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TRANSDERMAL DRUG DELIVERY SYSTEM A REVIEW; AND IT'S APPLICATION IN PRESENT SCENARIO

[1]Vaishnavi R. Shukla, [2]Dr. Dhananjay M. Patil, [3]Dr. Vinod A. Bairagi
[1]M.Pahrmacy, [2] Associate Professor, [3]Principal
Pharmaceutics Department,
K.B.H.S.S. Trust's Institute Of Pharmacy Malegaon Camp, Nashik,
Maharashtra, India-422003.

Abstract:
A recent drug delivery technique is to inject the medication into systemic circulation at a defined rate using skin as the application site. The transdermal drug delivery route has attracted researchers because of the many related biomedical advantages. In addition to the formulations currently being developed, new medications are being designed using the transdermal system due to the current enormous advantage of this route of administration. It offers a non-invasive drug administration route, although its applications are restricted by low permeability to the skin. Transdermal drug delivery is one of the most promising methods of drug use. Medication delivery with transdermal patch systems exhibits slow, regulated release and absorption of drugs. The concentration of plasma drugs doesn't change significantly over time. Transdermal delivery system is a growing market that is expected to expand in the near future with the discovery of new applications and technologies for drug treatment. Transdermal delivery has many advantages over conventional drug administration, avoids hepatic first-pass metabolism, potentially reduces side effects, and improves patient compliance.Innovative research using penetration-enhancing strategies, such as iontophoresis, electroporation, microneedle and sonophoresis, is promising the successful use of these drugs as consumer-friendly, transdermal dosage forms in clinical practice. This review outlines the promising new technologies involved in improving transdermal permeation.

Keywords: - *Transdermal, Skin, Drug Delivery, Technologies.*

Corresponding author:
Vaishnavi R. Shukla,
Pharmaceutics Department,
K.B.H.S.S. Trust's Institute Of Pharmacy Malegaon Camp,
Nashik, Maharashtra, India-422003.

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INTRODUCTION:

The goal of several drug delivery systems is to achieve a therapeutic amount of the drug into a specific site in the body to accomplish instantly to sustain the desired drug concentration. The novel drug delivery system are advanced through the application of the approach and capability of controlled release drug administration that not only develope the dynamic life of actual drug but also minimizes the opportunity and amount of testing that is needed for the FDA approval And which can make the clinically well established drugs to their therapeutic best.

Transdermal drug delivery system is inventive drug delivery system which is designed for the skin application to gain systemic effect.[1] In recent years, the progress of transdermal dosage forms has been attracting and developing the attention for the several advantage and important that this administration route offers. Transdermal drug delivery system is when correlated with conventional formulation, which broadly shows better and higher compliance. [2]

Transdermally practiced drug avoid the first pass metabolism because the drug goes directly into systemic circulation. Through the dermal patches we try to overcome the adversity which is accomplice with oral route like poor bioavailability and GI irritation.

For the study of transdermal drug delivery system, the transdermal patch of lorazepam was prepared and evaluated. The lorazepam is an antidepressant, anxiolytic agent which having the suitable feature for the transdermal delivery. In 1981 the transdermal patch was first approved by FDA and it was developed by DJ Richard. The first historic FDA label is approval and reported in 1981 by the company Mutual Parma. [3]

The lorazepam is a lipophilic drug with CNS activity. The in vivo studies have been indicated that it is relatively 88-92% constrained to plasma protein and has elimination half life ranging from about 11 to 16 hrs. A transdermal patch has the different components along with the linear, adherents, drug reservoirs, and the drug release membrane which can play an important role in the release of the drug over the skin [4]

Different types of patches along with numerous methods of application have been discovered to deliver the drug and release from the transdermal route. [5]

ADVANTAGE AND DISADVANTAGE OF TRANSDERMAL DRUG DELIVERY SYSTEM:

Attending a broad view over the transdermal patch has been deliberate its advantage and disadvantage below.

