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Transdermal Patch Using Iontophoretic Drug Delivery System

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ABSTRACT

Conventional dosage form has various drawbacks regarding Bioavailability and Permeability to overcome this a novel approach is the formulation of a transdermal system. It is patient convenience as there is no painful insertion in the skin, continuous release of drug achieved with this treatment the avoidance of hepatic first-pass metabolism is achieved When TDDS is combining with iontophoretic drug delivery the bioavailability has shown to increase the main advantage is delivery of ionic drug molecule, and protein/peptides using a lower current intensity with a less time required for the pharmacological effect. This article will ensure the overview of Transdermal drug delivery, the formulation of a patch, how the permeability of API can be increased by using the iontophoretic drug transmission pathway.

INTRODUCTION

The transdermal therapeutic system is defined as self-contained, distinct dosage forms which, when enforced to the surface of the skin, deliver the drug(s), through the skin, at a controlled rate to the whole blood plasma. The transdermal patch was 1st approved by the FDA in 1981, and it allows continuous entry of API with short biological half-lives, maintains the drug concentration in the therapeutic window. It is a peculiar drug delivery approach that improvises the drug release kinetics, TDDS gained significant importance during the last few years over conventional drug delivery. Percutaneous absorption is the main route in TDDS.

Iontophoresis is dependent on the "similar charges drive off", while "reversed charges engaged". The effect of enforced electric current on the migration of charged molecules through the skin an aspect is named electromigration. Transdermal iontophoresis is a useful physical enhancement technique used to achieve controlled delivery of API across the skin. Various studies have given the results that an increase in the drug concentration enhance iontophoretic flux. However, there is a limitation in achieving TDDS of high molecule weight like peptides, protein, and oligonucleotide which are water loving. (9)

Skin as a site of drug Absorption:

The skin of a moderate grown-up body mask around $2m^2$ of surface area and receives approximately one-third of all blood moving the whole body. A moderate human skin surface is obvious to encompass, 40-70 hair lobe and 200-250 sweat ducts on each square centimeter of skin area for many decades, the skin is been frequently used as the site for deposition of dermatological drugs to accomplish a localized pharmacologic effect in the skin tissue. Ions pick the way with minimum electrical blocking and that is Stratum corneum. The use of hydrocortisone for dermatitis, benzoyl peroxide for acne, and neomycin for superficial infection.

Mechanism of skin permeation:

Drug molecules can enter by three routes: (1)

