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INTRANASAL GEL TO TREAT PARKINSON DISEASE

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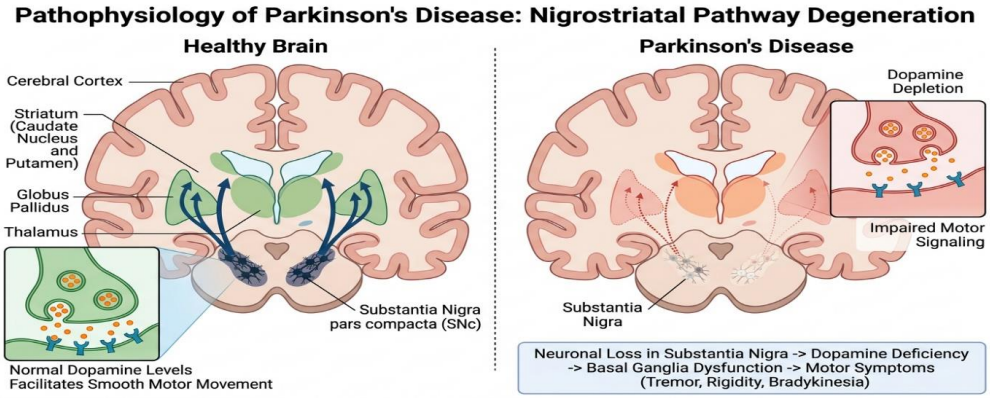
1. INTRODUCTION

Parkinson disease the second most common neurodegenerative disease caused due to the degeneration of dopaminergic neuron in substantial nigra results in the depletion of striatum dopamine.[1] The symptoms of this disease are classified into motor and non-motor symptoms. The motor symptoms in this includes muscle tension, shaking, rigidity, difficulty in walking or even in performing basic activities.[2] The non motor symptoms consist of memory loss, personality change, urinary and stool incontinence and dementia these symptoms are mostly seen in elderly population.[3] The diagnosis or the detection of Parkinson disease is done by bradykinesia, rest tremor, rigidity and loss of postural reflexes. Some other diagnostic measure for the clinical factors is bulbar dysfunction, neuro ophthalmological abnormalities and respiratory distribution.[4] The treatment is further characterized in to three groups. That are pharmacological treatment encompasses levodopa, carbidopa, dopamine agonists, MAO-B inhibitor, COMT inhibitor, anti -cholinergic and amantadine.[5] The non-pharmacological treatment comprises of physical, occupational, speech and nutritional therapy and exercises.[6] The last treatment form is surgery process that includes DBS (improves electrodes in subthalamic nucleus) and lesioning surgery (small lesion create targeted area of brain to disrupt abnormal drug activity).[7] Due to these traditional routes of administration or mode of treatment many difficulties were faced like difficulty in penetrating the BBB (blood brain barrier) and CSF (blood-cerebrospinal fluid), extensive first pass metabolism, enzymatical degradation, organ toxicity etc.[8]

1.1 Pathophysiology

The pathophysiology of Parkinson disease initiates from destruction of dopaminergic neuronal cell in the substantia nigra in the basal ganglia that further degenerates the dopaminergic nigrostriatal pathway that results in depletion of dopamine storage. The imbalance in the level of acetylcholine and dopamine neurotransmitters in corpus striatum the impairment of extrapyramidal tracts controlling complex body movement result in tremors, rigidity and bradykinesia.[9]



1.2. Intranasal Gel

In 1989 William Frey introduced intranasal administration to brain.[10] By this method BBB is bypassed and enables the delivery of small molecules and large protein substances to CNS, avoiding first pass metabolism in liver, reduces degradation by gastrointestinal enzyme and systematic toxicity.[11,12] Intranasal gel has some additional advantages like faster onset of action, enhancing efficacy, reduces toxicity and painless easy self-administered formulation.[13]

1.21 Pathway of drug to brain via intranasal administration

The nasal cavity has a large surface area that is well vascularized with relative permeability and epithelial endothelial basement membrane with pores making it suitable site for absorption.[14] The medication travels to CNS by two pathways that are the direct pathway (olfactory nerve and trigeminal nerve) and indirect pathway (systemic routes).

1.211 Direct pathway

The olfactory pathway is the main transport pathway for drugs from nose to brain. The drug transmits to brain via three different pathways. Firstly, is the intracellular or axonal transport which is done by receptor mediated endocytosis crossing the cribriform plate to reach the olfactory bud that further diffuses in various parts of brain like amygdala, hypothalamus and cortex.[15,16] Second pathway is the para cellular route that is within the nasal cavity due to continuous regeneration of neuronal and basal nerve cell causing the cell junction to form tight junction that provides a base for paracellular movement and further it crosses the nasal epithelium to reach olfactory bud and CNS within few minutes.[17] The third pathway is the perineural route in this the perineural space is the area between neuron and myelin sheaths through which the substance moves to olfactory nerve.[18] After the olfactory pathway trigeminal pathway comes under the category of direct pathway. The trigeminal nerve consists of three branches: the ophthalmic, maxillary and mandibular nerves that carry motor and sensory impulse to brain. same as olfactory the tree pathways are intracellular in which the substance internalized with trigeminal neurons by endocytosis and further reaches olfactory bud through exocytosis and finally reaches the brain stem.[19] In paracellular pathway the drug passes through the TJs of trigeminal nerve that further migrates through paracellular spaces of nasal epithelium to reach CNS.[20] The last pathway is the perineural pathway in which the drug moves with the trigeminal nerve crosses the cribriform plate and reaches the brain stem.[21]

