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A REVIEW ON NANOPARTICLE EMBEDED NASAL GEL FOR THE TREATMENT OF DISEASES

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ABSTRACT

In-situ gels are formulation that are in sol form before administration in the nasal cavity, after administration suddenly they will get converted to gel form.The formation of gel depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation, from which the drug gets released in a sustained and controlled manner. The *in situ* gel forming polymeric formulations offer several advantages like sustained and prolonged action in comparison to conventional drug delivery systems. With a brief introduction to nasal drug delivery, in this paper, the use of novel mucoadhesive *in situ* gels for the intranasal delivery of drugs is reviewed along with methods available for evaluation of *in situ* gels.

INTRODUCTION

***In situ*-based gels** are systems that exhibit sol-to-gel transition at the site where they are administered into the body. They are liquid when administered and undergo a sol-to-gel transition induced by external stimuli such as temperature, pH, ion change and magnetic field or in the biological environment. The global prevalence of neurological disorders is rising and yet we are still unable to deliver most drug molecules, in therapeutic quantities, to the brain. The blood brain barrier, consists of a tight layer of endothelial cells surrounded by astrocyte foot processes and these anatomical features constitute a significant barrier to drug transport from the blood to the brain. One way to bypass the BBB and thus treat diseases of the brain is to use the nasal route of administration and deposit drugs at the olfactory region of the nares; from where they travel to the brain.

Nanoparticle (NP) loaded *in situ* gel is considered to be a promising strategy for anti-depressant delivery without doing any modification in drug molecule. This is effective drug delivery system for brain targeting due to their rapid uptake by brain, biodegradable and bio acceptible nature. Nanosized drug carriers were shown to enhance the delivery of drugs to CNS compared to equivalent drug solution formulations. The nasal administration of drug loaded lipid nanoparticles showed effectiveness in treating central nervous system (CNS) disorders, particularly neurodegenerative diseases, because the nasal route (also called intranasal route) allows direct nose-to-brain drug delivery by means of lipid nanoparticles. Extensive studies report that, when administered intranasally, vaccines can induce both local and systemic immune response

MECHANISM OF NASAL DRUG ABSORPTION

Two mechanisms have been considered predominantly out of several mechanisms that have been proposed. The first involves an aqueous route of transport, which is known as the paracellular route. Feature of this mechanism involves. This route is slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. Poor bioavailability was observed for a drug with a molecular weight greater than 1000 Daltons, The second involves transport through a lipoidal route is also known as the trans cellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. For examples, chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport.

POSSIBILITIES FOR THE USE OF THE NASAL CAVITY FOR DRUG DELIVERY

The easy accessibility and available surface area make the nose a possibly viable drug delivery organ. Pharmaceutical product development is an essential task which is directly dependent on its therapeutic objectives. The aspects to be considered for product development depend on whether it is intended for: Local delivery

Nasal delivery is a logical delivery choice for local (or topical) treatment as it provides the minimal potential for systemic adverse effects when compared to the oral route of administration, and hence, relatively low doses are effective when administered through nasal route with less systemic toxic effects. Prominent therapeutic classes of drugs delivered are decongestants for cold nasal symptoms and antihistamines and corticosteroids for allergic rhinitis .

Systemic delivery

The intranasal administration of drugs is an effective way for the systemic availability of drugs as compared to oral and intravascular routes of administration. It provided fast and extended drug absorption than oral and parenteral administration. Therapeutic classes of drugs delivered include analgesics (exmorphine), cardiovascular drugs as propranolol and carvedilol, hormones such as levonorgestrel, progesterone, and insulin, anti-inflammatory agents as indomethacin and ketorolac, and antiviral drugs (acyclovir). Some examples which are available in the market include zolmitriptan and sumatriptan for the treatment of a migraine and cluster headaches .

