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Novel strategies for Neuro-Dysfunction management through Percutaneous Route: A Current Perspective.

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ABSTRACT

Neurodegenerative disorders are conditions in which cells of the brain and/or spinal cord degenerate. 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. As the human outer skin 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: Parkinson's disease, Neurological behaviors, BBB, Nanotechnology, Skin.

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INTRODUCTION

The brain 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[1]. Parkinson's disease (PD) is a progressive neurodegenerative disease characterized typically by motor features of tremor, rigidity and bradykinesia due to the depletion of dopaminergic nigrostriatal neurons. Though the treatment methods are available, the treatment of predominantly non-motor feature are remain a challenge which is caused by the degeneration of non-dopaminergic neurons[2].It is a chronic progressive neurodegener- active disorder that occurs mostly in older persons but that can appear in much younger patients. It is the second most common neurodegenerative disease[3]. Other neurodegenerative disorders can mimic idiopathic PD. These include Dementia with Lewy Bodies (DLB), Corticobasal Degeneration (CBD), Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP). The major focus of this work will be idiopathic PD and not these other parkinsonian-like syndromes. Parkinson's disease has been recognized since the early 1800's when the physician after whom the disease is named first described it. Sometimes called paralysis agitans, PD is uncommon in young people, especially those under[4].Exposure to environmental toxins in these areas is suggested to be a possible etiologic factor.[5,6] The prevalence of PD is expected to rise dramatically over the next 20 years as Americans age. Consequently, it will continue as an important health issue and strong economic drain due to its direct and indirect costs[3]. The economic and human burden may prove to be substantial especially in developed nations where average lifespans are continuously increasing[7].

Historical background of Parkinson's disease:

Parkinson's disease was first medically described as a neurological syndrome by James Parkinson in 1817, though fragments of Parkinsonism can be found in earlier descriptions (Parkinson 1817)[8]. Although PD has a worldwide distribution, incidence rates may vary among populations. As many as one million Americans are affected by PD and nearly 60,000 new cases are diagnosed each year. Worldwide, an estimated 7 to 10 million people are thought to be affected. Men are 1.5 times more likely to have PD than women[9]. A population based study of US Medicare beneficiaries found a mean prevalence of 1.6% for PD among persons 65 years and above. Less blacks and Asian Americans are affected than whites. Higher rates of PD are existent in the Midwest/Great Lakes region and the northeastern US seaboard. The results are, however, somewhat contradictory.

Thus, while the prevalence of PD has been reported to be relatively low in South African and Nigerian blacks, blacks living in Mississippi are affected to a comparable degree as the white population. Also, an autopsy study found that black Africans have an equivalent prevalence of incidental Lewy body disease as compared with white populations. Similarly, while lower prevalence rates have also been reported in some Oriental populations, the prevalence of PD in Taiwan is much higher and closer to that in Western countries. Even if population differences in PD incidence do exist, the question still remains as to the relative contribution of genetic or environmental variations to such differences.[10]

Etiology:

The main factors responsible for Parkinsonism are as below:

1- Abnormal protein processing-

Although genetic mutations have only been associated with rare forms of parkinsonism, the discovery of these genes has provided a tremendous insight into the pathogenesis of PD. The role of abnormal protein processing in particular has now been recognized as a major mechanism of cell death not only in genetic forms of parkinsonism,[11,12] but also in sporadic PD28 and in other neurodegenerative disorders[13]. Mutations in three identified genes have been associated with parkinsonism:-*synuclein*, on locus 4q21-23,[14,15] *parkin* on locus 6q25.2-27 and ubiquitin C-terminal hydrolase L1 (*UCH-L1*), on locus 4p14.[16]

2-Genetic factors-

There is increasing interest in the heritability of PD. This heightened interest was greatly promoted by the clinical observation of familial aggregation of PD cases and by the discovery of families with genetic forms of parkinsonism. Nevertheless, we have already noted that familial aggregation does not necessarily imply genetic causation and that most PD cases test negative for known mutations. In fact, a recent large twin study comparing clinical concordance rates between monozygotic and dizygotic twins detected increased concordance only in monozygotic twins who developed PD symptoms before the age of 50 years; no increased concordance was found in those who manifested disease at a later age. A recent epidemiological, statistical and mathematical study on PD patients and their parents showed that the child's risk of PD was related to the child's age at the time the parent developed PD rather than the parental age at onset of PD. Thus, the younger the child at the time the parent developed PD, the higher the risk for the child. This relationship was especially apparent when the affected parent was the mother. The degree to which parents and children share their environment usually decreases with age[17].

