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REVIEW ARTICLE

A NOVAL TRANSDERMAL DRUG DELIVERY SYSTEM AND ITS POSSIBLE EVALUTATION: A REVIEW

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ABSTRACT

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. The human skin is a readily accessible surface for drug delivery because it is one of the most readily accessible organs of the human body. There are many advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. During the past three decade, there are number of drugs formulated in the patches formulation 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 aim of this article reviews the selection of drug moiety, polymer, and method for which the patch to be formulated and followed by its possible evaluations.

KEYWORDS: TDDS, Bioavability, Iontophoresis, Electroporation , Sonophoresis, Microneedles

INTRODUCTION:

Over the past three decades, the TDDS has become an emerging tool for the treatment of the disease of skin because human skin is a readily accessible surface for drug delivery a transdermal patch is a medicated adhesive patch which is placed on the skin for deliver a specific dose of medicament through the skin and into the bloodstream. It is a self contained, discrete dosage forms which, when applied to the intact skin, which deliver the drug, through the skin at controlled rate to the systemic circulation[1]. Transdermal drug delivery systems (TDDS) is, also known as patches. Patchs are formulated to deliver a therapeutically effective amount of drug across a patient's skin. Transdermal delivery provides a leading edge over oral and injectables routes by increasing patient compliance and also avoiding the first pass metabolism respectively[2]. Patches not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with having short biological half-lives and eliminates pulsed entry into systemic circulation, which causes undesirable side effects. In the pharmaceutical point of view there are various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc. emerged. A part from all of these TDDS having Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, The pharmacological response, both the desired therapeutic effect and the undesired adverse effect, of a drug is dependent on the concentration of the drug at the site of action, which in turn depends upon the dosage form and the extent of absorption of the drug at the site of action. Traditional way to take medications tablets and injections but there is new options are becoming increasingly popular. One highly successful alternative delivery method is the transdermal[3]**.** The first Transdermal system, Transderm-SCOP was approved by FDA in 1979[4] The common ingredients used in Transdermal drug delivery systems (TDDS)[6] and their function is shown in table no 1 and well explain by figure no 1.

Table No 1: Ingredient of Transdermal drug delivery systems (TDDS)

Ingredients	Function	Example
Drug	Drug is in direct contact with release liner	Nicotine, Methotrexate
Liners	Protects the patch during storage	Polyester film.
Adhesive	to adhere the patch to the skin for systemic delivery of drug	Acrylates, Polyisobutylene, Silicones
Permeation enhancers	Controls the Release of the drug	Terpenes,Terpenoids, Pyrrolidones..
Backing layer	Protect patch from outer environment	Cellulose derivatives, pvc, etc.

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Figure 1: Reservoir Transdermal

ADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEMS [TDDS]:

- It avoidance the hepatic first pass metabolism[8].
- It is having an ability to discontinue administration by removal of the system.
- The ability to control drug delivery for a longer time.
- The ability to modify the properties of the biological barrier to absorption[9].
- They can avoid gastrointestinal drug absorption difficulties which are caused by gastrointestinal pH, enzymatic activity, and drug interactions with food, drink, and other orally administered drugs.
- Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastro-intestinal irritation, low absorption, decomposition due to hepatic *"first- pass"* effect, formation of metabolites that cause side effects, short half - life necessitating frequent dosing etc[10].
- Self administration is possible with these systems.

DISADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEMS [TDDS]:

The major disadvantages of transdermal drug delivery are that there is chances of local irritation will develop at the site of application. Erythema, itching, and local edema can be caused by the drug, and adhesive, or other excipients in the patch formulation.

MECHANISM OF ACTION OF TRANSDERMAL PATCHES: [11]

The application of the transdermal patch and the flow of the active drug constituent from the patch to the circulatory system via skin occur through various methods.

