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Intra nasal *in-situ* gel freighted with Nano naturaceuticals for neurological diseases - from bench to bed side

Indira Muzib Yallamalli*[1], Arunakumari Dommaraju[1], Ramji Ambedkar Yellamelli[2]

[1]*Institute of Pharmaceutical Technology, Sri PadmavatiMahilaVisvavidyalayam, Tirupati, Chitoor district, Andhra Pradesh, India-517502*

[2]*College of Veterinary Science, Sri Venkateswara Veterinary Univesity, Garividi, Vizayanagaram, Andhra Pradesh, India-535101*

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Abstract

The treatment for acute or chronic neurodegenerative diseases is the most exigent aspect in many aspects, as the drug should cross the blood-brain barrier. At present many formulations have been developed for synthetic drugs to target the drug to the brain through various routes. Among them,the nasal route is one of the most prominent routes to target the drug to the brain, where the drug can bypass the BBB. There are many natural drugs, Phytoconstituents also available for the treatment of neurodegenerative diseases. Because of the many advantages like natural, safe, easily available, biocompatible, low cost, etc., of natural drugs over synthetic drugs, the researchers were focused on the development of the formulations of natural drugs for various diseases. But here, the challenging concept is the delivery of the active Phytoconstituents to the brain through the nasal route as the molecular weight of the drugs is rate limited. Among the nasal formulations, *in-situ* gel systems are the trending research work carrying. So the review was focused on the overview of the available Phytoconstituents to treat brain disorders and how the drugs target the brain through the nasal route. A brief about nasal anatomy, the pros and cons of nasal drug delivery and nasal *in-situ* gels was also noted. The review summarizes the available nanoformulations for the Phytoconstituents to target the drug to the brain through the nasal route.

* **Corresponding Author:** Dr. Y.Indira Muzib ✉ yindira1415@gmail.com

Introduction

Brian is a mesmerizing organ known for its entanglement. This fragile organ was protected by the skull structure outside and inside,which consists of mainly two protective barriers, namely the blood-brain barrier (BBB) and the blood-cerebro spinal fluid barrier (BCSF), which hinder the treatment strategies endorsed for the therapeutic determination. Because of this fragility, the time period will be more for the development of CNS drugs than the NON-CNS drugs (Dong, 2018). The CNS disorders such as epilepsy, dementia, Parkinson's, Alzheimer's, brain tumors, meningitis, and brain tumors, can be managed by both natural and unnatural drug molecules but greatly depends upon the means of attaining higher drug levels at the targeting sites (Goyal D *et al.,* 2017).However, the synthetic drug molecules havea low molecular weight compared to the natural ones and the research was expanded.

Presently the research on natural drugs is gaining much interest because of their bio-friendly nature and supremacy over synthetic drugs (Borris, R. P. 1996). Most natural molecules havea high molecular weight, so the physico chemical properties of the drug mainly domineer its ability to penetrate the drug through these barriers and to exhibit therapeutic outcomes (Yu *et al.,* 2019). So the only option to target the drug molecules inthe brain is bypassing the barriers. To bypass the drug molecules through these protective barriers of brain to present their therapeutic effect, the nasal route drug delivery is the only choice (Khan *et al.,* 2017). There is scientific growth supporting nasal drug delivery owing to the fact that a confirmed concentration of drug can cross BBB. One more satisfaction of this route is that it deliversboth intra-cellular and extra-cellular drug transport pathways to the CNS, which further depends on added factors like physico chemical properties of the drug and receptors present in the olfactory region.

Nasal anatomy

The human nasal region divides into two equal symmetrical halves. There are four regions in both halves, as shown in Fig.1.

Nasal drug delivery

There are two pathways for the drug to target the brain.

Direct pathway

The nasal cavity is divided intoboth the respiratory and olfactory regions through the trigeminal nerve. The drug can enter the systemic circulation or directly to the brain tissues through the respiratory region, but in the olfactory region drug directly diffuses to the brain through the olfactory mucosa pathway, which is a direct pathway (Gao, 2016).

