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"APPROACHES FOR DRUG PERMEATION THROUGH TRANSDERMAL DRUG DELIVERY"

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Abstract: Transdermal drug delivery system (TDDS) utilizes the skin as executable route for drug administration but the foremost barrier against drug permeability is the stratum corneum and therefore, it limits therapeutic bioavailability of the bioactive. To improve characters transdermal drug delivery system (TDDS) was emerged which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific) placement within the body. Transdermal drug delivery system (TDDS) are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. Skin is an effective medium from which absorption of the drug takes place and enters into systematic circulation over a period of time. This review emphasizes a new era of delivery of drug and serves as an enlightening tool for the visionaries working in the concerned area.

Keywords: Transdermal route, patch, adhesives, penetration pathway.

Introduction: Transdermal patches are pharmaceutical preparations of various sizes that include one or more active ingredients and are designed to be placed to intact skin in order to deliver the active ingredient to the systemic circulation after passing through the skin barriers and avoiding the first pass effect [2]. Transdermal patches are a non-irritating, non-invasive method of administering medications since they are continuously released, showing their effects for the precise amount of time. It is a desirable alternative to conservative techniques for systemic medication administration [2]. The aim of dosage design for transdermal product is to minimise drug retention and metabolism in the skin while maximising drug flux through the skin into the systemic circulation [2]. Transdermal drug delivery systems (TDDS) are defined as self-contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation.

Controlled release drug delivery system, a novel drug delivery approach evolves, which facilitates the drug release into systemic circulation at a predetermined rate. Transdermal drug delivery systems (TDDS), which can transport medications via the skin portal to systemic circulation at a predetermined pace over a long period of time [1].

The stratum corneum serves as the foremost barrier to drug permeability in transdermal drug delivery systems (TDDS), which in turn reduces the therapeutic bioavailability of the bioactive substances [13].

Anatomy of Skin :

The primary site for transdermal drug delivery is the skin. A typical adult's body has a surface area of around 2 m2, and it receives one-third of the blood that circulates within it. It is elastic, rugged and under normal physiological conditions, self-regenerating. Only a few millimetres (2.97 mm) of skin thickness separates the body's vital organs and blood circulation system from the outside world. It protects the body from microbial invasion and acts as a defence against chemical and physical assaults. The epidermis, dermis, and subcutaneous fat tissue are the three tissue layers that make up the skin's multiple layers, which may be seen under a microscope [29].

1.Epidermis: The epidermis is uppermost layer, the stratum corneum, is made up of broad, flat, polyhedral, plate-like envelopes packed with keratin, which is produced from dead cells that have migrated up from the stratum granulosum. The majority of the dead, nuclear-free cells that make up this epidermal layer. New cells from the stratum germinativum continuously replace these dead cells when they slough off on the surface in the thin, air-filled stratum disjunctum (basale). The stratum corneum is made up of 10 to 15 layers of corneocytes, and its thickness vary depending on whether it is moist or dry state upto 40 μm.

It is primarily made up of keratin-rich corneocytes that are arranged in a multi-layered "brick and mortar" structure inside an intercellular matrix made up of long chain ceramides, free fatty acids, triglycerides, cholesterol, cholesterol sulphate, and sterol/wax esters. Keratinocytes in the middle to upper portion of the stratum granulosum release their lamellar contents into the intercellular space, resulting in the formation of the intercellular lipid matrix. The initial stratum corneum layers reorganise to create broad intercellular lipid lamellae, which unite to form lipid bilayers. The functioning of the lipid phase differs from that of other biological membranes as a result of the composition of the stratum corneum's lipids. The stratum corneum must contain water because it works as a plasticizer to keep the stratum from cracking. Water is an essential component of the stratum corneum, which acts as a plasticizer to prevent cracking of the stratum corneum and is also involved in the generation of natural moisturizing factor which helps to maintain suppleness. It is crucial to identify the main route of drug permeation within the stratum corneum in order to comprehend the physicochemical characteristics of the diffusing drug and vehicle influence across stratum corneum. When a molecule takes the transcellular route, it enters and diffuses through the keratinocyte, but then it must enter and diffuse through the estimated 4–20 lipid lamellae between each keratinocyte in order to reach the next one. This series of partitioning into and diffusing across multiple hydrophilic and hydrophobic domains is unfavorable for most drugs. Therefore the intercellular route is now considered to be the major pathway for permeation of most drugs across the stratum corneum [11].

A. Stratum Corneum: This is the skin's outermost layer, commonly known as the horney layer. approximately 10 mm thick while dry, but when fully hydrated, swells to several times this thickness. It has 10 to 25 layers of corneocytes, which are dead, keratinized cells that are lying parallel to the skin's surface. Although flexible, it is largely impermeable. The principal barrier to penetration is the stratum corneum. On a dry weight basis, the horney layer's constituents—75–80% proteins, 5–15% lipids, and 5–10% ondansetron material—have a significant impact on the barrier nature of the layer. Alpha-keratin makes up the majority of protein fractions (70%) with some beta-keratin (10%) and cell envelope (5%). The anatomical site affects the lipid composition (neutral lipids, sphingolipids, polar lipids, cholesterol). A distinctive characteristic of mammalian cells is their lack of phospholipids.

b. Viable epidermis: The thickness of this layer, which lies beneath the stratum corneum, ranges from 0.06 mm on the eyelids to 0.8 mm on the palms. It is made up of different layers as it advances inward, and including stratum basale, stratum lucidum, stratum granulosum, and stratum spinosum. The epidermis is constantly renewed by cell division in the basal layer, which makes up for the loss of dead horney cells from the skin's surface [5, 13, 16].

