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A NOVEL APPROACH IN DISORDER MANAGEMENT BY TRANSDERMAL PATCHES: A REVIEW

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ABSTRACT

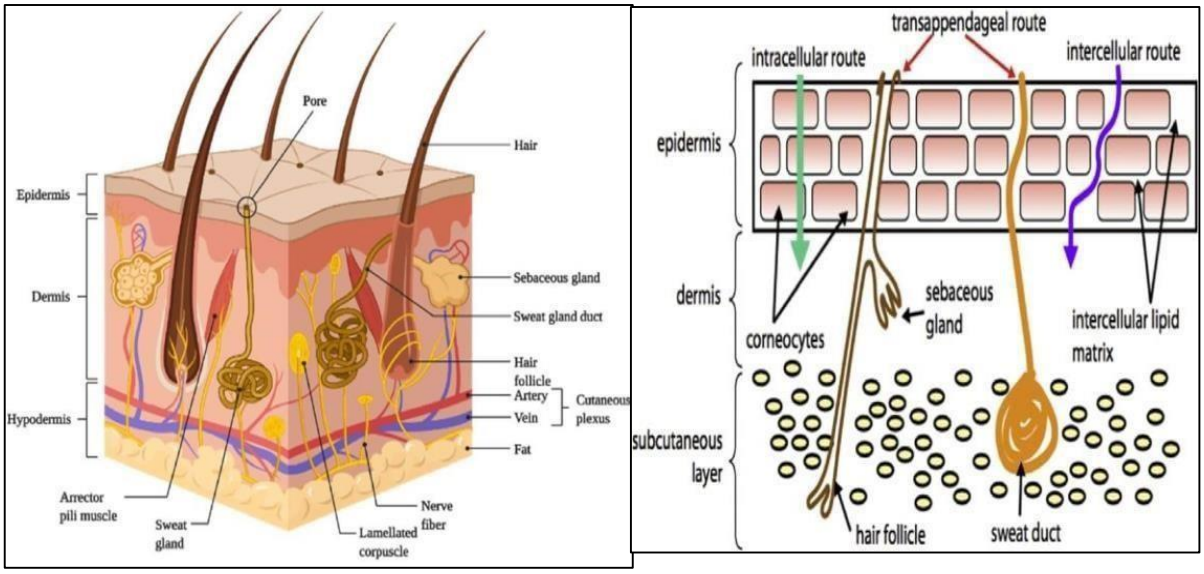
Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery. Transdermal drug delivery has evolved throughout time, with the development of passive and active technologies that have resulted in enhanced distribution, accuracy in drug dosage, and better fulfilment of the requirements of the individual. Transdermal patch of asenapine in schizophrenia offers another strategy for treatment to improve compliance and ease of administration. Hypertension is one of the largest deaths causing disease for the mankind which also uses transdermal patches, concentrations of polymer, plasticizer and penetrant were varied. Topical delivery methods have been used since the dawn of time, employed to cure a wide range of aliments and for aesthetic purposes. When compared to other transdermal drug delivery allows a controlled release of the medicine into patients, often by either a porous membrane or by body heat melting small layers of medication embedded in the adhesive. One of the diabetes mellitus treatments that can reduce pain is using insulin patch technology as a transdermal treatment. Transdermal delivery of Non-steroidal anti-inflammatory drugs and antiviral agents drugs has advantages of avoiding hepatic firstpass effect, gastric irritation and delivering the drug for an extended period of time at a sustained level. Vasomotor symptoms (VMS) associated with menopause can cause significant discomfort and decrease the quality of life for women in perimenopausal and post-menopausal stages of life. Hormone therapy is the mainstay of treatment for menopausal symptoms and is currently the only therapy proven effective for VMS.

KEYWORDS: Transdermal drug delivery system, Stratum corneum, Schizophrenia, Diabetes mellitus, Nonsteroidal anti-inflammatory drugs, Hormone therapy, Vasomotor symptoms.

INTRODUCTION

Transdermal drug delivery systems (TDDS) are dosage forms designed to deliver a drug through the skin into the bloodstream. For systemic drug delivery through skin, its morphological, biophysical and physicochemical properties must be considered; transdermal delivery improves compliance and avoids first-pass metabolism compared to injectables and oral routes.[1] Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which causes side effects. So, various forms of Novel drug delivery systems are emerged.[2]

Transdermal drug delivery is limited by the skin's tough, lipid-rich stratum corneum, which restricts penetration of most biopharmaceuticals and small molecules.[3] The stratum corneum is hydrophilic in nature that confines percutaneous formulations to creams, gels, ointments, and non-invasive patches.[4] As a heterogeneous barrier with complex physiology (fig1 a), skin causes high variability in topical pharmacokinetics. Molecules traverse the SC via transcellular, intercellular, or appendageal routes, predominantly reaching the viable epidermis by passive diffusion shown in fig1 b.[3]



(a) **(b)**

Figure 1: (a) Systemic representation of anatomical structure of the human skin. (b) Routes of percutaneous absorption.

