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Review Paper

Advancements and Applications of Transdermal Drug Delivery Systems (TDDS)

Sharvari Gurav*, Shruti Kalebere, Sudesh Patil, Umesh Kolap, Dr. Shobhraj Malavi

Genesis Group of Institutions, Radhangari 529/30, Near Gaibi Titta, Radhanagari Road, Opposite to Bharat Petroleum, Tal -Radhangari Dist-Kolhapur,416212

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ABSTRACT

The controlled drug delivery category includes transdermal drug delivery systems (TDDS), which are designed to distribute medications via skin at a pre-established and regulated rate. Approximately 74% of medications used orally now are discovered to be less effective than expected. A transdermal medication delivery device was developed to enhance such qualities. The practice of administering a medication through the layer of skin to provide a systemic effect is known as transdermal drug delivery, which is different from traditional topical delivery of drugs. Drug patches for clonidine, fentanyl, lidocane, nicotine, nitro-glycerine, estradiol, oxybutynin, scopolamine, and testosterone are available today. Combination contraceptive and hormonal substitute patches are also available. Generally, the patches last one to seven days, depending on the medication. The markets for non-medicated patches include skin care, nutritional, and thermal and cold patches attempting to deliver medications through the skin at a regulated and fixed rate. Theses patches are used in several diseases such as hypertension, alzheimer, breast cancer, diabetes, HIV obligates, schizophrenia. Numerous advantages come with this strategy, including longer therapeutic effect, less side effects, higher bioavailability, improved patient adherence, and easy medication termination. Understanding the drug's transportation mechanism, kinematics and physiological chemical properties of the drug compound is essential for achieving optimal efficacy. The concepts of different physical methods to enable transdermal medication distribution were the main emphasis of this iontophoresis, and electrophoresis these are some examples. Physical processes involve electrical, magnetic, chemical, and mechanical energy.

***Corresponding Author:** Sharvari Gurav
Address: *Genesis Group of Institutions, Radhangari 529/30, Near Gaibi Titta, Radhanagari Road, Opposite to Bharat Petroleum, Tal -Radhangari Dist-Kolhapur,416212*
Email ✉: sharvarigurav2003@gmail.com
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INTRODUCTION

Transdermal drug delivery system is the method that uses the human skin as a entrance for the administration of the medication molecules. Transdermal drug delivery system falls under the category of controlled drug delivery system whose goal is to administer the medication through the skin at a predetermined and regulated rate[1].Transdermal drug delivery system has raised interest in drug. delivery through the skin for systemic drug delivery and local effects on skin (topical delivery). Among the many significant benefits that the skin provides as a drug delivery system are the following: the ability to minimise Plasma levels are in contrast to oral treatment; the ability to provide a sustained release of the drug at the site of application; the ability to quickly terminate therapy by removing the device or formulation; the capacity to prevent problems with elimination time effects, the pH level, and stomach discomfort; the first-pass metabolism of the liver, which increases the drug's bioavailability; the ability to minimise fluctuations in the amount of drug blood plasma levels; and the avoidance of injection pain[2].For transdermal delivery, a small molecular size, adequate solubility in the carrier, short half-life, low dosage, and suitable lipophilicity are all required[3].

Advantages of (TDDS)-

1.Self-administration and continuous, prolonged medication release are both possible.
2.Avoids longer, multi-day dosing intervals as well as peak and trough medication levels.
3.Avoids gastrointestinal discomfort, enzymatic breakdown by the gastrointestinal system, and first-pass hepatic metabolism.
4.Patient compliance is improved by less frequent dosage.
5.For individuals who are unable to take oral drugs, an alternate method.

Disadvantages of (TDDS)-

1.Only medications that may be administered through the skin are tiny lipophilic ones.
2.Because patch size restricts the amount that may be administered, the drug molecule needs to be strong.
3.Unsuitable for high dosages of drugs.
4.The type of patch and the surrounding environment can affect adhesion.
5.Hypersensitivity responses and skin inflammation are possible [1].