Indirect pathway

Here,mucociliary clearance and enzymatic degradation are the two important factors thataffect the drug to reach the brain. So these factors can be overcome by formulating the drug to a lipophilic nature and targeted to the brain,which is an indirect pathway(Pires PC, Santos AO, 2018). Drug targeting to the brain is clearly demonstrated in Fig. 2.

Overcome the limitations

As shown in Table 1 (Dhakar *et al.,* 2011; Illum, 2002), to overcome the cons of nasal delivery, the following factors can be considered.

- The factor of mucociliaryclearance can be overcome by formulating the drug to intra- nasal *in-situ* gel.
- By nanoparticle drug carriers, we deliver the natural CNS drugs, which are high molecular weight.

Intra nasal in-situ gel

As *in-situ* gels consist of both the merits of solution and gels dosage forms, these are extensively used in the drug delivery system. *In-situ* gel is a polymeric system that initially exists as an aqueous solution but, after administration, immediately converts into firm gel due to the physiological environment (Pires and Santos, 2018). The physiological factors which affect the formulation are temperature, ion concentration, and water content. Based on the mechanism, these are divided into two types (Fig.3),1. Physical cross-linking 2. Chemical cross-linking. Physical cross-linking is generally used because of its superiority

phenomenon, which can be done by temperature modulation, pH change and addition of ions (Jeong *et al.,* 2012; Niranjan *et al.,* 2013).

Generally, there are two methods for the preparation of *in-situ* gels.1.Cold method 2.Hot method. Based on the influence of temperature on the solubility of the polymer, the method was selected (Patel *et al.,* 2012).The generally used polymers in nasal delivery are limited, such as poloxamer, chitosan, gellan gum, pectin, carbopol, and glyoglucon(Mishra *et al.,* 2012).

Thermo responsive systems

In this system, only at this temperature range of 25-37^{o}C the formulation changes from sol-to-gel. Below or above this temperature range, gelation time may increase or decrease, which results in hindering the handling or may induce the leakage of liquid formulation from the outer regions of the nostrils. Polymers play an important role in the gelation time factor. The synthetic polymers used for thermo-responsive systems: The most commonly used one is poloxamer 407 (Pluronic f127) because of its thermo-sensitive property. Based on micellization property, it shifts to gel. By the addition of various polymers which have mucoadhesive properties like carbopol 934P, PEGS like PEG400, PEG4000, PEG6000, PEG8000, Carrageenan, HPMC K4M, PVPK30, Sodium alginate, Tamarind seed gum one or combinations, the *in-situ* gel formulation was developed (Balakrishnan *et al.,* 2015).

The natural polymers used for the thermo-responsive systems: Xyloglucans and Chitosan are the most commonly used natural polymers that have thermosensitive and mucoadhesive properties (Mahajan H. S *et al.*, 2013). The mucilage extracted from the *Ficus.Carica* reported that it has mucoadhesive properties and also it is more effective compared to synthetic ones like HPMC and Carbopol 934P (Basu and Bandyopadhyay 2010). Natural polymers have the advantages of cost-effective, biocompatible and biodegradable. There are some polymers like N-[(2-hydroxy-3-trimethylammonium) propyl] chitosan chloride, a synthetic polymer having thermosensitive and mucoadhesive properties which arederived from the natural chitosan polymer (Wu J *et al.,* 2007). This type of polymer has both advantages of synthetic and natural ones.

Ion-responsive systems

The polymers gellan gum and pectin undergo gelation under physiological ion concentration. Gellan gum is an anionic polysaccharide when it comes in contact with the cations present in the nasal secretions, especially Ca^{+2} enables gel formation (Grasdalen and Smidsrød 1987). An ordered firm three-dimensional network structure was formed with the interaction of cations of the nasal fluid by the functional groups of the pectin. Li *et al.,* 2015, utilized the synergetic response of the thermo-responsive and ion-responsive systems. Poloxomer 407 as thermo-responsive and deacetylated gellan gum as ion-responsive polymers were used for the gel formulation and reported with synergetic effects like higher retention time in the nasal mucosa, superior pseudoplastic behavior and enhancing drug absorption.

PH-responsive systems

Mostly polymers containing weak acidic or weak basic moieties are proffered to be used as p^{H}-sensitive polymers. Acidic group like –COOH containing polymers gets deprotonated at basic p^{H} to get a negative charge and vice-versa, resulting in the expansion of the materials because of the repulsion of the similar charged groups.