COMPONENTS	FUNCTION	EXAMPLES
Drug	Drug is in direct contact with release liner.	Nicotine, Methotrexate and Estrogen.
Liner	Protects the patch during storage.	Polyester flim.
Adhesive	Serves to adhere the patch to skin for systemic delivery of drug.	Acrylates, Silicon, Polyisobutylene
Permeation enhancers	Control the release of the drug.	Terpenes, Terpenoids. Solvents-Alcohol, Ethanol. Surfactants-SLS, Pluronic F127.
Backing layer	Protect patch from outer environment.	Cellulose derivatives, Polyvinyl alcohol, Polypropylene silicon rubber.

Table 1: Components of patch.[5]

ADVANTAGES OF TDDS

1. Avoids first-pass metabolism.
2. Provides steady drug levels with fewer side effects.
3. Reduces plasma fluctuations, suitable for short half-life or low therapeutic index drugs.
4. Allows quick discontinuation in toxicity.
5. Lowers dosing frequency, improving compliance.
6. Prevents GI irritations and poor absorptions.
7. Achieves therapeutic effect with lower dose.
8. Enhances adherence.

LIMITATIONS OF TDDS

1. Skin irritation and dermatitis from the drug, excipients or enhancers takes place.
2. Drug molecules (>500Da) are difficult to penetrate.
3. Drugs with very low or high partition coefficient fail to reach blood circulation.

Many approaches have been attempted to deliver medicament across the skin layers. Major considerations for enhancing are physical enhancers and chemical enhancers.[6] To achieve systemic effect, consider SC, drug properties, application site, skin blood flow, additives, body temperature, and patch. Table 1 contains the components of patch. Dosage is controlled by the active surface of the patch.[7]

INFLUENCE OF HUMAN BIOLOGY ON PERFORMANCE OF TDS

Percutaneous drug delivery delivers medication into systemic circulation through the skin.[8,9] Male and female skin differ mainly in pore size (larger in male) and pH (lower in men), but in vivo studies show no significant difference in nicotine permeation to support gender based variations. Transdermal drug delivery (TDD) should be avoided if the skin is diseased because certain skin conditions can damage the skin's natural barrier. This barrier normally controls how much of a drug passes through the skin into the body. When the barrier is damaged, it can allow too much drug to be absorbed, which may cause harmful side effects. So, using TDD on damaged or diseased skin increases the risk of overdosing or adverse reactions.[9] Characterizing and predicting heat effects on TDS and topical systems is vital for regulatory evaluation and safety assurance.[10]

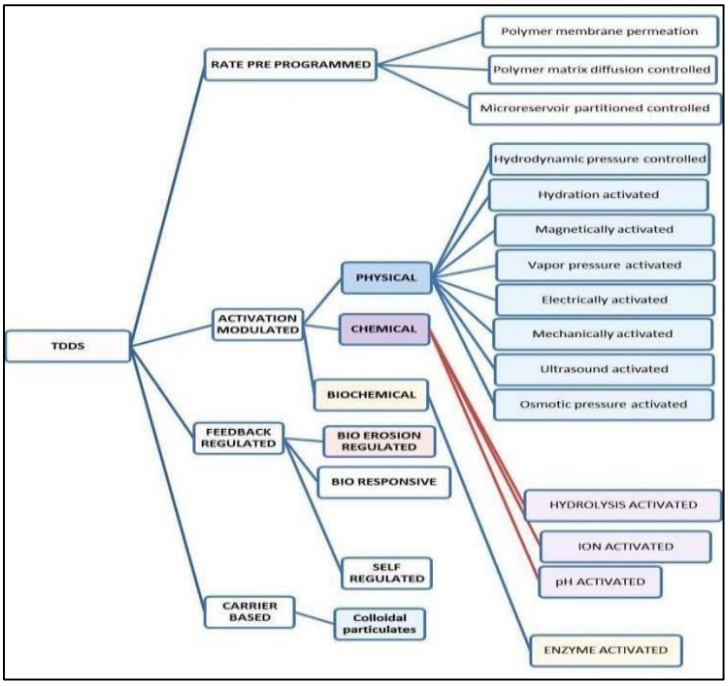


Figure 2: Classification of TDDS.