1.212 Systemic pathway

As a strong vascularization of nasal cavity medication can enter the CNS through the blood stream. Both small and large molecules can flow continuously and enter the circulatory system. So, in this pathway the drug must pass the BBB to reach the CNS. Due to the crossing of the BBB the medicinal success rate limits and lengthens the time for therapeutic benefits to manifest.[22] The drug administered by the intranasal route a portion of medication travels to the gastrointestinal track via ciliary movement where it gets indirectly absorbed by the gastrointestinal system.[23]

2. RESEARCH HYPOTHESIS

The two plants that we will be using are velvet seeds and Tulsi.

2.1 Velvet seeds

Scientific name *Mucuna pruriens* belonging to family *Fabaceae* (*Leguminosae*) subfamily *Faboideae* and tribe *Phaseoleae*.[24] The species is diploid and widely distributed in tropical and subtropical region usually in Africa, Asia and America.[25] These seeds are containing L-dopa as the major bioactive constituent. As per literature the L-dopa content in the seeds is 1.79%-7%. Various other constituents like phenolic acids, flavonoids, tannins, saponins, phytates, oligosaccharides, trypsin inhibitor and cyanogenic compounds are also present.[26]

In accordance to the parkinsonian effect of velvet seeds clinical trial has being conducted in which 15 and 30 gm of velvet seed powder along with carbamazepine (200/50 mg) was given to 8 patients. The longer duration of action suggested that the velvet seeds can actually benefit Parkinson patients.[27]

2.2 Tulsi

Scientific name Ocimum sanctum belonging to the family Lamiaceae is also known as queen of herbs. This is because Tulsi act as anti-microbial, anti-inflammatory, neuroprotective agent etc. the extract of Tulsi leaves shows effect on Parkinson disease that is indicated by rotenone and a catalepsy induced by haloperidol in rats and muscle rigidity in mice.[28]

The intranasal gel from velvet seeds and Tulsi will hand in hand improve the motor symptoms and dopamine level. As compared to oral administration the gel will enhance the delivery to the brain via olfactory pathway leveraging L-dopa from velvet seeds and neuroprotective effect from Tulsi.

3. MATERIAL AND METHODS

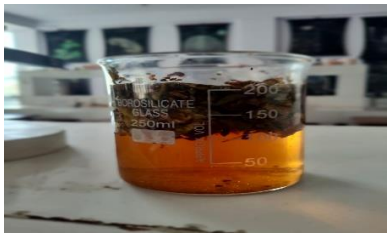
In this formulation we use velvet seeds (as API) which contains natural L dopa. The other plant is Tulsi its leaf extract has neuroprotective effect and deals with muscle rigidity.[26-28] Gelatin in this formulation is used as natural mucoadhesive polymer.[29] Other is Glycerin which is a solubilizing agent that prevents the gel from drying or even can be considered as gelling agent in combination with gelatin.[30] Then Methyl paraben which act as preservative at 0.05% w/v pr 0.1% w/v. Distilled water that acts as vehicle. At last Sodium hydroxide which act as buffer to reach a pH 5.8-7.0.[31]

We prepared the intranasal gel by **HOT METHOD**. Usually used for gellant gum or pectin, this involves dissolving polymers in hot water and cooling them before adding the drug.

Extraction of velvet seeds was performed by maceration method by dissolving the drug in vehicle (distilled water) for 24 hours and then filter the mixture to get the solvent or the extract as shown in figure 1.[32]

Extraction of Tulsi performed by hot maceration method by dissolving the drug in vehicle (distilled water) and boil it for 30 min then filter the same for the solvent or the extract as shown in figure 2.[33]

[Figure 1]

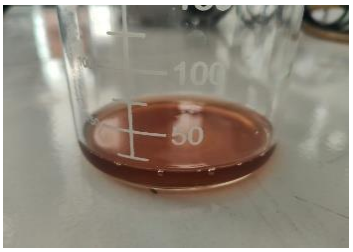


[Figure 2]

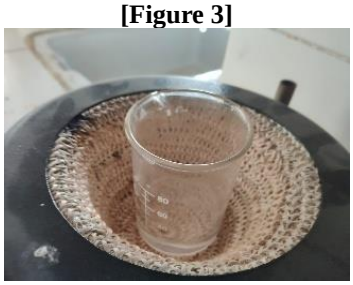
4. Procedure

The preparation of intranasal gel performed by mixing 10gm of gelatin and 100ml of water. Heat the solution in the temperature 70 degree Celsius until a homogeneous mixture is formed shown in figure 3.[34] Take 5ml of the solution from the above mixture. Add 5 ml of velvet seed extract and 5 ml of Tulsi in it after checking the optimum pH as shown in figure 4.[35] In another beaker add 7 ml glycerin and 20 ml of water and heat it again at temperature 70 degree Celsius as shown in figure 5. While the mixture is maintained at the temperature of 50 degree Celsius add the gelatin mixture to it with continuous stirring. Add 1 drop of methyl paraben in the solution as preservative. Add NAOH ad stirs constantly to maintain the pH of the gel.[36] Then place it in room temperature for 1-2 hrs. to set the gel as the final product is given in figure 6.