2. Dermis: The dermis is a 3 to 5 mm thick layer made up of a connective tissue matrix that contains nerves, lymphatic vessels, and blood vessels. The constant blood supply plays a crucial role in stabilizing body temperature by providing the skin nourishment and oxygen while also eliminating pollutants and waste. Capillaries provide sink conditions for molecules that penetrate the skin barrier and extend to within 0.2 mm of the skin's surface. Transdermal permeation is basically driven by the concentration difference across the epidermis, which is caused by the blood supply's low dermal concentration of permeate[5,13,16].

3. Hypodermis: The dermis and epidermis are supported by the hypodermis, or subcutaneous fat tissue. It acts as a place to store fat. This layer regulatees nutritional support, mechanical protection, and assistance with temperature regulation. It connects the body's major blood vessels and nerves to the skin and may contain organs that detect pressure [5,13,16].

. Drug penetration across the skin and their percutaneous distribution are inhibited by the stratum corneum's stratum corneum's barrier function due to its extremely well-organized structure.

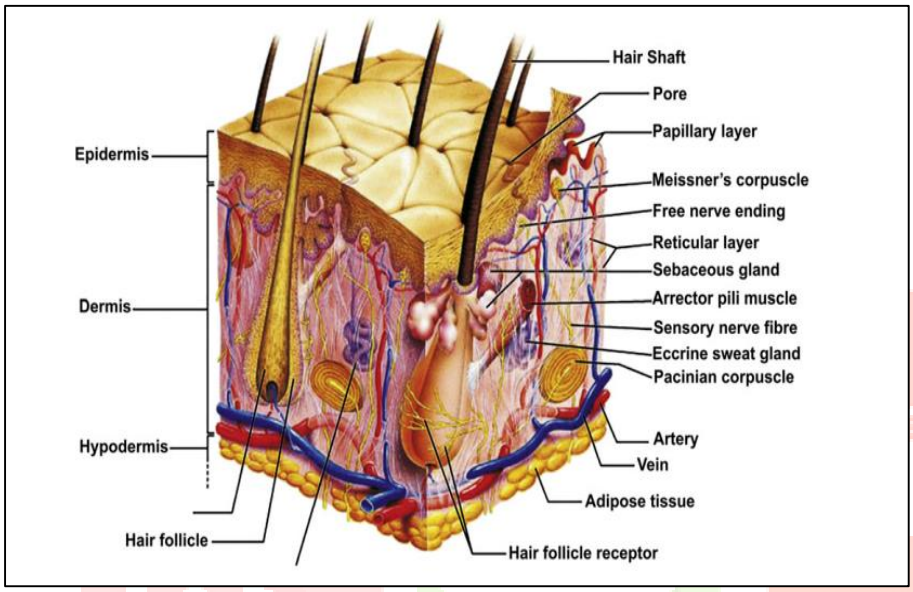

Fig.1. Transdermal patch showing different components.

A transdermal therapeutic system is essentially a multi laminate structure that is composed of following constituents: 1. Drug; 2. Polymer matrix; 3. Penetration enhancers; 4. Adhesives; 5. Backing membrane; 6. Release linear.[2]

Main Ingredients Used For the Preparation of Transdermal Drug Delivery System.

Drug- Drug reservoir is direct contact with release liner.

Physicochemical Properties[1,3,4, 5]:

The drug should have a molecular weight less than 500 daltons.

The drug should have affinity for both lipophilic and hydrophilic phases.

The drug should have a low melting point.

Hydrogen bonding groups should be less than 2.8

The drug should have some degree of solubility in both oil and water (ideally greater than 1 mg/ml).

Biological properties [1,3,5]:

The drug should be potent with a daily dose of the order of a few mg/day. The half life ($t_{1/2}$) of the drug should be short.

The drug must not induce a cutaneous irritation or allergic response.

Drugs which degrade in the G.I. tract or/are inactivated by hepatic first-pass effect are suitable candidates for transdermal delivery.

Tolerance to the drug must not develop under the near zero-order release profile of transdermal delivery.

Drugs which have to administered for a long period of time or which cause adverse effects to non-target tissues can also be formulated for transdermal delivery.

Narrow therapeutic window.

Polymers: Polymers are the backbone of TDDS, which control the release of the drug from the device. Polymer matrix can be prepared by dispersion of drug in liquid or solid state synthetic polymer base. Additionally they should provide consistent and effective delivery of a drug throughout the product's intended shelf life and should be of safe status[1] .

Backbone of TDDS, which control the release of the drug. Polymer should be chemically non-reactive, should not decompose on storage, should be non toxic, cost should not be high[11].

Natural polymers: e.g. cellulose derivatives, zein, gelatine, starch and chitosan , etc.

Synthetic elastomers: e.g. polybutadiene, hydrin rubber, polyisobutylene, silicon rubber, nitrile, butylrubber etc.

Synthetic polymers: e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, epoxy, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate, hydroxypropylcellulose etc[1,3,4,8].

Polymers used in transdermal system in versatile manner such as:

➢ Rate controlling membrane: It control the release of drug by disperse through an inert polymer matrix. The polymer powder blended with drug moiety by physical manner and then moulded in to desired shape with required thickness and surface area.

➢ Adhesive: make an intimate contact between the skin and transdermal system. It carries the drug which is dissolved or dispersed in solution or suspension form. The quality of drug diffused in to skin depending on the holding power.

➢ Pressure sensitive adhesive: Hitherto the rapidity of transdermal system can be done by pressure sensitive adhesive.

Liners- It provides the protection of patches during storage and the liner should be removed previous touse**.**Protects the patch during storage. The liner should be removed before its use. It is composed of a base layer, which may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinylchloride), and a release coating layer made of silicon or Teflon. Other materials include polyesters, foil, Mylar and metallized laminate.

The material properties to be considered for a release liner are as follows: Must be chemically inert.

Should not permeate the drug.

Affinity towards water should be null. Material should not crack, craze, or react in any way with the mechanism that are used for penetration in active transdermal drug delivery systems[2,3,8,15]

Adhesive- It served to adhere the components of the patch together along with adhering the patch to skin.

