Journal of Pharmaceutics & Drug Development
Volume 10 | Issue 2
ISSN: 2348-9782

Review Article Open Access

Review on Transdermal Drug Delivery System-Focus on Innovative 2 Transdermal Dosage Forms

Bedre Ashwini[1,*], **Bhoge Durga**[2], **Pradyumna Ige**[3]

Abasaheb Kakade College of B.Pharmacy, Bodhegaon, Tal. Shevgaon Dist. Ahmednagar

[*]**Corresponding Author:** Bhoge Durga, Abasaheb Kakade College of B.Pharmacy, Bodhegaon, Tal. Shevgaon Dist, Ahmednagar, 414503, Tel: 9373384856, E-mail: durgabhoge03102000@Gmail.com

Citation: Bedre Ashwini, Bhoge Durga, Pradyumna Ige (2023) Review on transdermal drug delivery system-Focus on innovative transdermal dosage forms. J Pharma Drug Develop 10(2): 204

Received Date: June 15, 2023 **Accepted Date:** July 15, 2023 **Published Date:** July 24, 2023

Abstract

The transdermal drug delivery system is technique that provides drug through the intact skin. Skin penetration enhancement techniques have been developed to increase the bioavailability of drug substance. These review describes various transdermal patches available in market, types of patches, basic components, polymer used in formulation. The novel drug delivery method do well and complete with those already on the market the main problem that requires consideration include device design and safety, efficacy, ease of handling and economical. Transdermal drug delivery system represent the most attractive method among these because of its low rejection rate, magnificent, ease of administration and better convenience and compliance with patient. This review article provide an overview of transdermal drug delivery system contains various innovative dosage forms. In comparison transdermal patch are effective due to its easy to apply and non-invasive.

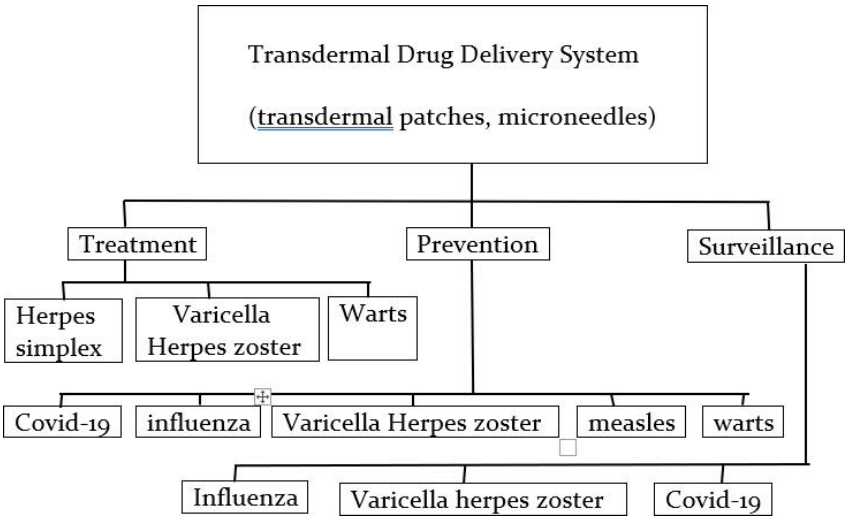
Keywords: Transdermal Drug Delivery; Enhancement Methods; Bioavailability; Matrix System; Transdermal Patch; Transdermal Gels; Transdermal Spray

Introduction

"Transportation of drug across the skin into the systemic circulation is known as transdermal drug delivery system". OR Transdermal Drug Delivery System also called as "patch" are dosage forms designed to therapeutically Effective amount of drug across a patient's skin. Transdermal Drug Delivery System established itself as an fundamental segment of novel drug delivery system. Transdermal Drugs are corrective separate dosage forms. It transfer the drug through intact skin at a controlled rate into the systemic circulation. Transdermal Drug Delivery System is a not causing or suffering physical pain method of delivering drugs. Compared to injection delivery, Transdermal Drug Delivery System avoid pain, bruising, and bleeding, which improves patient acceptance and compliance. The aim of dosage design for transdermal products is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drugs the skin.

Transdermal Drug Delivery is an attractive substitute for oral drug administration is it bypass first pass metabolism gastrointestinal effects and moreover, it can overcome the poor patient conformity associated with other drug delivery routes. Depending on the delivery route, there are many types of administration modalities, Such as oral administration route, intravenous injection, mucosal administration, and lung in halation. Among them, the transdermal drug delivery System represents an attractive approach. Transdermal Drug Delivery system useful to various diseases such as Parkinson's disease, Alzheimer's disease, anxiety, skin cancer, female sexual disfunction Cardiovascular disease, postmenopausal bone loss, and urinary incontinence.

One of the major drawbacks of transdermal Drug Delivery Systems has been their inability to deliver the drugs through the skin within the desired therapeutic range. To overcome this limitation, many studies have been concluded on new drug delivery methods using emerging micro and nanotechnologies.



Flowchart 1: TDDS for fighting common viral Infection [4]

Transdermal route has compete with oral treatment as the most successful New research area in drug-delivery, as oral treatment involves achievement, and maintenance of drug concentration in the body within a beneficially productive range by introduction in the body follows a peak & through profile leading to a significant chance of adverse effects or therapeutic failure; large amount of drug is lost in the surrounding area of the target organ and close attention. Conservation is required to monitor therapy to avoid overdosing [4]. Transdermal drug delivery System is one of the system lying under the Category of controlled drug delivery, in which the purpose is to deliver the drug between, the skin in a predetermined and controlled rate.

Historical Background of Transdermal Drug Delivery System

The use of the skin for delivery of various kinds of compounds has been widely explored over many centuries. The ancient popula-

tions in Africa administered different types of traditional plants and minerals topically for cosmetic purposes or treatment of skin diseases For example, in 4000 BC, ancient Egyptians had discovered the use of natural resources, such as henna, red ochre's and kohl, for skin care and cosmetics.

In 1500 BC, they wrote hundreds of drugs and prescriptions on a papyrus paper, namely Ebers Papyrus. One example of the information written in this book was the use of the tiger nut for covering skin wounds. Some thousand years later, Galen, a Greek physician, introduced the first cold cream containing an emulsion of vegetable oil, beeswax and water for skin treatment. They used the cold cream for skin wounds, burns and joint pains, due to its perceived antimicrobial activity. This invention was followed by the utilisation of bandages and plasters by ancient Chinese populations for administrating herbal mixtures. They mixed herbal ingredients with natural rubber gums and applied the plaster to the skin for localised treatment. One of primary transdermal formulations found in the fifteenth century was Unguentum Hydrargyri, an ointment formulation containing mercury for treatment of syphilis in 1880, a plaster-based formulation was developed by a German pharmacist, Paul Carl Beiersdorf, to treat skin disorders. One of the most well-known plasters was Emplastrum belladonna made of Atropa belladonna leaves for treatment of tuberculosis and tumours. However, it was not always fully believed that drugs could be delivered into the circulation. Then, in the twentieth century, some incidents of accidental intoxication were observed, for example poisoning by spills of phenol on the skin. This phenomenon gave significant insights into the understanding of topical and transdermal drug delivery systems. As a result, in the 1950s, the first transdermal product in the form of an ointment was released to treat angina pectoris, namely Nitrol® (2% nitro-glycerine ointment). Nevertheless, this product had limitations, in terms of the application and the frequency of administration Therefore, scientists were incentivised to develop 'measured-dose' transdermal delivery systems for different drugs to reduce the frequency of administration. The first transdermal product containing scopolamine (Transderm Scop®) was marketed in 1979. This product was used over 3 days for the treatment of motion sickness at sea. The development of Transderm scup® had proven that transdermal delivery of scopolamine could reduce some of the side effects of this drug, when compared to oral administration. Consequently, some other APIs were formulated into transdermal dosage forms following the scopolamine-containing product, CatapressTTS®, a clonidine loaded transdermal patch, was released in 1984 to treat hypertension. Additional transdermal products were also developed and marketed in 1986 (Estraderm®) and 1990 (Harbitrol® and Duragesic®). From 1991 until 2004, marketed transdermal products were dominated by hormone containing contraceptives, such as estradiol, testosterone, ethynyl estradiol, norelgestromine and levonorgestrel. This suggested that at the beginning, transdermal products were dominated by hormones containing contraceptive, such as estradiol, testosterone, ethynyl estradiol, and levonorgestrel [10]

Anatomy & Physiology

The skin is the most readily accessible organ of the body and acts as a barrier against the micro and macromolecules of the environment because of its low permeability to such substances The skin of an average adult body has approximately 2m2 surface area and it receives about one-third of the total blood circulating throughout the body [10].

