A Review Article on Transdermal Drug Delivery System

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Abstract*— Transdermal drug delivery has made an important contribution to medical practice . Transdermal drug delivery system (TDDS) is the system in which the delivery of the active ingredient of drug occurs through skin by which therapeutic efficacy and safety of drug get improved with increased bioavailability and with reduced size and dose. Tdds received broad attention as novel tool for controlled release. In this tdds drugs enter into the body using skin as medium and then drug enters into systemic circulation to avoid first pass metabolism . The tdds dosage form designed in the form of patches . The permeation of Transdermal patches crosses the skin through matrix and reservoir system . This review article provides overview of Transdermal drug delivery sytem , its advantages , disadvantages , factors effecting Tdds , skin as barrier , formulation design and evaluation methods .

I. INTRODUCTION

Transdermal fix (Skin patch) utilizes a unique film to control the rate at which the fluid medication contained in the repository inside the fix can go through the skin and into the circulatory system. A few medications should be joined with substances, for example, liquor, that increment their capacity to enter the skin to be utilized in a skin fix. Drugs regulated through skin patches incorporate scopolamine (for movement infection), nicotine (for stopping smoking),estrogen (for menopause and to forestall osteoporosis after menopause), dynamite (for angina), and lidocaine to free the agony from shingles (herpes zoster). Atoms of insulin and numerous different substances, in any case, are too huge to even think about going through the skin. Patches applied to the skin dispose of the requirement for vascular access by needle or the utilization of siphons. Transdermal patches were created during the 1970s and the first was endorsed by the FDA in 1979 for the therapy of movement disorder. It was a three-day fix that conveyed scopolamine. In 1981, patches for dynamite were supported, and today there exist various patches for medications like clonidine, fentanyl, lidocaine, nicotine, dynamite, oestradiol, oxybutinin, scopolamine, and testosterone. There are likewise mix patches for contraception, as well as chemical substitution. Contingent upon the medication, the patches commonly last from one to seven days.

Definition
medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream.

Advantages

1. Topical patches are an effortless, harmless method for conveying substances straightforwardly into the body.
2. Skin patches over a controlled, consistent conveyance of drug throughout longperiods of time.
3. Topical patches over a choice to individuals who can't, or rather not take prescriptions or enhancements orally.
4. Avoidance of first pass digestion of medications.
5. Easy end of medication conveyance in the event of harmfulness.
6. Reduction of dosing recurrence an upgrade of patient consistence.(1,2)

Disadvantages

1. Molecular size limitation
2. High expense
3. Transdermal medication conveyance frameworks could be unacceptable for drugs that bother or sharpen skin.
4. Variation in hindrance work
5. Cannot have Pulsatile formed drug discharge
6. Low porousness limits (3,4)

Factors affecting transdermal bioavaibility

Two central point influence the bioavaibility of the medication by means of transdermal courses:
(1) Physiological elements (2) Formulation factors

Physiological variables incorporate

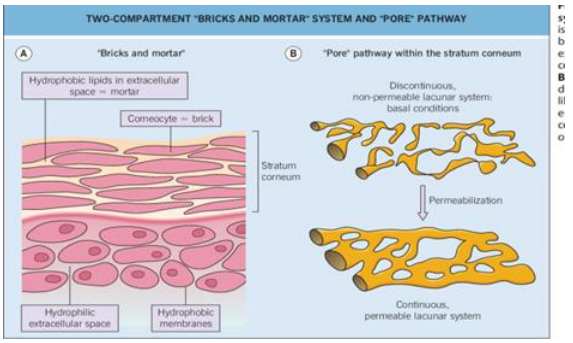
1) Stratum corneum layer of the skin
2) Anatomic site of use on the body
3) Skin condition and infection
4) Age of the patient
5) Skin digestion
6) Desquamation (stripping or chipping of the outer layer of the skin)
7) Skin disturbance and refinement

Definition factors incorporate

1) Physical science of transport
2) Vehicles and film utilized
3) Penetration enhancers utilized
4) Method of utilization
5) Device utilizeds