The Transdermal drug delivery device is firmly attached to the skin using pressure-sensitive adhesive (PSA). The three main polymer classes considered for TDDS's possible medical uses are:

Polyisobutylene type pressure sensitive adhesives.

Acrylic type pressure sensitive adhesives.

Silicone type pressure sensitive adhesives [2,3,15]

An integral element that maintains close contact between the delivery system and the skin is the adhesive. It carries the drug, which can either be distributed or dissolved in the matrix, or the compartment containing the drug (solution or suspension) is separated from the adhesive layer by a membrane that regulate diffusion. The medication permeates through this adhesive membrane to reach the skin. Because the patch lifts or falls off, the drug delivery from the patch is reduced due to a smaller surface area of contact[13].

Membrane: It regulates what further drug is released from the multi-layer patches. Termed " permeation enhancer". These substances modify the skin's ability to act as a barrier to the flux of a desired penetrant, hence increasing skin permeability [1]. It is hypothesized that penetration enhancers will have an influence on one or more of these epidermal layers in order to increase drug penetration [3,11]. The penetration enhancer should have the following properties: the ability to work selectively, reversibly, and for a predictable period; it should be pharmacologically inactive; nontoxic; nonallergenic; and nonirritating. The penetration enhancer should have the following properties: the ability to work selectively, reversibly, and for a predictable period; it should be pharmacologically inactive; nontoxic; nonallergenic; and nonirritating [13].

a. Solvents: Compounds increase penetration possibly by swallowing the polar pathway and/or by fluidizing lipids. Water, alcohols (methanol and ethanol), alkyl methyl sulfoxides-(dimethyl sulfoxide), dimethyl acetamide and dimethyl formamide, miscellaneous solvents (propylene-glycol, glycerol, isopropyl-palmitate)etc.

b. Surfactants: Compounds are proposed to enhance polar pathway transport, especially of hydrophilic drugs. Commonly used surfactants are: Anionic-surfactants (Dioctyl-sulphosuccinate, Sodium-laurylsulphate,Decodecyl-methylsulphoxide), nonionic-surfactants (Pluronic F127,Pluronic F68).

c.Bile salts: Sodium taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.

d.Binary systems: Eg. Propylene glycol-oleic acid and 1,4-butane diol-linoleic acid.

e.Miscellaneous chemicals: Eg. Urea, N,Ndimethyl-m-toluamide, Calcium thioglycolate, Anticholinergic agents [1,4].

Backing: It shields the patches from the outside environment. While being flexible, backing materials need to have a high tensile strength. Backing membranes are adaptable and offer a strong attachment to the drug reservoir. They also accept printing and stop the medication from escaping the dosage form through the top. It is an impermeable material that safeguards the product while it is applied to skin.

Eg. metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (aluminium foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminium foil disc)[2,3,4,5,15].

The three principal mechanisms of enhancement are as follows:

a) interactions with the intercellular lipids;

b) interactions with the intracellular keratin; and

c) the penetration of large amounts of enhancers or so-called co-solvents into the SC with a continued to improve dissolving capacity of the barrier for drugs and/or co-enhancers [13, 14].

A skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream[5].

A transdermal patch is defined as medicated adhesive patch which is placed above the skin to deliver a specific dose of medication through the skin with a predetermined rate of release to reach into the bloodstream [8].

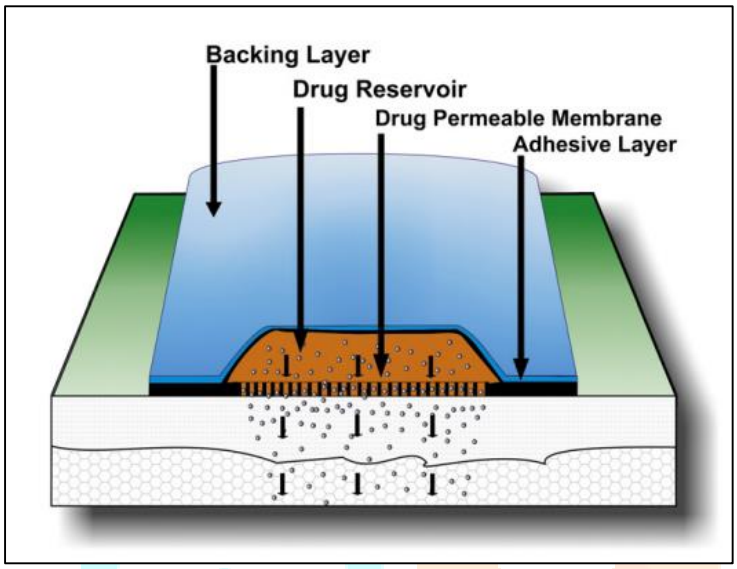

Fig.2. Anatomy of skin

Ideal properties of drug for Tdds [9, 11]

Table 1. Properties of transdermal delivery.

Parameters	**Properties**
Dose	Should be low (less than 20mg/day)
Half life	10/less(hrs)
Partition Coeffient	Log P(octanol- water) between 1-3
Therapeutic index	Should be low
pH of saturated aqueous solubiity	5-9
Molecular weight	<400 da
Skin permeability coefficient	>0.5*10-3cm/h
Skin reaction	Non irritating non sensitizing
Oral bioavailability	Low

Recent advances in transdermal delivery system [6]

1. Patch technology for protein delivery
2. Testosterone transdermal patch system in young women with spontaneous premature ovarian failure
3. Transdermal patch of oxybutynin used in overactive bladder
4. Nanotechnology gaining hold
5. Pain relief
6. Poke with patch approach
7. Coat and poke approach
8. Biodegradable micro needles
9. Hollow micro needles

Advantage [2, 3, 4, 5, 8, 11, 29]

Avoidance of first pass metabolism.

