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A REVIEW ON THE IMPORTANCE OF TRANSFEROSOMES AND TRANSDERMAL PATCHES

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ABSTRACT

Novel drug delivery systems are now a days is creating a new interest in development of drug deliveries. Vesicular drug delivery system is also a part of these novel drug delivery systems. TDDS is the permeability of the skin, it is permeable to small molecules, lipophilic drug and highly impermeable to the macromolecules and hydrophilic drugs. Transferosomes have recently been introduced, which are capable of transdermal delivery of low as well as high molecular weight drugs. This offers several potential advantages over conventional routes like avoidance of first pass metabolism, predictable and extended duration of activity, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and pharmacological response and have been applied to increases the efficiency of the material transfer across the intact skin, by the use of penetration enhancers. It is suitable for controlled and targeted drug delivery and it can accommodate drug molecules with wide range of solubility. Due to its high deformability it gives better penetration of intact vesicles. They are biocompatible and biodegradable as they are made from natural phospholipids and have high entrapment efficiency. The preparation variables are depending upon the procedure involved for manufacturing of formulation and the preparation procedure was accordingly optimized and validated. It increases stability of labile drugs and provides control release. Transferosomes thus differs from such more conventional vesicles primarily by its softer, more deformable, better adjustable artificial membrane.

KEYWORDS: Transdermal, Transferosomes, penetration enhance, biocompatible, biodegradable, deformability, entrapment efficiency, artificial membrane.

INTRODUCTION ON TRANSFEROSOMES

Orally administered drugs experience a hostile environment in the gastrointestinal (GI) tract, where most drugs are degraded in variable pH conditions, or face solubility issues and most importantly first-pass metabolism. In case of parenteral preparation, disadvantages are a lack of drug reversal, hypersensitivity reaction, risk of infection, emboli and cost. Some drugs much bitter in taste, swallowing of such a bitter medication in oral delivery and pain associated due to needle in parenteral delivery make them less patient compliance. From last few decades, considerable attention has been focused on the development of topical delivery of drugs because a number of advantages with this route.[1] Topical drug delivery means the application of drug to skin for localized effect and in transdermal drug delivery system (TDDS) skin is used as a potential route for the delivery of systemic action of drugs. TDDS is one of the systems with high patient compliance. Some potential advantages of transdermal route found over other conventional routes such as oral- and parenteral-like avoidance of first-pass metabolism, predictable and extended duration of activity, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels, inter- and intra-patient variations and most importantly, it provides patients convenience.[2,3] However, it also has some disadvantages such as possibility of local irritation effect, erythema, itching and low permeability in the stratum corneum.[4]

The skin has shown a promising route for the delivery of drugs in recent times. Surface area and ease of administration make it the best alternate choice for drug delivery. The major drawback of transdermal drug delivery systems (TTDs) is it has less permeability for hydrophilic drugs and macromolecules find it difficult to permeate the skin. Several different types of methods have been developed to overcome this problem. To date many physical and chemical approaches have been applied to increase the efficacy of the material to transfer across the intact skin, by use of the penetration enhancers, iontophoresis, iontophoresis and the use of colloidal carriers such as lipid vesicles (liposome and

pro-liposomes) and non-ionic surfactant vesicles (noisome and pro-noisome).[5]

A new vesicular derivative, the "transferosomes", has paved the way to minimize the defective transdermal permeation of a number of low and high molecular weight drugs, which has been found to be one of the major advancements in vesicle research. Cevc's group introduced transferosomes in 1991, which are prepared from phospholipids and surfactants (edge activators). Transferosomes is derived from the Latin word 'transfer' meaning 'to carry across' and the Greek word 'soma' for a 'body'. Transferosomes is a trademark registered by the German company IDEA.[6]

TDD is a painless method of delivering drugs systemically by applying a drug formulation onto intact and healthy skiaren.[7] The drug initially penetrates through the stratum corneum and then passes through the deeper epidermis and dermis without drug accumulation in the dermal layer. When the drug reaches the dermal layer, it becomes available for systemic absorption via the dermal microcirculation.[8-10]

They can improve patient compliance and provide a controlled release of therapeutic agents. It can provide a non-invasive alternative to parenteral routes, thus circumventing issues such as needle phobia.[11,12]

