INTERNATIONAL JOURNAL OF PHARMACOLOGY AND THERAPEUTICS
eISSN 2249 – 6467

Review Article

DRUG DELIVERY TO CNS THROUGH SKIN: A NOVEL APPROACH.

Navneet Saini[1], Manoj Kumar Katual[1], Navjyot Kaur[1], Manvir Singh[1], S.L.Harikumar[2].

1-Rayat-Bahra Institute of Pharmacy, Education City, Hoshiarpur, Punjab, India.

2- University School of Pharmaceutical Sciences ,Rayat-Bahra University, Mohali,Punjab,India.

Corresponding author: - Mr. Manoj Kumar Katual

ABSTRACT

As the surface area of human outer skin is 100m2 approximate, and proved it to be the largest organ of sense of body, that can be potentially used for the delivery of multiple therapy for the successful management of neurobehavioral disorders. Various novel approaches can be introduced for which further study is essential .The focus on this route has not been in limelight till yet. Transdermal drug delivery is helpful for topical and local action of the drug. . For the patients who have difficulties swallowing solids or liquids, a transdermal drug delivery may offer great advantages over conventional delivery methods. Drug delivery directly to the brain interstitium has recently been markedly enhanced through the rational design of polymer-based drug delivery system. After the oral administration of drugs, the huge variations were associated in plasma levels with regular gastintestinal symptoms including nausea, vomiting, diarrhea, constipation, anorexia, abdominal pain and abdominal distention. This drug administration route could therefore allow optimal therapeutic dose, potentially further improving the effectiveness of treatment. The transdermal delivery bypasses the first past metabolism and lesser side effects. This route may be explored for the delivery of nano-sized pharmaceuticals to the CNS as an alternate route.

Keywords: Percutaneous route, Neurological behaviors, BBB, Nanotechnology, CNS.

INTRODUCTION

The CNS is a delicate organ, and evolution built very efficient ways to protect it. Unfortunately, the same mechanisms that protect it against intrusive chemicals can also frustrate therapeutic interventions. Many existing pharmaceuticals are rendered ineffective in the treatment of cerebral diseases due to our inability to effectively deliver and sustain them within the brain. General methods that can enhance drug delivery to the brain are, therefore, of great interest**. [1].**
Drugs are currently being developed for the treatment of serious brain disorders including glioblastoma, Parkinson's disease, and Alzheimer's disease. These include chemotherapeutic drugs and those based on neurotrophic factors such as glial cell-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and neurturin (NTN). Neurotrophic factors have therapeutic potential for neurological disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD), and administration of GDNF and NTN has shown promise in preclinical studies. Despite their safety and effectiveness in preclinical studies, success of

chemotherapeutic drugs and neurotrophic factors in clinical trials has been limited in part by the blood-brain barrier (BBB), which naturally protects the brain from potentially harmful agents**.[2]**

Blood Brain Barrier :

To maintain normal brain function, the neural environment must be preserved within a narrow homeostatic range; this requires a tight regulation of transportation of cells, molecules and ions between the blood and the brain. Such tight regulation is maintained unique anatomical and physiological barrier, formed collectively in the central nervous system (CNS). Three barrier layers contribute to the separation of the blood and neural tissues:

(1) A highly specialized endothelial cells (EC) layer comprising the blood–brain barrier (BBB) and partitioning the blood and brain interstitial fluid,

(2) The blood-CSF barrier (BCSFB) with the choroid plexus epithelium which secretes the specialized cerebral spinal fluid (CSF) into the cerebral ventricles,

(3) The arachnoid epithelium separating the blood from the subarachnoid CSF. The BBB components include the EC layer and its basement membrane, adjoined by tight cell-to-cell junction proteins with specific transport mechanisms and pinocytic vesicles. The endothe-lium is surrounded by cellular elements including pericytes**. [3]**

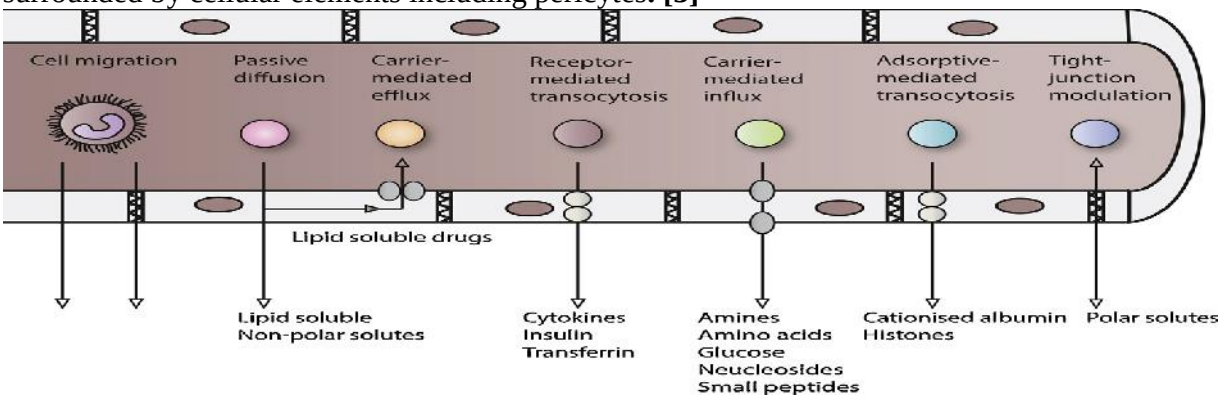


Fig.1. Potential routes for infiltration and transport across the endothelial cells of BBB.**[4]**

Cells may cross the BBB through or adjacent to the tight junctions. Solutes may passively diffuse through the cell membrane. Active efflux carriers may pump some of these passively penetrating solutes out of the endothelial cell. Carrier-mediated influx (passive or secondarily active) can transport essential polar molecules, such as amino acids, glucose and nucleosides into the CNS. Receptor-mediated transcytosis (RMT) can transport macromolecules such as peptides and proteins across the endothelium. Adsorptive-mediated transcytosis (AMT) is induced non-specifically by positivelycharged macromolecules and can result in passage across the BBB. Tight junction modulation may occur, affecting the permeability of the paracellular aqueous diffusional pathway**. [4]**

Blood to Brain Transportation:

Membrane diffusion: Many endogenous molecules and drugs diffuse through the cell membranes that comprise the BBB. Lipid solubility/hydrogen bonding correlates directly and the square root of the molecular weight inversely with the rate of passage across the BBB. However, even water soluble molecules, as exemplified by morphine and some peptides, can cross to some degree by this mechanism to induce CNS effects. Charge, protein binding, tertiary structure, or other factors can be in uential or even predominant for specific substances .Substances with molecular weights greater than about 400 ± 600 Daltons are unable to cross the BBB by membrane diffusion.

Subsequent work showed that the four substances examined by Levin with molecular weights over 400 Daltons are all substrates for the p-glycoprotein eflux system Other studies have shown that substances with molecular weights over 5000 Daltons are capable of crossing the BBB by transmembrane diffusion. As such, Levin's study illustrates the dangers of not considering eflux systems as a reason for a lower than expected penetration of the BBB. Blood to brain saturable transport: The rate of entry into the CNS is limited for large, water soluble substances unless they are transported across the BBB. The presence of a transporter typically increases the rate of entry by tenfold or more. Transport systems exist for almost every substance which the brain requires but cannot synthesize (e.g., essential amino acids, vitamins, free fatty acids, glucose, minerals, nucleic acids, and electrolytes.**[5]**

The Drug Delivery to CNS through Transdermal Drug Delivery System:

A Transdermal patch is a medicament adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. A drug is applied in a relatively high dose to the inside of a patch, which is worn on the skin for an extended period of time.Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration in the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow. **[6]**

Types of Transdermal Patches:

A. Single-layer Drug-in-Adhesive: The adhesive layer of this system contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

B. The multi-layer drug in adhesive: The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. One of the layers is for immediate release of the drug and other layer is for control release of drug from the reservoir. The multi-layer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing.

C. Reservoir: Unlike the Single-layer and Multi-layer Drug-in-adhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system the rate of release is zero order 8.

D. Matrix: The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it. Also known as a monolithic device. **[7]**

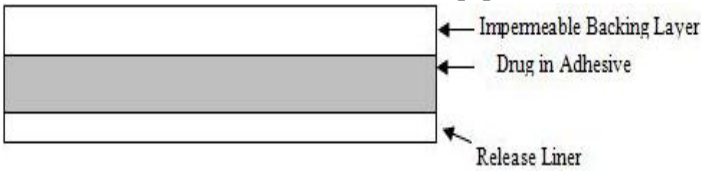


Fig. 2: Design of drug in adhesive type transdermal patch **[8]**

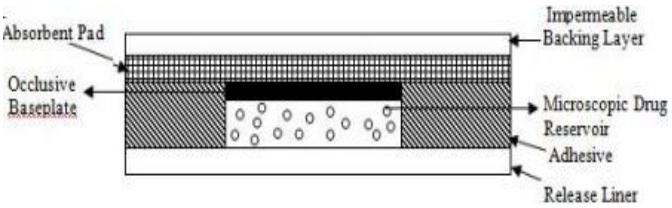


Fig. 3: Design of reservoir type transdermal patch **[9]**

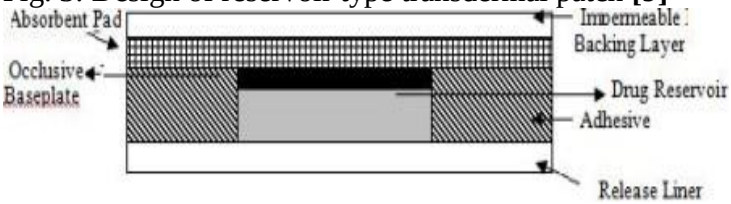


Fig.4: Design of matrix type transdermal patch **[10]**

Basic components of transdermal drug delivery systems:

1. The components of transdermal devices includes:
2. Polymer matrix or matrices.
3. The drug.
4. Permeation Enhancers.
5. Liner - Protects the patch during storage. The liner is removed prior to use.
6. Adhesive - Serves to adhere the components of the patch together along with adhering the patch to the skin.
7. Membrane - Controls the release of the drug from the reservoir and multi-layer patches.
8. Backing - Protects the patch from the outer environment.

Fig no.5: Component of transdermal patch **[11]**

Polymer matrix: The polymer controls the release of drug from the devices. The following criteria should be satisfied for a polymer to be used in a transdermal system.

a) Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that specific drug diffuses properly and gets released through it.

- The polymer should be stable.
- The polymer must be non reactive with the drug.
- The polymer can be easily manufactured.
- It can be fabricated easily into the desired product.
- It must be economic.
- The polymer and its degradation product must be non-toxic.
- They are not antagonistic to the host.
- The mechanical properties of the polymer should not deteoriate excessively when large amount of active agent or incorporated into it.

b).Polymers used in transdermal system:

A polymer is a very large organic molecule made up from many smaller molecules joined together. The small molecules are known as monomers and most polymers are made up of one or two different types of monomer.

The Drug – Drug solution in direct contact with release liner. For successfully developing transdermal delivery system, the drug should be choosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.

- .Physiochemical Properties

- The drug should have are molecular weight less than approximately 1000 Daltons.
- The drug should have affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conductive to successful drug delivery via the skin.
-The drug should have a low melting point.

- Biological Properties

-. The drug should be potent with a daily dose of the order of a few mg per day.
- The half life (t1/2) of the drug should be short.
- The drug must not induce a cutaneous or allergic response.
- Drug which degrade in the G.I tract or 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 profil of transdermal delivery.
- Drugs which have to be administered for a long period of time or which cause adverse effects to non-target tissues can also be formulated for transdermal delivery.

Permeation Enhancers: These are compounds which promotes skin permeability by altering the skin as barrier to the flux of a desired penetrant. The flux J of drugs across the skin can be written as:

J= D dc/dx,

Where, D is the diffusion coefficient and isa function of the size, shape and flexibility of the diffusing molecules as well as the membrane resistance. C is the conc. of the diffusion species. X is the spatial coordinate. The permeation enhancers may be classified under the following categories:

a. Solvents
b. Surfactants
c. Binary systems
d. Miscellaneous chemicals

Solvents**:** These compounds increased penetration possibly by swelling the polar pathway or by fluidizing lipids.

Selection criteria for the solvents**:** The solvent must be possessed following criteria:

_ The solvent must be non reactive with the drug.
_ The solvent can be easily vapourised.
_ It must be economic.
_ The solvent must be non-toxic.
_ They are not antagonistic to the host.

Examples: Water, Organic Solvents- Chloroform, methanol,ethanol, acetone etc.
Alkylmethylsulfoxides- Dimethylsulfoxides,alkylhomologs of methylsulfoxide, dimethyl acetamide and dimethylformamide.
Pyrrolidones- 2-pyrrolidone, N-methyl 2pyrrolidone.Laurocapram (azone)
Miscellaneous solvents- Propylene glycol,glycerol, silicon fluids, isopropyl palmitate.

