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Nasal Route: A Potential Alternative for Antiparkinsonism Drug Delivery

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Abstract: Nasal administration has now been perceived as very optimistic route for delivery of therapeutic compounds. It has been proved that low absorption of drugs can be countered by using absorption enhancers or increasing the residence time of drug in the nasal mucosa and also by using mucoadhesive polymers. In this manner it is possible to efficiently deliver challenging drugs such as low molecular weight polar molecules, antiparkinsonism drugs and macromolecular polysaccharides. This review emphasizes on different delivery systems or routes and different drugs that are used for the treatment of parkinsonism disease. It also focuses on the strategies to improve nasal absorption release kinetics of drugs to prolong therapeutic effects and reducing the frequency of administration.
Key words: Nasal Route, Antiparkinsonism Drug Delivery.

INTRODUCTION:

In 1817 James Parkinson published and described the clinical features of Parkinsonism disease.[1] He provided a visual and detailed description of symptoms and discussed progressive worsening of the disorder. Parkinsonism disease is a leading cause of neurological disability; it is the second most common progressive neurodegenerative disorder. The effect of the parkinsonism disease reaches 1-2% in people over the age of 50. It has no gender preference and has a worldwide distribution. [2] The symptoms of parkinsonism disease are largely related to progressive loss of dopamine in the basal ganglia. The symptoms are described in Table 1. The main cause of the Parkinson's disease is unknown, but it is well-characterized. The degeneration of brain cell occurs primarily in the midbrain region area called as substantia nigra. Normally, substantia nigra brain cells communicate with another region of the brain called as the striatum via chemical messenger called dopamine also loss of cell in the substantia nigra results decrease in the levels of available dopamine. The exogenous substitution with dopamine agonists on the dopamine prodrug, levodopa corrects the mechanical disorders at early stage of parkinsonism disease. The levodopa is converted into dopamine after its administration and stored in the dopaminergic neurons, still levodopa is considered as best drug in the treatment of parkinsonism disease.

Table1: Symptoms of parkinsonism disease.

PRIMARY MOTOR SYMPTOMS	SECONDARY MOTOR SYMPTOMS
Bradykinesia (slowed movement)	Micrographia (small handwriting)
Muscle rigidity (stiffness)	Dysarthria (soft, muffled speech)
Resting tremor (shaking; usually more pronounced on one side of the body)	Reduced arm swing on the affected side of the body
Postural instability (poor balance)	Short-stepped or shuffling gait
	Reduced eye blinking and frequency of swallowing
	Depression and anxiety
	Sleep disorders
	Low blood pressure

DRUGS FOR PARKINSONISM DISEASE:-
Parkinson's disease is a chronic disorder that requires broad-based management including patient and family education, support group services, general wellness maintenance, physiotherapy, exercise. There are number of drugs which are used in the treatment of parkinson's disease. These contains agonists of dopamine (e.g. apomorphine), cholinesterase inhibitors (e.g. donepezil) etc and provide safety, compliance, feasibility and short term/long term efficacy to the patients. [3] The drugs are shown in Table 2.

Table2: Drugs for parkinsonism disease.

S.NO.	CATEGORY OF DRUG	PHARMACOKINETIC	DOSE & MARKETED PRODUCT
I	DOPAMINERGIC SRUGS (A) DOPAMINE PRECURSOR (LEVODOPA)	❖ It absorbed by small intestine by on active transport system. ❖ Decarboxylation Occurs in peripheral tissue like cut wall, liver & kidney ❖ It Do not cross BBB & enzyme inhibitor is needed like benserazide.	Dose: 2-3g/day Marketed product: - Levopa, braopal (0.5g tab).
	(B) PERIPHERAL DECARBOXYLASE INNHBITOR :- (CARBIDOPA & BENSERAZIDE)	❖ Both Extracerebral dopa decarboxylase inhibitors. ❖ They donot penetrate BBB & also donot inhibit conversion of levodopa to dopamine in brain. ❖ On-off effect is minimized Since Cerebral dopamine levels are more sustained.	Dose :- CARBIDOPA : 7-5 100 mg BENSERAZIDE :- 100-200 mg Marketed Product :- Benspar, Madopar (Benserazide (25 mg) + Levodopa (100mg) }] Capsule
	(C) DOPAMINERGIC AGONIST :- (BROMOCRIPTINE) (ROPINROLE & PRAMIPERXOLE)	❖ Bioavailability is lower by high first pass metabolism in liver. ❖ Metabolites are excreted mainly in bile & plasma t ½ in 3 hours. ❖ It's rapidly absorbed orally & bound 40% to plasma protein with t1/2 of am 6 hrs.	Dose :- 1.25 mg once at night (LD') 5 to 10 mg thrice daily (HD) Marketed Product :- Proctinal, Parlodel, Sicriptin, bromogen (1.25, 2.5 tabs) Dose :- Ropinirole :- 0.25 mg (LD') 4.8 mg (HD) Marked Product: - Requip – 0.25 to 5 mg tab. Pramipexole :- 0.125 mg (LD') 0.5 – 1.5 mg. (HD) Marketed Product: - Mirapes, sifrol, Mirapexin.