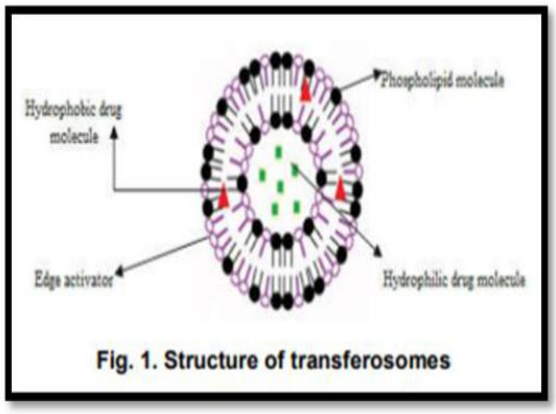

Fig. 1. Structure of transferosomes

Advantages

1. Transferosomes can squeeze themselves through constrictions of the skin barrier that are very narrow, such as 5 to 10 times less than the vesicle diameter, owing to their ultra-deformability and elastic properties.
2. High vesicle deformability facilitates the transport of drugs across the skin without any measurable loss in intact vesicles and can be used for both topical, as well as systemic, treatments.
3. They are made up of natural phospholipids and EAs, therefore promisingly biocompatible and biodegradable.
4. Transferosomes carriers are very versatile and efficient in accommodating a variety of agents nearly independent of their size, structure, molecular weight, or polarity.
5. Transferosomes are an obvious choice for a sustained drug release, as well as a predictable and extended duration of activity.
6. They are capable of increasing the transdermal flux and improving the site-specificity of bioactive agents.
7. Avoiding the first-pass metabolism, which is a major drawback in oral drug administration, results in optimized bioavailability of the drug.
8. Minimize the undesirable side effects of the drug, as well as protect the drug from metabolic degradation; moreover, the utility of short half-life drugs.

Disadvantages

1. Transferosomes are considered as chemically unstable due to their tendency to oxidative degradation.
2. The oxidation of transferosomes can be significantly decreased when the aqueous media is degassed and purged with inert gases, such as nitrogen and argon.
3. Storage at a low temperature and protection from the light will also reduce the chance of oxidation.
4. Post-preparation processing, such as freeze-drying and spray-drying, can improve the storage stability of transferosomes.
5. Another obstacle to utilizing transferosomes as a drug delivery system is a difficulty to achieve the purity of natural phospholipids.
6. Therefore, synthetic phospholipids could be used as alternatives.
7. The expensiveness of transferosomal formulations is associated with the raw materials used in lipid excipients, as well as the expensive equipment needed to increase manufacturing.
8. Hence, the widely used lipid component is phosphatidylcholine, because it is relatively low in cost.[13-15]

Composition of transferosomes

Transferosomes is a self-adaptable and optimized mixed lipid aggregate and is composed of two main aggregates namely,

1. Firstly, an amphipathic ingredient (phosphatidylcholine), in which the aqueous solvents self-assemble into lipid bilayer that closes into a simple lipid vesicle.
2. Secondly, a bilayer softening component (such as a biocompatible surfactant or amphiphilic drug) increases lipid bilayer flexibility and permeability.

An edge activator consists usually of single chain surfactant that causes destabilization of the lipid bilayer thereby increasing its fluidity and elasticity.
The newer elastic vesicles were introduced by Van den berg in 1998, consisting of non-ionic surfactant as the edge activator.

Flexibility of transferosomes membrane can be altered by mixing suitable surface active agents in the proper ratios.

The resulting, flexibility and permeability optimized, transferosomes vesicle can therefore adapt its shape easily and rapidly, by adjusting local concentration of each bilayer component to the local stress experienced by the bilayer. Therefore, the transferosomes thus differs from such more conventional vesicle primarily by its "softer", more deformable, and better adjustable artificial membrane.[16]

Materials commonly used for the transferosomes preparation are summarized in Table 1:

Ingredient	Examples	Functions
Phospholipid	Soya Phosphatidylcholine Egg Phosphatidylcholine Disteryl Phosphatidylcholine	Vesicle forming Componet
Surfactant	Sodium Cholate Sodium deoxy Cholate Tween 80 Span 80	For Providing Flexibility
Alcohol	Ethanol Methanol	As a Solvent
Dye	Rhodamine-123 Rhodamine-DHPE Flurescein-DHPE Nil red 6 Corboxy fluorescence	For Confocal ScaningLaseer Microscopy (CSLM) Study
Buffering Agent	Saline phosphate buffer (PH 6.5) 7% v/v ethanol Tris buffer (PH 6.5)	As a hydrating medium

Mechanism of action

The natural transdermal water activity variation across the skin layers creates a powerful force that activates the Transferosomes, causing the widening of intercellular connections and the formation of transcutaneous channels with a diameter of 20-30 nm. These pathways are created to allow ultra-deformable microscopic Transferosomes to pass through the epidermal layers furthermore, the osmotic gradient created by body heat evaporating moisture from the skin's superficial layers is used as a driving force to facilitate the flexible passage of therapeutic agents from the site of application to the specific area for local or system therapies in effective therapeutic concentrations with minimal systemic toxicity. Therefore, transferosomes uptake is a function of hydration gradient that exists across the epidermis, stratum corneum, and ambient atmosphere.[17]