The skin is largest single organ in the human body. It is divided into three layers

Epidermis

Dermis

Hypodermis

It is composed of dead, flat-tened, keratin -rich cell, corneocyte.

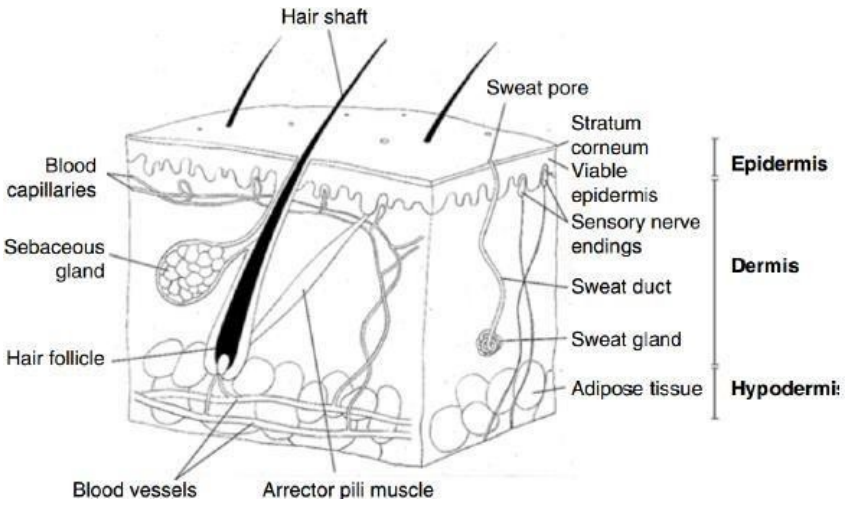


Figure 1: Vertical section of human skin

Epidermis

The multilayered epidermis varies in thickness, depending on cell size & number of cell layers of epidermis, ranging from 0.8mm on palms. It consists outer stratum corneum & viable epidermis,

Stratum Corneum

The cells are keratinised. The cell out lines are indistinct & the nuclei are absent. The stratum corneum is the principal barrier for penetration of drug. The lipids are arranged in multiple bilayers. This layer is thickest at the sole & the palm & thinnest at the lip. Hairs, loops, nails, feathers, Scales, etc.

Viable Epidermis

This is situated beneath the stratum corneum & varies in thickness from 0.06mm on the eyelids to 0.8mm on the palms.

Dermis

Dermis consists of extensive microvasculature network structure like sweat glands, hair, follicles. Inner & larger (90%) skin layer comprises primarily of connective tissue & provides to epidermis layer of skin. It also provides nutrients & oxygen to the skin while removing toxins & waste products. The dermis contains nerve endings, sweat glands, hair follicles & blood vessels.

Hypodermis

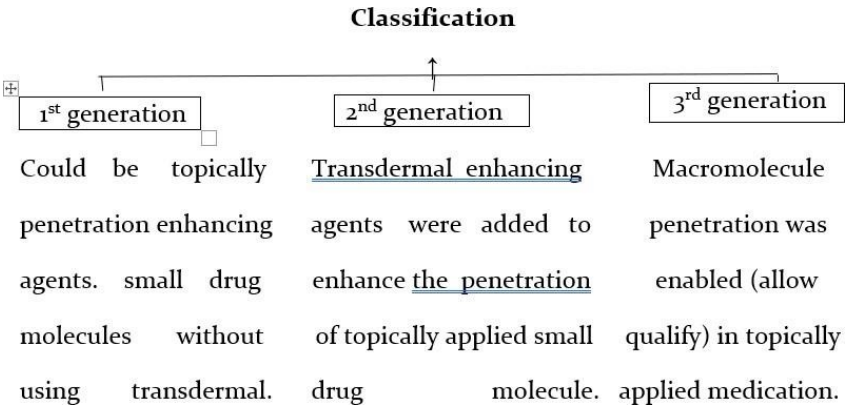
The hypodermis or subcutaneous fat tissue support the dermis & epidermis. It serves as a fat storage area. The thickness of this layer is 4 to 9 mm on average. When a molecule reaches intact skin, it contacts with the cellular debris, normal flora of microorganisms, sebum & other materials.

Function of Skin

Protection, Sensation, Temperature regulation, Immunity, Excreation, etc.

Classification of Transdermal Drug Delivery System

Classification of transdermal drug delivery Systems has proceeded through three generation on the basis of drug molecule Size and the presence of penetration enhances material.



Flowchart 2: classification of TDDS

Penetration Enhancement Techniques for Transdermal Drug Delivery System

Skin penetration enhancement techniques have been developed to improve bioavailability and increase the range of drugs for which topical and transdermal delivery is a viable option [6] Permeation Enhancers: These are the substances that promote skin permeability by altering the skin as a barrier to flux of a desired penetrant. OR The substance that are capable of promoting penetration of drugs into skin and transdermal therapeutic system offers a more reliable mean of administering drug through the skin. The greatest obstacle in the Transdermal Drug Delivery is stratum corneum, as it provides a rate limiting step for the delivery of most of the drugs. The most common active methods of skin permeation are Jet injections, iontophoresis, electroporation, ultrasound, micro needles, power injection, and ablation and tope stripping [1].

Types of Penetration Enhancers or Enhancement Techniques

Table 1: Types of penetration enhancers or enhancement techniques

Sr.no	Types of penetration enhancement technique	Mechanism of action	Examples
1	Physical enhancer	In which the increase the penetration by using ultrasound magnetic and physical separation methods.	1]electrophoresis 2]sonophoresis 3]iontophoresis 4]radio frequency 5]thermophoresis 6]needleless injection 7]magnetophoresis 8]phonophoresis 9]hydration of SC 10] stripping of SC
2	Chemical enhancer	In chemical enhancer technique three types of mechanism are included: 1. disturbing of the ordered structure of SC 2. interact with the intracellular protein 3. improve drug partition via SC.	1]azones 2]pyyolidones 3]cyclodextrines 4]oxizolidinones 5]sulphoxide & chemical like dimethyl sulphoxide (DMSO),Dimethyl acitamide (DMAC) 6]Amides & amines 7]Fatty acids 8] Surfactants
3	Biochemical enhancer	Performed by changing substance or molecule to suitable form.	1] Synthesis of bio convertible prodrug 2] Coadministration of metabolite inhibitor of skin.
4	Natural enhancer	It increased 1]diffusion coefficient 2]partition coefficient 3]solubility of drug 4]extraction of lipids 5]terpenes molecule molecular orientation with lipid layer	1] terpenes:-limonene linalool 2] Essential oil –neem oil chenopodium, basil oil.

5	Drug vehicle based enhancers	Exchange of enhancers with stratum corneum	1] ion pair & complex coacervates
6	Miscellaneous enhancer	Various types of mechanism are present in these technique	1] phospholipids 2] clofibric acid

It is categorized as following types

Chemical penetration Enhancers

Physical penetration Enhancers

Biological penetration Enhancers

Chemical Penetration Enhancers

Chemicals that helps the penetration of topically applied drugs are used as accelerations, absorption promoters or penetration enhancer. They are added to the formulation to increase the skin permeability, by reversibly altering the physiochemical nature of the stratum corneum to reduce its diffusion resistance [9]. The enhancer should have a solubility parameter similar to that of skin. Some of the most used permeation enhancer are, fatty acids and esters (oleic acid), alcohol (methanol) glycol (propylene glycol) sulphoxide (DMSO), acone (lauracapran) and surfactant (anionic surfactant), Terpenes (mentnone) Chemical permeation enhancers act by: Increasing the thermodynamic activity of the drug when functioning as a co solvent, increasing the partition coefficient of the drug and Condition the stratum corneum to promote drug diffusion.

Mechanism of Action

Solubilizing the skin-tissue

Interaction with intercellular lipids. (Disruption of highly ordered lamellar structure)

Interaction with intracellular protein (to promote permeation of drugs via corneocyte layer)

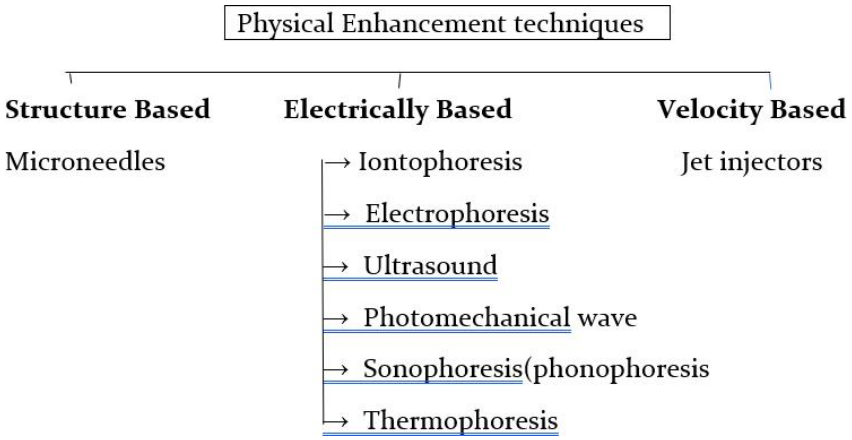
Improve partition of the drugs, co-solvents into stratum corneum.

