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Review Article

Advances in Transdermal Drug Delivery: Strategies, Challenges and Clinical Application

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ABSTRACT

Being a non-invasive and productive replacement for oral and parenteral methods, transdermal delivery systems for drugs (TDDS) have become an important advancement in pharmaceutical technology. This study gives a complete overview of TDDS, highlighting how it can improve patient compliance, avoid first-pass metabolism, and keep stable plasma drug concentrations. The stratum corneum is the main barrier to drug penetration, according to the article, which explores the basic structure of the skin. The drug reservoir, polymer matrix, and pressure-responsive adhesives which are all essential parts of a transdermal patch are. The present piece spends a lot of time examining different permeation enhancement strategies, from chemical enhancers to physical approaches including iontophoresis, sonophoresis, and microneedles, respectively. The report also describes the essential evaluation characteristics needed for quality control, including thickness, folding durability, and Franz cell-based in-vitro diffusion testing. TDDS has been highlighted as a key element in modern personalised medicine in the review's conclusion, which also discusses the present difficulties and potential pitfalls of "smart" transdermal products and vesicular carriers.

INTRODUCTION

TDDS makes it easier for drugs to enter the bloodstream through the skin, allowing for systemic circulation. However, the oral route is preferred as a better drug delivery method due to its many advantages, including painless administration, patient compliance in the absence of a medical professional, and the availability of a variety of formulations, including tablets, capsules, syrups, emulsions, suspensions, and many more. There are still a lot of issues with oral medication distribution, with first pass metabolism and GIT pH being the main factors to consider when creating the dose form.[1]

Therefore, the parentral route is the next most effective method to declare the medication directly

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into systemic circulation with 100% bioavailability4 in order to address the mentioned primary problem. There are still a lot of issues with oral medication distribution with first pass metabolism and git pH being the main factors to consider when creating the dose form therefore the parentral route is the next most effective way to declare the drug directly into systemic circulation with 100 % bioavailability in order to address the aforesaid essential problem.[1]

However there are drawbacks to this approach as well including as discomfort during application increased expense extremely low patient compliance difficulty with the self-administration in the absence of a medical professional and particle size because tdds transports medication into the systemic circulation through diffusion processes following skin application it may be preferred as a favourable route to address the shortcomings of both the oral and parental routes.[1]

A group of physicochemical technologies that can govern the transport and release of pharmacologically active molecules into cells, tissues, and organs such that these active substances can have the best possible effects are collectively referred to as drug delivery systems (DDS). To put it another way, DDS encompasses drug formulations and methods of administration that effectively deliver the medication to maximise therapeutic efficacy while minimising side effects. There are numerous administration methods, including by mouth, percutaneous therapy, lung respiration, buccal administration, and intravenous injection, depending on the delivery route. The transdermal drug delivery system (TDDS) is one of the more attractive methods.[2]

Unlike classical direct administration strategies that require needle-based injections, TDDS has become known as one of the most extensively studied methods of noninvasive drug delivery into the body through the skin. The delivery of several therapeutic drugs has been greatly impacted by TDDS, particularly in the areas of hormone therapy, pain management, and the treatment of pathologies affecting the central nervous system and cardiovascular system. Since TDDS does not need transit via the gastrointestinal tract, there is no loss from first-pass metabolism, and medications can be provided without interference by intestinal flora, pH, or enzymes.[2]

TDDS can also be used to regulate medication release in compliance with intake limitations, adding adds to the method's high persistence.But because of the natural barrier to the skin, it still does not reach its full potential. The skin, which has a multilayered structure and is the body's outermost organ, serves to shield the body from external hazards like heat, chemicals, and toxins. Such skin can be differentiated into two layers: the dermis, which makes skin cells and contains blood arteries, and the epidermis, which serves as a barrier. Each layer comprises components that obstruct transdermal permeability.[2]

First, the corneal layer, the outermost layer of the epidermis, has the skin barrier effect, which is the ability to prevent substances on the outside. When it comes to the movement of materials with enormous mass, the barrier effect is quite significant. It has been recognised in TDDS that the intracellular pathway operates to deliver drugs with tiny molecular weights.[2]

2. POLYMER

The macromolecules designated as polymerisation are produced when two or more monomer units are joined jointly. In pharmaceutical formulations, these structures are regarded as the basic element. Although they manage drug release, these polymers are key to the formulation of TDDS.

TDDDS are simply dependent on three types of polymers: natural, semi-natural, and synthetic.[1]

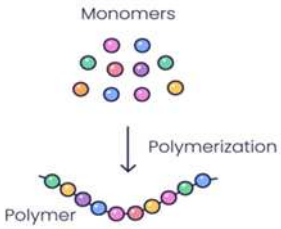

FIG. 1: POLYMER

TYPES OF POLYMERS

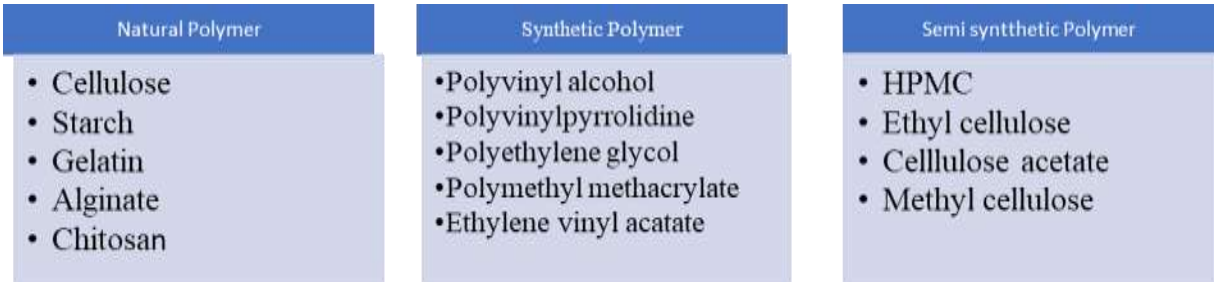

FIG. 2: CLASSIFICATION OF POLYMER

3. TRANSDERMAL PATCH

Although by mouth is the most prevalent drug delivery method, it has several drawbacks, such as first pass metabolism and drug degradation in the gastrointestinal tract as a result of pH, enzymes, etc. A unique drug delivery process originated to address these issues. It was applied topically. Transdermal delivery method or patches. This technique creates medicated adhesive patches that, when applied to the skin, supply a therapeutically effective dose medicament.[3]

