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INTRANASAL MUCOADHESIVE DRUG DELIVERY FOR PARKINSONISM WITH CENTELLA ASIATICA

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ABSTRACT

Parkinson's disease (PD) is an important age-related neurodegenerative disorder. Resulting from the loss of dopamine-producing neurons in the substantia nigra pars compacta of midbrain, characterized by motor and non- motor symptoms. Nowadays, 80% of people use medicine which is directly or indirectly derived from plants. There are many traditional plants responsible for neuroprotective property. This review focus on *Centella asiatica*, could offer a useful support to the Parkinsonism therapy by acting as a neuroprotective antioxidant and thus prevent the neuronal damage in brain regions associated with Parkinsonism. The Asiaticoside, present within the *Centella asiatica* extract are simpler in neuro protecting activity from oxidative stress. Therapy through intranasal administration has been an accepted sort of treatment within the Ayurvedic system of Indian Medicine. Intranasal (IN) drug delivery used for treating various CNS diseases like Alzheimer's, Schizophrenia, Meningitis, and Parkinson's diseases. IN delivery also offers the advantage of straight forward administration, cost effectiveness and convenient. But in some cases low duration thank to mucocilliary clearance may be a major challenge in nasal drug delivery. The utilization of mucoadhesive can resolve this problem by localizing the formulation during a particular region of the nasal cavity, thereby improving the bioavailability of medicine. Meaning that mucoadhesive based drug delivery will be better in combination with intranasal route.

KEYWORDS: Parkinsonism, *Centella asiatica*, Intranasal delivery, Mucoadhesive based drug delivery.

INTRODUCTION

Parkinson's disease (PD) is an important age-related neurodegenerative disorder.[1] Resulting from the loss of dopamine-producing neurons in the substantia nigra pars compacta of midbrain, which in turn disrupt the normal balance between dopamine and acetyl choline in the basal ganglia, characterized by motor and non- motor symptoms.[2] Motor symptoms include rigidity, tremor, bradykinesia (slowness) and postural instability.[3] Nonmotor symptoms[4] of PD include depression, cognitive impairment, and constipation, disturbances of sleep patterns, anosmia, and disturbances of some autonomic functions. Dopamine is a neurotransmitter essential for normal functioning including support, voluntary motion, and control of posture. That is dopaminergic activity is mediated by dopamine and cholinergic activity by acetyl choline.[5] A balance between two kinds of activity produces normal motor functions. A relative excess of dopaminergic activity and cholinergic activity will produces involuntary movements and rigidity, akinesia.

Peoples with Parkinson's disease also loss the nerve endings that produce nor epinephrine, the main chemical messenger of sympathetic nervous systems which controls many automatic functions of the body such as blood pressure, heart rate. The loss of nor epinephrine might help explain some of the non movement features of Parkinson's such as irregular blood pressure, decreased movement of food through digestive tract, fatigue, and postural hypotension that happens when person stands up from a lying down or sitting position.

This chronic progressive neurodegenerative disorder is also called as "shaking palsy"[6], described by James Parkinson, published his monograph in 1817 that is "An essay on the shaking palsy". In this report, he described the clinical syndrome or a neurological illness now called as Parkinson's disease (Paralysis Agitans), consisting of resting tremor with lessened muscular power, in parts are not in proper action and even when supported.

The main pathological feature of this disorder is loss of dopamine-producing neurons in the substantia nigra pars compacta, associated with presence of cytoplasmic protein aggregates called Lewy bodies.[7] This preferential loss of dopamine producing neurons results in marked impairment of motor functions. The Lewy Body Dementia (LBD) is a disease related with abnormal deposition of a protein called α-synuclein[8] in the brain. These deposits is called Lewy bodies which affect chemicals in the brain whose changes further leads to problems with movement, thinking, behavior and mood.

The diagnosis of PD is principally clinical, although specific investigations can help the differential diagnosis from other forms of Parkinsonism. When patients are diagnosed at first time, a substantial proportion of dopaminergic neurons in the SNpc have already been lost, and this neurodegeneration has spread to other central nervous system regions.

Currently available treatments mainly focuses on symptomatic relief with drugs aiming to either restore the level of dopamine in the striatum or to act on striatal post-synaptic dopamine receptors.[4] That is, the currently available treatments offer good control of motor symptoms like rigidity, tremor, bradykinesia (slowness) and postural instability but do not halt the evolution of the disease, the increasing disability and the progression of neurodegeneration. Further investigation on novel therapies to replenish the loss of dopaminergic cells or even reduce the rate of neurodegeneration remains in the research setting, with some in the early stages of clinical trials.

AETIOLOGY

PD is idiopathic in nature, but both genetic and environmental factors affect this multifactorial disease. And also age is the biggest risk factor for PD, The incidence of the disease rises with age to 93.1 (per 100,000 person-years) in age groups between 70 and 79 years.[3]

Genetics factors

The minority of cases (10–15%) due to family history, and around 5% due to Mendelian inheritance. The genes that are responsible for Parkinson's disease are called "PARK" genes.[8] There is 23 PARK genes have been connected to PD. Mutations in these PARK genes either demonstrated as, Autosomal dominant (e.g., α-synuclein gene (SNCA), Leucine Rich Repeat Kinase 2 (LRRK2), Ubiquitin C-terminal Hydrolase1 (UCHL1)) and Autosomal recessive inheritance (e.g., Parkin REB E3 Ubiquitin Protein ligase (PRKN), PTEN- Induced Putative Kinase1 (PINK1), and Deglycase (DJ-1)). In case of autosomal dominant PD the first type of familial PD caused by a point mutation in the α-synuclein gene. Gene duplication or triplication as well as four additional point mutations, have now been associated with autosomal dominant PD. But these mutations are rarely occurs. The most common autosomal dominant monogenic PD is caused by mutations in the gene encoding leucine-rich repeat kinase 2 (LRRK2). Six LRRK2 mutations have been confirmed as pathogenic. Autosomal recessive PD typically present with an earlier onset. Three of the PARK genes causing autosomal recessive PD have been connected to mitochondrial homeostasis (PRKN, PINK1,

and DJ-1). Specifically, the proteins parkin and PINK1 (encoded by the PRKN gene) are both involved in the same mitochondrial quality control pathway, with PINK1 recruiting parkin to dysfunctional mitochondria and thus initiating mitophagy. Mutations in Parkin REB E3 Ubiquitin Protein ligase (PRKN) gene are the most common cause of autosomal recessive familial PD, occurring in up to 50% of all early-onset cases.