ADVANTAGE:

1. It is very convenient method and has only once weekly application that is a simple dosing regimen can aid in the patient adherents to drug therapy.
2. The particular patients who cannot accept oral dosage forms. TDDS can be used as an alternative route of administration.[6]
3. It is one of the great applications in the patient who are nauseated or unconscious.
4. Dermal patches are painless, unoffensive way to delivered the substances into the body [7].
5. They administer the extended therapy with a single application and improving compliance over the other dosage forms compelling more frequent dose administration.
6. First pass metabolism can be avoided in TDDS.[8]

DISADVANTAGES:

1. At the site of application, it may provide the local irritation.
2. Binding of drug through the skin may cause the dose dumping phenomenon.
3. Transdermal therapy is not achievable for certain potent drugs.[10]
4. Transdermal therapy is not for the ionic drugs.
5. The transdermal drug delivery system is not applicable for the pulsatile fashion. [11]

BASIC COMPONENTS OF TDDS:

The components of the transdermal device include;

1. Polymer matrix
2. Drug
3. Permeation enhancers
4. Adhesive
5. Backing layer
6. Release linear
7. Other exexcipent

1. Polymer matrix:

Polymer is the backbone of the transdermal system. Which control the release of drug from the various devices. Polymer matrix can be prepared by dispersion of drug in liquid or solid-state polymer base. The polymers which are used for TDDS and it can be described as,

- Natural polymer - Zein, gelatin, waxes, cellulose derivative, shellac, proteins, gum and their derivative, starch, natural rubber, etc.

- Synthetic polymer - Hydrin, Polybutadien, rubber, polysiloxane, silicon rubber, nitrile, neoprene, etc.[12]

2. Drug:

The transdermal route is very inviting option for the drug delivery with their applicable pharmacology & physicalchrmistry. For developing a successfully transdermal drug delivery system the drug should must be choosen with extream care. The following are important properties of drug delivery. [13]

Physicochemical properties:

- The drug should have molecular weight with less than 1000 Dalton relatively.
- It should have the properties for both lipophilic and hydrophilic phase with the extreme barrier characteristic which should not conductive to successful drug delivery via the skin.
- The drug should must have low melting point. [14]

Biological properties:

- The drug should be potent with daily of the order of a few mg/day.
- The drug should have a short half life and be a non irritating. [15].

3. Permeation enhancers:

This compound is useful to increase the permeability of stratum Corneum. An approach is the commonly research for promoting permeation through the skin with the poorly penetrating drug molecules with the help of the incorporation of chemicals penetration enhancer to the TDDS. [16]

There are mainly three approaches for the permeation enhancement.

- Chemical approach-

This includes;

- ➢ Synthesis of lipophilic analogs;
- ➢ Delipidization of stratum Corneum;
- ➢ Co-administration of the skin permeation enhancers.

Some examples;

1) Sulfoxides: Dimethylsulfoxide, Decylmethasulfoxide;
2) Alcohols: Ethanol;
3) Polyols: propylene glycol;
4) Alkenes: long chain alkanes (C7 - C10)
5) Terpenes: Eugenol.

- Biological approach

This includes;

1) Synthesis of Bio-convertible pro-drug and;
2) Co- administration of skin metabolism inhibitors.

- Physical approach

This includes;

1) Iontophoresis;
2) Sonophoresis;
3) Thermal energy. [17]

4. Adhesive:

The adhesive fulfills the property so, as they serve the system to the skin surface and maintain the position. Even though in presence of water after removal of the patch any traces of adhesive are washed with soap and water. Pressure sensitive adhesive are used to accomplished the contact between patch and skin. The adhesion must be understood by three phenomenons they are namely; [18]

1. Peel: The resistant against the breakage of the bond.
2. Track: With the little contact of pressure the polymer adhere to substrate.
3. Creep: The viscous relaxation of adhesive bond is upon to the shear.