		❖ Reducing frequency of on-off effect.	
	(D) SELECTIVE – MAO-B-INHIBITOR (SELEGILINE)	❖ Attenuates Motor fluctuation & decreasing wearing off effect. ❖ It inc. intraneuronal levels of dopamine. ❖ It irreversibly inhibits MAO-B enzyme in nerve endings.	Dose: - 5 mg twice a day breakfast & lunch. Marketed Product: - eldepryl 5,10 tab. Selgin 5 mg Tab.
	(E) DOPAMINE FACILITATOR (AMANTADINE)	❖ It stimulates/Promotes the release of dopamine stored in synaptic terminals. ❖ It's well absorbed long half life and excreted unchanged by kidney. ❖ It reduces reuptake of the released dopamine by pre synaptic neuron.	Dose : - 100 mg twice in a day Marketed Product : Amantrel 100 mg tab.
	(F)COMT INHIBITORS (ENTACAPONE & TOLCAPONE)	❖ When peripheral decarboxylation of LD is blocked by CD/BS is metabolized by COMT to 3-0-Methyldopa. ❖ It allows larger fraction of administered dose to cross to brain & plays important role in degradation of DA in brain. ❖ COMT inhibitor preserves DA formed in striatum & supplement the periphery effect.	Dose: - 100 -200 mg twice or thrice daily. Marketed Product: - COMTAN Tablets.

II	CENTRAL ANICHOLINERGIC AND ANTIHISTAMINICS DRUGS (Trihexyphenidyl, Procylidine, Biperiden, Orphanodrine,	❖ These agents block the effect of excess acetylcholine in corpus striatum. ❖ It is used in combination with levodopa to obtain better control on disease.	DRUG	DOSE	MARKETED PRODUCT
			Trihexyphenidyl	2-10 mg/day	Pacitane, Carbenz (2 mg tab.)
			Procylidine	5-20 mg/day	Kemdrin (2.5,5mgtab)
			Biperiden	2-10 mg /day	Biperiden 2 mg

		Orphanodrine	(Oral,i.m., i.v.)	tab., 5mg/ml inj.
				Dispal, Orphipal (50 mg tab.)
Promethazine)		Promethazine	100-300mg /day	
				Pheneragan (10,25 mg tab.0
			25-75 mg/day	

Abbreviations: **LD', Low dose: HD, high dose: MAO, monoamine oxidase: CD, carbidopa: BS, benserazide: COMT, Catechol-o-methyl transferase: DA, dopamine: i.m., intramuscular: i.v., intravenous: LD, levodopa:**

VARIOUS APPROACHES USED IN TREATMENT OF PARKINSONISM DISEASE:

1. ORAL ADMINISTARTION:-

1.1 Immediate-release drug delivery:-

The first marketed product containing a combination of levodopa and carbidopa was an immediate-release (IR) oral dosage form under the trade name of Simenet® and other commercialized products like Madopar® which contained levodopa, peripheral decarboxylase inhibitor and benserazide. Under conventional oral medication, in early stages of disease the response of levodopa is very beneficial because the buffering and compensatory mechanisms are highly intact, With the progression of the disease, patients become very sensitive to rapid fluctuations in plasma levodopa concentrations and dopaminergic terminals continue to degenerate and are no longer able to buffer the exogenous levodopa adequately, as a result patients experience one or more periods during the day when the dose of levodopa wears off. After the administration of an immediate release tablet, the plasma levodopa level rises and falls rapidly because of the short plasma half-life of the drug (1 h), its dependence to enzymatic conversion, and its narrow absorption window at the upper part of the small intestine. [4] The dopamine receptors are thus stimulated in a frequent abnormal and intermittent fashion, thereby developing an oscillating clinical response during chronic treatment of parkinsonism disease. The repeated dosing of levodopa cause pulsatile stimulation of D1 and D2 receptors and subsequent desensitization, which may also induce dyskinesis. These abnormal involuntary movements occur in 75% of patients after about 6 years of levodopa therapy. As parkinsonism disease evolves, the brain loses its ability to regulate dopamine function as both storage and release become impaired. Consequently, a long-duration response to a single levodopa dose is gradually replaced by a shortening interval of effect and a need for more drug.[5] The "on–off" effect comprises an "on" state when the patient has a good response from levodopa and an "off" period characterized by a sudden loss of benefit when the plasma level of the drug falls.[6] Usually, a wearing off phenomenon can be defined to be present when an adequate dosage of levodopa does not lose for at least 4 h. However, in the late stages of the disease, the duration of the "on" response becomes shorter. In addition to the apparent tolerance that appears with a chronic intake of levodopa, interpatient variability can result in adverse events or decreased efficacy. [7] Conventional administration schemes shown their limitation when connected with motor fluctuations that appear over years of treatment and proposed a new dispensing device that was able to deliver individual doses of levodopa and carbidopa.

1.2 Liquid and dispersible drug delivery:-

Levodopa may decrease the t_{max} because its gastric emptying is less dependent on pylorus contraction when compared to conventional solid dosage forms the but it shows similar pharmacokinetic parameters and plasma levodopa levels were found to be more stable under liquid administration.[8] This clinical benefit was probably due to the ability of patients to fractionate the liquid dose more easily, according to their requirements. Dispensable products could be more beneficial in treating morning motor disturbance in parkinsonism disease patients undergoing long term levodopa therapy. Indeed, a long-term levodopa administration causes increased levodopa bioavailability due to a deteriorated metabolism. [9] With liquid formulations providing an immediate levodopa supply, the time taken to reach the "on" response in the morning could be shorter than that required with a standard solid dosage form. Solid dosage forms as well as liquid/dispersible preparations provide an immediate supply of levodopa and, associated with the short half-life of this drug, lead to a more intermittent delivery resulting in the appearance of peaks and troughs in plasma levodopa levels. [10] Ultimately, they failed to provide adequate relief

because the therapeutic index narrows as parkinsonism disease progresses.