They come in various sizes and contain several components. Applying them to clear skin permits the active molecules to get through skin barriers and into the systemic circulation. They vary in various shapes and contain various components. Placing them to skin that is healthy allows the active substances to penetrate through skin barriers and enter systemic circulation. A transdermal patch with a high dosage of medication that is left on the skin for a long time and diffuses into the circulation of the blood.[3]

Generally, there are three ways that medicines can get into the skin:

a) By method of hair follicles.

b) By means of sebaceous glands.

c) Through the sweat duct.

It isolates the patch while in storage. During using, the liner requires to be peeled out. It is an integral part of primary encapsulation, which prevents pharmacological leakage from the polymer matrix.

Adhesive: This substance is used to join the fix's components and bind it to the skin. Adhesives include silicon-based adhesive polymers, polyacrylate, and polyisobutadiene. Membrane

Drug release from reservoirs and multi-layer patches is controlled by the membrane. [4]

Materials like chitosan and poly-2-hydroxyethylmethacrylate are regularly employed to make it. High-density polyethylene, silicones, polyester elastomers, polyacrylonitrile, and ethylene vinyl acetate copolymer are a few examples. The drug's active component comes into intimate contact with the release liner. Polymer: The polymer must be chemically and environmentally compatible with medicine and other additives including adhesives, plasticisers, and permeation enhancers.[4]

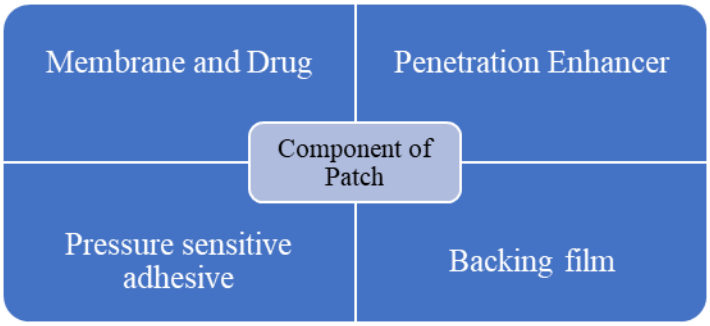

FIG. 3: COMPONENTS OF PATCH

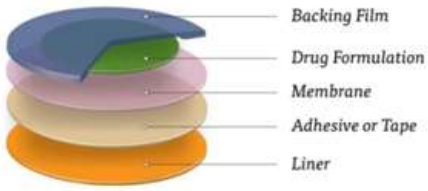

FIG. 4: STRUCTURE OF PATCH

3.1 TYPES OF TRANSDERMAL PATCH

1. Adhesive using a single-layer drug: The bonding agent layer of this kind of patch is in care of both medication release and adhering the several layers and all of the components to the skin. A interim liner and backing surround the adhesive layer.[4]

2. Adhesive with multiple layers of drug: In that both sticky layers are in charge of medication release, this kind of patch is identical to a single-layer patch.But in this method, there is a further layer that the adheres to the medicine and usually is (though not always) separated by a membrane. Additionally, this patch offers both permanent and temporary lining material layers.[4]

3. Reservoir: In this approach, the substance is released across the micropore rate-controlled membrane whenever a drug reservoir is positioned between the support material and the rate-control membrane. The medication may be distributed in a rigid polymer matrix within the reservoir compartment or is available as a gel, suspension, or solution.[4]

4. Matrix: The adhesive and backing material, whose serve as the formulation's outer layer, are the primary features of the matrix system. To create a matrix film, medications are first combined with other additives like polymers and enhancers to make a viscous solution. The solvent is then evaporated.[4]

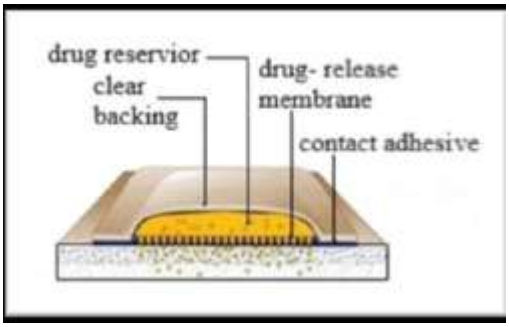

FIG. 5: STRUCTURE OF TRANSDERMAL PATCH

4. PERMEATION ENHANCER

By diminishing the skin's impenetrability, penetration improvement agents aid in the planned drug's (penetrant's) movement through the skin. Pharmacologically inert, nonirritating, nontoxic, nonallergic, compatible with medications and excipients, odourless, tasteless, colourless, practical, and having good solvent qualities are some of the desired features for permeation enhancers.The ability of the penetrant (drug) to enter the skin in amounts adequate to sustain therapeutic levels is essential for the success of a topical matrix patch. Chemical enhancers are often utilised in the formulation process of transdermal drug delivery systems (TDDS) since they aid in lowering the skin's permeation barrier qualities.[6]