There are mainly three types of adhesive which are generally used that are;

a. Silicon type of adhesive;
b. Polyacrylate based adhesive and;
c. Polyisobutylene adhesive. [19]

5. Backing layer:

The backing layer is flexible and Impermeable to the drug and permeation enhancers. The backing membrane is important for the entire system together and at the time it protects the drug reservoir. [20] The most generally used backing materials are polyester, siliconised, polyethylene terapthalate, aluminized polyethylene terapthalate and aluminum foil of metalized polyester laminated with polyethylene.[21]

6. Release Liners:

The patch is covered by a protective liner that is removed and release immediately before the application of the patch to the skin. Therefore, it is regarded as a part of the primary packaging product. Rather than a part of dosage form for the delivery of the drug. The release liner is made up of different components such as a base layer which is may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinyl chloride) and the release coating layer is made up of silicon or Teflon. [22]

7. Other excipients:

Different types of excipents are also used in the TDDS such as chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare the drug reservoir. To provide the specific plasticity to the transdermal patches various types of plasticers are used such as disbutyl pthalate, polyethylene glycol and propylene glycol.[23]

BIOACTIVITY OF TDDS: - [24]

Other dosage forms are administering to delivered the drug to the systemic circulation is which often generate a highly alternative levels in the blood and

tissue, with specifically after repeating dosing. Whereas the transdermal method is solution of this problem which is minimized. To determine the transdermal route, it is necessary a workable alternative, which one must ask that what problems is exist with the different dosage forms of a particular drugs. In most of cases, the therapeutic effect of drug is based on the drug concentration. There is an upper and lower limit of drug which criticizes a "Therapeutic window ". In order to achieve a systemic level in transdermal system, the drug must first dissolved in the matrix and then migrate from the matrix through the skin and into plexus. Pharmacokinetic treatment of percutaneous absorption is generally depending on the drugs permeating through skin.

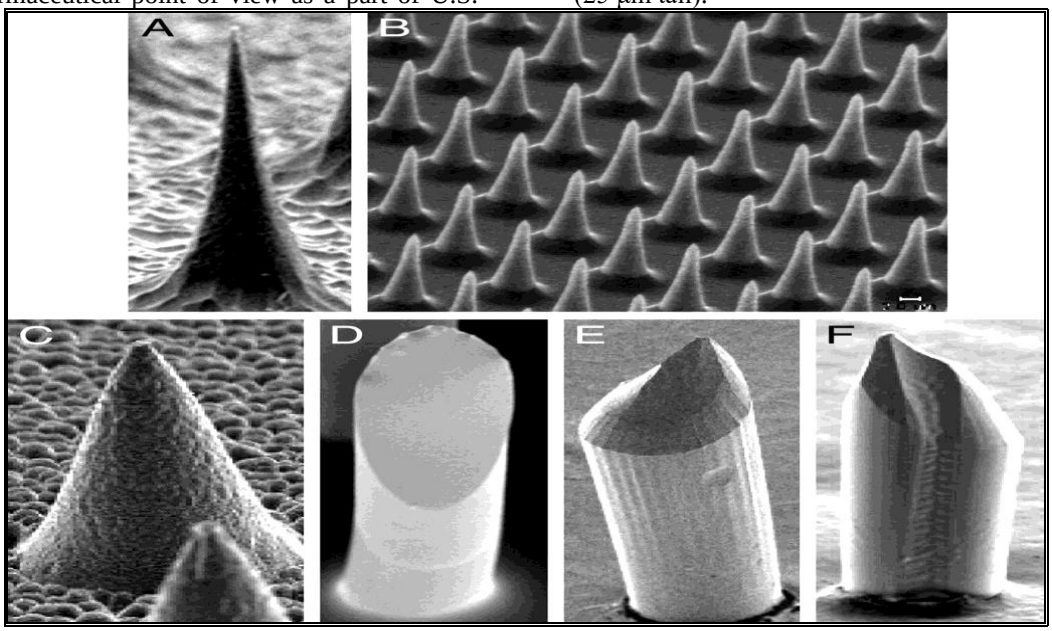
The researchers were shows that metabolites are formed in the smaller amounts and that the combination of unchanged drug and its metabolite was less using in percutaneous route. They also showed that the skin is rate limiting and indicating that by the adjusting drug loading, vehicle components and surface area, prolonged steady state blood levels can be sustained. The use of pharmacokinetic parameter it provides an innovative tool for the development of transdermal system. The parameters are also important from the biopharmaceutical point of view as a part of U.S. food and Drug Administration review for market approval in order to support for drug labeling.