Surfactants**:** They enhance polar pathway transport ofhydrophilic drugs. Examples: Pluronic F127.

Binary system: These systems apparently open up the heterogeneous multilaminate pathways as well as the continuous pathways. e.g: oleic acid and propylene glycol.

Miscellaneous chemicals: These mainly include urea,a hydrating and crytolytic agents .Other Excipients:

Adhesives: The adhesive must be fulfill the following criteria:

a) Should not irritate or sensitized the skin during the contact time.

b) Should adhere to the skin aggressively.

c) Its position should not be disturbed by the activities such as bathing, exercise etc.

d) Should be easily removed.

e) Should not leaved and unwashable residue on the skin.

f) Should have excellent contact with the skin at microscopic and macroscopic level.

The phase adhesive system should also fulfill the following criteria:

- Physical and Chemical compatibility of the drug, excipients and enhancers device of which it is a part.
- Permeation of drug should not be effected.
- The delivery of simple or blended permeation enhancers should not be effected.

Backing membrane: Backing membranes are:

- Flexible.
- They provide a good bond to the drug reservoir.
- Prevent drug from leaving the doses form through the top.
- It is permeable substance that protects the product during use on the skin.**[12]**

The skin:

Microscopically, the skin is a multilayered organ, composed of many histological layers.

The skin or cutaneous membrane covers the external surface of the body. It is the largest organ of the body in surface area and weight. Skin consists of two main parts, the superficial, thinner portion, which is composed, of epithelial tissue is the epidermis and dipper thicker layer Dermis.**[13]**

Drug molecules can penetrate by three pathways:

- Sweat ducts
- . Hair follicles
- Sebaceous glands Or Directly across the stratum corneum**.[14]**

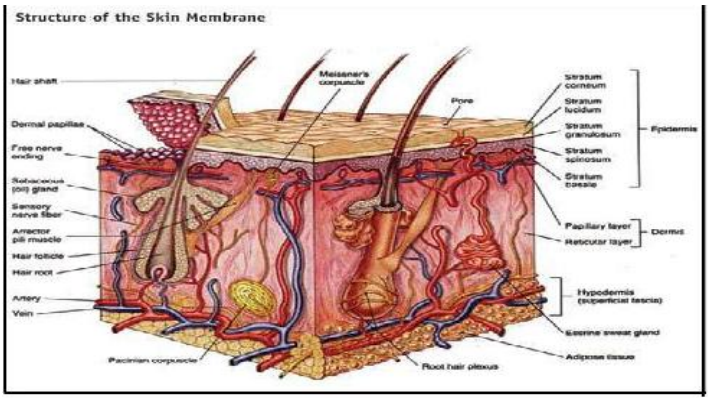


Fig no. 6: Anatomy of Human Skin **[15]**

Drug Release mechanism from transdermal Patches:

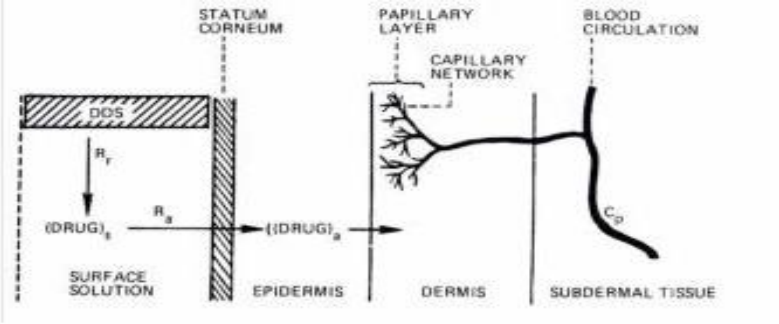


Fig no.7: Schematic representation of the relationship between the rate of drug release (Rr) from a transdermal system and the rate of release of absorption (Ra) by the skin **[16]**

General aspects to be considered for TTs

Before the drug is absorbed by the vascular network and/or lymphatic system in the dermis, it has to overcome several hurdles.

- The stratum corneum (SC), the main diffusion barrier of the skin.
- Antigen presenting cells of viable epidermis reporting to the immune system like Langerhans cells and also cells filtering UV radiation or forming a barrier against chemicals
- Immune and inflammatory cells of the dermis which react on any mechanically or chemically induced irritation, like the mast cells. If the outermost skin layer has to be interrupted by microneedles or laser beams, location of nerve endings in the dermis has to be considered as well.

In passive diffusion controlled systems the drug molecule can take different routes to cross the SC. The para- or intercellular tortuous route between the corneocytes is seen as the principal transport pathway for most lipohilic drugs. Following this route the drug has to diffuse through bilayers of ceramides, which are associated with free fatty acids (and their esters) and cholesterol. Structural properties of the paracellular lipid matrix fit the barrier needs of skin by being simultaneously robust and impermeable.Human skin has on average about 100 to 200 sweat pores/cm^2. Hair follicle density is in the same order of magnitude depending on age and region of the skin. Depending on physicochemical properties of the drug and formulation drug, uptake by this pathway may also not be negligible despite the small skin area fraction of about 0.1%.The transcellular pathway requires repeated drug partition and diffusion across structured bilayers, and seems to be usually less important.**[17]**

Different area of body to which Transdermal patch is applied:

Table 1: Regional variation of stratum corneum **[18]**

Sr.no.	Skin region	Thickness microgram.
1.	Abdomen	15.0
2.	Volar forearm	16.0
3.	Scrotum	5.0
4.	Back of hand	49.0
5.	Palm	400.0
6.	Plantar	600.0

Neurodegenerative disorders:

Neurodegenerative disorders are conditions in which cells of the brain and/or spinal cord degenerate and die. The brain and spinal cord are composed of neurons with different functions such as controlling skilled movements, processing sensory information, storage of information and making decisions. Cells of the brain and spinal cord do not usually regenerate, so damage to the nervous system can be devastating. Normally, the neurodegenerative process begins long before any symptoms appear. Neurodegenerative diseases result from deterioration of neurons or their myelin sheaths which over time will lead to dysfunction and disabilities. Neuro degenerative diseases markedly affect the lives of millions and lead to a growing public health challenge with increased costs for individuals and society. The prevention and treatment of these neurodegenerative disorders represent a critical goal of medical research today. Most of these disorders increase with age. Today, there are 25 million suffering from dementia and it is generally believed that the prevalence will be 130 million demented persons by 2050. The lack of effective treatments that can halt or reverse the disease process indicates a huge medical need. In recent years the knowledge of these disorders has moved from description of symptoms to a mechanistic understanding on a molecular level. The key molecular events in these diseases are today believed to be protein misfolding and spreading of soluble protein aggregates that lead to neuronal dysfunction, cell death, brain damage and symptoms of disease. Each neuro degenerative disease is characterised through its unique aggregated protein. The hallmark of Alzheimer's disease is ß-amyloid (Aß), whereas α-synuclein is the key protein in Parkinson's disease and Dementia with Lewy bodies (DLB). Other examples of misfolded proteins causing diseases are SOD1 in ALS (Amyotrophic Lateral Sclerosis or Lou Gehrig's disease), huntingtin in Huntington's disease, and prion proteins in Creutzfeldt-Jacob's disease. An attractive treatment strategy is to inactivate these toxic proteins. Today, there are neither cures nor effective treatments that consistently slow or halt the course of these devastating neuro degenerative diseases. Bio Arctic is committed to bring hope to people with neurodegenerative diseases and to change the future for people with Alzheimer's, Parkinson's, ALS, Huntington's, and other neurodegenerative diseases through innovative research.[**19]**

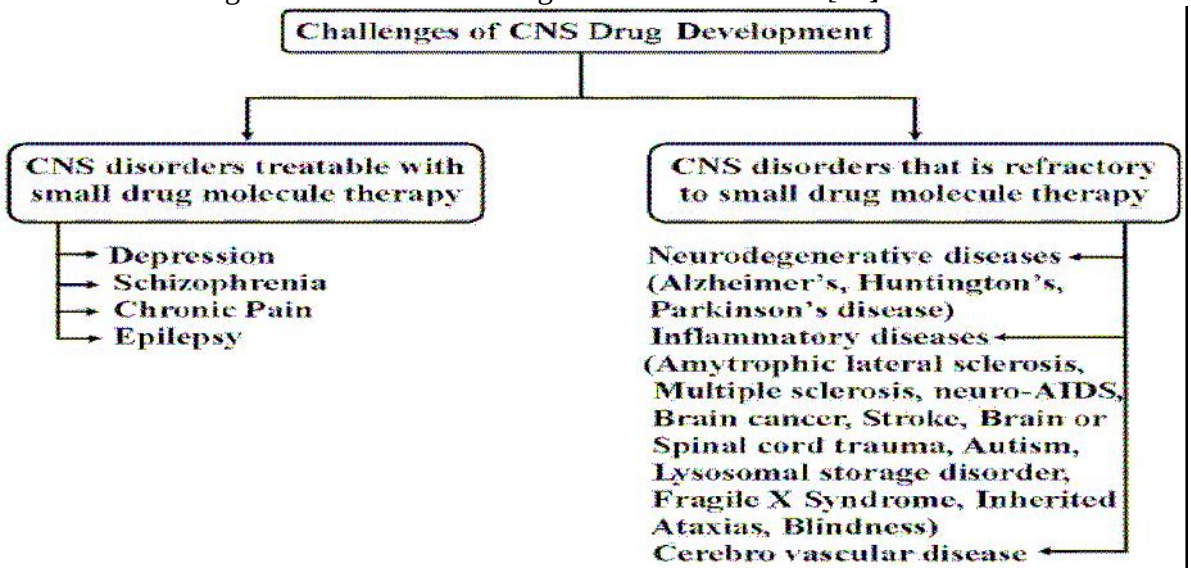


Fig no. 8: Schematic representation of challenges faced during CNS Drug development **[20]**

Parkinson's disease: Parkinson's disease (PD) is the second most common neurodegenerative disorder. The characteristic is the damage of the nigrostriatal dopaminergic systems that causes the loss of dopamine inside the brain. In, Parkinson's disease**,** the pigmented neurons of the substantial nigra, locus caeruleus, and other brain stem dopaminergic cell groups are lost. The cause of the disease is not known. Symptoms are bradykinesia, resting tremor and rigidity. PD patients also suffer from sleep disorders, neuropsychiatric issues and cognitive dysfunction. PD affects the basal ganglia.**[21]**

Alzheimer's Disease: Dementia is an overall term for diseases and conditions characterized by a decline in memory or other thinking skills that affects a person's ability to perform everyday activities. Dementia is caused by damage to nerve cells in the brain, which are called neurons. As a result of the damage, neurons can no longer function normally and may die. This, in turn, can lead to changes in one's memory, behavior and ability to think clearly. In Alzheimer's disease, the damage to and death of neurons eventually impair one's ability to carry out basic bodily functions such as walking and swallowing. People in the final stages of the disease are bed-bound and require around-theclock care. Alzheimer's disease is ultimately fatal.**[22]**

Epilepsy: An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition. An epileptic seizure is the clinical manifestation of an abnormal and excessive discharge of a set of neurons in the brain. The definition of epilepsy requires the occurrence of at least one epileptic seizure.**[23]**

Transdermal Drug Delivery System for Neuro-degenrative Disorders:

This list includes transdermal patches and delivery systems approved by the US Food and Drug Administration. The recently approved product for a given drug or drug combination administered by a given delivery method is shown:

Table No.2: Marketed Formulations Available as Transdermal Delivery System **[24]**

Drug/API	Indication	Mfg. Company	Approval year
Selegiline (Emsam)	Depression	Somerset Pharmaceuticals	Feb 2006
Rivastigmine(Exelon)	Alzheimer disease	Novartis Pharmaceuticals	July ,2007
Methylphenidate (Daytrana)	Attention deficit hyperactive disorder (ADHD)	Noven Pharmaceuticals	April, 2006
Rotigotine/Neupro	Parkinson's disease	Schwarz Pharma (Mequon, WI, USA)	2007

Ropinirole Transdermal System: is a D2 receptor agonist and acts by dopaminergic stimulation of the central and peripheral receptors to offer symptomatic relief in Parkinson's disease. Transdermal route of delivery bypasses first pass metabolism (bioavailability of ropinirole is 50%) and can achieve stable plasma levels when applied once daily. Rotigotine, another dopamine agonist, which is formulated as a patch for passive delivery offers the advantage of once daily use and prolonged effect also a patch can be withdrawn at the occurrence of side effects like nausea, dizziness, hallucinations and orthostatic hypotension associated with peripheral receptor stimulation of ropinirole hydrochloride.

limitation However, like oral administration a patch formulation limits the use to specified doses and does not allow the physician to make adjustments to the dose tailored to the needs of a patient's condition. Ropinirole, which is also a small molecular weight dopamine agonist, will face a similar challenge when administered by transdermal route. Ropinirole base is unstable; hence, formulation of a passive transdermal system is difficult.