1. Perspiration ducts

2. Hair lobes

3. Sebum glands Or Precisely through the stratum corneum

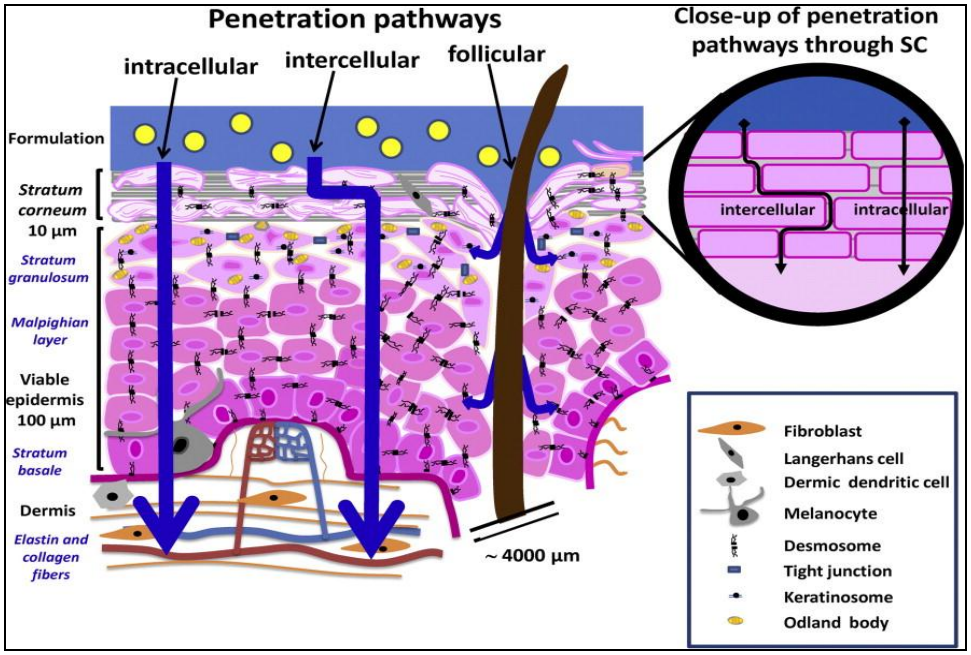

Fig. 1: Achievable drug penetration routes across human skin

The lipid-rich and structurally complex intercellular region of stratum corneum are said to operate a major role in percutaneous absorption. Stratum corneum allows a relatively lipophilic molecule to pass to the lower skin layer. The transport of such molecule across is by Passive diffusion the permeation rate through the stratum corneum is represented by [6]

$$\frac{dm}{dt} = \frac{DC_0K}{h}$$

Where,

dm- The amount of diffusant passed through the layer in time dt.

C_0- Drug concentration in donor solution

k- The partition coefficient of the diffusant in the middle of the membrane and solution.

D- Diffusion coefficient of the membrane.

h- Membrane thickness.

Percutaneous penetration of fragment is a stepwise mechanism involving: [16]

i. Penetration: The entry of a fragment into a particular layer of the skin;

ii. Partitioning from the stratum corneum into the aqueous feasible epidermis;

iii. Movement through the feasible epidermis and into the uppermost dermis;

iv. Transport: The infiltration of molecules from one layer into another, which is distinct both functionally and structurally from the first layer;

v. Absorption: The movement of a fragment into the plasma circulation.

Transdermal drug delivery:

Transdermal drug transmission is a term that is confined to a situation in which a drug diffuses through different layers of the skin into the systemic circulation to bring out a curative response. An example would be a transdermal clonidine patch for the treatment of Hypertension, a local anesthetic patch for that the drug is intended to show pharmacological action at the required site.

Transdermal drug delivery also described as "patches" this is a self-administered dosage form design to deliver a competent bulk of API over perfect skin. **(4)** The earliest transdermal patch authorized for integral transmission in 1979 was a patch for continuous, three days transmission of scopolamine in the cure of motion sickness. The main advantage of this system is that there is a disciplined release of drug and painless drug delivery. [4]

Absorption of drugs over the skin is affected by the number of factors such as skin site, skin thickness, skin temperature, body temperature, blood flow rate, lipid concentration, Number of the hair follicle, hydration status, ph of the skin, principle of stratum corneum, sweat gland.