Physical Penetration Enhancers

Physical penetration Enhancers are again divided into following types

Microneedles

Micro needles (MNs) are micron-sized needles, on a solid support, with needle heights ranging between 25 and 2000 μm. These needles can pierce the SC and create micro conduits, following insertion into the skin. The first concept of MN was introduced by Gerstel and Place in their patent, entitled 'Drug Delivery Device [21]. It is on effective technique for transdermal drug delivery. It is solid or hollow cannula with on insertion length of 20 to 1500 microns and the external diameter not more than 30 microns. In which various types of microneedles involved that are solid microneedles, Coated microneedles, Dissolving microneedles, Hollow microneedles, Hydrogel-forming microneedles, For example: Insulin, glucagon, and growth hormone [7].



Flowchart 3: Physical Enhancement Techniques

Electrically Based

Iontophoresis: (Into = ion Phoresis = transfer). It is a process of Transdermal Drug Delivery System by using of a voltage gradient on the skin. The permeation of ionized drug molecules across Biological membrane under the influence of electrical current. Iontophoresis is a painless method. It discovered by lue due 1903. The efficacy of iontophoresis depends on the polarity, valency and mobility of the drug molecule, nature electrical cycle.

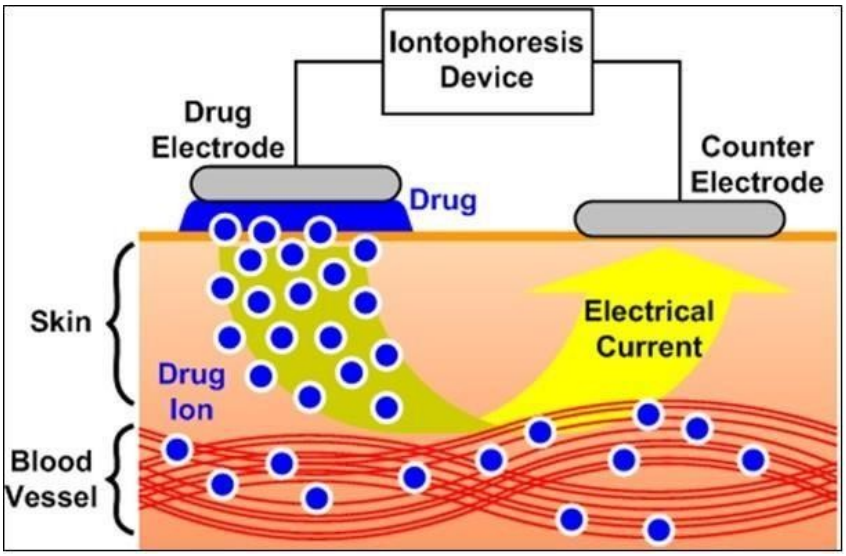
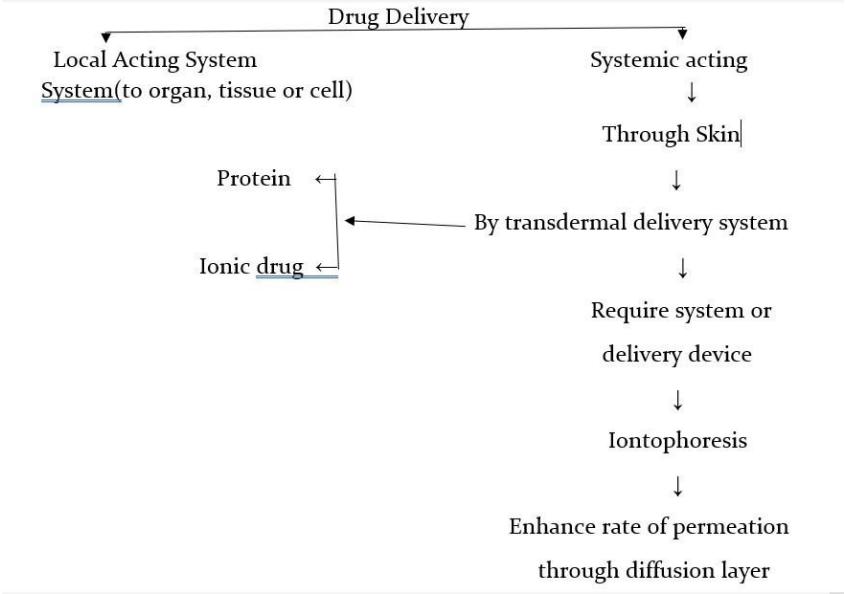


Figure 2: Mechanism of Iontophoresis

Electrophoresis

Electrophoresis is a separations technique that is based on the mobility of ions in an electric field. Electrophoresis method is used only those substances that high voltage electric pulse that ranges from 5 to 500 v for short period of time that leads to formation of pores which increases the permeability of skin or safe and painless drug administration, electric pulses are introduced using closely, positioned, electrodes. The major limitation of electrophoresis is insufficiency quantitative delivery, Apoptosis, with high field and harm to unstable drug.

Mechanism of Action



Flowchart 4: Drug Delivery System

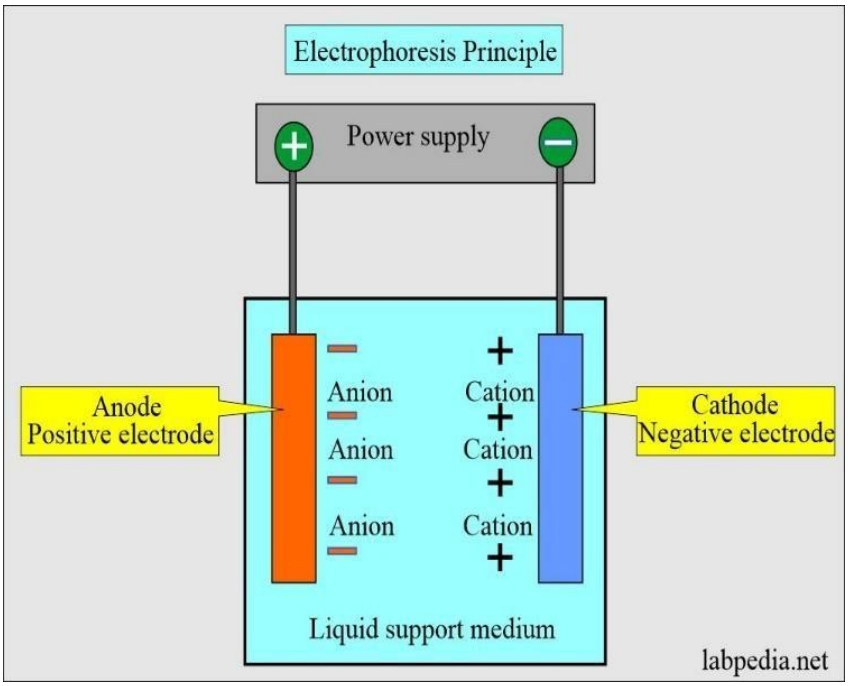


Figure 3: Electrophoresis in TDDS

This electro kinetic phenomenon was observed for the first time in 1807 by Ferdinand reuse (Moscow state university).

1939 zone electrophoresis developed

1950 Agar gel electrophoresis

1955 starch gel (smithies)

1957 cellulose acetate (kohn)

1959 Acrylamide gels 1st used (Raymond and win Straub).

1961 IEF (svensson)

1964 disc gel electrophoresis (Ornstein and Davis).

Ultrasound

Ultrasound also called as sonophoresis or phonophoresis. This frequency of ultrasound higher than 20kHz.The proposed mechanism behind the increase in skin permeability is attributed to the formation of gaseous cavities within the intercellular lipids on exposure to ultrasound resulting in disruption of the SC .The ultrasound technology are used in diagnostic techniques, obstetric ultrasonography, therapeutic procedures. Ultrasound is used to identify the growth of fetus.

The SonoPrep® device (Sontra Medical Corporation) uses ET low frequency ultrasound (55 kHz) for an average duration of per 15 s to enhance skin permeability. This battery operated handling device consists of a control unit, ultrasonic horn with control panel, a disposable coupling medium cartridge, and a return electrode. The ability of the SonoPrep® device to reduce the time of onset of action associated with the dermal delivery of local anesthetic from EMLA cream recently was reported.