Table 1: Genes responsible for Parkinsonism[14]

Gene	Locus	Phenotype	Inheritance
α-synuclein	4q21-23	Early onset PD	Autosomal dominant
Parkin	6q25.2-27	Juvenile onset PD	Autosomal recessive
UCH-L1	4p14	Typical PD	Autosomal dominant
PARK3	2p13	Typical PD	Autosomal dominant
PARK4	4p14-16	PD/ Essential tremor	Autosomal dominant
PARK6	1p35-35	Early onset PD	Autosomal recessive
PARK7	1p36	Early onset PD	Autosomal recessive
PARK8	12p11.2-q13.1	Typical PD	Autosomal dominant

3-Environmental factors

Several epidemiological studies have given support to the environmental hypothesis of PD. Most studies agree on the role played by pesticide exposure and smoking on the risk of PD. While the exposure to pesticides may be associated with an increased risk of PD, smoking seems to play a protective role. Other factors often imputed to increase the risk of PD (e.g., head trauma) have not been supported by consistent evidence[18]. In addition, many of these factors may be associated with one another, which poses difficulties in teasing apart their individual contribution, if any. For example, rural living, well water drinking, and farming activity may be compound risk factors[17]**.** Young-onset parkinsonism in particular has been associated with exposure to well water. While no toxic constituents have been identified, well water drinking may simply be a marker for rural environment, which might, in turn, point to pesticide exposure. Dietary factors have also been purported to have an effect on the risk of PD[19].Thus, for example, consumption of products containing niacin may reduce the risk; diets heavily dependent on animal fat, on the other hand, may increase the risk of PD. No evidence has yet been provided to support a role for antioxidants (e.g., vitamin E) as potential neuroprotective agents[19].

Mechanism of cell death in PD.

It has already seen that abnormal protein processing is likely to play a pivotal role in cell death in PD and, perhaps, in other neurodegenerative disorders as well. This will focus on other factors i.e oxidative stress, mitochondrial dysfunction, apoptosis, excitotoxicity, and inflammation that may also be involved. None of these factors should, however, be seen as mutually exclusive. Abnormal protein processing, for example, may increase the susceptibility to oxidative stress (and vice versa). Impaired mitochondrial function may promote both excitotoxicity and free radical damage. Naturally, environmental toxins could act at any of these stages, with the common end result of selective nigral death. Following figure represents the possible mechanism of cell death.

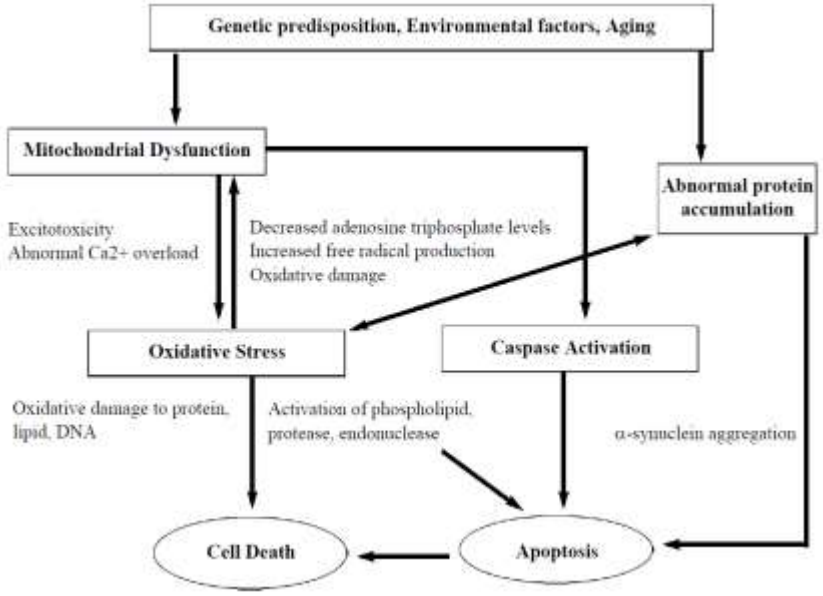

Figure 1: Mechanism leading to cell death in P.D[20]

Symptoms:

Parkinson's disease is a common progressive neurodegenerative disorder characterized by massive depletion of striataldopamine (DA) as a result of degeneration of dopaminergic (DAergic) neurons in the substantianigra. Clinically, the disease is manifested by both motor and non-motor symptoms. The cardinal motor symptoms include bradykinesia, restingtremor, rigidity and disturbance of posture and gait, and non-motor symptoms are diminished sense of smell, depression and sleep disturbance. So far, the etiopathogenesis of nigral DAergic neuron loss in PD is unclear[7].

Pathophysiology:

The pathological definition of PD is loss or degeneration of the dopaminergic (dopamine-producing) neurons in the *substantianigra* and development of Lewy Bodies (a pathologic hallmark) in dopaminergic neurons. Pathologic changes may precede obvious symptoms by two decades or more. This preferential loss of dopamine producing neurons results in marked impairment of motor control. Lewy Bodies, or abnormal intracellular aggregates, contain various proteins including alpha-synuclein and ubiquitin that impair optimal neuron functioning. Recent publications suggest that environmental stress and aging itself may promote neuropathology. Specifically, exposure to environmental toxins (e.g., pesticides), drugs of abuse, or the stress of the aging process promotes a chronic low-level inflammation in the brain (Inflammaging). This inflammatory process over time generates cellular senescence in brain neurons. From a pathologic perspective, the brain's substantianigra pars compacta and the pontine locus ceruleus are affected