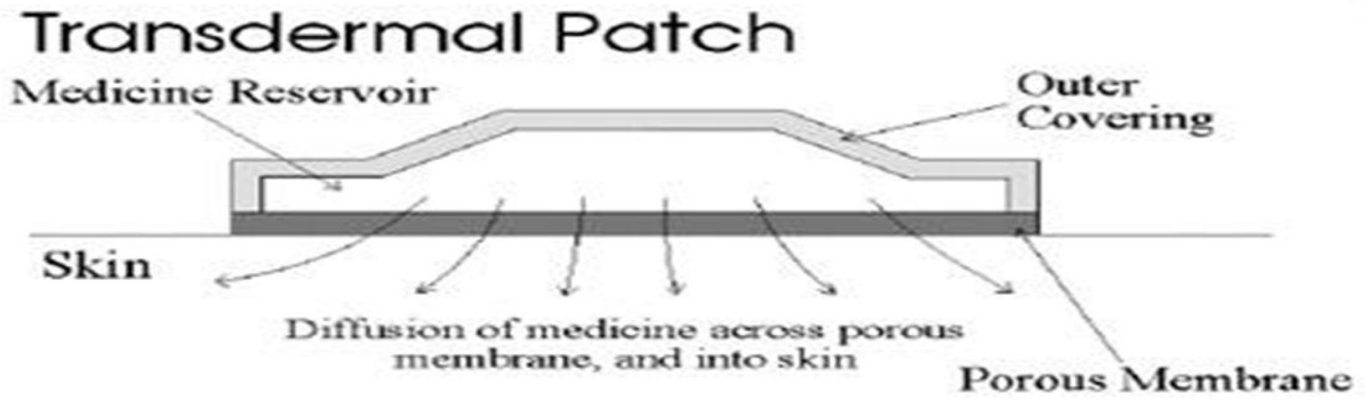

Figure 2: Mechanism of Action of Transdermal Patch

1. Iontophoresis
2. Electroporation
3. Ultrasound
4. Microscopic projection

1. INOTOPHORESIS:

It passes a few milliamperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier. This technique is mainly used of pilocarpine delivery to induce sweating as part of cystic fibrosis diagnostic test.and for lidocaine appears to be a promising approach for rapid onset of anesthesia.

2. ELECTROPORATION:

Electroporation is a technique of application of short, high-voltage electrical pulses to the skin. After electroporation, the permeability of the skin for diffusion

of drugs is increased by 4 time of magnitude. The electrical pulses are believed to form transient aqueous pores in the stratum corneum, through which drug transport occurs.

3. ULTRASOUND:

Use of ultrasound, particularly low frequency ultrasound, has been shown to enhance transdermal transport of various drugs including macromolecules. It is also known as sonophoresis[12] reported on the use of low-frequency sonophoresis for topical delivery of EMLA cream.

4. MICROSCOPIC PROJECTION:[13]

Microscopic projections is known as microneedles which are used to facilitate transdermal drug transport through needles ranging from approximately 10-100 µm in length are arranged in arrays. When pressed into the skin, the arrays make microscopic punctures that are large amount to deliver macromolecules, but small enough that the patient does not feel the penetration or pain[48]. The drug is surface coated on the microneedles to aid in rapid absorption. They are used in development of cutaneous vaccines for tetanus and influenza.

TYPES OF TRANSDERMAL PATCHES: [14-18]

1. SINGLE-LAYER DRUG-IN-ADHESIVE:

The inclusion of the drug directly within the skin-contacting adhesive is come under the single-layer drug in adhesive system. In this transdermal system design, the adhesive not only serves to affix the system to the skin, but also serves as the formulation foundation, containing the drug and all the excipients under a single backing film. The rate of release of drug from this type of system is dependent on the diffusion across the skin. Shown in figure no 3.