Iontophoresis is an active enhancement technique where low current intensities are applied to the skin for topical or transdermal delivery of charged or neutral molecules. It works on the principle of electrorepulsion, i.e. like repels like and electroosmosis where neutral molecules are transported from anode to cathode along with the bulk solvent flow .A programmed iontophoretic system can allow precise and controlled delivery of therapeutic agent. Transdermal delivery of dopamine agonists like ropinirole hydrochloride, apomorphine, rotigotine and 5-OH-DPAT using iontophoresis has been studied due the advantages offered by this technique.**[25]**

Selegiline Transdermal System (EMSAM®): is a transdermally administered antidepressant. When applied to intact skin, EMSAM is designed to continuously deliver selegiline over a 24-hour period.EMSAM systems are transdermal patches that contain 1 mg of selegiline per cm2 and deliver approximately 0.3 mg of selegiline per cm2 over 24 hours. EMSAM systems are available in threesizes: 20 mg/20 cm2, 30 mg/30 cm2, and 40 mg/40 cm2 that deliver, on average, doses of 6 mg, 9 mg, or 12 mg, respectively, of selegiline over 24 hours.

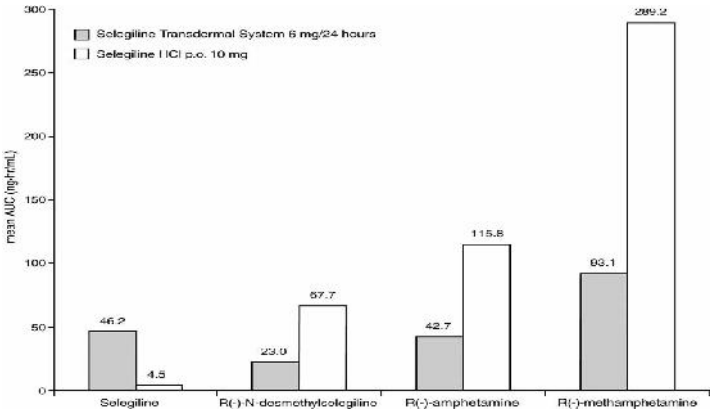


Fig No.9: Average AUCinf (ng•hr/mL) of selegiline and the three major metabolites estimated for a single, 24-hour application of an EMSAM 6 mg/24 hours patch and a single, 10 mg oral immediate release dose of selegiline HCl in 12 healthy male and female volunteers.**[26]**

NEUPRO® (rotigotine transdermal system):

NEUPRO® is a dopamine agonist indicated for the treatment of:

1. Parkinson's disease.
2. Moderate-to-severe primary Restless Legs Syndrome.

Parkinson's disease: Initially, 2 mg/24 hours for early-stage disease or 4 mg/24 hours for advanced-stage disease. The dose may be increased as needed by 2 mg/24 hours at weekly intervals, up to 6 mg/24 hours for early-stage disease and up to 8 mg/24 hours for advanced-stage disease.

Transdermal System: 1 mg/24 hours, 2 mg/24 hours, 3 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, and 8 mg/24 hours of rotigotine**.**

Table no. 3 Nominal Dose, Drug Content, and Transdermal System Size **[27]**

NEUPRO Nominal Dose	Rotigotine Content per System	NEUPRO System Size
1 mg/24 hours	2.25 mg	5 cm2
2 mg/24 hours	4.5 mg	10 cm2
3 mg/24 hours	6.75 mg	15 cm2
4 mg/24 hours	9 mg	20 cm2
6 mg/24 hours	13.5 mg	30 cm2
8 mg/24 hours	18 mg	40 cm2

Rivastigmine Transdermal system: Rivastigmine is a cholinesterase inhibitor that inhibits both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) . The efficacy of oral rivastigmine has been demonstrated in pivotal clinical trials involving more than 3000 AD patients and 500 PDD patients.Rivastigmine is a small molecule (<400 Da), and is both lipophilic and hydrophilic. These properties mean that rivastigmine can pass easily through the skin into the bloodstream as well as through the blood–brain barrier, making it well-suited to transdermal delivery. Its high potency is also advantageous since it allows a transdermal patch to be small and discreat. These properties, combined with improved patch technology, constituted the basis for the development of rivastigmine transdermal patch, the first Transdermal option for the symptomatic treatment of mild to moderate AD. The pharmacokinetic profile of the rivastigmine patch was compared to that of the rivastigmine capsule in an open-label, ascending dose study of 51 AD patients. Rivastigmine capsule was rapidly absorbed, with a median tmax of 1 h for all doses. In comparison, tmax with rivastigmine patch was reached at approximately 8 h for all patch sizes, reflecting the more gradual increase in plasma concentration with Transdermal administration.

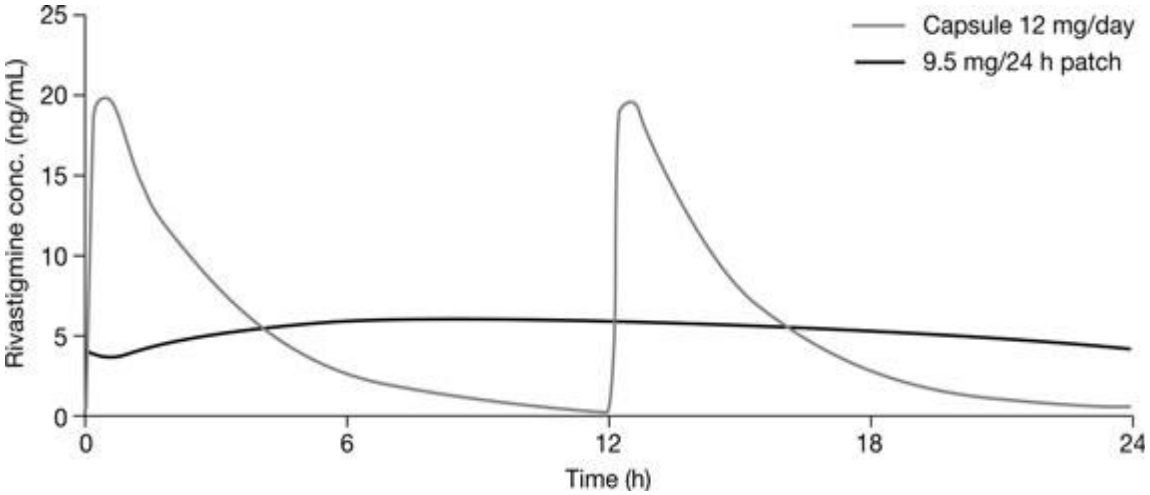


Fig No.10 Mean plasma rivastigmine levels following administration of 9.5 mg/24 h patch versus 12 mg/day capsules (adjusted for baseline weight and gender) **[28]**

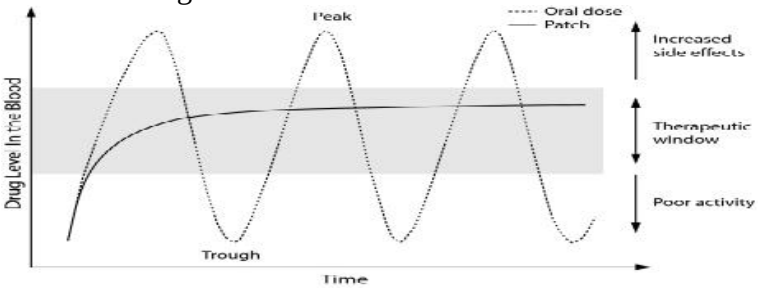
Other drugs used in neurodegenerative disorder are as follows:

Table No.4 other psychotropic drugs studied as Transdermal drug delivery system**[29]**

Drug	**Transdermal drug delivery technology**	**Category**
Aripiprazole	Reservoir Patch	Atypical antipsychotic
Haloperidol	Matrix patch	Atypical antipsychotic
Lorazepam	Matrix patch	Antianxiety
Oxazepam	Matrix patch	Anti anxiety
Clonazepam	Gel	Anti anxiety
Propranolol	Matrix patch	Antianxiety
Impramine	Gel	Antidepressant
Amitriptyline	Gel	Antidepressant

T**ransdermal versus Oral Drug Delivery System:**

The oral dosage form shows fluctuation in peak plasma concentration and there is more dosing intervals due to which there are chances of more side effects . and after some time the drug concentration goes in a sub therapeutic level.but the Transdermal drug delivery system provide a zero order drug release pattern with in a therapeutic window with lesser chances of side effects and less dosing interval.



FigNo.11 An Illustration Comparing the Pharmacokinetic Profiles of Oral and Transdermal Medications **[30]**

OBJECTIVE OF THE STUDY:

The main objective of the present work is given as follows:

1. The main objective is to gain all the background information about the drug delivery to the central nervous system through the skin.
2. To acquire the knowledge regarding the Transdermal drug delivery system, the advantages and disadvantages , the types and the method to prepare it.
3. To correlate between the Transdermal drug delivery and other dosage system.
4. To gain the knowledge regarding the MOA of the drug delivery to the CNS through Transdermal patches.
5. To know about the newer technique and advancement in the flied of drug delivery system to the CNS.
6. To know the pros and cons of the Transdermal drug delivery system in treatment.
7. To know about the various disorders of the CNS and drugs available for them.
8. To know about the various drugs available for disorder of CNS in Transdermal patches.
9. The study and work achieved so far regarding it i.e. prior art to Transdermal drug delivery.

The unsolved issue in use and the success rate by Transdermal delivery in CNS disorders.

REVIEW OF LITERATURE:

Ranendra Narayan Saha *et al* reported that drug delivery to the brain is always a challenging task for the formulation scientists because of low permeation due to presence of blood brain barrier (BBB) with tight junctions in the brain endothelial cells. Even though numerous traditional approaches such as prodrugs, disruption of blood brain barrier have shown some success to overcome these challenges, researchers are continuously working for alternatives for better delivery of drug to brain. Recent advances in nanotechnology offer an appropriate solution for the drug delivery problems associated with the brain targeted drug delivery. The present review describes various nanotechnology based formulations such as polymeric nanoparticles, solid lipid nanoparticles, liposomes, dendrimers, miscelles and nanoemulsions which have been widely used for the better delivery of the drugs across blood brain barrier. Furthermore, components of blood brain barrier, general transport mechanisms across BBB and possible mechanisms of enhanced transport of nanoformulations to the brain have been discussed in detail. Moreeover several ligand based targeted systems for the active drug delivery to the brain have also been discussed**[31]**.

Rajesh Mujoriya *et al* Since 1981, transdermal drug delivery systems have been used as safe and effective drug delivery devices. Their potential role in controlled release is being globally exploited by the scientists with high rate of attainment. If a drug has right mix of physical chemistry and pharmacology, transdermal delivery is a remarkable effective route of administration. Due to large advantages of the TDDS, many new researches are going on in the present day to incorporate newer drugs via the system**[32]**.