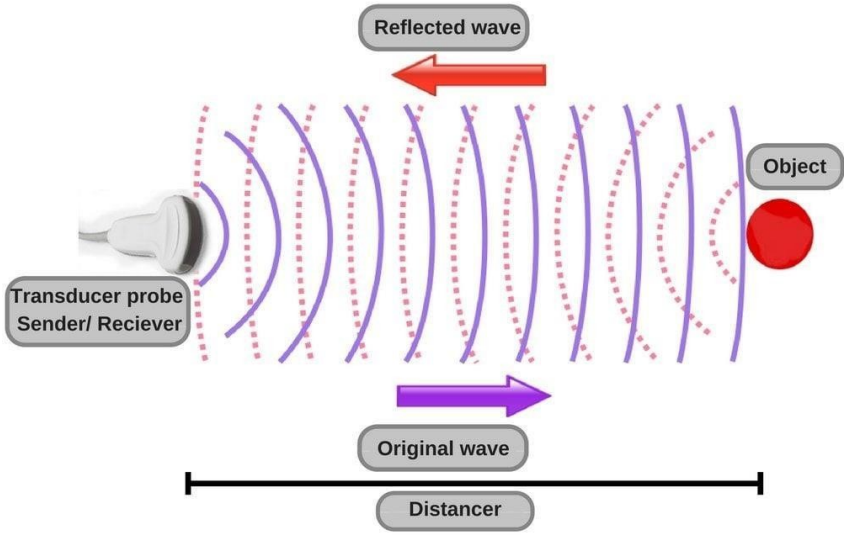


Figure 4: Ultrasonic radiation

Photomechanical Wave

Photomechanical wave also called as laser generated stress wave. Photomechanical waves significantly lead to the stratum cornera highly permeable to drug substance through a possible permeabilization mechanism due to development of transient channels. In photomechanical wave the frequency of ultrasound transducer frequency is ~20 kHz.

Sonophoresis

It also known as high frequency ultrasound sonophoresis allow strict control of transdermal diffusion rates, and greater patient approval. The mechanism of drug penetration through this method is not yet completely understood, and problems related this sonophoresis is device availability, optimization duration and treatment cycles, and undesirable side effects. In sonophoresis zirconium and thorium crystals are used to produce the ultrasonic radiations .The frequency of sonophoresis device is 20 kHz.

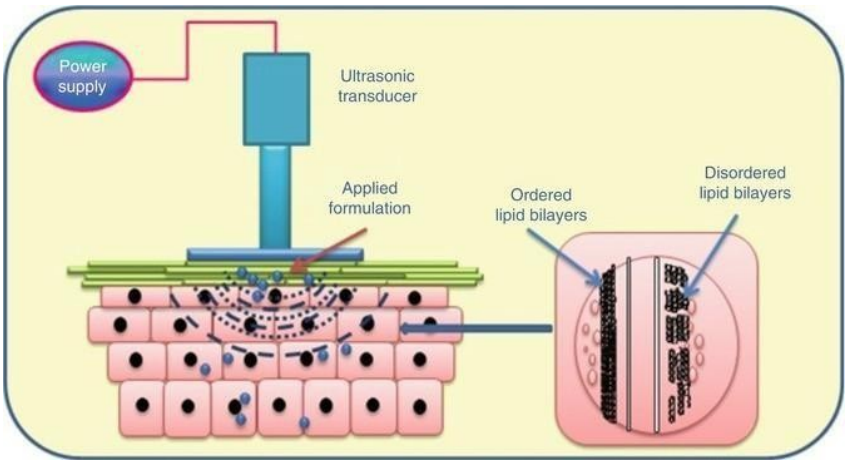


Figure 5: Sonophoresis

Thermophoresis

The effect of elevated temperature on percutaneous absorption was initially reported by blank, scheuplein, and Macfarlane 1967.Thermophoresis also called as thermal ablation and temperature. The evaporation of stratum corneum by the or by using thermophoresis. The temperature become high i.e. above 100°c and leads to vaporization of keratin cell are occurred. It is the ideal and precise technique for control drug delivery [2].

Jet-Injectors

The concept of skin penetrating jet injectors dates back over 50 years .It is type of injection that is used for the delivery the drug in the body Eg; Vaccines, insulin, Lidocaine. In high velocity jet injectors are used in transdermal drug delivery system because that expel out drug in the skin.

Jet Injectors have occurred in Five Areas

Pharmacokinetics (insulin and radioisotope maker)

Tissue penetration and reaction (penile injection (rat)

Pain and compliance issues (alone and in comparison to traditional needle injection

General safety consideration (potential for the accidental introduction of infections material across the skin)

New clinical application (combination with iontophoresis for the delivery of diclofenac and angiotensin)

Ideal Properties of Penetration Enhancers [12]

It should be pharmacologically inert

It should be non-toxic

It should be non-allergic

Onset of action predictable

Suitable duration of action

One direction only

Chemically and physically compatible with drug substance

It should be non-irritant

It should not be expensive

Cosmetically acceptable with suitable skin feel

Factors Affecting Transdermal Drug Delivery System

Five types of factors that affects the transdermal drug delivery system they are as following: Physiological factors, Biological factors, Pharmacokinetic factors, Formulation related factors and Environmental factors

Table 2: Factor Affecting Transdermal Drug Delivery System

Physiological factors	1) skin irrigation
	2) temperature
	3) PH
	4) drug concentration
	5) diffusion co-efficient
	6) solubility
	7) partition coefficient
	8) molecular weight
	9) molecular size
	10) ionization
	11) melting point
	12) release characteristic
	13) Composition of drug
Biological factors	1) skin poisonousness
	2) allergic reaction
	3) site of application
	4) skin metabolism
	5) skin permeability
	6) age
	7) gender
	8) blood flow
	9) disease condition
Pharmacokinetic related factors	1) half-life of product
	2) volume of distribution

	3) total body clearance
	4) therapeutic plasma concentration
	5) bioavailability of product
Formulation related factor	1) current strength
	2) current density
	3) pulsed current
	4) duration of application
	5) Electrode material

Basic Components of Transdermal Formulations

Drug, polymer matrix. Permeation enhancer, pressure sensitive adhesives (PSA), backing layer (BL), release liner (RL) and other excipients (OE).

Drug: Selection criteria for drug. Molecular weight less than 500D. Drug have low melting point .Drug have short half-life, i.e.1-6 hrs. It should be non- irritant.

Polymer Matrix

In which drug are bound with various types of polymers such as, Natural polymers, synthetic polymers, and synthetic elastomers.

Physicochemical characteristics:

Drug should supposed to low molecular weight

Drug lower melting point temperature

Drug hydrophilic and lipophilic property

Table 3: Polymer use in TDDS

Sr.no	Natural Polymers	Synthetic Elastomers	Synthetic Polymer
1	Cellulose	polybutadiene	Polyvinyl alcohol
2	Natural rubber	Butyl rubber rubber	polyurea
3	waxes	polysiloxane	polyethylene
4	starch	Hydrin rubber	polyester
5	proteins	Butyl rubber	Polyvinyl acetate
6	gelatine	neoprene	polyethylene
7	Methyl cellulose	Silicone rubber	Acetyl copolymer

Permeation Enhancer

These are the substances that promote skin permeability by altering the skin as a barrier to flux of a desired penetrant OR The substance that are capable of promoting penetration of drugs into skin and transdermal therapeutic system offers a more reliable mean of administering drug through the skin. The greatest obstacle in the Transdermal Drug Delivery is stratum corneum, as it provides a rate limiting step for the delivery of most of the drugs [9]. The most common active methods of skin permeation are Jet injec-

tions, iontophoresis electroporation, ultrasound, micro needles, power injection, and ablation and tope stripping.

Pressure Sensitive Adhesives

In pressure sensitive adhesive all types of transdermal drug delivery possible. Development of new polymers such as, hydrogels, hydrophilic polymers. Physical and chemical modification are needed to developed or improve drug delivery [15].

Baking Layer

Baking laminates are selected for appearance, pliability and blockage. Baking layer is outer most layer of patch. It is made up of aluminum film, poly olefin film, poly ester film, polyethylene film, etc. backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept Printing [17].

Release liner: In these system the storage condition of patch is covered by a protective cover and that is removed by before the application of patch to the skin.The liner should be chemically inert. The release liner is composed of base layer may be barriers like paper fabric, polyethylene, polyvinyl chloride. And release coating layer composed of silicon or Teflon.