TYPES OF TRANSDERMAL PATCH

a) Single layer drug in adhesive: In this type, the adhesive layer contains the drug, adheres the layers, and releases the drug to the skin; it is bordered by a temporary liner and backing.

b) Multi-layer drug in adhesive: This type is similar to single-layer patches. It has an immediate drug release layer, a controlled release adhesive layer that releases the drug, plus a temporary liner and permanent backing.

c) Vapour patch: In this patch, the adhesive layer both holds layers together and releases vapour. Vapour patches, used for essential oils in decongestions, also improve sleep and reduce smoking.

d) Reservoir system: In this system, the drug reservoir lies between an impervious backing and a rate controlling membrane, through which the drug is released. The reservoir may contain the drug as a solution, suspension, gel, or within a solid polymer matrix.

e) Matrix system

1. **Drug-in-adhesive system:** In this type, the drug reservoir is made by dispersing the drug in an adhesive polymer and spreading it on an impervious backing via solvent casting or melting. Protective un-medicated adhesive layers are applied on top.
2. **Matrix-dispersion system:** In this type, the drug is evenly dispersed in a hydrophilic or lipophilic polymer matrix and placed on an occlusive base within a backing layer. The adhesive is applied around the edge as a rim, not on the reservoir face.

f) Micro-reservoir system: This system combines reservoir and matrix-dispersion types. The drug is suspended in a water-soluble polymer solution, then evenly dispersed in a lipophilic polymer, forming microscopic drug reservoirs. This unstable dispersion is stabilized by immediate in situ cross-linking using cross-linking agents.[6,11,12,13]

EVALUATION PARAMETERS

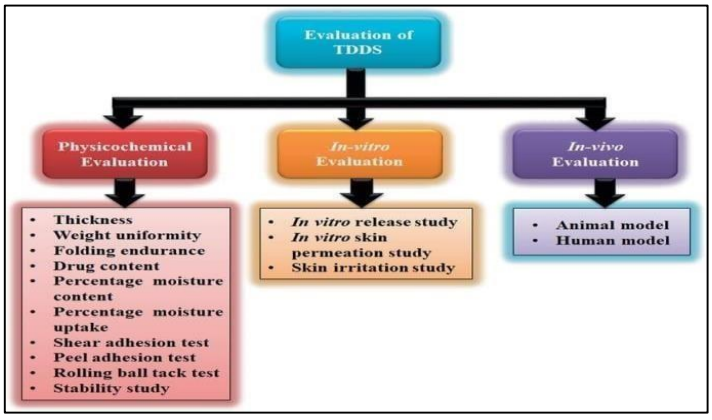


Figure 3: Evaluation parameters of TDDS.

DISORDERS

1. CENTRAL NERVOUS SYSTEM

a. SCHIZOPHERNIA

Schizophrenia is a chronic psychiatric disorder marked by disrupted thoughts, perceptions, emotions, and social interactions.[14] It presents with positive(hallucinations), negative (emotional and behavioural deficits), and cognitive symptoms that may be subtle.[15,16] Key features include delusions, disorganized speech or behaviour, flat effect, anhedonia and avolition.[14] Symptoms listed, for a significant period of time during, a month period: delusions, hallucination, disorganized speech, grossly disorganized or catatonic behaviour and negative symptoms.[17]

Schizophrenia pathophysiology involves neurotransmitter imbalance, brain structural changes, environmental factors, and genetic risk. Dopamine hypothesis suggests agonist triggers or worsen psychosis, while antipsychotics act via D2 receptors. Reduced dopamine disrupts basal ganglia motor control, whereas excess dopamine in the mesolimbic pathway drives positive and negative symptoms.[18]

First generation and second generation anti-psycotics are used. The drug used in TDDS treatment is Asenapine- a second generation drug that blocks 5HT-2A receptors and less adverse effects. It is formulated in both sublingual and transdermal from named Saphris and Secuado respectively. The patch is applied once in a daily for 24 hrs on upper arm, upper back, or abdomen. Drug metabolism takes place by cytochrome P-450. Reported adverse reactions are dizziness, dryness, pain, irritation. Side effects are headache, hypertension and constipation.[19]

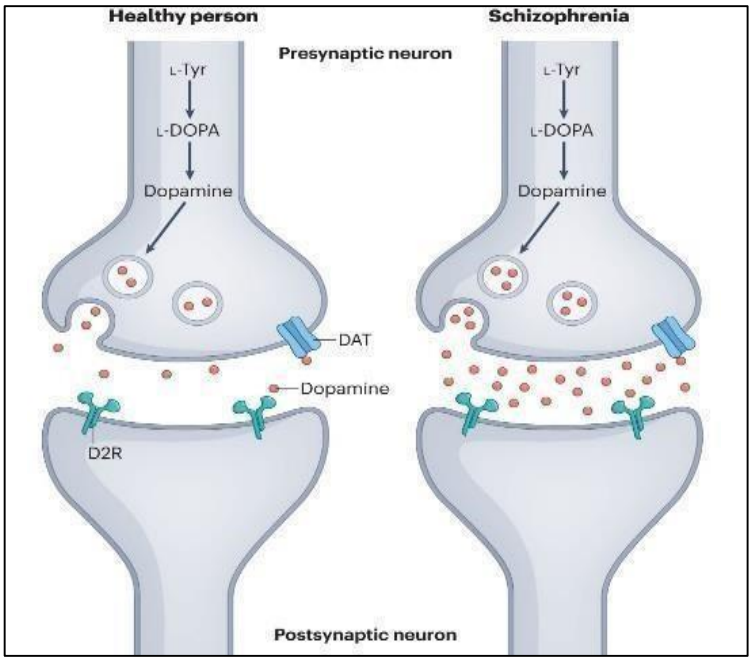


Figure 4: Pathophysiology of SZ.

b. DEPRESSION

Depression is a mood disorder causing a persistent feeling of sadness and loss of interest. It's disorder features are sadness, emptiness or irritability with somatic cognitive changes.