1.3 Sustained-release drug delivery:-

Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum effects. The main advantage of these dosage forms over immediate release (IR) dosage forms lies in the plasmatic concentrations which can easily be leveled in the therapeutic range of the drug over an extended period of time with reducing dose frequency (increased patient compliancy), thus it limits side effects and reduce plasmatic peaks. To compare the pharmacokinetic parameters and the efficacy on parkinsonism disease patients of the controlled-release (Sinemet® CR) versus the standard formulation (Sinemet®) many clinical trials have been conducted. [11-12] The formulations are composed of levodopa and carbidopa. The controlled release system contains 200 mg of levodopa and 50mg of carbidopa, whereas a half-dose of both drugs is incorporated in the standard Sinemet®.[13] After oral administration of the controlled release system no initial peak of levodopa was observed. [14] The t_{max} obtained for levodopa from Sinemet® CR (t_{max} = 4 h) was almost double that of the standard Sinemet® (t_{max} = 2.5 h) and was associated with much slower increase in plasma levodopa levels.[15] Due to lower frequency of administration the controlled release formulation provided less variability in plasma levodopa levels. [16] The decrease in the number of administration of levodopa and carbidopa were observed which greater with the standard dosage form But the amount of levodopa and carbidopa still remains in the upper part of the small intestine. [17] Possibly due to the narrow absorption window, it should be feel that the bioavailability of Sinemet® CR was found to be lower in the fasting state than in fed condition, due to a faster gastric emptying. [18]

1.4 Gastroretentive drug delivery:-

Gastroretentive dosage forms (GRDFs) are a drug delivery formulation that are designed to be retained in the stomach for a prolonged time and release there their active materials and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract. This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged retention in the upper GI tract can greatly improve their oral bioavailability and/or their therapeutic outcome. To prolong the residence time of delivery

systems in the stomach different approaches have been proposed which includes the use of passage-delaying agents , swelling and expanding systems, bioadhesive systems , high-density, and floating dosage forms. [19-23] Only limited gastroretentive systems have been developed with success which contains levodopa. [24] A new controlled-release gastroretentive dosage form (CR-GRDF) comprised of unfolding membranes has also been investigated. The CR-GRDF were composed of an inner layer contains a polymer-drug matrix (ethylcellulose-levodopa 1:1) framed with rigid polymeric strips (l-polylactic acid-ethylcellulose 9:1) covered on both sides by two outer layers (composed of enzymatically hydrolysed gelatin, methacrylic acid copolymer type B, glycerine and glutaraladehyde (48:30:20:2)). Hence the CR-GRDFs were retained in the stomach for at least 24 h which was analyzed through X- ray.

2.   INTRAVENOUS ADMINISTRATION:-

Injection of levodopa directly to the systemic circulation may be needed for several reasons: (a) to overwhelmed the unpredictable absorption after oral intake, (b) to provide a direct drug supply, (c) to maintain constant brain levodopa concentration and (d) to Increase bioavailability as well as decrease its variability with the age and sex. [25] The efficacy of a saline solution of levodopa (2 mg/ml) was evaluated on 27 parkinsonism disease patients in fasted condition. A 200mg dose of carbidopa was orally administered 1 h prior to starting the infusion. Firstly, a rapid intravenous (IV) loading (10 min) produced a transient peak in plasma levodopa concentration. Afterwards, a 90min constant-rate infusion led to a target steady-state plasma concentration of 600 ng/ml. [26] Chronic intravenous (IV) administration of levodopa is not clinically practicable and cooperation is hard to obtain from patients with dementia, making injection quite difficult. The passage through the blood–brain barrier is not bypassed this technique, which limits the amount of the circulating dose available to the brain. Because of this, implantable systems that may provide a direct supply of levodopa to the brain were developed and evaluated.

3.   IMPLANTABLE ADMINISTRATION:-

For a long-term therapy implantable systems are designed and these systems provided continuous progressive supply of the incorporated drug for a long period of time. Once they are implanted, no further invasive administration is needed until the complete release of the active drug. However, these systems are usually limited by their small size, and the constituting polymers must be biocompatible. Depending on the

approach developed to achieve the controlled administration of the therapeutic agent (e.g. diffusion or activation), the type of polymer includes biocompatible compounds such as ethylene-vinyl acetate derivates, polyethylene glycol, silicone elastomer, lipidic materials, PLA and PLGA. [27] By using solvent evaporation technique the microsphere of levododpa and carbidopa were prepared sepeartely. [28] The biodegradable polymers, poly (l-lactides) (l-PLA), poly (d,l-lactides) (d,l-PLA), and poly(d,l-lactide-co-glycolide) (PLAGA), were dissolved in dichloromethane prior to being addedto a solution containing an aqueous emulsifying agent [PVA:SO or NaCMC:SO (4:1, w/v)]. The size of microsphere ranging from 20-40um were sterilized by gamma irradiation after the production. With the help of Dissolution tests (USP I, HCl 0.1N, pH 1.2, 900 ml, 50 rpm) it has been demonstrated that the polymers were able to provide a sustained release of levodopa and carbidopa for 10 h.

4.   PULMONARY ADMINISTRATION:-

It is a non-invasive route which provides rapid and efficient delivery of levodopa to the brain but due to the fast drug absorption through the alveoli, it can also be used as rescue therapy when an immediate supply of levodopa is needed as it avoids the first-pass liver metabolism. The principal mechanisms contributing to lung deposition are inertial impaction, sedimentation and diffusion that contributes to lung deposition. [29] The main parameters influencing lung deposition is the aerodynamic diameter (da) of the inhaled particles, particles with a mean geometric diameter (dg) ranged between 1–5µm are known to provide an optimal deposition and large porous particles (dg >5µm) have shown similar behavior due to their low mass density (<0.4 g/cm3).