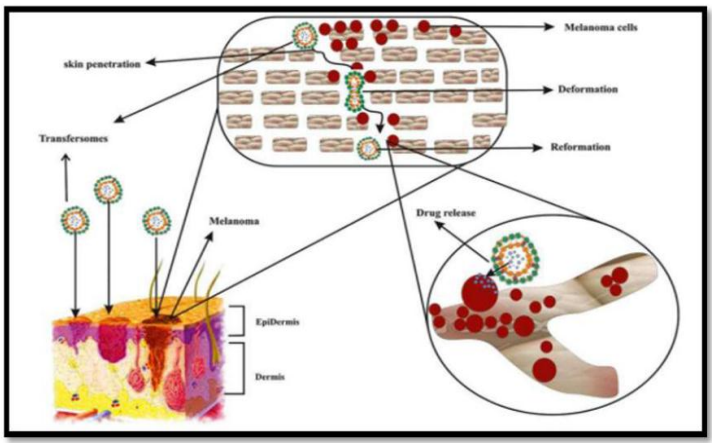

Figure 2: Schematic representation of mechanism of action.

Preparation methods of transferosomes

1. Thin Film Hydration Technique / Rotary Evaporation-Sonication Method

Drug, Phospholipid along with surfactants was placed in a round-bottomed flask. The solvent system is then added to the mixture and the ingredients were dissolved in the solvent (Chloroform: methanol) by handshaking. The flask was attached to a rotary evaporator and immersed in a water bath maintained at 60°C, rotated with 100rpm for 45min. The formation of the thin film at the bottom was observed. The thin film is hydrated using 6.8 pH buffer. The resultant solution was sonicated in probe sonicator for 30mins.

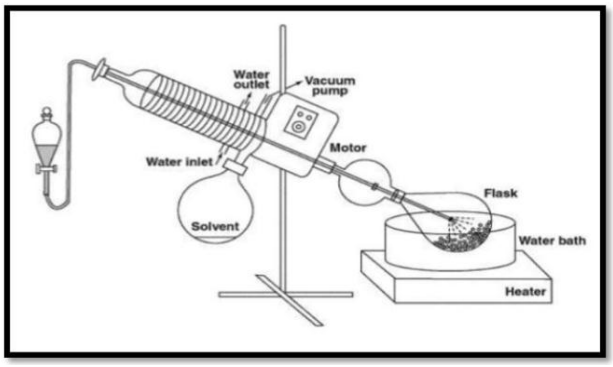

Figure 3: Schematic representation of thin film hydration technique method.

2. Vortexing - Sonication Method

In this method, mixed lipids (i.e. such as phosphatidylcholine, EA and the therapeutic agent) are blended in a phosphate buffer and vortexed to attain a milky suspension. The suspension is sonicated, followed by extrusion through poly-carbonate membranes.

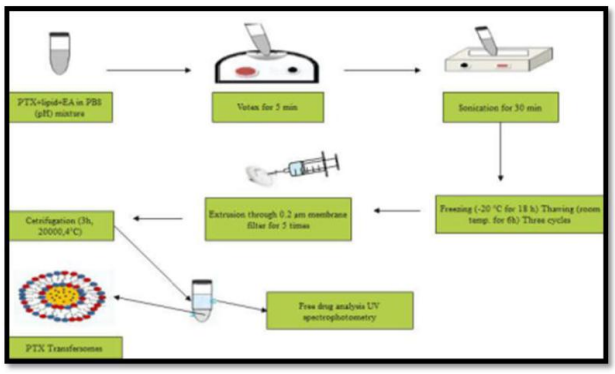

Figure 4: Schematic representation of vortexing sonication method.

3. Modified handshaking process

In an ethanol: chloroform (1:1) combination, the drug, lecithin (PC), and edge activator are dissolved. Above the lipid transition temperature (43°C), the organic solvent is evaporated with hand shaking. Rotation causes the formation of a thin lipid layer inside the flask wall. The thin layer is let to dry overnight to ensure complete evaporation of solvent. The film is then hydrated for 15 minutes at room temperature with phosphate buffer (pH 7.4) and moderate shaking. At 2-8°C, the Transferosomal suspension hydrated for a further hour.

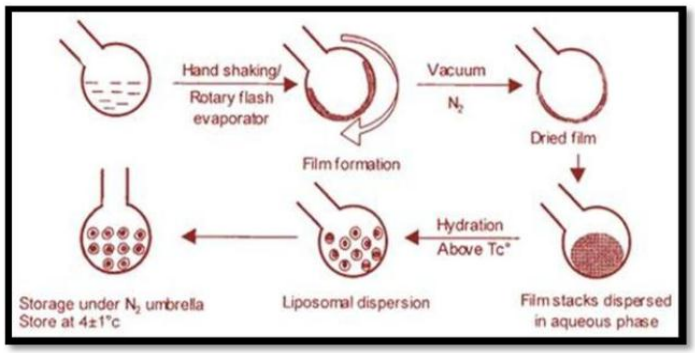

Figure 5: Schematic representation of modified handshaking method.