CNS 5-HT involvement in major depression is indicated by SSRI efficacy, implicating receptor regulation, signalling, gene expression, and neurotransmitter availability.

SSRIs, SNRIs, Atypical antidepressants, SDAMs, TCAs, MAOIs are the drugs used in depression.[20]

Selegiline transdermal system was designed to treat MDD and overcome dietary safety concerns that exist with the conventional oral MAOIs.[21] MAO(A) inhibition and tyramine presser effects in the brain results in the antidepressant effects of selegiline. MOA(A) inhibition prevents dietary tyramine breakdown, risking fatal hypertensive crisis. At higher doses of 9mg and 12mg, a tyramine restricted diet is recommended.[22] The STS appears to be well-tolerated with application site reactions as the most common adverse reaction and low rates of weight gain and sexual dysfunction.[21]

Figure 5: Different doses of STS.

2. CARDIOVASCULAR SYSTEM

a. HYPERTENSION

Hypertension is a cardiovascular disease that leads to high death rate and disability worldwide. The Global Burden of Disease study reported 5.2 million cardiovascular deaths in developed and 9.1 million in developing countries.[23]

Clonidine is a centrally acting antihypertensive drug having plasma half-life of 8-12h and peak concentration occurs in 2-4h.[24] It reduces blood pressure in patients from mild to moderate hypertension.[25] Both transdermal and oral form of clonidine showed similar efficacy.[26]

Mao Zhenmin et al.,[27] prepared, a new type of polyacrylates polymer synthesized in lab by UV curing method and studied in membrane controlled drug release systems. In this method, membranes were photosynthesized by UV radiation of mixtures of three acrylate monomers: 2-hydroxy-3-phenoxypropylacrylate, 4-hydroxybutyl acrylate and sec-butyl tiglate in different ratios photo initiator, benzoyl peroxide. The effects of monomers ratios, membranes were characterized by FTIR, DSC, and SEM. It was found that the new type of membranes could control clonidine linear release in the transdermal drug delivery system.

Ming KEG et al., characterized a newly developed clonidine transdermal patch, KBDtransdermal therapeutic system, for the treatment of attention deficit hyperactivity disorder in children. In-vivo release, penetration, and in-vivo pharmacokinetics in rabbits were investigated. Pharmacokinetics of KBD-transdermal therapeutic system (2.3 mg/2.5 cm^2) in rabbits were compared with Catapres-TTS (2.5 mg/3.5 cm^2). The transdermal penetration rate of clonidine was mainly controlled by the ethylene vinylacetate membrane used in the patch. A single dose of patch was administered to rabbits (n=6 each) and removed after 168 h. The average half-life, T_{max}, C_{max} and C_{ss} values of clonidine in rabbits following administration of KBD-transdermal therapeutic system were 19.27’4.68 h, 52.56’25.77 h, 27.39’9 ng/ml, and 25.82’9.34 ng/ml, similar to those of Catapres-transdermal therapeutic system, respectively. The clonidine plasma concentration of KBD-transdermal system reached a steady state at 24h through 168h. The in vitro release rate of the clonidine significantly correlated with in the in vivo absorption rate ($p<0.001$).[28]

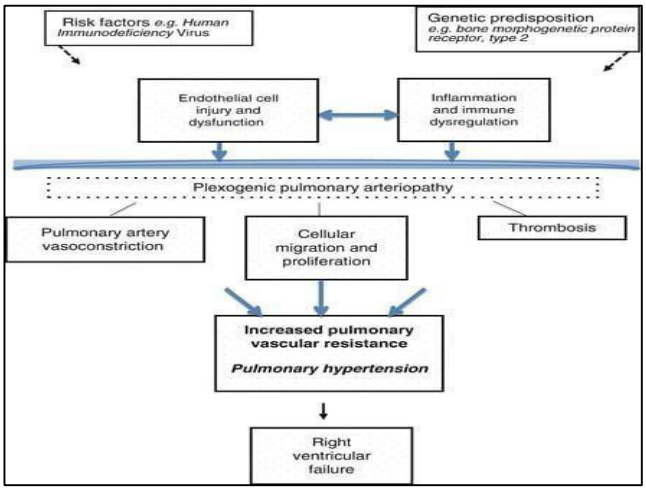


Figure 6: Pathophysiology of hypertension.

b. CORONARY ARTERY DISEASE

Coronary Artery Disease is characterized by the development of atherosclerosis in the coronary arteries, which can sometimes be asymptomatic.[29] The pathophysiology of Coronary Artery Disease is atherosclerosis plaque formation. Plaque is build-up of fatty material that narrows the arterial lumen and impedes blood flow. Atherosclerosis begins with fatty streaks formed by foam cells macrophages. Plague may stabilize with a fibrous cap and calcification or progress to significant obstruction. Plague rupture exposes tissue factor causing thrombosis.[30]

The transdermal patch used for coronary artery disease is Nitroglycerin patch.