MODIFIED TRANSDERMAL TECHNOLOGIES: -

1. Microfabricated microneedle:

Arrays of micrometer scale needles could be used to deliver drugs, protein and particles across the skin in a minimally invasive manner. Hypodermic needles have provided a extremely useful standard for the drug delivery over a century, but a advances in biotechnology make their limitation increasingly apparent. As devices, those transport the molecules of nanometer dimensions, and the millimeter in large length scale for conventional needles and that cause a pain and limited targeted delivery. [25] Therefore, we sought to test the hypothesis that needles of micrometer dimensions can create the transport pathways large enough for small drugs like macromolecules and nanoparticles and it avoid the pain and facilate a highly localized intracellular target. [26]

Solid microneedle made from silicone, rubber, and metal, imaged by electron microscopy scanning. (A) Silicone microneedle (150 μm tall) from an array of 400 needles cut from a silicone substrate. (B) List segment containing 160,000 silicone microneedle (25 μm tall). [27]



Fig(1):- Solid microneedle fabricated out of silicon, polymer, and metal, imaged by scanning electron microscopy. (A) Silicon microneedle (150 μm tall) from a 400-needle array etched out of a silicon substrate. (B) Section of an array containing 160,000 silicon microneedles (25 μm tall). (C) Metal microneedle (120 μm tall) from a 400-needle array made by electrodepositing onto a polymeric mold. (D–F) Biodegradable polymer microneedle with beveled tips from 100-needle arrays made by filling polymeric molds. (D) Flat-bevel tip made of polylactic acid (400 μm tall). (E) Curved-bevel tip made of polyglycolic acid (600 μm tall). (F) Curved-bevel tip with a groove etched along the full length of the needle made of polyglycolic acid (400 μm tall). The microelectronics innovation has afforded tool for highly precise, reproduces and various methods to fabricated the structure of micrometer dimensions. The lithography based approach produce a large arrays of microneedle that can be inserted into skin, cell and tissues. Microfrabicated microneedle are painless disrupt the barrier of the skin and they create a pores resulting in an increased in a penetration. [27]

2. Macroflux®:-

Macroflux® technology is another innovative novel transdermal drug delivery that ALZA corporation was developed a to deliver the biopharmaceutical drug in a controlled reproducible manner that enhance the bioavailability and efficacy without discomfit to the patient. [28] Macroflux® has area of up to 8cm^2 and contain as many as 300 micro projection per cm^2 with the separated micro projection length it being with <200um. And the mostly adhesive patch size is 10cm^2.Macroflux® skin patch technology give the rapid and reproducible intraceutaenous administration of drug coated antigen. [29]