❖ **Skin and drug permeation**

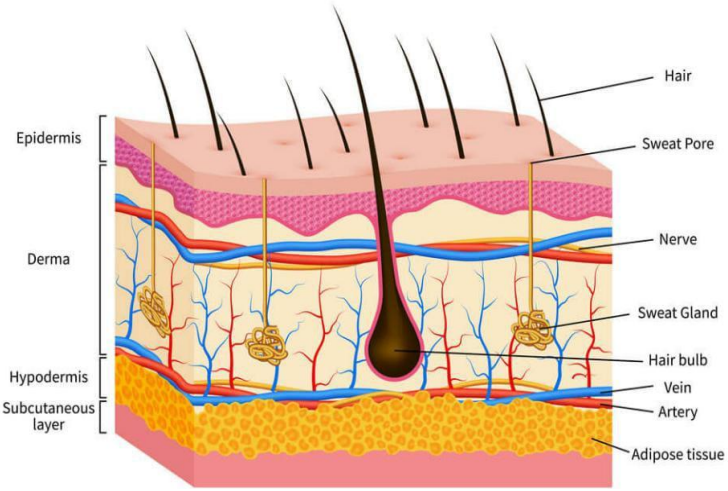


Fig. No. 1 skin

At almost 15% of the total weight of an adult, the skin is the largest part of a human being. Among its many essential roles are defence against external physical, chemical, and challenges from biological processes, avoiding too much body fluid loss, and aiding in thermoregulation. Subcutaneous tissue, dermis, and epidermis are the three layers of skin

1.Epidermis-

The epidermis is consisting primarily of dendritic cells and keratinocytes. Pilosebaceous apparatuses, nails, and sweat glands are examples of derived structures that originate from the epidermis, a layer that is constantly renewing.

2.Dermis-

The dermis gives the skin its pliability, flexibility, and tensile strength. It also makes up the majority of the skin. It has receptors for sensory inputs, binds water, helps regulate body temperature and protects the body from mechanical damage. The dermis and epidermis work together to maintain the properties of both tissues [4].

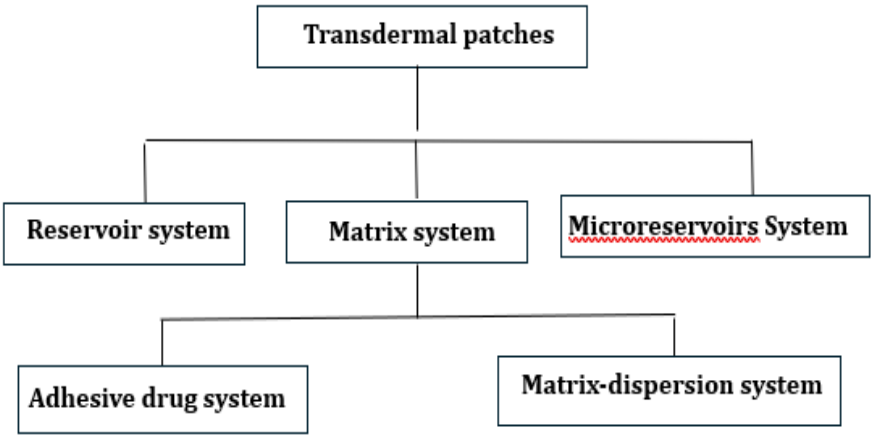
3.Hypodermis-

The hypodermis, another name for the subcutaneous tissue, is not regarded as genuine component of the organized connective tissue. It`s made up of fibrous, white connective tissue with a loose texture that contains lymph and blood vessels. The majority of researchers believe that the medicine enters the bloodstream through the skin before arriving at the hypodermis, where the fatty tissues act as a drug store [3].

❖ **Transdermal patches:**

It is a patch that delivers a prescribed dosage of medication via the skin at a predefined rate of release into the bloodstream [5]. A small molecular size, sufficient solubility of carrier, short half-life, low dosage, appropriate lipophilicity are all necessary for transdermal administration [1]. A medicated adhesive patch called a transdermal patch is applied on the skin layer to administer a prescribed dosage of medication at a predetermined release rate[5]. However, the stratum corneum act as a barrier to the patches, making it difficult for larger medications to get through the layer of stratum corneum by adding enhancers this can be addressed [3].

- **Types of transdermal patches-**



1. Reservoir system-

This transdermal system embeds the drug reservoir between a rate-controlling microporous or non-porous membrane and an impermeable backing

layer. Only the rate-controlling membrane allows the medicine to be released.