Nitrates are well absorbed via mucosa, GI tract, and skin; nitroglycerin is available as oral, sublingual, buccal, spray, transdermal and IV forms.[31]

During clinical trails, it has been discovered that nitroglycerin inactivated itself during prolonged delivery, each branded patch was to be administered once daily with a 12h 'rest cycle' in between each.[32] Volatilization of nitroglycerin did not seem to be the problem. Unintentional transmission through interpersonal touch, on the other hand, was a challenge, as illustrated by a spousal headache following intercourse with a spouse who had rubbed a nitroglycerin patch on his penis to relieve erectile dysfunction.[33,34] The nitroglycerin patches manufactured till now are shown in the table 2 below.

TRADE NAME	LAUNCHED BY	SITE OF APPLICATION	DURATION OF APPLICATION
Transderm-Nitro®	Ciba Pharmaceuticals Company	Chest, shoulder, upper arm, or back	12-14h
Nitro-Dur®	Key Pharmaceuticals	Chest, shoulder, upper arm, or back	12-14h
Nitrodisc®	Key Pharmaceuticals	Chest, shoulder, upper arm, or back	12-14h

Table 2: The US FDA has licensed commercially viable transdermal patches.

3. DIABETES MELLITUS

Diabetes mellitus, now common in the community, is a condition caused by increased blood glucose due to progressively reduced insulin secretion.[35] Hyperglycemia, an early symptom of diabetes mellitus, is marked by elevated blood sugar levels above 200 mg/dl.[36] Diabetes is a metabolic disorder caused by insufficient insulin production or ineffective use of insulin from pancreas, leading to hyperglycemia.[37] Diabetes mellitus is a chronic disease that weakens immune function, increasing susceptibility to infections.[38] Diabetes is divided into:

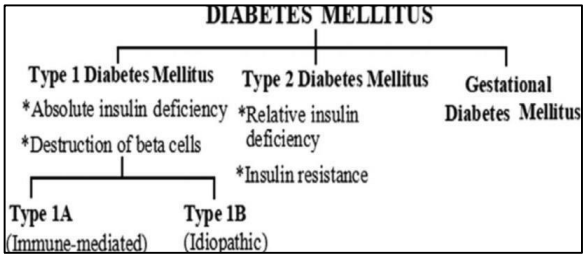


Figure 7: Types of diabetes.

Insulin is a vital hormone that regulates metabolism, consisting of two chains: A chain with 21 amino acids and a B chain with 30 amino acids, both linked by two disulfide bridges.[39] (Figure 8)**.**

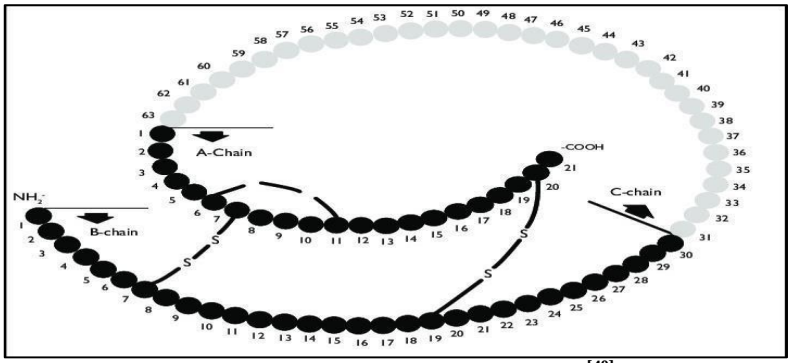


Figure 8: Insulin composing chains.[40]

When the body receives a signal that there is increase in blood glucose levels, it triggers insulin secretion from the pancreas. According to Merentek in Muhammad[41], insulin secretion depends on blood glucose levels, voltage-sensitive calcium channels, and ATPsensitive K+ channels. Increased ATP/ADP block K+ channels, causing plasma membrane depolarization. This process triggers voltage-gated Ca^{2+} channels to open, allowing Ca^{2+}influx and activating granule exocytosis.[42] The process of cellular insulin secretion can be seen in figure 9 below.