Environmental factors

The cause of Parkinson's disease is not known. But various epidemiologic studies indicate that there is number of factors which may increase the risk of developing PD. These include exposure to pesticides, well water, herbicides, wood pulp mills, industrial chemicals, farming, and living in a rural environment. And also a number of exogenous toxins have been related to the development of parkinsonism, including trace metals, organic solvents, cyanide, lacquer thinner, carbon disulfide and carbon monoxide. The most evidence for an environmental factor in PD relates to the toxin 1, 2, 3, 6-methyl-phenyl-tetrahydropyridine (MPTP). It can easily cross blood brain barrier because of lipophillic nature then metabolized to produce a neurotoxin MPP+(1- methyl-4-phenyl pyridinium), mitochondrial complex –I inhibitor. This is absorbed by dopaminergic neurons via dopamine transport results oxidative stress and decrease in ATP generation. Rotenone (a pesticide) is a powerful selective complex-I inhibitors cause oxidative stress and lead to selective dopaminergic depletion. Paraquat (herbicide, structurally similar to MPP+) weak inhibitor of mitochondrial complex –I, is reported to show loss of dopaminergic neurons in the substantia nigra. And also Lewy body like structure has been observed in rodent studies.

Ageing

Age is the major risk factor for the progression and development of Parkinson's disease (PD).[9] PD is an important example of an age-related disease. Normal ageing may be related to very mild Parkinsonian signs, whereas PD has a very distinct clinical picture. Ageing is associated with increased free radical production, mitochondrial dysfunction, and oxidative stress, which may lead to DNA mutations and genomic instability. And also PD reflects a failure of the normal cellular compensatory mechanisms in vulnerable brain regions, and this vulnerability is increased by a genetic susceptibility acted upon by other environmental and genetic factors and mostly by age. The accumulation of age-related somatic damage combined with a failure of compensatory mechanisms may lead to an increased prevalence

and an acceleration of PD with age. So ageing is the main modifying factor on the phenotypic presentation of PD.

PATHOGENESIS

There are number of mechanism have been implicated in PD pathways[10] (figure 1). Altered protein handling, oxidative stress, mitochondrial dysfunction, and inflammatory change are considered to lead to cell death and dysfunction by autophagy or apoptosis.

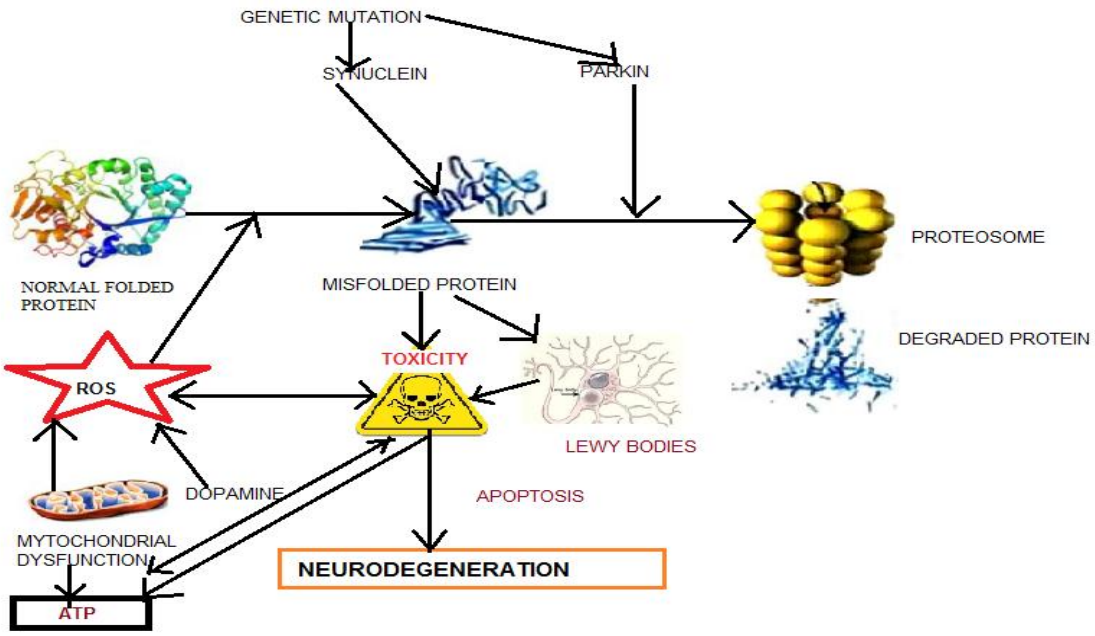

Figure1: Mechanism of neurodegeneration.

α-synuclein misfolding and aggregation has long been associated with the death of dopaminergic neurons. That is α-synuclein present in the brain is mostly unfolded form without its tertiary structure. In aqueous solution they form tetramers that resist aggregation. But upon interaction with negatively charged lipids like phospholipids, which make up the cell membrane, this α-synuclein fold into α-helical structures. In PD this protein adopts a β-sheet-rich amyloid-like structure that is more prone to aggregation.

Also in most of the studies have been found that SNpc of PD brains reported a deficiency of the mitochondrial complex-I, which is a vital component of the electron transport chain. Complex -I deficiency also found in platelets and skeletal muscle of PD patient compared to healthy ones. MPTP when oxidized to form MPP+, a toxic metabolite absorbed by dopaminergic neurons via dopamine transport leads to complex-I inhibition. Thus results oxidative stress and decrease in ATP generation. Other toxins and pesticides include

Paraquat, rotenone, and maneb. Mitochondrial dysfunction may leads to dopamine cell death due to energy depletion. The known genes responsible for PD also play a role in mitochondrial dysfunction. Includes PINK1 and parkin (PARK2 and PARK6, respectively) vital components responsible for the removal of dysfunctional mitochondria, a process called mitophagy. Mutations in either gene will lead to impaired mitochondrial quality control and which cause autosomal recessive PD. Also α-synuclein interferes with mitochondrial function. It can interact with the mitochondrial membrane and accumulate inside the organelles. This leads to the damage of complex-I activity, to mitochondrial dysfunction and increased oxidative stress.