5.   NASAL ADMINISTRATION:-

Conventionally, the nasal route has been used for delivery of drugs in the treatment of local diseases. It has been recognized that the importance of the nasal cavity as a potential route for non-invasive drug delivery. The nasal cavity possesses many benefits like large surface area for absorption with a highly vascularised subepithelial layer. The direct transport of absorbed drug into the systemic circulation avoids the first-pass metabolism by the liver, bypasses the blood–brain barrier and results in preferential absorption to the cerebrospinal fluid.[30] The small volume of the aqueous secretions present in the nasal cavity limits the dissolution of an instilled compound. Butylester levodopa (BELD) is a best example because it offers the best solubility and Lipophilicity compared to the

other alkyl ester prodrugs of levodopa. [31] It is seen that in a rat model, the absolute bioavailability of levodopa following nasal administration of BELD was found to be around 90% (vs. 5% per os). Therefore the early conversion of BELD into dopamine in the nasal cavity minimized the peripheral side effects.

6.   RECTAL ADMINISTRATION:-

The mode of delivery as a non-invasive route has also been explored for levodopa. Unfortunately, when levodopa was given rectally alone, there was no rise in plasma level and no clinical benefit. [32] This lack of absorption was attributed to the relative alkanility of the rectal secretions. Clinical improvement following rectal administration of a strongly acidic suspension of levodopa-carbidopa absorption of levodopa could be enhanced in association with salicylates. This phenomenon was shown to be concentration and pH-dependent. Salycilate facilitates the rectal absorption of numerous drugs, especially in their ionic form. Although the disappearance of levodopa in the perfusate was higher at pH <5 and >7, the enhancement of the drug absorption by salicylate was not due to the formation of a complex as the absorption rate of the adjuvant administered alone did not depend on the presence of levodopa in the perfusion. By the use of irritating adjuvants, like salicylate, which is used to enhance the absorption of levodopa, should be avoided for patients weakened by the disease. To avoid the use of absorption enhancers the rectal administration of aqueous solutions (pH 5.5) containing several short-chain alkyl esters prodrugs of levodopa was evaluated in rats, mice and beagle dogs. [33] In all species, the prodrugs absorption and resulting bioavailability was greater than those obtained with levodopa itself.

7.   TRANSDERMAL ADMINISTRATION:-

For providing a progressive supply of levodopa to the systemic circulation without adverse complications transdermal route appear to be a better route. Moreover, this route of administration is very useful for drugs that undergo extensive first-pass metabolism such as levodopa controlled transdermal delivery system based on iontophoresis and ion-exchange fiber was proposed by. [34] An insoluble organic polymer which having negatively charged radicals attached to it that can attract and hold cations in a surrounding solution called cation exchange resins. thus with the help of these resins the dissolved levodopa could be loaded in a cation-exchange resin, the optimal pH of the solution was fixed at 2.0 to avoid the alkaline oxidation of the colorless hydroquinone groups to the corresponding colored quinone functions. Due to its

zwitterionic form, the complete dose of levodopa was already released after 2 h when the dosage form was immersed in an in vitro saline solution. In contrast, permeation studies performed on cadaver human skin showed that only 25% (w/w) of levodopa crossed the epithelium barrier after 2 h. Therefore, it seemed that the ionic-exchange system failed to control the release of levodopa since the release rate of the drug was determined by the skin. To promote the transport of the ionic compound through the skin a constant iontophoretic current of 0.5mA/cm2 was applied. A three- to four fold increase in transdermal levodopa permeation was clearly observed. [35] To provide a constant supply of levodopa most of the drug delivery systems have failed. Consequently, the plasma level cannot be sustained for a prolonged period of time, thereby involving fluctuations in the therapeutic response. According to the drug delivery system considered, the inability to provide suitable plasma concentrations of levodopa is partially created by the complexity of the transport processes and the extensive metabolization of the drug. In order to avoid the problems connected with the route of administration and with the pharmaceutics concept of the dosage form to the delivery of levodopa directly to its absorption zone is one of the interpretations.

8. INTRADUODENAL ADMINISTRATION:-
Infusion of levodopa/carbidopa continuously constitutes a useful method for the most severely fluctuating parkinsonism disease patients. A constant supply of dopamine can mimic the dopaminergic stimulation seen in the normal state by avoiding the fluctuations in dopamine levels that accompany intermittent oral levodopa dosing, thus facilitating more normal control of movement. [36] With the help of portal pump a water-based gelling suspension of levodopa and carbidopa administered intraduodenally, through a percutaneous endoscopic gastrostomy. The dispersion contains micronized levodopa (20 mg/ml) and carbidopa (5 mg/ml) dispersed in a 1.8% aqueous methylcellulose solution.[37] As the course of parkinsonism disease is a slow progression of symptoms, increasing dosage of levodopa had to be applied for longer duration therapy (e.g. 4–7 years). Although reduced variation of levodopa delivery to the absorption site reduced several long-term pathophysiological changes, the loss of dopamine neurons progressively diminished the synaptic storing capacity.

NASAL ROUTE:-
Nasal drug delivery has now been recognised as very promising route or delivery of therapeutic compounds

including biopharmaceuticals.[38-39] The delivery of drugs for the treatment of nasal disease like nasal allergy, nasal congestion and nasal infection which follows certain mechanisms as shown in figure 1.