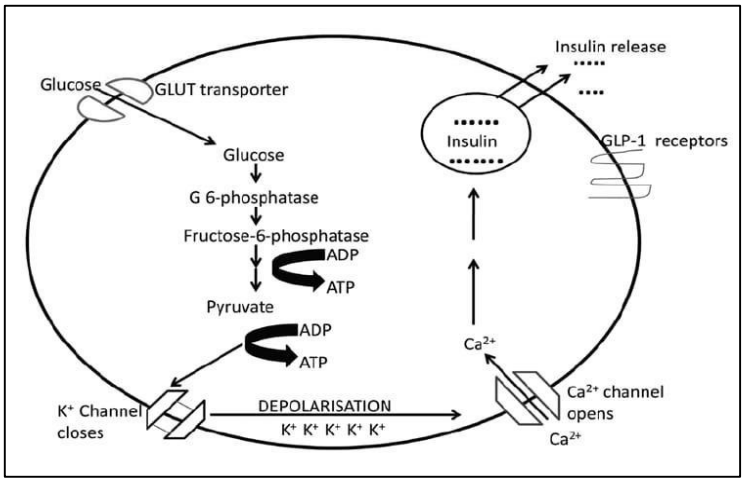


Figure 9: Cellular process of Insulin secretion.

Insulin patch technology: A transdermal insulin patch is an adhesive device consisting drug molecules, applied to the skin that delivers the correct drug dose systemically at set intervals.[43] For instance, drug transport can be blocked by large skin chemicals, thus microneedles-short (50-900µm) and thin (300µm)- were developed to penetrate the nerves painlessly. The insulin patch activates when glucose fills the artificial vesicles, where glucose oxidase converts it into gluconate. This process needs constant oxygen and may cause mild hypoxia in diabetes mellitus patients due to the hydrophobic-to-hydrophilic shift of 2nitroimidazole molecules. As a result, the artificial vesicles start to fall apart and rapidly send insulin into the bloodstream.[44]

This insulin release increases as glucose levels rise from normoglycemic to hyperglycemic. The insulin patch shows promise as a transdermal treatment for diabetes, delivering faster effects than oral or injected drugs, without causing pain.[45]

4. ANTI-INFLAMMATORY AGENT

Inflammation is the process that follows infection or tissue injury and helps maintain homeostasis but can cause tissue damage through fibroplasia, leukocytosis, and excess production of cytokines and other mediators like tumor necrosis factor-α-alpha, interleukin IL-6 and IL -8. Inflammation is also a key physical trigger of the immune response.[46] Superficial pain originates from skin and mucosal nociceptors and is often linked to inflammation and swelling.[47] The primary goal of inflammatory response is to localize and eliminate harmful agents, then remove damaged tissue to promote healing.[48]

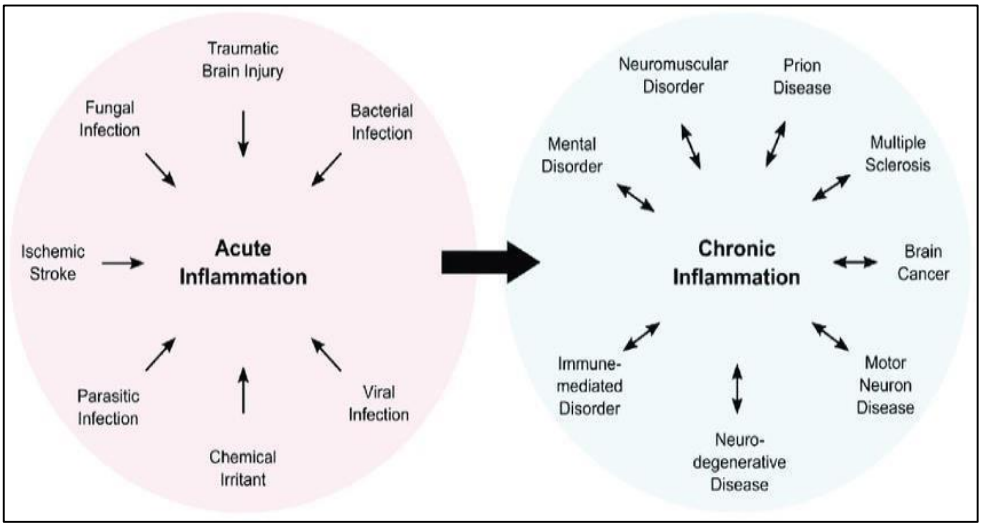


Figure 10: Causes of inflammation.