SKIN AS A BARRIER TO DRUG PERMEATION

The peripheral few microns of the skin, the SC, helps to the obstruction capacity of the skin. This layer of the skin is the most impermeable, framing a cover of compacted keratin-filled corne ocytes appended in a lipophilic network. The lipids of this grid are recognizing in many regards:



- From the skin surface to the foundation of the SC, they give the main constant stage
- Among the biomembranes,the nonappearance of phospholipid is specific and is a creation (ceramides, free unsaturated fats, and cholesterol) that is extraordinary
- The SC lipids exist as multilamellar sheets despite the fact that it is having a shortage of polar bilayer framing lipids
- The basically soaked, long-chain hydrocarbon tail helps a profoundly requested, interlock design. In any case, the resistivity of the layer can't be totally clarified by the strange lipid framework, and the design of the SC through and through has been proposed to assume a part in the boundary property of the film. The corneocyte looking like a physical gathering is proposed to grant the film impermeable to water as for other biomembranes. Also, by the perception studies confining a few permeants, in the intercellular channels by active investigation of the in vivo skin infiltration paces of model mixtures and by proof from thermotropic biophysical investigations of lipid areas the vehicle job of this pathway gets besides support

- Transdermal permeation pathways

Transdermal permeation can take place by diffusion through

A. Through the SC: Through the transcellular course, medications can go through the corneocytes profoundly hydrated keratins are available in corneocyte, which gives a watery climate to which the hydrophilic medications can pass. Subsequently, the transcellular pathway is a dominating pathway for hydrophilic medications

B. Intercellular permeation: In intercellular pathway, the drug diffusing takes place by means of the continuous lipid matrix
C. Transappendaged permeation: Just 0.1% of the skin surface region is covered by the hair follicle and sweat organs which limit the region accessible for the applied medication detailing to interact with it. For some medications, a fluid pathway is thought of as alluring yet as the perspiration is going against the dispersion pathway of permeant, penetration might be restricted. Lipid-rich sebum fills the sebaceous organ, which might introduce an obstruction for hydrophilic medications .(5,6)

PERMEATION ENHANCERS

Permeation enhancers are the mixtures which advance skin porousness . They are a significant component in a TDDS which is utilized to work on the transition (J). Motion can be characterized as how much material moving through the unit cross segment region at that point (t) .

Ideal properties of penetration enhancers:

- They should be pharmacologically dormant, nonallergic, nonirritating, and nontoxic
- It should have similarity with excipients and drugs
- It should not have any pharmacological action in the body
- Cosmetically it should be adequate
- It should be scentless, boring, and boring
- It ought to permit restorative specialists into the body yet ought to keep the deficiency of endogenous material from the body, i.e.,they should work unidirectionally
- It should have substance and actual solidness
- It should have a reproducible and unsurprising term of activity .(7,8)

ENHANCERS OF TDDS

Enhancers assemble the penetration of pervasion by upsetting the design of skin's outer layer i.e layer cornium and growing penetrant dissolvability. Aggravation either by the technique for compound which might impact both the intracellular and extracellular design. Interference might be a direct result of protein denaturation, fluidization and randomization of intercellular lipids or intercellular delamination and augmentation. Enhancers of transdermal medicine movement structure are actual enhancers, particulate systems, and compound enhancers.

Particulate framework

The enhancers of transdermal drug movement sytem are liposomes, microemulsion, transfersome, noisomes and nanoparticles are the instances of particulate strategy for overhaul.

Physical enhancers

The enhancers of transdermal prescription movement system are the iontophoresis, electroporation, magnetophoresis, microneedle and ultra sound (in any case called phonophoresis or sonophoresis) techniques are representations of actual strategy for development that have been used for overhauling percutaneous entry (and maintenance) of various kinds of therapeutic subject matter experts.