4. Reverse-Phase evaporation method

In a glass beaker, the components such as cholesterol and phospholipids are added. The surfactant is then added to same beaker and dissolved in a separate solvent solution. The beaker is left at room temperature for 24 hours to produce a thin layer. The drug solution is poured over the thin film and sonicated for 2 minutes at a frequency of 20 KHz using a probe sonicator. After that, the film is hydrated in phosphate buffer saline (pH 7.4) with edge activator before being sonicated for 2 minutes to get transferosomal suspension. After that, different transferosomal suspensions should be filtered using Whatman filter paper (No. 40).

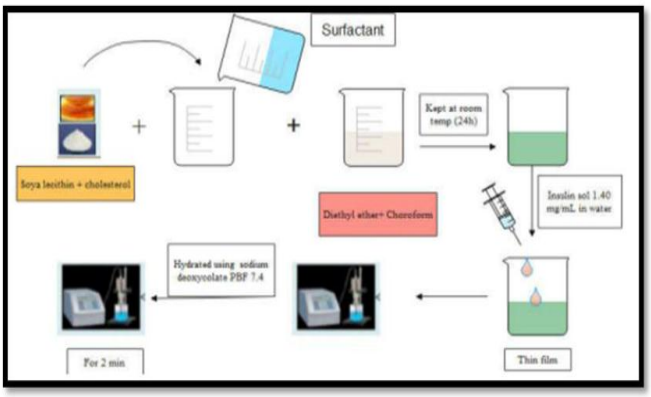

Figure 6: Schematic representation of reverse phase evaporation method.

5. Ethanol injection method

The organic phase is made by dissolving the phospholipid, edge activator, and lipophilic drug in ethanol and stirring for the appropriate amount of time until a clear solution is obtained. The water-soluble compounds are dissolved in the phosphate buffer to form the aqueous phase. This is the time to incorporate the hydrophilic medication. Both solutions are heated to 45–50 °C. After that, the ethanolic phospholipid solution is injected dropwise into the aqueous solution while stirring continuously for the period specified. Transferring the resulting dispersion into a vacuum evaporator and then sonicating for particle size reduction is how ethanol is removed.[18-23]

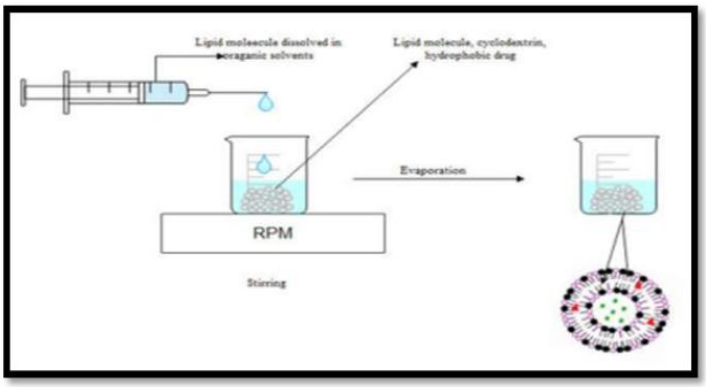

Figure 7: Schematic representation of ethanol injection method.

Optimization of formulation containing transfersomes

There are some process variables such as lecithin, surfactant ratio, effect of various solvents, effect of various surfactants, and hydration medium. This could affect the preparation and properties of the transferosomes. Procedure for preparation of transferosomes will accordingly optimize and validate. The process variables depend on the procedure for manufacturing of formulation. Entrapment efficiency of drug is the tool used for optimization. Other variables were kept constant at the time of preparation of particular system.[24]

Characterization of transferosomal formulations

Determination of vesicle size, polydispersity Index and Zeta potential

The vesicle size, PDI, and zeta potential of the prepared transferosomes were determined based on laser diffraction using the Malvern Master seizer by diluting the sample using water as dispersant.

Entrapment efficiency

The percentage of drug entrapped in the transferosomal suspension was determined by disrupting the vesicles. Transferosomes containing drug were separated from entrapped drugs by centrifugation at 14,000 rpm for 30 min. The supernatant was filtered and assayed.

$$EE\% = \frac{\text{actual drug loading}}{\text{theoretical drug loading}} \times 100\%$$

Drug content determination

The amount of drug contained in the transferosomal suspension was determined by dissolving 100 ml of the formulation in 10ml of ethanol. Analysis of the mixture was done.

Turbidity measurement

Nephelometer is one of the methods which generally used for turbidity measurement in aqueous solution.

Degree of deformability or permeability measurement

Permeability study is one of the important and unique parameters for characterization in case of transferosomes. The deformability study is done by taking pure water as standard. Transferosomes preparation is passed through a number of pores of known size (through a sandwich of different microporous filters, with pore diameter between 50 and 400 nm, depending on the starting transferosomes suspension). Particle size and size distributions are noted after each pass by DLS measurements.