4.1 IDEAL PROPERTY

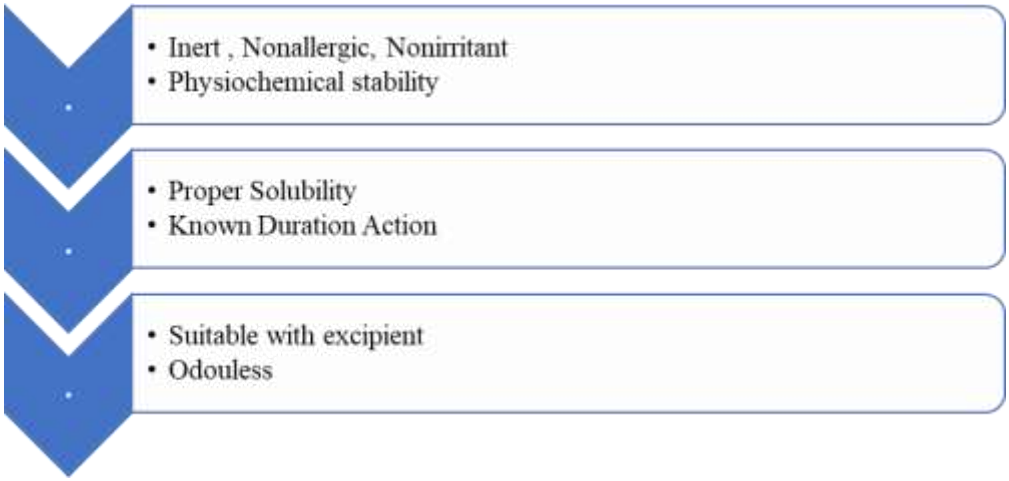

FIG. 6: IDEAL PROPERTY OF PENETRATION ENHANCER

4.2 APPROACH OF PENETRATION ENHANCER

4.2.1 CHEMICAL PROCESS:

Mechanism: it has three essential avenues that penetration boosters take:

1. Breaking the stratum of corneum's extraordinarily orderly structure.

2. Interaction with intercellular proteins.

3. Better medication redistribution in the stratum corneum with the aid of a co-enhancer (solvent) the enhancers work by adjusting either of the three pathways.

This can be executed in two ways: by either swelling the solvent or by causing a conformational shift in the skin proteins. For instance, the stratum corneum expands lipophilic due to the fatty acid enhancers. The enhancers' goal is to enhance the drug's dispersion on the sc so that it disintegrates into the skin's surface.[7]

The use of alcohol may increase superficial penetration by a number of procedures, involving standardised stratum corneum expansion, lipid and protein extraction, and hence a raising the drug's solubility or partitioning into the host skin in formulation . Here are a few cases: Polyols or ethylene glycol and water (PG): Propylene glycol increases the flow of ketoprofen, heparin sodium hydrochloride, and verapamil hydrochloride. propane glycol inhibits the ketoprofen receptor flow at high concentrations. When azone and propylene glycol are combined, the cyclosporine flux is enhanced. PG enters the hydrogen bonding sites by solvating SC keratin.[7]

4.2.2 PHYSICAL METHOD

Drug diffusion, emigration, or electro-osmosis via the skin over a concentration gradient are all part of the mechanism. The majority of the fluid and counterions move in the same way during electro-osmosis. The motion of this fluid flow without the focus gradient is the foundation of iontophoresis. The skin has perhaps negative charge under normal circumstances, and the cations are generated by counterions. Flow occurs from cathode to anode in compliance with the electro-osmotic principle. By raising their flow, this optimises the absorption of cationic treatments. Iontophoresis was originally carried out with continuous DC current, whereas pulsed DC frequencies are now also used to boost penetration.[7]

TABLE 1: CLASSIFICATION OF PENETRATION ENHANCER

Class	Subclass	Examples
Natural	Terpenes	Menthol, Limonene, Cineole
	Essential oil	Basil oil, Niaoli oil , Rosemaryoill
	Fatty Acid	Oleic acid, Linolic acid
	Other	Aloe vera , Papain
Synthetic	Sulfoxides	DMSO
	Azones	Laurocapram
	Pyrrolidones	NMP
	Surfactant	Tween 80 , Span 20

5. STRATUM CORNEUM

Except for the manufacture of vitamin D, virtually all epidermal action can be described as protective, and almost all of these crucial protective activities further relate to the SC. The place of certain specialised defensive functions in the corneocyte or additional cellular matrix is mostly determined by the SC's structural configuration into a two-compartment system.A variety of functions has to be present in the SC interstices due to lamellar bodies standard LB, which secrete a range of proteins and lipids into the extracellular chambers.[8]

SC, which is a multifaceted tissue consisting up of lipid-deficient fibroblasts embedded in a fat-rich extracellular matrix that maintains the barrier, is generated as an outcome of epidermal transition. The corneal LB, a distinct lipid and enriched with hydrolase secretory organelle, is produced by a very active lipid-synthetic factory that acts in all of the nucleated cell layers of the epidermis.[8]

Although corneocyte peptides have been thoroughly investigated as markers of epidermal differentiation, it is unclear how they perform in the permeability barrier. However, it is generally recognised that these anucleated cells carry out additional vital epidermal tasks.By acting as "spacers," or driving water and living things to go through a convoluted, extracellular hydrophobic channel, and by acting as a scaffold for lamellar cellular membrane organization, corneocytes have a significant effect on permeability of the barrier.[8]