Saravanakumar K *et al* , studied that Transdermal drug delivery system is the system in which the delivery of the active ingredients of the drug occurs through the skin. Transdermal drug delivery can improve the therapeutic efficacy and safety of drugs because drug delivered through the skin at a predetermined and controlled rate. Skin is the important site of drug application for both local and systemic effect. The permeation of transdermal patches were crosses the skin through matrix and reservoir systems. Various techniques are available to prepare the transdermal patches such as solvent evaporation, solvent casting techniques. It provides more bioavailability when compared with the other route of administration respectively.**[33]**

Miriam Isaac *et.al* reported that Adherence to medications and dose optimization can be affected by several physiological and psychological factors such as undesirable side effects, dosing regimen, route of administration, nature of illness, belief systems and personal attributes Innovations in transdermal delivery systems (TDS) have made important contributions to medical practice by providing advances in the delivery of treatment with existing and novel drugs. TDS have significant advantages (over other routes of administration, such as providing prolonged and steadier drug levels, the ability to interrupt treatment abruptly by removing the patch and less frequent dosing. Drug delivery through skin means avoidance of gastrointestinal incompatibility and hepatic first pass metabolism, without the unpleasant and painful experiences with injections or rectal applications.**[34]**

Mark R. Prausnitz *et al* reported that The past twenty five years have seen an explosion in the creation and discovery of new medicinal agents. Related innovations in drug delivery systems have not only enabled the successful implementation of many of these novel pharmaceuticals, but have also permitted the development of new medical treatments with existing drugs. The creation of transdermal delivery systems has been one of the most important of these innovations, offering a number of advantages over the oral route. In this article, we discuss the

already significant impact this field has made on the administration of various pharmaceuticals; explore limitations of the current technology; and discuss methods under exploration for overcoming these limitations and the challenges ahead**[35]**

Chen JJ *et al* reporte that Rotigotine is a highly lipophilic dopamine-receptor agonist and the first transdermally delivered agent to demonstrate efficacy and safety as monotherapy in early Parkinson's disease and to reduce "off" hours in levodopa-treated patients with advanced Parkinson's disease. The rotigotine pharmacophore is nonergolinic and demonstrates high affinity for dopamine D(2) and D(3) receptors. With once-daily application, the patch matrix provides continuous, nonfluctuating plasma drug levels at steady state, resulting in continuous and steady plasma and brain levels and striatal dopamine-receptor stimulation. In early Parkinson's disease, doses of rotigotine up to 8 mg/24 hours demonstrate comparable efficacy to ropinirole (at doses up to 12 mg/day); in advanced Parkinson's disease, doses of rotigotine up to 16 mg/24 hours demonstrate comparable efficacy and tolerability to pramipexole (at doses up to 4.5 mg/day). In the registration trials for early and advanced Parkinson's disease, the adverse effects most commonly observed with rotigotine were minor application site reactions, dizziness, nausea, and somnolence. Doses of transdermal rotigotine can be titrated to a maintenance dose within 2-3 weeks, and the once-daily regimen minimizes complexity of therapy. The transdermal delivery system is also an advantage when nonoral administration is desired, and the 24-hour, continuous, nonfluctuating drug levels can improve early morning and nocturnal symptoms of Parkinson's disease. Thus, transdermally delivered rotigotine is a clinically innovative and useful addition to the dopamine-receptor agonist class. This review summarizes the key pharmacologic and clinical data for rotigotine and provides a focused clinical context for its use in early-to-advanced Parkinson's disease, as well as a brief summary for its role in restless legs syndrome**[36]**

Nogid A.*et al* In clinical trials, rotigotine transdermal system at doses ranging from 4.5 to 67 mg/d was associated with significant clinical benefit in patients with early and advanced PD. In 4 randomized, doubleblind, placebo-controlled trials of 6 months' duration, patients receiving rotigotine transdermal system had significant improvements on the Unified Parkinson's Disease Rating Scale (UPDRS) part II (activities of daily living) that ranged from -0.3 to -4.2, compared with +0.92 to -2 for placebo ($P < 0.001$, rotigotine transdermal system vs placebo). In one trial that included pramipexole as an active comparator, the change in UPDRS II at 6 months was -4.2 in the rotigotine transdermal system group and -4.6 in the pramipexole group (P = NS, rotigotine transdermal system vs pramipexole). Changes on the UPDRS III (motor examination) at 6 months ranged from -3.58 to -8.7 with rotigotine transdermal system, compared with +0.38 to -4.3 in the placebo group and -10.3 in the pramipexole group ($P < 0.001$ vs placebo; P = NS vs pramipexole). The change in "off" time at 6 months ranged from -2.1 to -2.7 hours with rotigotine transdermal system, compared with -0.9 hour with placebo and -2.8 hours with pramipexole ($P < 0.001$ vs placebo; P = NS vs pramipexole). The proportion of patients achieving a >30% reduction in "off" time ranged from 55.1% to 59.7% of patients receiving rotigotine transdermal system, compared with 34.5% to 35.0% of patients receiving placebo and 67.0% of patients receiving pramipexole ($P<0.001$ vs placebo; P = NS vs pramipexole). The most commonly reported adverse event was application-site reaction, occurring in 9% to 46% of patients receiving rotigotine transdermal system, compared with 5% to 13% of patients receiving placebo. Other adverse events occurring in >20% of patients receiving rotigotine transdermal system were somnolence(8%\2-33%)and nausea(12%-49%). Less than 5% of patients assigned

to rotigotine transdermal system discontinued study medication because of an adverse drug event.Present review highlights various drug delivery systems used for delivery of pharmaceutical agents mainly antibiotics, antineoplastic agents, neuropeptides, and other therapeutic substances through the endothelial capillaries (BBB) for CNS therapeutics. In addition, the use of ultrasound in delivery of therapeutic agents/biomolecules such as proline rich peptides, prodrugs, radiopharmaceuticals, proteins, immunoglobulins, and chimeric peptides to the target sites in deep tissue locations inside tumor sites of brain has been explained. In addition, therapeutic applications of various types of nanoparticles such as chitosan based nanomers, dendrimers, carbon nanotubes, niosomes, beta cyclodextrin carriers, cholesterol mediated cationic solid lipid nanoparticles, colloidal drug carriers, liposomes, and micelles have been discussed with their recent advancements. Emphasis has been given on the need of physiological and therapeutic optimization of existing drug delivery methods and their carriers to deliver therapeutic amount of drug into the brain for treatment of various neurological diseases and disorders. Further, strong recommendations are being made to develop nanosized drug carriers/vehicles and noninvasive therapeutic alternatives of conventional methods for better therapeutics of CNS related diseases. Hence, there is an urgent need to design nontoxic biocompatible drugs and develop noninvasive delivery methods to check posttreatment clinical fatalities in neuropatients which occur due to existing highly toxic invasive drugs and treatment methods.**[37]**

William A. Banks *et al* reported that The successful treatment of Alzheimer's disease (AD) will require drugs that can negotiate the blood–brain barrier (BBB). However, the BBB is not simply a physical barrier, but a complex interface that is in intimate communication with the rest of the central nervous system (CNS) and influenced by peripheral tissues. This review examines three aspects of the BBB in AD. First, it considers how the BBB may be contributing to the onset and progression of AD. In this regard, the BBB itself is a therapeutic target in the treatment of AD. Second, it examines how the BBB restricts drugs that might otherwise be useful in the treatment of AD and examines strategies being developed to deliver drugs to the CNS for the treatment of AD. Third, it considers how drug penetration across the AD BBB may differ from the BBB of normal aging. In this case, those differences can complicate the treatment of CNS diseases such as depression, delirium, psychoses, and pain control in the AD population.**[38]**

Nida akhtar *et al*, studied that With the advent of modern era of pharmaceutical dosage forms, transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. Transdermal patches are polymeric formulations which when applied to skin deliver the drug at a predetermined rate across dermis to achieve systemic effects. The number of drugs formulated in the patches has gained tremendous potential to deliver the drug via transdermal route. Controlled absorption, more uniform plasma levels, improved bioavailability, reduced side effects, painless and simple application and flexibility of terminating drug administration by simply removing the patch from the skin are some of the potential advantages of transdermal system. Numerous studies have been conducted to evaluate the potential of patches for efficacious transdermal delivery. The present review focuses on the preclinical and clinical aspects of drug delivery of various therapeutic categories through transdermal patches emphasizing enhanced safety and efficacy via these carriers**[39]**

B.W Barry *et al* Optimisation of drug delivery through human skin is important in modern therapy. This review considers drug–vehicle interactions (drug or prodrug selection, chemical potential control, ion pairs, coacervates and eutectic systems) and the role of vesicles and particles (liposomes, transfersomes, ethosomes, niosomes). We can modify the stratum corneum

by hydration and chemical enhancers, or bypass or remove this tissue via microneedles, ablation and follicular delivery. Electrically assisted methods (ultrasound, iontophoresis, electroporation, magnetophoresis, photomechanical waves) show considerable promise. Of particular interest is the synergy between chemical enhancers, ultrasound, iontophoresis and electroporation.**[40]**

Robert A. Hauser *et al* reported that Levodopa has been the mainstay of treatment for Parkinson's disease (PD) for more than 40 years. During this time,researchers have strived to optimize levodopa formulations to minimize side effects, enhance central nervous system (CNS) bioavailability, and achieve stable therapeutic plasma levels. Current strategies include concomitant treatment with inhibitors of dopa decarboxylase (DDC) and catechol-*O* - methyltransferase (COMT) to prolong the peripheral levodopa half-life and increase CNS bioavailability. Levodopa combined with DDC inhibition is the current standard method of delivering levodopa for symptomatic treatment of PD.Recent research suggests that continuous dopaminergic stimulation that more closely approximates physiological stimulation may delay or prevent the development of motor fluctuations ('wearing off') and dyskinesias. Strategies currently being used to achieve more continuous dopaminergic stimulation include the combination of an oral levodopa DDC inhibitor with a COMT inhibitor and the enteral infusion of a levodopa gel formulation. Attempt are underway to develop oral and transdermal very long-acting levodopa preparations**[41]**

Gordan MN *et al,* reported that,the comparison between te orl and Transdermal seligeline , These studies compared the dose-response effects of oral vs. transdermal selegiline on antidepressant-like activity and brain monoamine oxidase (MAO) activities in rats. Rats received selegiline by gavage (0-100 mg/kg) or via transdermal patches (0-4.8 cm2, 0-8.7 mg/kg) daily for 7 days; antidepressant-like activity was determined using the forced-swim test. Following behavioral testing, cerebral cortices were assayed for MAO-A and MAO-B activities. Doses of selegiline that selectively inhibited MAO-B (3 and 10 mg/kg/day by gavage and 0.4 mg/kg/day via patch) did not alter either immobility or latency time. However, the oral administration of 30 or 100 mg/kg/day or the transdermal administration of 8.7 mg/kg/day, doses that led to greater than 70% inhibition of MAO-A, decreased immobility time significantly. The IC50s for inhibition of MAO-A following oral and transdermal administration for 7 days were 19.8 and 1.1 mg/kg, respectively. Results indicate that both oral and transdermal selegiline have antidepressant-like activity as assessed by the forced-swim test, and that transdermal administration, which bypasses first-pass metabolism, allows for using lower doses than oral administration.**[42]**

LeWitt PA *et.al* to assess safety, tolerability, and efficacy outcomes of an overnight switch from oral ropinirole, pramipexole, or cabergoline to rotigotine, a dopaminergic agonist with transdermal delivery over 24 hours in subjects with established Parkinson disease (PD). In this open-label multicenter study, we hypothesized that the selected doses of transdermal rotigotine would provide at least equivalent antiparkinsonian actions in subjects with idiopathic PD not adequately controlled with oral ropinirole (up to 9 mg/d), pramipexole (up to 2 mg/d), or cabergoline (up to 3 mg/d). The tolerability of the rotigotine switch was evaluated by the number of subjects completing the scheduled 28-day treatment period, need for rotigotine dose reductions, and dropouts due to adverse events. Efficacy assessment relied on changes in Unified Parkinson's Disease Rating Scale from the baseline to the end of treatment in PD symptoms and subject preference of dopaminergic agonist.**[43]**

Vishal Gupta1e*t al*, reported that Drug therapy is a process for cure the patient diseases. And in this study several studies can involve such as Photodynamic therapy (PDT), Music therapy,

and Chewing gum as drug delivery system. Photodynamic therapy is a relatively new procedure used for the treatment of acne. Music has frequently been used as a therapeutic agent from the ancient times. The concept of Music Therapy is dependent on correct intonation and right use of the basic elements of music. Chewing gum is an obvious drug delivery system for local treatment of diseases in the oralcavity and in the throat, as sustaining the release of active substances may deliberately prolong exposure. **[44]**

Archana K. Gaikwad *et.al* reported that the conventional oral dosage forms have significant setbacks of poor bioavailability due to hepatic first pass metabolism. To improve characters of transdermal drug delivery system (TDDS) was emerged, which will improve the therapeutic efficacy and safety of drugs by specific sites within the body, thereby reducing both the size and number of doses. Skin is an effective medium from which absorption of the drug takes place and enters into systematic circulation over a period of time. The present article reviews the selection of drug candidates and polymers suitable to be formulated as transdermal system, advantages, disadvantages of formulation design and the methods of evaluation.**[45]**

Rahul v. Wagh *et al* reported that Transdermal Drug Delivery System is the system in which the delivery of the active ingredients of the drug occurs through the skin. Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery. Transdermal drug delivery systems (TDDS) are dosage forms involves drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation. This review article covers a brief outline of the trasdermal drug delivery system, advantages over conventional drug delivery system, Layers of the skin, various components of transdermal patch, penetration enhancers, and evaluation of transdermal system and applications of Transdermal patch.**[46]**

Jain Amit K, *et al* reported that The goal of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. Polymers are the backbone of a transdermal drug delivery sys- tem. Systems for transdermal delivery are fabricated as multi- layered polymeric laminates in which a drug reservoir or a drug–polymer matrix is sandwiched between two polymeric layers: an outer impervious backing layer that prevents the loss of drug through the backing surface and an inner polymeric layer that functions as an adhesive and/or rate-controlling membrane. To be successfully used in controlled drug delivery formulations, a material must be chemically inert andfree of leachable impurities. It must also have an appropriate physical structure, with minimal undesired aging, and be readily processable. **[47]**