The material will regain its original shape due to the withdrawal of repulsion as the p^{H} becomes normal (Kim Y.-H *et al.,* 1994). Sherje and Londhe 2018, developed a p^{H} responsive cyclodextrin-based intra-nasal *in-situ* gel of paliperidone for the treatment of schizophrenia. They reported satisfactory mucoadhesion and sustained drug release. Makwana *et al.,* 2016, formulated a p^{H}-responsive ophthalmic *in-situ* gel of ciprofloxacin hydrochloride. Sodium alginate was used as a polymer that interacts with the Ca^{+2} divalent cation present in the lachrymal fluid, which results in calcium alginate.

Table 1. Pros and cons of intra nasal delivery.

Pros	Cons
• It is a safe, non-invasive, rapid and convenient method for drug delivery to brain	• Mucociliary clearance is the major factor which affect the absorption of drug
• It enhances the bioavailability of CNS drugs by avoiding the GI degradation, hepatic first pass metabolism	• High molecular weight drugs may result in decreased permeability
• Drug was directly targeted to the brain, so that quick onset of action, and absorption can be enhanced	• In cold and allergic conditions nasal decongestion may interfere in the drug delivery
• Best alternative route of parental administration. So it is patient compliance because of self-medication.	• Due lack of proper administration, mechanical loss of drug dosage may occur
• Cost effective	

Natural drugs used for the brain disorders

Because of the biodegradable and biocompatible nature of natural herbal drugs, many brain disorders like Alzheimer's, Parkinson's, dementia, depression, epilepsy, schizophrenia, anxiety, etc., can be treated over synthetic ones. This review mainly discussed the natural drugs used for brain disorders and how to target them to the brain. Table 2 embellishes the various natural drugs used for numerous neuro disorders.

Nanoparticles of natural drugs

Over the decades, numerous nanoparticulate drug delivery systems have flourished and been employed to enhance the pharmacokinetic and pharmacodynamic profile of the therapeutics which istargeted to the brain. The application of nanotechnology has been fascinatingover the past few years because of its advantages, like targeting drug delivery, increasing bioavailability, and decreasing the dose, thereby associated side effects (Ghaffari and Dolatabadi, 2019).The lack ofa proper delivery system for these natural drugs limits their use;being a macro molecule, these are unable to penetrate through biological barriers and not able to reach the specific target sites. So wide research was ongoing in the design of the various Nano drug carriers which target the brain (Olivier, 2005). Nanoparticulate intra-nasal drug delivery has gained interest recently because of precedence. Through the nasal route, the active pharmaceutical ingredient (API) was directly targeted to the brain for both local and systemic action. Though there are numerous synthetic CNS drugs that are formulated into intra-nasal *in-situ* gel, the research is evolving around the natural CNS drugs targeted to the brain through an intra-nasal *in-situ* gel using nanocarriers. This review is mainly fascinated by the natural drugs targeted to the brain bypassing the obstructive barriers of the brain through the nasal route using nanocarriers.

Curcumin, a Phenolic compound extracted from the *Curcuma longa* used as a spice in many Indian dishes, is reported as an anti-brain tumor especially used for Alzheimer's disease (AD) (Tsai *et al.,* 2011, Roney *et al.,* 2005). The aqueous solubility of curcumin was limited. It is reported that in the aqueous buffer, pH=5.0, the solubility of curcumin is only 11ng/ml (Dhule *et al.,* 2012). So there is a need to improve the solubility of curcumin through the application of solubilization techniques or else by nanotechnology. Wang *et al.,* 2012, prepared micro emulsion-based intra-nasal *in-situ* gel of curcumin by ion sensitive gelling system. The bioavailability of curcumin was increased to 55.82%, and brain targeting efficiency was 6.50. The brain tissue distribution was higher compared to intravenous. Sumeet sood*et al.,* 2014, prepared curcumin nanoemulsion of intra-nasal *in-situ* gel and optimized using box-behnken design. The formulation did not show any toxicity, which is carried out SK-N—SH cell line studies and nasal ciliotoxicity studies and reported as a safe formulation for nasal delivery. Arun raj *et al.,* 2019, developed a transferosomal intra-nasal *in-situ* gel of curcumin and optimized it using design expert software. Reported that the drug was released in a controlled manner and increased bioavailability. The concentration of curcumin in the brain was higher compared to the intravenous administration.