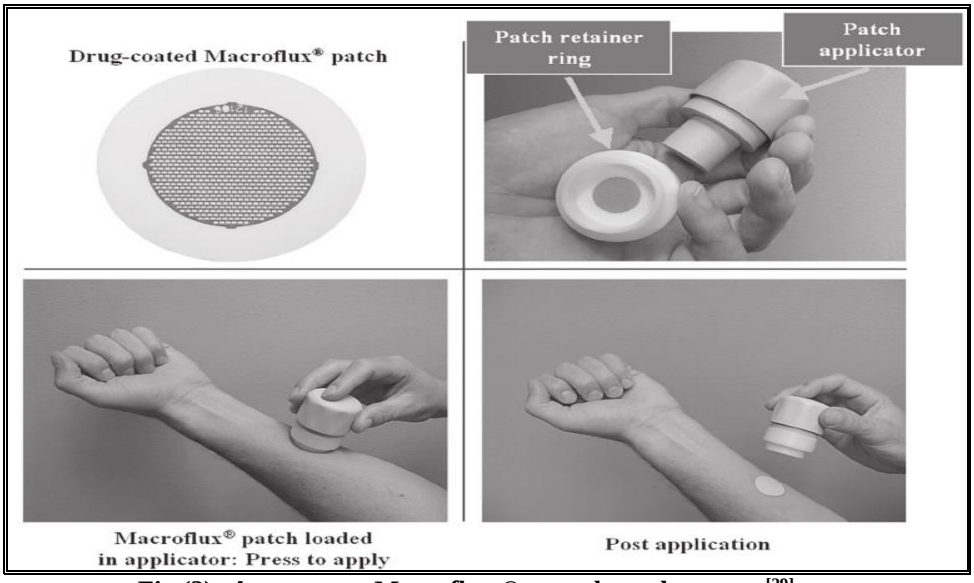


Fig (2):-A prototype Macroflux ® transdermal system. [29]

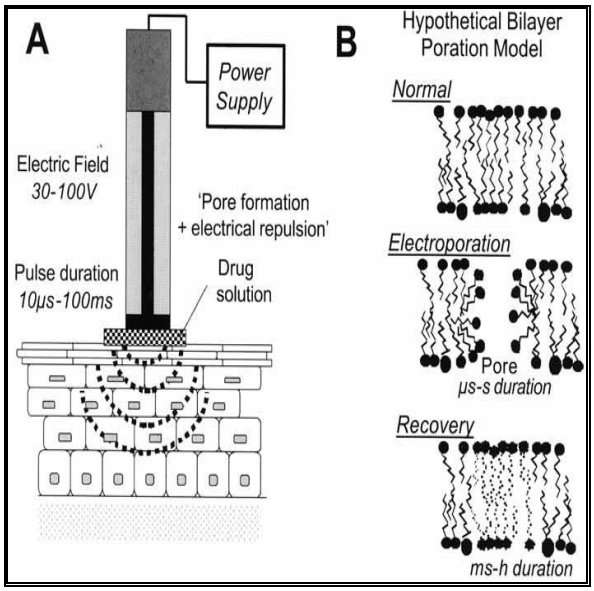
Three types of Macroflux® have been designed and tested in preclinical studies, They include;

a. Dry-coated Macroflux®; A system is for short duration of administration that consist of a drug with coated microjection arrays that adhere to a flexible polymeric adhesive backing membrane.
b. D-Trans® Macroflux®; A system is for short duration of administration that consist of a micro projection array that is coupled with a drug reservoir.
c. E-Trans® Macroflux®; A system is for pulsatile Orit demand on the delivery of a micro projection array that coupled with an electro transport system.

In this study, we were demonstrated that micro projection patch technology provide and facilitate the controlled transdermal ODN delivery. [30]

3. Electroporation: -

Electroporation has been demonstrated in various different mammalian, yeast, plant, bacteria and other cells as well as in artificial spherical and planner membranes. In electroporation, cells are provisionally encoverd to high intensities of electric pulse which leads to the forming of aqueous pores in the lipid bilayer of the stratum Corneum. Hence, it's allowing the diffusion of drug through the skin. [31]



Fig(3):- The basic design of electroporation delivery devices. (A) Drug is placed on the skin beneath the electroporation probe. Short pulses of high voltage current are passed through the probe and drug molecules are hypothesized to move into the skin through a combination of pore formation and electrical repulsion. (B) Pores are hypothesized to form in the intercellular bilayers via momentary realignment of lipids that recover their original position at various times after the electrical pulse. [31]

Electroporation was basically used to transfer the cells with macromolecules by altering the DNA by their cell membranes in a reversible manner. [32] Electroporation of skin of desire a high voltage in there order that is greater than 50v . The studies have been clearly reported that the electroporation is very effective for the transdermal delivery of proteins and peptides.

