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Transdermal Drug Delivery: A Review

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ABSTRACT: Transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. An easy, painless, and convenient mode of application. Provides stable plasma level time profiles over extended time periods. The main route for penetration of drugs is generally through the epidermal layers, rather than through the hair follicles or the gland ducts, because the surface area of the latter is rather small compared to the area of the skin. Transdermal drug delivery is the noninvasive delivery of medications from the surface of skin. Various drugs can be used for transdermal drug delivery like Lercanidipine hydrochloride, fentanyl, nicotine, scopolamine, clonidine, buprenorphine, rivastigmine etc. For treating various diseases with the utmost patient convenience. Recently 100 patches were under clinical trials studies, so demand for transdermal patches is a never-ending process.

KEYWORDS: Transdermal Drug delivery, Patch, Treatment

I. INTRODUCTION:

Definition: Transdermal drug delivery system can be defined as the topically administered medications in self-contained, discrete dosage forms of patches which when applied to the skin deliver the drug, through the skin portal to systemic circulation at a predetermined and controlled rate over a prolonged period of time in order to increase the therapeutic efficacy and reduced side effect of drug.

It is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream.
An ideal dosage form would be maintaining the drug concentration in the blood at a constant level nearly coinciding with the minimum effective concentration (MEC)of the drug throughout the period. This leads to the concept of controlled drug delivery. The primary objective of controlled drug delivery is to ensure safety and efficacy of the drugs as well as patients' compliance [1].

A.Advantages: [2-4]

Administration can be visually confirmed. Produce excellent prolonged effects. Avoid first pass hepatic metabolism. Maintains constant blood levels for a longer period of time. Decrease the dose of administration. Decrease unwanted/side effects. Decrease gastro-intestinal side effects. Easy to discontinue in case of toxic effects. Increased patient compliance. Great advantage for patients who are unconscious. Provides an ability to modify the properties of biological barriers to improve absorption. Relatively large area of application in comparison to buccal/nasal cavity. Self-administration is possible. The drug input can be terminated at any point of time by removing the transdermal patch. Avoid the pain on injection.

B.Disadvantages: [4-6]

Drugs must have some desirable physic-chemical properties to penetrate through the stratumcorneum. Local irritation at the site of administration may be caused by drug, adhesive/other excipients in patch. In the TDDS formulation the components may produce skin irritation, local edema or erythema. Poor skin permeability limits the number of drugs that can be delivered in this route.TDD cannot achieve high drug levels in blood/plasma.TDD cannot deliver ionic drugs.
Drugs are metabolized by the skin and undergoes protein binding in skin are not suitable in
TDD cannot deliver the drugs in pulsatile fashion.

C.Genarations of transdermal patches:
1) First Generation: TDDS include traditional patches such as clonidine or estrogen. Delivery of small lipophilic, low dose drugs.
2) Second Generation: Uses chemical enhancers and iontophoresis

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3) Third Generation: TDDS use Novel technologies to increase the scope of molecules that can be delivered through the skin. Ex. Microneedles, thermal ablation, or microdermabrasion.

D.Use of TDDS:

TDDS maintains drug concentration within the therapeutic window for prolong period of time ensuring that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration.

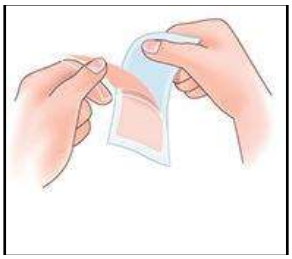

Fig no1: Transdermal patch

E.Topical drug delivery:
Term utilized for application of dosage forms to the controlled area of skin to get the localized effect.
Dermatological disorders: eczema, psoriasis
Infections: Bacterial and fungal.
Treatment is not intended for systemic effect.
Drugs: corticosteroids, antifungals, antivirals, antibiotics, antiseptics, local anesthetics and antineoplastics.
Dosage forms: solutions, emulsions, powders, creams, pastes, gels, ointments, lotions.
Topical preparations used as protectives, cleansing agents' emollients and adsorbents.