Penetration ability

Fluorescence microscopy can generally use for evaluation of penetration ability of transferosomes.

Occlusion effect

Occlusion of skin is considered to be useful for permeation of drug in case of traditional topical preparations. However, the occlusion also proves to be harmful for elastic vesicles. Hydrotaxis is the major driving force for permeation of vesicles through the skin is hydrotaxis (movement in the direction) of water, from its relatively dry surface to water rich deeper regions. It affects hydration forces as it prevents evaporation of water from skin.

Surface charge and charge density

Surface charge and charge density of transferosomes can be determined using zetasizer.

Comparison Study with other Vesicles

Confocal scanning laser microscopy (CSLM) study allows researchers to compare transferosomes to liposomes, noisome, and other types of nanoparticles, as well as investigate the process of transferosomes penetration. The process involves the use of a lipophilic fluorescent marker that can produce light. The light that is emitted is used for additional detection.[25-33]

Applications of transferosomes

1. Delivery of insulin

Transferosomes is one of the successive ways to deliver such large molecular weight drugs on the skin. Insulin is generally administered by subcutaneous route that is inconvenient for patient. Encapsulation of insulin in transferosomes (transfersulin) overcomes all problems arises with conventional insulin delivery. After application of transfersulin on the intact skin, therapeutic effect observed after 90-180 min, depending on the carrier composition.

2. Delivery of corticosteroids

Problems arise with corticosteroids delivery is mask by incorporation it into transferosomes. Site specificity and overall drug of corticosteroid delivery into skin by optimizing the percutaneously administered drug dose safety is achieved by transferosomes encapsulation. Dose required for biological activity of corticosteroid is less by use of transferosomes technology.

3. Delivery of proteins and peptides

Transferosomes have been widely used as a carrier for the transport of proteins and peptides also safely given by means of transferosomes technology. Proteins and peptide has problem i.e., it is difficult to transfer into the body, as they are large biogenic molecules, GI tract degradation is problem arise when given orally. That's reasons why these peptides and proteins still given by means of injectable. A number of approaches have been developed to improve this condition. Transferosomes is somewhat identical to that resulting from subcutaneous injection of protein suspension in terms of bioavailability. On repeated percutaneous application, transferosomes preparation of protein also induced a strong immune response. For example, the adjuvant immunogenic serum albumin in transferosomes.

4. Delivery of interferon (INF)

INF also delivered using transferosomes as a carrier, for example, leukocyte-derived INF-α is a naturally occurring protein having antiviral, anti-proliferative, & some immunomodulatory effects. Transferosomes as drug delivery systems have the potential for providing controlled release of the administered drug and increasing the stability of labile drugs.

5. Delivery of anticancer drugs

Transferosomes technology provides a new approach for cancer treatment, especially skin cancer. Result found to be favourable when methotrexate was tried for transdermal delivery using transferosomes technology.

6. Delivery of anaesthetics

Application of transferosomes-containing anaesthetics induces a topical anaesthesia, under suitable conditions, within 10 min. Effect when we said in case of pain & sensitivity is nearly as strong (80%) as of a comparable subcutaneous bolus injection, but transferosomal anaesthetics preparation has last longer effect.

7. Delivery of non-steroidal anti-inflammatory drugs (NSAIDs)

Problems arise with most of NSAIDs are a number of GI side effects. This can be overcome by transdermal

delivery using transferosomes. Studies have been carried out on diclofenac and ketoprofen. Ketoprofen in a transferosomes formulation gained marketing approval by the Swiss regulatory agency (Swiss medic) in 2007; the product is expected to be marketed under the trademark "Diractin." Further therapeutic products based on the transferosomes technology, according to IDEA AG, are in clinical development.

8. Delivery of herbal drugs

Herbal drug also delivered by transferosomes approach shows the better topical absorption of transferosomes of capsaicin in comparison to pure capsaicin.

Another most important application of transferosomes is transdermal immunization using transferosomes loaded with soluble protein like integral membrane protein, human serum albumin and gap junction protein. These approach offers at least two advantages, first they are applicable without injection and second, they give rise to relatively high IgA levels.

Peripheral drug targeting: the ability of transferosomes to target peripheral subcutaneous tissues is due to minimum carrier associated drug clearance through blood vessels in the subcutaneous tissues.

Transferosomes have the potential for the controlled release of the administered drug and increasing the stability of labile drugs due to the incorporation of phospholipids.