In general, non-steroidal anti-inflammatory drugs (NSAIDs) can be used to treat pain and inflammation. NSAIDs inhibit cyclooxygenase enzymes (COX-1 and COX-2), blocking thromboxanes and prostaglandins (PGE2) synthesis.[49] COX enzymes are released during pain and inflammation, while thromboxanes and PGE2 mediate allergic responses like vasoconstriction and inflammation.[50]

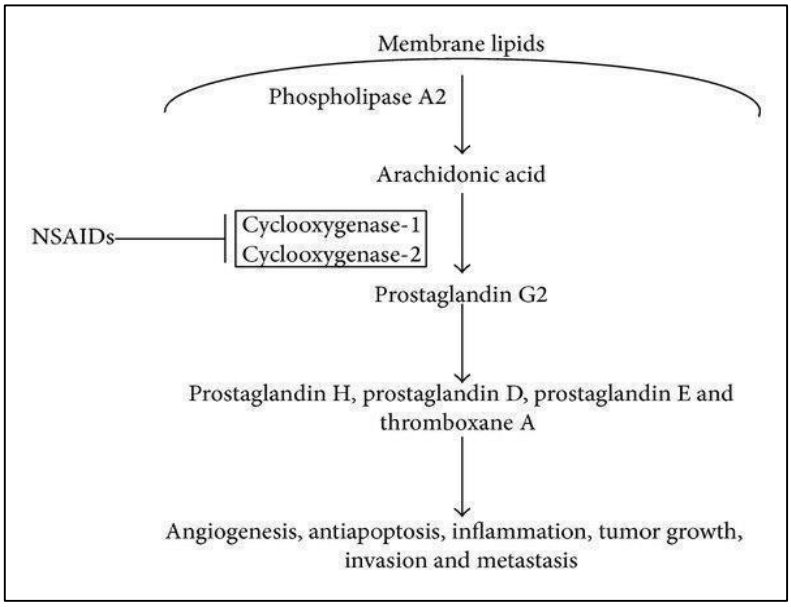


Figure 11: Mechanism of inflammation.

Transdermal drug delivery (TDD) is now a preferred alternative to oral and parenteral NSAID administration.[51] Among various advantages, one key advantage of transdermal delivery is bypassing liver metabolism and GI absorption, reducing the risk of bleeding and irritation. TDD systems deliver a controlled drug dose through the stratum corneum into the systemic circulation.[52] The drug used as anti-inflammatory agent is diclofenac sodium.

Diclofenac sodium patches using chitosan and polyvinyl alcohol (PVA) cross-linked with sodium tripolyphosphate have been shown to enhance transdermal drug permeation across rabbit skin. Diclofenac sodium patches were analysed by ultraviolet spectrophotometry, showing satisfactory physicochemical parameters. Postsurgical pain, caused by inflammation, has always been challenging for surgeons and patients; NSAIDs are commonly used to reduce this response.[53] Diclofenac sodium, an aryl acetic acid derivative, is a commonly used NSAID alone or with others.[54] It is a nonselective COX inhibitor that works by blocking the COX enzyme.[55] A benefit of transdermal medication is that it offers controlled drug release into circulation compared to other types like oral or topically.[56] The transdermal diclofenac patch (Nu Patch) is also used to relieve postoperative pain. It is applied once within 24 hours span, providing fast reliefwith minimal side effects. The patch to be used should be applied to hairless skin.[57] The patch reaches plasma levels of 20-50 ng/ml, lower than the oral routes.[58]

5. REPRODUCTIVE SYSTEM

Hormone therapy in postmenopausal women: Menopause is a biological process which causes decline of ovarian function and estradiol production, leading to follicle depletion and permanent cessation of menstruation.[59] The menopausal transition occurs naturally over years or suddenly due to ovary removal, chemotherapy, or radiational therapy. Natural menopause is confirmed after 12 months of amenorrhea, indicating near-complete ovarian hormone cessation.[60]

Declining estradiol levels during pre and post-menopause causes symptoms like hot flashes, breast tenderness, insomnia, migraines, and premenstrual dysphoria. Vasomotor symptoms (VMS) including hot flashes and night sweats, are the most common effects of menopause. Long-term estrogen loss raises the risk of cardiovascular disease, osteoporosis, and vaginal or vulvar atrophy.

For the treatment of mild VMS, lifestyle changes, alone or with nonprescription remedies, are generally the first-line treatment options [NAMS 2007]. Lifestyle modifications include keeping the environment cool, regular exercise, maintaining a healthy weight, avoiding hot foods and drinks that trigger hot flashes, and practicing relaxation techniques. Systemic hormone therapy (HT) is the standard treatment for moderate-to-severe VMS (NAMS 2007) and the only option consistently shown to significantly reduce its severity and frequency.[61,62]

All transdermal HT products share the clinical benefits of transdermal estradiol. While equivalent estradiol doses

likely offer similar efficacy across delivery systems, but differences in application and formulation may affect patient acceptance and compliance. The first transdermal HT delivery technology was the reservoir patch, featuring a drug reservoir, backing layer, and alcohol-based membrane to control drug release.[63,64] Reservoir patches offer more stable estrogen levels than oral forms but can cause local irritation in upto 46% of users.[65]

Matrix patches were the next advancement in transdermal patch technology. This design contains the active ingredients in a polymer or textile pad placed directly on the skin. This design offers more consistent drug delivery than reservoir patches. Matrix patches also tend to cause fewer skin reactions, thanks to the absence of alcohol and improved air circulation.[66] The latest advance in matrix patches is dot matrix technology, combining drug and adhesive in one layer. Dot matrix patches are smaller, thinner and offer the most consistent drug delivery with the lowest local irritation among transdermal patches.[67]