F. Transdermal drug delivery:
Involves drug diffusion through distinct layers of skin into systemic or blood circulation to provoke therapeutic effects.
Transdermal patch of clonidine(hypertension)and nitroglycerin(angina)
Drugs: scopolamine, nitroglycerin, clonidine, diclofenac, indomethacin, nicotine, estradiol, testosterone etc. [7].

Adherence to prescriptions and portion enhancement can be influenced by a few physiological and mental factors, for example, bothersome results, dosing routine, course of organization, nature of disease, conviction frameworks and individual ascribes [8].

2. Approaches used in Development of Transdermal Drug Delivery Systems:

II. FORMULATION

A. Rate-programmed transdermal DDS:
1) Polymer Membrane Permeation-Controlled TDDS.
2) Adhesive diffusion controlled TDDS.
3) Matrix dispersion controlled TDDS.
4) Micro-reservoir type controlled TDDS.

1) Polymer membrane Permeation-controlled TDDS:In this system, the drug repository is implanted between an impenetrable sponsorship layer and a rate controlling film. The medication delivers just through the rate controlling membrane, which can be miniature permeable or non-permeable. In the medication repository compartments, the medication can be as a solution, suspension or gel or scattered in a strong polymer network. On the external surface of the polymeric film a flimsy layer of medication – compatible, hypoallergenic adhesive polymer can be applied. The rate controlling variable of medication release: polymer composition, permeability coefficient and thickness of the rate controlling film.

2) Adhesive diffusion controlled TDDS:The medication repository is shaped by scattering the medication in a glue polymer and afterward spreading the sedated polymer glue by dissolvable projecting or by liquefying the adhesive in instances of hot-soften adhesives onto an impenetrable backing layer. The medication supply layer is then covered by a non-medicated rate controlling adhesive polymer of consistent thickness to create an adhesive diffusion controlling drug delivery system.

3) Matrix dispersion controlled TDDS: The medication is scattered homogeneously in a hydrophilic or lipophilic polymer network. This medication containing a polymer circle at that point is fixed onto an occlusive base plate in a compartment manufactured from a drug impermeable backing layer. Rather than applying the adhesive on the substance of the medication supply, it is spread along the boundary to form a strip of adhesive rim.

4) Micro-reservoir type controlled TDDS:This drug delivery system is a blend of reservoir and matrix dispersion-controlled systems. The drug supply is shaped by first suspending the medication in a watery arrangement of water-dissolvable polymer and afterward scattering the

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arrangement homogeneously in a lipophilic polymer to frame a great many inaccessible, minute circles of drug reservoirs.The thermodynamically shaky scattering is settled rapidly by promptly crosslinking the polymer in situ. A transdermal system, restorative system accordingly shaped as a medicated disc situated at the middle and encompassed by an adhesive rim [9].

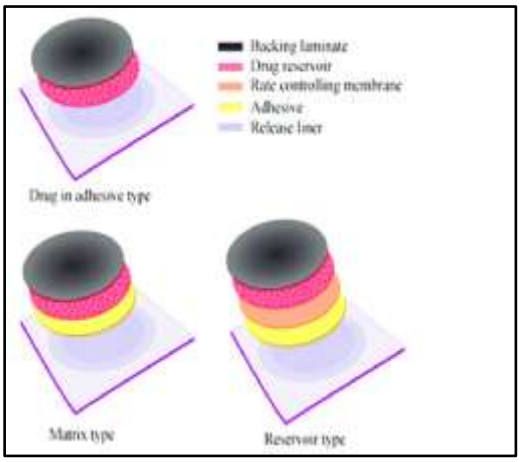

Figure2: Approaches in formulation of transdermal patches

B.Physical stimuli-activated TDDS:

1) Structure based:
- Microneedles
- Macro fluxMDTS

2) Electrically based:
- Iontophoresis
- Ultrasound
- Photochemical Waves
- Electroporation
- Electroosmosis

3) Velocity based:
- Powder jet
- Needle free injection

4) Others
- Transferosomes
- Medicated tattoos
- Skin abrasion
- HeatLaser radiation
- Magnetophoretic [10].