Since transferosomes obtain similar bioavailability to subcutaneous injection. Human serum albumin was found to be effective in producing the immune response when delivered by transdermal route encapsulated in Transferosomes.[34-40]

Introduction on transdermal patches

Most of the chronic diseases have genetic, hereditary cause or lifestyle borne like hypertension, asthma, diabetes, addiction etc. It is desirable, from the standpoint of pharmacodynamics to maintain the drug concentration in plasma within a therapeutic effective range for long periods.[41] However, even if the drug is well absorbed orally, it will run through entero-hepatic cycle. In some cases it will decrease the systemic availability of drug as it undergoes hepatic first pass metabolism. This effect will establish a significant difference between claimed (theoretical) and attained (practical) bioavailability of drug moiety.[42]

To compensate the loss, massive dosing will make the product bulkier, process uneconomical and may cause toxicity in some cases. Among conventional dosage forms, continuous i.v. infusion is the sole exception that will bypass the hepatic cycle and also releases the drug following zero order kinetics for long term, hence minimizes overdosing.[43,44] Therefore, attention has been given to develop transdermal drug delivery system with the large surface area of skin as the site of application.[45]

Transdermal patch generally refers to topical application delivers agents to healthy intact skin either for localized treatment of tissues underlying the skin or for systemic therapy. Transdermal Patch offers many advantages over the conventional dosage forms or controlled release oral systems. Transdermal patch provides constant blood levels, avoids first pass metabolism, increased patient compliance, and avoids dose dumping. The application of transdermal delivery to a wider range of drugs is limited due to the significant barrier to penetration across the skin which is allied primarily with the outermost stratum corneum layer of the epidermis.

Formulation on skin can be classified into two categories according to the target site of the action. One has systemic action after drug uptake from the cutaneous micro vascular network and other exhibits local effects in the skin. Transdermal drug delivery can closely mimics the slow intravenous infusion without its potential hazards and also offer another most important advantage in allowing the patient to terminate the drug therapy by simply removing the patch at desired time if toxicity develops.[46]

Patches applied to the skin eliminate the need for vascular access by syringe or the use of pumps and today there exist a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, nitro-glycerine, oestradiol, oxybutynin, scopolamine, and testosterone. There are also combination patches for contraception, as well as hormone replacement. Depending on the drug, the patches generally last from one to seven days. Transdermal drug delivery systems (TDDS) are the topically applied "patches" designed to deliver a therapeutically effective dose of a drug across the patient's skin at a controlled rate for the systemic effect.[47]

Despite the interests and the merits in this drug delivery system, only very few drug candidates have been approved for transdermal delivery. Besides skin toxicity of the drug or drug excipients, the major obstacle facing this route of delivery is the barrier nature of the skin which limits the number of molecules permeating it to only few that can meet certain criteria. Such molecules should possess appropriate physicochemical properties such as low melting point (< 10 mg). Only few drugs meet these criteria. Several percutaneous research strategies are available including in vivo and in vitro permeation studies.[48]

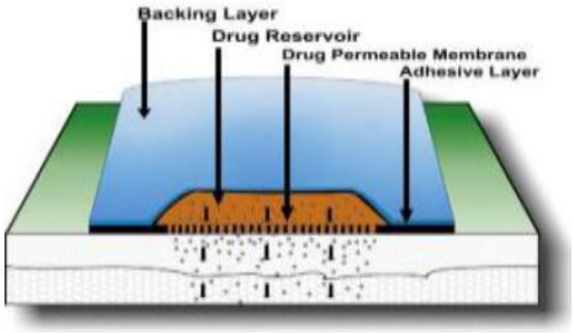

Fig. no. 8: Transdermal patch showing its different components.

Table 2: Some marketed transdermal products.

PRODUCT	DRUG	MANUFACTURER	INDICATION
Alora	Estradiol	TheraTech/proctol and Gamble	Postmenstrual syndrome
Androderm	Testosterone	Theratech/GalxosmithKline	Hypogonadism in males
Catapres-TTS	Clonidine	ALZA/Boehinger Ingelheim	Hypertension
Climaderm	Estradiol	EthicalHoldings/Wyeth-Ayerest	Postmenstrual syndrome
Climara	Estradiol	3M Pharmaceuticals/Berlex Labs	Postmenstrual syndrome
Deponit	Nitroglycerine	Schwarz pharma	Angina pectoris
Duragesic	Fentanyl	Alza/ Janssen pharmaceutical	Moderate /severe pain
Estraderm	Estradiol	Alza/Novartis	Post menstrual syndrome
Fempatch	Estradiol	Parke-davis	Post menstrual syndrome
Habitraol	Nicotin	Novartis	Smoking cessation
Minitrann	Nitroglycerine	3M pharmaceuticals	Angina pectoris
Nicoderm	Nicotin	Alza/glaxo smithkline	Smoking cessation
Nitrodisc	Nitroglycerine	Roberts pharmaceuticals	Angina pectoris
Nitro-dur	Nitroglycerine	Key pharmaceuticals	Angina pectoris
Prostep	Nicotine	Elan Corp./Lederle Labs	Smoking cessation
Testoderm TTS	Testosterone	Alza	Hypogonadism in males
Transderm	Scopolamine	Alza/Novartis	Motion sickness
Transderm	Nitroglycerine	Alza/Novartis	Angina pectoris