Because they are easily readily accessible have a thin SC, the human biceps and side stomach are the best areas for impedance analysis in an in vivo study.. In addition to its tremendous area and low thickness, the vertebrate abdomen is ideal for in vitro studies of any kind. Studying the skin's anatomy is essential to revealing the skin impedance model. In this case, the skin structure will be portrayed from the outward to the innermost layer. The physical basic concepts of skin transfer are then explored. In the end, the model of skin interference is studied.[9]

The skin of rodents plays an important role to the body's defence. The three principal layers of human skin are the dermis, viable epidermis, and SC. likewise there are some horizontal skin appendages, such as hair follicles and sweat glands. The corneum stratum the outermost layer,

has been suggested that it is the largest impediment to transdermal transfer. The thickness of SC varies widely between normal people and body sections. The forearm's thickness is said to be among 10 and 40 μm. Corneocytes, which are dead cells without nuclei embedded in the packed and well-organised lipid matrix, make up the vast majority of SC. SC's moisture content is preserved at roughly twenty percent.[9]

SC's level of moisture stays stable at approximately twenty percent. The repellent features of a skin and the small sized transport channel, which has a high skin impedance , are expected to be established by this kind of structure and constitution. In a nutshell when the frequency is less than 1000 Hz, high skin impedance produced on by the SC layer can be measured. The saturated lipids which include ceramides, cholesterol, and free fatty acids can act as an additional permeability barrier .[9]

Transdermal transport may be harmed by SC defects, while it is still unsure to what degree. In conclusion, because of its unique physiological structure, the SC traits will substantially influence the examination of skin permeability and the determination of surface conductivity. The real-time skin epidermis, which is the layer under SC, is contrasted with the divided dead cells of SC. With the exception of some areas like the palm and sole, the average thickness corresponding to viable epidermal layer Epithelial cells, follicular epidermis, and a few concomitant oedema, such as hair follicles, sebaceous glands, and glands for sweat, together up the viable keratin.[10]

The SC operates as simultaneously an inside-out barrier to uphold skin hydration and an outside-in barrier against foreign irritants. The SC's insolubility and its tightly packed, highly cross-linked proteins have made it difficult to thoroughly analyse its barrier nature using conventional imaging methods. In this examination, we used conventional imaging mass spectra (MS) to assess the SC with the objective to get overcome these challenges.[10]

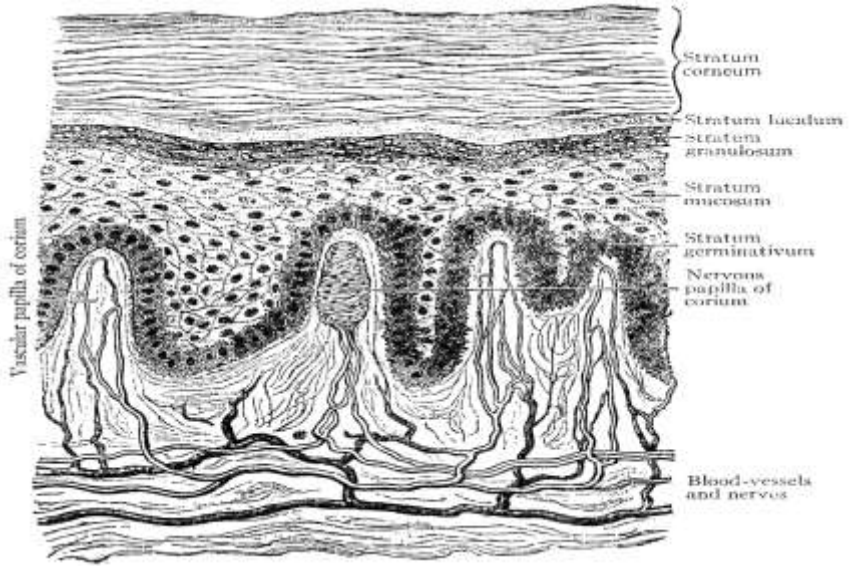

FIG. 7: STRUCTURE OF SKIN

By ionising molecules from each X-Y point then back analysing the ionised molecules and protein ion fragments by MS to determine them by their mass-to-charge ratio (m/z), conventional spectroscopy MS of biological samples enables visualisation of the distribution spatially of molecules on a sample, typically involving a thin cellular section. The SC has been considered as a

homogeneous barrier, and it is unclear if it is composed of layers with different purposes. Topically applied tiny molecules could travel more in upper layers compared with lower ones, as indicated by previous studies. The SC has been considered as a homogeneous barrier, and it is unclear if it is composed of layers with different purposes.[10]

6. MICRONEEDLE (MN)

The intention of MN technology, also known as an active transdermal delivery method, is to replace conventional syringe injections. The medicine is delivered via a minimally invasive procedure using the MN array, which permeates the stratum corneum. These arrays are made up of tiny needles that range in height between 25 to 2000 μm. Medicines and vaccine delivery, beauty care, and illness testing are just a few of the uses for MNs. This review paper provides more representations of MN's array of structural shapes, forms, materials, and methods of fabrication.[11]

From the use of substantial amounts syringes to the current contemporary aesthetics of microneedles, tiny needles notions have evolved over time.MNs can be generated primarily because of their capacity to pierce the skin without splitting or bending. The MN manufacturing difficulty has been addressed using into account a number of aspects, including material, process of manufacture, and design. Different types of MNs have been created using an assortment of materials. These materials encompass silicon, metals, ceramics, and polymers. Biomedical applications such as medication delivery, the creation of tissues, and biomedical devices have employed the use of an assortment of material types.[11]