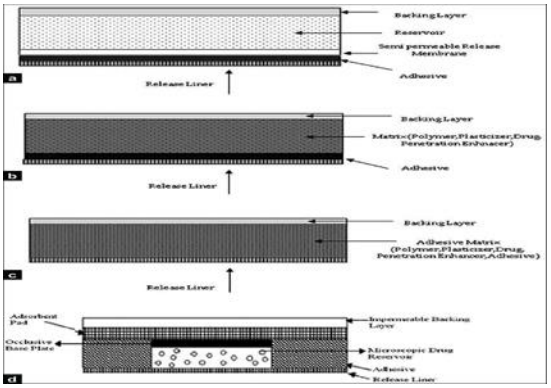
Chemical enhancers

The enhancers of transdermal drug transport structure by technique for synthetic compounds are sulphoxides, glycols, alkanols, terpenes, etc. Synthetic compounds that advance the invasion of topically associated prescriptions are by and large suggested as catalysts, maintenance advertisers, or entry enhancers (9)

FORMULATION DESIGN

A transdermal therapeutic system is essentially a multilaminate structure that is composed of following constituents:

1. Drug
2. Polymer matrix
3. Penetration enhancers
4. Adhesives
5. Backing membrane
6. Release linear.



1. Drug

Transdermal course of organization can't be utilized for a wide range of medications. It relies on ideal physicochemical properties of the medication, its organic properties. Furthermore, thought of the pharmacokinetic and pharmacodynamic properties of medication is essential. The main necessity of medication to be conveyed transdermally is shown by need for controlled conveyance, for example, short half-life, antagonistic impact related with other course or a perplexing oral or I.V. portion routine . The medication boundary expected for ideal medication contender for transdermal medication conveyance can be partitioned into:

- Physicochemical properties

1. The medication ought to have a sub-atomic weight not exactly around 1000 Daltons
2. The medication ought to have liking for both-lipophilic and hydrophilic stages. Outrageous apportioning trademark are not helpful for fruitful medication conveyance by means of the skin
3. The medication ought to have a low softening point
4. Since the skin has pH of 4.2 to 5.6, arrangements which have this pH range are utilized to keep away from harm to the skin.

Anyway for various medications, there may likewise be critical transdermal retention at pH values at which the unionized type of the medication is overwhelming.

- Organic properties

1. The medication ought to be strong with an everyday portion of the request for a couple of mg/day
2. The half life t½ of the medication should be short
3. The medication ought to be non-bothering and non unfavorably susceptible
4. Drugs which corrupt in the gastro gastrointestinal (GI) lot or inactivated by hepatic first-pass impact are appropriate possibility for transdermal conveyance.

2. Polymer

Propels in transdermal medication conveyance innovation have been quick a result of the complexity of polymer science that currently permits joining of polymers in transdermal framework (TDS) in satisfactory amount. The delivery rate from TDS can be customized by differing polymer organization. Choice of polymeric layer is vital in planning an assortment of film penetration controlled TDS.

1. The polymer ought to be synthetically non receptive or it should be an inactive medication transporter.
2. The polymer should not deteriorate on capacity or during the life expectancy
3. Atomic weight, actual trademark and synthetic usefulness of the polymer should permit the dissemination of the medication substance at beneficial rate
4. The polymer and its decayed item ought to be nontoxic. It ought to be biocompatible with skin
5. The polymer should be not difficult to make and create into wanted item. It ought to permit consolidation of a lot of dynamic specialist.(10)

3. Penetration enhancer

A methodology generally explored for advancing pervasion through the skin ineffectively infiltrating drug particles is the fuse of compound entrance enhancer to the TDDS. Then again, actual component, for example, intophorosis and phonophoresis can be utilized for specific instances of medication. There are chiefly methodologies for the entrance upgrade .

- Chemical approach

this includes:

a) Synthesis of lipophilic analogs
b) Delipidization of stratum corneum
c) Co-administration of skin permeation enhancers. This chemical approach can further be classified according to their chemical class

(i) Sulfoxides
Dimethyl sulfoxide, decylmethal sufoxide
(ii) Alcohols:
Ethanol
(iii) Polyols:
Propylene glycol
(iv) Alkenes:Long chain alkanes (C7-C16)
(v) Fatty acids: oleic acid
(vi) Esters: Isopropyl myristate
(vii) Amines and amides: Urea, dimethyl acetamide, dimethyl formamide
(viii) Pyrrilidones: N-methylpyrrilidone, azones
(ix) Terpenes: Eugenol
(x) Surface active agents: Cationic surfactants
(xi) Cyclodextrines. Biochemical approach This includes:
(a) Synthesis of bio-convertible pro-drugs and
(b) Co-administration of skin metabolism inhibitors. Physical approach This includes:
(a) Iontophoresis;
(b) Sonophoresis: Ultrasonic energy
(c) Thermal energy;
(d) Stripping of stratum corneum and
(e) Hydration of stratum corneum.(11)