by typical abnormalities of PD patients including depigmentation, neuronal loss and gliosis. By the time PD symptoms occur, about 60-70 percent of the neurons in the substantianigra pars compacta are gone. Genetic nutations that code proteins of the central nervous system play a role in neuronal death. Specifically, alpha-synuclein becomes abnormal and self-aggregates. This aggregated, insoluble alpha-synuclein is a major constituent of Lewy Bodies, cellular inclusions that are the hallmark of PD. In addition, systems designed to break down abnormal proteins like the ubiquitin - proteasome system also become impaired. Other impaired processes that may play a role in PD are mitochondrial dysfunction or abnormal oxidative stress through reactive oxygen species causing neuronal degeneration. Some researchers use the theories of Braak and colleagues to explain PD pathophysiological progression. Called the dual-hit hypothesis, the theory suggests that an unknown, possibly viral, pathogen enters the brain through the olfactory route. Notably, PD patients often have prodromal olfactory deficits. Or the swallowing of nasal secretions introduces the pathogen to the gut and it enters the vagus nerve and the CNS. Pathologic support for this hypothesis derives from the identification of Lewy Bodies in the intestinal structures, vagus nerve, and brain structures.

Table 2:Traditional drugs and novel delivery system for the treatment of PD[20]

S.N	Drug	Dosage	Trade name	Formulation
1	Levodopa	0.1,0.25,0.5g	Dopar	Oral tablets
2	LD/Carbidopa	20mg/5Ml	Duodopa	Suspension of micronised LD/Carbidopa in microcrystalline methylcellulose gel for enteral delivery. Indicated for patients affected by PD with fluctuating motor functions
3	LD/Benserazide	100/25mg or 200/50mg	Madopar	Oral capsules, Oral breakable tablets.
4	COMT Inhibitors			
	• Tolcapone	100/200mg	Tasmar	Oral film coated tablets.
	• Entacapone	200mg	Comtan	Oral film coated tablets.
5	MAO-B Inhibitors			
	• Selegiline	5mg	Eldepryl	Oral capsules.
	• Selegiline	1.25mg	Zelapar	Sublingual tablets.
	• Resagiline	0.5-1mg	Azilect	Oral tablets.

6	ErgolineDopamine Receptor Agonists			
	Bromocriptine	2.5 mg	Parlodel	Oral snap tabs.
		5mg	Parodel	Oral capsules.
	Pergolide	0.05/0.25/1mg	Permax	Oral tablets.
		1-2mg		
	• Cabergloine	0.2/0.5/1mg	Cabaser	Oral tablets.
	• Lisuride	2.5µg/h($10cm^2$)	Dopergin	Oral tablets.
	• Lisuride	5µg/h($20cm^2$)	Nenad	Transdermal patch.
	Dihydroergocriptina	5mg	TDS	Oral capsules.
	Dihydroergocriptine	10mg	Daverium	Oral capsules.
			Daverium	
7	Non-Ergotine Dopamine Receptor Agonists			
	• Pramipexole	0.125/0.25/0.51/1.5mg	Mirapex	Oral tablets.
		0.25/0.5/1/2/3/4/5mg		
	• Ropinirole	2/4/8mg	Requip	Oral tablets.
		2mg/24hr		
	• Ropinirole	4mg/24hr	Requip	Extended-release tablets.
	• Rotigotine	6mg/24hr	XL	Transdermal patch.
		8mg/24hr	Neupro	
		5mg/ml		
		10mg/ml		
	• Apomorphine	10mg/ml		Continuous infusion
		10mg/ml	Apo-go	Subcutaneous injection.
			PFS	Subcutaneous injection.
			Apokyn	Subcutaneous injection.
			Apo-go Pen	
			Apo-go Amp.	

Novel strategies for improved Parkinson's Management:

1. Transdermal drug delivery

The skin as a site of drug delivery has a number of significant advantages over many other routes of drug administration, including the ability to avoid problems of gastric irritation, pH and emptying rate effects, avoid hepatic first-pass metabolism thereby increasing the bioavailability of drug, reduce the risk of systemic side effects by minimizing plasma concentrations compared to oral therapy, provide a sustained release of drug at the site of application, rapid termination of therapy by removal of the device or formulation, the reduction of fluctuations in plasma levels of drugs and avoid pain associated with injections[21]

Anatomy and Physiology of Human Skin:

Human skin comprises of three distinct but mutually dependent tissues namely:

1. The stratified, a vascular, cellular epidermis
2. Underlying dermis of connective tissues
3. Hypodermis.

Epidermis

The multilayered envelop of the epidermis varies in thickness, depending on cell size and number of cell layers, ranging from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Stratum corneum and the remainder of the epidermis, also called viable epidermis, cover a major area of skin.[21]

Stratum corneum:

This is the outermost layer of skin, also called horney layer. It is approximately 10 mm thick when dry but swells to several times this thickness when fully hydrated. It contains 10 to 25 layers of parallel to the skin surface, lying dead, keratinized cells, called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principal barrier for penetration. The barrier nature of the horney layer depends critically on its constituents: 75 to 80% proteins, 5 to 15% lipids, and 5 to 10% ondansetron material on a dry weight basis. Protein fractions predominantly contain alpha-keratin (70%) with some beta-keratin (10%) and cell envelope (5%). Lipid constituents vary with body site (neutral lipids, sphingolipids, polar lipids, cholesterol). Phospholipids are largely absent, a unique feature of mammalian membrane.