Avoidance of gastro intestinal incompatibility.

Predictable and extended duration of activity.

Minimizing undesirable side effects.

Provides utilization of drugs with short biological half lives, narrow therapeutic window.

Enhance therapeutic efficacy.

Drug administration stops with patch removal.

Improved patient compliance.

Avoiding the deactivation by digestives and liver enzymes.

Has a constant serum drug level.

Alternative for drugs that cannot be taken orally.

Alternative for nauseated or unconscious patient

Gives a constant plasma drug level.

Can be discontinued by removing patch anytime.

Reduces systemic drug interaction.

Offers long duration of action.

Self administration can be done.

Disadvantage [2, 3, 5]

Only small, lipophilic drugs can be delivered currently through.

Drug molecule must be potent because patch size limits amount.

Drugs with very low or high partition coefficient fail to reach blood circulation.

Easy elimination of drug delivery in case of toxicity.

Drugs that are highly melting can be given by this route due to their low solubility both in water and fat.

Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation.

Many hydrophilic drugs cannot pass or very slowly permeates the skin.

Many problems like itching, erythema, edema can be observed.

The barrier function of the skin may change from person to person, or with ages or with different sites on same person.

Uneconomical system of drug delivery.

TDDS is not compatible with ionic drugs.patch

Dumping of dose may occur.

The delivery system cannot be used for drugs requiring high blood levels.

Types of transdermal patches [2,3, 4, 7, 8, 17, 18]

1. **Single layer drug in adhesive:** The drug is contained in the adhesive layer. The drug reservoir is completely enclosed in a moulded compartment made of a rate-regulating polymeric membrane and a drug-impermeable metallic plastic lamination. The drug particles are suspended in an unleachable, viscous liquid medium or dispersed in a solid polymer matrix in the drug reservoir compartment.The rate of release of drug from this type of system is dependent on the diffusion across the skin.
   dQ/dT=Cr/1/Pm+1/Pa
   Where, Cr is the drug concentration in the reservoir compartment and Pa and Pm are the permeability coefficients of the adhesive layer and the rate controlling membrane, Pm is the sum of permeability coefficients simultaneous penetrations across the pores and the polymeric material. Therefore,
   Pm= $K_{m/r}$.Dm/hm and
   Pa= $K_{a/m}$.Da/ha
   Where, Km/r and Ka/m are the partition coefficients for the interfacial partitioning of drug from the reservoir to the membrane and from the membrane to adhesive respectively;
   Dm and Da are the diffusion coefficients in the rate controlling membrane and adhesive layer, respectively; and
   hm and ha are the thicknesses of the rate controlling membrane and adhesive layer.
2. **Multi layer drug in adhesive**: Drug-in-Adhesive in that the drug is incorporated directly into the adhesive. the multi-layer encompasses either the addition of a membrane between two distinct drug-in-adhesive layers or the addition of multiple drug-in-adhesive layers under a single backing film. It contains a immediate drug release layer and other layer will be a controlled release along with the adhesive layer.
   The rate of drug release in this system is defined by:
   Ka/r . Da dQ/dt = Cr ha
   Where Ka/r is the partition coefficient for the interfacial partitioning of the drug from the reservoir layer to adhesive layer.
3. **Drug reservoir in adhesive:** The Reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive.
   $$\frac{dQ}{dt} = \frac{K_{a/r} \cdot D_a}{h_a(t)} A(h_a)$$
   The thickness of the adhesive layer for drug molecule to diffuse through increases with time ha (t). To compensate for this time dependent increase in the diffusional path due to the depletion of drug dose by release, the drug loading level is also increased with the thickness of diffusional path A (ha)
4. **Drug Matrix-In-Adhesive:** The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the release liner.
   The rate of drug release from this type of system is defined
   $dQ/dT=ACpDp^{1/2}/2t$
   Where, A is the initial drug loading dose dispersed in the polymer matrix and
   Cp and Dp are the solubility and diffusivity of the drug in the polymer respectively. Since, only the drug species dissolved in the polymer can release,
   Cp is essentially equal to CR, where
   CR is the drug concentration in the reservoir compartment.

5. **Vapour Patch**: The role of adhesive layer not only serves to adhere the various layers together but also serves as release vapour.

Tdds Classification Based On Their Technical Sophistication [7]:

A) Rate Pre Programmed Drug Delivery System It involves the system design that delivers medicaments by controlling molecular diffusion of drug molecules across the skin barrier within or surrounding the delivery system.

1. Polymer membrane permeation controlled drug delivery system: It's to do with the way the drug is contained in a drug reservoir. This is covered with a semi-permeable polymer membrane with a particular permeability that controls the release. Potential developments using the technique of membrane permeation include gel diffusion controlled drug delivery systems, gastric fluid resistance intestinal targeted controlled release gastrointestinal devices, and microporous membrane permeation controlled gastrointestinal delivery devices.

2. Polymer matrix diffusion controlled drug delivery system It is developed by dispersing drug particles in carrier matrix (in a homogenous manner) that is rate controlling.

3. Microreservoir partitioned controlled drug delivery systemIt involves dispersion of micro particles of suspension of drug (aqueous in nature) in a polymer using high energy dispersion.

B) Activation Modulated Drug Delivery System This type of delivery system can be achieved by

1-Physical means

- Osmotic pressure activated drug delivery system.
- Hydrodynamic pressure controlled drug delivery system.
- Vapour pressure activated drug delivery system.
- Mechanically activated drug delivery system.
- Magnetically activated drug delivery system.
- Electrically activated drug delivery system.
- Ultrasound activated drug delivery system.
- Hydration activated drug delivery system.