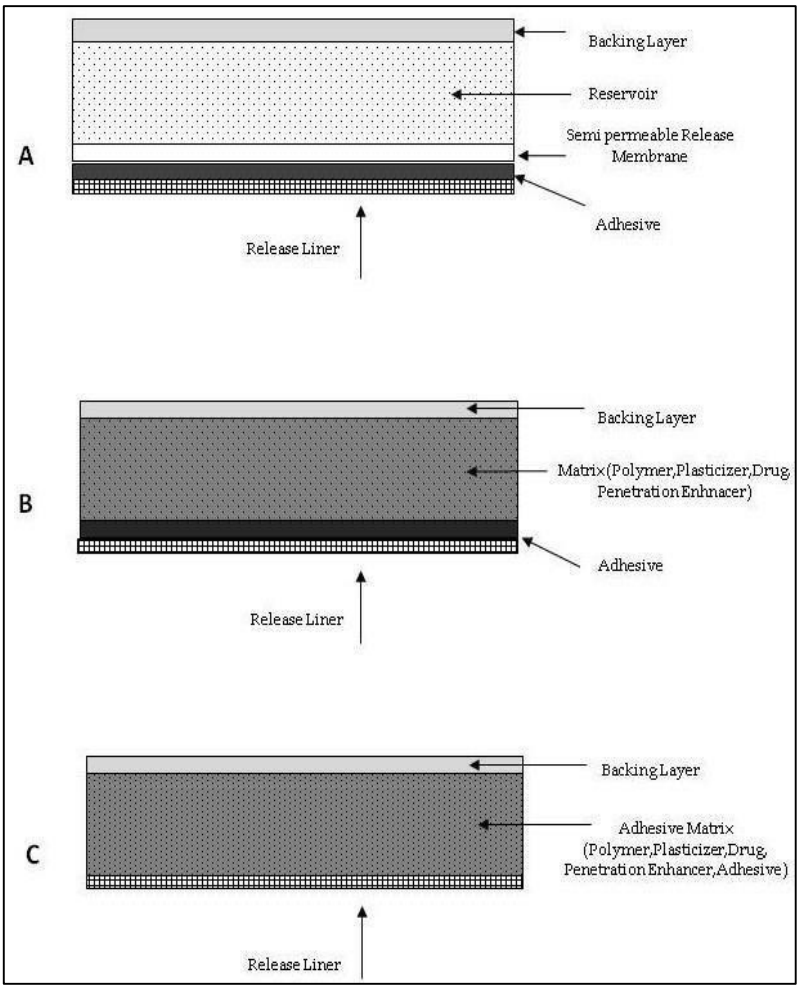


Figure 12: Modifications in HT patches. (a) Reservior patch, (b) Matrix patch, (c) Adhesive patch.

CONCLUSION

A review of TDD systems and an investigation into how 3DP can benefit drug delivery techniques are presented here. Specifically, tailored formulation approaches would be favoured as patients can move away from the 'one size fits all approach' to a more customized approach. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substances into promising deliverable drugs. The asenapine transdermal system for the treatment of adults with SZ provides a promising option for pharmaceutical treatment of both positive and negative symptoms. The advantages of transdermal delivery system include sustained release and avoidance of first-pass drug metabolism. Reduction of side effects like weight gain are another benefits of asenapine treatment. More studies are needed to address the lack of understanding surrounding the diagnosis of SZ and time of onset in relation to the efficacy of asenapine in specific patients. The brief overview of the different antihypertensive drugs revealed that, by delivering drug through the transdermal route improves bioavailability as well as improves the patient compliance by many fold. Insulin patch technology holds great potential to be utilized in treating diabetes mellitus by reducing blood glucose levels. NSAIDs may increase local soft tissue and joint concentrations and also reduces the side effects associated with oral administration. Terpenes (anethole)

along with propylene glycol and polyethylene glycol as penetration enhancers could be effective in achieving therapeutic plasma levels for AZT of the various HT options, transdermal delivery is emerging as an increasingly attractive option given for potential of an improved safety profile. Due to their lack of first-pass hepatic metabolism, transdermal products achieve clinical benefits while minimizing patient exposure to estrogens, which is consistent with the most recent clinical guidelines. The latest development in percutaneous drug delivery, estradiol transdermal spray, offers both the female patient and the clinician a unique option among the hormone therapy armamentarium for the individualized treatment of VMS due to menopause.

But the demerit is that, all the drugs cannot be given as transdermal delivery because the drug should have specific Physicochemical property which should be suited to permeate through skin. The development of success TDDS depends on proper selection of drug, polymer as well as other additives. It is possible that patients with specific epigenetic markers or mutations may respond differently to various therapies.

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