Michael N Pastore1,*et al* reported that Transdermal patches are now widely used as cosmetic, topical and transdermal delivery systems. These patches represent a key outcome from the growth in skin science, technology and expertise developed through trial and error, clinical observation and evidence-based studies that date back to the first existing human records. This review begins with the earliest topical Therapies and traces topical delivery to the present-day transdermal patches, describing along the way the initial trials, devices and drug delivery systems that underpin current transdermal patches and their actives. This is followed by consideration of the evolution in the various patch designs and their limitations as well as requirements for actives to be used for Transdermal delivery. The properties of and issues associated with the use of currently marketed products, such as variability, safety and regulatory aspects, are then described. The review concludes by examining future prospects for transdermal patches and drug delivery systems, such as the combination of active delivery systems with

patches, minimally invasive microneedle patches and cutaneous solutions, including metered-dose systems.**[48]**

V. Kalvimoorthi1 *et al,* reported that The conventional oral dosage forms have some drawbacks like poor bioavailability, first pass effect, frequent dosing which may be inconvenient to patients. The transdermal drug delivery system is one of the novel drug delivery system which overcome the problems arises from conventional dosage forms. A transdermal patch is an adhesive patch that has a coating of drug, the patch is placed on the skin to deliver particular amount of drug into the systemic circulation over a period of time. This review gives valuable information about the TDDS like it advantages, disadvantages, types of TDDS,different methods for formulation of transdermal patches, different evaluation of Transdermal patches. Skin permeation enhancement techniques have been developed to improve the bioavailability the number of transdermal patches is formulated from past few decades. This painless drug delivery system is slowly gaining and will be one of the important drug deliveries in future.**[49]**

Neha D. Singh *et al* reported that The objective of this study was to investigate the effect of modulated current application using iontophoresis- and microneedle-mediated delivery on transdermal permeation of ropinirole hydrochloride. AdminPatch_ microneedles and microchannels formed by them were characterized by scanning electron microscopy, dye staining and confocal microscopy. In vitro permeation studies were carried out using Franz diffusion cells, and skin extraction was used to quantify drug in underlying skin. Effect of microneedle pore density and ions in donor formulation was studied. Active enhancement techniques, continuous iontophoresis (74.13_2.20 mg/cm2) and microneedles (66.97_10.39 mg/cm2), significantly increased the permeation of drug with respect to passive delivery (8.25_2.41 mg/cm2).Modulated iontophoresis could control the amount of drug delivered at a given time point with the highest flux being 5.12_1.70 mg/cm2/h (5–7 h) and 5.99_0.81 mg/cm2/h (20–22 h).Combination of modulated iontophoresis and microneedles (46.50_6.46 mg/cm2) showed significantly higher delivery of ropinirole hydrochloride compared to modulated iontophoresis alone (84.91_9.21 mg/cm2). Modulated iontophoresis can help in maintaining precise control over ropinirole hydrochloride delivery for dose titration in Parkinson's disease therapy and deliver therapeutic amounts over a suitable patch area and time**[50]**

Sravanthi Anampally *et al*: reported that Ropinirole free based used as the drug entity was prepared from its hydrochloride salt. Suitability of the polymers in the form of drug-excipient compatability was determined prior to formulation development using FTIR. Patches were developed usingsolvent evaporation technique. Limonene was used as a penetration enhancer. Moisture absorption, moisture content and mechanical properties, drug content, *in vitro* drug release, drug-excipient compatibility, *in vitro* skin permeation were the *in vitro* parameters measured. Short-term stability, skin irritation and *in vivo* drug release were measured with one optimized formulation. Results and discussion:Ropinirole free base was used successfully in the preparation of the patches. FTIR studies indicated no interaction between the drug and the polymers of this study. Formulations developed were strong and not brittle with uniform drug release. Patches containing higher HPMC generally showed higher drug release and permeation. Drug release and permeation decreased with increase in the concentrations of Eudragits. Drug release studies indicated Higuchi model for all the patches with a diffusion mechanism of non-fickian type.Short-term stability studies indicated that ropinirole was stable in the patches. Patches did not cause any skin irritation. *In vivo* the optimized patch sustained drug release for

24 hours upon one time administration. Conclusion: Clinically viable ropinirole Transdermal patch can be successfully prepared from its base form using HPMC/Eudragits.**[51]**

I˙smail tuncer degˇ i˙m, *et al* reported that Bromocriptine (BRC) has been mainly used for the inhibition of lactation, treatment of menstrual disorders, Parkinson disease, breast tumours, infertility and brain tumours as a dopamine agonist in clinics. BRC formulations have some side effects and bioavailability problems because of hepatic first pass effect. Transdermal application could be an alternative route to overcome all these problem and penetration properties of BRC has not been studied yet. Therefore, it was aimed to investigate the effectiveness of transdermal formulation of BRC which is applicable to the skin. For this purpose, a number of BRC gel formulations (Carbopol-934 (C- 934), chitosan (CH) and Gantrez-SP215 (G-SP215) were developed and the effectiveness and bioavailability of the formulations were compared in rabbits. Commercial BRC tablets (Parlodel®) were also But current given to rabbits orally and plasma levels were compared. The effects of two different penetration enhancers, sodium taurocholate (ST) and ethoxydiglycol-Transcutol® (TR) on the BRC penetration were also investigated. The skin samples from the dorsal part of the rabbit were removed after CH gel application and investigated under electron microscope to understand the effects of the gel on the penetration and the possible penetration mechanisms through skin were also discussed. In conclusion, CH gel formulation was found to be the best formulation and comparable blood BRC concentrations were obtained when applied to the rabbit skin. Higher blood levels were obtained with the use of CH. The main penetration process was found to be through transcellular route but some other mechanisms were also found to be incorporated, after microscopic investigation. CH gel was found to be a useful carrier for BRC administration through dermal route and the penetration enhancing effect and the mechanism of CH gel were first established in this study. It was concluded that transdermal delivery of BRC may be a very promising alternative route to the oral route for the treatment**[52]**

Seema ArkvAnshi et al reported that As skin is a readily accessible organ of the body, it acts as the portal of entry for extraneous substances for their effective transdermal delivery.Possessing various advantages, it has the limitation of low permeability of drugs across it, limiting the efficacy of drugs. Therefore, various carrier systems have been developed to enhance the permeation deep into the systemic circulation. The potential of using the intact skin as the portal for drug administration to the human body has been recognized for several decades. With the advent of modern era of pharmaceutical dosage forms,transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. Transdermal patches are polymeric formulations which when applied to skin deliver the drug at a predetermined rate across dermis to achieve systemic effects. The number of drugs formulated in the patches has gained tremendous potential to deliver the drug via transdermal route. Controlled absorption, more uniform plasma levels, improved bioavailability, reduced side effects, painless and simple application and flexibility of terminating drug administration by simply removing the patch from the skin are some of the potential advantages of transdermal system. Numerous studies have been conducted to evaluate the potential of patches for efficacious transdermal delivery. The present review focuses on the preclinical and clinical aspects of drug delivery of various therapeutic categories through transdermal patches emphasizing enhanced safety and efficacy via these carriers.**[53]**

Cummings J *et al,*reported that the dual cholinesterase inhibitor rivastigmine is approved in capsule form in many countries for the symptomatic treatment of dementia associated with Alzheimer disease (AD) and Parkinson disease (PD). All orally administered cholinesterase

inhibitors are associated with central cholinergic gastrointestinal side effects, particularly during the titration phase, which are believed to be caused by a rapid increase in brain acetylcholine levels after effective inhibition of the target enzymes. A recently developed rivastigmine transdermal patch may have the potential to reduce such side effects. Pharmacokinetic studies have shown that transdermal administration of rivastigmine prolongs t(max), lowers C(max), and reduces fluctuations in plasma concentration. The 10-cm(2) rivastigmine patch provides comparable exposure (area under the curve, AUC) to the highest capsule dose (6-mg BID) and may be the target maintenance dose for most patients, delivering optimal rivastigmine exposure to produce a therapeutic effect. The potential of a patch to improve the tolerability of rivastigmine (e.g., nausea and vomiting) while permitting similar exposure to the highest doses of capsules may, in turn, lead to improved efficacy and compliance**.[54]**

A. Kurz *et al,* reported that the 9.5 mg ⁄ 24 h rivastigmine patch was shown to provide comparable exposure to the highest recommended doses of capsules (12 mg ⁄ day) with significantly lower maximum plasma concentration (Cmax 8.7 vs. 21.6 ng ⁄ ml) and slower absorption rate (tmax 8.1 vs. 1.4 h). In a clinical trial of 1195 AD patients, this translated into similar efficacy with three times fewer reports of nausea and vomiting (7.2% vs. 23.1%, and 6.2% vs. 17.0% respectively). Consequently, more patients in the 9.5 mg ⁄ 24 h patch group achieved their target therapeutic dose at the end of the study, compared with those in the 12 mg ⁄ day capsule group (95.9% vs. 64.4%). The rivastigmine patch provides continuous drug delivery over 24 h and similar efficacy to the highest recommended dose of oral rivastigmine with improved tolerability. This may allow patients to achieve optimal therapeutic doses and to benefit from a longer duration of treatment**.[55]**

Oertel W *et.al* , reported that transdermal patches are used for the treatment of various diseases including neurologic and psychiatric disorders such as Parkinson disease (PD), major depression, and attention deficit hyperactivity disorder. They are believed to offer many advantages over conventional oral therapies. By providing smoother, continuous drug delivery and steadier plasma levels, patches may reduce the incidence of side effects, thus making optimal therapeutic doses easier to attain and potentially improving treatment efficacy and compliance. Drug delivery systems such as patches that are more patient- and caregiver-friendly may enable patients to continue treatment for longer periods and to attain greater, more sustained treatment benefits. To date, approved therapies for Alzheimer disease (AD), including cholinesterase inhibitors and memantine, are orally administered. Potential advantages associated with patches provide a therapeutic rationale to offer additional benefits in AD patients. Rivastigmine is well suited to patch administration because it is a small, potent molecule that is both lipophilic and hydrophilic. A rivastigmine patch has been developed and may provide a promising new approach to dementia therapy**.[56]**

Chan AL *et.al* , reported that there is increasing interest in the potential of transdermal drug delivery systems for the treatment of neurological disorders, especially in the elderly. In this population, the higher incidence of chronic diseases, such as diabetes mellitus, cardiovascular disease, neurological disease and chronic pain, has dramatically increased the need for long-term medications. Additionally, elderly patients often have a combination of several chronic diseases, meaning drug delivery, drug-drug interactions, absorption/blood concentrations, toxicity and compliance are of concern for patients as well as for their caregivers and physicians. Recent efforts have focused on developing pharmaceutical preparations that overcome these issues. For example, rate-controlled drug delivery systems have been under active development. Transdermal drug delivery systems have been developed to deliver phenserine, rivastigmine,

nicotine and estradiol for the management of cognitive and behavioural dysfunctions in patients with Alzheimer's disease because this form of administration has several advantages, including maintenance of sustained therapeutic plasma concentrations of drugs, easy application and reduced systemic adverse effects. Thus, transdermal drug delivery for elderly patients offers promise as the ideal therapeutic approach to treating Alzheimer's disease.This article reviews the technical principles underlying the development of transdermal drug delivery systems, focusing on cholinesterase inhibitors, and the prospects for future development. The clinical performance of transdermal patches, again with emphasis on cholinesterase inhibitors, is also reviewed.**[57]**

Miriam Isaac *et al*, reported that adherence to prescribed psychiatric and nonpsychiatric medication is a serious issue in people with mental illness that can contribute to poor health outcomes. Some of the factors influencing adherence include side effects of medication and the ease of use. With mental healthcare provision increasingly focusing on a community model of health delivery, there seems to be a renewed interest in addressing complex dilemmas of safety and adherence to treatment. The use of alternative methods of safely delivering medication in innovative ways may resolve some of these difficulties. There has been little discussion about the wider use of transdermal patches in the field of psychiatry in published literature. This article describes the findings from the literature on key principles underlying Transdermal delivery strategies, the scope of clinical use in psychiatric illness and explores its challenges and advantages.**[58]**

Ball AM *et al,* reported that Transdermal drug delivery capitalizes on an attractive route of drug delivery, as it avoids the need for painful i.v. drug administration, i.v. site access, and syringe disposal and is an option for drug delivery to patients who are unable to swallow oral medications. Specific transdermal drug designs have advantages and disadvantages, including the ability to alter the patch size or readily manipulate the products. Transdermal drug delivery systems currently available include drug reservoir and microreservoir membrane-modulated systems, drug-in-adhesive layer designs, and matrix patches. Maximizing patient response to transdermal drug formulations may also rely on a number of other practical concerns, including patient dexterity, dose reproducibility, storage and stability of the remaining portion, and decreased adhesive efficacy. Adhesives in transdermal precuts may be locally irritating, and prolonged use and high dosages have resulted in dermatological reactions to some patches. Patients may also develop contact sensitization or systemic sensitization to the transdermal formulation itself. When a transdermal product regimen is initiated, caregivers should be mindful of the product's primary features and educate patients accordingly, specifically addressing where and how to apply the patch, duration of patch use, and procedures for properly changing and storing patches.**[59]**