Other excipients: It is inactive substance that are used in formulation along with active ingredients to formulate medicament called as excipients. It is used to increase the bulk of formulation and long term stabilization. Examples of excipients ; diluents, binders , lubricants, glidents , colorant's , disintegrating agents ,plasticizer , sweetener's , and adhesive etc. Adhesive: The binding of TDDS on skin done by pressure sensitive adhesive (PSA).The adhesive tape fixed on the device and extending peripherally.

Both adhesive systems should accomplish the following characteristics.

It must be adhere to skin without disturbed by daily activities like bathing, exercise

It's easily removed without any adverse effects

The adhesive residues not to be retaining on the surface of skin

It must be an outstanding contact with skin

Dosage Forms of Transdermal Drug Delivery System

Transdermal patch

Transdermal film

Transdermal gel

Transdermal spray

Transdermal injection

Transdermal tape

Transfersomes

Ethosomes

Transdermal Patch

The first transdermal system containing scopolamine was approved in the United States in 1979; the US Food and Drug Administration (FDA) approved nicotine patches in 1984. A decade later, transdermal patches for pain relief, analgesic activity, and contraception and hormone replacement therapy were FDA approved and marketed, and the progress in this field continues today. The FDA has approved in 1981 to prevent the nausea and vomiting related with motion sickness. The FDA has approved till 2003 more than 35 transdermal patches cross 13 molecule. The transdermal patch are helpful for avoiding the first pass effect and also used to target drug delivery [14]. The development of transdermal patch various physiological factors should be considered such as nature of substance, molecular weight , partition co- efficient , HLB value , strength of substance. Transdermal patch is an adhesive patch that has a coating of drug that is deposit on the skin to transfer dose of medicine into the blood over period of time [16]. In transdermal drug delivery system various types of mechanism are involved to control manage the drug concentration, or controlled. Dose of drug, such as single layer or multilayer drugs in the adhesive System matrix system.

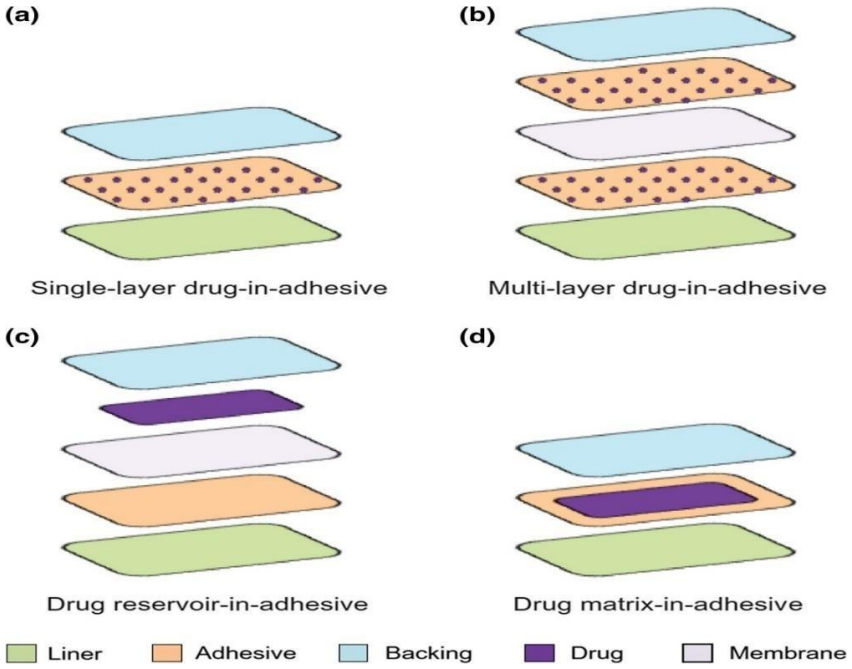


Figure 6: Types of transdermal patches

Types of Transdermal Patches: (Classification) in the Transdermal Patches 5 Types

Single-layer, drug-in-Adhesive, Multi-layer Drug-in-Adhesive, Reservoir, Matrix, Vapour patch.

Single-Layer Drug-in Adhesive

A single layer of polymer with adhesive - properties is used as a reservoir for drug dispersion. In this type the adhesive layer contains the drug. The Drug that adheres or deposited in single polymer layer and it is released from the backing laminate layer that supports the drug reservoir. The adhesive layer is surrounded by a temporary liner and a backing layer. Eg. Daytrana® [5].

Multi-Layer Drug in Adhesive

It also similar to the single layer. But it contains an immediate drug release layer & other layer will be a controlled release along with the adhesive layer. The adhesive layer helps to drug release process. The multi- layer drug patches are relief pain.

Vapour Spray Transdermal Patches

Vapour transdermal patches contains single layer of drug in adhesive polymer with Vapour release property. A number of Vapour dermal patches are available in the markets for different- different uses [14]. Eg. Nicodermal CQ®, altacura®

Reservoir

In these system the drug is insert between an impermeable backing layers. The backing layer composed of impermeable metallic plastics and porous polymeric membrane. In the drug reservoir compartment, the drug can be in the form of solution, Suspension, gel or dispersed in a solid. Drug in the transdermal patch is controlled by molecular dispersion of the drug in the drug in a polymer matrix part of the preparation [16].

Examples: Transdermal - Nitro®, Transdermal - Scop®, Catapres®

Matrix System

Drug-in-Adhesive System

In this type the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose [16].

Matrix-Dispersion System

In this type the drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim. Miscellaneous transdermal patches [13]. Other FDA approved transdermal matrix delivery systems are transdermal patches with adhesive tapes, transdermal gel, transdermal spray, iontophoresis delivery, and phonophoresis delivery [16].

Evaluation of Transdermal Patches: [16]

Interaction studies

Thickness of the patch

Weight uniformity

Folding endurance

Percentage Moisture content

Percentage Moisture uptake

Water vapour permeability (WVP) evaluation

Drug content

Uniformity of dosage unit test

Polari scope examination

Shear Adhesion test

Peel Adhesion test

Thumb tack test

Flatness test

Percentage Elongation break test

Rolling ball tack test

Quick Stick (peel-tack) test

Probe Tack

In vitro drug release studies

In vitro skin permeation studies

Skin Irritation study

Table 4: FDA Approved Transdermal System

Sr.no	Drug	Uses	Approval	Mechanism
1	Scopolamine	Motion Sickness	1979	Passive diffusion
2	Clonidine	Hypertension	1984	Passive diffusion
3	Estradiol	Menopausal symptoms	1986	Passive diffusion
4	Fentanyl	Chronic pain	1990	Iontophoresis
5	Nicotine	Smoking Cessation	1991	Passive diffusion
6	Testosterone Gel	Testosterone deficiency	1993	Passive diffusion
7	Lidocaine	Post-Herpetic Neuralgia	1999	Sonophoresis
8	Norelgestromin	Birth prevention or contraception	2001	Passive diffusion
9	Oxybutynin	OAB (over active bladder)	2003	Passive diffusion
10	Methylphenidate	Minimal brain damage	2006	Passive diffusion
11	Selegeline	Depression	2006	Passive diffusion
12	Diclofenac Epolamine	Acute pain	2007	Passive diffusion
13	Rivastigmine	Mental illness	2007	Passive diffusion
14	Ganisetron	Highly emetogenic chemotherapy	2008	Passive diffusion
15	Buprenorphine	Chronic pain	2010	Passive diffusion
16	Sumantriptan	Migraine	2013	Iontophoresis
17	Asenapine	Antipsychotic	2019	Passive diffusion
18	Lievonorgestrel + Ethinyl Estradiol	Contraception	2020	Passive diffusion

19	Ketorolac tromethamine	Antipyretic analgesic	2021	Passive diffusion
20	Covide-19 smart vaccine patch	Viral infection	2021	Passive diffusion
21	Rivastigmine single-day transdermal patch	Mental illness	2021	Passive diffusion
22	Rivastigmine multi-day transdermal patch	Mental illness	2021	Passive diffusion
23	Antiretroviral (ARV) lidocaine/capsaicin/menthol	Pain relieving	2022	Passive diffusion

Table 5: Marketed products of transdermal patches

Sr.No	Brand name	Drug	Indication	Manufacture company
1	Nicotine	Nicotine	Pharmacological smoking cessation	Novartis
2	Alora	Estradiol	Postmenstrual Syndrome	TheraTech
3	Neupro	Rigotine	Early-stage idiopathic Parkinson's disease	UCB & Schwarz Pharma
4	Matrifen	Fentanyl	Pain relief patch	Nicomedia
5	Climara	Estradiol	Postmenstrual Syndrome	3M pharmaceutical
6	Nitro disc	Nitro-glycerine	Angina pectoris	Roberts pharmaceutical
7	Estraderm	Estradiol	Postmenstrual Syndrome	Alza /Novartis