2. The matrix dispersion system-

a. Adhesive drug system

This kind creates the drug reservoir by first dispersing drug in a sticky polymer, then distributing the formulated sticky polymer on an impermeable backing layer by making a melting or solvent casting method (for hot melt adhesives).

b. Matrix-dispersion system-

The medication is uniformly distributed inside the matrix of lipophilic or hydrophilic.

3.Microreservoirs Systems-

This TDDS integrates a reservoir and matrix dispersion system. The medication is dissolved within aqueous solution of a water-based polymer, and the solution is then evenly dispersed in a lipophilic polymer. This process produces thousands of microscopic drug reservoir spheres [(1)].

❖ **Materials used to make patches:**

1. **Drug reservoir and polymer matrix–**

The polymer regulates the release of drug from patches in TDDS. As a result, the polymers employed in TDDS need to be chemically and biocompatible with medications and other system elements like PSA and filtration enhancers. In addition, polymers need to deliver drugs consistently and effectively.

2. **Membrane-**

In a multilayer patch, the discharge of the medication from the reservoir is regulated by the membrane. Polyurethane, silicone rubber, and ethylene vinyl acetate are a few examples. These function as a membrane to control the release of drugs [(5)].

3. **Permeation Enhancers-**

Permeation Enhancers work to raise the permeability of the skin to the intended therapeutic level. Non-hazardous, hypoallergenic, intolerant controlled and pharmacologically inactive, the capacity to act specially for a predictable duration, chemical and physical suitability for drugs and other ingredients and inodorous and uncoloured are the ideal characteristics of enhancers.

4. **Adhesives-**

Adhesives that are sensitive to pressure and it is a substance that sticks to the surface —for example, Silicon-based adhesives, polyacrylate, polyisobutylene, and other PSA polymers are frequently utilized in TDDS.

5. **Backing films-**

The backing films are chosen based on the elasticity, look, and backing layer, the material's chemical resistance must be taken into account.

6. Additional excipients, including plasticizers or solvents

(a) Solvent:

To make drug reservoirs, the solvents dichloromethane, methanol, acetone, chloroform, and isopropanol are utilized.

(b) Plasticizers:

The material is also made more malleable by the addition of plasticizers such as dibutyl phthalate, triethyl citrate, polyethylene glycol, and propylene glycol [(3)].

❖ **Factors influencing drug delivery system**

A. Biological Factors-

(i)Skin age: More pores can be found in younger skin than in older skin. Youngsters are particularly vulnerable to contaminants entering their bodies through their skin. Thus, skin aging is one of the factors affecting medicine penetration in TDDS.

(ii)Blood supply: Transdermal absorption may be impacted by modifications in peripheral circulation

(iii)Skin site: Site-specific variations exist in skin thickness, and density. These factors have more effect of drug penetration.

(iv)Skin metabolism: Hormones, steroids, chemicals that cause cancer, and several drugs are metabolized by skin. Therefore, the effectiveness of a drug is determined by skin metabolism.

(**v)Species differences:** The penetration is affected by species-specific differences in skin thickness, appendage density, and keratinization.

B. Physicochemical factors-

(i)Skin hydration: When the skin comes in contact with water it becomes more permeable. Hydration is important factor in improving skin permeation.

(ii)Temperature and pH: Drug penetration increases as increase in temperature. Percentage unionized drug determines the concentration of drug in the skin. Two crucial variables influencing medication penetration are pH and temperature.

(iii)Diffusion coefficient: The drug penetration is determined by its diffusion coefficient.

(iv)Partition coefficient: Appropriate action requires the optimal partition coefficient(K). Excessive K-containing drugs are not yet ready to exit the lipid layer of the skin. Additionally, medications with low K will not penetrate.

(v)Molecular size and shape: Molecular weight and drug absorption are negatively correlated; tiny molecules absorb drugs more quickly than large ones.

C. Environmental factors-

(i) Sunlight: It causes the blood vessel walls to thin, which results in bruising and only minor harm in the areas exposed to the sun. Additionally, freckles or solar lentigo are examples of pigmentation, the most obvious pigment alteration brought on by the sun.

