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A review on in situ gel therapy for epilepsy via nasal route

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Abstract
The currently available antiepileptic drugs are typically administered via oral route which commonly exhibit high systemic distribution into non-targeted tissues, leading to peripheral effects and limited brain uptake. In order to improve the efficacy and tolerability of the antiepileptic drug therapy, alternative administration strategies have been investigated. Olfactory epithelium situated on the roof of nasal cavity is said to deliver nasally administered medications directly to brain. Nasal in situ gel in which liquid solution of drug formulation get converted into semisolid when it comes in contact with nasal mucosa. In situ gelling has many approaches like temperature induced, pH induced, osmotically induced, ion cross linking etc. The development of nasal in situ gel leads to various advantages like decrease frequency of drug administration, low dose requirement, increase patient compliance.

Keywords: Epilepsy, intranasal route, nasal in situ gel

Introduction

Epilepsy [1]

Epilepsy is a disorder of the central nervous system characterized by brief episodes (seizures) of loss or disturbances of consciousness, with or without characteristic body movements (convulsions), sensory or psychiatric phenomena.

Table 1: Classification of Epileptic Seizures [2, 3]

Seizures Types	Characterization
Focal (partial) Seizures	Origin within networks limited to one hemisphere; only a certain area of the body is usually involved. - Retained consciousness (simple partial seizure). - Loss of consciousness (focal dyscognitive seizure) (complex partial seizures).
Generalized Seizures	Simultaneous arising from both cerebral hemispheres with symptom manifestation bilaterally in the body.
Tonic-clonic (grand mal)	Abrupt loss of consciousness followed by tonic contraction of the muscles which then evolves to clonic convulsive movements. - Tonic phase: rigid, violent and sustained contraction of whole body musculature. Momentary cessation of breathing and tongue biting. - Clonic phase: repetitive spasms and rhythmic jerking of the extremities. It is characterized by a progressive muscle relaxation until the end of the ictal phase.
Absence	Sudden, brief lapses of consciousness without loss of postural control.
Myoclonic	Sudden, brief and arrhythmic muscle contractions that may involve the whole body or certain focal areas.
Clonic	Repetitive rhythmic clonic jerks with impairment of consciousness and a short post-ictal phase.
Tonic	Tonic contraction of the face, neck, axial, or appendicular musculature lasting from 10 to 60 seconds. Usual upward deviation of the eyes.
Atonic	Sudden loss of postural muscle tone and consciousness that usually cause abrupt falls.
Unknown	Seizures that cannot be clearly diagnosed into one of the preceding categories due to incomplete data.

Symptoms of epilepsy [3]

- Confusion, Loss of consciousness or recognition, uncontrolled movement, often including jerking and pulling, Repetitive movements, Convulsing.

Causes of epilepsy [3]

- Oxygen deprivation, Birth asphyxia, Brain infection (meningitis, encephalitis, brain abscess), Traumatic head or brain injury, Stroke, Brain tumor, Alzheimer's disease, Withdrawal from alcohol.

Pathophysiology of epilepsy [4]

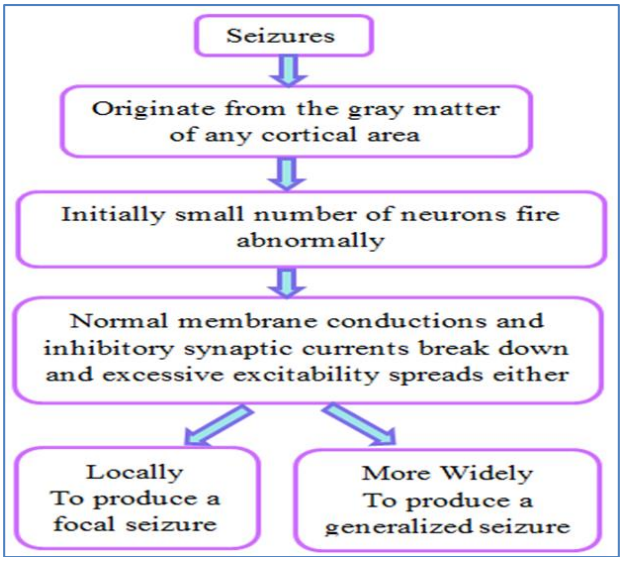

Fig 1: Pathophysiology of Epilepsy

Management of epilepsy [5]