[Figure 3]



[Figure 4]



[Figure 5]

[Figure 6]

4.1 Evaluation of Intranasal Gel

1. Physical evaluation

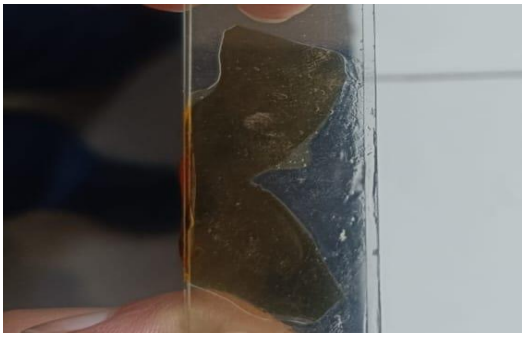
The physical parameters such as color of the herbal gel were observed manually. The prepared gel of velvet seeds and Tulsi formulation was yellow with homogeneous appearance.

2. Homogeneity

The visual inspection of the developed formulation was done for homogeneity. They are observed for there appearance and presence of any aggregation.[37] The gel formulation was found homogenous and lump free.

3. Spreadability

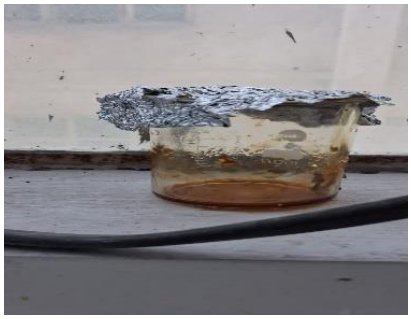
Spreadability was measured on the basis of slip and drag characteristics of gel. In this 2g and above of gel was taken in a ground slide another slide of same diameter as ground slide was taken and was pressed for 5 minutes.[38] The gel covering the top slide was noted 7.8 cm. The gel is easily spreadable by small amount of shear shown in figure 7.



[Figure 7]

4. Stability

The stability of the product was tested by keeping the sample for a week in room temperature and in a refrigerator. The product after 3 days started to turn black at room temperature as shown in figure 8 but was found to be stable when kept in a refrigerator.



[Figure 8]

5. Measurement of pH

The pH of the intranasal gel formulation was 7.07shown in figure 9 that is generally accepted and well tolerated but is slightly higher than nasal physiological range (6.2-6.4) and shows no deviation over time.[39]

[Figure 9]

5. DISCUSSION

An intranasal gel made from Mucuna pruriens (Velvet Seeds) extract, which contains L-DOPA, and Ocimum sanctum (Tulsi) leaf extract, may be a promising option for treating Parkinson's disease. This gel can deliver medication directly to the brain via the nose, bypassing the blood-brain barrier. The gel has a pH of 7.07, is spreadable, and keeps its consistency when stored in the refrigerator. Gelatin and glycerine help the gel stick inside the nose and dissolve properly, supporting fast effects and limited side effects. Oral L-DOPA treatments are less effective due to poor absorption and breakdown before reaching the brain, which can cause unstable dopamine levels. Intranasal delivery provides improved bioavailability, as seen in other drugs like apomorphine. Using velvet bean as the L-DOPA source works well for sustained symptom relief. Tulsi leaf may help protect nerve cells by lowering oxidative stress and reducing muscle rigidity.

6. CONCLUSION

An intranasal gel containing Mucuna pruriens and Ocimum sanctum (Tulsi) is a good, non-invasive therapy option that can be used for the management of Parkinson's disease. Through the use of the nose-to-brain pathway, this gel formulation eliminates the shortcomings of oral formulations due to their inability to penetrate the BBB, the extent of first-pass effect, and the possibility of enzymatic breakdown. The gelatin was effectively employed as a mucoadhesive polymer while a hot process was used to obtain an ideal homogeneous and spreadable gel product. The formulation appears to be stable when kept under refrigeration and therefore holds promise for future applications. Combining the intrinsic ability of Mucuna pruriens as an L-Dopa source and Tulsi's neuroprotective and anti-inflammatory properties, this combination could be an effective means of treating motor as well as non-motor symptoms associated with Parkinson's. The nasal route has the added advantage of being less complicated compared to the oral route especially when dealing with elderly patients. Not only will the use of the nasal route result in quick relief from symptoms but it will also minimize cases of systemic toxicity due to the drug.

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