(ii) Cold season: Dry and itchy skin is a common side effect of the cold season. In response to the drying impacts of the weather, the skin produces more oil. Dry skin symptoms can be lessened with the use of a decent moisturizer. Additionally, maintaining moisturized and glowing skin can be achieved by drinking lots of water.

(iii) Air pollution: Drug distribution through the skin is impacted by dust because it blocks the pores and raise germs on the surface of skin, which can result in acne or patches. Chemical that is invisible Air pollutants have the ability to disrupt the skin's natural defences by dissolving the natural oils that keep the skin hydrated and supple [(1)].

Table No. 1 Transdermal patches that are commercially available for longer than 24 hours of continuous medication delivery.

Drug therapy	Uses	The frequency of use	The variety of adhesive	The period of approval
Estradiol[(6)]	Prevention of menopausal symptoms	Two times a week	Blend of silicone and acrylate	The year 1998

Levonorgestrel [7][8]	Avoiding symptoms associated with menopause	Once every week	Acrylate	The year 2003
Oxybutynin [9] [10]	Therapy for an overactive bladder	Two times a week	Acrylate	The year 2003
Buprenorphine [11]	Enduring persistent pain	Once every week	Cross-linking polyacrylate with aluminium	The year 2011
Clonidine [12]	Management of Hypertension	Once every week	PIB	2022
Donepezil hydrochloride[13]	Alzheimer's disease	Once every week	Acrylate	2022

Table No. 2 Recent studies on transdermal patches have focused on long-acting reservoir types.

Sort of patches	Drug	Uses
Gel-oriented	Imipramine hydrochloride [14] Raloxifene [15]	Management of depressive disorders Treating cancer of the breast
loaded lipidic vesicles	Insulin [16] [17] Paroxetine [18]	Diabetes mellitus Depressive disorder
loaded nanoparticle	Repaglinide [19]	Type 2 diabetes

Table No. 3 Transdermal patches of the long-acting matrix kind

Sort of patch	Drug	Uses
patch based on a matrix	Olanzapine [15] Amlodipine [20] Letrozole [21] Diclofenac, Ibuprofen, Ketoprofen, Loxoprofen, Naproxen, Diflunisal, Suprofen, and Flurbiprofen [22]	Bipolar disorder combined with schizophrenia High blood pressure Cancer of the Breast Handling of Pain
Matrix patches based on ions and ions	Gliclazide [23]	Diabetes type II

Table No. 4 Currently being developed are formulations for long-acting transdermal microneedles (MN).

Sort of patch	Drug	Uses
Polymer MNs	Rilpivirine[24] Huperzine[25]	HIV medical care Management of Alzheimer's
Shell-core polymeric MNs	Levonorgestrel [26]	Management of Birth control
MNs filled with nanocarriers	Ivermectin [27] Minoxidil [28]	Parasitic illness Androgenetic Hair Loss
Inflatable MNs	Cabotegravir sodium [29]	Management of HIV

❖ **Development of equipment for transdermal delivery**

Electrical, physical and mechanical stimuli are external stimuli are known to increase the

permeability of medications and biomolecules via skin, in contrast to topical drug administration [30]. With the right tools, active transdermal delivery, or TDDS, is a method that has been shown to deliver drugs into the skin quickly and reliably. Additionally, the therapeutic efficacy of prescribed drugs can be accelerated by this enhanced TDDS mode [31].

