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TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

A Transdermal Patch is a Medical Adhesive Patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. First-generation transdermal delivery has delivered small, lipophilic, low dose drugs. Second-generation transdermal delivery has used ultrasound, iontophoresis and chemical enhancers in delivering the drug. Third-generation transdermal delivery has used microneedles, electroporation, thermal ablation, microderm abrasion, in topical application. The main aim of transdermal drug delivery system is to deliver the drug into systemic circulation with minimal inter and intra subject variability.

KEYWORDS: Transdermal skin, permeation enhancers, evaluation studies.

INTRODUCTION

Transdermal Drug Delivery Systems Transdermal drug delivery systems are topically administered medicaments in the form of patches that deliver the drugs for systemic effects at a predetermined and controlled rate. As it is one of the most promising methods for drug application. Transdermal delivery of drugs through the skin to the systemic circulation provides a suitable route of administration for a variety of clinical indication.[1] Delivery of drugs through the skin for systemic effect, called transdermal delivery was first used in 1981, when Ciba-Geigy +marketed Transdermal V (present day marketed as Transderm Scop) to prevent the nausea and vomiting associated with motion sickness. Once they apply on unbroken skin they deliver active ingredients into systemic circulation passing via skin barriers.[2] A transdermal patch containing high dose of drug inside which is retained on the skin for prolonged period of time, which get enters into blood flow via diffusion process. Drug can penetrate through skin via three pathways) through hair follicals. b) Through sebaceous glands. c) Through sweat duct. Transdermal drug delivery systems are used in various skin disorders, also in the management of angina pectoris, pains, smoking cessation & neurological disorders such as Parkinson's disease.[3]

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.

DISADVANTAGES

- 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
- Skin permeability is also a limiting factor
- Drugs requiring higher blood levels are difficult to formulate as transdermal drug delivery systems. May lead to skin irritation and allergic response.

TYPES OF TRANSDERMAL PATCH

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.[4]

Multi-layer Drug-in-Adhesive: The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. 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.[5]

Reservoir: Unlike the Single-layer and Multi-layer Drug-in adhesive 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.[6]

Matrix: 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.

Vapour Patch: In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour.[7] 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.[8]

VARIOUS METHODS FOR PREPARATION OF TDDS

Circular Teflon mould method: 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. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Plasticizer (e.g., Di-N-butylphthalate) is added into the drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular Teflon mould.[9] The moulds are to be placed on a levelled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 h. The dried films are to be stored for another 24 h at 25±0.5°C in a desiccators containing silica gel before evaluation to eliminate aging effects. These types of films are to be evaluated within one week of their preparation.[10] Films were cast from organic and aqueous solvents using various bioadhesive polymers namely: sodium carboxymethyl cellulose (Na-CMC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC) and Carbopol 934. The prepared films were subjected to investigations for their physical and mechanical properties, swelling behaviours, in-vitro bioadhesion, drug permeation via bovine buccal mucosa and in-vitro drug release.[11] These properties were found to vary significantly depending on the preparation methods, the type of the polymers and the ratio of addition of both plasticizer (i.e. polyethylene glycol) and film forming agent (ethyl cellulose and polyvinylpyrolidene). The obtained results indicated that the concentration of ketorolac in the oral cavity was maintained above 4.0 µg/mL for a period of at least 6 h. This film showed promising results for using the ketorolac buccoadhesive route of administration topically and systemically.

Asymmetric TPX membrane method: A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be 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 adhesive. These are fabricated by using the dry/wet inversion process. TPX is dissolved in a mixture of solvent (cyclohexane) and nonsolvent additives at 60°C to form a polymer solution. The polymer solution is kept at 40°C for 24 hrs and cast on a glass plate to a pre-determined thickness with a gardner knife.[12] After that the casting film is evaporated at 50°C for 30 sec, then the glass plate is to be immersed immediately in coagulation bath (maintained the temperature at 25°C). After 10 minutes of immersion, the membrane can be removed, air dried in a circulation oven at 50°C for 12 h. Membranes, fabricated by the dry/wet inversion method, were applied to transdermal delivery of nitroglycerin (NTG), a drug for treating angina pectoris. The flux of NTG through the TPX membrane was measured in-vitro by a Franz cell. The results indicated that the NTG flux through asymmetric TPX membranes is strongly dependent on the membrane structure, which can be varied by adding non solvents in the casting solution. By adding different kinds of non-solvents and adjusting the added amounts, membranes with different NTG-release rate can be fabricated. It was also found that, with suitable drug formula, the NTG dissolution rate of a prototype TPX patch is comparable to that of a commercial patch, Transderm-Nitro.[13]

Mercury substrate method: The drug is dissolved in polymer solution along with plasticizer. It is followed by stirring for 10 - 15 minutes to produce a homogenous dispersion and poured into a levelled mercury surface, covered with inverted funnel to control solvent evaporation have studied that transdermal matrix type patches of terbutaline sulphate were fabricated using ethyl cellulose and cellulose acetate polymer. The transdermal patches of terbutaline sulphate were prepared by solvent casting technique employing a mercury substrate. In the present investigation various polymeric transdermal patches of terbutaline sulphate were prepared. The effect of permeability enhancer on the permeability of drug from cellulose acetate and ethyl cellulose patches was studies. The polymeric combinations showed good film forming properties and the method of casting on mercury substrate was found to give good films have studied transdermal patches containing glibenclamide (1.06 % w/v, i.e. 13.5 mg/cm^2) were prepared by solvent castine technique employing mercury as substrate to formulate transdermal patches using Eudragit RL 100, Eudragit RS 100, Polyvinyl pyrollidone (PVP) as polymers, glycerol and propylene glycol as a plasticizers and Span 80 as a permeation enhancer by solvent casting method. The formulation containing Eudragit RL 100 with propylene glycol as plasticizer showed complete and prolonged release with 98.02 % at the end of 24 h.[14]