4 . Adhesive layer
The glue should forces' adequate property in order to solidly tie down the framework to the skin surface and to keep up with it ready however long wanted, even within the sight of water. After expulsion of fix, any hints of cement left behind should be equipped for being washed with water and cleanser. Pressure delicate glues are utilized to accomplish contact between the transdermal fix and the skin. Bond is perceived to be the net impact of three peculiarity's in particular

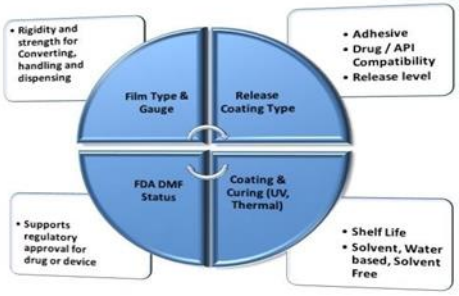
1. Peel: The obstruction against the breakage of the cement bond
2. Track: The capacity of a polymer to stick to a substrate with little contact Pressure and
3. Creep: The thick unwinding of the cement bond upon shear.

The ideal characters of adhesive materials are
1. High biocompatibility (low irritancy, harmfulness, hypersensitive response and so forth)
2. Great Adhesive (cement) to slick, wet, badly crumpled and furry skin
3. Great climate opposition against water and stickiness
4. Simple to eliminate from the skin
5. High porousness of dampness to keep away from exorbitant impediment and for the actual medication
6. Non-responsive towards drug.

There are three kinds of Adhesive(glue) utilized for the most part
1. Silicone type Adhesive
2. Polyisobutylene Adhesive and
3. Polyacrylate based Adhesive. (12)

5. Backing layer
The support layer should be impermeable to medication and pervasion enhancers. The support layer effectively holds the whole framework together and simultaneously safeguards the medication repository from openness to the climate, which could bring about the breakage or loss of the medication by volatilization. The most usually utilized sponsorship materials are polyester, aluminized polyethylene terapthalate, siliconised polyethylene terapthalate and aluminum foil of metalized polyester covered with polyethylene.(13)

6 . Release liner
The peel strip prevents the loss of the drug that has migrated into the adhesive layer during storage and protects the finished device against contamination. Polyesters foils and other metalized laminates are typical materials which are commonly used.



year	Generic name	indication	Mechanism/ technology
2004	Lidocaine/ultrasound	Local dermal anaeesthesia	sonophoresis
2005	Lidocaine/tetracaine	Local dermal analgesia	Heat assisted system
2006	Fentanyl/iontophoresis	Acute post operative pain	iontophoresis
2006	Metylphenidate	ADHD	Passive diffuion
2006	Selegiline	Depression	Passive diffuion
2007	Diclofenac epolamine	Acute pain	Passive diffuion
2007	Rivastigmine	Dementia	Passive diffuion
2008	Granisetron	Chemo-induced emesis	Passive diffuion
2009	Capsaicin	Neutropathy pain	Passive diffusion
2010	Buprenorphine	Chronic pain	Passive diffusion
2012	Rotigotine	Parkinsons disease	Passive diffuion
2013	Sumatriptane	migraine	iontophoresis

EVALUATION TESTS

Drug content determination: A precisely gauged piece of film is disintegrated in 100 ml of dissolvable in which the medication is solvent and afterward the arrangement is shaken persistently for 24 hr in shaker hatchery. Then, at that point, the entire arrangement is sonicated. After brooding and ensuing filtration, drug in arrangement is assessed by spectrophotometrically at proper weakening.