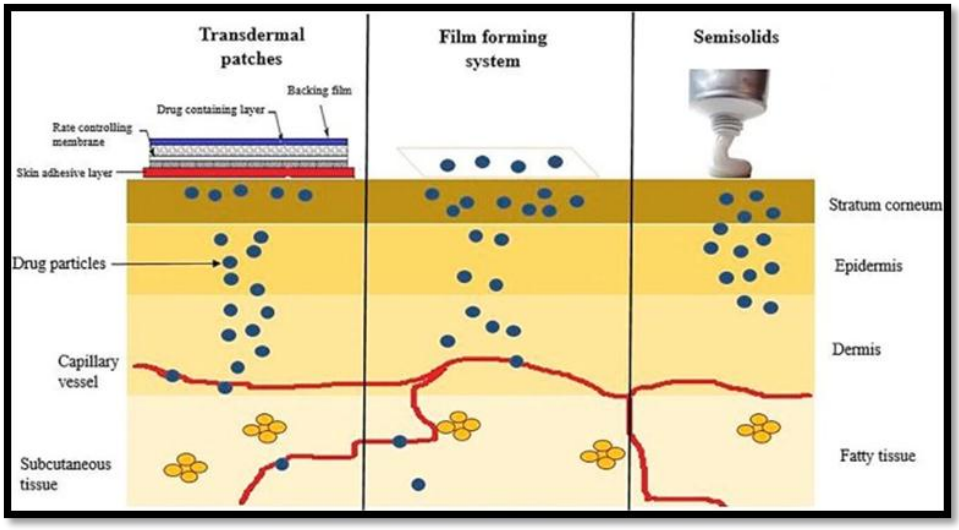

Fig. 2: Shows the correlation of drug liberated from Different dosage form

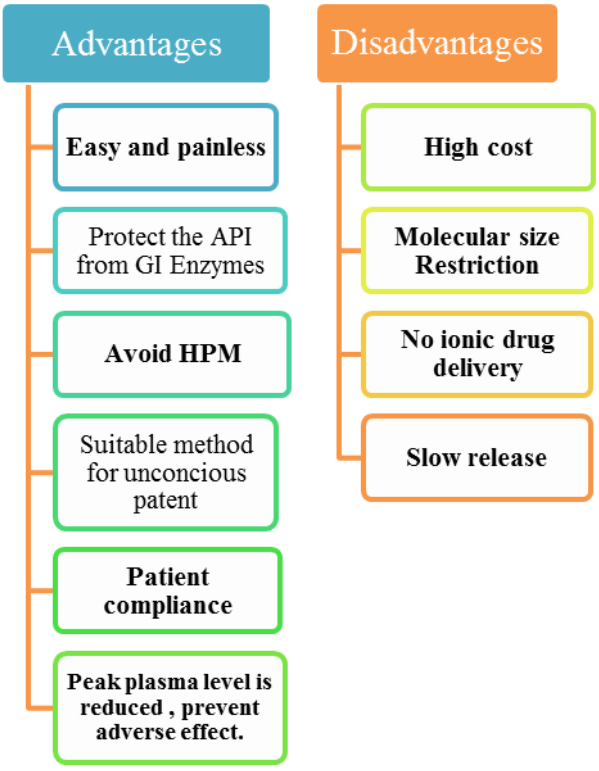

Fig. 3: Advantages & Disadvantages of TDDS

A transdermal patch has several components like [4]

Liner, drug, adhesive, drug reservoir, backing membrane, penetration enhancer.

Liner: [13]

For the time being, a patch is enclosed by a defensive liner that is detached and removed before the function of a patch to the skin.

The release liner is having a base layer that may be nonocclusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride) and release coating layer manufactured up of silicon or Teflon. Different earthly used for TDDS liners include polyester foil and metalized laminate that look over the patch during storage. The liner is detached before to application.

Drug: [13]

The drug solution is in direct contact with a release liner.

e.g.: Nicotine, Methotrexate, and Estrogen**.**

Drug selection criteria [4] [8]

1. The API shall have a molecular weight of less than 1000 Da.
2. The API shall have affection for lipophilic and hydrophilic patches.
3. An API shall have a less melting point.
4. The API shall be effective in a low daily dose.
5. The half-life of API shall be short.
6. The drug should not induce the allergic process.
7. The release should not change to zero-order kinetics.
8. Less Melting point below 6-7.

Adhesives: [13]

The attachment of TDDS is an important factor in security, potency, and quality of the product. Thus, adhesives are a vital component that plays a mellow connection between the delivery system with the membrane. It is analogous to drug delivery and curative effect. It

bears the drug that can either be break up or soften in the matrix or the cell containing drug (solution or suspension).

Properties:

Easily removable

Inexpensive

Nonirritant

No unwashable residue

Excellent skin contact

Compatibility with the drug

Permeation enhancers: [13]

(a) Solvent:

Mentioned below compounds enhances diffusion likely by bumping the polar route. e.g.: Water alcohols–Methanol & ethanol, /Dimethyl acetamide, PG, and Glycerol

(b) Surfactants:

The strength of a surfactant to alter the entrance is a mechanism of the polar head group and the hydrocarbon chain length.

i) Anionic surfactant: - SLS, Diacetylsulphosuccinate

ii) Nonionic Surfactant:-Pluronic F1, Pluronic F68

iii) Bile Salt: - Sodium taurocholate, Sodium deoxycholate

Backings: [13]

Backings are selected to look, plasticity, and demand for a barrier. Examples of backings are polyester film, polyethylene film, and polyolefin film, and aluminum vapor coated layer.