Table 2: The Main Clinically Approved Antiepileptic Drugs

First Generation	Second Generation	Third Generation
Phenobarbital	Zonisamide	Stiripentol
Phenytoin	Vigabatrin	Pregabalin
Primidone	Lamotrigine	Rufinamide
Ethosuximide	Oxcarbazepine	Lacosamide
Carbamazepine	Gabapentin	Retigabine
Valproic acid	Topiramate	Perampanel

The Mechanisms of Action of Anti-Seizure Drugs Fall Into Three Major Categories: [6]

1. The first mechanism is to limit the sustained, repetitive firing of neurons an effect mediated by promoting the inactivated state of voltage-activated Na^+ channels.
2. A second mechanism appears to involve enhanced γ-amino butyric acid (GABA)–mediated synaptic inhibition; an effect mediated either by a presynaptic or postsynaptic action. Drugs effective against the most common forms of epileptic seizures, partial and secondarily generalized tonic-clonic seizures, appear to work by one of these two mechanisms.
3. Drugs effective against absence seizure, a less common form of epileptic seizure, work by a third mechanism, inhibition of voltage-activated Ca2+ channels responsible for T-type Ca2+ currents

Diagnosis of epilepsy [7]

- Electroencephalograph (EEG), Complete blood count (CBC), Blood Glucose, Kidney function tests, Liver Function tests, Tests for infectious diseases.

Available dosage forms [8]

Table 3: Dosage Forms of Antiepileptic Class Drugs

AED's	Dosage Form	Drugs
Phenobarbitone	Tablet / Syrup 100ml / Injection	Barbinol
Primidone	Tablet / Capsule	Mysoline
Phenytoin	Capsule(ER)	Dilantin, Phenytek
Carbamazepine	Extended-Release Capsules 100 mg, 200 mg and 300 mg	Carbatrol, Equetro
	Immediate-release Tablet 200mg	Tegretol
	Chewable Tablet 100mg	Epitol
Oxcarbazepine	Film-coated tablet	Trileptal
	Extended-release tablet	Oxtellar XR
Diazepam	Tablet (2 mg, 5 mg or 10 mg)	Valium
Lorazepam	Tablet 1mg	Ativan
Lamotrigine	Chewable tablets (2,5,25mg) Oral Disintegrating tablets (25 mg, 50 mg, 100 mg, 200 mg)	Lamictal
Gabapentin	Capsule(100 mg,300mg,400 mg)	Neurontin
	Tablet (300 mg or 600 mg)	Gralise

Introduction to Nasal Delivery [9-11]

- The nasal cavity is easily accessible, rich vascular plexus at the same time permits topically administered drugs to rapidly achieve effective blood levels while avoiding intravenous catheters and avoids immense pain.

- The human nasal cavity has a total volume of about 16 to 19 ml, and a total surface area of about 180 cm^2, and is divided into two nasal cavities by the septum. The volume of each cavity is approximately 7.5 ml, having a surface area approximately 75 cm^2.
- Nasal secretions originate mostly from submucosal glands, but are also contributed to by goblet cells and transudate from plasma. Mucus is composed of water (95%), glycoproteins (2 %), albumin, immunogobulins, lysozyme, lactoferrin and other proteins (1%), inorganic salts (1%) and lipids (<1%).
- Post drug administration into the nasal cavity, a solute can be deposited at one or more of anatomically distinct regions, the vestibular, respiratory and olfactory regions showing in following figure,