1. Iontophoresis-

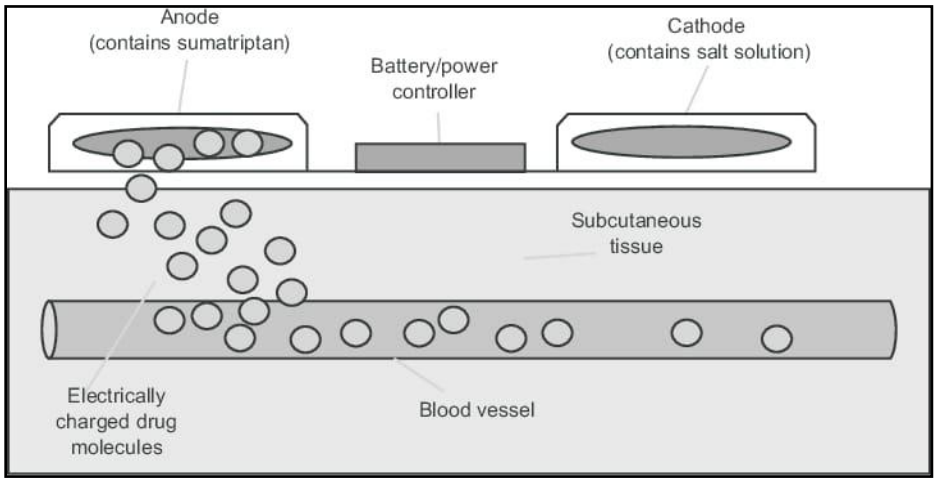


Fig No. 2 Iontophoresis

Whenever there is a slight externally applied potential difference (less than 0.5 mA/cm2), iontophoresis facilitates the transport of ions across the membrane. It has been shown to enhance penetration via the skin and speed up the release of certain medications with subpar penetration and absorption characteristics [32]. Through the creation of an electrochemical potential gradient, this method has been employed for transferring ionic or non-ionic medications in vivo [33].

2.Nanocarriers:

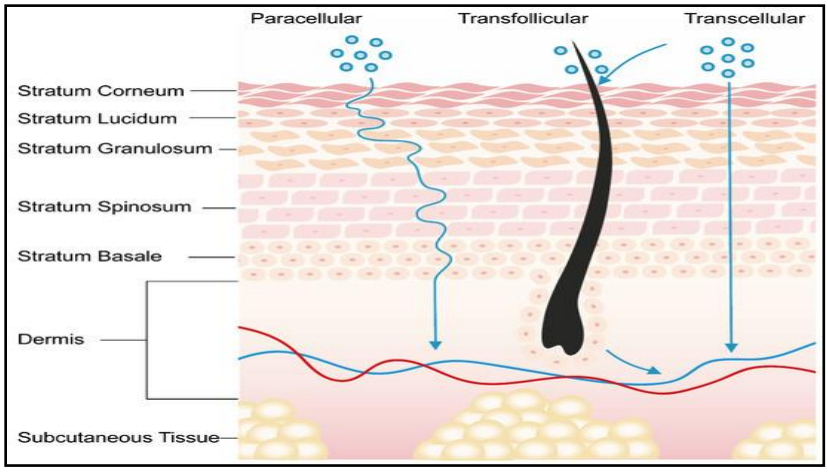


Fig No. 3 Nanocarriers

The drug aims to minimize side effects while getting to the right place. Adherence to your treatment plan is improved by employing nanocarriers, which reduce the frequency of application and facilitate compliance. Nanocarriers improve patient adherence and make it simpler to follow your treatment plan by reducing the frequency of administrations. It is

therefore a common option for those with sensitive skin since it increases patient comfort and the treatment's overall safety profile.

3.SLNs and NLCs:

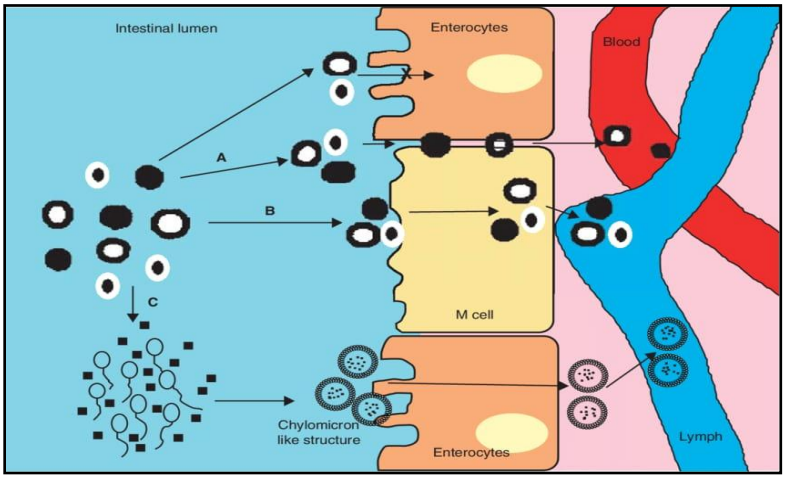


Fig No. 4 SLNs and NLCs

Drugs are encapsulated or embedded within the lipid membranes of solid lipid nanoparticles (SLNs), in this system lipids are used as a carrier. Compared to SLNs, non-lipid carriers (NLCs) offer benefits such a greater drug-loading capacity and more potential because they integrate solid and liquid lipids to transport medications. In order to improve the overall efficacy of drug delivery, SLNs have also demonstrated by ensuring in enhancing the stability, bioavailability, and ease of distribution of medications to certain tissues or cells. Because of the similarities in their characteristics, we selected SLNs as drug carriers. For example, we supply medications like ibuprofen and methotrexate through NLCs. They have a lot of potential as a means of distributing medications and are capable of carrying a lot of drugs. Improved drug absorption and effectiveness could result from increased interaction within the lipid nanoparticles and skin cells. Because lipid nanoparticles target certain cells or tissues, offer regulated drug release, and inhibit disintegration, they may improve medication delivery [34].

4.Electroporation:

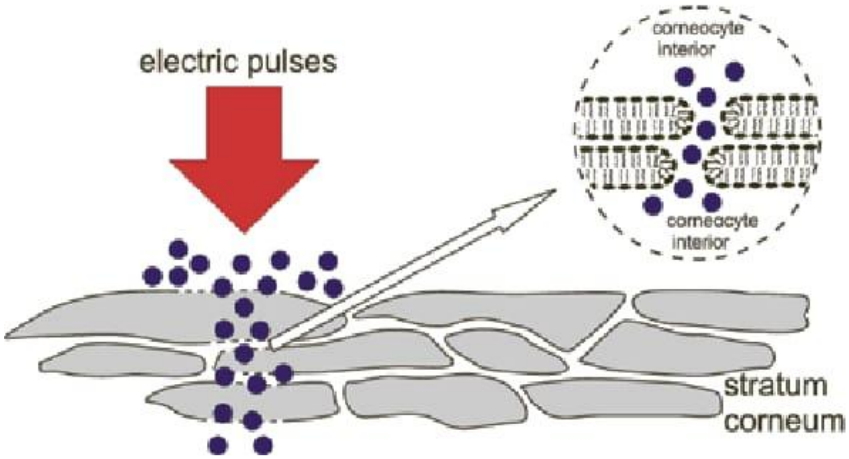


Fig No. 5 Electroporation

Short, high voltage electrical pulses with a 5-500V holes in the SC, increasing the permeability of the drug particles. By disrupting the SC's barrier properties, electroporation aims to improve drug delivery through the skin and encourage drug transport.

5.Microneedles:

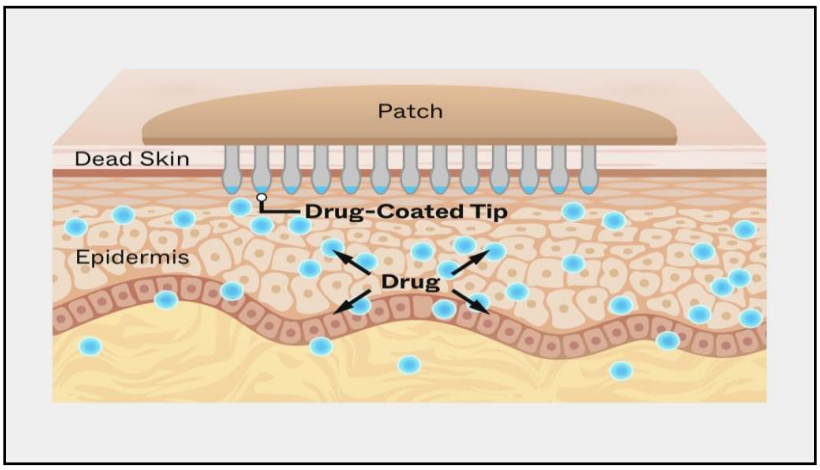


Fig No. 6 Microneedles

Microneedles are tiny needle-shaped structures that facilitate the passage of larger molecules via the stratum corneum layer. Drugs will more easily diffuse across the blood vessel-rich dermal layers thanks to this route.