Because of dysfunctional protein clearance systems there is an accumulation of dysfunctional protein occurs which leads to further toxicity and neurodegeneration. There are two main protein clearance systems within cells that are responsible for the removal of dysfunctional proteins:

1. Ubiquitin-proteasome system (UPS)
2. Autophagy-lysosome pathway

The UPS is primarily responsible for breaking down abnormal proteins, and "tagging" them with ubiquitin and then transporting them to the proteasome for degradation. Proteosomal abnormalities characterized by abnormal protein accumulation. In PD, catalytic activity of UPS reduced compared to healthy brains. The Autophagy-lysosome pathway is divided into three: Chaperone-Mediated Autophagy (CMA), macroautophagy and microautophagy. CMA is a more selective process, here molecular chaperones target the specific proteins and then transport them to the lysosome for degradation. In macroautophagy, an intracellular component, that is cytosolic proteins, are engulfed by the autophagosome, which then fuses with the lysosome, leading to the breakdown of its contents. Finally in microautophagy, the lysosome alone engulfs and destroys cytoplasmic components. And also the microglia-induced inflammatory processes may be contributing to the degeneration of these cells. There is also α-synuclein which directly trigger microglial activation and thus initiate inflammatory processes.

Also oxidative stress plays an important role in pathogenesis pathway. That is, the oxidative metabolism of dopamine will yield hydrogen peroxide (H2O2) and other reactive oxygen species (ROS). Oxidant stress and consequent cell death could develop in the SNpc when there is (a) Increased dopamine turnover, resulting in formation of excess peroxide; (b) an

increase in reactive iron, which can promote $OH^{\cdot}$ Formation; (c) a deficiency in glutathione (GSH) thereby diminishes the brain's capacity to clear H_2O_2. In PD brains, demonstrate decreased GSH, increased iron and oxidative damage to lipids, proteins and DNA, suggesting that the SNpc is in a state of oxidant stress. Although Glutamate excitotoxicity induces the dopamine neuronal death, cognition impairment and movement disorders. That is, Glutamate is the major excitatory neuro transmitter in the central nervous system (CNS). If glutamate is not removed promptly in the synaptic cleft. It will largely stimulate the glutamate receptors and induce excitotoxic effects on the CNS.

PHARMACOLOGIC TREATMENTS

There are several pharmacological treatments[11] that can help to alleviate some of the symptoms of PD. But, these are not a cure and clinical symptoms will reappear when the time passes.(Figure 2)

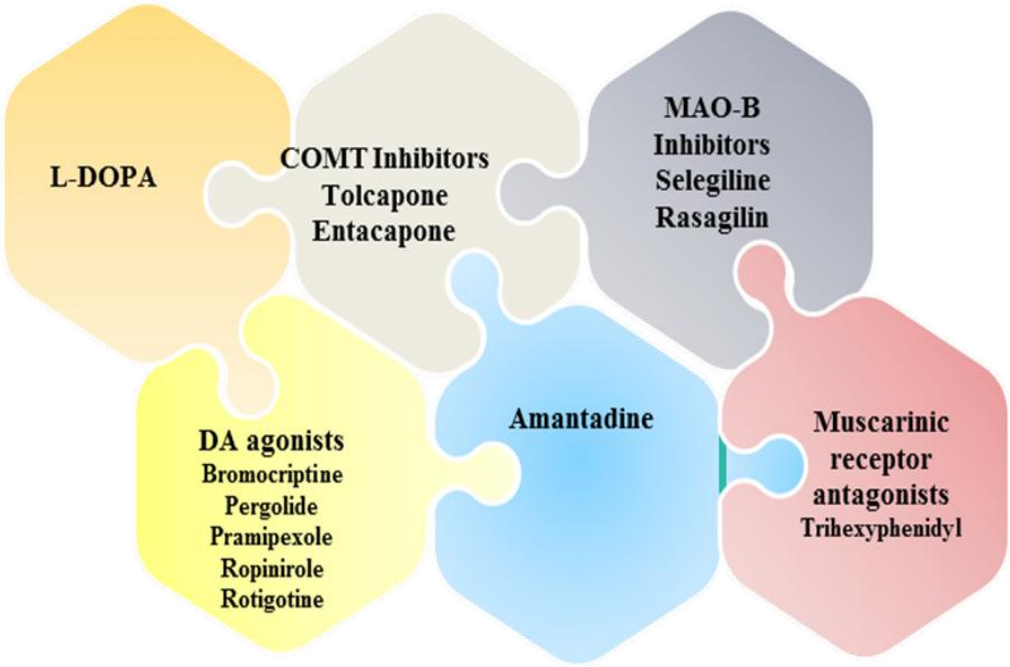

Figure 2: Pharmacological treatments.

1. L- DOPA

Levodopa (L- DOPA) is the precursor of the neurotransmitter dopamine. When this given orally as large daily doses some of them is able to escape metabolism in the blood stream and they enter into brain. Surviving dopamine neurons convert this into dopamine by

decarboxylation (removal of COOH). To increase the delivery of levodopa to the brain L-DOPA is supplemented with carbidopa(an analogue of levodopa), which helps to inhibit decarboxylation of levodopa to dopamine prior to crossing blood brain barrier(DA cannot cross BBB)As a result greater amount of levodopa are able to reach the brain, enabling the administration of lower dose of drug and thereby reducing the risk of severe side effects.

2. Dopamine receptor agonists

These are work by binding to dopamine receptors on dopaminergic neurons (The neurons that normally synthesize and use dopamine) in the absence of neurotransmitters. Stimulation of these receptors increases dopaminergic activity in the brain, thereby reducing the severity of Parkinsonism symptoms.

3. COMT AND MAO-B Inhibitors

COMT (Catechol-O-Methyl Transferase) inhibitors, such as Tolcapone and Entacapone, block the COMT enzyme which is responsible for enzymatic breakdown of dopamine. These drugs commonly given in conjugation with combination of levodopa and carbidopa. Since they inhibit COMT degradation of levodopa in the peripheral tissue thus increasing half-life of levodopa in the blood. This leads to greater amount of the drug to cross the BBB.

MAO-B (Monoamine Oxidase B) inhibitors slow down the degradation of dopamine in the brain.