2-Chemical means

- pH activated drug delivery system
- Ion activated drug delivery system
- Hydrolysis activated drug delivery system

3-Biochemical means

- Enzymes activated drug delivery system

C) Feedback Regulated Drug Delivery System The release of the drug molecules from the transdermal system is facilitated by a agent that triggers the release of drug, such as biochemicals in the body and also regulated by its concentration through some feedback mechanism.

- Bio-erosion regulated drug delivery system.
- Bio-responsive drug delivery system.
- Self regulated drug delivery system.

D) Carrier Based Drug Delivery System Colloidal particulates carrier system

This involves vesicular system like hydrogels, liposomes, niosomes, nanocapsules, nanoparticles, polymeric complexes, microspheres, nanoerythrosomes, transferosomes, dendrimers, aquasomes, etc.

Factors affecting transdermal patch permeability [1,3]

Physicochemical properties of the penetrate molecules:

Partition coefficient: Drugs that are water and lipid soluble are more quickly absorbed through the skin. It has been demonstrated that as the length of the lipophilic alkyl chain increases, the membrane partition coefficient grows exponentially. By changing the carrier, one can also affect the partition coefficient of a pharmacological molecule.

pH conditions: The use of solutions with extremely high or low- pH values might harm the skin. Moderate pH levels can modify the ratio of charged to uncharged species and their transdermal permeability, which can have an impact on the flux of ionizable medicines.

Penetrate concentration: Assuming membrane limited transport, increasing the concentration of dissolved drug causes a proportional increase in flux. At concentration higher than the solubility, excess solid drug functions as a reservoir and helps to maintain a constant drug concentration for a prolonged period of time.

Release characteristics: Whether the drug molecules are dissolved or suspended in the delivery system. The interfacial partition coefficient of the drug from the delivery systems to the skin tissue and pH of the vehicle.

Composition of the drug delivery system: The composition of the drug delivery system not only affects the rate of the drug release but also the permeability of stratum corneum by means of hydration, mixing with skin lipids, or other sorption promoting effects.

Enhancement of transdermal permeation: Most of the drugs the penetration can be improved by the addition of a sorption or permeation promoter into the drug delivery system.

Physiological And Pathological Condition of the Skin:

Reservoir effect of the horny layer: The reservoir effect is due to the irreversible binding of a part of the applied drug with skin. This binding can be reduced by the treatment of the skin surface with anionic surfactants.

Lipid Film: The lipid film on the skin surface acts as a protective layer to prevent the removal of moisture from the skin and helps in maintaining the barrier function of the stratum corneum.

Skin Hydration: Hydration of the stratum corneum can enhance transdermal permeability, although the degree of penetration enhancement varies from drug to drug. Skin hydration can be achieved simply by covering or occluding the skin with plastic sheeting, leading to the accumulation of sweat and condensed water vapour. Increased hydration appears to open up dense, closely packed cells of the skin and increase its porosity.

Skin temperature: Raising skin temperature results in an increase in the rate of skin permeation due to increased diffusivity due to enhanced thermal energy. Altered solubility of drug in skin tissues Increased vasodilatation of skin vessels. Skin age, blood supply, and regional skin site are considered.

Penetration pathway:

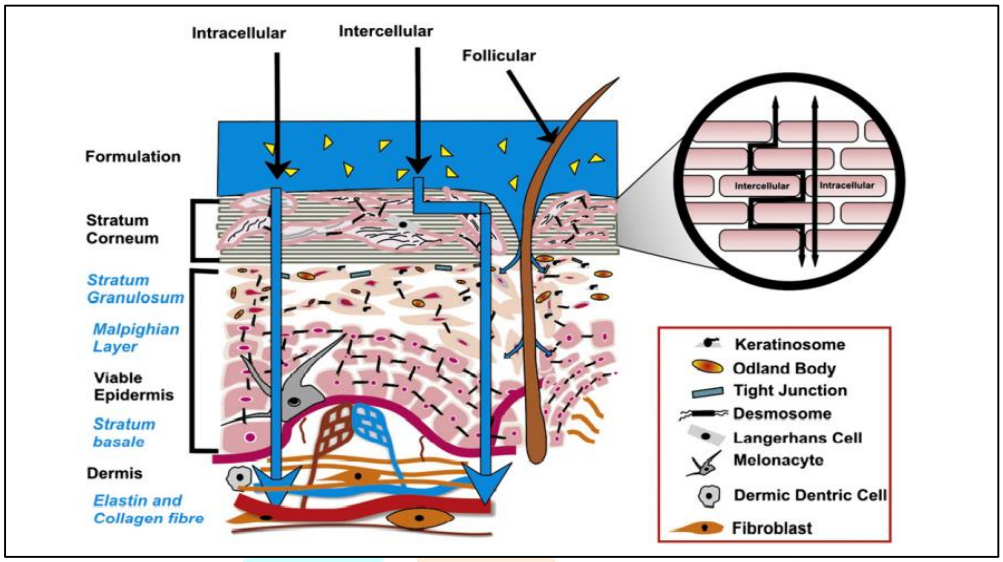

Fig.3. Diagrammatic representation of penetration pathways along with differentiation in the major route.

Recent techniques for enhancing techniques in TDDS [7]:

A] Structure based enhancement techniques:

1. Transdermal Patches A transdermal patch or skin adhesive patch is that device which is loaded with drug candidate and usually applied on the skin to transport a specific dose of medication across the skin and into the blood circulation.

2. Microfabricated microneedles These are the medical devices that combine the advantages of a transdermal patch and a hypodermic needle to administer medications effectively across the membrane. The device comprises of a reservoir for the medicine and a few protrusions (microneedles) that extend from the reservoir. These aid in delivering the drug by penetrating the stratum corneae and epidermis**.**

Poke with patch approach- Involves piercing into the skin followed by application of the drug patch at the site of treatment.

Coat and poke approach- Needles coated with the drug are inserted into the skin and release of medicament is then occurs by dissolution.

