less (hrs.)
3	Molecular weight	Greater than 400da
4	Skin permeability coefficient	Less than 0.5*10-3cm/h
5	Skin reaction	Non-irritating, non-sensitizing
6	Oral bioavailability	Low

Some Transdermal Drugs for Systemic Delivery Launched in the USA and EU (Pastore et al.,2015)

Drug (Trade name, year of FDA Approval)	Type	Indication	Patch Design	Site of Application	Duration of Application
Buprenorphine (Butrans®, 2010)	Therapeutic	Chronic Pain	DIA	the side of the chest, the upper back, the upper chest, or the upper outer arm	7 days
Clonidine (Catapres-TTS®, 1984)	Therapeutic	Hypertension	Reservoir/Membrane	Upper outer arm or upper chest	7 days
Oestradiol (Alora®,1996)	Therapeutic	Female HRT	DIA	Lower abdomen, the top of the buttocks, or the outside of the hip	3-4 days
Rivastigmine(Exelon®,2007)	Therapeutic	Alzheimer's & disease	Matrix	Upper/lower back, upper arm or chest	24 hr
Nicotine (Nicorette® Invisipatch®)f	OTC	Smoking Cessation	Matrix	A clean, intact, dry &hairless skin of the thigh, arm or chest	16 hr
Diclofenac epolamine (Flector®),2007	Topical	Topical treatment acute pain	DIA	The most painful area	12 hr

Backing Laminate: It is anappurtenant material that is rubber to medicine and conjointly to permeation enhancers. They ought towith chemicals compatible with the drug, enhancer, adhesive and different excipients.

Ex: Vinyl, Polyethylene and Polyester films (Ezhumalai, 2011).

Release Liner: This is the primary packaging material that can protect the patch during application. It is made up of base layer which may be

- Non-occlusive (e.g. paper fabric)
- Occlusive (e.g. polyethylene, polyvinylchloride)

It is made up of silicon or Teflon. Release liner should be chemically inert & it should be permeable to drug, penetration enhancers & water.

Other Excipients like Plasticizers and Solvents

- Solvents: Chloroform, methanol, acetone, isopropanol and dichloromethane.
- Plasticizers: Dibutylpthalate, triethyl citrate, polyethylene glycol and propylene glycol (Hiren, 2011).

The polymer solution is cast on a glass plate after being maintained at 40°C for 24 hours. The casting film is then evaporated at 50°C for 30 seconds, after which the glass plate must be immediately submerged in a coagulation bath with a constant temperature of 25°C. The membrane can be extracted after 10 minutes of soaking and allowed to air dry for 12 hours in a circulation oven at 50°C.

Circular Teflon Mould Method: In 1989, Baker and Heller made the discovery. As an organic solvent, polymeric solutions in various ratios are utilised. The answer is then split into two halves. The prescribed amount of medicine is dissolved in one portion, while varied concentrations of enhancers are dissolved in the other, and the two parts are then combined. The drug polymer solution is then given a plasticizer (such as Di-n-butyl phthalate). The entire mixture must be mixed for 12 hours before being placed into a Teflon mould with a circle shape. In order to manage solvent vaporisation in a laminar flow hood model with an air speed of 0.5 m/s, the moulds must be set on a flat surface and covered with an inverted funnel. 24 hours are given for the solvent to evaporate. A dry film was then formed and must be stored for an additional 24 h at 25 ± 0.5 °C in a desiccator containing silica gel prior to evaluation to eliminate the effects of aging.

Mercury Substrate Method: In this method, the drug and plasticizer are dissolved in the polymer solution. It was stirred for 10-15 min to

produce a uniform dispersion, after which it was poured onto a flat mercury surface, covered with an inverted funnel to control solvent evaporation.

By Using "IPM Membranes" Method: In the combination of water & polymer (propylene glycol containing Carbomer 940 polymer) drug get dispersed and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous via way of means of the addition of triethanolamine. If the drug solubility in aqueous answer could be very bad then answer gel is receivedvia way of means ofthe usage of Buffer pH 7.4. The shaped gel might beincludedwithinside the IPM membrane.

By Using "EVAC Membranes" Method*:* For the preparation of TDS, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membrane is wanted as pricemanages membrane. If the drug is insoluble in water then use propylene glycol for gel guidance. Drug is dissolved in propylene glycol, carbopol resin may bedelivered to the above answer and neutralized via way of means ofthe usage of 5% w/w sodium hydroxide answer. The drug (in gel form) is located on a sheet of backing layer over layingthe desired area. A price controlling membrane may belocated over the gel and the rimsmay be sealed via way of means of warmth to acquire a leak evidence device. Aliquot of the organic solution is introduced into the sphericalbell-bottom flask at 37°C, when complete drying second aliquots (0.5ml) of the {answer} is to be added. Afterthe last loading, the flask Preparation of TDDS by victimization Proliosome: By carrier methodology using film deposition technique pro-liposomes are prepared. Drug and phospholipidmagnitude relationought to be 0.1:2.0 taken as an optimized one from previous references. For the preparation of proliosome in 100ml round bottom flask take 5mg of diuretic powder, then it'sunbroken at 60-70°c temperature and therefore the flask is turned at 80-90 rate and dried the mannitol at vacuum for thirty minutes. when drying, the temperature of the water bathtub is adjusted to 20- 30°C.