Percentage Moisture content: The pre-arranged films are weighed independently and kept in a desiccators containing calcium chloride at room temperature for 24 hr. The movies are weighed again after explicit stretches until they show a steady weight. The percent dampness content is determined by utilizing the recipe. Rate dampness content = Initial weight - Final weight/last weight ×100

Percentage moisture uptake: Gauged films are to be taken in a dessicator at room temperature for 24 hr. These are then taken out and introduced to 84% relative sogginess using absorbed game plan of potassium chloride a desicator until a steady weight is achieved. Rate sogginess take-up is found out by using the condition. Rate dampness uptake= Final weight-Initial weight/Initial weight X 100

Water vapour penetrability assessment (WVP): Water fume permeability can be settled with foam dressing framework the air compelled oven is displaced by a trademark air dispersal oven. The WVP can be constrained by the going with condition. WVP = W/A Where, WVP is imparted in gm2 each 24 hr, W is the proportion of fume infiltrated through the fix.

Folding Endurance: A piece of specific locale is to be cut consistently, again and again fell at a similar spot till it broke. The amount of times the film could be fallen at a similar spot without breaking gave the assessment of the collapsing perseverance.

Thickness of the patch: The thickness of the fix which is drug stacked is estimated at various focuses by utilizing a screw measure and decides the normal thickness and standard deviation of the pre-arranged fix.

Flatness: A transdermal fix ought to have a smooth surface and shouldn't tighten with time. This can be exhibited by evenness study. For evenness study, one strip is cut from the middle and two from each side of patches. The length of the each strip is estimated and variety long is determined by deciding percent tightening. 0% choking is comparable to 100 % evenness.

Weight variation: The arranged patches are dried at 600ºc for 4hr preceding testing. A predefined territory of patch is to be cut in diverse parts of the patch and say something computerized equalization. The normal weight and standard deviation qualities are to be calculated from the individual weights.

In-vitro permeation: The in-vitro saturation examination of made transdermal patches was finished by using a rat stomach skin and franz dispersion cell. The skin was sandwiched in supporter and receptor compartments of the franz dispersion cell. A 2.2 cm estimation of the fix was set in close contact with the layer cornium side of the skin, the top side was utilized as a help film spread with aluminum.Teflon dab was set in the receptor compartment stacked with 12 ml of standard saline. The cell substances were mixed in an alluring stirrer at a temperature of 37 ± 5°C was kept up all through the test. 1ml of test was removed through the testing port at particular time spans for a period of 24 h, all the same volume of phosphate support pH 7.4 after each withdrawal. By then the examples were examined by utilizing spectrophotometrically (14,15)

Recent Advances of TDDS

. Few of the latest research done in the field of transdermal patches are stated below

Pain-free diabetic monitoring using transdermal patches:

The primary model fix measures around 1cm and is made utilizing polymers and meager metallic movies. The 5×5 testing cluster can be obviously seen, as well as their metallic interconnections. Whenever the seal is compromised, the interstitial liquid, and the biomolecules contained in that, becomes open on the skin surface. Using micro-heating components incorporated into the primary layer of the fix nearest to the skin surface, a high-temperature heat heartbeat can be applied locally, penetrating the layer corneum. During this removal interaction, the skin surface encounters temperatures of 130°C for 30ms span. The temperature lessens quickly from the skin surface and neither the living tissue nor the sensitive spots are impacted. This easy and bloodless cycle brings about disturbance of a 40-50μm width area of the dead skin layer, roughly the size of a hair follicle, permitting the interstitial liquid to cooperate with the fix's cathode destinations. (16)

Transdermal patch of oxybutynin used in overactive bladder:

The item is a transdermal fix containing Oxybutynin HCl and is supported in US under the brand name of Oxytrol and in Europe under the brand name of Kentera. OXYTROL is a flimsy, adaptable and clear fix that is applied to the mid-region, hip or butt cheek two times week after week and gives persistent and steady conveyance of oxybutynin more than a three to multi day span. OXYTROL offers OAB patient's ceaseless successful bladder control with a portion of the incidental effects, for example, dry mouth and obstruction experienced with and oral definition. In many patients these aftereffects anyway are not an irksome.(16)

Nanotechnology gaining hold:

Another enhancer that is acquiring headway is microneedles. This innovation joins the benefit of a needle and the transdermal fix. The gadgets are dime-sized bits of polymer with many empty microneedles somewhere in the range of 100 and 1,000 micrometers in length. These little needles infiltrate the top layers of skin and permit the medication to go through effortlessly. This innovation can be joined with an electronically controlled micropump that conveys the medication at explicit times or upon request. Once supported by the FDA, these gadgets would permit the patient or doctor to control the time and portion of the medication being conveyed. These gadgets can possibly put tranquilizes exactly into the area where exceptional invulnerable cells live, making these medications equipped for regulating the resistant framework, without breaking a sweat. Alza is utilizing a somewhat unique minor departure from the utilization of needles. . The organization has fostered the licensed Macroflux transdermal innovation that utilizes microprojections to make shallow pathways through the dead skin boundary. The tips of the projections contain dynamic medication - a speedy bolus.(17)

CONCLUSION

Tdds is fastest growing sector within the pharmaceutical industry. Tdds offers numerous advantages to patients with a good efficacy and safe compliance. Advances in drug delivery systems have increasingly led to controlled administration with

fewer side effects and increased efficiency and consistent medication administration.

REFERENCES

[1] Sampathkumar KP, Debjit B, Chiranjib B and Chandira RM: Transdermal drug delivery system- a novel drug delivery system and its market scope and opportunities. International Journal of Pharmacy and Bio Sciences 2010; 1:1-21.

[2] Patel D, Patel N, Parmar M and Kaur N: Transdermal drug delivery system: Review. international Journal of Biopharm and Toxicological Research 2011; 1: 61- 80

[3] Jain A, Mishra A, Nayak S and Soni V: Transdermal delivery of antihypertensive agents: A tabular update. International Journal of Drug Delivery 2011; 3: 1-13.

[4] Patel RP and Baria AH: Formulation and evaluation considerations of transdermal drug delivery system. International Journal of Pharmaceutical Research 2011; 3: 1-9.

[5] Lee, A.Y. Molecular Mechanism of Epidermal Barrier Dysfunction as Primary Abnormalities. Int. J. Mol. Sci. 2020, 21, 1194. [CrossRef] [PubMed]

[6] Basler, K.; Bergmann, S.; Heisig, M.; Naegel, A.; Zorn-Kruppa, M.; Brandner, J.M. The role of tight junctions in skin barrier function and dermal absorption. J. Control. Release 2016, 242, 105–118. [CrossRef] [PubMed]

[7] Arunachalam A, Karthikeyan M, Kumar VD,Prathap M, Sethuraman S, Ashutoshkumar S,Manidipa S. Transdermal Drug DeliverySystem: A Review. Current Pharma Res. 2010(1):70-81.

[8] Willams AC, Barry BW. Penetration Enhancers.Adv. Drug Del. Rev 2004; 56: 603-618. 30.Pellet M, Raghavan SL, Hadgraft J, Davis AF.The application of supersaturated systems topercutaneous drug delivery, In: Guy R.H and Dekker, Inc., New york 2003, pp. 305-326

[9] Bhargava T, Ramchandani U, Shrivastava SK and Dubey PK: Current trends in NDDS with special reference to NSAIDs. International Journal of Pharmacy and Bio Sciences 2011; 2-114

[10] Siepmann et al., 1998. The criteria forthe polymers are (Chien, 1987; Vyas and Khar, 2002;Mishra, 1998)

[11] Barry, 1987 , walker and smith 1996

[12] according to Hock and William (1999), Qvist et al. (2002), Govil et al. (1993) and Govil (1988) , Qvist eadministration according to Govil (1988)

[13] Chein YW. Transdermal drug delivery and delivery system. In, novel drug deliverysystem, vol. 50, Marcel Dekkar, Inc., NewYork, 1992; 031-381.

[14] Malthiowitz.Z.E, Chickering.D.E, Lehr.C.M, Bioadhesive drug delivery systems; Fundamentals, novel approaches and development, Marcel Dekkar, Inc., NewYork, Basel.

[15] Shah S.Transdermal Drug Delivery Technology revisited: Recent Advances pharmainfo.net.2008;6(5)

[16] Morrow T. Transdermal Patches Are More Than Skin Deep. Managed care. I serial online] 2004 [cited 2011 feb 4). Available online.