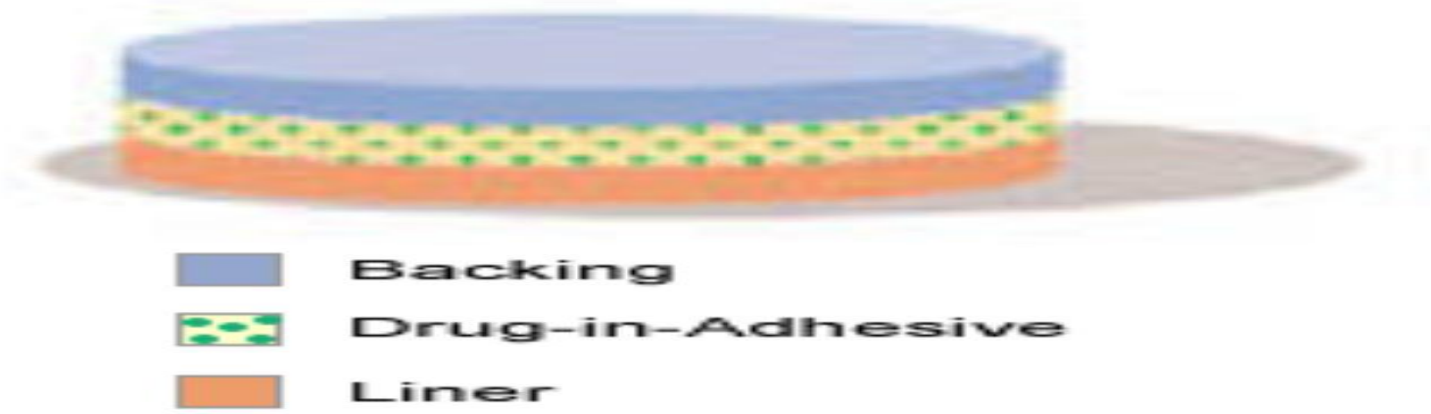

Figure 3: Single-Layer Drug-In-Adhesives

2. MULTI -LAYER DRUG IN ADHESIVE:[49]

Multi -layer drug in adhesive is quite similar to the single layer but it contains an immediate drug release layer which is different from other layer which will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing. Shown in figure no 4.

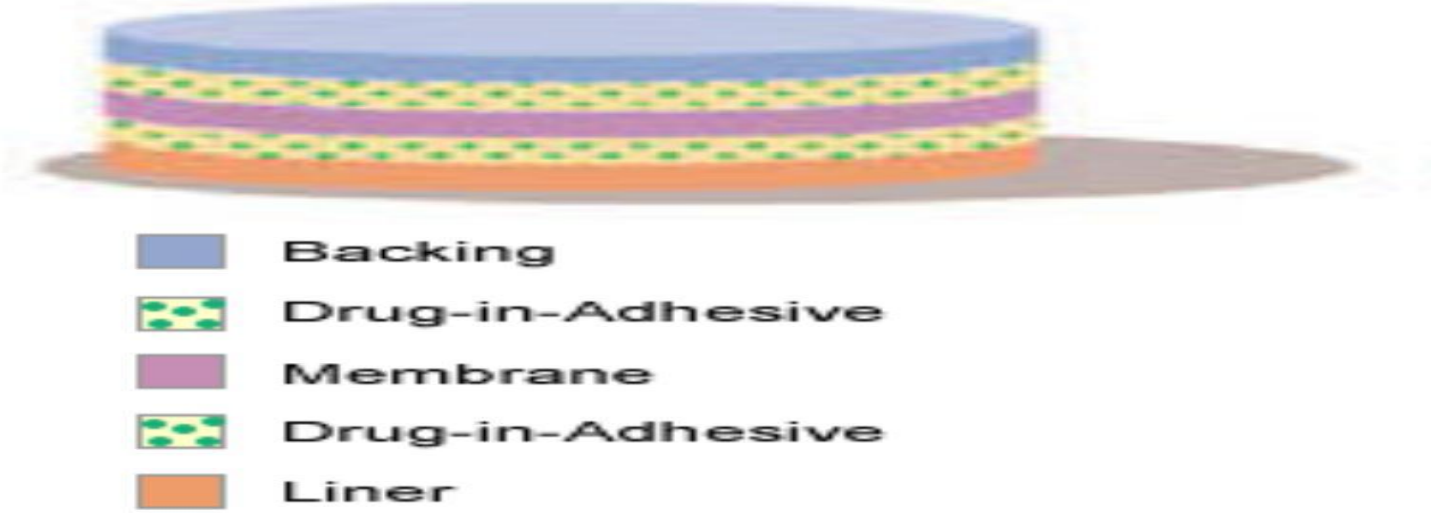

Figure 4: Multi -Layer Drug in Adhesive

3. RESERVOIR:

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 are shown in figure no 5. This patch is also backed by the backing layer. In this type of system the rate of release is zero order.