Dermis

Dermis is a 3 to 5 mm thick layer and is composed of a matrix of connective tissue which contains blood vessels, lymph vessels, and nerves. The continuous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of permeate very low, and the resulting concentration difference across the epidermis provides the essential driving force for transdermal permeation.

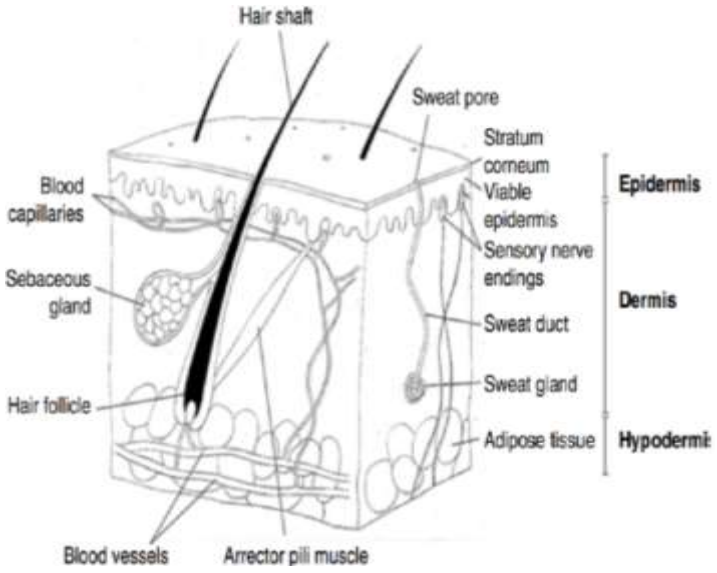

Figure 2: Anatomical structure of human skin[22]

Hypodermis

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area

Various permeation techniques used for drug penetration through the percutaneous route.

The permeation of drugs through the skin includes the diffusion through the intact epidermis through the skin appendages (hair follicles and sweat glands). These skin appendages form shunt pathways through the intact epidermis, occupying only 0.1% of the total human skin. It is known that drug permeation through the skin is usually limited by the SC.

1-The intercellular lipid route-

Interlamellar regions in the SC, including linker regions, contain less ordered lipids and more flexible hydrophobic chains. This is the reason for the nonplanar spaces between crystalline lipid lamellae and their adjacent cells outer membrane. Fluid lipids in skin barrier are crucially important for trans epidermal diffusion of the lipidic and amphiphilic molecules, occupying those spaces for the insertion and migration through intercellular lipid layers of such molecules.[22]The hydrophilic molecules diffuse predominantly laterally along surfaces of the less abundant water filled interlamellar spaces or through such volumes; polar molecules can also use the free space between a lamella and a corneocyte outer membrane to the same end.

2-The transcellular route-

Intracellular macromolecular matrix within the SC abounds in keratin, which does not contribute directly to the skin barrier but supports mechanical stability and thus intactness of the SC. Transcellular diffusion is practically unimportant for transdermal drug transport.[21] The narrow

aqueous transepidermal pathways have been observed using confocal laser scanning microscopy. Here, regions of poor cellular and intercellular lipid packing coincide with wrinkleson skin surface and are simultaneously the sites of lowest skin resistance to the transport of hydrophilic entities. This lowest-resistance pathway leads between clusters of corneocytes at the locations where such cellular groups show nolateral overlap.[23]The contribution to transdermal drug transport can increase with pathway widening or multiplication, eg, that which is caused by exposing the SC to a strong electrical (electroporation/iontophoresis), mechanical (sonoporation/sonophoresis), or thermal stimulus, or suitable skin penetrants. Recently, follicular penetration has become a major focus of interest due to the fact that drug targeting to the hair follicleis of great interest in the treatment of skin diseases.

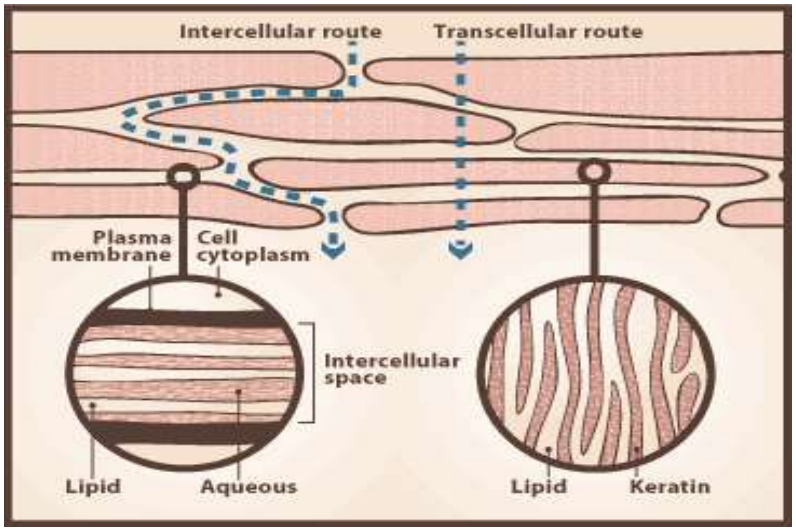

Figure 3:Mechanism of Transdemal drug delivery system.[22]

A transdermal patch is used to deliver a specific dose of medication through the skin and into bloodstream. Transdermal patches products were first approved in 1981,FDA.Transdermal delivery provides controlled, constant administration of the drug, and allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation.[22] An innovative delivery strategy for treating PD is a skin patch, or transdermal therapeutic system (TTS), which offers considerable advantages over parenteral or oral administration of anti-Parkinson therapy, patch use could enhance plasma concentration, reduce gastrointestinal variations and avoid first-pass metabolism, as well as simplifying the daily dosing schedule and ensuring a short plasma elimination half-life of the drug after patch removal. Furthermore, there are indications that patient compliance may be increased with TTS treatment.