Table 2. Natural drugs used for the neuro disorders.

Plant name	Active constituent	Activity	Reference
Hypericum perforatum	HypercinPseudo hypercin	Anti depressent	Schultz, *et al.,* 1998
Piper methysticum	Piperdine Kava pyrones	Sedative Anxiolytic hallucinogen	Harrer and Schulz 1994
Valeriana officinalis	Balerenal Bornyl formate Euginyl isovalerate eugenol	Anxiety,sleepdisorder seizures	Choudhary, *et al.,*2013
Ginkgo biloba	Ginkolides	Alzheimers Anxiety	Bihaqi, *et al.,* 2011
Centella asiatica	Asiaticosides Asiatic acid Madacassic acid Betulic acid	Anxiolytic Epileptic Anti-depressant	Joseph, *et al.,* 2005
withaniasomnifera	Withaferin withanolides	Anti-depressant	Bhattacharya *et al.,* 1997
Rauwolfia serpentine	Respirine Ajmaline serpentine	Schizophrenia	Choudhary *et al.*, 2013
Catharanthus roseus	Vincristine vinblastine	Alzheimers	Kundu *et al.,* 2016
Curcuma longa	curcumin	Protects against synaptic dysfunction	Chang, *et al.,* 2016
Acorus calamus	asarone	Sedative, capable of improving memory power	Zanoli, *et al.,* 1998
Emblica officinalis	Vit.C phyllemblin	Anti-cholinesterase activity	Joseph, *et al.,* 2005
Magnolia officinalis	Honokiol 4-methyl-honokiol magnolol	Neurosis Anxiety Stroke dementia	Lee *et al.,* 2003
Uncariarhynchophylla	Rhynchophylline isorhyncholhylline Corynoxeine isocornoxine	Neuro ischemia	Liu RH, 2003
Ziziphus spinosa	Jujuboside-A Jujuboside-B action	anti-calmodulin	Ying-Jun *et al.,* 2005
Llexparaguariensis	Theophylline theobromine	Dementia Parkinson's disease	Prediger, *et al.,* 2008
Evolvulusalsinoides	Betaine Evolvine	dementia	Gupta, *et al.,* 2007
Glycyrrhiza glabra	glychrrhizin	Improves memory on scopolamine induced neurodisorders	Dhingra, *et al.,* 2004
Terminalia chebule	Phenolic acids	Enhance memory and promote longevity	Misra, 1998
Panex ginseng	ginsenosides	Congestiveand physical sluggishness	Chen ,*et al.,* 2003
Allivum sativum	Allium cepa	hyperlipidemia	Oi Y, *et al.,* 1999
Lycopersicon esculentum	lycopene	Huntington's odisease	
Tripterygium wilfordi	triptolide	Alzheimer's disease	Allison, *et al.,* 2001
chlorophyta	trehalose	Huntington's disease	Liu R, *et al.,* 2005
Ananas comoscus	Quercetin hesperdine	Reduce stress in epileptic condition	Lopez-Lopez, *et al.,* 2004
Botanical berries	resveratrol	Alzheimer's disease	Bertelli, *et al.,* 2002
Baccopamonnieri	Bacoside-A Bacoside-B Betulic acid	Improves memory power, reduce the stress in epileptic condition	Mishra, *et al.,* 2006
Lyciumbarbarum	L.Barbarum	Alzheimer's disease	Ho YS, *et al.,* 2010