Table 1: Various drug used in Transdermal drug delivery system:

Drug	Polymer	System	Purpose
Tenoxicam	Eudragit L-30, D-55	Reservoir Type	Used to cure the rheumatic diseases
Anastrozole	_	Matrix Type	Hormone-sensitive breast cancer
Meloxicam	Sodium methoxide PVP, DIPAa	Drug-in-adhesive Type	Rheumatic diseases and osteoarthritis.
Avobenzone	HP-β-CD	_	chemical sunscreen
Diltiazem	HPMC	Matrix Type	Diltiazem is used to treat hypertension
Nortriptyline hydrochloride	HPMC	Matrix Type	Depression.
Benztropine	_	Drug-in-adhesive Type	Parkinson disease
Ketoprofen	Sodium polyacrylate	Matrix Type	NSAID
Glipizide	Eudragit RL-100/ Eudragit RS-100	Matrix Type	Type 2 diabetes
Estradiol	N-methyl-2-pyrrolidone	Reservoir, Matrix Type	Used to treat menopause symptoms
Nicotine	Carbopol	Matrix Type	Nicotine replacement therapy (NRT)
Primaquine	Ethyl cellulose	Matrix Type	Treatment of malaria.
Dexamethasone	Povidone	Matrix Type	Antiemetic therapy

Strategies in the development of transdermal patches: [2]

1. Polymer Membrane transport

2. Polymer Matrix dispersion

3. API Reservoir Gradient / Adhesive distribution Type System.

4. Microreservoir Dissolution Controlled TDDS.

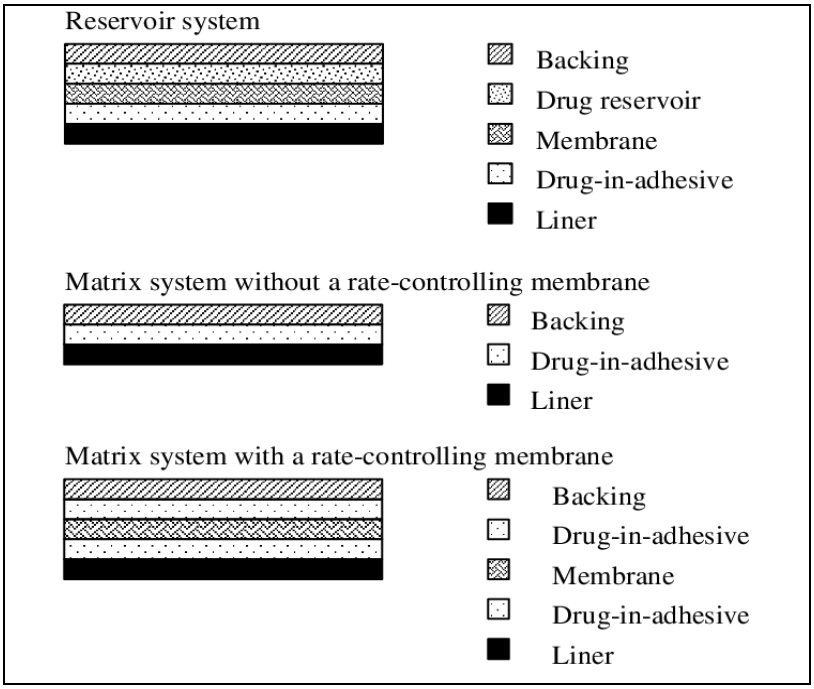

Fig. 4: Represent the Types of transdermal patches that are commercialized

Table 2: Absolute properties of transdermal drug delivery system

Sr. no	Properties	Range
1	Shelf life	Shall be up to 2.5 years
2	Patch size	Shall be less than 40mm^2
3	Dose frequency	Once a daily- once a week
4	Appearance	Shall be clear or white
5	Packaging properties	Shall be easily removable of a release liner
6	Skin reaction	Shall be non-irritating
7	Release properties	Shall have consistent PK & PD profile over time