Advantages of tdds

- ✓ Avoids vagaries associated with gastro – intestinal absorption due to pH, enzymatic activity, and drug food interactions.
- ✓ It is a substitute for oral route
- ✓ Avoids first pass effect (drug deactivation by digestive and liver enzymes)
- ✓ It avoids the risks and inconveniences of i.v therapy
- ✓ Provides predictable extended duration of activity
- ✓ Extends the activity of drugs with short half – lives
- ✓ Multi day therapy with single application
- ✓ Provides capacity to terminate drug effects rapidly.
- ✓ Rapid identification of medication in emergency e.g., non-responsible unconscious or comatose patients.
- ✓ Minimize inter and intra patient variation
- ✓ Provides suitability for self-administration.
- ✓ Reduces daily dosing, thus improving patient compliance.

Limitations of tdds

- ✓ Limited time that the patch can remain affixed.
- ✓ Variable intra and inter individual percutaneous absorption efficiency.
- ✓ Skin rashes and sensitization.
- ✓ Bacterial and enzymatic drug metabolism under the patch
- ✓ Complex technology / high cost[49,50]

Need for transdermal patches

Transdermal drug delivery is the delivery of medicament through the dermal route of administration by over coming to the first-pass metabolism, gastrointestinal complications, and oral incompatibilities of various

drugs. This route of administration of drugs shows better plasma concentration with enhanced bioavailability compared to other formulations containing same medicament. The patches having more than one medicament are very useful for managing different disease states of the patient with minimal medication prescription, thereby achieving best outcomes with patient care-oriented therapy. The major side effects such as Lacto-acidosis, drug toxicities can be reduced through using of transdermal patches.

This is patient-friendly as it is easy to use if any of the situations and even care takes can also administer to patients in case patient is having neurological and psychological diseases. The transdermal system is a less painful route of administration, minimally invasive technique, ensuring better patient comfort for drug administration and increased to a great extent due to novel inventions and recent developments.[51]

Approaches in the development of transdermal system

Several technologies have been successfully developed to provide a rate control over the release and the transdermal permeation of drugs. These technologies are as follows:

- ✓ Adhesive dispersion type system
- ✓ Membrane permeation controlled system
- ✓ Matrix diffusion controlled system:
- ✓ Micro reservoir type controlled system.[52]

Preparation of transdermal patch

The prepared transferosomal formulations were incorporated into transdermal patches by solvent casting method using aluminium foil as a backing membrane. The optimum ratio of two polymers were taken. Plasticizer was added to the formulation. The solution was kept undisturbed for 24 h. Then, with the help of syringe, the solution was poured into a glass ring. The solvent was allowed to evaporate for 6 h in a thermostatically controlled oven at 60 °C. The patches were stored in an airtight container under ambient conditions for 7 days prior to use.[53]

Transferosomal patch characterizations

Physical appearance

All the prepared patches were visually inspected for color, clarity, flexibility, and smoothness.

Uniformity of weight

About five patches of individual batches were weighed and calculation of the average weight was done.

Thickness

Thickness of patch was measured using Vernier callipers. Thickness was determined by taking three different positions and average was calculated. The uniformity of the patch reflects the accuracy of the dose in each patch.

Tensile strength

Tensile strength was measured in kg/cm^2 by enacting the weight onto the specified area of film till it breaks. This was done to find out the flexibility/ elasticity of the patch/film may be encountered at the time of transportation and storage.

Tensile strength = Tensile load /cross sectional area

Percent elongation

It would be defined as the ratio of the length of patch in normal position to stress condition. Here, stress conditions would be stated as stretching the patch to the point till it breaks down and measuring the largest length of the intact patch before breaking.

Elongation break = Final weight – Initial weight /Initial weight x 100

Percentage Moisture content

The patch was weighed and placed in desiccators having calcium chloride and dried for at least 24 h. The moisture content was the difference of the initial weight taken and constant weight was reported in terms of percentage (by weight) moisture content.

$$\% \text{ Moisture Content} = \frac{\text{(Initial weight - Final weight)}}{\text{Initial weight}}$$

Percent moisture uptake

A patch was weighed and kept in a desiccator at room temperature for 24 hours and exposed to 84% relative humidity (a saturated solution of potassium chloride) in a desiccator until a constant weight for the patch is obtained.

$$\% \text{ Moisture Uptake} = \frac{\text{(Final weight - Initial weight)}}{\text{Initial weight}}$$

Water vapour transmission

Glass vials approx. 5 ml capacity of equal diameter were taken for transmission study. All vials washed thoroughly and dried in an oven completely. Weigh about 1 gm of anhydrous/ fused calcium chloride and kept in respective vials. Fix the films on the brim of vials and weigh individually then kept in closed desiccator containing saturated solution of potassium chloride to maintain humidity approx. 84%. The vials were weighed in 6, 12, 24,36, 48, and 72 hours respectively.