- The solid microneedle operates on the ‘poke and patch’ approach. Formulations or particles are introduced straight penetrates through the layer of dermis by forming microchannels
- Hypodermic needles are similar to these microstructures in appearance. The drug is administered as a liquid formulation under pressure.
- One technique for dissolving microneedles is called "poke and flow." These microneedles, which are composed of materials likes sugar and polymer, are loaded with the medication.

6.Thermophoresis:

A temperature differential can be produced in a number of ways. One method is resistive heating, often known as Joule heating. This process, which is mostly based on Ohm's law, generates heat by applying electrical resistance to an electrical conductor. Another method of creating temperature gradients in microscale devices is by using heated or cooled channels; heat transfer occurs from the cold to the hot channels in a one-dimensional system. Knowing the thermophysical parameters of both channels allows one to approximate their temperature characteristics.

7.Needle-free injection:

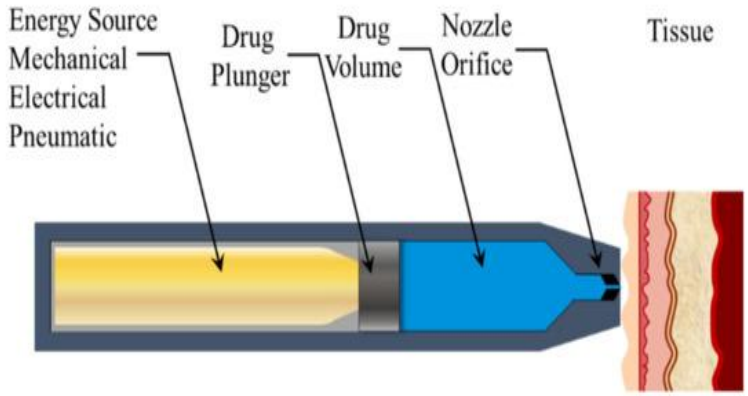


Fig No. 7 Needle-free injection

One of the most significant developments in the field of transdermal drug delivery system is the creation of needle-free injection technology (NFIT). In contrast to conventional techniques, this technology eliminates the necessity for hypodermic needles when administering medication via skin injection. Rather, a variety of forces are used, including electrophoresis, shock waves, Lorentz forces, and gas pressure. These devices function better than traditional syringes in terms of painless drug delivery.

8.Photomechanical waves:

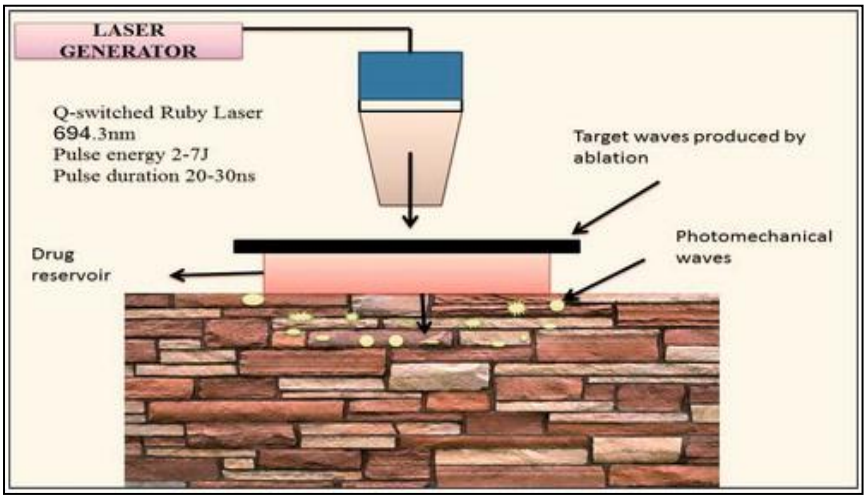


Fig No. 8 Photomechanical waves

Photomechanical waves (PWs) are pressure waves with a large amplitude produced by Q switches or mode-locked lasers. PWs' immediate touch with the biological target makes them special. PW efficiency is determined by the conversion of mechanical and wave energy. PW-mediated transdermal medication distribution is most likely motivated by the hydrophilic portions of the lacuna system's lipid structure being especially susceptible to these electrical alterations. The following parameters are used to maximize PW-mediated transdermal distribution:

- PW can be used to transport peptides and proteins.
- These parameters consist of pulse duration, wavelength [35].