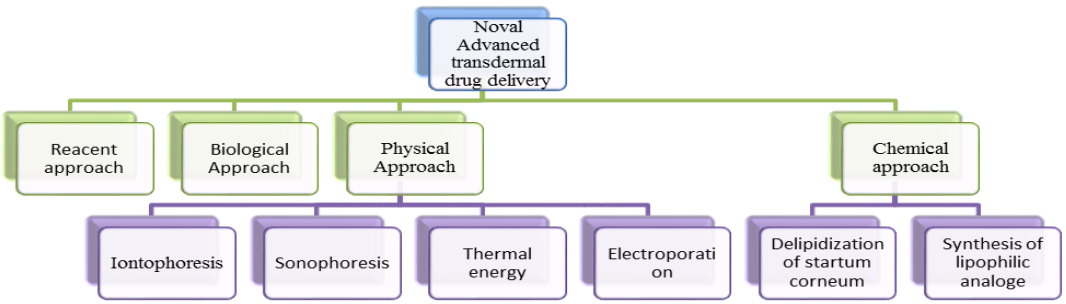

Fig. 5: Novel advanced transdermal technologies

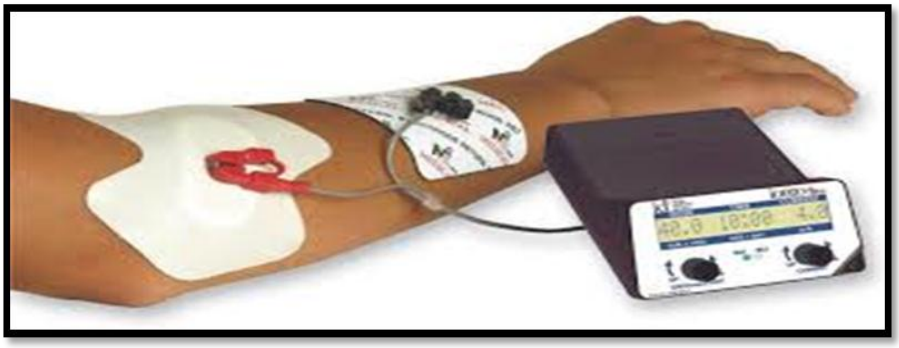

Fig. 6: Iontophoresis drug delivery system

History and development of iontophoresis: [9]

The iontophoretic drug delivery method was described by Private in the year 1747. The two well-known scientists named Galvani and Vota in the 18th century. [3]

The history of iontophoresis has been detailed by [24] earliest and well- documented experiments were done by Ludec at the beginning of the 20th century he demonstrated the importance of polarity when using a direct current to administer strychnine and cyanide to two rabbits [23] Additionally, up to the last few generations, iontophoresis has come to be a nearly new technique for its benefit in the transmission of charged ions and large molecule through the skin for systemic circulation.

Physical enhancement techniques are designed to convey the drug through smaller skin areas. **[8]**

1. Iontophoretic Delivery Principles And System Components [9] [25]

Iontophoresis is depending on the principle that "similar charges resist", while "reversed charges pull toward each other". A set of electrodes is been utilized to form the repulsive and attractive forces this supply the foreign energy to run the ions over the skin, leading to improvement of drug diffusion.

This fundamental has led to the progression of two types of elementary system, anodal and cathodal iontophoresis, both having the primary set of electrodes (anode and cathode), API, and salt reservoirs, and a current origin. Positively charged ions could be conveyed by keeping them beneath the positive electrode (anode) by cause of repulsion and at the same time creating attractive force by keeping the negative electrode at a distal location of the skin.

At the same time, negatively charged ions through the body (primarily Cl^-) move toward the anode. This system is called anodal iontophoresis.