Biodegradable microneedles- Involves encapsulation of the drug within the biodegradable, polymeric microneedles, which is then inserted into the skin.

Hollow microneedles- Involves injecting the drug through the needle with a hollow bore.

3.Macroflux: These are objects with a surface area of around 8 cm and 300 micro projections per cm2, each of which is less than 200 m in length. There are three different varieties of Macroflux. They consist of, Dry-Coated Macrofluxsystem: This is a short-term delivery system that uses a microprojection array coated with medication and attached to a backing made of an elastic polymer.

4. Metered-Dose Transdermal Spray (Mdts) It is a liquid preparation in the form of solution that are used topically which is made up of a vehicle that is volatile come non volatile in nature, which consists the completely dissolved medicament in solution.

B] Electrically based enhancement techniques:

1. Iontophoresis : It involves passing of current (few milliamperes) to skin limited to a certain area using the electrode remains in contact with the formulation which is to be administered.

2. Ultrasound In this technique, there is a mixing of drug substance with a coupling agent (usually with gel, cream or ointment) that causes ultrasonic energy transfer from the system to the skin. This involves rupturing the lipids present in stratum cornea, which allows the medicament to permeate via biological barrier.

3. Photomechanical Waves: Through a potential permeabilisation process caused by the creation of transient channels, photomechanical waves greatly contributed to the stratum cornea becoming highly permeable to drug material.

4. Electroporation It this method, short and high-voltage electrical pulses are applied to the skin thus the diffusion of drug is improved with the increasing permeability. The electrical pulses are considered to form small pores in the stratum cornea, through which transportation of drug occurs. For the safe and painless administration, the electrical pulses introduced by closely spaced electrodes to reserved the electric field within the stratum cornea.

5.Electro-Osmosis To the porous membrane which is having some charge, a voltage difference is applied to it, thus a bulk fluid or volume flow takes place with no concentration gradients. This process is known as electro-osmosis.

C] Velocity based enhancement techniques

1. Needle-Free Injections • Intraject • Implaject • Jet Syringe • Iject • Mini-ject

2. Powderject Device High-speed gas flow is used to drive the solid medication particles across the skin. This is made of two polycarbonate membranes sandwiched between a drug cassette containing powdered drug and a gas canister that allows helium gas at high pressure to enter a chamber at one end. The gas expands quickly after release due to the instantaneous rupture of both membranes, which creates a forceful motion resembling a wave that moves down the nozzle. This moves at a pace of 600 to 900 m/s.

D] Other techniques:

1. Transfersomes This device penetrates the skin barrier along the skin moisture gradient. Transfersome carriers can create a drug depot in the systemic circulation that is having a high concentration of drug. Transfersomes contain a component that destabilizes the lipid bilayers and thus leading to the deformable vesicles.

2. Medicated Tattoos Med-Tats is a modification of temporary tattoo which contains an active drug substance for trandermal delivery. This technique is useful in the administration of drug in those children who are not able to take traditional dosage forms.

3. Skin Abrasion This involves direct removal or disruption of the upper layers of the skin to provide better permeation of topically applied drug substance. In general, one approach is adopted to creates micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules is generally known as Microscissuining.

4. Controlled Heat Aided Drug Delivery (CHADD) System: It is easier for pharmacological compounds to reach the bloodstream by applying heat to skin, which increases skin temperature and, as a result, blood vessel permeability and microcirculation. A small heating unit that is attached to a common patch device makes up the CHADD system. An oxidation reaction occurs inside the device, which typically produces brief bursts of low-intensity heat.

5. Laser Radiation: This entails exposing the skin to the laser beam, which causes the stratum cornea to be ablate without harming the epidermis that is still in contact with it. This method of stratum cornea removal is thought to enhance the administration of hydrophilic and lipophilic drugs.

6. Magnetophoresis The effect of magnetic field on diffusion flux of drug substance was found to enhance with increasing applied strength.

Various method for preparation of TDDS[7]:

a. **Asymmetric TPX membrane method** : For this, a heat-sealable polyester film (type 1009, 3m) with a concave of 1 cm diameter will be utilised as the backing membrane to manufacture a prototype patch. A TPX poly(4-methyl-1-pentene) asymmetric membrane is used to cover the concave membrane, which is then sealed with an adhesive.
b. **Circular teflon mould method:** Solutions with different ratios of polymers are utilised in an organic solvent. Half as much of the same organic solvent is used to dissolve the calculated amount of medication. The second half of the organic solvent is used to dissolve enhancers at various concentrations before they are applied. The plasticizer di-N-butylphthalate is included in the drug polymer solution. The entire mixture must be agitated for 12 hours before being placed into a teflon mould. In order to manage solvent vaporisation in a laminar flow hood model with an air speed of 0.5 m/s, the moulds must be put on a flat surface and covered with an inverted funnel. For 24 hours, the solvent is allowed to evaporate. The dry films must be kept at 250.5°C for an additional 24 hours. Before evaluation, the dried films must be kept for a further 24 hours at 250.5°C in a desiccator containing silica gel to counteract the effects of ageing. Within a week of preparation, the type films must be reviewed.
c. **Mercury substrate method:** This approach involves dissolving the medication and plasticizer in a polymer solution. The aforementioned solution must be agitated for 10 to 15 minutes to provide a uniform dispersion before being placed over a mercury surface that has been.
d. **By using IPM membranes" method:** In this procedure, the medication is dissolved in a solution of water and carbomer 940 polymer that contains propylene glycol, and it is then swirled for 12 hours in a magnetic stirrer.
e. **By using EVAC membranes" method**: To prepare the target transdermal treatment system, polyethelene (PE) and ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. When the drug is not soluble in water, gel is created using propylene glycol. The medication is dissolved in propylene glycol, and then carbopol resin is added and the solution is neutralised with a 5% w/w sodium hydroxide solution. On top of the medication is a backing layer sheet covering the designated area (in gel form). A rate-regulating membrane will be placed over the gel and the edges to form a leak-proof device.
f. **Aluminium backed adhesive film method:** If the loading dose is larger than 10 mg, transdermal drug delivery systems may result in unstable matrices. It is appropriate to use adhesive film with an aluminium backing. Chloroform is the preferred solvent for its manufacture because it is soluble in the majority of medications and adhesives. Chloroform is used to dissolve the medicine, and then adhesive material is added and dissolved in the drug solution. Aluminum foil is used to line a mould made of aluminium, and cork blocks that fit snugly around the edges are used to blank off the ends**.**
g. **By using free film method:** Casting on the surface of the mercury creates a free film of cellulose acetate. Chloroform is going to be used to make a 2% weight-to-weight polymer solution. Plasticizers must be added at a 40% weight-to-weight (w/w) concentration in the polymer. In a glass petri dish with mercury on the surface, five ml of polymer solution was added to a glass ring. An inverted funnel is positioned over the Petri dish to manage the solvent's rate of evaporation. After the solvent has completely evaporated, the mercury surface is observed to detect the film formation. In a desiccator, the dry film will be separated and kept until use between wax paper sheets. Free films of various thicknesses can be made by altering the volume of polymer solution.