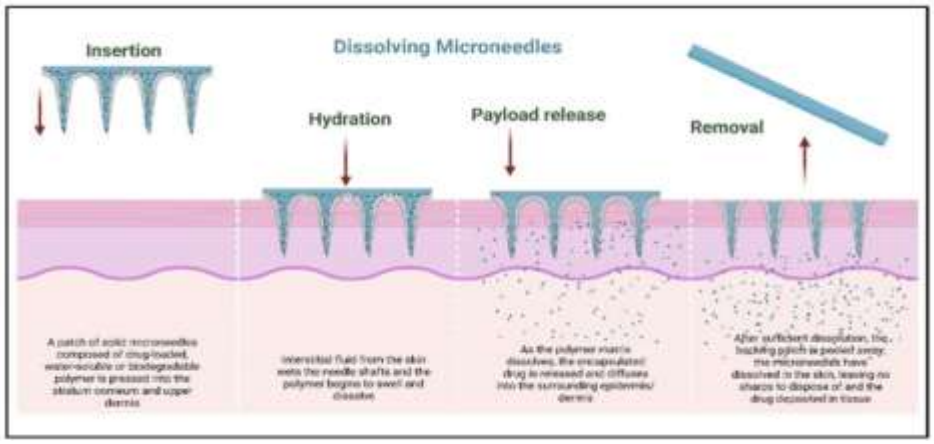

FIG. 8: APPLICATION OF MICRONEEDLES

Multipurpose silicon MNs permit ongoing, uninterrupted administration of medications across various physiological areas. MNs carrying glucocorticoid greatly decreased fluid retention and inflammatory in the knee joints of rats with osteoarthritis. Meloxicam is not highly dissolves in water. Similar to other NSAIDs, it may have gastrointestinal adverse effects that reduce patient adherence. Furthermore, because osteoarthritis (OA) is a chronic condition, pharmaceuticals used to treat it tend to be used over long periods of periods.[12]

In along with meloxicam for osteoarthritis, MNs innovation was also used to treat rheumatoid arthritis as well, using an array of additional drugs, such as methotrexate,, artemether alkaloids, capsaicin, and Etanercept (EN). Consequently, MN transdermal circulation offers a possible mode of administration towards therapy of arthritis. The

use of this method uses a minimally involved delivery system to regulate the rate of drug release, lower the required dosage amount, and mitigate the incidence of drug-related side effects. [12]

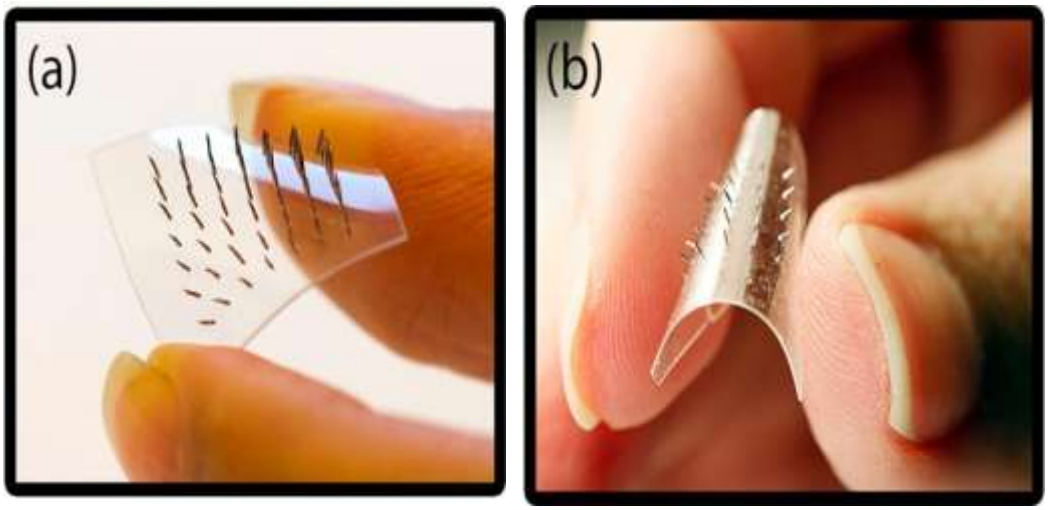

FIG. 9: MICRONEEDLES

The micrometer-sized crystalline lipophilic medication was changed into a micrometer-sized amorphous form appropriate for transdermal diffusion. In addition, it built the DMN framework for delivery via the transdermal layer. Regular patches usually have simple microstructure and release medicine more slowly, which reduces their therapeutic effect and wider medical usefulness. MNs, on one another hand, have porous microstructures. In order to facilitate either controlled, or sustained pharmaceutical release, they can use polymeric polymeric substances with multifunctional antibacterial capabilities to incorporate skin regeneration or the formation of cutaneous replacement factors or medication.[12]

In terms of architecture and design, solid small needles constitute one of the most fundamental There is no prescription drugs or excipient in these solid-material microneedles. The primary goal is to pre-treat the skin by penetrating the stratum corneum and epidermal layer with micron-sized holes that momentarily break the skin barrier before cutting deeply enough to induce unpleasant sensations or bleeding.A prescription drug formulation—such as a gel, lotion, or patch—is applied to the skin area that has been broken down by these robust microneedles.[13]

This substantially raises drug porousness and absorption through the system by enabling drug diffusion within the microchannels entering the dermal capillaries. The above method improves usability by minimising the thick, impenetrable stratum corneum, particularly for peptides that normally have low skin contact. Another advance in microneedle systems is coated microneedles, a procedure in which drug is directly applied to the surface of solid microneedles. The medication diffuses into the tissues beneath after dissolving off the microneedle after being put into the skin.[13]