ChellanVijayaRaghavan *et al*`reported that Alzheimer’s disease (AD) is the most common neurodegenerative disorder characterized by memory dysfunction, loss of lexical access spatial and temporal disorientation. The targeted drug delivery to the central nervous system for the diagnosis and treatment is restricted due to the presence of blood brain barrier (BBB). Recent advances in nanotechnology have provided solutions for delivering drugs across blood brain barrier. Various approaches like liposomes, polymeric nanoparticles, solid lipid nanoparticles, quantum dots, dendrimers, nanogels are available to target the drugs across BBB. Recently surface modified nanocarriers can be used to target the drugs to BBB. Therefore, the present review focuses on surface modified polymeric nanocarriers to cross BBB including dug transport of functionalised nanocarriers via receptor mediated targeting as well as *in vitro* model to cross the BBB.**[60]**

Vaibhav Rastogi *et al* Transdermal drug delivery system (TDDS) is one of the systems lying under the category of controlled drug delivery, in which the aim is to deliver the drug through the skin in a predetermined and controlled rate. It has various advantages, like prolonged therapeutic effect, reduced side-effects, improved bioavailability, better patient compliance and easy termination of drug therapy. The stratum corneum is considered as the rate limiting barrier in transdermal permeation of most molecules.There are three main routes of drug penetration, which include the appendageal, transcellular and intercellular routes. Skin age, condition, physicochemical factors and environmental factors are some factors that are to be considered while delivering drug through this route. Basic components of TDDS include polymer matrix, membrane, drug, penetration enhancers, pressuresensitive adhesives, backing laminates, release liner, etc. Transdermal patches can be divided into various systems like reservoir system, matrix system and micro-reservoir system, which are used to incorporate the active ingredients into the circulatory system via the skin. After preparation of transdermal patches, consistent methodology are adopted to test the adhesion properties, physicochemical properties, *in vitro* drug release studies, *in vitro* skin permeation studies, skin irritation studies and stability studies. According to the duration of therapy, various drugs are commercially available in the form of transdermal patches.**[61]**

Kalpana S Paudel *et al* reported that Transdermal drug delivery is an exciting and challenging area. There are numerous transdermal delivery systems currently available on the market. However, the transdermal market still remains limited to a narrow range of drugs. Further advances in transdermal delivery depend on the ability to overcome the challenges faced regarding the permeation and skin irritation of the drug molecules. Emergence of novel techniques for skin permeation enhancement and development of methods to lessen skin irritation would widen the transdermal market for hydrophilic compounds, macromolecules and conventional drugs for new therapeutic indications. As evident from the ongoing clinical trials of a wide variety of drugs for various clinical conditions, there is a great future for transdermal delivery of drugs.**[62]**

Vijay S Jatav1 *et al,* reported that transdermal administration of drugs is an another way of administration that can significantly deliver larger molecules in potent quantities that overcome the problem with the oral administration such as poor bioavailability due to first pass metabolism and sometimes responsible for rapid blood level. Drugs that are given by transdermal route may enhance the potency as well as safety of drugs. One such advance has been the development of transdermal patch delivery systems. Transdermal drug technology specialists are continuing to search for new methods that can effectively and painlessly deliver larger molecules in therapeutic quantities to overcome the difficulties associated with the oral route. Transdermal drug delivery system is the system in which the delivery of the active ingredients of the drug occurs by the means of skin. Skin is an effective medium from which absorption of the drug takes place and enters the circulatory system. Various types of transdermal patches are used to incorporate the active ingredients into the circulatory system via skin. The patches have been proved effective because of its large advantages over other controlled drug delivery systems. New transdermal drug delivery system (TDDS) technologies now have been developed that is considered to be helpful in rate controlled delivery of drug that is difficult to administer**.[63]**

Harneet Marwah *et al* , reported that today, _74% of drugs are taken orally and are not found to be as effective as desired.To improve such characteristics, transdermal drug delivery was brought to existence. This delivery system is capable of transporting the drug or macromolecules painlessly through skin into the blood circulation at fixed rate. Topical administration of

therapeutic agents offers many advantages over conventional oral and invasive techniques of drug delivery. Several important advantages of transdermal drug delivery are prevention from hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. Human skin surface, as a site of drug application for both local and systemic effects, is the most eligible candidate available. New controlled transdermal drug delivery systems (TDDS) technologies (electrically-based, structure-based and velocity-based) have been developed and commercialized for the transdermal delivery of troublesome drugs. This review article covers most of the new active transport technologies involved in enhancing the Transdermal permeation via effective drug delivery system.**[64]**

Su Y *et al,* reported that the development of drugs that act in the CNS has been significantly impeded by the difficulty of delivering them across the blood-brain barrier (BBB). This article aims to provide the reader with a critical overview of important issues in the discovery and development of drugs that need to enter the brain to elicit pharmacological activity, focusing particularly on i) the role of drug transporters in brain permeation and how to manipulate them to enhance drug brain bioavailability; ii) the successful application, limitations and challenges of commonly used in vitro and in vivo methodologies for measuring drug transport across the BBB, and iii) a discussion of recently developed strategies (e.g., modulation of efflux transporters by chemical inhibitors and the employment of delivery vectors taking advantage of native transport systems at the BBB) for facilitating drug penetration into the brain**.[65]**

William A *et al* reported that banks substances cross the blood-brain barrier (BBB) by a variety of mechanisms. These include trans-membrane diffusion, saturable transporters, adsorptive endocytosis, and the extracellular pathways. Here, we focus on the chief characteristics of two mechanisms especially important in drug delivery: transmembrane diffusion and transporters. Transmembrane diffusion is non-saturable and depends, on first analysis, on the physicochemical characteristics of the substance. However, brain-to-blood efflux systems, enzymatic activity, plasma protein binding, and cerebral blood flow can greatly alter the amount of the substance crossing the BBB. Transport systems increase uptake of ligands by roughly 10-fold and are modified by physiological events and disease states. Most drugs in clinical use to date are small, lipid soluble molecules that cross the BBB by transmembrane diffusion. However, many drug delivery strategies in development target peptides, regulatory proteins, oligonucleotides, glycoproteins, and enzymes for which transporters have been described in recent years. We discuss two examples of drug delivery for newly discovered transporters: that for phosphorothioate oligonucleotides and for enzymes**.[66]**

Robert W. Lee *et al* reported that the principal driving force behind transdermal flux is the concentration gradient. An in vitro Franz cell study was conducted using human cadaver skin to compare the relative flux rates obtained for Estrasorb (containing about 9% w/w ethanol), a commercial estradiol gel (containing about 40% w/w ethanol), and a 100% ethanolic solution of estradiol (Figure 2.8). The three formulations were applied on the skin at equivalent estradiol concentrations and the concentration of drug that permeated across the skin into the donor compartment was measured as a function of time. The results indicated that there was no significant difference between the 100% ethanolic solution and Estrasorb – while the gel exhibited one-fourth the rate of drug transfer of Estrasorb. This supports the claim that the composition of the MNP formulation promotes improved product–skin interactions and drives the API more efficiently across the skin – in a comparable fashion to a pure drug solution**.[67]**

Himanshu Gupta *et al,* reported that There are many ways to deliver drugs into the body, viz oral (through swallowing), sub mucosal (through buccal and sublingual mucosa), parenteral

(through injection), transdermal (through skin), pulmonary (through inhalation) etc. Among these deliveries oral delivery (by swallowing) is widely accepted. In oral drug delivery, many scientific challenges and breakthrough technologies are required to generate novel dosage forms raising drug delivery to higher level. Some are self emulsifying systems, solid self nanoemulsion, polymeric micelles, spray freezing, pH controlled systems, time delayed system, osmotic pumps, prodrugs etc. This paper reviews recent patents, technologies and products with their importance, manufacturing and novel approaches implemented till date to overcome the challenges in oral drug delivery systems.**[68]**

Sandeep Karki *et al* reported that **,**Pharmaceutical scientists throughout the world are trying to explore thin films as a novel drug delivery tool. Thin films have been identified as an alternative approach to conventional dosage forms. The thin films are considered to be convenient to swallow, self administrable, and fast dissolving dosage form, all of which make it as a versatile platform for drug delivery. This delivery system has been used for both systemic and local action *via* several routes such as oral, buccal, sublingual, ocular, and transdermal routes. The design of efficient thin films requires a comprehensive knowledge of the pharmacological and pharmaceutical properties of drugs and polymers along with an appropriate selection of manufacturing processes. Therefore, the aim of this review is to provide an overview of the critical factors affecting the formulation of thin films, including the physico-chemical properties of polymers and drugs, anatomical and physiological constraints, as well as the characterization methods and quality specifications to circumvent the difficulties associated with formulation design. It also highlights the recent trends and perspectives to develop thin film products by various companies**.[69]**

Bhalekar R. Mangesh *et al* ,reorted that Piroxicam is class II drug and has low oral bioavailability owing to low aqueous solubility. Long-term administration of piroxicam is reported to produce gastrointestinal toxicity. The objective of this study was to improve the permeation of piroxicam by incorporating as piroxicam loaded solid lipid nanoparticles (pirox-SLNs) into a transdermal patch. Method: Pirox-SLN's (average particle size 248.87 ± 6.481 nm and entrapment efficiency 84.48% ± 1.08%) upon optimization, were prepared by pre-emulsion sonication method and were incorporated into ethyl cellulose and polyvinyl pyrrolidone matrix patch prepared by solvent evaporation method. Results& Discussion: The prepared transdermal patches were evaluated for thickness, weight variation, flatness, folding endurance, and drug content which were found to 0.31 ± 0.04 mm, 0.17 ± 0.03 g, 99.5% ± 0.3%, 35 ± 1.34 and 95.74 ± 0.4, respectively. *Ex-vivo* skin permeation of the prepared formulation was studied on rat skin and the drug release from patch incorporated with SLNs was found 66.6% up to 24 h, significantly less as compared to plain piroxicam patch having release of 88.01%, however, the slow release from the SLN patch was attributed due to slow release of the drug from SLN. *Ex-vivo* skin permeation studies on pirox-SLN containing patches showed satisfactory flux (17.16 µg/cm2/h) compared with that of plain piroxicam patches (4.6 µg/cm2/h). The skin irritation test showed that the prepared transdermal patch were free of skin irritants. Conclusion: It was concluded that SLN's can be successfully used as a carrier for enhancing transdermal permeation of piroxicam and thus the bioavailability.**[70]**

Chellan Vijaya Raghavan *et al,* reported that Alzheimer's disease (AD) is the most common neurodegenerative disorder characterized by memory dysfunction, loss of lexical access spatial and temporal disorientation. The targeted drug delivery to the central nervous system for the diagnosis and treatment is restricted due to the presence of blood brain barrier (BBB). Recent advances in nanotechnology have provided solutions for delivering drugs across blood brain

barrier. Various approaches like liposomes, polymeric nanoparticles, solid lipid nanoparticles, quantum dots, dendrimers, nanogels are available to target the drugs across BBB. Recently surface modified nanocarriers can be used to target the drugs to BBB. Therefore, the present review focuses on surface modified polymeric nanocarriers to cross BBB including dug transport of functionalised nanocarriers via receptor mediated targeting as well as *in vitro* model to cross the BBB**.[71]**

Vijay K Ramanan *et al* reported that The discovery of causative genetic mutations in affected family members has historically dominated our understanding of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal dementia (FTD), and amyotrophic lateral sclerosis (ALS). Nevertheless, most cases of neurodegenerative disease are not explained by Mendelian inheritance of known genetic variants, but instead are thought to have a complex etiology with numerous genetic and environmental factors contributing to susceptibility. Although unbiased genome-wide association studies (GWAS) have identified novel associations to neurodegenerative diseases, most of these hits explain only modest fractions of disease heritability. In addition, despite the substantial overlap of clinical and pathologic features among major neurodegenerative diseases, surprisingly few GWAS-implicated variants appear to exhibit cross-disease association. These realities suggest limitations of the focus on individual genetic variants and create challenges for the development of diagnostic and therapeutic strategies, which traditionally target an isolated molecule or mechanistic step. Recently, GWAS of complex diseases and traits have focused less on individual susceptibility variants and instead have emphasized the biological pathways and networks revealed by genetic associations. This new paradigm draws on the hypothesis that fundamental disease processes may be influenced on a personalized basis by a combination of variants – some common and others rare, some protective and others deleterious – in key genes and pathways. Here, we review and synthesize the major pathways implicated in neurodegeneration, focusing on GWAS from the most prevalent neurodegenerative disorders, AD and PD. Using literature mining, we also discover a novel regulatory network that is enriched with AD- and PD-associated genes and centered on the SP1 and AP-1 (Jun/Fos) transcription factors. Overall, this pathway- and network-driven model highlights several potential shared mechanisms in AD and PD that will inform future studies of these and other neurodegenerative disorders**.[72]**