Benefits of TTS System.

- Patches are easy to apply, non-invasive and painless.

- Drug can be delivered over a long period of time.
- Reduces dosing frequency as a single patch continuously delivers the drug for prolonged period of time.
- Suitable for drugs that are degraded in stomach pH, intestine or metabolized by liver as drug in TDDS avoids first pass metabolism by directly absorbing into the systemic circulation.
- Suitable for old age peoples who cannot take medicines orally.
- Suitable for drugs which are irritating by oral route and decreases drug side effects.
- In case of toxicity drug delivery can be stopped by removing the patch.
- Self-administration is possible.
- Patches are cost effective.
- Reduces inter and intra patient variability.

Risks of TTS System.

- Although Transdermal drug delivery systems possess numerous advantages but these also have some disadvantages as follow:
- Difficult to administer large dose i.e. more than 10 mg/ day.
- Ionic drugs create problems.
- Drugs having size more than 500 Dalton are not suitable for TDDS.
- Drugs in high concentration may cause skin irritation.
- Difficult to achieve high plasma drug concentration.
- Long term adherence creates discomfort to patients.
- Drugs with very low or high partition coefficient fail to reach systemic circulation.

Transdermal drug delivery in Parkinson's Management.

The appeal of transdermal administration of medication as a means of achieving a constant rate of drug delivery is well recognized and the technique has been applied successfully in the treatment of a number of disease processes. Nitroglycerin (glyceryl trinitrate) patches for coronary artery disease, clonidine patches for hypertension, scopolamine patches for motion sickness, and nicotine patches for smoking cessation are all examples of currently used transdermal treatment approaches. With a transdermal system, a constant supply of drug can be delivered, even though the half-life of the drug might be quite short; moreover, the drug can be easily removed should adverse effects develop. Levodopa itself has generally not been regarded as a candidate for

transdermal administration because it has poor solubility and stability, but several DA agonists have demonstrated a capability for transdermal absorption.

1-Naxagolide:

The naphthoxazine derivative, naxagolide [(+)-4-propyl-9-hydroxynaphthoxazine (PHNO, MK-458)] is a very potent DA agonist that was the subject of some excitement and extensive testing in the 1980s in both animals and humans. It was also known to be soluble in both aqueous and lipid media, making it a candidate for transdermal application. Subsequent testing demonstrated that, in addition to being effective when administered via the, oral route, naxagolide also produced clinical improvement in both primates and humans when applied transdermally. A delay of 4-6 hours, correlating with rising plasma naxagolide concentrations and reflecting the time for naxagolide to permeate the epidermis below the skin patch and reach the dermal capillaries, was noted between patch application and onset of clinical benefit. Clinical response and plasma concentration elevations persisted for several hours after removal of the patches, also reflecting the reservoir provided by the skin and subcutaneous tissues. Adverse effects generated by naxagolide were similar to those produced by other DA agonist drugs, including drowsiness.

2-Rotigotine

Yet another DA agonist has been the object of extensive testing over recent years and is still under active investigation. Rotigotine (N-0923) is a non-ergot aminotetralin derivative that, along with most other D Aagonists employed or tested in PD, predominantly stimulates the D2 receptor. It is the (–)-enantiomer of the racemic agonist, N-0437animal models, it produced responses predictive of antiparkinson activity in humans, but it was found to undergo extensive gastrointestinal and first pass hepatic metabolism that rendered it inactive when administered orally. Because of its lipid solubility and ability to penetrate the skin, it was felt to have potential as an agent delivered via the transdermal route. The primary adverse effects noted were hypotension and nausea.

Intranasal drug delivery for PD.

Nasal drug delivery, has received a significant attention in recent years as a convenient and reliable route, not only for local but also for the systemic administration of drugs [26].Whenever systemic effects are intended oral drug delivery is the most desirable route for drug administration. Oral route remains the most popular for systemic drug administration but low oral bioavailability of some compounds has prompted the search of more effective routes for their systemic delivery. Researchers developed the parenteral route of drug administration to solve the above problem. For the past few years, the transdermal route has been selected for delivery of certain drugs. But because of the low permeability of the skin to many drugs its use is limited. Now a day, nasal

mucosa is an alternate route to achieve faster and higher drug absorption. The nasal cavity offers a number of unique advantages such as easy accessibility, good permeability especially for lipophilic, low molecular weight drugs, avoidance of harsh environmental conditions and hepatic first pass metabolism, potential direct delivery to the brain, and direct contact for vaccines with lymphatic tissue and action as inducer as well as effector of the mucosal immune system. Nasal route provide a large surface area for permeation of drug due to the presence of villi and microvilli.[27]

1-Anatomy and physiology of human nasal system.