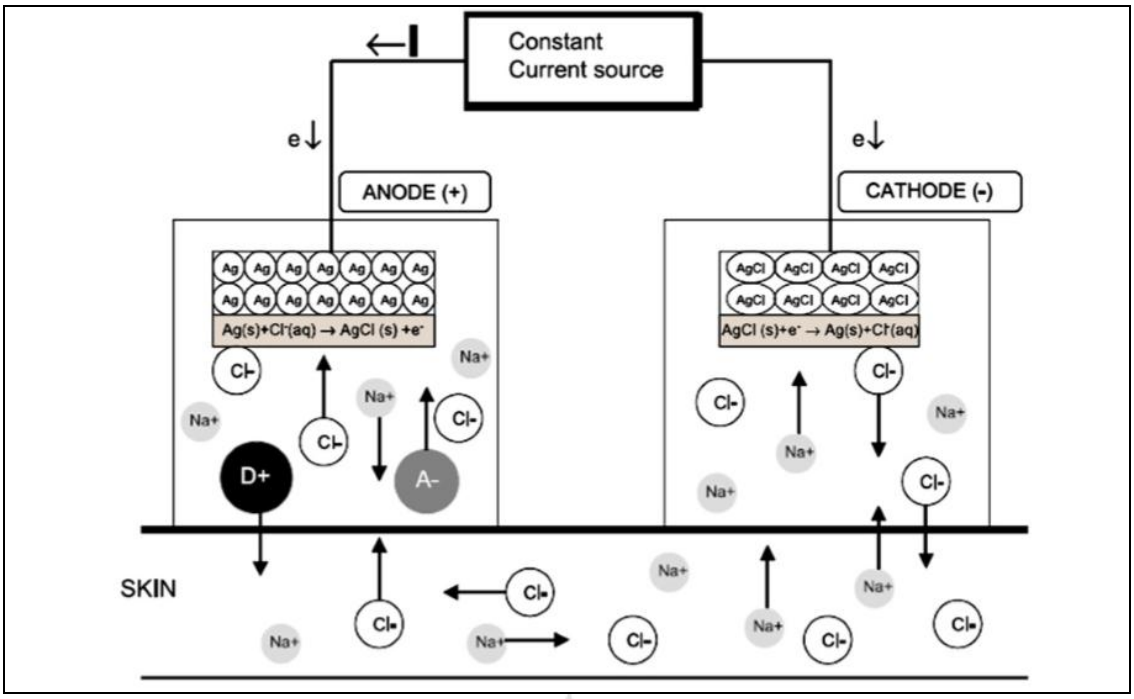

Fig. 7: Represent the movement of ions in iontophoresis

Ideal drug candidate for Iontophoresis

Aqueous Solubility: > 1 mg/ml

Charge: pKa or pl< 4 (for acids) > 7.4 (for bases)

Dosage given:

- 20 – 50 mg/day for Mwt < 1000 Da
- 2 – 5 mg/day for 1000 Da<Mwt<5000 Da
- < 1 mg/day for Mwt > 5000 Da
- pKa – Ionization constant and pl – Isoelectric point

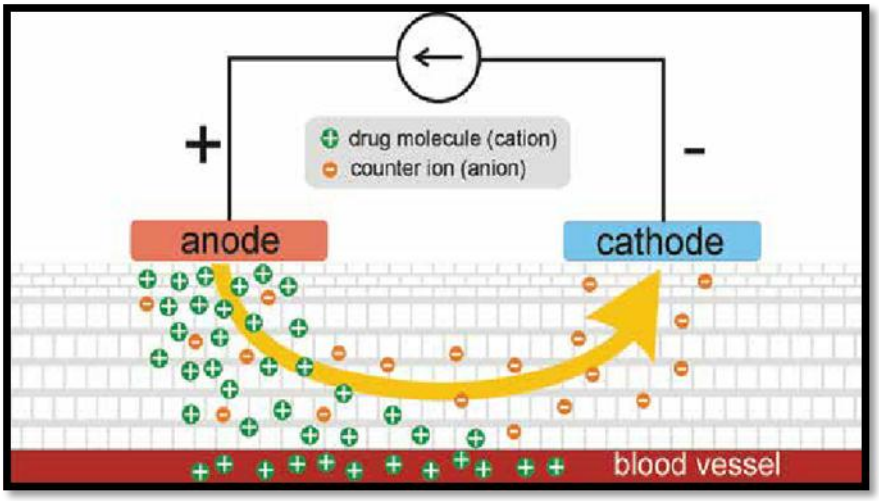

Fig. 8: Represent the mechanism of iontophoresis

Drug Transport in iontophoresis [9] [15]

The vast quantity of iontophoretic diffusion takes place due to the outcome of the supplied electric current on the movement of the charged molecule across the skin, this aspect is called electro-transfer or electro-repulsion. The supplied electric current likewise gives rise to a water transit anomaly, called electro-osmosis, which give to the iontophoretic shipment of a molecule. Iontophoresis can be utilized to supply a dose of a drug. A wide variety of API have been approved for their application in iontophoresis propranolol hydrochloride, [28] [29] buspirane hydrochloride, [30] insulin. [31] Iontophoretic shipment is essentially directed by electro-repulsion and electro-osmosis, also to a lesser degree through passive diffusion. So, the entire iontophoretic flow, J_{total}, can be shown as: [32]

$$J_{total} = J_e + J_c + J_p$$

Where J_e = flux contribution due to electrorepulsion,

J_c= flux contribution due to passive diffusion.