Mechanisms:-
1. The first mechanism includes transport of drug across the nasal epithelium into the systemic circulation (blood)[40-41] and subsequently into the brain after crossing the blood brain barrier.
2. The second mechanism involves, passage through olfactory region into cerebrospinal fluid and finally into the brain.
When drug is administered through nasal cavity (nasal administration) it passes through mucociliary clearance and enzymatic barrier. [42] Then the drug passing through this barrier will be absorbed across nasal epithelium and reaches the systemic circulation. Then it will be eliminated by a normal clearance mechanism after showing its pharmacological effect at the target tissue/organ. Mucociliary clearance will force the drug towards the gastrointestinal tract via the nasopharynx, and give the possibility that the drug will be absorbed from gastrointestinal tract.[43]

BARRIERS IN NASAL DRUG DELIVERY:-
1.   **Different Routes:-**
A number of routes were followed for the treatment of parkinsonism disease but still the problem occurs in these routes. In case of oral route, the immediate release solid systems fail to produce the clinical effects because levodopa is not absorbed through oral mucus. [44] Due to this problem liquid and dispersible formulations were developed, but parkinsonism treatment being long therapy and these preparation only provide immediate supply of levodopa with short half life and due to narrow therapeutic index. These entire drawbacks strongly led to the development of sustained release dosage form, which provide smoother levodopa plasma profile. The alternative of this formulation are dual release systems which determine the rate of gastric emptying and extent of its absorption but they also failed in providing the continuous supply of levodopa at its absorption site. Gastroretentive dosage forms were developed to obtain lesser-fluctuating plasma concentrations, thereby establishing a possibly more stable clinical effect. Dysphagia, unpredictable gastric emptying and subsequent erratic absorption of levodopa have lead drug development to focus on numerous alternative routes of administration. Non-oral formulations may be more suitable but also more reliable in avoiding pulsatile stimulation of dopamine receptors and the subsequent motor complications. [45] Intravenous

administration of levodopa is not clinically practicable and cooperation is hard to obtain from patients with dementia, making injection quite difficult. Moreover, this technique does not bypass the passage through the blood–brain barrier, which limits the amount of the circulating dose available to the brain. Because of this, implantable systems that may provide a direct supply of levodopa to the brain were developed. Also pulmonary delivery provided levodopa and dopamine levels four- to twofold superior on both sides of the striatum. [46] This route should be reserved for "rescue therapy" due to the rapid onset response that it provides. Transdermal route is another option for the administration of those drugs which undergoes first pass metabolism like levodopa and Intraduodenal infusion of levodopa and carbidopa are very useful for continuous supply of dopamine to the patient. Apart from all these routes a number of issues has to be addressed like first pass metabolism, compatibility of polymers, continuous supply of drug, adhesiveness of the polymers, irritation property The data are shown in Table 3.

Fig. 1: Possible mechanisms of drugs after nasal administration.
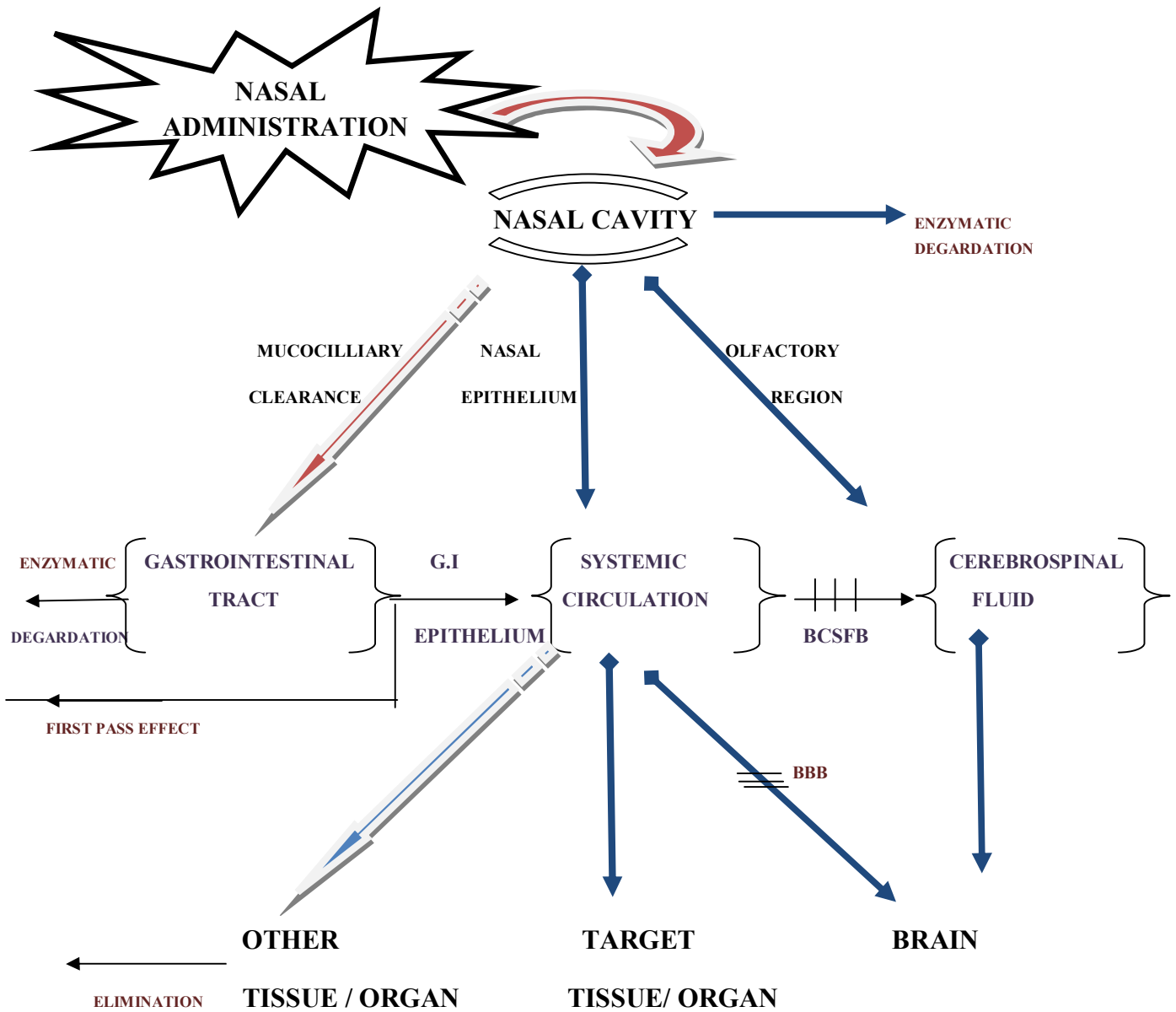
BBB --- BLOOD BRAIN BARRIER
BCSFB --- BLOOD CEREBROSPINAL BFLUID BARRIER