The human nose has two primary functions, the first is olfaction – the sense of smell and the second function is filtration, heating and humidification of the inhaled. The nasal cavity refers to the interior of the nose. It is the entry point for inspired air and the first of a series of structures which form the respiratory system. The cavity is entirely lined by the nasal mucosa. It is one of the anatomical structures which form the physical barriers of the body's immune system. These barriers provide mechanical protection from the invasion of infectious and allergenic pathogens. The human nasal cavity is divided into two nasal cavities by the septum. It has a total volume of about 16 to 19 ml, and a total surface area of about 180 cm2. The volume of each cavity is approximately 7.5 ml, having a surface area approximately 75 cm2.The nasal cavity extends from the external opening, the nostrils, to the pharynx (the upper section of the throat), where it joins the remainder of the respiratory system. It is separated down the middle by the nasal septum. It is nothing but the piece of cartilage which shapes and separates the nostrils. Each nostril can be further divided into roof, floor, and walls. The nasal cavity can be divided into the vestibule, respiratory and olfactory sections. Nasal vestibule is the anterior part of the nasal cavity inside the nostrils, and it is about 0.6cm2 in area.[28] The nasal vestibule is the dilated area at the nostril opening. The nasal portion is covered by a stratified squamous epithelium and keratinized epithelium with sebaceous glands. Respiratory region Largest part of the nasal cavity is respiratory region, also called conchae, is the cavity and it is divided in superior, middle and inferior turbinates which are projected from the lateral wall. The nasal respiratory mucosa, considered the most important section for delivering drugs systemically, is constituted by the epithelium, basement membrane and lamina propria. The nasal respiratory epithelium consists of pseudo stratified columnar epithelial cells, globet cells, basal cells and mucous and serous glands. Many of the epithelial cells are covered on theirapical surface with microvilli and the major part of them also has fine projections, called cilia. Olfactory region Location of olfactory region is at the roof of the nasal cavity and extends a short way down the septum and lateral wall[29].Neuroepithelium

which is the only part of the CNS, is directly exposed to the external environment. The olfactory receptors (receptors for smell sensations) are found in this section of the nasal cavity. The small serous gland (glands of Bowman) produces secretions acts as a solvent for odorous substances.[27]

Advantages of Naso-Brain drug delivery:

- Absorption of drug is rapid via highly vascularized mucosa.
- Availability of large nasal mucosal surface area for dose absorption.
- Onset of action is rapid.
- Non invasive and easy for administration.
- Bypass the BBB.
- Degradation of drug observed in GIT is avoided.
- Hepatic first pass metabolism is absent.
- Nasal bioavailability of small drug molecules is good.
- Bioavailability of large drug molecules can be increased by means of absorption enhancers.
- Unsuitable drug candidates for oral route can be successfully given via nasal route.
- Alternate to parenteral route especially for proteins and peptides.
- Convenient route for the patient on long term therapy.
- Improved bioavailability.
- Side effects are reduced due to low dose.
- Patient convenience and compliance is improved.
- A self-administration is possible.
- Direct transport into systemic circulation and CNS is Possible.
- Offers lower risk of overdose
- Does not have any complex formulation requirement

Disadvantages of Naso-Brain Drug delivery:

- Residence time of drug reduces due to the mucociliary clearance
- It is not applicable to all drugs
- Due to the lack of adequate aqueous solubility it shows insufficient absorption
- Depending on aqueous solubility of drug it require high volume of dose (25-200ml)
- Some drugs can cause nasal irritation
- Some drugs may undergo metabolic degradation in the nasal cavity
- It is less suitable for chronically administered drugs
- Those drugs which require sustained blood levels should not be considered for nasal

delivery as there is no conventional way of formulating sustained release type nasal dosage forms.

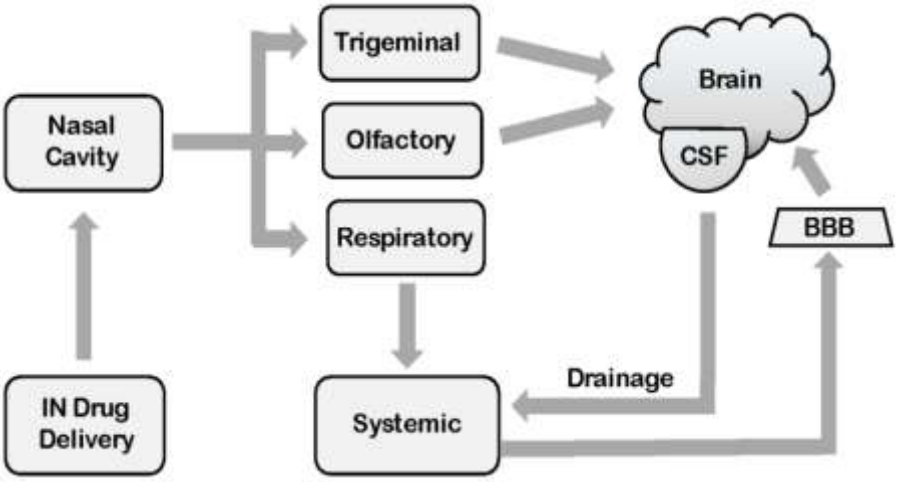

Figure 4: Different pathway for Naso-Brain drug administration.