Transdermal Film

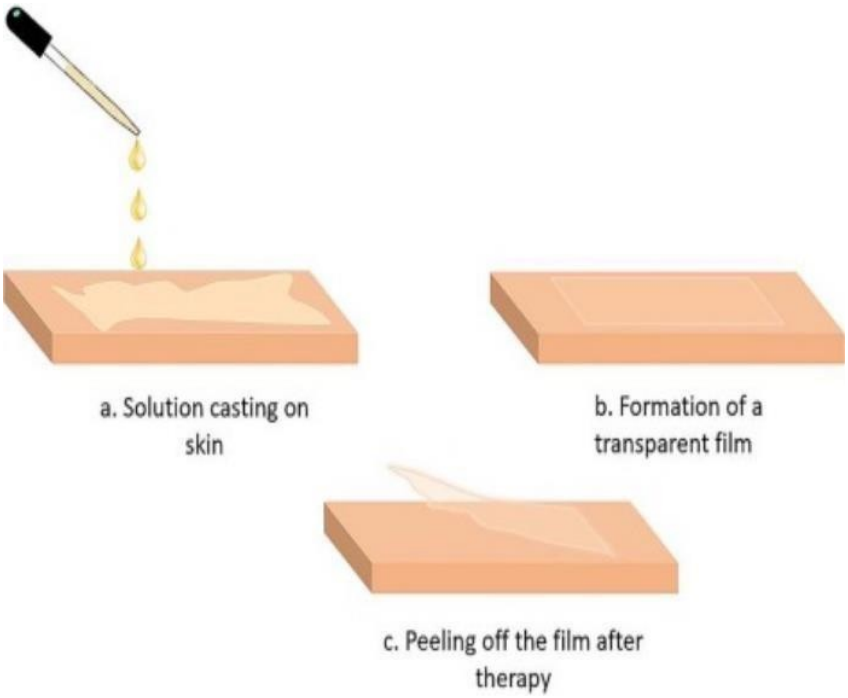


Figure7: Formation of film in TDDS

Film forming system (FFS) is a novel approach which can be used as an alternative to conventional topical and transdermal formulations. It is defined as non-solid dosage form that produces a film in situ, i.e. after application on the skin or any other body surface. These systems contain the drug and film forming excipients in a vehicle which, upon contact with the skin, leaves behind a film of excipients along with the drug upon solvent evaporation. The formed film can either be a solid polymeric material that acts as matrix for sustained release of drug to the skin or a residual liquid film which is rapidly absorbed in the stratum corneum [10] .

Mechanism of Film Formation

Film forming system is directly applied on a skin in the form of thin and transferent form. After application of the film forming system the composition of film formulation changes due to loss of various substance like volatile oils. During these process concentration of drug substances are increases and arrive at Saturation level on the skin membrane. The saturation method explains by Fick's law of diffusion that are as following [10]

J h = DKCv

where,

J = rate of drug permeation per unit area of skin per unit time (flux)

D = diffusion coefficient of drug CV = concentration of drug

h = thickness of barrier to diffusion

In the above equation the stability of drug substances is directly proportional to the thermal behaviour.

Uses of Film

It is used in the field of surgery or wound care. Film forming solutions or gels have been used as tissue glues for the closing of operative wounds. It also helps to delivery of active ingredients. It also act as barrier membrane in the industry. Protect of workers from acid, base, other chemicals, UV rays, and infra-red rays [10].

Table 6: Materialistic film forming system

Sr.no	Product	Drug	Formulation type	Use
1	Lamisil once	Terbinafine hydrochloride o	Film forming solution	Fungal infection
2	Axiron	testosterone	Film forming spray	Muscle development
3	Liquid-patch	Testosterone hydrocortisome	Film forming spray	Itching reduce pain
4	Dura peel	ropivacane	Film forming gel	inflammation
5	Pharmadur	hydroquinone	Film forming emulsion-gel	Melasma , post-inflammatory

Transdermal Gel

Table 7: Marketed product of transdermal gel

Sr.no	Product Name	Drug	Manufacturer
1	Miconaz- Hemulgel	Miconazole nitrate, Hydrocortisone	Medical union pharmaceuticals
2	Execs gel	Adapalene	Zee laboratories
3	Clinagel	Clindamycin phosphate allantois	Stiegel Parma
4	Pernox gel	Benzoyl peroxide	Cosmo remedies Ltd
5	Zorotene gel	Tezarotene	Elder pharmaceuticals

The term 'Gel' was introduced in the late 1800 to name some semisolid material according to their physiological characteristics rather than molecular composition. The U.S.P. defines gels as a semisolid system consisting of dispersion made up of either small

inorganic particle or large organic molecule enclosing and interpenetrated by liquid. Gels are a substantially dilute cross-linked system, which exhibits no flow when in the steady-state [8]. Gels as DDS: The field of pharmaceutical developing steadily over the year, become & has today invaluable in helping to keep us healthy & prevent disease. The nature of these carriers progressed over the years form Ceramics, to natural, to synthetic materials.

Classification of Gels

Gels- Nature of Colloid

Inorganic Gels.

Organic

Confining the pharmaceutical or other effect of the drug to the surface. Of the skin. Science has been Semi-solid formulation in all their diversity doming the system for topical delivery, but foams Spray, medicated powders, Sol", & even medicated adhesive systems are in use. Most widely used. Semisolid preparation for topical drug delivery includes get gels, creams & ointments.

Nature of solvent

Hydro Gels

Organo Gels

Characteristics of Gels

The topical gel should not be tacky!

Ideally, the gelling agent for pharmaceutical or cosmetic use should be inert, safe, & should not react with other formulation components.

It should possess Suitable antimicrobial activity against microbial attack.

The gels intended for ophthalmic use should be sterile.

The phenomenon occurs this process is referred Syneresis Ageing

Application of Gels

Gels are applied directly to the skin, mucus membrane or the eye to provide local action. They acts as long acting form of drug injected! Intramuscularly or implanted into the body. Gelling agents are useful binders in tablet useful binders in tablet granulation, protective colloids in suspensions, thicken are in oral liquid, and cosmetically gels have been Suppository bases [8].

Transdermal Spray

The drug delivery systems are mainly used in pain management, contraception, infections, allergies, inflammation and urinary incontinence. Sprays are dosage forms in which polymeric solution of drug is sprayed over the intact skin so as to get a sustained release of drug from the polymeric matrix. The drug is present in saturated form in the polymer matrix. As the organic solvent vehicle evaporates, slowly the drug diffuses through the polymer matrix and passes from the skin barrier [11]. Numerous technologies have been developed to overcome the relatively low skin permeability, including spray-on transdermal systems. Transdermal spray is in the form of solution of medicament is sprayed over the skin to get the pain relief or produce sustained release effects. A me-

tered dose transdermal spray delivers the medication to the skin. It works similar to transdermal patches and transdermal gels. Sprays are similar that of the aerosols system. Aerosols system made up of metals, glasses.

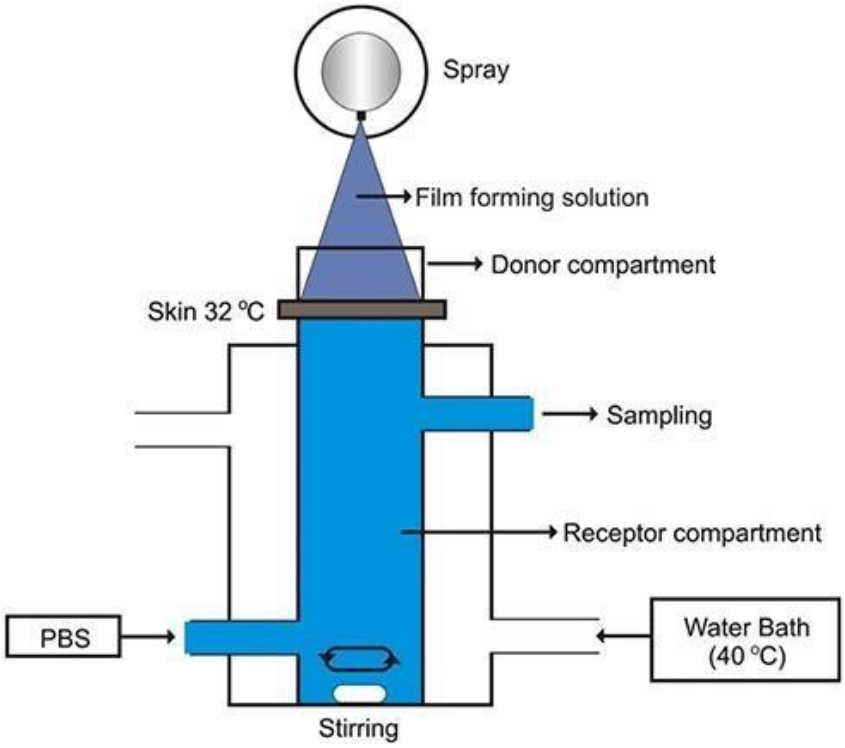


Figure 8: Film forming Transdermal spray.