Naringenin is a natural flavonoid found in many berries like grapes, blueberries, blackberries, mulberries,oranges, tangerine, etc., and also in tomatoes. Naringenin was confirmed that could be used in cerebral ischemia (Wang Y *et al.,* 2017) and also it has an antioxidant effect (Renugadevi J and S. M. Prabu, 2009).So it can be used in the epileptic condition to reduce the stress especially in the time of seizures and also in Parkinson's disease. Being a very low bioavailability (Madsen H. L *et al.,* 2000) and poor water solubility drug (Yu J *et al.,* 2005), we need to increase the bioavailability by applying various formulation techniques. Ahmad Niyaz *et al.,* 2020 developed an intra-nasal *in-situ* gel nanoemulsion of

naringenin and evaluated all the cerebral ischemic parameters and toxicity studies were also carried. They reported the neurobehavior activity was improved significantly and no toxicity was found, reported as a safe formulation. Gaba B *et al.,* 2019, formulated a nanoemulsion of vitamin-E-loaded naringenin for intra-nasal delivery to manage the oxidative stress in Parkinson's disease and also they examined the synergetic effect of Vit E and naringenin in*in-vivo* studies. They are successful in targeting the brain and increasing in bioavailability of naringenin to treat Parkinson's disease, which is studied against the standard drug Levodopa.

Resveratrol is a natural polyphonic acid found in various botanical berries like grapes, blueberries, blackberries, mulberries, etc., which has antioxidant properties(Kim JH *et al.,* 2016) and is used for Parkinson's disease. It acts as an antioxidant by increasing the levels of glutathione, vitamin E, vitamin C and beta-carotene (Summerlin N *et al.,* 2015).

Table 3. Olfactory area differences in various species.

Species	Body weight (kg)	Nasal cavity volume (NCV) (cm^3)	Nasal cavity surface area (NCSA) (cm^2)	Relative surface area (NCV/NCSA) (cm^{-1})	Olfactory epithelium	Olfactory epithelium
Mouse	0.03	0.03	25	96.3	47	1.37
Rat	0.25	0.26	13.4	51.5	50	6.75
Rabbit	3	6	61	10.2	10	6
Human	70	25	160	6.4	8	12.5

The disadvantage ofResveratrol is it has very low bioavailability and undergoes extensive hepatic and pre-systemic metabolism (Teskač K and J Kristl, 2010). Ananoemulsion of vitamin E loaded Resveratrol through intra-nasal delivery to reduce stress during Parkinson's disease was designed. The optimized formulation showed high scavenging efficiency (Pangeni R *et al.,* 2014). Hao J *et al.,* 2016, fabricated*an in-situ* gel of nanosuspension resveratrol for intra-nasal delivery. The residence time in the nasal cavity was enhanced using this formulation and the targeting efficiency was shown as 458.2%. The*in-situ* gel loaded with resveratrol cubosomes was developed for nasal delivery and optimized using factorial design. When compared to the oral delivery of resveratrol, the nasal delivery showed significantly higher for $C_{max}$and AUC.

The half-life and bioavailability of the nasal formulation were more than the oral route delivery; this may conclude that the *in-situ* gel has better retention in the nasal cavity (Ahirrao M and S. Shrotriya, 2017). Rajput *et al.,* 2018 designed a nanostructured lipid carrier of resveratrol loaded in the *in-situ* gel for the treatment of Alzheimer's disease. The optimized formulation showed fivefold higher permeation through the nasal cavity compared to the suspension-based *in-situ* gel. The formulation showed significant improvement in memory function in rats comparedto the orally administeredresveratrol suspension (Rajput A *et al.,* 2018). Salem H. F *et al.,* 2019, formulated resveratrol transferosomes based on an intra-nasal *in-situ* gel. All the pharmacokinetic parameters like $t_{1/2}$, AUC, C_{max}, T_{max} and MRT showed a significant increase compared to the oral administration of resveratrol suspension.

Eugenol, an essential oil found in the clove tree, rose oil, cinnamon and valerian are highly used as spices in Indian dishes (Umezu T *et al.,* 2006). Because of having antioxidant and neuroprotective potential, it is used to treat various neurological disorders like cerebral ischemia (Yanpallewar S *et al.,* 2004). Begin a plant-derived phytochemical, eugenol easily prone to light and oxygen sensitivity and volatility (Choi M.J *et al.,* 2009). To protect the eugenol was encapsulated and administered the drug orally, but the oral administration showed low bioavailability and various adverse effects like nausea, vomiting, headache and dizziness (Gaysinsky S *et al.,* 2005). So the alternative route of administration for eugenol to treat various neurological diseases is the nasal route.