Table3:   Different Routes or formulation for treatment of parkinsonism disease.

S.No.	DRUGS USED IN PARKINSONISM DISEASE	ROUTES OR FORMULATION FOR TREATMENT OF PARKINSONISM DISEASE	REFERENCES
1.	Levodopa	Oral route and dual release formulation	[67]
2.	Levodopa and carbidopa	Oral route and controlled release formulation	[68]
3.	Levodopa	Oral route	[69]
4.	Levodopa	Oral route	[70]
5.	Levodopa ethyl ester	Oral route and oral solution formulation	[71]
6.	Levodopa and carbidopa	Oral route and sustained release floating, minitablet formulation	[72]
7.	Levodopa and carbidopa	Oral route and immediate and controlled release formulation	[73]
8.	Levodopa and carbidopa	Oral route and controlled release formulation	[74]
9.	Levodopa and carbidopa	Oral route and controlled release formulation	[75]
10.	Levodopa	Oral route and sustained release floating dosage form	[76]
11.	Levodopa	Intravenous infusion / route	[77]
12.	Levodopa and carbidopa	Intravenous infusion / route	[78]
13.	Levodopa	Intravenous route	[79]
14.	Levodopa	Pulmonary route	[80]
15.	Levodopa and carbidopa	Rectal route	[81]
16.	Levodopa	Rectal route	[82]
17.	Levodopa	Transdermal formulation and hydrogel formulation	[83]
18.	Levodopa	Duodenal infusion / route	[84]
19.	Levodopa	Duodenal infusion / route	[85]
20.	Levodopa	Intraduodenal route and water based formulation	[86]
21.	Levodopa	Intestinal infusion / route	[87]

2.   Enzymatic degradation:-

Another contributing factor to the low bioavailability of peptides and proteins across the nasal mucosa is the possibility of an enzymatic degradation of the molecule in the lumen of the nasal cavity or during passage through the epithelial barrier. These sites both contain exo peptidases such as mono and diamino peptidases that can cleave peptides at their N and C termini and endopeptidases such as serine and cysteine, which can attack internal peptide bonds. [47] The use of enzyme inhibitors and saturation of enzymes may be approaches to overcome this barrier. [48] In summary, the nose offers unique merits as administration site for drug delivery. Thus low permeability for polar and high molecular drugs, rapid clearance of the delivery system from the cavity and possible enzymatic degradation of the in the nose may be encountered. These challenges can be faced by various approaches, such as use of bioadhesive and absorption enhancers.

3.   Mucociliary clearance:-

The fast clearance of the administered formulation from the nasal cavity may be attributed to the mucociliary clearance mechanisms. This is especially the case when the drug is not absorbed rapidly enough across the nasal mucosa. It has been seen that for both

liquid and powder formulations, which are not bioadhesive, the half life for clearance is 15 - 30 min. [49-50] The use of bioadhesive excipients in the formulations is an approach to overcome the rapid mucociliary clearance. The clearance may also be reduced by depositing the formulation in the anterior, less ciliated part of the nasal cavity thus results to improved absorption. [51-52]

4.   Low bioavailability:-
The most important point which limiting the absorption of polar drugs in nasal cavity and also large molecular weight polar drugs such as peptides and proteins having low membrane permeability, during across the membrane either by paracellular. [53] Larger peptide and proteins also passes the nasal membrane bit in low amount by endocytotic transport process. The absorption of polar drug can be improved by co-administrating the absorption enhancing agents, by using surfactants, bile salts and its derivative, fatty acid and its derivative. Absorption enhancer act by altering the permeability of epithelial cell layer by modifying the phospholipid bilayer, leaching of proteins from the membrane, and some of these also show effect on tight junction and worked as enzymatic degradation inhibitor. [53-54] Some other enhancers like cyclodextrin and chitosan shows enhancing effect. Because some surfactants cause damage to mucosa therefore the selection of absorption enhancer is most important in terms of potential and systemic nasal toxicity. [55]