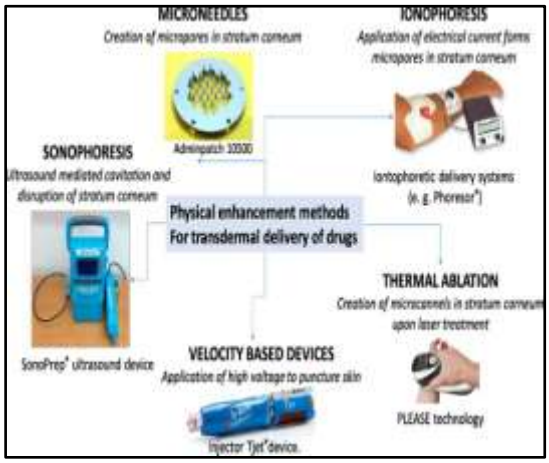

Figure3: Methods to Enhance Transdermal Drug Delivery

III. METHOD OF PREPARATION OF TRANSDERMAL PATCHES:

1.Asymmetric TPX membrane method
2. Circular Teflon mold method
3. By using "IPM membranes" method
4. By using "EVAC membranes" method
5. Aluminum backed adhesive film method
6. Preparation of TDDS by using Proliposomes
7. By using free film method [11-12]

IV. 4. EVALUATION PARAMETERS

1) Thickness of the patch
2) Folding endurance
3) Percentage Moisture content
4) Content uniformity test
5) Drug content
6) Shear Adhesion test
7) Peel Adhesion test
8) Water vapor transmission studies (WVT)
9) Rolling ball tack test
10) Quick Stick (peel-tack) test
11) Probe Tack test
12) Weight variation

In Vitro drug release studies

1) Skin irritation study
2) Stability studies [13-14].

Table 1: List of Marketed formulations

Brand Name	Drug	Manufacturer	Indications
Nupatch 100	Diclofenac diethylamine	Zydus cadila	Anti-inflammatory
Matrifen^{R}	Fentanyl	Nycomed	Pain relief patch

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Neupro	Rigotine	UCB and Schwarz Pharma	Early-stage idiopathic parkinson's disease
Emsam	Selegiline	Somerset pharmaceuticals	Major depressive disorder
Salonpas	Menthol (Methyl Salicylate)	Hisamitsu pharmaceutical	Muscle and joint pain
Lidoderm	Lidocaine	Hind Health Care	Postherpetic neuralgia pain
Testoderm	Testosterone	Alza	Testosterone deficiency

Table 2: List of Marketed preparations

Brand Name	Manufacturer Name	API
SonoDerm	Imarx	Insulin
Intraject	Weston medical	Vaccines
Oxytrol	Watson Pharma	Oxybutynin
Habitrail	Novartis	Nicotine
Chadd	ZarsInc	S-caine

Use of Transdermal patches and its role in various treatments:

a) Oxybutynin transdermal patch:J. Salinas Casado.et has explained the role of oxybutynin an antimuscarinic transdermal patch for treating overactive bladder, a condition in which bladder muscles contract uncontrollably and cause frequent urination when urgently needed to urinate. oxybutynin transdermal patch releases about 3.9mg/ml twice/week [15].

b) Nitroglycerin transdermal patch:Nitroglycerin transdermal patch used for antianginals treatment. Kounis et al. have demonstrated that the reactions to such patches are mostly irritative and only minimally allergic. In the suspicion of ACD to patches made of nitroglycerin[16].0.1mg/hr-0.8mg/hr, onepatch /day having nitrate free period of 10-12 hrs duration needed to prevent toleranceExample; Nitro-dur 02, Nitro-dur 03, minitran, nitrek etc