Nasal vaccines

During inhalation nasal mucosa is the first site of contact with inhaled antigens, and therefore, its use for vaccination, especially for respiratory infections, has been extensively evaluated. In fact, nasal vaccination is a promising alternative to the classic parenteral route because it can enhance the systemic levels of specific immunoglobulin

Central nervous system (CNS) delivery through nasal route

The intranasal route has encouraging approach for the delivery of drugs to the brain. The delivery of drugs to CNS from the nasal route may occur through olfactory neuroepithelium. Drug delivery through nasal route into CNS has been reported for Alzheimer's disease, brain tumours, epilepsy, pain, and sleep disorders. The treatment of Parkinson's disease is classified as a symptomatic and neuroprotective therapy. Presently, there is no proven neuroprotective therapy for the treatment of the disease. In cases of severe Parkinson's syndrome disease, when the medication is longer effective, brain surgery, which involves deep brain stimulation, is performed so as to manage the motor symptoms.

The drugs that are used to treat the disease are classified as dopamine precursors, dopamine agonists, monoamine oxidase B inhibitors and anticholinergic. These classes of drugs suffer from some side effects, as illustrated in Table 1. A brain tumour is characterized by an abnormal growth of tissue in the brain or central spine, disrupting the function of the brain, which can be either cancerous or non-cancerous. Tumours are classified based on where the cells originated. They are classified as benign when they originate from cells within the brain and do not spread into other tissue; malignant brain

tumours that spread into other tissues and grow rapidly, thus invading the surrounding brain tissue; primary tumours that start in cells of the brain and can spread to other parts of the brain or to the spine; metastatic brain tumours that begin in another part of the body and then spread to the brain. The risk factors are viral infection, chemicals, ionizing radiation and genetic manipulation. Brain tumours are difficult to treat. Some of the drugs used for the treatment of brain cancer are temozolomide, lomustine, bevacizumab, carmustine wafer, etc.

***In Situ* Gels**

In situ-based gels are systems that exhibit sol-to-gel transition at the site where they are administered into the body. They are liquid when administered and undergo a sol-to-gel transition induced by external stimuli such as temperature, pH, ion change and magnetic field or in the biological environment. They exhibit good properties, which make them useful for drug delivery such as: they are highly compatible with a range of drugs, which are soluble, insoluble, low and high molecular weight drugs; they are less invasive and can be used to obtain high drug concentrations at the desired site of action with reduced systemic side effects; biocompatibility; biodegradable and exhibit sustained drug release over an extended period, thereby enhancing patient compliance. The aforementioned properties make them useful for nose-to-brain delivery.

***In Situ*-Based Gels for the Delivery of Anti-Parkinson Drugs**

Anti-Parkinson drugs such as levodopa are used for the treatment of Parkinson's disease, and its use is limited by its poor bioavailability, which is characterized by its low brain uptake. Its poor bioavailability is attributed to the irregular gastrointestinal metabolism of the drug before it attaches to the L-amino acid carrier that transports the drug actively through the duodenum where it enters the bloodstream .Sharma et al. incorporated chitosan nanoparticles loaded with levodopa prepared by ionic gelation technique using sodium TPP (1 mg/mL) onto a thermo-reversible gel prepared from Pluronic PF127 (Poloxamer 407) . (Table 2). The formulations were characterized, followed by *in vitro* drug release studies, which revealed that the formulation obeyed the Hixson-Crowell model (drug release by dissolution with changes in the surface area and diameter of the formulation). The addition of polycations enhanced the drug absorption of the formulation on the nasal mucosa by opening the junctions between epithelial cells and delaying mucociliary clearance. *In vivo* studies on Swiss albino rat models further showed that intranasal administration of the chitosan nanoparticles resulted in an enhanced brain uptake of the drug when compared to the gel formulation, suggesting that the viscosity of the gel reduced the brain uptake of the drug. Increasing the mucoadhesive polymer resulted in an increased gelation temperature, and increasing amantadine reduced the gelation. A concentration of 16% of Pluronic F127 was found to be suitable for the sol-to-gel transition of the formulation at ambient nasal temperatures. These systems are potential therapeutics for the treatment of Parkinson disease. The formulation was stable, which was evidenced by the repeatable drug release profiles of the Fickian mechanism (a transport process in which the polymer relaxation time is greater than the solvent diffusion time), followed by an anomalous drug release mechanism (a combination of diffusion and erosion controlled drug release) after storage of the formulation at 4 _C for eight weeks. There was no significant cellular toxicity to the human nasal epithelial cells up to 4 mg/mL and up to 1 mM. The % drug release from the formulation was in a range of 43–44% *in vitro*. Khan et al. reported mucoadhesive *in situ* gel formulation prepared from chitosan and hydroxyl propyl methyl cellulose for intranasal delivery of ropinirole to the brain *In vivo* brain uptake of ropinirole in albino rats following intranasal administration of 99mTc (Technetium 99m)-ropinirole-loaded gel AUC (area under the curve) (0–480 min) was 8.5-times when compared to the intravenous administration prepared thermosensitive gel for intranasal delivery of rasagiline mesylate, a drug for the treatment of Parkinson's disease .The gels were prepared from a combination of poloxamer 407 and poloxamer 188 in a 1:1 ratio with mucoadhesive polymers, namely: carbopol 934 P and chitosan. *In vivo* performance of the formulation in New Zealand white rabbits suggested that the