STRATEGIES TO ENHANCE NASAL ABSORPTION:-
To improve the nasal absorption of different drugs like peptides and proteins, antiparkinsonism drugs there are several strategies by which improve the nasal absorption are described as follows:-
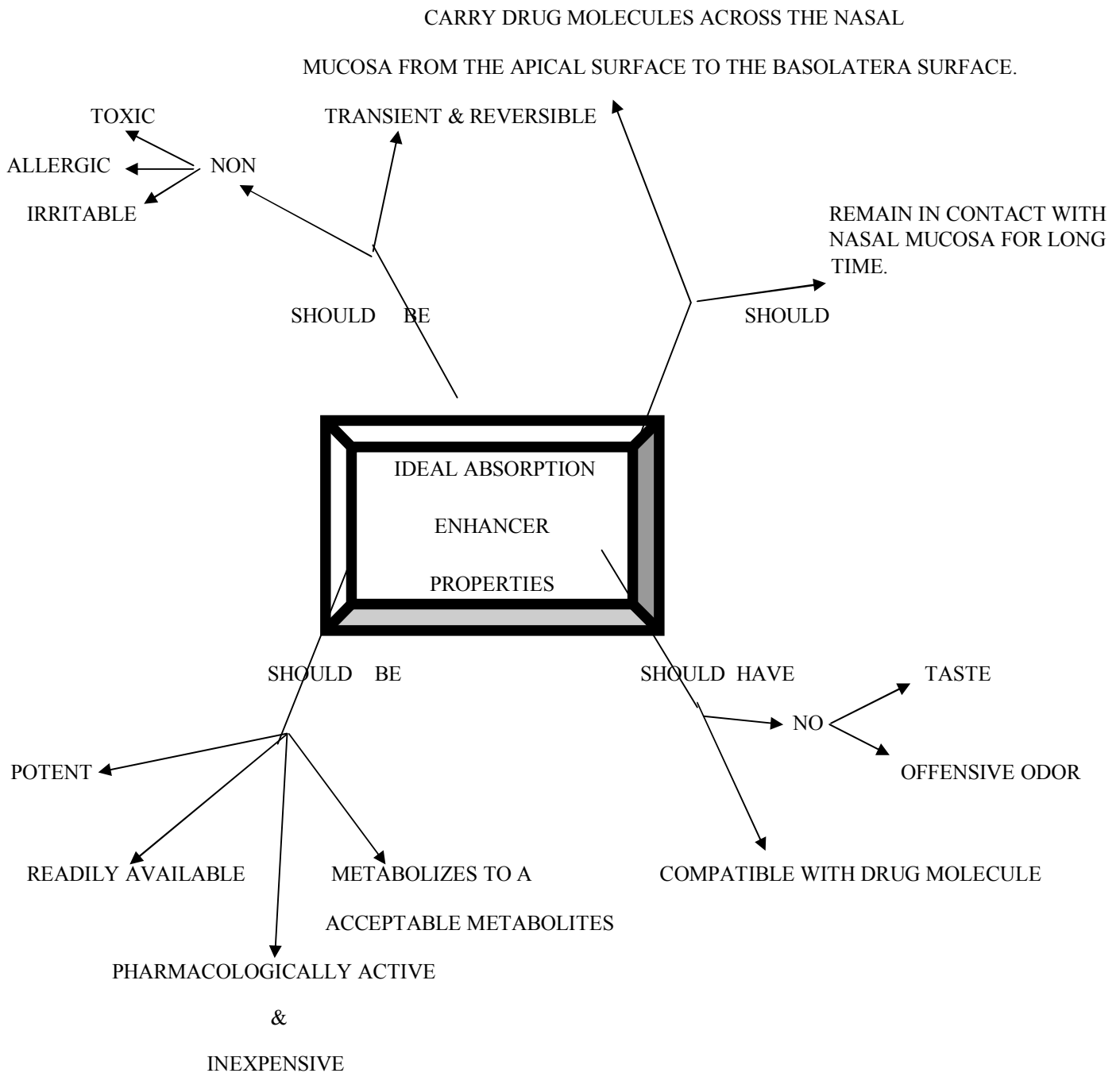
1.   Use of absorption enhancer:-
The optimum absorption enhancers have following functions like increasing membrane fluidity, opening of tight junctions, or inhibiting enzymatic activities in the nasal tissue. Absorption enhancers are classified on chemical basis which is better than based on mechanism of action. [56-57] The examples and requirements for an ideal absorption enhancer are shown in table 4 and Figure 2.

Table 4: Different examples of nasal absorption enhancers with their mechanism of action.

ABSORPTION ENHANCERS	MECHANISM OF ACTION	EXAMPLES
Bile salts(and derivative)	Disrupt membrane, Open tight junctions, enzyme inhibition, mucolytic activity	Sodium glycocholate,sodium deoxycholate
Surfactants	Disrupt membranes	Saporin, sodium lauryl sulphate
Fatty acids	Disrupt membranes	Sodium caprylate, phospholipids, sodium laurate
Chelating agent	Open tight junction	Salicylates, Ethylene diamine tetraacetic acid
Enzyme inhibitors	Enzyme inhibition	Bestatin, amastatia
Miscellaneous	Cyclodextrins	Disrupt membranes, open tight junctions
Bioadhesive materials powders	Carbopol, starch microspheres,chitosan	Reduce nasal clearance, open tight junctions
Liquids	Chitosan, carbopol	Reduce nasal clearance, open tight junctions

Fig. 2: The properties of ideal absorption enhancer.

CARRY DRUG MOLECULES ACROSS THE NASAL

MUCOSA FROM THE APICAL SURFACE TO THE BASOLATERA SURFACE.

TOXIC   TRANSIENT & REVERSIBLE

ALLERGIC ← NON

IRRITABLE

REMAIN IN CONTACT WITH
NASAL MUCOSA FOR LONG
TIME.