Microneedles typically are coated by dip-coating, meaning they are submerged in a drug-containing solution.To maximise delivery efficiency, the pharmaceutical should also normally be concentrated nearer to the microneedle tip, which actually breaches the skin. Coated microneedles are effective, but a capacity to load drugs is limited, in particular for high-dose therapies.[13]

Although the amount of medication given can be doubled by several coating cycles, this also

enhances sophistication and material consumption. The active pharmaceutical substance is embedded in dissolving microneedles, a sophisticated drug delivery technology composed solely of biodegradable or water-soluble materials. These microneedles are made to totally dissolve in the skin, removing a chance of needle reuse or damage and producing no sharps waste. They are usually made by pouring drug-polymer combination into moulds and allowing them solidify, a step known as solvent casting.[13]

Common polymers that are safe, biocompatible, and able hone in hard structures with embedded prescriptions include carboxymethyl cellulose molecule (CMC), methyl cellulose, and sugars like sucrose and trehalose, among other substances.The substance is contained in the outermost section of these microneedles, which penetrates the skin first. It must have enough mechanical strength to break the skin without disintegrating. Low viscosity is also necessary to effectively satisfy mould voids without causing inflated bubbles.[13]

When surrounded by liquids from the body, the cross-linked, hydrophilic molecules that form up gelatin microneedles progressively swell and do not disintegrate. The drug has been combined into the backing patch, base substrate, and microneedle tip in these systems, which are intended for extended-term drug delivery.[13]

7. CONTROLLED RELEASE DRUG RELEASE

This drug delivery strategy keeps a steady quantity of a medication in the blood and tissue for a period of time. Pharmacokinetics (PK) curves show how a drug's plasma concentration fluctuates over time for both conventional as well as controlled dosage methods. Bolus PK, where the drug level varies above and below the minimal effective concentration, is typical for multiple dosing with oral tablets or injections in a traditional delivery system. By contrast, a single dosage of controlled drug administration from a particular formulation or device demonstrates zero-order PK in the controlled delivery system. Within the therapeutic window, the pharmaceutical levels are persistently maintained.[14]

To avoid unexpected drug effects on other organs, it is important to target the substance to the place where the targeted pharmacological activity is essential. Localised delivery, ligand attachment as usual, and antibody tagging may achieve this. Targeting distributing drugs to specific regions, such as the brain, bone, and testicles, is constrained by biological barriers. Alternatives that can get past the barriers and reach the target site are medications made with nanocarriers and permeation enhancers.[14]

To get the greatest in vitro in vivo co-relationship (IVIVC), suitable models from animals must be constructed for each type of delivery technology. This aids in crossing the gap between conclusions of clinical study and in vivo animal experiments. Determining the correct biomaterial and designing the dosage form reflect substantially on pharmaceutical administration methods. In this regard, if it is necessary for the pharmaceutical to be released after rectal injection, the biomaterial needs to have a melting point of in excess of 37 °C or be soluble at that pH.[14]

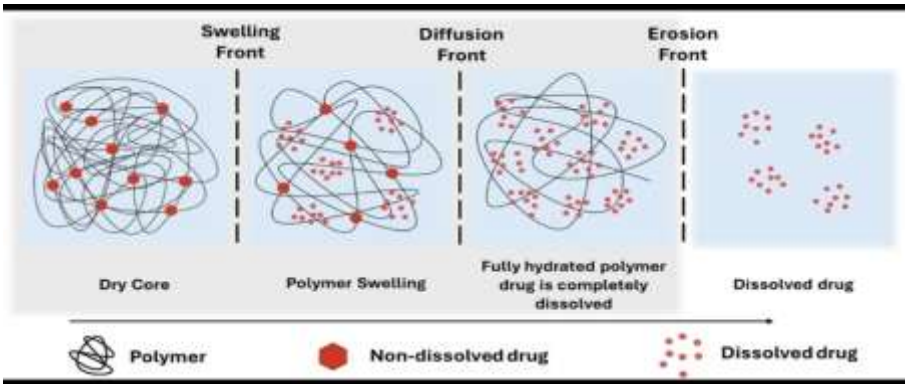

FIG. 10 : CONTROLLED DRUG DOSAGE FORMS

7.1 TYPES OF CONTROLLED RELEASE

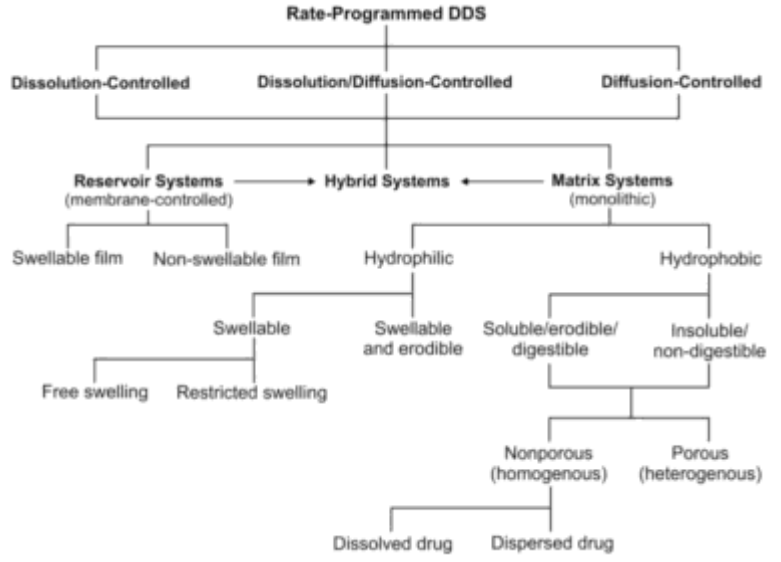

FIG. 11: TYPES OF CDDS

There are two types of diffusion-controlled systems: homogeneous or matrix systems and membrane-controlled systems. In membrane-controlled systems, a thin polymeric membrane encompasses the drug, which remains in the core as a reservoir. The membrane may be non-porous or porous. medications are offered by diffusion through the membrane, and the rate of release is determined by the membrane's thickness, porosity, and the physical properties of the medications (dosage, protein binding, segregation coefficient, molecular dimensions and diffusivity). Tablet encapsulation and press coating are common strategies used to create membrane-controlled reservoir systems.[14]