Although major progress has been made regarding intranasal drug delivery, there is still a distinct lack of information regarding this topic. This novelistic route demands attention of scientists around the globe due to the rapid increase in the aging population and the increasing susceptibility of patients to neurological disorders around the world. Intranasal drug delivery has got the attention of many researchers due to its application in various diseases related to CNS. This system has clinical benefits like reduced dose hence lower incidence of systemic adverse effects, and more patient compliance. The advantages of intranasal delivery are numerous and very importantly it is rapid and non-invasive. It reduces systemic exposure and thus reduces the side effects. It also bypasses the BBB and delivers the drug directly into the CNS. It acts as an alternative to parenteral and oral route for delivery of some drugs.[29]

OBJECTIVE OF THE STUDY:

The major focus of this review article is-

- To gain all the background information about the Neurodegenerative disorders, etiology and novel treatments feasible.
- To update the novel techniques and advancements in the field of drug delivery system.
- To collect information regarding the drugs used in the treatment.
- To review the combination therapy of drugs (if any available) for the best possible results.
- To gain all the background information about the drug delivery to the central nervous system through the skin.
- To acquire the knowledge regarding the Transdermal drug delivery system, the
- advantages and disadvantages , the types and the techniques involved.
- To correlate between the Transdermal drug delivery and other dosage system.

- To gain the knowledge regarding the MOA of the drug delivery to the CNS through
- Transdermal patches.
- To know about the newer technique and advancement in the flied of drug delivery system to the CNS.
- To know about the various drugs available for disorder of CNS in Transdermal patches.
- The study and work achieved so far regarding it i.e. prior art to Transdermal drug delivery

LITERATURE REVIEW:

Adnan Azeem *et.al* (2011) made oil based nanocarrier system for transdermal delivery of ropinirole. They focused precisely on pharmacokinetic, biochemical and mechanistic assessment of transdermal nanoemulsion gel in rats induced with Parkinson lesioned brain by 6-OHDA.[30]

SandhyaGoyal *et.al* (2015) prepared in-situ gel of levodopa using chitosan-thioglycolic acid conjugate and musk ketone by efflux transport modulation for brain targeting. They formulatedpluronic thermosensitive nasal gel of levodopa for brain targeting using chitosan-thioglycolic acid conjugate as P-gp efflux transport inhibitor and nitromusk (musk ketone) as fragrance compound that stimulates the sensation and thus permeability in the nasal cavity.[31]

Devang Bhatt *et.al* (2011) formulated nanosuspension of Ropinirole Hydrochloride for oral delivery**.** Ropinirole hydrochloride alleviates this deficiency by stimulating striatal dopamine receptors. Ropinirole hydrochloride has got complete but variable oral absorption with less bioavailability approximately 50%. Hence, nanoparticles of Ropinirole hydrochloride was developed to improve drug diffusion profile and hence the oral bioavailability.[32]

SnehPriya *et.al* (2015) formulated Solid Lipid Nanoparticles of Ropinirole Hydrochloride. From the results, they concluded that drug released from SLNs follows sustained release pattern and it will enhance the overall activity of the drug.[33]

Nishan N.Bobade *et.al* (2015) conducted research on design and *in-vitro* characterization of novel phase transition systems for nasal drug delivery. Phase transition systems of Ropinirole HCL for nasal drug delivery were prepared with muco-adhesive polymer such as chitosan and various grades of Hydroxyl Propyl Methyl Cellulose (HPMC) sodium beta glycerophospate.[34]

HardikA.Shah *et.al* (2016) prepared transdermal patch and proniosomal gel of Ropinirole Hydrochloride. They concluded that proniosomal gel system have shown great potential for delivery of Anti-Parkinson drugs. The proniosomal gel also appears to be an effective alternative vehicle for delivering adrug through the topical and transdermal route.[35]

Bhosale Nilesh R *et.al* (2011) made transdermal patch of Ropinirole Hydrochloride. According to them the conventional multidose antiparkinsons therapy leads to re-emergence of Parkinson's symptoms, due to fluctuations in serum levels of drug. The rational strategy to overcome this drawback is to minimize the fluctuations by fabricating sustained release formulations. Their aim was to develope transdermal patch of Ropinirole HCl to show its prolonged release.[36]

Chandrakantsing.V*et.al* (2013) fabricated and evaluated novel surface modified polymer–lipid hybrid nanoparticles (PLN) as robust carriers for intranasal delivery of ropinirole hydrochloride. They fabricate these nanoparticles with the application of Box-Behnken design. Their findings suggested that investigated carrier system could offer an exciting mode of neurotherapeutic delivery to CNS.[37]

Omidreza Jafarieh *et.al* (2014)prepared mucoadhesive nanoparticles of Ropinirole for intranasal drug delivery. Their purpose was to investigate the possibility of targeting an anti-Parkinson's drug ropinirole (RH) to the brain using polymeric nanoparticles.[38]

ShahdabMd *et.al* (2012) investigated the potential use of chitosan nanoparticles as a delivery system to enhance the brain targeting efficiency of bromocriptine (BRC) following intranasal (I.N.) administration**.**[39]