The components of spray is

Propellant

Container

Valve and actuator

Product concentrate

Propellant: it develops proper pressure with on the container and also helps to expel out the drug from the container.

Container: The pressure of container must be 140 to 180 psig. Container made up of metals: aluminum, stainless steel, tinplated steel. Glass: uncoated glass, and plastic coated glass.

Valves: it is easy to open and close and competent of transferring the content in the desired form such as spray, foam, solid stream etc.

Product concentrate: active substances or mixture of active substances and other necessary agents such as solvents, antioxidants and surfactant.

Transdermal Injection

Transdermal is a route of administration wherein active ingredients are delivered across the skin for systemic distribution. Examples include transdermal patches used for medicine delivery. The drug is administered in the form of a patch or ointment that delivers the drug into the circulation for systemic effect.

In transdermal injection four types of injection are involved;

Subcutaneous injections

Intramuscular injections

Intravenous injections

Intradermal injections

Advantage of transdermal injection:

•Rapid and uniform absorption of the drug, especially the aqueous solutions

•Rapid onset of the action compared to that of the oral and the subcutaneous routes.

Transdermal Tape

Transdermal tape is easy for applications as well as invasive method. The tape stripping process is performed after an appropriate incubation time post topical application of the test composition. The composition may be removed or left on the skin to provide the original amount of components to be used during the measurement. The adhesive tape is placed on the skin surface and is always removed from the same selection. It is important that the adhesive tape is always flattened with the same force as the roller to eliminate the effect of creases and recesses on tape stripping. In addition, the removal rate is an important factor. The slower the adhesive tape removal rate, the higher the adhesion of the SC [3] these product also analyzed various techniques like high performance liquid chromatography, atomic absorption spectroscopy and infra-red spectroscopy.

Transfersomes

The name means "carrying bodies'. Transfersomes word is derived from the Latin word 'transferee' which means 'to carry across' and the Greek word "soma' which is used for a body [18]. Transfersomes are a type of liposomes. It is novel method of transdermal drug delivery system. Transfersomes are a form of elastic vesicles and it is a modernist class of liposome. It is discovered by Gregor cave in 1991. The main components of Transfersomes are phospholipids, surfactant and water. In Transfersomes both hydrophilic as well as hydrophobic drug are present. In which the elastic vesicles are helps system to pass through narrow pathway between skin cell to mediate drug transport containing both hydrophilic as well as hydrophobic drug in aqueous core as well as vesicles bilayer. Transfersomes: skin delivery of peptides and proteins Cave et al. reported that Transfersomes could deliver insulin to the systemic circulation in therapeutic amounts equivalent to subcutaneous injection. Insulin delivery from Transfersomes composed of phosphatidylcholine incorporating sodium cholate was compared with conventional liposomes and mixed micelles applied to the skin of both mice and humans. Given the size (a molecular weight of ~ 6000 Da) and polarity of insulin, passive permeation across intact human or animal skin is negligible. However, Cave et al. reported that radiolabelled insulin delivered in Transfersomes permeated the skin to reduce blood glucose levels in mice. There was a 30- min lag time relative to a subcutaneous injection of the same formulation, but overall efficacy of delivery was comparable. Conventional liposomes and mixed micelles did not deliver insulin, demonstrating that the penetration achieved by Transfersomes was not due to the components of the formulation [6].

Advantages of Transfersomes

They carry high as well as low molecular weight of drugs.

They are biocompatible.

They are biodegradable.

They have high entraptment efficiency.

Disadvantages of Transfersomes

They are chemically unstable.

Deficiency of purity of natural phospholipids.

It is expensive.

Ethosomes

Ethosomes are nothing but the ethanolic liposome. The concept of Ethosomes was first discovered by the Touitou in 1997. The main components of Ethosomes are phospholipids alcohol and water. Ethosomes are non-invasive method that helps to rich the drug molecule into the systemic circulation. Ethosomes are non-invasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation. Ethosomes are soft, malleable vesicles tailored for enhanced delivery of active agents [19].

Work of Ethosomes

Vesicles, ethanol, and skin lipids interact synergistically in ethosome function because ethosome and skin lipids interact better than liposomes, they improve the distribution of active ingredients over liposomes. When ethanol interacts with the lipid molecules in the polar head group region, the transition temperature of the lipids in the stratum corneum is decreased. These cause the drug to be delivered into the deep layers of the skin by increasing fluidity and lowering lipid multilayer density. Furthermore, ethanol imparts smoothness and flexibility to vesicles, facilitating deeper penetration into the epidermal layer [20].

Advantages of Ethosomes

It increase's the permeation of drug through the skin

Delivery of large molecule is possible

It is non-invasive method

High patient compliance

Disadvantages of Transfersomes

Poor yield

Adhesive may not adhere to all type of skin

May not be economical

Loss of during transfer from organic to water media

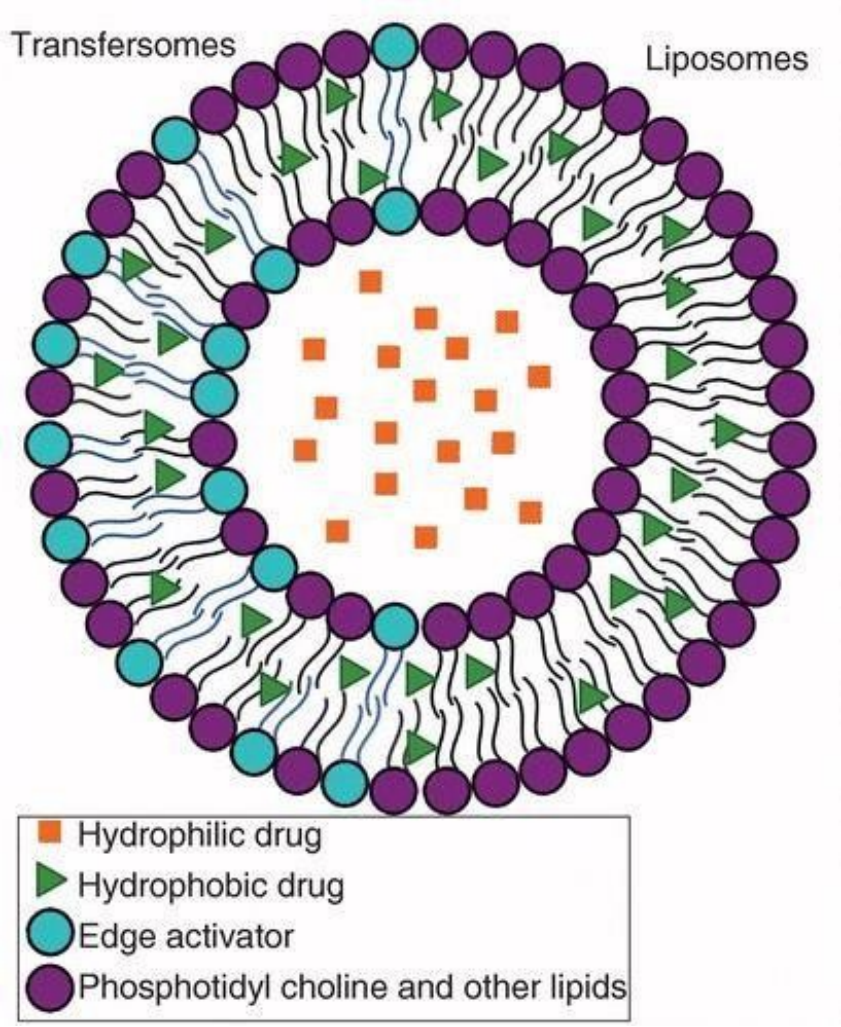


Figure 9: structure of Transfersomes

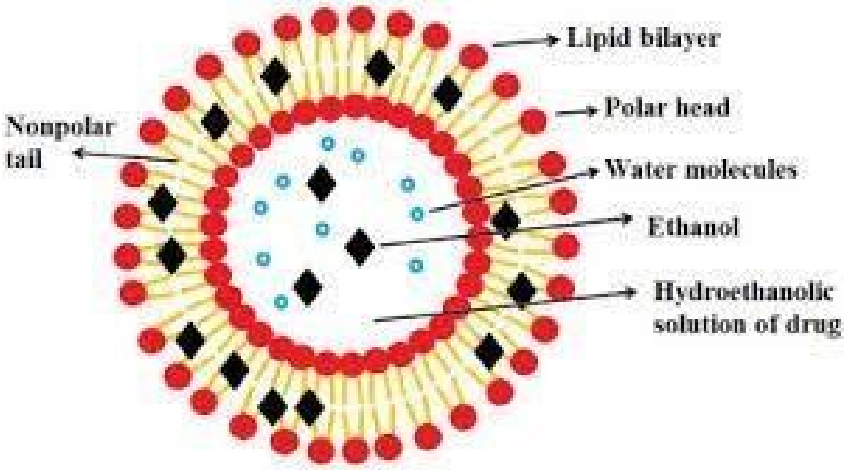


Figure 10: structure of Ethosome.