Electronsport technology offers a more invasive attractive to parental systemic drug delivery. The electronic control of drug delivery that is grant to rapid onset of action of the drug and which makes the possible demand. The patient dosing and there patterned in a modulated drug delivery. [33]

4. Iontophoresis: -

Iontophoresis is defined as 'The abutment of ionizaionizable drug permeation cross the skin by the enforced a electrical potential in which the driving force may be simply the feature of electrostatics repulsion. [34] In generally the iontophoresis devices consist of a battery, electrode, drug reservoir and microprocessor controller. There are simple three explanations of iontophoresis for how they work and increase the transdermal drug delivery [35].

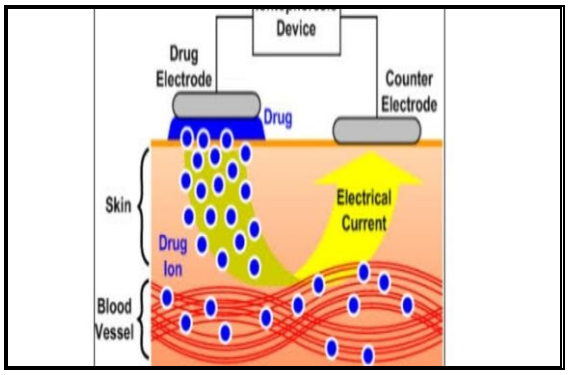


Fig (4):-Transdermal drug delivery by iontophoresis [35]

The first, proposes is that the drug are forced to across the skin by a simple electronic repulsion or similar charges. The second, explanation is the advice that the electric current enhances the permeation rate by inhibiting the skins ability to perform the protective or efficacy barrier function. The third, state explained that the iontophoresis cause by a water as a very important and effective penetration enhancer, to penetrate in the stratum Corneum by electro-osmosis. Dissolved drug can be carried out by the across the skin along with penetrating the water during the process of iontophoresis. To date, clinical studies have been criticizing that to only smaller molecules such as keterolac, dexamethasone, etofenmate, naproxen, lidocaine, cortisone and fentanyl. Iontophoresis have better efficacy and safety properties for the various drug delivery. [36]

5. Ultrasound:-

Ultrasound (sonophoresis, ultraphonophersis and phonophoresis) are the technique which is used for increasing the skin permeation of drug using the specific ultrasound (20 KHz to 16MHz) as a physical force. The combination of ultrasound and topical drug therapy where used to achieve a therapeutic drug concentration at specific site of the skin membrane. [37]

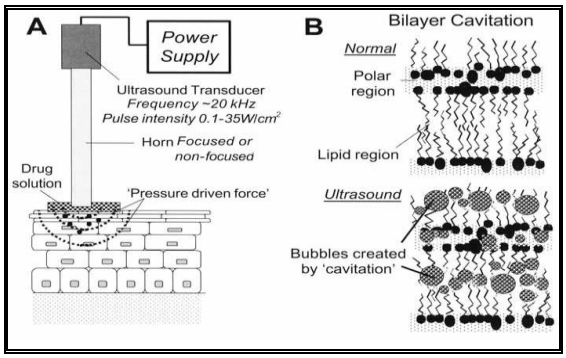


Fig (5) :- The basic design of ultrasonic delivery devices. (A) Drug is placed on the skin beneath the ultrasonic probe. Ultrasound pulses are passed through the probe and drug molecules are hypothesized to move into the skin through a combination of physical wave pressure and permeabilisation of intercellular bilayers. (B) The formation of bubbles in the intercellular lipid space caused by cavitation increases bilayer fluidisation and resultant permeability.[37]