Ravi Kant Upadhyay *et al* reported that the use of ultrasound in delivery of therapeutic agents/biomolecules such as proline rich peptides, prodrugs, radiopharmaceuticals, proteins, immunoglobulins, and chimeric peptides to the target sites in deep tissue locations inside tumor sites of brain has been explained. In addition, therapeutic applications of various types of nanoparticles such as chitosan based nanomers, dendrimers, carbon nanotubes, niosomes, beta cyclodextrin carriers, cholesterol mediated cationic solid lipid nanoparticles, colloidal drug carriers, liposomes, and micelles have been discussed with their recent advancements. Emphasis has been given on the need of physiological and therapeutic optimization of existing drug delivery methods and their carriers to deliver therapeutic amount of drug into the brain for treatment of various neurological diseases and disorders. Further, strong recommendations are being made to develop nanosized drug carriers/vehicles and noninvasive therapeutic alternatives of conventional methods for better therapeutics of CNS related diseases. Hence, there is an urgent need to design nontoxic biocompatible drugs and develop noninvasive delivery methods to check posttreatment clinical fatalities in neuropatients which occur due to existing highly toxic invasive drugs and treatment methods**.[73]**

Roberto Bernabei1 *et al* ,reported that The incidence of dementia syndromes such as Alzheimer's disease (AD) or Parkinson's disease dementia (PDD) increases with age: approximately 10% of people over the age of 65 years may develop AD,5 and dementia has been reported in as many as 80% of older PD patients (mean age 73 years).These dementia syndromes are characterised by a progressive deterioration of cognition and the emergence of behavioural and psychological symptoms and functional decline, which makes conducting everyday tasks increasingly challenging. Cholinesterase inhibitors such as rivastigmine, donepezil and galantamine – which have been widely available in oral formulations – and memantine form the mainstay of treatment for AD. Currently, rivastigmine is the only treatment approved for the treatment of mild to moderate PDD. However, due to the multitude of risk factors that individuals with dementia face, i.e. typically being older, with co-morbidities, high medication burden and memory deficits, this patient population is especially vulnerable to treatment non-compliance. Transdermal patches provide smooth and continuous drug delivery across the skin barrier and into the bloodstream. They have the potential to provide more gradual rises in maximal plasma concentration (Cmax) and to prolong the time to Cmax (tmax), thus avoiding the rapid rise and fall of concentrations seen with oral therapies.**[74]**

Gagan Hans,*et al* reported that Psychiatric comorbidity was present in 47% of the studied patients. There was predominance of Major Depressive Disorder and the Adjustment Disorder, both of which constituted approximately 80% of the total diagnoses. Major Depressive Disorder was the most common psychiatric disorder followed by Adjustment Disorder, present in 41.5% and 39.4% of the patients. A large number of the cancer patients were found to be unaware of their diagnosis. The knowledge about the cancer diagnosis significantly increased the chances of developing a psychiatric disorder in the patients. The p-value of the comparison between the "aware" and the "unaware" patients for the presence of the psychiatric comorbidity was significant (0.005). Over all, findings indicate strong and immediate relationship between the diagnosis of cancer and psychiatric comorbidity as also between the awareness of the cancer diagnosis and psychiatric comorbidity.**[75]**

Inayat Bashir Pathan *et al* reported that Skin as an important site of drug application for both local and systemic effects. However in skin, the stratum corneum is the main barrier for drug penetration. Penetration enhancement technology is a challenging development that would increase the number of drugs available for transdermal administration. The permeation of drug through skin can be enhanced by both chemical penetration enhancement and physical methods. In this review, we have discussed the chemical penetration enhancement technology for transdermal drug delivery as well as the probable mechanisms of action.**[76]**

Vaibhav Rastogi *et al* reported that Transdermal drug delivery system (TDDS) is one of the systems lying under the category of controlled drug delivery, in which the aim is to deliver the drug through the skin in a predetermined and controlled rate. It has various advantages, like prolonged therapeutic effect, reduced side-effects, improved bioavailability, better patient compliance and easy termination of drug therapy. The stratum corneum is considered as the rate limiting barrier in transdermal permeation of most molecules. There are three main routes of drug penetration, which include the appendageal, transcellular and intercellular routes. Skin age, condition, physicochemical factors and environmental factors are some factors that are to be considered while delivering drug through this route. Basic components of TDDS include polymer matrix, membrane, drug, penetration enhancers, pressuresensitive adhesives, backing laminates, release liner, etc. Transdermal patches can be divided into various systems like reservoir system, matrix system and micro-reservoir system, which are used to incorporate the

active ingredients into the circulatory system via the skin. After preparation of transdermal patches, consistent methodology are adopted to test the adhesion properties, physicochemical properties, *in vitro* drug release studies, *in vitro* skin permeation studies, skin irritation studies and stability studies. According to the duration of therapy, various drugs are commercially available in the form of transdermal patches**.[77]**

DISCUSSION:

The treatment of CNS diseases is particularly challenging because the delivery of drug molecules to the brain is often precluded by a variety of physiological, metabolic and biochemical obstacles that collectively comprise the BBB, BCB and BTB. The present outlook for patients suffering from many types of CNS diseases remains poor, but recent developments in drug delivery techniques provide reasonable hope that the formidable barriers shielding the CNS may ultimately be overcome. Drug delivery directly to the brain interstitium has recently been markedly enhanced through the rational design of polymer-based drug delivery systems. Substantial progress will only come about, however, if continued vigorous research efforts to develop more therapeutic and less toxic drug molecules are paralleled by the aggressive pursuit of more effective mechanisms for delivering those drugs to their CNS targets. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. TDDS a realistic practical application as the next generation of drug delivery system.Transdermal drug delivery systems have been used as safe and effective drug delivery devices since 1981. A lot of progress has been done in the field of Transdermal Patches. Due to large advantages of the Transdermal Drug Delivery System, this system interests a lot of researchers. Many new researches are going on in the present day to incorporate newer drugs via this system. Transdermal dosage forms may provide clinicians an opportunity to offer more therapeutic options to their patients to optimize their care. In recent years the use of a number of biophysical techniques has aided in our understanding of the nature of the stratum corneum barrier and the way in which chemicals interact with and influence this structure. A better understanding of the interaction of enhancers with the stratum corneum and the development of structure activity relationships for enhancers will aid in the design of enhancers with optimal characteristics and minimal toxicity. The Transdermal route is an extremely attractive option for the drug with appropriate pharmacology and physical chemistry. The Transdermal drug delivery system has potential advantages of avoiding hepatic first pass metabolism, maintaining constant blood level for longer period of time resulting in a reduction of dosing frequency, improved bioavailability, decreased gastrointestinal irritation that occur due to local contact with gastric mucosa and improved patient compliance.16 Recently ,it is becoming evident that the benefits of intravenous drug infusion can be closely duplicated , without its hazards by using the skin as a part of drug administration to provide continuous Transdermal drug infusion through intact skin

Neupro® is an innovative alternative to oral Parkinson's therapy. With Neupro®, patients will benefit from stable plasma levels, as well as the nonergolinic structure of rotigotine. Neupro® may also offer additional benefits, such as improved early-morning motor and night-time Parkinson's symptoms. Once daily application and ease of use may be the reason for improved compliance with the patch as reported by patients. The development of modern and novel drug delivery systems to circumvent the BBB. This is due to the significant challenge faced by industry, government and academics in seeking effective drug therapies for the increasing incidence of brain disease associated with an ageing population. In this review, we looked at the

barrier issue from a biological and pathological perspective to provide a better insight to the challenges and opportunities associated with the BBB. We need to remind ourselves that we are developing drug delivery systems which ultimately will transport a drug to a diseased brain, not a healthy one.

It is desired to develop low dose maintenance therapy of psychotropic drugs which can minimize the risk of major side effects and address the problems of poor compliance in patients. Transdermal drug delivery of psychotropic drugs is able to provide optimum amount of drug to control the disease condition along with minimum side effects. This can lead to cost effectiveness of healthcare treatment for long term management of psychiatric disease. But the successful development of the transdermal system depends upon the choice of drug. The drug should permeate the skin in adequate amount to produce the desired therapeutic effect. The opportunities for transdermal drug delivery are expanding through the application of new formulation technologies and active delivery systems. However, for these novel delivery methods to succeed and compete with those already on the market, the primary issues that require consideration include device design and safety, efficacy, ease of handling and cost effectiveness. Today, a large number of candidates for transdermal delivery have evolved along with greater acceptance. Transdermal drug delivery market is growing and there is a prospect of higher growth in this market over the next several years. Transdermal drug delivery of psychotropic drugs is expected to have a profound impact on patient care.

CONCLUDATORY COMMENTS:

As the Human skin is the largest organ in the body having the surface are of 100 m^2 approx, which can be potentially used for the delivery of multiple therapy for the successful management of neuro-degenerative disorders. Various novel approach can be introduced for which further study is essential .The focus on pecutaneous route has not been in lime light till yet .Transdermal patches provide smooth and continuous drug delivery across the brain barrier and into the bloodstream. They have the potential to provide more gradual rises in maximal plasma concentration (Cmax) and to prolong the time to Cmax (tmax), thus avoiding the rapid rise and fall of concentrations seen with oral therapies. Consequently, drug levels may be maintained within the theoretical optimal ‘therapeutic window’, with smaller fluctuations between peaks and troughs that may be associated with side effects and reduced efficacy, respectively. Bioavailability following transdermal administration has repeatedly been shown to be greater than with oral delivery for some drugs. A drug released across the skin directly into the bloodstream is free from interactions in the gastrointestinal tract and bypasses first-pass metabolism in the liver. Transdermal patch promises a new, effective, convenient and simple treatment option for various neurodegenerative disorders. Favoured by care-givers in terms of ease of use and following the schedule, a patch has many clinical advantages over conventional oral therapy. Economic evaluation suggests that by improving patient outcomes in general, in terms of cognition, clinical global impression and daily activities, the Transdermal patch represents a clinically valuable, cost-effective option for the treatment of various neurodegenerative disorders. Future studies are anticipated to provide further evidence that a Transdermal patch actually improves compliance to pharmacological therapy among patients with neurodegenerative disorders, potentially resulting in a good, cost-effective and well-perceived treatment option.

ACKNOWLEDGEMENT:

The authors are highly thankful to all staff members of Rayat-Bahra Institute of Pharmacy, Education City, Hoshiarpur, Punjab, India and University School of Pharmaceutical Sciences, Rayat-Bahra University, Mohali, Punjab, India for their constant encouragement and moral support for preparing this article.