4. Muscarinic receptor antagonists

Abnormal activity of neurotransmitter Acetyl choline is also responsible for producing certain Parkinsonism symptoms. This activity is mediated by binding of Ach to muscarinic Ach receptors present in the brain. Thus these agents blocks the receptors and reducing the symptoms.

5. Amantadine

It is an antiviral drug, which is used in the treatment of influenza A infection and also has some ability to reduce Parkinsonism symptoms like bradykinesia (slowness of movement) and tremor. It has been found to trigger the release of dopamine from neurons in the brain.

If these drugs taken for longer period of time there is hallucination, confusion, nausea, vomiting, leg swelling, discoloration as side effects which will be suffered by the patients.

So based on different journal being acknowledged it has been found that herbal drug is having much better effectiveness with lesser side effects. The utilization of herbal drugs and its development has expanded enormously in recent years. Nowadays, 80% of people use medicine which is directly or indirectly derived from plants. Even though treatments with herbal drug have the potential for curing diseases, the utilization of the herbal plant is increasing rapidly. Herbal products have their own advantages and disadvantages but nowadays herbal drugs are more popular among the people due to their advantages.[12]

Under these circumstances traditional knowledge on medicinal plants and current scientific information on their phyto-chemical constituents may pay way for finding cure for this disease. Use of medicinal plants and its bioactive compounds can serve as an alternative therapy for modifying or slowing down the disease progression. There are many traditional plants responsible for neuroprotective property, includes *Centella asiatica, Mucuna pruriens, Withania somnifera, Bacopa monnieri, Gingko biloba, Panax ginseng, Scutellaria baicalensis.*[13]

Nagaraja Haleagrahara et al., (2010) presented a study on Neuroprotective effect of *Centella asiatica* extract (CAE) on experimentally induced Parkinsonism, It implies that *Centella asiatica* could offer a useful support to the Parkinsonism therapy by acting as a neuroprotective antioxidant and thus prevent the neuronal damage in brain regions associated with Parkinsonism.[14] Many studies especially in animal experiments and in human interventions have shown its wide pharmacological activities in brain improvement and neuroprotective effects.[15] Based on the literature review *Centella asiatica* is been found to be a better option in Parkinson's disease.

Centella asiatica

It consists of dried whole plants of *Centella asiatica* belongs to the family Apiaceae. It is a stoloniferous perennial herb, faintly aromatic, has been used as a medicinal herb for thousands of years. It is commonly known as Indian Pennywort, Brahmi, Mandukaprnika, Mutthil and also kwon as Saraswati plant, Kodangal and Brahma Manduki.[16]

Figure 3: *Centella asiatica* plant leaves.

Figure 4: *Centella asiatica* whole plants.

Centella asiatica mostly found in sub tropical and tropical regions of India up to an altitude of 600m. Stem is glabrous, striated, rooting at the nodes. Centella asiatica flourishes extensively in shady, marshy, damp and wet places like paddy fields, river banks forming a dense green carpet and instead of clayey soil, the sandy loam (60% sand) is found to be the foremost fertile soil for its regeneration. The leaves, which are edible, are in yellowish-green color, thin, alternate with long petioles, orbicular and quite characteristic reniform, oblong-elliptic shapes with seven veins Flowers are in fascicled umbels, each umbel consisting of 3-4 white to purple or pink flowers, flowering occurs within the month of April- June. Fruits are borne throughout the season in approx 2 inches long, oblong, globular in shape and strongly thickened pericarp. Seeds have pedulous embryo which are laterally compressed.[17]

Centella asiatica is an ancient traditional medicinal herb with high pharmaceutical applications. It is widely used in India, China, and Malaysia, South Africa and Madagascar for treating various diseases. It is traditionally used as a brain tonic in ayurvedic medicines.[18] The whole plant or its parts like leaves, roots are also used for medicinal application and its chemical constituents used for different conditions like skin disorders, asthma, ulcers and body pain, for improving memory, as a brain tonic and in treatment of leprosy, dropsy, leucorrhoea, elephantiasis, gastric catarrh, kidney troubles, and in maternal

health care, in urethritis, in treatment of stomach disorders and also as a vegetable in house hold purpose.[19] The components present in the plant extract show excellent radical scavenging activities, which decreases amyloid-β (Aβ) deposition in the brain. It has high antioxidant activity, antifungal and antimicrobial activities. It contains various micronutrients like Fe, Cu, Zn, Mn, Mg this can be used in dietary supplements.[18] In India it is one of the traditional herbs used for treating Parkinsonism, preventing oxidative stress, and promoting memory enhancement, revitalizing the nerves and brain cells, hence also called as "Brain food".[20]

The leaves of C. asiatica contain various sorts of terpenes such like monoterpenes, sesquiterpenes and triterpenes.[21] The aerial parts of *C. asiatica* contain triterpenes, phenols and cadiyenol while the basis also contains monoterpenes, sesquiterpenes and triterpenes in additionally to some minerals. Asiaticoside appears to be liable for most of the pharmacological activities of *C. asiatica* reported. In animal studies, Asiaticoside has been shown to exhibit central nervous system protective effects.[21] The present study implies that *Centella asiatica* enriched with polyphenols and triterpenes could also be particularly useful xenobiotics detoxifying agents because it could decrease lipid peroxidation and enhance brain anti-oxidants and significantly prevent the brain from neuro-toxic effects.[14] *C. asiatica* could offer a useful support to the Parkinsonism therapy by acting as a neuroprotective antioxidant and thus prevent the neuronal damage in brain regions related to Parkinsonism. Thus *C. asiatica* extract enriched with bioflavonoid and triterpenes could also be considered as a strong neuroprotective agent for membrane molecular medicine. The Asiaticoside, present within the *Centella asiatica* extract are simpler in neuro protecting activity from oxidative stress. Asiaticoside shows anti-inflammatory, antipyretic activity and antioxidant, within the central nervous system, Asiaticoside also attenuates neurochemical, neurobehavioral, and histological changes. Another study demonstrated that Asiaticoside shows anxiolytic effects in both acutely and chronically stressed animals.[22] Also *Centella asiatica* contains many phytoconstitutents used for several medical applications.

Constituents present

Centella asiatica contains various phytoconstitutents[23], which liable for various medical conditions.

Glycosides: Asiaticoside A & B, madecassoside & centelloside. Upon hydrolysis these glycosides yield the triterpene acids like centellic acid, asiatic acid.