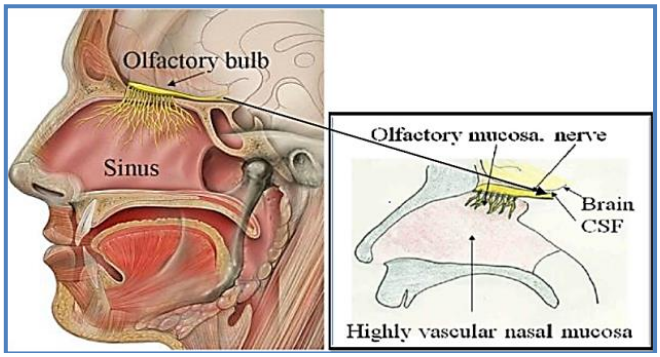

Fig. 2: Representation of Olfactory Bulb

Advantages of nasal dosage form

- Easy to administration, non-invasive, rapid and comfortable.
- For direct delivery of drug to the central nervous system via the olfactory region, thus by-passing the blood brain barrier.
- Hepatic first – pass metabolism is absent.
- Easy accessibility to blood capillaries.
- Rapid drug absorption and Quick onset of action.
- Drug degradation is absent.
- Avoid side effects like nausea and vomiting which is normally seen after oral administration.
- Convenient route for long term therapy.
- Polar compounds particularly suited for nasal route.

Disadvantages of nasal dosage form

- High permeability of the nasal mucosa may leads to toxicity.
- Lack of adequate aqueous solubility.
- Entire dose limit volume of 25–200 µl (0.025-0.2 ml)
- Once the drug administered cannot be removed.
- Delivery is expected to decrease with increasing molecular weight of drug.
- Some therapeutic agents may be susceptible to partial degradation in the nasal mucosa.
- Nasal congestion due to cold or allergies.
- There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs.

Physiological factors affecting nasal absorption [11]

A) Effect of deposition on absorption

- Deposition of the formulation in the anterior portion of the nose provides a longer nasal residence time. The anterior portion of the nose is an area of low permeability, while posterior portion of the nose is where the drug permeability is generally higher, and provides shorter residence time.

B) Nasal blood flow

- Nasal mucosal membrane is very rich in vasculature and plays a vital role in the thermal regulation and humidification of the inhaled air. The blood flow and therefore the drug absorption will depend upon the vasoconstriction and vasodilatation of the blood vessels.

C) Effect of enzymatic activity

- Several enzymes that are present in the nasal mucosa might affect the stability of drugs. For example, proteins and peptides are subjected to degradation by proteases and aminopeptidase at the mucosal membrane. The level of aminopeptidase present is much lower than that in the gastrointestinal tract. Peptides may also form complexes with immunoglobulin in the nasal cavity leading to an increase in the molecular weight and a reduction of permeability.

D) Effect of mucociliary clearance

- The absorption of drugs is influenced by the residence (contact) time between the drug and the epithelial tissue. The mucociliary clearance is inversely related to the residence time and therefore inversely proportional to the absorption of drugs administered.

E) Effect of pathological condition

- Intranasal pathologies may affect the nasal mucociliary transport process and/or capacity for nasal absorption.

Introduction to Nasal Insitu Gel [12]

- Gel is the state which exists between solid and liquid phase. The solid component comprises a three dimensional network of inter-linked molecules which immobilizes the liquid phase.
- In situ gelation is a process of gel formation at the site of action after the formulation has been applied at the site. In situ gel phenomenon based upon liquid solution of drug formulation and converted into semi-solid mucoadhesive key depot.

Principle of gelling [12]

Main principle of In-situ gelling for nasal formulation is to be applied in nasal fluid. In this process after administration of drug solution is converted into gel in nasal cavity.

Properties of nasal in situ gel [13]

- It should have long residence time.
- It should be low viscous.
- Free flowing allow for reproducible administration to nasal cavity.
- The nasal in-situ gel follows phase transition mechanism and shear forces in nasal cavity wall.