To increase the bioavailability, the residence time should be increased, which can be attained by formulating the eugenol to intra-nasal *in-situ* gel using various mucoadhesive polymers. Ahmad N *et al.*, 2017, developed an *in-sit* gel of chitosan-coated-PCL-Nan particles for nasal delivery. The AUC, Cmax and $t_{1/2}$ showed a significant increase when comparedto the IV administration of eugenol. They reported the developed formulation is safe as it doesn't show any toxicity.

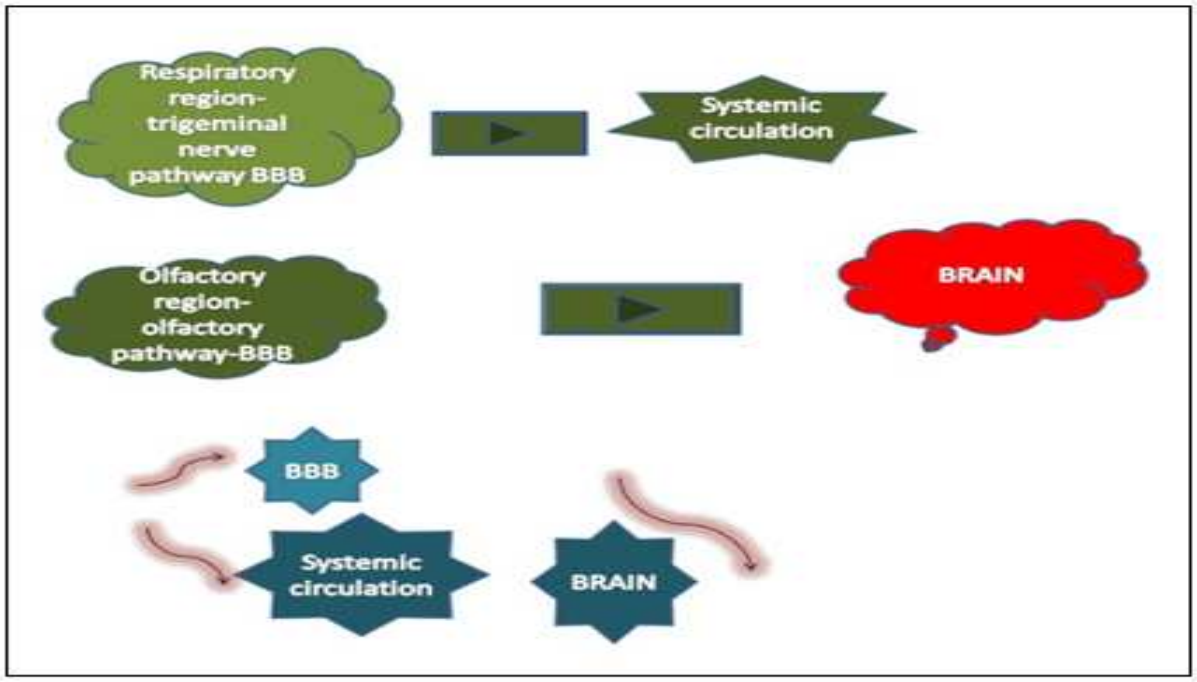

Fig. 1. Permeability of the drugs in the nasal region.

Ginko biloba is an herbal plant containing a vast Phytoconstituents like terpene lactones, sesquiterpines, flavonoids like kaempferol, quercetin, myricetin, flavones like catechin, flavones, biflavones, carotenoids, volatile terpenes, organic acids like ginkgolic acid and lipids. Many experimental studies showed it is used in the treatment of various neurological disorders like dementia, anxiety, fear, Alzheimer's disease, and asthenic syndrome (Bunyatyan N *et al.,* 2019).

The temperature-sensitive nasal *in-situ* gel of Ginko biloba extract was designed and evaluated for *in-vitro* drug release. They reported the formulation has good transdermal delivery with sustained release characteristics (Kapoor L, 1990).

Centella asiatica, also known as Brahmi, claimed to enhance memory power and intelligence (Mohandas Rao K *et al.,* 2006). Many papers reported that the extract of *Centellaaciatica* is used to treat neurological diseases like depression, anxiety and Alzheimer's disease. Balakrishnan *et al.,* 2015, designed carbopolgel-based formulation loaded with nanoemulsion of *Centellaaciatica* extract for nasal delivery. The drug showed a sustained release pattern for upto 48 hours. By varying the concentration of Carbopol, the retention time in the nasal site also varies. As the polymer concentration increases, the retention time there by the bioavailability of the drug also increases.