Triterpene acids: Madecassic, Asiatic, centellic, centoic, centic, centellic, brahmic & isobrahmic acid.

Alkaloids: Hydrocotylin from dried plants.

Flavanoids: kaempferol and quercetin.

Volatile & Fixed oil : fatty oil consists of glycerides of stearic, oleic, palmitic acids

Vitamins: vitamin B1, B2, A, C, niacin and carotene.

Total ash contains iron, phosphate, calcium, magnesium, chloride, sulphate, potassium and sodium.

Centella asiatica are often administered in various forms like dried powders, infusions, capsules, tinctures and also topically administered forms.[15] Therapy through intranasal administration has been an accepted form of treatment in the Ayurvedic system of Indian Medicine. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. Advances in biotechnology have made available a large number of protein and peptide drug for the treatment of a variety of diseases. As per various literatures review nasal administration is one among the simplest routes for delivery of drug to brain. Meaning the intranasal drug delivery used for treating various CNS diseases like Alzheimer's, Schizophrenia, Meningitis, and Parkinson's diseases.[24] SL Jyothi *et a*l., (2017)[24] presented a study on Nose to Brain Drug Delivery: The intranasal route of drug delivery system is an appropriate pathway for delivery of medicine to the brain directly and therefore the passage of medicines to blood brain barrier through nasal pathway.

Intranasal Drug Delivery

The nasal routes are often used for both local and systemic drug delivery. Localized nasal drug delivery is typically wont to treat conditions associated with the cavity, like rhinitis, congestion, and sinusitis. The cavity offers many advantages for systemic delivery sort of a large area for drug absorption, Rapid attainment of therapeutic drug levels within the blood, High drug permeability, Potential direct drug delivery to the brain along the olfactory nerves, Bypassing of hepatic first-pass metabolism, Direct contact site for vaccines with lymphatic tissues and Avoidance of harsh environmental and gastrointestinal conditions.[25]

A wide range of pharmaceutical dosage forms including suspensions, solutions, emulsions, gels, drops and sprays, powders, micro particles and liposome are often given intranasally wont to achieve drug actions. Meaning the cavity is an easily accessible route which is

usually well tolerated. The abundance of blood vessels within the nasal mucosa contributes to drug absorption, which is nearly adequate to intravenous injections in some instances.[26] CNS disorders can treated by giving these forms by intranasally to realize desired drug action.

Different Routes for Intranasal Delivery of Drug to Reach Brain

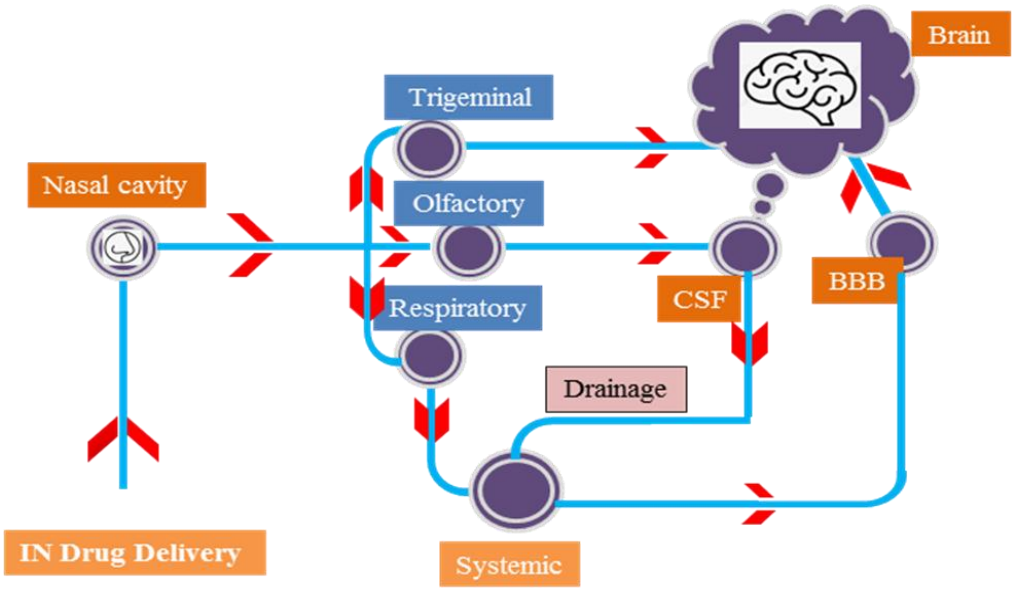

Figure 5: Pathway of nose to brain delivery.[25]

The most direct pathway to the brain is that the trigeminal nerve and olfactory pathway. The three various routes includes

1. Taken up by the trigeminal network then transferred to the cerebrospinal fluid and therefore the brain.
2. Taken up by the nasal epithelium and is transferred to the brain parenchyma through olfactory bulb.
3. Taken up by the epithelium of respiratory system directing the drug to systemic circulation which is further delivered to the brain through BBB.

Drug transport route

1. If intranasally administered drugs survive mucocilliary clearance within the vestibular region then moves to the posterior region of cavity which then contact with respiratory epithelium within the respiratory region. A number of them are absorbed through epithelium into blood or the lymphatic system is being transport to systemic circulation.
2. When the drug reaches the respiratory epithelium, a number of them could also be transported through the branches of trigeminal nerves then being internalized to peripheral

trigeminal neurons by endocytosis. Then being delivered afterward to brain stem and other hind brain and fore brain.

3. When the drugs reach the innermost region, they will be transported to the brain by three different routes

(a) Intracellular (neuronal)

(b) Extracellular

(c) Transcellular transport across the basal epithelial cells

(a) Intracellular(neuronal)

After internalization drug into the neurons then the drug or formulation may enter into olfactory sensory neurons by endocytosis or pinocytosis. Then transport along the neurons into olfactory bulb they're released by exocytosis. Then further distributed to different brain region. It's a slow process takes hours to days.

(b) Extracellular

Transport across the space between cells, which is along channel near the olfactory nerves. It requires only several minutes to succeed in olfactory bulb and other brain region. These are much faster transport. Extracellular transport because the dominant pathway to direct nose to brain.

(c) Transcellular transport across the basal epithelial cells

The transcellular route provide drug to lamina propria. Then enter into the brain through passive diffusion or active transport. These are mainly liable for the transport of lipophillic molecules.