Devices for ReservoirsIn this approach, a medication core is packaged in a water-insoluble polymeric molecule. Drug will partition into the membrane and exchange with the fluid surrounding the particles (or) tablet.Using a rate-limiting membrane, the active substance spreads into the surrounding environment. The drug in question delivery rate in reservoir systems remains essentially unaltered.Matrix Equipment the medicinal product or active constituent spreads across the polymer matrix in the matrix devices in order to create an unified system called a matrix system. When drugs moves from its polymer matrix into the surrounding environment, diffusion gets place. With this kind of system, the rate of

release commonly reduces as it goes on when the active agent needs a longer diffusion time to release due to an increasing distance distance travelled.[15]

Substances having controlled dissolution Very permeable polymers or microencapsulation manage the drug's rate of dissolution in these products. The treatment may dissolve after the covering has been removed. The rate of medication release can be altered by altering the coat's composition and thickness. To supply a pulse dose quickly following administration, some preparations comprise an amount of the entire dose as an instant release component. It is common to encapsulate or assemble the pellet dosage forms of standardised or dissolution-controlled commodities such as standardised tablets.[15]

There are two groups of dissolution-controlled products.

A. Control of Encapsulation Dissolution : A dissolved slowly substance is bound to individual drug molecule particles or granules adopting these technologies. The coated particles can be put in capsules or compacted straight into tablets. Microencapsulation influences the drug's rate of dissolution and, thereby, its availability for absorption. The medication may collapse when its cover gets removed. The rate of releasing drugs can be regulated by adjusting the coat's composition and thickness.[15]

B. Control of Matrix Dissolution :Combining the medication with a slow-dissolving carrier is a different procedure in this system. Here, the drug's rate .The rapidity at which the dissolve fluid accesses the matrix, porosity, the presence of hydrophobic additives, the system's wetting capacity, and the particle's surface each affect release.[15]

7.2 FACTOR AFFECTING DESIGN OF CONTROLLED DRUG DELIVERY SYSTEM

Physiological properties

a. Aqueous Solubility's

b. Partition coefficient (P-value)

c. Drug pKa

d. Drug stability

e. Molecular size & molecular weight

Biological factors

a. Absorption

b. Biological half life

c. Dose size

8. FIRST PASS METABOLISM

The amount that gets the site of action decreases if an agent is metabolised in the liver, gut wall, or gastrointestinal tract before it enters the systemic circulatory system. This effect, often known as "first-pass" metabolism or the "first-pass" effect, generally arises from liver metabolism. The 20-fold contrast between the therapeutic parenteral and oral doses can be addressed by the metabolization of propranolol to an inactive molecule. Grapefruit juice can improve the bioavailability of medications including felodipine, terfenadine, and ciclosporin4 by slowing the intestinal digestion enzymes; in many instances, this interaction has been lethal. Glyceryl trinitrate, for instance, can be provided sublingually, buccally, transdermally, and other meds (like morphine) can be provided rectally so as not to damage the liver.[16]

PGP should be considered to be one aspect of the "first-pass effect" given that it hinders absorption in the intestinal tract. Indeed, it can serve as a "gatekeeper" or "set up" for forthcoming CYP actions. The inhibition and induction of PGP mostly impact the pace of medication absorption, while the inhibition and production of colonic CYP3A enzyme enzymes from metabolic processes alter drug absorption.[16]

First pass metabolic process, sometimes referred to as a pre-systemic process metabolism, describes the way a drug-like molecule undergoes metabolic processes prior to entering the systemic circulation. It is most common in treatments taken orally, while it may occur as well through other methods of administration. Whenever first-pass metabolism normally takes place, a drug's bioavailability is often decreased. While alternative methods of administration, including injections via IV, require a qualified person to provide a dose, oral dosage is a standard method for delivery when creating prescription drugs for the pharmaceutical business.[16]