Drug and lecithin are dissolved during aappropriate organic solvent mixture, a 0.5ml containing pro-liposomes are connected in a lyophilized and later on drug loaded diuretic powders (proliosome) are placed in a desiccator night long then sieved through a hundred mesh. The collected powder is transferred into a glass bottle and hold on at the freeze temperature till characterization. During this method first of all cellulose ester free film is ready by casting it on mercury surface. And 2% w/w compound answer is prepared by using chloroform. Plasticizers are to be admixed at an amount of 40% w/w of compound weight. Then five mil of polymer answer is poured during a glass ring that is placed over the mercury surface in a glass Petridis. The speed of evaporation of the solvent will be controlled by putting an inverted funnel over the Petridis. The film formation is noted by perceptive the mercury surface when complete evaporation of the solvent. The dry film will be separated out and hold on between the sheets of paper in a desiccator till use. By this method we will prepare free films of various thickness will beready by dynamic the amount of the compound answer (Ashok Kumar, 2010; MdIntakhab Alam, 2013).

Factors Affecting Transdermal Patches

There are various factors which affects the action of transdermal patches. These are given below:

Physicochemical Properties

- Partition coefficient
- Molecular size
- Solubility/melting point
- Ionization

Physiological & Pathological Conditions of Skin

- Reservoir effect of horny layer
- Lipid film
- Skin hydration
- Skin temperature
- Regional variation
- Pathological injuries to the skin
- Cutaneous self-metabolism
- Skin barrier properties in the neonate and young infant
- Skin barrier properties in aged skin (14)

Advantages

- 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 (15,16).

Disadvantages

- Chances of allergic reactions at the site of application like-itching, rashes, local 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 (17,18).

Simvastatin

Simvastatin (SMV) is a lipid-lowering medication (statin). Previous research suggested that statins may have anti-inflammatory properties distinct from their lipid-lowering effect. (19,20)As a result, statins may potentially have an impact on a variety of inflammatory disorders. According to the Biopharmaceutics Classification System (BCS), SMV is a Class II medication with low bioavailability (5%) due to its slow rate of solubility and first pass metabolism. (21,22) SMV's poor oral bioavailability must be improved, which requires an increase in solubility.(23)

Nano Particles: Particulate dispersions or solid particles with a size between 10 and 1000 nm are referred to as nanoparticles. The medication is broken down, confined, encapsulated, or joined to a nanoparticle matrix. Depending on the preparation technique, one can produce nanoparticles, nanospheres, or nano-capsules. Nanospheres are matrix systems in which the drug is physically and evenly spread, whereas nano-capsules are systems in which the drug is contained to a cavity and enclosed by a special polymer membrane. Biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymers like poly(ethylene glycol), or "long-circulating particles," have gained popularity in recent years,have been considered as possible drug delivery systems because to their capacity to transport proteins, peptides, and genes as well as their capacity to circulate for an extended length of time and target a specific organ. (24-27)

Advantages of Nanoparticles

- After parenteral delivery of a medication, passive and active drug targeting may be accomplished by simply changing the particle size and surface properties of nanoparticles.
- By adding targeting ligands to the surface of the particles or by using magnetic guiding, site-specific targeting may be accomplished.

- The system may be employed for a variety of delivery methods, such as intra-ocular, nasal, parenteral, and oral.(28)

Limitation of Nanoparticles

- Physical handling of nanoparticles in liquid and dry forms can be challenging due to particle aggregation caused by small size and vast surface area.
- Large surface area and tiny particle size also easily lead to burst release and little drug loading. Before nanoparticles may be employed clinically or made commercially available, several practical issues must be solved.(29,30)

Clinical trials, Marketed Products, and Analyses (31): According to a search done in December 2019 (Watkinson, 2013), ClinicalTrials.gov currently has over 900 trials that use the word "transdermal" in their description. Unfortunately, the same four drugs (nicotine, oestradiol, fentanyl, and testosterone) are the subject of many trials, and the fact that most of the trials focus on a small number of drugs is not surprising given the exclusive nature of marketed transdermal drugs, the selective nature of the skin as a barrier to diffusion, and the physicochemical and pharmacokinetic properties of marketed transdermal drugs (Watkinson, 2013). In addition, a lot of the case studies deal with chronic pain and nausea, or they examine the effects of different pharmaceuticals when given through different delivery methods like injections or lozenges versus patches. In addition to their different pharmacokinetic characteristics, certain transdermal medicines for systemic distribution that have been introduced in the USA and EU are listed in Table 2 and Table 3, respectively (Pastore et al., 2015). These tables highlight additional criteria for marketed passive transdermal candidates as well as potential constraints.

CONCLUSION

Since the first TDP and 3DP were introduced over 40 and 30 years ago, respectively, it is clear that there is room for innovation in drug delivery methods in the pharmaceutical industry. Here, a review of TDD systems and an analysis of the potential advantages of 3DP for drug delivery methods are presented. Particularly, patients can switch from the "one size fits all" strategy to a more personalised approach by using bespoke formulation options. Despite all the research, 3DP of API formulations and TDD systems are still in their early stages because many regulatory concerns must be resolved before the techniques are widely used and because many medications continue to be unsuitable for them. As methods to create MN or micro molds for MN castings, inkjet and photopolymerization-based technologies have dominated. The advantages of 3DP over current or dispersible or hypodermic delivery are highlighted in published research. The former and latter lessen the negative effects of metabolism and bioavailability and the invasive and waste-producing injections, respectively. The pharmaceutical business is aware of the benefits and drawbacks of 3DP, so it is critical that AM is efficiently incorporated into pharmaceutical manufacturing so that its advantages can be quickly felt in patient healthcare.

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