intranasal administration of the formulation exhibited a better drug bioavailability of six-fold higher than the oral solution. Nasal mucosal integrity studies indicated maintained integrity of the nasal mucosa of rats after chronic administration of the formulation. The brain uptake of the formulation was significantly ($p < 0.01$) high when compared to the drug solution. Rasagiline mesylate's poor bioavailability is attributed to its rapid absorption and first-pass metabolism, which is overcome when administered intranasally, resulting in extended residence and contact time with nasal epithelium and enhanced drug absorption from the nasal cavity. High Cmax revealed the rapid absorption of the drug, and the high AUC0–¥ values suggested complete absorption of the drug from the gel formulations Rao et al. prepared thermoreversible nasal gels by the cold method from Pluronic F-127 and hydroxyl methyl propyl cellulose, and ropinirole, an anti-Parkinson drug with poor oral bioavailability, was loaded onto the gel. Formulations exhibited gelation at the nasal temperature, and the time of gelation was less than the mucociliary clearance time. The nasal residence time of the formulation was influenced by the mucoadhesion and enhanced strength of the gel. The formulations' ex vivo drug release was 56–100% over a period of 5 h. Histological study of sheep nasal mucosa revealed that the gel had a protective effect when compared to the free drug, which was characterized by cellular damage. The brain uptake of the drug after nasal administration was five-fold when compared to the administration of the formulation intravenously, revealing the system as a potential delivery system for anti-Parkinsonian drugs. The drug delivery from the formulation to the brain was via the olfactory nerves Pharmaceutics, *11*, x 9 of 17 Pluronic F-127 and hydroxy methyl propyl cellulose, and ropinirole, an anti-Parkinson drug with poor oral bioavailability, was loaded onto the gel [61]. Formulations exhibited gelation at the nasal temperature, and the time of gelation was less than the mucociliary clearance time. The nasal residence time of the formulation was influenced by the mucoadhesion and enhanced strength of the gel. The formulations' ex vivo drug release was 56–100% over a period of 5 h. Histological study of sheep nasal mucosa revealed that the gel had a protective effect when compared to the free drug, which was characterized by cellular damage. The brain uptake of the drug after nasal administration was five-fold when compared to the administration of the formulation intravenously, revealing the system as a potential delivery system for anti-Parkinsonian drugs. The drug delivery from the formulation to the brain was via the olfactory nerves

EVALUATIONS:

Gelling temperature and gelling time

Gelling temperature refers to the temperature when the meniscus of the formulation would no longer move upon slanting the test tubes at 90 °. The gelling temperature was determined by placing the test tube, containing sufficient quantity of the prepared solutions, in a water bath at 4 ℃. The temperature of water bath was increased slowly at a constant rate of 1 ℃ every 2 min. Gelling time of formulations was determined using the procedures described by Miller and Donovan The delivery systems exist in sol form before administration, however, once they are administered; they undergo gelation to form a gel. Gelling time was recorded as the time for first detection of gelation. The sol-gel transition temperature (Tsol-gel) of the prepared *in situ* gel formulations was evaluated by transferring 2 ml of the prepared formulation to a test tube (10 ml), with a diameter of 1.0 cm. After sealing with a parafilm, the tube was kept in a circulation water bath at 37 ℃. Following each temperature setting, equilibration was allowed for 10 min. Finally, the test tube was placed horizontally to observe the state of the sample and to examine the gelation.