If this is often given by intranasal route (IN), the nasal mucosa is nearby the brain, Cerebro Spinal Fluid (CSF) and therefore the drug concentrations can exceed plasma concentrations. IN delivery provides a noninvasive method of bypassing the BBB to rapidly deliver therapeutic agents to the brain, spinal cord, lymphatics and to the vessel walls of the cerebrovasculature for treating central nervous system (CNS) disorders. IN delivery also offers the advantage of straightforward administration, cost effectiveness and convenient. But in some cases low duration thank to mucocilliary clearance may be a major challenge in nasal drug delivery. The utilization of mucoadhesive can resolve this problem by localizing the formulation during a particular region of the nasal cavity, thereby improving the

bioavailability of medicine. Meaning that mucoadhesive based drug delivery will be better in combination with intranasal route.

Mucoadhesive-based Drug Delivery Systems

Mucoadhesion is that the attachment of medicine alongside an appropriate with carrier to the mucus. Mucus membrane or Mucosa is that the moist tissue that lines organs and body cavities like nose, gut, mouth rectum, genital area, and eye lid.[27] Anatomical features are different in varying body location. The drugs are formulated as sprays, powders, compacts, films or semisolids. For instance, powders and nanoparticles are wont to facilitate drug administration to the nasal mucosa. Oral strips were used for tongue or cavity. Compacts are used for drug delivery to the mouth.

As compared to oral controlled release systems, mucoadhesive delivery systems have several advantages by virtue prolongation of duration, rapid absorption, enhanced bioavailability thanks to its area and high blood flow, by pass the primary pass hepatic metabolism, avoiding the degradation of gastrointestinal enzymes, intimate contact between dosage form and absorptive mucosa, reduced dose and minimize side effect.[28]

Mucoadhesive formulation use polymers as adhesive component. These polymers are often water soluble, when utilized in a dry form they attract water from mucosal surface and this water transfer results in strong force thus increasing the retention time over mucosal surface this results in adhesive interaction prolonged contact time of a drug with a body tissue by employing a bioadhesive polymer can significantly improve the performance of the many drugs.[29]

Advantages

Mucoadhesion drug delivery system has many advantages like.[29]

Prolonged retention time.

Rapid onset of action.

Enhanced bioavailability of drug thanks to avoidance of first pass metabolism.

Enhanced absorption of drug thanks to increased blood supply.

Enhanced efficacy of the active substance.

Better patient compliance thanks to the straightforward drug administration.

Prevention of drug degradation within the GIT thanks to the presence of acid.

It is often easily used in case of unconscious and fewer co-operative patients.

Due to the high extent of perfusion the speed of drug absorption is quicker.

The side effect which will arise thanks to oral administration, such as, nausea and vomiting, they will be avoided completely.[30]

Disadvantages[31]

If mucosal drug delivery systems adhere too tightly because it's undesirable to exert an excessive amount of force to get rid of the formulation after use, otherwise the mucosa might be injured.

The lack of standardized techniques often results in unclear results.

Medications administered orally don't enter the blood stream immediately after passage through the buccal mucosa.

Costly drug delivery system.

Some patients suffer unpleasant feeling.

Drugs, which are unstable at buccal pH, can't be administered by this route.

Drugs could also be swallowed alongside the saliva and lose the benefits of buccal route.

In case of vaginal drug delivery, the drug has got to be stable within the acidic vaginal pH.

In case of ocular formulations, the formulation may cause uneasiness and blurring.

In case of nasal formulations, the presence of the formulation may stimulate sneezing and subsequent dislodgement of the formulation.

Sites for Mucoadhesive Drug Delivery Systems

The common sites of application where mucoadhesive polymers have the ability to deliver pharmacologically active agents include oral cavity, nasal cavity, GIT, eye conjunctiva, and vagina.[31]

The buccal cavity has a very limited surface area of around 50 cm^2 but the easy access to the site makes it a preferred location for delivering active agents.[31] It is the most appropriate site for oral controlled drug delivery system because it increases the residence time in the buccal mucus membrane which leads to pharmacological actions of drug in the controlled manner.[29]

The sublingual mucosa is relatively more permeable than the buccal mucosa due to the presence of large number of smooth muscle and immobile mucosa, which results in quick absorption, suitable bioavailability and are appropriate, approachable, and well received. Though sublingual mucosa has many advantages but still it is not convenient for oral

transmucosal delivery system because it has unequal and moveable mucus which are washed by saliva and causes low residence time. So these delivery systems are generally coated with a drug and water impermeable film so as to prevent the washing of the active agent by the saliva.[32]

Like buccal cavity, nasal cavity also provides a potential site for the development of formulations where mucoadhesive polymers can play an important role. The nasal mucosal layer features a area of around 150–200 cm^2. One of the key advantages provided by intranasal drug delivery is that the cavity provides an outsized highly vascularised area through which first-pass metabolism are often avoided, as blood is drained directly from the nose into the circulation. Successful nasal delivery has been obtained using solutions, gels, powders, and micro particles.

GIT is additionally a possible site which has been explored for an extended time for the event of mucoadhesive based formulations. The modulation of the transit time of the delivery systems in a particular location of the gastrointestinal system by using mucoadhesive polymers has generated much interest among researchers around the world.

The delivery of therapeutic agents to the eye could also be achieved using various sort of dosage forms including liquid drops, gels, ointments and solid ocular inserts (both degradable and nondegradable). Due to the continual formation of tears and blinking of eye lids, there's a rapid removal of the active medicament from the ocular cavity, which ends up within the poor bioavailability of the active agents. This can be minimized by delivering the drugs using ocular insert or patches.

The vaginal and therefore the rectal lumen have also been explored for the delivery of the active agents both systemically and locally. Vaginal drug delivery offers many advantages; the avoidance of hepatic first-pass metabolism, a decrease in hepatic side effects and avoidance of pain, tissue damage, and infection commonly observed for parenteral drug delivery routes of administration. While the vagina provides a promising site for systemic drug delivery due to its large area, rich blood supply and high permeability, poor retention thanks to the self-cleansing action of the vaginal tract is often problematic. However, residence times within the vagina tend to be much above at other absorption sites like the rectum or intestinal mucosa.