c) Lercanidipine hydrochloride patch:Mamatha et al., has done an experiment on lercanidipine hydrochloride drug which is an hypertensive drug by transdermal route. Absorption studies were performed using rat abdominal skin where permeability studies obtained from solutions of 8 & 12% namely A1,A2,A3....A6 are shown absorption rate 82%,74.5%, 63.2%.....53.5% respectively. In the present study, it was observed that as the concentration of hydrophilic polymer (HPMC) increased in the formulations, the drug release rate increased substantially. in case of humans lercanidipine hydrochloride orally administered at the dose of 10-20mg/day

d) Transdermal delivery of combined hormonal contraception:Rosanna M Galzote et al has made a review on combined hormonal contraception through transdermal drug delivery route combination of 150 micrograms norelgestromin and 35 microgram ethinyl estradiol patch\week for three weeks. She has concluded that two new patches have been developed, one containing gestodene and Ethinylestradiol (EE) in Europe and another containing levonorgestrel and EE. Overall, the patch provides an alternative to combined oral contraceptives for women who want autonomy and the benefit of not needing to take a pill daily, with similar efficacy and tolerability.[18]

e) Transdermal delivery of proteins:Hari Priya kalluri et al., has reviewed that combined protein drug delivery through skin can be enhanced by using techniques like chemical enhancers, iontophoresis, microneedles, electroporation, sonophoresis, thermal ablation, laser ablation, radiofrequency ablation and noninvasive jet injectors, along with this mechanisms, sterility requirement and commercial development of products [19].

f) Rotigotine patch:Rotigotine transdermal patch used to treat signs of Parkinson's convulsions. Chang Qing Zhou et al., has done a systematic review and meta-analysis of rotigotine patch in the treatment of Parkinson disease, to evaluate the efficacy, tolerability, and safety of rotigotine transdermal patch [21]Example; NEUPRO R 2mg /24hrs

g) Domperidone bilayer matrix transdermal patch:Domperidone was used in the treatment

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of motion sickness.S.K. Madishetti et al has developed a bilayer matrix type of patch by using a film casting technique with a polymer polyoxyethylene lauryl ether (Brij-35) was incorporated as a solubilizer, d-limonene and propylene glycol were employed as permeation enhancer and plasticizer respectively. HPMC and eudragit were used as secondary layers. The studies show that this patch was effectively used to treat motion sickness showing drug release about 90.7% and drug permeability 6806.64 micrograms /24hrs [22].

h) Analgesic transdermal patchFentanyl transdermal duragesic a small patch and once it can be applied, the active pain medication is slowly absorbed through skin into blood stream that is one patch /12-24 hrs

i) Transdermal patch for smoking cessation:Jose Juan Escobar-Chavez et al., has formulated a Nortriptyline hydrochloride(NTP-HCL) patch using polymers like chitosanPluronic F-127 and 1-dodecanol (3rd patch) provided a reasonable flux of NTP-HCl across the skin than other patches. Iontophoresis is the applied mechanism but it does not increase the penetration of NTP-HCl across the skin.Some transdermal drugs for systemic delivery launched in the USA & EU [24].

j) Topiramate transdermal patch :Topiramate is used to treat migraine formulated in transdermal matrix dispersion controlled release TDDS has been ensuring that sustained drug release performance of about F1-F25 formulations were varied between 40.19% to 97.03% by altering the polymers . highest sustained release performance shown by the polymers like HPMCK15, Eudragit 400 and lowest performance by HPMCK15 ,Carbopol.

Fig no 4: Clonidine Patch

Fig no 5: Fentanyl Patch

V. CONCLUSION

Transdermal patches can offer advantages to patients over oral plans as far as usability, straightforward treatment regimens, evasion of the primary pass impact, and shirking of high greatest plasma focuses with quick changes in medication levels, without the intrusive systems related with intravenous treatment. Transdermal medication conveyance framework might be ideal for some infused just as orally given medications, yet numerous medications can't enter the skin layer viably due to low porousness of skin boundary.

These are largely present day plans in grid patches, created to give proper medication dose in a worthy and all-around endured structure.

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