Transcorneal penetration [5, 11]:

Intra cellular penetration: Drug molecule passes through the cells of the stratum corneum. Seen in case of hydrophilic drugs. As stratum corneum hydrates, water accumulates near the outer surface of the protein filaments. Polar molecules appear to pass through this immobilized water.

Inter cellular penetration: Non-polar substances follow the route of intercellular penetration. The molecules dissolve in and diffuse through the non- aqueous lipid matrix imbibed between the protein filaments.

Transappendegeal penetration: This is also called as the shunt pathway . The drug molecule may transverse through the hair follicles, the sebaceous pathway of the pilosebaceous apparatus or the aqueous pathway of the salty sweat glands.T he relative ability to partition into each skin phase. The transdermal permeation can be visualized as composite of a series in sequence as:

1. Adsorption of a penetrant molecule onto the surface layers of stratum corneum.

2. Diffusion through stratum corneum and through viable epidermis.

3. Finally through the papillary dermis into the microcirculation.

Diffusion through the stratum corneum is the rate-limiting step. The stratum corneum acts like a passive diffusion medium.

Mechanism of Action of Transdermal Patches[2]:

Different processes are used for the transdermal patch's operation and the movement of the active medicinal ingredient from the patch via the skin to the circulatory system. A systemically active medicine must possess certain physicochemical qualities that facilitate the drug's absorption through the epidermis and entry into the microcirculation in order to reach a target tissue.

Kinetics of transdermal permeation[4,8]:

1. Sorption by stratum corneum.

2. Penetration of drug through epidermis.

3. Uptake of the drug by the capillary network in the dermal papillary layer.

Various methods used to enhance skin penetration[3,6 ,11, 18]:

Table 2. Methods of enhancing skin penetration

Active/ Vehicle interaction	**Vesicles**	**Stratum corneum modified**	**Stratum corneum bypassed/ removed**	**Electrically assisted methods**	**Particles**
Drug/ Prodrug	Liposomes and analogues	Hydration	Microneedles:	Phonophoresis	Liposomes
Chemical potential	Liposomes and analogues	Chemical enhancers	Ablation	Iontophoresis	Niosome
Ion pair/ Coacervates	Lipid nanoparticles		Follicular delivery	Electroporation	Transferosome
Eutetic systems	High velocity particles			Photomechanical wave	Magnetophoresis

Evaluation:

1. Interaction studies [6, 7]:

Interaction studies are taken out by Thermal analysis, Fourier transform infrared spectroscopy (FTIR), ultra violet (UV) and chromatographic techniques by comparing their physicochemical properties like assay, melting point, wave numbers, and absorption maxima.

2. Physical evaluation of transdermal system:

Surface pH [21]:

The film was put in glass tube containing 10ml DW, after one hour, the pH of film surface measured by using digital pH meter, this method done in triplicate.

Film thickness [8]:

The thickness of film is measured by using micro meter, electronic vernier callipers, with a least count of 0.01mm, dial gauge, or screw gauge. Thickness is measured at five different points on the film and average of five readings is taken.

Flatness[3,5,8]:

For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

% constriction= L1-L2/L2*100

L1= Initial length of each strip

L2= Final length of each strip

Uniformity of weight [3,5,7]:

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight

Weight Variation [24]:

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Content uniformity test [11]:

10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have 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. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test 1

Folding Endurance [3,5,7,8, 14, 15]:

It determines the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking is folding endurance value.

Tensile Strength [3,8,24,25]:

The polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted.

Tensile strength=applied force/ cross section area= m*g/b*t

Where, S = tensile stress in 980 dynes/cm2, m = mass in grams, g = acceleration due to gravity (980 dynes/cm 2) b = breadth of strip in centimeters, t = thickness of strip in centimeters.

Thickness of the patch [3,5,7,8,11, 24,25]:

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch. The thickness of transdermal film is determined by traveling microscope dial gauge, screw gauge or micrometer at different points of the film.

Drug content determination[3, 25]:

An accurately weighed portion of film (about 100 mg) is dissolved in 100 ml of suitable solvent in which drug is soluble and then the solution is shaken continuously for 24 h in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.

Elongation break test [8]:

The elongation break is to be determined by noting the length just before the break point. The elongation break can be determined by the formula:

Elongation break = $(\boldsymbol{Final\ length} - \boldsymbol{Init}\ )\ \boldsymbol{Initial\ length}$

Moisture content[3,8, 11]:

The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula.

% moisture content= Initial weight-Final weight/Final weight* 100

Uptake Moisture[3,7,8,11]:

Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved.