The use of ultrasound (specifically HIFV) is introducing or gaining the rapid clinical acceptance data for as a tumor therapy, lithotripsy and various other surgical instruments. It is also used to enhances the drug concentration of protein, RNA/DNA, and some other compounds into cells and tissues. Basically, a proper selection of the ultrasound parameter is nesscary to induce the a better or higher enhancement of transdermal drug transport by the sonophoresis technique. Therefore, it is an object of a present senerio to innovate or to provide a various method for enhancing the transdermal transport for better technology. [38]

6. Laser radiation and photomechanical waves: -

Laser have been used in various clinical therapies for decades, therefore their effect on the biological membrane are well established. Laser treatment are mostly used in various determatological conditions such as acne, confer facial rejuvenation, etc. Where the laser radiation is destroys the targeted cells and tissue. Such direct and controlled exposure of the radiation of laser to skin results in ablation of the stratum Corneum without damaging the epidermis. Pressure waves are generated by the intense laser radiation, without any effect on the skin and increase the permeability of the skin. The important

parameter which affecting delivery such as pressure peak, rise time and duration which have been demonstrated. A design concept for a transdermal drug delivery patch based on the uses of pressure waves. [39]

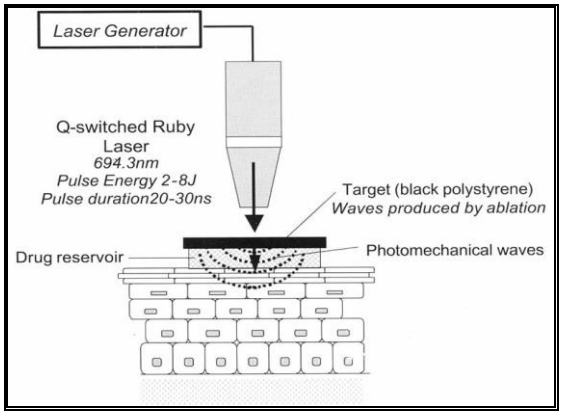


Fig (6):-The basic design of photomechanical wave delivery devices. A drug reservoir backed with a laser target material (e.g. black polystyrene) is placed on the skin. A laser is fired over the application site which hits the target material resulting in the formation of photomechanical waves which are hypothesized to increase the permeability of the stratum Corneum allowing the facilitated passage of drug molecules from the reservoir into the skin. [39]

7. Metered Dose Transdermal spray:-

It is a liquid preparation which is form of solution that are used for topically which is made up of volatile compounds that are nonvolatile in the nature. Which consist of different dissolved medicament in solution. The use of MDTS have ability for the better permeation of the drug through skin. Different types of penetration enhancers such as ethanol and azone are used commonly for the preparation of the solution. The MDTS have the following important advantage that are; [40]

1. Improved cosmetics acceptability.
2. Dose flexibility and efficacy.
3. Simplicity of manufacturers.

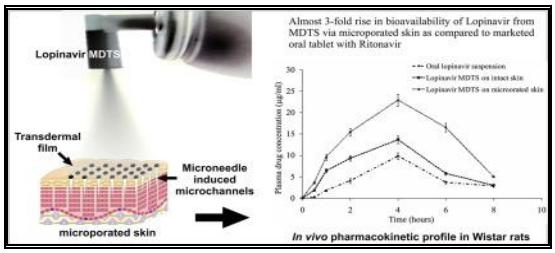


Fig (7):- Meter dose transdermal spray for delivery. [40]

8. Transfersomes:-

To date, the most advantageous transdermal drug carrier is the newly advanced and patented. The transfersomes which pass through the skin barrier along with the transcutaneous moisture gradient. The transfersomes are form of elastic and deformable vesicles, which are firstly introduced by described by Cevc in the early 1990's. Transferosomes are permeate to intact vesicles that are claimed the vesicles pass through the skin layer to the systemic circulation. Transfersomes are composed of the lipid such as phospholipids, phosphatidycholline and also consist of surfactant such as sodium chlorate, deoxycholate, span 80, Tween 80. They are typically 100- 400nm in diameter and have a rigid structure. [41]