"IPM membranes" method: The drug is dispersed in a mixture of water and propylene glycol containing carbomer-940 polymers and stirred for 12 h in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of tri-ethanolamine. Buffer (pH 7.4) can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM (isopropyl myristate) membrane have studied the drug-in-adhesive transdermal patch and evaluated for the site-specific delivery of anastrozole. Different adhesive matrixes, permeation enhancers and amounts of anastrozole were investigated for promoting the passage of anastrozole through the skin of rat in-vitro. The best skin permeation profile (in-vitro) was obtained with the formulation containing DURO-TAK® 87-4098 (pressure sensitive adhesive), IPM 8% and anastrozole 8%. For local tissue disposition studies, the anastrozole patch was applied to mouse abdominal skin, and blood, skin, and muscle samples were taken at different times after removing the residual adhesive from the skin. High accumulation of the drug in the skin and muscle tissue beneath the patch application site was observed in mice and compared with that after oral administration. These findings showed that anastrozole transdermal patches were an appropriate delivery system for application to the breast tumour region for site-specific drug delivery to obtain a high local drug concentration.[15]

"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 have studied the irritation of transdermal devices delivering levonorgestrel and the permeation enhancer ethyl acetate with or without ethanol were evaluated in rabbits. Erythema and oedema were assessed 24, 48 and 72 h and 7 days after application of the 24-h delivery system. The devices were found to be mild to moderately irritating, with erythema the primary manifestation. No differences were observed between devices using pure ethyl acetate or ethyl acetate-ethanol (7:3 v/v) as enhancers. Devices using pure ethanol as an enhancer gave levels of irritation similar to those using ethyl acetate ethanol or pure ethyl acetate.[16]

Evaluation of Transdermal Patches: Development of controlled release transdermal dosage form is a complex process involving extensive research. Transdermal patches have been developed to improve clinical efficacy of the drug and to enhance patient compliance by delivering smaller amount of drug at a predetermined rate. This makes evaluation studies even more important in order to ensure their desired performance and reproducibility under the specified environmental conditions. These studies are predictive of transdermal dosage forms and can be classified into different types including physicochemical evaluation, in-vitro evaluation, and in-vivo evaluation. After the successful evaluation of physicochemical and in-vitro studies, in-vivo evaluations may be conducted.

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.

Drug content determination: It can be determined by completely dissolving a small area ($1cm^2$) 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 applied as the gold standard to determine chemically the content of active constituent for each unit dose. The test is completed by performing assay to find out the content of drug material contained in polymeric film of the patch. According to USP the procedure consists of two stages. First stage consists of assaying the randomly selected ten units. It is followed by second stage to be performed on twenty more units when the first stage fails. Initially ten patches are selected and content is determined for individual patches. Test passes when all 10 unit doses have content ≥ 85 % and ≤ 115 % (RSD < 6%). 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. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If RSD of all the 30 units is < 7.8%, not more than one value is outside 85–115%, and no value is outside75–125%, the batch passes the test if not fails the test.

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.

Moisture Uptake: Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated.[18]

Flatness: A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. 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.

L2 = Final length of each strip
L1 = Initial length of each strip

Folding Endurance: Evaluation of folding endurance 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.

Tensile Strength: To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation. 'F' is the force required to break; 'a' is width of film; 'b' is thickness of film; 'L' is length of film; 'l' is elongation of film at break point. In another study, tensile strength of the film was determined with the help of texture analyser. The force and elongation were measured when the films broke.[19]

Water vapour transmission studies (WVT): WVT is determined by taking one gram of calcium chloride in previously dried empty vials having equal diameters. The polymer films are pasted over the brim with the help of adhesive like silicon adhesive grease and then allowed to set for 5 minutes. The vials are accurately weighed and placed in humidity chamber maintained at 68% RH. The vials are then weighed repeatedly up to seven consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch In other reported method, desiccators are used to place vials, in which 200 mL of saturated sodium bromide and saturated potassium chloride solution are placed. The desiccators are tightly closed and humidity inside the desiccator is measured by using hygrometer. The vials are then weighed before and after placing in the desiccator and procedure. 'W" is the increase in weight in 24 h; 'S' is area of film exposed (cm^2); 'T' is exposure time.

Microscopic studies: Distribution of drug and polymer in the film can be studied using scanning electron microscope. For this study, the sections of each sample are cut and then mounted onto stubs using double sided adhesive tape. The sections are then coated with gold-palladium alloy using fine coat ion sputter to render them electrically conductive. Then the sections are examined under scanning electron microscope contact between the patch and the skin. The adhesion of a TDDS to the skin is obtained by using PSAs, which are defined as adhesives capable of bonding to surfaces with the application of light pressure. The adhesive properties of a TDDS can be characterized by considering the following factors.

Peel Adhesion properties: It is the force required to remove adhesive coating from test substrate. It is tested by measuring the force required to pull a single coated tape, applied to substrate at 180° angle. The test is passed if there is no residue on the substrate.[20]

CONCLUSION

Transdermal drug delivery is hardly an old technology, and the technology no longer is just adhesive patches. Due to the recent advances in technology and the 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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