9.Magnetophoresis:

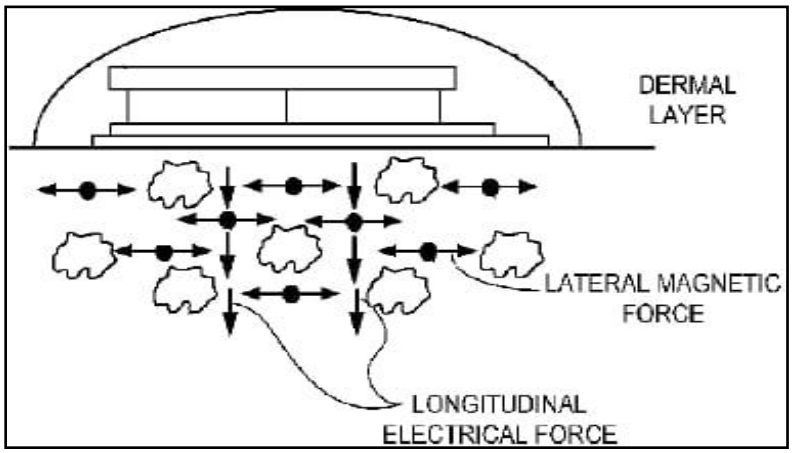


Fig No. 9 Magnetophoresis

Transdermal magnetophoresis is the process of facilitating drug transport via the skin by means of a magnetic field. The skin may change structurally as a result of magnetic field exposure, making it more permeable. In vitro drug penetration studies over the pig epidermis were conducted using varying magnetic field intensities. When the applied magnetic field is stronger, the higher "flux enhancement factor" for the drug penetration. "Magnetokinesis"

10.Ultrasound waves:

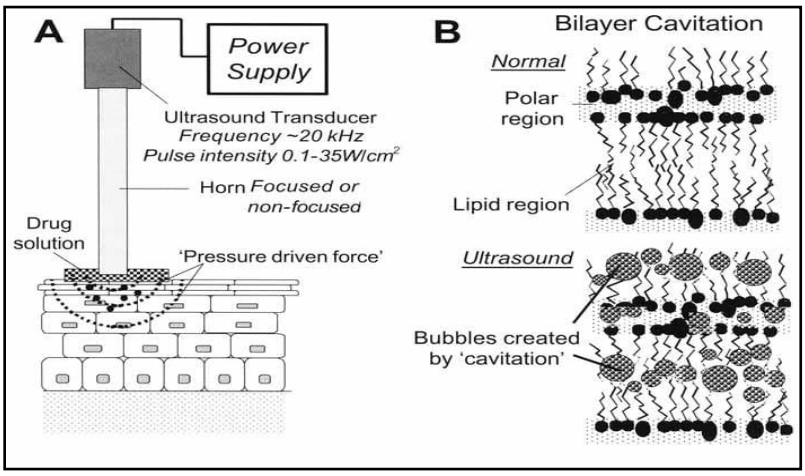


Fig No. 10 Ultrasound waves

Waves of ultrasound from the 1950s, while digital polyarthritis was treated with hydrocortisone, ultrasound techniques have been studied. The waves of pressure that are 20 kilohertz or higher than the boundaries of a person's hearing range are referred to as ultrasonic waves. Three frequency bands are used to categorize acoustic energy: Frequencies higher than 3 MHz are referred to be high-frequency sonophoresis [36]

CONCLUSION:

The category of controlled drug delivery includes transdermal drug delivery system (TDDS), which are developed to distribute medications via the skin at a predefined and regulated rate. To enhance these qualities, a transdermal medication delivery method was developed. In contrast to conventional topical drug delivery, transdermal drug delivery includes delivering a medication through the skin to provide a systemic impact. There are numerous advantages to this strategy, including longer therapeutic effect, reduced side effects, enhanced absorption, improved patient adherence, and easy

drug withdrawal. One important advantage that can be applied to the effective treatment of illnesses is the capacity of physical approaches to minimize discomfort. Additional clinical research is required to fully understand these drug delivery techniques.

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