In-situ gelling nasal inserts

These are the solid dosage form consisting of sponge-like hydrophilic polymer matrix structures in which the drug is loaded. It is a promising drug delivery system; once it comes into contact with the nasal mucosa, the sponge hydrates and formsa firm gel and releases the drug in a controlled pattern. These are high potential for systemic administration. Freeze drying and lyophilization are techniques used to produce the *in-situ*gelling nasal inserts.

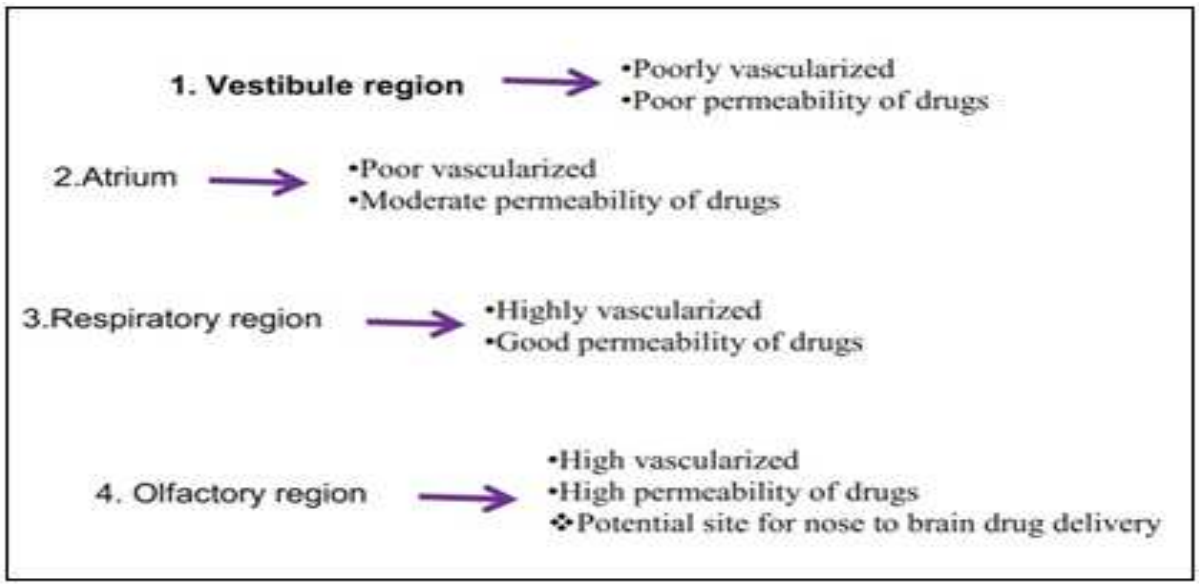

Fig. 2. Target the drug to brain.

The selection of polymers is the most important step in the formulation. Generally, high molecular weight polymers are selected because it results in high viscosity gels, low dissolution rate and retention time in the nasal cavity also increases. Generally,Carrageen gum is the choice of polymer because of its strong retarding nature and sodium alginate is also used because of its bio-adhesion nature (Zaman M *et al.,* 1999). Bertram and Bodmeier 2012, investigated the effect of polymer weight and polymer blends on the *in-situ* gelling nasal inserts using OxymetazolineHcl and Diprophyllin as model drugs. Carrageenan gum and sodium alginate in different concentrations and in different ratios with/withoutthe drug are used. Viscosity, bioadhesion potential, water uptake, mass loss, contact angle, *invitro* drug release and mechanical properties are examined.

The effect of polymer blend ratio on the drug release is more than the effect of polymer molecular weight. Werner *et al.,* 2004, designed intra-nasal inserts of estradiol by complexation with methyl beta cyclodextrin (MβCD). Different hydrophilic polymers like HPMC, PVP 90, Carrageenan gum, sodium alginate and xanthan gum are used for comparison in terms of drug release from the complex. The bioadhesive potential of the HPMC K15M is reduced by the addition of MβCD. The drug release pattern from the complex is as follows: HPMC E5>PVP 90>sodium alginate>xanthan gum> Carrageenan gum.