Viscosity of solution: Viscosity of the *in situ* gel systems was determined using Brookfield viscometer DV-II+Pro coupled with S-94 spindle. The prepared gel formulations were transferred to the beaker. The spindle was lowered perpendicularly into the gel at l00 rpm and temperature was maintained at 37 ± 0.5 ℃. The viscosity was determined during the cooling of the system All the measurements were performed in triplicates.

Table 1. Some drugs used for the treatment of selected neurological diseases.

Drugs	Application	Route of Administration	Side Effects
Donepezil	All stages of Alzheimer's disease	Oral	Nausea, increased bowel movements, loss of appetite.
Galantamine	Mild to moderate Alzheimer's disease	Oral	Nausea, increased bowel movements, loss of appetite.
Rivastigmine	Mild to moderate Alzheimer's disease	Orally and transdermally	Dizziness, constipation, headache
Memantine	Moderate to severe Alzheimer's disease	Oral	Dizziness, constipation, headache
Donepezil and Memantine	Moderate to severe Alzheimer's disease	Oral	Nausea, increased bowel movements, loss of appetite, dizziness, constipation, headache.
Beta interferon	Relapsing-remitting multiple sclerosis	Subcutaneous and intramuscular	Myalgia, headache, anemia, nausea.
Glatiramer acetate	First clinical episode of multiple sclerosis	Subcutaneous	Nausea, vomiting, body ache.

Table 2. Intranasal administration of bioactive agents via *in situ* gels.

Bioactive Agents	Formulation Composition	Neurological Disorder	Efficacy
Levodopa	Pluronic F127, chitosan	Parkinson's syndrome	Delayed mucociliary clearance
Rasagiline Mesylate	Poloxamer 407, poloxamer 188, carbopol 934 P and chitosan	Parkinson's syndrome	6-fold higher drug bioavailability
Ropinirole	Chitosan, hydroxyl propyl methyl cellulose	Parkinson's syndrome	Enhanced brain uptake of drug *in vivo*
Amantadine	Pluronic F127, carboxymethylcellulose	Parkinson's syndrome	No cellular toxicity to human nasal epithelial cells
Geniposide	Poloxamers (P407, P188) and hydroxypropyl methylcellulose	Alzheimer's	*In vitro* release profile of the drug was zero-order, and the ex vivo release mechanism was the Weibull model

Table 3. Summary of the reported studies investigated as nasal mucoadhesive *in situ* gels.

Polymer	Gelling Agent	Drug
Chitosan	Hydroxypropyl methylcellulose	Ketorolac tromethamine
Pectin	Hydroxypropyl methylcellulose	Ketorolac tromethamine
Carbopol 934P	Hydroxypropyl methylcellulose	Sodium cromoglycate
Pluronic F68	Xanthan gum	Rizatriptan benzoate
Pluronic F 127	Carbopol 974P	Sumatriptan succinate

Rheological properties of *in situ* gels: The rheological properties of *in situ* gel formulations were investigated using Brookfield LVDV-E Viscometer (Brookfield Engineering Laboratories, Inc, USA). The temperature was initially maintained above 40 °C. The rheological properties were measured by increasing the spindle rotational speed from 0.3 to 100 rpm, and the shear rate (g), shear stress (t), and viscosity (h) were recorded. All the measurements were performed in triplicates.

Determination of pH: One ml of the prepared gels was transferred to a 10 ml volumetric flask, and the solution was diluted with distilled water. The pH of resulting solution was determined using a digital pH meter, which was previously calibrated using phosphate buffers at pH 4 and pH 7

Drug content assay: One ml of the prepared formulation was dispersed in 10 ml of methanol for 2–3 min with occasional shaking. The resulting solution was filtered through a 0.45 µm filter paper and was diluted with methanol. The amount of loratadine in the formulation was determined spectrophotometric ally.