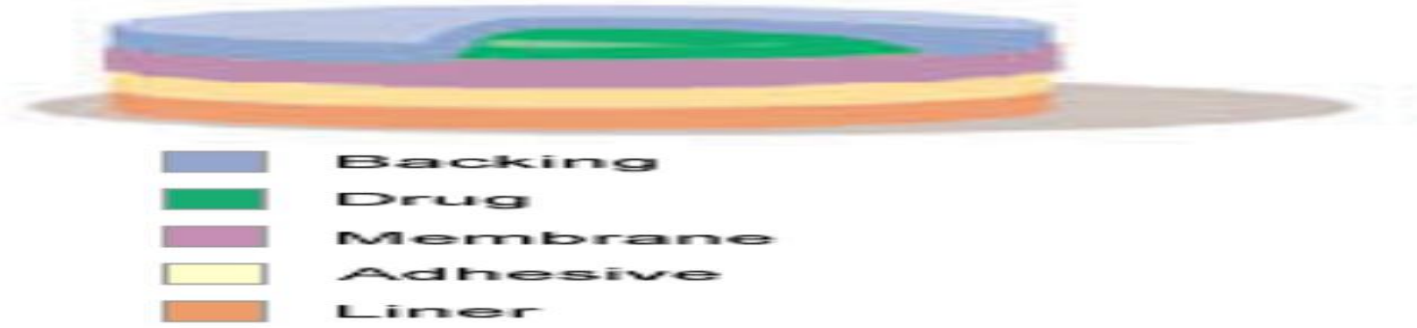

Figure 5: Reservoir

4. MATRIX TRANSDERMAL PATCHES:

In this system the active drug in this type of patch is contained in a polymer matrix. The drug is released at a rate governed by the components in the matrix. In a matrix patch (Figure no 6), the drug, adhesive, and polymer matrix are combined. Matrix patches are not designed to provide true zero-order release because as the drug closest to the skin is released, the drug deeper within the patch must travel a longer distance to reach the skin[50]. The first transdermal patches incorporated the reservoir technology, and this type of patch maintains a reasonable share of the market. However, most transdermal patches reaching the market today use the matrix technology. Matrix patches may be smaller and thinner than their reservoir predecessors due to advances in design. Therefore, these new patches have the benefit of improved patient acceptability.

Figure 6: Matrix Transdermal Patches

5. VAPOUR PATCH:

The vapour patches are new on the market and they release essential oils for up to 6 hours. In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour this patches is useful to release essential oils and are used in cases of decongestion mainly.

EVALUATION PARAMETERS OF TRANSDERMAL PATCHES:[19,20,21]

Evaluation studies of Transdermal patches are more important because of their desired performance and reproducibility under the specified environmental conditions. So evalutation parameter can be divided in to three broad categories:

1. **Physicochemical evaluation.**
2. **In vitro evaluation.**
3. **In vivo evaluation.**

1. PHYSICOCHEMICAL EVALUATION:

There are various physicochemical evaluation parameter for Transdermal patches such as Thickness, Drug content, Percentage moisture content, Percentage moisture uptake, weight uniformity, Folding endurance, Content uniformity test, Flatness, Water vapour permeability test, Thumb tack test, Probe tack test, Rolling ball tack test, Peel tack test etc.

a. THICKNESS OF PATCH:[34]

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

b. DRUG CONTENT:[35]

An accurately weighed portion of film (about 100 mg) is dissolved in 100 ml of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution by appropriate dilution is estimated spectrophotometrically.

c. PERCENTAGE MOISTURE CONTENT:[36]

The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24h. The films are weighed again after a specified interval until the show a constant weight. The percent moisture content is calculated as the difference between final and initial weight with respect to final weight.

d. PERCENTAGE OF MOISTURE UPTAKE:

A Weighed Film Kept In a desiccator at room temperature for 24 h was taken out and exposed to 84% relative humidity (a saturated solution of aluminum chloride) in a desiccator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.

e. 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;

Tensile Strength= F/A.B (1+L/L)

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.

f. CONTENT UNIFORMITY TEST:[46]

10 patches are selected and content is determined for individual patches. 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 these 20 patches have range from 85% to 115%, then the transdermal patches pass the test.

g. UNIFORMITY OF WEIGHT:[45]

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.

h. FOLDING ENDURANCE:[47]

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 is folding endurance value.

i. 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. 0% constriction is equivalent to 100 % flatness.