Transmission rate = (Final weight – Initial weight) x Area x Time x 100

Folding endurance

Measurement of folding endurance was done manually. A part of patch (2 × 2 cm^2) was cut and folded at one place till it breaks. The brittleness of the patch was determined by the number of times the patch folded at the same place.

In vitro dissolution studies

A vertical type of the Franz Diffusion cell was used for permeation study. The receptor compartment having

diffusion area of 2.303 cm^2 and 22.5 ml phosphate buffer at pH 6.8 as the receptor fluid stirred at 100 rpm, and was maintained at 37 ± 0.5°C throughout the experiments. A semi-permeable membrane was used for the study (Stat-M®). Samples are withdrawn through the sampling port of the diffusion cell at predetermined time interval over 24 hours and are analysed. The amount of the drug permeated was estimated by plotting cumulative amount permeated against time.

Skin irritancy studies

The skin irritancy can be performed on healthy rabbits / mice albino / rats and potential of transdermal system can be evaluated by modified Draize test. The dorsal surface of given test animal is to be cleaned and remove the hair from the clean surface then applied rectified sprit. Applied the transdermal formulation over the clean surface for 24 hour. After this period, remove the formulation and observed the status of skin. The score are given from 0 to 4 depending the degree of erythema as follows: zero point given for no erythema, 1 point for slight erythema-(barely perceptible-light pink), 2 points for moderate erythema(dark pink),3 points for moderate to severe erythema(dark pink) and 4 points for severe erythema (extreme redness).

Confocal laser scanning microscopy

Depth of skin penetration of a patch can be assessed using CLSM. Transdermal formulation is applied non-occlusively for 8 hours to the dorsal skin. The mice is sacrificed by heart puncture, dorsal skin is excised and washed with distilled water. The excised skin is then placed on aluminium foil and the dermal side of the skin is generally teased off any adhering fat and/ or subcutaneous tissue. These are then cut in to pieces of $1mm^2$ and tested for probe penetration. The full skin thickness is optically scanned at different increments through the z-axis of a CLS microscope.

Stability studies

The stability of active component is a major criterion in determining acceptance or rejection of transdermal system. The stability studies were performed as according to ICH guidelines as at different temperature and relative humidity 25-30^oC (60% relative humidity) and 45- 50^oC (75% relative humidity) over a period of 60 days. The sample were withdrawn at 0,3,6, and 9 weeks respectively and were analysed for their physical appearance, drug content and in-vitro diffusion studies.

In-vivo studies

These studies are the true depiction of formulation performance. The variables which were not considered during in-vitro study taken in to account now. In-vivo studies of transdermal system can be done by using following models such as Animal Models, Human volunteers, Biophysical Model.[49-51]

Applications of tdds

- ✓ Hisetal, used in the treatment of multiple sclerosis may be formulated in TDDS using oleic acid as permeation enhancer to achieve sufficient drug delivery.
- ✓ Diclofenac sodium, celecoxib used as Non-Steroidal Anti Inflammatory Drugs (NSAIDs), formulated in TDDS may overcome the gastric lesions associated with oral dosing.
- ✓ Drugs used for long term dosing in the chronic diseases like captopril, verapamil, terbutaline sulphate, pinacidil, propranolol which have a short biological half-life, considerable first pass metabolism may be formulated as TDDS to achieve prolonged steady state plasma concentration.
- ✓ Hydrophilic polymers like polyvinyl pyrrolidine may provide faster drug release whereas hydrophobic polymers like ethyl cellulose can provide prolonged drug delivery.
- ✓ Gel formulation with lipid disperse system of beta histidine has potential for the development of an efficient controlled release transdermal system.
- ✓ Enhancer and co-solvent may synergistically enhance the delivery of peptides like thyrotropin releasing hormone across the human skin.
- ✓ Prazosin HCL in membrane controlled TDDS may deliver the drug enough to maintain the minimum effective concentration and can avoid hypotension associated with high initial oral dosing.
- ✓ TDDS of indomethacin in poly vinyl pyrrolidine polymer (acting as anti-nucleating agent) may provide better anti-inflammatory activity and lower ulcer indices compared to oral administration.[52-64]

CONCLUSION

Transdermal route of drug delivery does not allow transport of high molecular weight therapeutic agents and drugs because of the barrier properties of the stratum corneum layer of the skin. These Transferosomes are specially designed vesicles capable of responding to external stress by squeezing themselves through skin pores that are many times narrower than they are leading to increased transdermal flux of therapeutic agents. Transferosomes have beneficial advantages over other vesicular systems such as their high penetration power across skin, higher stability, systemic drug release possible and higher deformability than other vesicular systems such as noisome, ethosomes etc. These will ensures reproducible and efficient transcutaneous carrier and drug transport. Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility.[65]

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