Gel strength: Sample (50 g) was placed in a 100 ml graduated cylinder. Gelation was carried out by placing the formulations in a thermostat at 37 ℃. The strength of the gel was determined by measuring the time taken by a weight of 35 g to sink 5 cm in the gel

Spread ability: Spreadability was determined using a 10 × 4 cm rectangular glass slide. The sheep nasal mucosa from serosal side was tied on the surface of slide with a thread. The slide was kept in a hot air oven at 37 ℃ and one drop of gel was placed on the mucosa at an angle of 120 °. Spreadability was determined relative to the distance travelled by the drop of gel (liquid) before its gelation. Average of three readings was recorded

Mucoadhesive strength: *Ex vivo* mucoadhesive strength was determined using fresh sheep nasal mucosa. The mucosal membrane was separated by removing the underlying fat and loose tissues. The membrane was washed thrice with distilled water and phosphate buffer (pH 6.4). Modified balance method was used to design the experiment. The balance was equilibrated on both sides by placing one beaker on the left pan and a weight (5 g) on the opposite pan. The sheep nasal mucosa was cleaved into 1 cm^2 and glued with cyanoacrylate over the glass support so as to allow the smooth surface of nasal mucosa face the upper side of the glass. The glued sheep nasal mucosa was wetted with buffer by filling the beaker with the buffer on the right hand side of the balance by lowering the glass support. The above setup was placed below the right side of the pan.

***In vitro* drug release:** *In vitro* drug release of loratadine was determined using Franz-diffusion cell. The sheep nasal mucosa was prepared as described in the above procedures. The prepared nasal mucosa was mounted between the donor and receptor compartments. The receptor compartment was filled with phosphate buffer at 37 ℃. The solution was stirred at 100 rpm. The gel (10 mg) was placed on the nasal mucosa and the compartments were clamped together. One ml of the sample was withdrawn at predetermined time intervals (0, 0.5, 1, 2, 4, 6, 8, 10, and 12 h) from receptor compartments and immediately replaced using phosphate buffer pH 6.4. for drug content. The mechanism of drug release from the *in situ* nasal was determined by plotting the best fit of the release data in Higuchi and Korsmeyer-Peppas plots. The release rate constants *k* and *n* of each model were calculated by linear regression analysis using Microsoft Excel 2003 software. Coefficients of determination (R^2).

Accelerated stability studies: Stability studies were carried on *in situ* gel formulation according to International Conference on Harmonization guidelines. A sufficient quantity of *in situ* gel in nasal spray bottles was stored in desiccator, containing saturated solution of sodium. The desiccator was placed in hot air oven maintained at 40 ± 2 ℃, and the samples were withdrawn at 1, 2, 3, 5, and 6 months. Changes in the appearance, drug content, gelling strength, and *in vitro* drug release of the stored formulations were

investigated. Mean values from the three determinations were recorded.

Differential scanning calorimetry: Differential: scanning calorimetric thermograms of selected formulation were recorded. The samples were placed in sealed aluminium pans and scanned at heating rate of 10 °C min^{-1} over the temperature range of 30–200 °C.

CONCLUSION

Eventhough nasal drug delivery provides many advantages for the delivery of pharmaceuticals as well as biopharmaceuticals, certain disadvantages limit the use of nasal route of drug administration. Mucociliary clearance and rapid drainage of the liquid formulation are the main disadvantages of nasal route. These limitations can be minimised by the use of mucoadhesive polymers. Recent developments in the field of polymer science and technology has led to the development of various stimuli sensitive hydrogels like pH, temperature and ion sensitive which are employed for nasal drug delivery. In conclusion, the primary requirement of a successful controlled release product focuses on increasing patient compliance which the *in situ* gels offer. Exploitation of polymeric *in situ* gels for controlled release of various drugs provides a number of advantages over conventional dosage forms. Sustained and prolonged release of the drug, stability and biocompatibility characteristics make the *in situ* gel dosage forms exceptionally reliable. Use of biodegradable and water soluble polymers for the *in situ* gel formulations can make them more acceptable and excellent drug delivery systems.

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