% constriction =L 1 – L 2/L 1X 100

L2 = Final length of each strip

L1 = Initial length of each strip

j. ROLLING BALL TEST:

This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive. The less tacky the adhesive, the further the ball will travel.

l. PROBE TACK TEST:

Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack.

m. THUMB TACK TEST:

2. IN VITRO EVALUATION:[22 23,37]

The *in-vitro* permeation study of fabricated transdermal patches of was carried out by using excised rat abdominal skin and franz diffusion cell. The skin was sandwiched between donor and receptor compartments of

the diffusion cell. A 2.2 cm diameter patch was placed in intimate contact with the stratum corneum side of the skin; the top side was covered with aluminum foil as a backing membrane. Teflon bead was placed in the receptor compartment filled with 12ml of normal saline. The cell contents were stirred with a magnetic stirrer and a temperature of 37 ± 5°C was maintained throughout the experiment. Samples of 1ml were withdrawn through the sampling port at different time intervals for a period of 24 h, simultaneously replacing equal volume by phosphate buffer pH 7.4 after each withdrawal. Then the samples were analyzed spectrophotometrically at a suitable nm.

3. IN VIVO EVALUATION:[24,25]

- Animal models
- Human volunteers

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. 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. Clinical trials cab is conducted to assess the efficacy, risk involved, side effects, patient compliance etc.

FUTURE ASPECT OF IN TDDS:

1. SONOPHORESIS:

Ultrasound mediated transdermal delivery of key compounds was first reported in 1954 by Fellinger and Schmid through successful treatment of digital polyarthritis using hydrocortisone ointment in combination with ultrasound[26,27,28]. Sonophoresis is a process that exponentially increases the absorption of topical compounds (transdermal delivery) into the epidermis, dermis and skin appendages by ultrasonic energy[29]. Sonophoresis is a localized, non-invasive, convenient and rapid method of delivering low molecular weight drugs as well as macromolecules into the skin[30]. Mechanistically, sonophoresis is considered to enhance drug delivery through a combination of thermal, chemical and the true mechanical alterations within the skin tissue[31]. Ultrasound at various frequencies in the range of 20 kHz–16 MHz with intensities of up to 3W/cm2 has been used for sonophoresis[32,33].

2. PATCH TECHNOLOGY FOR PROTEIN DELIVERY:[34]

Transdermal delivery of large proteins is a novel and exciting delivery method. There is no commercial technology currently available that incorporates proteins into transdermal patches. TransPharma uses its unique printedpatch technology for transdermal delivery of proteins thereby complementing its ViaDerm delivery technology figure no 7.