REFERENCES

1. Ambikanandan Mishra, *et al*, *"Drug delivery to the central nervous system: a review"* Pharmacy Department, M.S. University of Baroda Shrenik P. Shah. Sun Pharma Advanced Research Center, Baroda, 2005,pg. no-.252-273,
2. http://d3nqfeqdtaoni.cloudfront.net/images/pdf/FUSBBBWorkshopSummaryFinal.pdf
3. http://dx.doi.org/10.1016/j.semcdb.2015.01.002 1084-9521/© 2015 Elsevier Ltd. All rights reserved
4. Serlin Y, *et al*. *"Anatomy and physiology of the blood–brain barrier"*. Semin Cell Dev Biol (2015),http://dx.doi.org/10.1016/j.semcdb.2015.01.002. page no. 1-2.
5. William A Banks *et al*, "*Physiology and pathology of the blood-brain barrier: implications for microbial pathogenesis, drug delivery and neurodegenerative disorder"*, Journal of NeuroVirology (1999) 5, 538-555.
6. http://www.jneurovirology.com1999 Journal of NeuroVirology, Inc.
7. Serlin Y, et al. "*Anatomy and physiology of the blood–brain barrier"*. Semin Cell Dev Biol (2015),p age no.3. http://dx.doi.org/10.1016/j.semcdb.2015.01.002.
8. Latheeshjlal.L, "*Transdermal Drug Delivery Systems: An Overview"*, International Journal of PharmTech Research coden (USA): IJPRIF ISSN: 0974-4304 Vol.3, No.4, pp 2140-2148, Oct-Dec 2011.
9. Latheeshjlal.L et al , "*Transdermal drug delivery system: An overview"* International journal of Pharmatech Research,vol 3 no. 4 ,page no.2140-2148.
10. Sonia dhiman, "*Transdermal patches: a recent approch to new drug delivery system"*, International Journal of Pharmacy and Pharmaceutical Sciences ISSN- 0975-1491 Vol 3, Suppl 5, 2011 pageno. 30.
11. Dipen Patel,*" Transdermal Drug Delivery System: A Review"*, The pharma innovation ,Vol. 1 No. 4 ,2012,page no. 68.
12. Vishal Gupta**,** *"Transdermal drug delivery: Past, present, future trends"*, International journal of pharmacy & life sciences, Vol 2(9): Sep., 2011] page no. 1101-1102.
13. Shinde P.V. et al, *"A Review on Advance Technologies for Developing Transdermal Drug Delivery Systems"*, Asian Journal of Pharmaceutical Technology & Innovations 02 (04); 2014; 01-15, Published on: 15-02-2014, page no. 2.
14. Shinde P.V. et al. "*A Review on Advance Technologies for Developing Transdermal Drug Delivery Systems Received"* Asian Journal of Pharmaceutical Technology & Innovations Published on: 15-02-2014, page no.5
15. Sonia Dhiman *et al;Transdermal Patches :A Recent Approach To Drug Delivery System* ; Indian Journals of Pharmaceutical Science, *ISSN*- 0975-1491,09 Aug 2011.
16. Richa Sachan, Meenakshi Bajpai, *Transdermal drug delivery system: a review*, International Journal of Research and Development in Pharmacy and Life Sciences, December - January, 2013, Vol. 3, No.1, pp 748-765.
17. http://www.americanpharmaceuticalreview.com/Featured-Articles/163672-Future-of-Transdermal-Drug-Delivery-Systems-TDDS.
18. Debjit Bhowmik, K.Rao.Pusupoleti2, *Recent Approaches in Transdermal Drug Delivery System* ,The Pharma Innovation Journals, Vol. 2 Issue 3 2013, page no.103
19. Professor J Jankovic, Department of Neurology, *Parkinson's Disease Center and Movement Disorders Clinic*, Baylor College of Medicine, Received 26 July 2007 Revised 3 September 2007, Accepted 4 September 2007.
20. Yasir Mehmood, *etal*, *Brain targeting Drug Delivery System: A Review* International Journal of Basic Medical Sciences and Pharmacy (IJBMSP) Vol. 5, No. 1, June 2015, ISSN: 2049-4963, page36

21. Faria Afroz *et al, Improvement in Drug Delivery System for Parkinson's Disease* ASEE 2014 Zone I Conference, April 3-5, 2014, University of Bridgeport, Bridgpeort, CT,USA.
22. Alzheimer's association, 2104 Alzheimer disease fact and figures, Alzheimer and dementia,volume 10 issue 2,page 5.
23. Suruchi Sharma *et al, Epilepsy – A Comprehensive Review*, International Journal of Pharma Research & Review, Dec 2013; 2(12):61-80page no. 61
24. Geeta aggarwal , "psychotropic drugs and transdermal delivery: an OverviewInternational Journal of Pharma and Bio Sciences V1(2)2010page no.6
25. Neha D. Singh and Ajay K. Banga, *Controlled delivery of ropinirole hydrochloride through skin using modulated iontophoresis and microneedles*, J Drug Target, Early Online: 1–13, Published online 11 January 2013,page 1-2
26. 021336s002lbl.pdf
27. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021829s002lbl.pdf.
28. https://www.neupro.com/
29. Prim Care Companion CNS Disord. 2011; 13(6): PCC.11r01149.
30. Geeta aggarwal,"psychotropic drugs and transdermal delivery: an overview, International Journal of Pharma and Bio Sciences V1(2)2010page no.6
31. Ranendra Narayan Saha *et al, Advances in Brain Targeted Drug Delivery: Nanoparticulate Systems*, Journal of Pharma Sci Tech Volume3(Issue1)2013;page no.1-8
32. Rajesh Mujoriya *et al ,A Review on Transdermal Drug Delivery System*, Research J. Science and Tech. *3(6): Sept.-Oct. 2011: 227-231*
33. Saravanakumar K, *transdermal drug delivery system: a review*, Journal of Global Trends in Pharmaceutical Sciences *6(1)-(2015) 2485 – 2490.*
34. Miriam Isaac *et al, "Transdermal patches: the emerging mode of drug delivery system in psychiatry"*,The Adv Psychopharmacol. 2012 Dec; 2(6): 255–263.
35. Mark R. Prausnitz *et al, "Current status and future potential of transdermal drug delivery"* ,Nature Reviews Drug Discovery 3, 115-124 (February 2004) |
36. Chen JJ, *et al, "Transdermal rotigotine: a clinically innovative dopamine-receptor agonist for the management of Parkinson's disease*, Pharmacotherapy". 2009 Dec;29(12):1452-67
37. Nogid A.*et al "Rotigotine transdermal system for the treatment of Parkinson's disease"* Biomed Res Int. 2014; 2014: 869269. Published online 2014 Jul 20.
38. William A. Banks' Drug delivery to the brain in Alzheimer's disease: Consideration of the blood–brain barrier, Advanced Drug Delivery Reviews, Volume 64, Issue 7, 15 May 2012, Pages 629–639 Delivery of Therapeutics to the Central Nervous System
39. Seema arkvanshi, nida akhtar,"*Transdermal delivery a preclinical and clinical perspective* of *drugs Delivered via patches"*, International Journal of Pharmacy and Pharmaceutical sciences ISSN- 0975-1491 vol 6, issue 5, 2014 *26-38.*
40. B.W Barry et al ' *"Novel mechanisms and devices to enable successful transdermal drug delivery"*, European Journal of Pharmaceutical Sciences, Volume 14, Issue 2, September 2001, Pages 101–114
41. Robert A. Hauser et al, *"Levodopa: Past, Present, and Future"* ,Eur Neurol 2009;62:1–8 Published online: April 30, 2009
42. GordanM N *et al, "oral versus transdermal selegiline antidepressant like activity in rat";*pharmacol biochem behave;19 july63(3):501-6
43. LeWitt PA et al, "*Overnight switch from oral dopaminergic agonists to transdermal rotigotine patch in subjects with Parkinson disease"*
44. .Vishal Gupta1et *al, "Transdermal drug delivery:Past,present,future trends* international journal of pharmacy & life sciences Vol. 2, Issue 9: Sep.: 20111096-1106
45. Archana K. Gaikwad *et al "Transdermal drug delivery system: Formulation aspects and evaluation"* Comprehensive Journal of Pharmaceutical Sciences Vol. 1(1), pp. 1 - 10, Feb. 2013
46. .Rahul v. wagh *et al, "Rrecen*t *approch in transdermal drug delivery system: an overview* .International journal of pharmaceutical research and bio-science,2015; Volume 4(3): 32-51
47. Jain amit k *et al, "A systematic review on transdermal drugDelivery system"* international journal of pharmaceutical studies and research /vol. Ii/ issue i/january-march, 2011/122-132
48. Michael n pastore *et al, "transdermal patches:history, development and pharmacology* british" journal of pharmacology (2015) 172 2179–2209 2179

49. V. Kalvimoorthi1 *et al,"Transdermal drug delivery system: an overview"*, international journal of pharmaceutical and chemical sciences, vol. 4(1) Jan-mar 2015, page no.89-101
50. Neha D. Singh *et al, "Controlled delivery of ropinirole hydrochloride through skin using modulated iontophoresis and microneedles"*, J Drug Target, Early Online: 1–13Published online 11 January 2013
51. Sravanthi Anampally et *al, development of ropinirole (free base) transdermal patch using blends of hydroxypropyl methylcellulose/eudragits and it' s in vitro/ in vivo characterizati* , ajprhc volume 3 issue 4 89-98
52. I˙smail tuncer deg˘ i˙m et *al, "transdermal administration of bromocriptine,* april 2003 *biol. pharm. Bull"*. 26(4), page no.501—505 (2003). vol. 26, no. 4.
53. Seema Arkvanshi *et al , "transdermal delivery a preclinical and clinical perspective of drugs Delivered via patches"*, International Journal of Pharmacy and Pharmaceutical Sciences Vol 6, Issue 5, page no. 26-38.
54. Cummings J *et al, "Pharmacokinetic rationale for the rivastigmine patch"*,Neurology. 2007 Jul 24;69(4 Suppl 1):S10-3.
55. A. Kurz *et al, "Pharmacokinetics of a novel transdermal rivastigmine patch for the treatment of Alzheimer's disease: a review"* ,The international journal of clinical practice, may 2009, 63, 5, 799–805.
56. Oertel W *et al, "Rationale for transdermal drug administration in Alzheimer disease*.**"** Neurology. 2007 Jul 24;69(4 Suppl 1):S4-9.
57. Chan AL *et al, **"**Transdermal delivery of treatment for Alzheimer's disease: development, clinical performance and future prospects**"**.* Drugs Aging. 2008;25(9):761-75.
58. Miriam Isaac *et al, "Transdermal patches: the emerging mode of drug delivery system in psychiatry"*, Ther Adv Psychopharmacol (2012) 2(6) 255–263
59. Ball AM *et al, "Optimizing transdermal drug therapy"*. Am J Health Syst Pharm. 2008 Jul 15;65(14):1337-46.
60. Chellan vijayaRaghavan *et al, "blood brain barrier: surface modified nanocarriers and in vitro models to treat alzheimer's disease - a review"*.International Journal of Advances in Pharmaceutical Research Feb. 2012/ Vol. 3 / Issue. 2 / 798 – 804
61. Vaibhav Rastogi *et al, "Transdermal drug delivery system: An overview"* Asian Journal of Pharmaceutics - July-September 2012 Volume 6 / Issue 3, page no. 161-169.
62. Kalpana S Paudel *et al, "Challenges and opportunities in dermal/Transdermal delivery"*, Ther Deliv. 2010 July ; 1(1): 109–131.
63. Vijay S Jatav *et al, "recent advances in development of transdermal patches" Pharmacophore* 2011, Vol. 2 (6), 287-297.
64. Harneet Marwah *et al, "Permeation enhancer strategies in transdermal drug delivery"* Drug Deliv, 2016; 23(2): 564–578.
65. Su Y *et al, "Drug delivery across the blood-brain barrier: why is it difficult? how to measure and improve it*?"Expert Opin Drug Deliv. 2006 May;3(3):419-35
66. William A Banks et al, "Characteristics of compounds that cross the blood-brain barrier" *BMC Neurology* 2009, 9(Suppl 1):S3 page no. 1-5.
67. Robert W. Lee *et al, "Micellar Nanoparticles: Applications for Topical and Passive Transdermal Drug Delivery"*, Handbook of Non-Invasive Drug Delivery Systems, ISBN 9780815520252, 2010 Elsevier Inc. page no. 45-46.
68. Himanshu Gupta *et al, "Recent Trends in Oral Drug Delivery: A Review"*, Recent Patents on Drug Delivery & Formulation 2009, *3*, 162-173
69. Sandeep Karki *et al, "Thin films as an emerging platform for drug delivery"* , asian journal of pharmaceutical s c i e n c e s 11 (2 0 1 6) page no.559–574
70. Bhalekar R. Mangesh *et al, "Solid Lipid Nanoparticles Incorporated Transdermal Patch for Improving the Permeation of Piroxicam*" Asian Journal of Pharmaceutics • Jan-Mar 2016 • 10 (1) | 45
71. Chellan Vijaya Raghavan *et al, "blood brain barrier: surface modified nanocarriers and in vitro models to treat alzheimer's disease - a review*" IJAPR / *Feb. 2012/ Vol. 3 / Issue. 2 / 798 – 804*
72. Vijay K Ramanan *et al, "Pathways to neurodegeneration: mechanistic insights from GWAS in Alzheimer's disease, Parkinson's disease, and related disorders*"Am J Neurodegener Dis 2013;2(3):145-175
73. Ravi Kant Upadhyay *et al , "Drug Delivery Systems, CNS Protection, and the Blood Brain Barrier*", Hindawi Publishing Corporation, BioMed Research International, Volume 2014, Article ID 869269, 37 pages

74. Roberto Bernabei *et al , "Clinical Benefits Associated with a Transdermal Patch for Dementia*" Department of Gerontology10.17925/ENR.2008.03.01.10 page 10-13
75. Gagan Hans *et al, "Psychiatric co-morbidity in patients suffering from cancer and its relationship to disease awareness*" Delhi Psychiatry Journal Vol. 18 No. 1 April 2015 page no 40 -47.
76. Inayat Bashir Pathan *et al , "Chemical Penetration Enhancers for Transdermal Drug Delivery"* SystemsTropical Journal of Pharmaceutical Research, April 2009; 8 (2): 173-179
77. Vaibhav Rastogi *et al, " Transdermal drug delivery system: An overview*" Asian Journal of Pharmaceutics - July-September 2012 page no.161-170