ChandrakantsingV.Pardeshi *et.al* (2012) prepared ropinirole hydrochloride loaded solid lipid nanoparticles (SLNs) for intranasal delivery by application of factorial design. Prime objectives of this experiment was avoidance of hepatic first pass metabolism and to improve therapeutic efficacy in the treatment of Parkinson's disease.[40]

Sumit Sharma *et.al* (2013) prepared thermo-reversible gel of Levodopa. In an attempt to improve brainuptake and to avoid degradation of levodopa in peripheral circulation and the use of carbidopain combination, nose to brain drug delivery of levodopa alone via the olfactory route and the trigeminal nerves has been investigated.[41]

AdanAzeem *et.al* (2009) investigated the potential of nanoemulsions as nanodrug carrier systems for the percutaneous delivery of ropinirole. The purpose of the study was to investigate the potential of nanoemulsions as nanodrug carrier systems for the percutaneous delivery of ropinirole.[42]

Paolo Blasi*et.al* (2011) aimed to optimize the formulation of lipid nanoparticles (NPs), intended for brain targeting, with the aid of a computer generated experimental design. According to this a computer generated experimental design and a response surface analysis it was possible to establish the best formulation conditions with a limited number of experiments.[43]

Ellisabetta Esposito *et.al* (2008) described a formulative study for the development of innovative drug delivery systems for bromocriptine. They concluded that nanostructured lipid carriers encapsulation may represent an effective strategy to prolong the half-life of bromocriptine.[44]

TingtingPu*et.al* (2016) developed a prolonged-release pramipexole (PPX) transdermal patch for the treatment of Parkinson's disease. As per their study development of a prolonged-release transdermal patch for PPX may be a feasible strategy for the treatment of PD, which will largely improve patient compliance.[45]

J.MGorell*et.al* (1998) described the risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. According to their research Farming as an occupation was significantly associated with PD (OR, 2.79; 95% CI, 1.03, 7.55), but there was no increased risk of the disease with rural or farm residence or well water use. The association of occupational exposure to herbicides or insecticides with PD remained after adjustment for farming. The association of farming with PD was maintained after adjustment for occupational herbicide exposure and was of borderline significance after adjustment for occupational insecticide exposure. These results suggest that PD is associated with occupational exposure to herbicides and insecticides and to farming and that the risk of farming cannot be accounted for by pesticide exposure alone.[46]

Carlo Ferrari *et.al* (1992) discussed Cabergoline in long-term therapy of hyperprolect- inemic disorder. In this study Cabergoline was administered orally at dose levels ranging between 0.2 and 3.5mg per week, given once weekly in 92 patients, twice weekly in 22, thrice weekly in 9 and daily in 4. Serum prolactin and progesterone levels, hematology, blood chemistry and electrocardiograms were frequently evaluated throughout treatment.[47]

Tsong-Long Hwang *et.al* (2009) developed perfluorocarbon nanobubbles for Apomor- phine delivery. The aim of the work was to develop acoustically active perfluorocarbonnanobubbles (PNs) for encapsulation of both apomorphine HCl and base forms to circumvent these delivery problems.[48]

G.L.Li *et.al* (2005) discussed transdermal iontophoretic delivery of apomorphine in patients improved by surfactant formulation pretreatment. Their aim was to further increase the transdermal transport rate of R-apomorphine, a nonocclusive pretreatment with an aqueous surfactant formulation in combination with iontophoresis was explored in vitro. They concluded that nonocclusive pretreatment with the surfactant formulation enhances the iontophoretic transport of R-apomorphine, and is a promising approach to achieve therapeutic concentrations of R-apomorphine.[49]

James W.Tetrud *et.al* (2004) prepared a novel formulation of selegiline for treatment of Parkinson. These studies clearly demonstrated that selegiline was safe and significantly improved on time in PD patients experiencing end-of-dose wearing off. However, certain levodopa-related side effects, such as nausea, psychosis, orthostatic hypotension, and dyskinesia, prompted reduction of levodopa, thus negating some of the levodopa-potentiating effects of the drug.[50]

Karin M.Jogra *et.al* (1999) studied the effect of Talcapone on the pharmacokinetics of Benserazide. The safety margin derived from this study, together with the absence of any organic toxic effects in clinical trials, show that the observed interaction between tolcapone and benserazide does not represent a safety concern for PD patients treated with this combination.[51]

DISCUSSION AND CONCLUDATORY COMMENT

Transdermal drug delivery is helpful for topical and local action of the drug. At present, it is the first option for the treatment of neurodegenerative-diseases. For the patients who have difficulties swallowing solids or liquids, a transdermal drug delivery may offer great advantages over conventional delivery methods. The treatment of Parkinson's disease is particularly challenging because the delivery of active molecules to the brain is often precluded by a variety of physiological, metabolic and biochemical obstacles that collectively comprise the Blood Brain Barrier (BBB), Blood Cerebrospinal fluid Barrier (BCB) and Blood-Tumor Barrier (BTB). The present outlook for patients suffering from many types of brain diseases remain poor, but recent developments in drug delivery techniques provides reasonable hope that the formidable barriers shielding the brain 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 system. 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 brain targets. .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 blood stream. 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 neurode-generative disorders. Favored 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.

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