Each site of mucoadhesion has its own advantages and drawbacks alongside the essential property of prolonged residence of dosage form at that specific site. In buccal and sublingual sites, there's a plus of fast onset alongside bypassing the first-pass metabolism, but these sites suffer from inconvenience due to taste and intake of food. Nasal and ophthalmic routes have another drawback of mucocilliary drainage that might clear the dosage form from the location. In GIT, there's an opportunity for improved amount of absorption due to microvilli, but it's a drawback of acid instability and first-pass effects. Rectal and vaginal sites are the best ones for the local action of the drug but they suffer from inconvenience of administration.[32]

Mucoadhesive Dosage Forms

Various dosage form includes.[31,32]

Tablets

Tablets are small, flat, and oval, with a diameter of roughly 5–8 mm. Unlike the traditional tablets, mucoadhesive tablets leave drinking and speaking without major discomfort. They soften, adhere to the mucosa, and are retained in position until dissolution and/or release is complete. Mucoadhesive tablets, in general, have the potential to be used for controlled release drug delivery, but coupling of mucoadhesive properties to tablet has additional advantages, for instance, it offers efficient absorption and enhanced bioavailability of the drugs thanks to a high surface to volume ratio and facilitates a way more intimate contact with the mucus layer. Mucoadhesive tablets can be tailored to adhere to any mucosal tissue including those found in stomach, thus offering the possibilities of localized as well as systemic controlled release of drugs. The application of mucoadhesive tablets to the mucosal tissues of gastric epithelium is employed for administration of medicines for localized action. Mucoadhesive tablets are widely used because they release the drug for a protracted period, reduce frequency of drug administration and improve the patient compliance. The major drawback of mucoadhesive tablets is their lack of physical flexibility, leading to poor patient compliance for long-term and repeated use.

Patches

Patches are laminates consisting of an impermeable backing layer, a drug-containing reservoir layer from which the drug is released during a controlled manner, and a mucoadhesive surface for mucosal attachment. Patch systems are almost like those utilized in transdermal drug delivery. Two methods wont to prepare adhesive patches include solvent

casting and direct milling. In the solvent casting method, the intermediate sheet from which patches are punched is ready by casting the solution of the drug and polymer(s) onto a backing layer sheet, and subsequently allowing the solvent(s) to evaporate. In the direct milling method, formulation constituents are homogeneously mixed and compressed to the specified thickness, and patches of predetermined size and shape are then cut or punched out. An impermeable backing layer can also be applied to regulate the direction of drug release, prevent drug loss, and minimize deformation and disintegration of the device during the appliance period.

Films

Mucoadhesive films may be preferred over adhesive tablets in terms of flexibility and comfort. In addition, they will circumvent the relatively short duration of oral gels on the mucosa, which are easily washed away and removed by saliva. Moreover, within the case of local delivery for oral diseases, the films also help protect the wound surface, thus helping to scale back pain, and treat the disease more effectively. An ideal film should be flexible, elastic, and soft, yet adequately strong to face up to breakage thanks to stress from mouth movements. It must also possess good mucoadhesive strength so as to be retained within the mouth for the specified duration of action. Swelling film, if it occurs, should not be too extensive in order to prevent discomfort.

Gels and ointments

Semisolid dosage forms, like gels and ointments, have the advantage of easy dispersion throughout the oral mucosa. However, drug dosing from semisolid dosage forms might not be as accurate as from tablets, patches, or films. Poor retention of the gels at the location of application has been overcome by using mucoadhesive formulations. Certain mucoadhesive polymers, for example, sodium carboxymethylcellulose, carbopol, and xanthan gum, undergo a phase transition from liquid to semisolid. This change enhances the viscosity, which ends up in sustained and controlled release of medicines. Hydrogels also are a promising dosage form for buccal drug delivery. They are formed from polymers that are hydrated in an aqueous environment and physically entrap drug molecules for subsequent slow release by diffusion or erosion. The application of mucoadhesive gels provides an extended retention time within the mouth, adequate drug penetration, also as high efficacy and patient acceptability. A major application of adhesive gels is that the local delivery of medicinal agents for the treatment of periodontitis, which is an inflammatory and communicable disease

that causes formation of pockets between the gum and the tooth, and can eventually cause loss of teeth. It has been suggested that mucoadhesive polymers could be useful for periodontitis therapy when incorporated in antimicrobial-containing formulations that are easily introduced into the periodontal pocket with a syringe.

The mucoadhesive dosage forms offer prolonged contact at the location of administration, and better patient compliance. The formulation of mucoadhesive drug delivery system is highly dependable upon the selection of suitable polymer with excellent mucosal adhesive properties and biocompatibility.[33]

CONCLUSION

Parkinson's disease (PD) is a chronic, progressive age-related neurodegenerative disorder. Resulting from the loss of dopamine-producing neurons in the substantia nigra. If the currently marketed drugs taken for longer period of time there is different side effects which will be suffered by the patients. So based on different journal being acknowledged it has been found that herbal drug is having much better effectiveness with lesser side effects. Use of medicinal plants and its bioactive compounds can serve as an alternative therapy for modifying or slowing down the disease progression. Therapy through intranasal administration has been an accepted sort of treatment within the Ayurvedic system of Indian Medicine. IN delivery also offers the advantage of straightforward administration, cost effectiveness and convenient. But in some cases low duration thank to mucocilliary clearance may be a major challenge in nasal drug delivery. The utilization of mucoadhesive can resolve this problem by localizing the formulation during a particular region of the nasal cavity, thereby improving the bioavailability of medicine. Meaning that mucoadhesive based drug delivery will be better in combination with intranasal route.

REFERENCES

1. Dauer W, Przedborski S.Parkinson's Disease: Mechanisms and Models Review. Neuron, 2003; 39: 889-909.
2. Radhakrishnan DM, Goyal V. Parkinson's disease: A review. Neurol India, 2018; 66(1): 26-35.
3. Abhijeet D. Kulkarni, Yogesh H. Vanjari, Karan H. Sancheti, Veena S. Belgamwar, Sanjay J. Surana, and Chandrakantsing V. Pardeshi. Nanotechnology-mediated nose to brain drug delivery for Parkinson's disease: a mini review. Journal of Drug Targeting, 2015; 15(2): 1-14.