Transferosomes have been increasingly used as a carrier for s ranging drugs such as including steroids, NSAID's and local anesthetics. Cevc et. Also reported that transfersomes could deliver insulin to the systemic circulation in therapeutic amount which is equivalent or similar to a subcutaneous injection. The advancement in the transfersomes offered a various drug delivery such as peptides and proteins and also antigens through the skin is very exciting but it requires a proper investigation. [42]

9. Medicated tattoo's:-

Med-Tats is a modification of a temporary tattoos which contain the active drug substance for the transdermal delivery. This technology is very useful for the administration of the drug to pediatric patients. Who are not able to take traditional dosage forms? [43]

In general the tattoos are understood as a patch like substances which is made of various polymer with their high quantity of coloring compound and materials during application on the skin layer surface it apply with gentle pressure.[44] The main application of these technology is used in the Cosmeceutical. A medicated tattoo is one of the upcoming approach or invention in the transdermal drug delivery. [45]

10. Magnetophoresis:-

Transdermal Magnetophoresis is one of important phenomenon of the application of magnetic field to enhance the proper drug via skin. The in-vivo studies demonstrated the more flexible and innovative Magnetophoresis transdermal patches system. [46]

The magnetically medicated drug permeation enhancement can be further enhances the ability by the addition of proper suitable chemical enhancers. The fact is that this technology can only be used with diamagnetic materials only that will serves as limitating factor in this method. But the applicability and probably showing action of this technology generate the interest in this method. [47]

RECENT TRENDS IN TDDS: - [48]

A rich area of researcher over the past 10 to 15 years has been concentrated on invention and

developing of transdermal technologies that uses a mechanical energy to increase the drug concentration through skin by either changing the skin barrier or energy of the molecules. Drug in adhesive technology has become the preferred system for the passive transdermal delivery; the two areas of formulation researcher are focused on the adhesive and various excipents. The pie diagram shows the fentanyl and nitroglycerin are the drugs which are mostly used in the market.

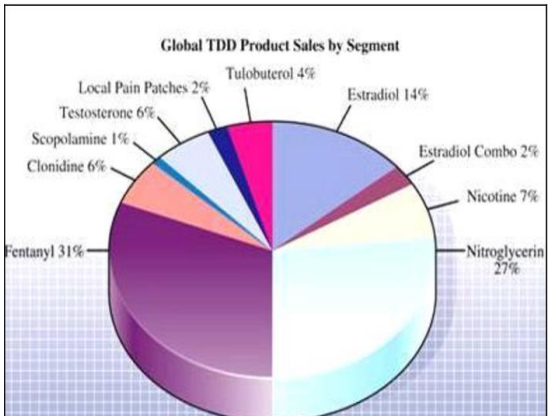


Fig (8):-TRANSDERMAL DRUG DELIVERY PRODUCT SALE GLOBALLY. [48]

The Recent advances in the TDDS include;

- Vereniciline patch for smoking cessation and high dose patch for fast metabolizes.
- Insulin patches for diabetes.
- Sufentanil patches for chronic cancer therapy.
- Clonidine patches for the trauma patients.
- Estrogen and testosterone patches for post menopause.
- Glyceryl trinitrate for acute stroke therapy.

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CONCLUSION AND FUTURE SCOPE:

Transdermal drug delivery system is innovative and extremely useful for the topical and local action of drug. The drug which shows the hepatic first pass effect and unstable GI conditions are suitable candidate for TDDS. The skin is the heart of TDDS which have a extremely good barrier functions and improve the ability of penetration of active ingredients, it is important for enhancement of strategies. The transdermal drug delivery have a very few side effect and increasing in there efficacy and shows the constant delivery. However, with our greater understanding of the structure and function of skin and now to ulter these properties more and more new drug products with different technologies are being developed for transdermal delivery. Transdermal system is very effective and which provide a more efficacy and less effect than other drug delivery system. The transdermal drug delivery system could be one day one of the best novel drug delivery system.

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