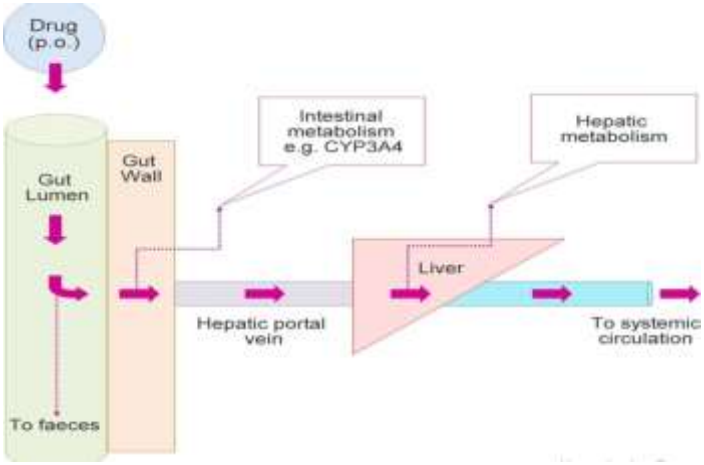

FIG. 12: EFFECT OF FIRST PASS METABOLISM

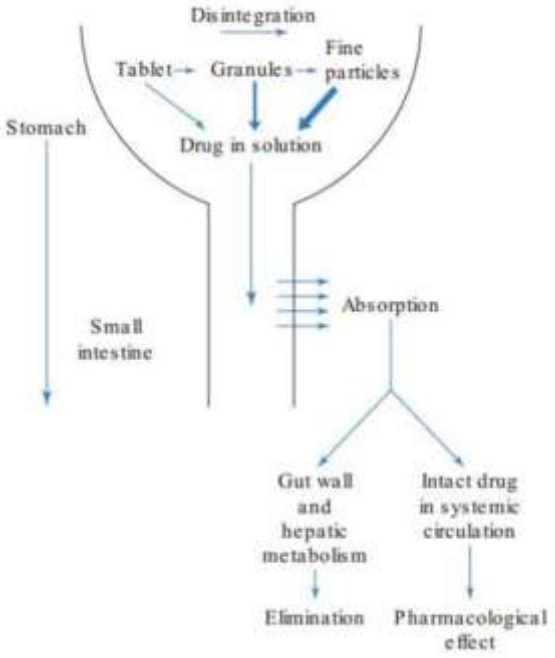

FIG. 13: ACTION OF FIRST PASS EFFECT

CONCLUSION

Transdermal drug delivery systems (TDDS) are a novel and promising way to get around the drawbacks of traditional drug delivery methods, especially parenteral and oral ones. TDDS improves medication bioavailability and guarantees controlled and prolonged drug release by avoiding first-pass metabolism and gastrointestinal degradation. Drug penetration into the stratum corneum has been greatly enhanced by the use of polymers, permeation enhancers, and cutting-edge technologies like microneedles. Notwithstanding difficulties with the skin's barrier qualities, ongoing developments in formulation and administration methods have increased the use of TDDS in a variety of therapeutic contexts. All things considered, TDDS provides a non-invasive, patient-friendly, and effective drug delivery platform with enormous potential for further pharmaceutical development. Drug penetration and controlled release across the skin have been greatly improved by the combination of polymers, permeation enhancers, and cutting-edge techniques like microneedles. Even though the stratum corneum is still a significant obstacle, ongoing research has produced creative solutions. TDDS reduces side effects and dosage frequency while simultaneously increasing treatment efficacy. TDDS offers a safe, non-invasive, and patient-centered strategy for the management of a variety of chronic and systemic disorders, and it has significant future promise thanks to continuous developments in materials and delivery technology

REFERENCES

1. Thakur G, Bassi P, Garg K, Kumari N. Transdermal drug delivery system: current progress and prospects for the future—an overview. Research Journal of Pharmacy and Technology. 2025;18(7):25-27
2. Jeong WY, Kwon M, Choi HE, Kim KS. Recent advances in transdermal drug delivery systems: a review. Biomaterials Research. 2021;25(1):24:
3. Tayal S, Jain A, Ansari MM. A review on transdermal patch: a novel approach for non-invasive drug administration. Asian J Basic Sci Res. 2025;7(2):141–150.
4. Shaikh N, Srivastava R. A review on transdermal drug delivery through patches. Int J Pharm Exp Dermatol. 2024:117.
5. Abiyyatun A, Wahyuning D N, Hendradi E. Transdermal patches: a review of a new drug delivery system approach. J Dermatol Venereol. 2020:25–31.
6. Das A, Ahmed AB. Natural permeation enhancer for transdermal drug delivery system and permeation evaluation: A review. Asian Journal of Pharmaceutical and Clinical Research. 2017;10(9):55-59
7. Roy N, Agrawal M, Chaudhary S, Tirkey V, Dhwaj A, Mishra N. Review article on permeation enhancers: A major breakthrough in drug delivery technology. International Journal of Pharmaceutical Sciences and Research. 2017;8(3):1001–1007.
8. Elias PM. Stratum corneum defensive functions: an integrated view. J Invest Dermatol. 2005 Aug;125(2):183-200. doi:10.1111/j.0022-202X.2005.23668.x.
9. Lu F, Wang C, Zhao R, Du L, Fang Z, Guo X, Zhao Z. Review of stratum corneum impedance measurement in non-invasive penetration application. Biosensors. 2018;8(2):31.
10. Kubo A, Ishizaki I, Kubo A, Kawasaki H, Nagao K, Ohashi Y, et al. The stratum corneum comprises three layers with distinct metal-ion barrier properties. Sci Rep. 2013;3:1731.
11. Aldawood FK, Andar A, Desai S. A comprehensive review of microneedles:

types, materials, processes, characterizations and applications. Polymers (Basel). 2021;13(16):2815. p. 45-53.

12. Sekar L, Seenivasan R, Reddy MV, Varma KD, Ahmed SS, Pachiyappan JK, et al. Advancements in microneedle technology: comprehensive insights into versatile drug delivery mechanisms. Int J Appl Pharm. 2024;16(2):75-77
13. Gandhat S, Ugale S, Kumavat S, Gadge K, Dandawate N, Bhor V. Microneedles in transdermal drug delivery: a comprehensive review. J Drug Deliv Ther. 2025.p.110-119
14. Adepalli S, Ramakrishna S. Controlled drug delivery systems: current status and future directions. Molecules. 2021 Sep 29;26(19):5905. p.265-287
15. Yadav U, Rao CMMP. Review on controlled release dosage forms. World J Pharm Med Sci. 2024;191-194
16. Elsevier. First pass effect [Internet]. Amsterdam: Elsevier; [cited 2026 Apr 17]. Available from: https://www.sciencedirect.com/topics/medicine-and-dentistry/first-pass-effect

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