SHOULD   BE   SHOULD

IDEAL ABSORPTION

ENHANCER

PROPERTIES

SHOULD   BE   SHOULD HAVE   TASTE

                                   NO

POTENT   OFFENSIVE ODOR

READILY AVAILABLE   METABOLIZES TO A   COMPATIBLE WITH DRUG MOLECULE

              ACCEPTABLE METABOLITES

PHARMACOLOGICALLY ACTIVE

              &

INEXPENSIVE

2.   Enzyme inhibitor:-
Another strategy for the protection of drugs like peptides and proteins and to prevent them from enzymatic degradation is by co-administering peptidase/protease inhibitors. The nasal tissue has various enzymes, including peptidases and proteases, which are present in the mucus, on the membrane surface, and in the intercellular space. [58] Among several known species of proteolytic enzymes, the predominant enzyme appears to be aminopeptidase. Some enzyme inhibitors like bacitracin, bestatin, and

amastatin have been found to be effective for improving the nasal absorption of various drugs. The control of the pH of the formulation can be a factor for reducing enzyme activity at the absorption site. [59]

3.   Chitosan:-
Chitosan, derived from crustacean chitin by a partial deacetylation process, is a type of polysaccharide consisting of glucosamine and N-acetyl-glucosamine, and has been widely investigated in the pharmaceutical field. Chitosan is a positively charged

polymer, and can form salts with inorganic and organic acids. [60] Although the chitosan of a pharmaceutical (good manufacturing practices) grade is a glutamate salt with an average molecular mass of approximately 250 kDa and degree of deacetylation of more than 80%. This chitosan salt is soluble in water upto ph of about 6.5. A broad range of molecular weights and salt forms is currently available. One of the important features of chitosan for nasal application is its bioadhesiveness. [61] Because of the positive charge, it can interact with the negatively charged sialic acid residues in the mucus layer, which can modify the mucociliary transport system. Another mechanism of action elucidated is a transient opening of the tight junctions in the cell membrane to allow polar drugs to pass through. [62] Furthermore, chitosan itself is not absorbed across the mucosa because of its high molecular weight and its toxicity by the nasal administration has been well studied, being non toxic and well accepted by patients. [63] The structure of chitosan and chitin as shown in figure 3.

Fig. 3: structure of chitin and chitosan.

CHITIN

&

CHITOSAN
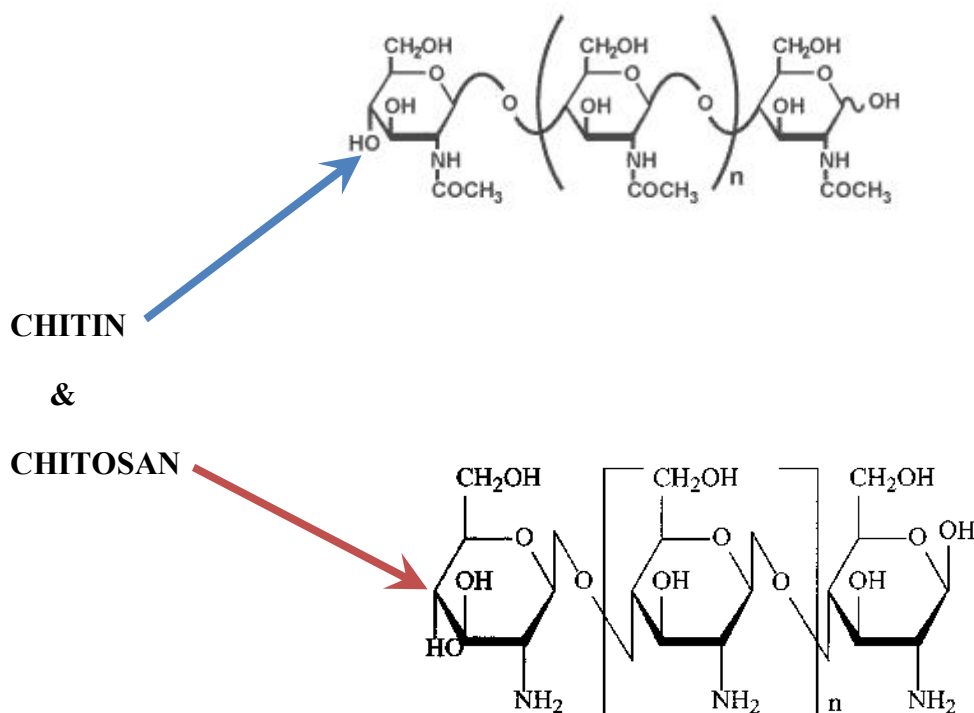
4.   Different formulations:-

4.1 Nasal drops

Nasal drops are one of the most simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of dose precision and therefore nasal drops may not be suitable for prescription products. [64] It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

4.2 Nasal powders

This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g., due to lack of drug stability. The advantages to the nasal powder dosage forms are the absence of preservative and superior stability of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particle size, aerodynamic properties

and nasal irritancy of the active drug and/or excipients. Local application of drug is another advantage of this system but nasal mucosa irritancy and metered dose delivery are some of the challenges for formulation scientists and device manufacturers. [65]

4.3 Nasal sprays

Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose from 25 to 200 µL. The particle size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly. Solution and suspension sprays are preferred over powder sprays because powder results in mucosal irritation. [66]

CONCLUSION:-

The administration of antiparkinsonism drugs through nasal route is one of the most attractive and convenient route. It reduces systemic exposure, side effects and also assures good compliance by patient undoubtly. Nasal drug delivery system bypasses the blood brain barrier and delivers the drug directly into the central nervous system and also act as a better alternative to parenteral and oral route for delivery of antiparkinsonism drugs. In conclusion, a better improvement may be in terms of strategies and safety aspects for nasal drug absorption and also further efforts will require ensuring the efficacy of the formulation.

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