Present Perspective

In recent years, the scale of TDDS in the domestic and overseas drug delivery system market has increased, as confirmed through increasing research studies, patents, and commercially available products from many companies and research institutes. In addition, micro needles are attracting great attention even among TDDS modalities, which complement the limitations of the existing simple application type and patch type needles and com- bine the advantages of micro needles to obtain higher treatment efficiency and effects [2]. For this, manufacturing and commercialization methods are being developed, with judicious implementation of latest technologies, such as 3D bio printing. Advances in these TDDSS could provide the driving force for controlling prevalence of diseases of cardiovascular and central nervous systems, diabetes, neuromuscular diseases, genetic diseases, and infectious and localized infectious diseases, while spear- heading advances in vaccination and supporting patient preference for self-administration of drugs for long-term treatment.

Future Perspective

The market for transdermal devices has been estimated at U.S. $2 billion and this figure represents 10% of the overall U.S. $28 billion drug delivery market. Such figures are surprising when we consider that the first transdermal patch was granted a licence by the FDA in 1979, and only an additional drugs have been approved since that time. This short list of "deliverables" highlights the physicochemical restrictions imposed on skin delivery. Transdermal drug delivery has experienced a healthy annual growth rate of 25%, which outpaces oral drug delivery (2%) and the inhalation market (20%) [2]. The most recent 'hype' for a drug delivery system is the use of micro needles with the main focus being on single- dose vaccine delivery. For instance, the Nano patch® required a second-order lower dose of antigen to be delivered to the skin to achieve antibody responses comparable to conventional I.V injection. The use of micro needles for long-term treatment of opiate and alcohol dependence with naltrexone, an opioid antagonist [2].

Discussion

Transdermal drug delivery system established itself as an integral part of the novel drug delivery system. Transdermal drug delivery systems is most convenient route for the transferring the drug through skin. The transdermal drug delivery system provides a major advantage over injectable or implantable and oral route by preventing the first pass metabolism. These system is easy to use and release drug in controlled manner as compared to other drug delivery system. However, with our greater understanding the structure and function of the skin and how to change these properties, to produce new drug products for transdermal drug delivery system. The transdermal drug delivery system can be delivered via skin to direct systemic circulation and the greater bioavailability of drug. Transdermal drug delivery system increases or improves patient compliance and effectiveness are individual aspects of new drug delivery system. These systems are rapidly developed and number of stable products are formulated. To overcome the problems related to oral drug delivery route, transdermal drug delivery system are used as an alternative route specially focus on improvement in the style of dosage formulation. The effective delivery is possible because of components like backing layer, release liner, polymer matrix these all components helps to successful delivery. These systems also helps to avoid many problems related to poor oral bioavailability. In the Transdermal Drug Delivery System various penetration techniques are used to increase the product flux without rupturing the viable cells and also the some natural product as potential drug are also used to increase the performance of drug molecules. In recent years there has been a search for natural compounds as a permeation enhancer to improve drug permeation. In most cases their enhancement effects are associated with toxicity their fore limiting their clinical application. This technology will help realize the development of new and improved devices that will be smaller, inexpensive, and invasive and more suitable with a wide range of biochemical and other uses. In transdermal technology various types of dosage forms are used to improve drug delivery that are patches, films, gels, spray and injection. Transdermal Patches are very to apply there in no need to physicians to explain the technique how to apply so the altimetry no need to pay fees to physician these is the major advantage

of these systems. In transdermal patches various types are used that helps to drug delivery at target organ or reach to the target site. Transdermal dosage forms used number of methods to enhance permeation .The one transdermal patch used any time and discard after three days. Transdermal dosage forms are easy for applications as well as non-invasive method and minimal pain. These systems mostly suitable for children and order patient because they irritate during therapy and because of these in proper dose given so the TDDS are used.

Conclusion

The TDDS are an excellent alternative to oral drug delivery system and hypodermic injection. This is more convenient and non-invasive method for drug delivery and better choice for those afraid of injections. Skin permeation enhancement techniques are rapidly developed to increase the drugs suitable for transdermal drug delivery system. For the successful drug implementation need of numerous considerations and the properties of the drug attributes of the transdermal devices, collection of status of patients is important for safe and successful drug delivery.

References

1. Arunachalam A, Karthikeyan M, Kumar DV, Prathap M, Sethuraman S et al. (2010) Transdermal drug delivery system: a review. J. Curr.Pharm Res 1: 70.

2. Brown MB, Martin GP, Jones SA, Akomeah FK (2006) Dermal and transdermal drug delivery systems: current and future prospects. Drug deliv 13: 175-87.

3. Jeong WY, Kwon M, Choi HE, Kim KS (2021) recent advances in transdermal drug delivery systems: A review. Biomater. Res 25: 1-15.

4. Wang FY, Chen Y, Huang YY, Cheng CM (2021) Transdermal drug delivery systems for fighting common viral infectious diseases. Drug Deliv. Transl. Res 11: 1498-508.

5. Singh A, Bali A (2016) Formulation and characterization of transdermal patches for controlled delivery of duloxetine hydrochloride. J. Anal. Sci. Techno 7: 1-13.

6. Benson HA (2005) Transdermal drug delivery: penetration enhancement techniques. Curr. Drug deliv 2: 23-33.

7. Escobar-Chávez JJ, Bonilla-Martinez D, Angélica M, Molina-Trinidad E, Casas-Alancaster N et al. (2011) Microneedles: a valuable physical enhancer to increase transdermal drug delivery. The J. Clin. Pharmacol 51: 964-77.

8. Verma A, Singh S, Kaur R, Jain UK (2013) Topical gels as drug delivery systems: A review. Int. J. Pharm. Sci. Rev. Res 23: 374-82.

9. Marwah H, Garg T, Goyal AK, Rath G (2016) Permeation enhancer strategies in transdermal drug delivery. Drug deliv 23: 564-78.

10. Kathe K, Kathpalia H (2017) Film forming systems for topical and transdermal drug delivery. Asian J pharm sci 12: 487-97.

11. Chavan P, Bajaj A, Parab A (2016) Topical sprays: novel drug delivery system. Int. J. Pharm.Chem. Res 2: 102-11.

12. Patil UK, Saraogi R (2014) Natural products as potential drug permeation enhancer in transdermal drug delivery system. Arch. Dermatol. Res 306: 419-26.

13. Kumar A, Kumar K (2020) Development and Evaluation of Matrix Type Transdermal Patches of Torasemide. J. Drug Deliv. Ther 10: 98-104.

14. SHINGADE GM (2012) Review on: recent trend on transdermal drug delivery system. J. drug deliv. Ther 2.

15. Wokovich AM, Prodduturi S, Doub WH, Hussain AS, Buhse LF (2006) Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute. Eur. J. Pharm. Biopharm 64: 1.

16. Al Hanbali OA, Khan HMS, Sarfraz M, Arafat M, Ijaz S et al. (2019) Transdermal patches: Design and current approaches to painless drug delivery. Acta Pharm 69: 197-215.

17. Sharma N, Agarwal G, Rana AC, Bhat ZA, Kumar D (2011) A review: transdermal drug delivery system: a tool for novel drug delivery system. Int J drug dev Res 3: 70-84.

18. Chauhan P, Tyagi BK (2018) Herbal novel drug delivery systems and transfersomes. J of Drug Deli and Therap 8: 162-8.

19. Godin B, Touitou E (2003) Ethosomes: new prospects in transdermal delivery. Critical Reviews™ in Therap Drug Carrier Syst 20.

20. Chauhan N, Vasava P, Khan SL, Siddiqui FA, Islam F et al. (2022) Ethosomes: A novel drug carrier. Annals of Medicine and Surgery 104595.

21. Halder J, Gupta S, Kumari R, Gupta GD, Rai VK (2021) Micro needle array: applications, recent advances, and clinical pertinence in transdermal drug delivery. Journal of Pharmaceutical Innovation 16: 558-65.