Elements to be considered in intra-nasal drug delivery

The foremost elements are head position, drug volume and mode of administration effects the deposition of formulation in the nasal cavity and passage to CNS through the nasal route. Many proved that altering the head position can alter the administration of formulation to the nasal cavity through the nostrils.

The head down and forward position is the favorable position for the drug to the brain via nasal delivery. But the position is not much comfortable and also it is inconvenient for the patients. So different devices are used for the convenient delivery of drugs throughthe nasal route. Devices such as sprays, nose droppers, and needleless syringes are used for the delivery of the formulation to the nasal cavity. Delivery volume is also an important factor to be considered, which affects the therapeutics of the drug. So the above-mentioned devices are used in metered values to achieve the perfect dose delivery factor (McDonough J *et al.,* 2010; Ehrick J. D *et al.,* 2013).

Olfactory area difference in animal species

The nasal mucosa and its physiology differ from one species to another.

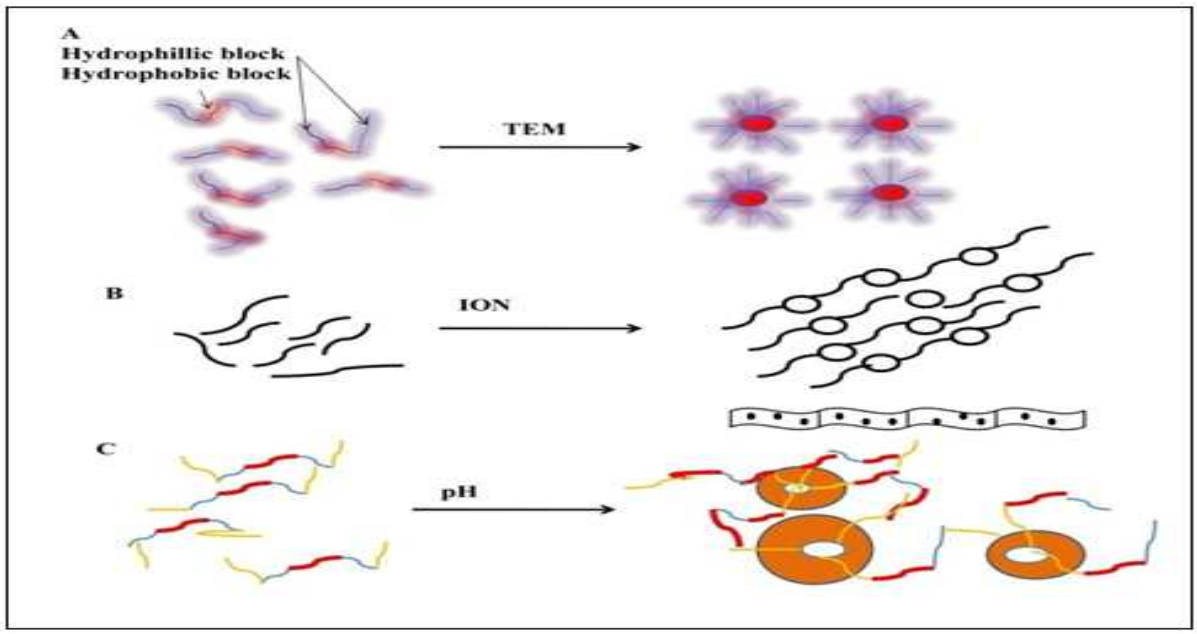

Fig. 3. Schematic presentation of *in-situ* gel by physical cross linking.

The most commonly used experimental animals are mice and rats. It is foreseen to the anatomical and histological differences when making out findings from animal experiments on humans which is described shortly in Table 3 (Gizurarson, 1990).

Conclusion

By taking into consideration all the aspects of nasal delivery, Intra nasal *in-situ* gelling system is the pre-eminent formulation for the natural drugs which have been destined for the brain to treat various neurological disorders. Research towards intra-nasal*in-situ* gel systems is much more exploring from groundwork to fact-finding.

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