4. A H V Schapira. Present and future drug treatment for Parkinson's disease. J Neurol Neurosurg Psychiatry, 2005; 76: 1472–1478.
5. Spehlmann R, Stahl SM. Dopamine acetylcholine imbalance in Parkinson's disease. The lancet, 1976; 307(7962): 724-726.
6. Parkinson J.An Essay on the Shaking Palsy.J Neuropsychiatry Clin Neurosci, 2002; 14(2): 223-236.
7. Schapira AH, Jenner P.Etiology and Pathogenesis of Parkinson's Disease. Movement Disorders, 2011; 26(6): 1049-1055.
8. Lotharius J, Brundin P.Pathogenesis of Parkinson's disease: dopamine, vesicles and α-synuclein. Neuroscience, 2002; 3: 932-942.
9. Hindle J V.Ageing, neurodegeneration and Parkinson's disease. Age and Ageing, 2010; 39: 156–161.
10. Olanow C W, Tatton W G.Etiology And Pathogenesis Of Parkinson's Disease. Annu. Rev. Neurosci, 1999; 22: 123-144.
11. Jankovic J, Aguilar L G.Current approaches to the treatment of Parkinson's disease. Neuropsychiatric Disease and Treatment, 2008; 4(4): 743–757.
12. Quazi MA, Molvi KI. Herbalmedicine: A comprehensive review. International journal of pharmaceutical research, 2016; 8(2): 1-6.
13. Divya S, Kavimani S, Sudha Rani S, Subashree S, Praveen Kumar S, Mahalakshmi G, Nirmala T, Samundeswari R, Sivassoupramanian D.Parkinson's Disease: A Phytochemical Approach. International Journal of Pharmacy Review & Research, 2014; 4(2): 111-119.
14. Haleagrahara N, Ponnusamy K.Neuroprotective effect of *Centella asiatica* extract (CAE) on experimentally induced parkinsonism in aged Sprague-Dawley rats. The Journal of Toxicological Sciences, 2010; 35(1): 41-47.
15. Hashim P.MiniReview Centella asiatica in food and beverage applications and its potential antioxidant and neuroprotective effect. International Food Research Journal, 2011; 18(4): 1215-1222.
16. Singh S, Gautam A, Sharma A, Batra A.Centella asiatica (L.): A Plant With Immense Medicinal Potential But Threatened. International Journal of Pharmaceutical Sciences Review and Research, 2010; 4(3): 9-17.
17. Mohd Moklas M A, Chiroma S M, Che Norma M, Taufik M, Amon Z, Jagadeesan S, Ibrahim B.Neuro-therapeutic Benefits of Centella asiatica on Some Neurodegenerative

Diseases: A Review. Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2017; 8(6): 549-556.

18. Byakodi M K, Bagewadi Z K, Uday M Muddapur. Phytoconstituents Profiling and Evaluation of Antimicrobial and Antioxidant Attributes of Methanolic Extract of Centella asiatica. Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2018; 9(3): 493-500.
19. Manisha V, Ajit K, Varsha G.Pharmacognostic standardization, phytochemical evaluation and wound healing activity of leaf extracts of *Centella asiatica*. International Journal of Innovative Pharmaceutical Sciences and Research, 2018; 6(09): 44-58.
20. Suryawanshi V.S, Biradar S R, Rachetti B D.Phytoconstituents of a valuable ayurvedic medicinal herb *Centella asiatica* (L.) URB. Trends in biotechnology research an international peer-reviewed journal, 2013; 2(1): 12-16.
21. Aziz Z, Chong N J.A systematic review on the chemical constituents of Centella asiatica. Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2011; 2(3): 445-459.
22. Qi F Y, Yang L, Tian Z, Zhao M G, Liu S B, An J Z.Neuroprotective effects of Asiaticoside. Neural Regeneration Research, 2014; 9(13): 1275-1282.
23. Pal R S, Pal Y.Pharmacognostic review and phytochemical screening of Centella asiatica Linn. Journal of Medicinal Plants Studies, 2016; 4(4): 132-135.
24. Gowda DV, Jyothi SL, Gupta N V, Osmani R A M.Nose to Brain Drug Delivery: New Perspectives for Old Problems -An Enlightening Review. Journal of Chemical and Pharmaceutical Research, 2017; 9(7): 111-122.
25. Sonvico F, Clementino A, Buttini F, Colombo, Pescina S, Guterres S S, Pohlmann A R, Nicoli S.Surface-Modified Nanocarriers for Nose-to-Brain Delivery: From Bioadhesion to Targeting. Pharmaceutics, 2018; 10: 34.
26. Shabana P, Bonthagarala B, Harini A L, Dasari V.Nasal Drug Delivery: A Potential Route for Brain Targeting. International Journal of Advances in Scientific Research, 2015; 1(02): 65-70.
27. Rhushikesh S, Suresh S.A review on mucoadhesive drug delivery system. International Journal of Research and Analytical Reviews, 2020; 7(1): 793-808.
28. Jyotsana M, Sagar B, Mahesh D.Mucosal drug delivery system. International Journal of Research in Ayurveda & Pharmacy, 2010; 1(1): 63-70.

29. Gurjeet Singh T, Dhiman S, Dhiman H, Arora S.Mucoadhesion Drug Delivery Sytem: A Propitious Approach. International Journal of Pharmaceutical Sciences Review and Research, 2018; 50(2): 72-88.
30. Singh R, Sharma D, Garg R.Review on Mucoadhesive Drug Delivery System with Special Emphasis on Buccal Route: An Important Tool in Designing of Novel Controlled Drug Delivery System for the Effective Delivery of Pharmaceuticals. Journal of Developing Drugs, 2017; 6(1): 1-12.
31. Dr.Khokan Bera, Dey T, Samanta B, Dr.Beduin Mahanti. Mucoadhesive Drug Delivery System: A Review Article. International Journal of Pharmacy and Engineering, 2020; 8(2): 944-960.
32. Boddupalli B M, Mohammed Z N K, Ravinder Nath A, Banji D.Mucoadhesive drug delivery system: An overview. Journal of Advanced Pharmaceutical Technology & Research, 2010; 1(4): 381-387.
33. Lalge M, Sharma P K, Bhandari A, Garud A, Garud N.Mucoadhesive drug delivery system: a review. Critical review in pharmaceutical sciences, 2014; 3(3): 17-29.