J_p = flux contribution due to passive diffusion.

pH shows a very important aspect in iontophoresis by maintaining a huge quantity of API in its ionized form. The essential pH in the ability of iontophoresis transport is shown by[26] useing constant current iontophoresis for transdermal transport of cytochrome C across porcine skin. [27]

Iontophoretic flow possess a straight dependency on the vitality of the supplied current, with the flux values growing linearly with the rise in current density (figure no 4.3).

Consolidation methods to enhance transdermal iontophoretic drug delivery

- Iontophoresis with electroporation.
- Iontophoresis with chemical enhancers.
- Iontophoresis along microneedles.
- Iontophoresis along sonophoresis
- Ion- exchange materials.
- Reverse iontophoresis.

Table. 3: Represent the approved drug for Iontophoretic technique

Drug	Iontophoretic system	Polarity	Purpose
Lidocaine	Lidosite®	+	Anesthetic
Botulinum	Iomed Phoresor® II	+	hyperhidrosis
Fentanyl HCl (Ionsys)	E-Trans, Activa Tek	+	Postoperative pain management
Lidocaine and epinephrine	Phoresor®	+	local dermal anesthesia
Corticosteroids	Ocuphor™	+	Retinal diseases
Glucose	GlucoWatch G2 Biographer	+	Monitoring glucose

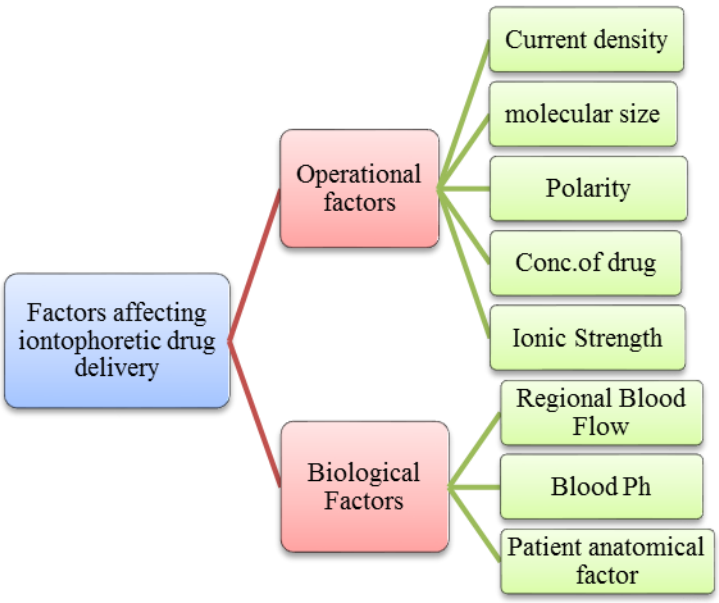

Fig. 9: Factors affecting Iontophoretic Drug Delivery

Evaluation of TDDS:

1. Physicochemical Evaluation. [(1) (7)]

1. The thickness of the patch: The thickness of the API weighted patch is measured in the distinct mark by using a digital micrometer, traveling microscope, dial gauge, screw gauge or micrometer on various points of the film.

2. Uniformity of weight: Weight fluctuation is conducted by alone measuring 10 different selected patches and considering the average weight. The formed patches were dried at 60°C for 4hrs earlier testing. A stated area of patch is been cut in different parts of the patch.

3. Drug content determination: An exactly measured area of the film (about 100 mg) is dissolved in 100 ml of the desired solvent in that drug is soluble and then the solution is agitated continuously for 24h in shaker incubator. Then that solution is sonicated and estimated using Uv or HPLC technique.

4. Content uniformity test: 10 patches are taken and content is checked for specific patches. If 9 out of 10 patches had content between 85%to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity.

5. Folding endurance: Evaluation of folding endurance contain knowing the folding strength of the films exposed to the periodic extreme situation of folding. Folding endurance is identified by repeatedly folding the film at the same place until it breaks. The number of times the films could be folded at the same place without breaking is folding endurance value.

6. Percentage Moisture content: The formed film is to keep in desiccators holding fused calcium chloride at room temperature for 24 hrs. After 24 hrs film is again reweighed and identifying percentage moisture content.