% moisture uptake= Final weight- Initial weight/Initial weight* 100

Water vapour transmission studies (WVT)[3,5,7, 8, 11,22,25]:

For the determination of WVT, Rao et al., (1997) weighed one gram of calcium chloride and placed it in previously dried empty vials having equal diameter. The polymer films were pasted over the brim with the help of adhesive like silicon adhesive grease and the adhesive was allowed to set for 5 minutes. Then, the vials were accurately weighed and placed in humidity chamber maintained at 68 % RH. The vials were again weighed at the end of every 1st day, 2nd day, 3rd day up to 7 consecutive days and an increase in weight was considered as a quantitative measure of moisture transmitted through the patch. Desiccators were used to place vials, in which 200 mL of saturated sodium bromide and saturated potassium chloride solution were placed. The desiccators were tightly closed and humidity inside the desiccator was measured by using hygrometer.

Water vapour transmission rate= Final weight- initial weight/time* area * 100

Swelling Index [3,21]:

The film capacity to uptake the water was measured by swelling index, the film was weighted on a apreweight slide (Wo) and dipping in petridish containing 50ml phosphate buffer pH 7.4, after that the slide was removed from petridish at regular time interval for one hour and reweight again (wt), the swelling index was measured according to following equation and done in triplicate.

SI= Wt – Wo /Wo x 100

3. **Adhesive studies [3]**:

The therapeutic performance of TDDS can be affected by the quality of contact between the patch and the skin. The adhesion of a TDDS to the skin is obtained by using PSAs, which are defined as adhesives capable of bonding to surfaces with the application of light pressure.

a.Peel Adhesion properties

b.Tack properties

c.Thumb tack test

d.Rolling ball test

e.Quick stick (Peel tack) test

f.Probe tack test

g.Shear strength properties or creep resistance

Shear adhesion test[7,8,11]:

This test determines the cohesive strength of an adhesive polymer. The level of cross-linking, the molecular weight, the make-up of the polymer, and the quantity of tackifiers used can all have an impact on the strength value. A stainless steel plate with an adhesive coated patch on top is stacked, and a predetermined

weight is suspended from the patch parallel to the plate. The cohesive strength is determined by how long it takes to remove the patch from the plate. The shear strength increases as the amount of time increases.

Peel adhesion test: Adhesion is the measurement of the patch strength between an adhesive and a substrate. The amount of force necessary to remove the adhesive coating from the steel test substrate. The sticky characteristics of a polymer depend on the type, quantity, molecular weight, and content of the polymer. The single patch was applied to a test surface made of steel and was dragged away from it at an angle of 180 degrees. No remnants on the test substrate suggest that the adhesive failed.

Tack properties [7,8]: Tack is the ability of polymer to adhere to a substrate with little fingure pressure It's important in transdermal systems which are applied with little figure pressure. Tack is dependent on molecular weight as well as composition of polymer and tackifying resins used in the polymer. Tests for tack include:

a.Thumb tack test: This is subjective test in which evaluation is done by pressing the thumb in to the adhesive. Experience is required for using the test.

b.Rolling ball tack test: This test involves measurement of distance travelled by a stainless steel along the upward face of adhesive. The diameter of ball is 7/16o inches and it released on inclined track having angle 22.5oMore the distance travelled, less the tacky polymer. Distance travelled by ball is measured in inches which determine the tackiness of polymer. It determines the softness of adhesive polymer.

c.Peel tack or quick stick test: The peel force is the force required to break the bond between the adhesive and the test substrate. The patch is pulled away from the substrate at 90o with speed 12 inches/minute. The value of force is expressed in grams/inch or ounces/inch.

d.Probe tack test : In this, the tip of probe with defined surface roughness brought in to contact with adhesive and when the bond is formed between the adhesive an probe, removal of probe at a fixed rate away from the adhesive which break the bond. The force required to break the bond is recorded as tack and it is expressed in grams.

4.In vitro drug release studies[3, 5, 7]:

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500- mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5- mL aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

There are various methods available for determination of drug release rate of TDDS.

The Paddle over Disc

The Cylinder modified USP Basket

The reciprocating disc

Diffusion Cells e.g. Franz Diffusion Cell and its modification Keshary- Chien Cell.

5.In-vitro skin permeation and release kinetics studies:

In-vitro studies greatly help in investigating the route of skin permeation and the rate of transfer through skin by which drug entered in to systemic circulation.

Franz Diffusion Cell: The in-vitro skin permeation of transdermal patches can be studied using Franz diffusion cell(most commonly used) with an effective permeation area of 1.0cm2 and receptor cell volume of 10 ml . The temperature is maintained at 32oC ± 1oC .The receptor compartment is filled with 10 ml PBS and is constantly stirred in a magnetic stirrer at 100rpm. The skin is mounted on a receptor compartment with the stratum corneum side facing upward in to the donor compartment. Samples are withdrawn through the sampling port of the diffusion cell at predetermined time interval over 24 hours and are analysed. The receptor phase is immediately replenished with equal volume of fresh diffusion buffer.

6.Skin irritacy studies[7,8,23]:

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..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).

7.Stability studies [7,8]:

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 25-30oC (60% relative humidity) and 45- 50oC (75% relative humidity) over a period of 60 days. The sample were withdrawn at 0,3,6, and 9 weeks respectively and were analyzed for their physical appearance, drug content and in-vitro diffusion studies.

Regulatory Strategy For Investigational New Drug Application And New Drug Application Submissions [3]

For Tdds

Standard irritation and sensitization studies should be performed with the patch itself in animals/ humans.

Negotiate the timing and implementation of the toxicology requirements. The dermatology division at FDA should review dermal aspects of the IND and New drug Application(NDA).

Primary review should occur at the division that handles the indication under study.

Dose ranging studies be required in Phase 2.Single Phase 3 study could be negotiated.

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