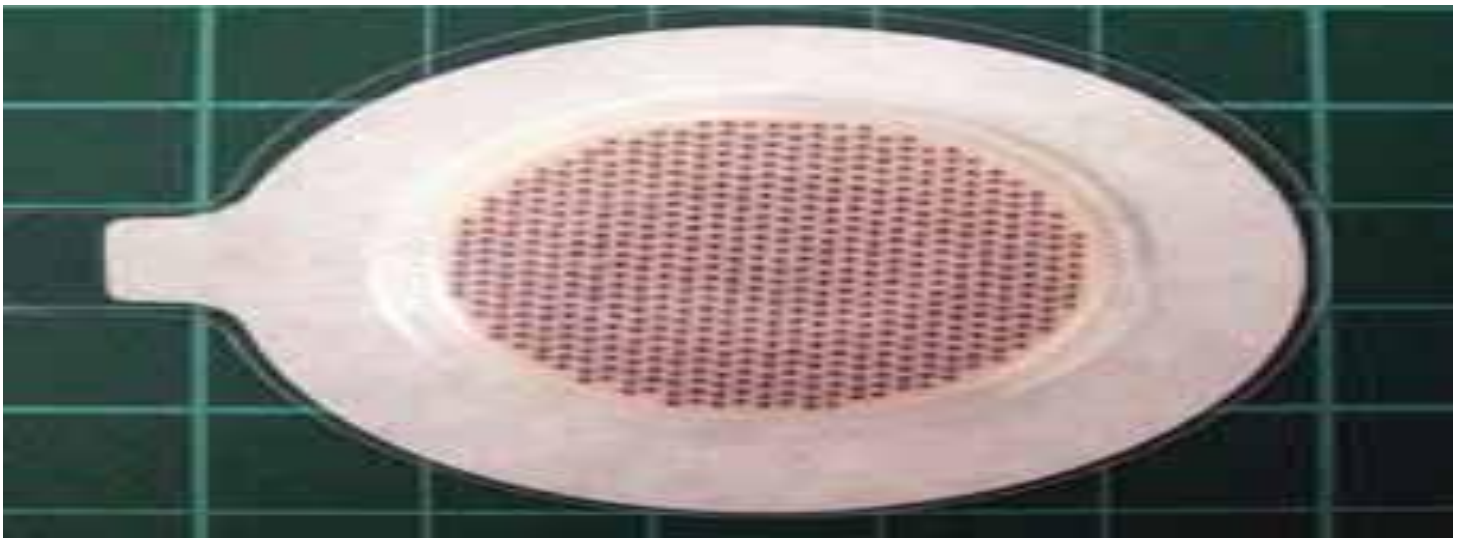

Figure 7: Patch for Protein Delivery

3. MICRONEEDLES AS A PENETRATION ENHANCER:

microns in length[39] and are fabricated in groups called arrays that can contain 150-650 microneedles/cm2. Some of the materials that have been used to make microneedles are silicon, metal, sugar, and plastics. Microneedles can be hollow and deliver drug through the pores of the needles or they can be coated with active ingredients that deliver the drug as the microneedles dissolve in the skin[40]. Solid microneedle arrays can even be effective in delivering drug simply by creating temporary holes in the stratum corneum that remain in effect long enough for an applied drug solution to enter the dermis.

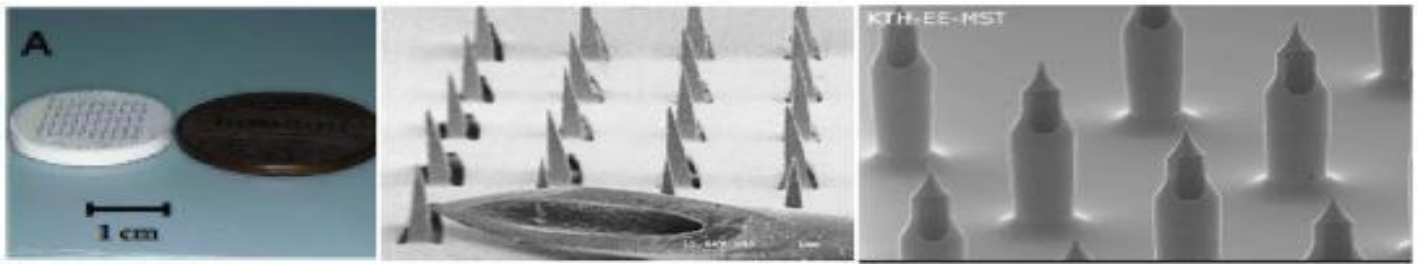

Figure 8: (from left to right) Dissolving microneedle array[41]; Solid microneedle array with hypodermic needle for comparison[42]; Hollow microneedle array[43]

CONCLUSION:

Transdermal drug delivery systems have been used as safe and effective drug delivery system since 1981. 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. Transdermal patches are divided into various types like matrix, reservoir, membrane matrix hybrid; micro reservoir type and drug in adhesive type transdermal patches and different methods are used to prepare these patches by using basic components of TDDS. Future aspects 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.

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