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

7. Shear Adhesion test:

This test is to be performed for the determination of the cohesive power of the adhesive polymer. It can be influenced by the polymer type, amount of tackifier added. An adhesive glaze tape is enforced on a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is known by analyzing the time it takes to pull the tape of plates.

8. Flatness: A transdermal patch must contain a smooth surface and that should not constrict with time. This can be determined by a flatness study. For flatness analysis, one strip is cut at the center and two from each side of the patches. The diameter of each strip is analyzed and change in length is measured by knowing percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

2. In vitro evaluation:-

1. In vitro API discharge studies : [5]

The paddle over disc method (USP apparatus V) is for the analysis of the release of the drug through the prepared patches. Dry films cut into a small shape, weighed, and packed over a glass plate with the adhesive. The glass plate is then placed in a 500 ml. phosphate buffer (pH 7.4), and the apparatus is equilibrated to 32± 0.5°C. The paddle is kept at a distance of 2.5 cm from the glass plate and regulated at a speed of 50 rpm. Samples (5- mL aliquots) can be

withdrawn at given time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC.

2. In vitro skin permeation studies: [7]

An in vitro permeation study can be carried out by using Franz diffusion cell The cell is containing two parts: donor and receptor. The receptor part has a volume of 5-12ml and an effective surface area of 1-5 cm2. The diffusion buffer is continued to stirring at 600rpm by the use of a magnetic bar. The temperature of the cell is maintained at 32 ± 0.5°C using a thermostatically controlled heater.

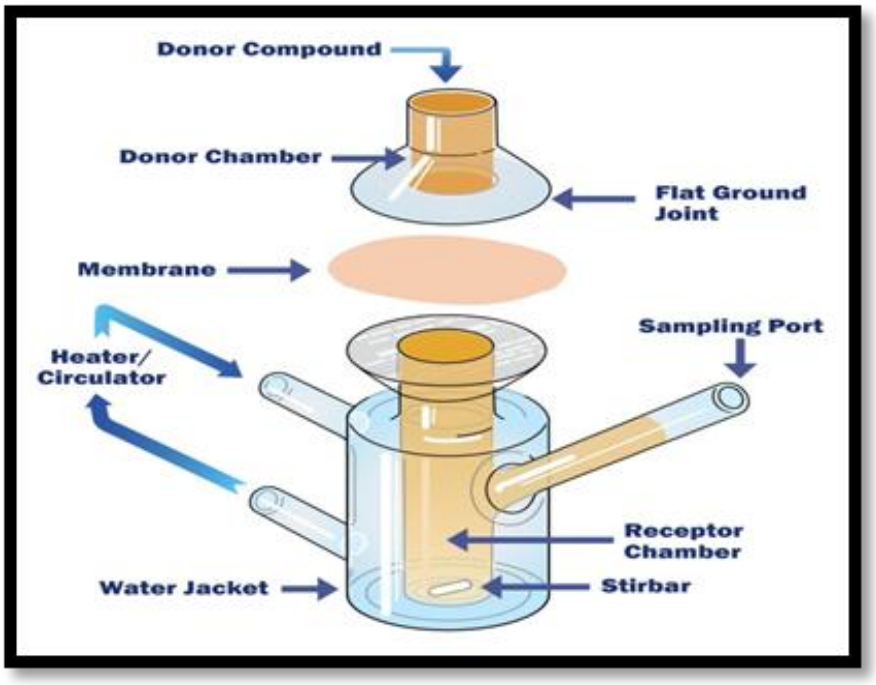

Fig. 10: Franz's diffusion cell

CONCLUSIONS:

Transdermal drug delivery systems represent a beneficial innovation for drug delivery, the use of TDDS is increasing rapidly in the present time particularly in patients who cannot swallow or remember to take their medications.

This transdermal iontophoretic technique increases the movement of API molecules through the membrane by the control of an externally supplied electric current and so it is one of the, most promising physical methods to increase the skin penetration of ionic drug molecules. The use of iontophoresis for the systemic delivery of new peptides and protein therapeutic

agents has attracted considerable recent interest from the biotechnology industry. This article presents the complete approach of the iontophoretic transdermal drug delivery system, delivery device, drug delivery mechanisms, basic iontophoretic principles.

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