Advantages of nasal in situ gel [14]

- Increased residence time of drug in nasal cavity.
- Decreased frequency of drug administration.
- Results in rapid absorption and onset of effect.
- Avoids degradation of drug in gastrointestinal tract

resulting from acidic or enzymatic degradation.
- Low dose required.
- Minimized local and systemic side effects.
- Improved bioavailability of drug.

Direct transport into systemic circulation and CNS is possible.

Approaches of in situ gelling system (15, 16)

Table 4: Approaches of In Situ Gelling System

Approaches of In Situ Gelling System		
A) Stimuli Responsive In Situ Gelling System 1) Temperature induced in situ gel system. 2) pH induced in situ gel systems.	B) Osmotically Induced In Situ Gelling System	C) Chemically Induced In Situ Gelling System 1) Ionic cross linking. 2) Enzymatic cross linking. 3) Photo polymerization.

A) Stimuli Responsive In Situ Gelling System

Physical or chemical changes in response to small external changes in the environmental conditions.

1) Temperature induced in situ gel system

- Temperature is the most widely used stimulus in environmentally responsive polymer systems. The change of temperature is not only relatively easy to control, but also easily applicable both *in-vivo* and *in-vitro*.
- These hydrogels are liquid at room temperature (20˚-25˚C) and undergoes gelation when in contact with body fluids (35˚-37˚C), due to increase in temperature. The polymers which show temperature induced gelation are poloxamers or pluronics, cellulose derivatives (methyl cellulose).

2) PH inducing in situ gelling system

- Polymers containing acidic or alkaline functional groups that respond to changes in pH are called pH sensitive polymers. The pH is an important signal, which can be addressed through pH-responsive materials.
- Gelling of the solution is triggered by change in pH. At pH 4.4 the formulation is free from is a free running solution which undergoes coagulation when the pH is raised by the body fluid to pH 7.4. The polymers which shows pH induced gelation are cellulose and its derivatives polyvinyl acetate, polyethylene glycol.

B) Osmotically Induced In Situ Gelling System

- In this method, gelling of the solution instilled is triggered by changes in the ionic strength. It is assumed that the rate of gelation depend on the osmotic gradient across the surface of the gel. The aqueous polymer solution forms a clear solution forms a clear gel in the presence of the mono or divalent cations. The polymer which shows osmotically induced gelation is gellan gum, alginates.

C) Chemically Induced In-Situ Gelling System

The chemical reaction which forms in-situ gel systems are ionic crosslinking, enzymatic cross linking and photo-polymerization

1) Ionic cross linking

- Ion sensitive polysaccharides such as carragenan, gellan gum, pectin, sodium alginate undergo phase transition in presence of various ions such as k^+, $Ca^{2+,}$ Na^+. These polysaccharides fall into the class of ion-sensitive ones. For example, Alginic acid undergoes gelation in presence of divalent cations example-Ca^{2+} due to the interaction with guluronic acid block in alginate chains.

2) Enzymatic cross linking

- In Situ formation catalyzed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and physicochemical approaches. For example an enzymatic process operates efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators.

3) Photo polymerization

- Photo polymerizable systems when introduced to the desired site via injection get photo cured in-situ with the help of fiber optic cables and then release the drug for prolonged period of time. A photo polymerization, biodegradable hydro gels as a tissue contacting material and controlled release carrier.

Polymer used in in situ gel [17]

➢ **Ideal characteristics of polymers**

- Its degradation products should be nontoxic.
- It should adhere quickly to moist tissue and should possess some site specificity.
- It should be a non-irritant to the mucous membranes.
- The cost of the polymer should be not too high, so that prepared dosage form remains Competitive.

Table 5: Bioadhesive Polymers Used In Nasal Drug Delivery

Polymer	Characteristics
Cellulose derivatives **Soluble**: Hydroxypropyl methylcellulose (HPMC) Hydroxypropyl cellulose(HPC) Carboxymethyl cellulose(CMC) **Insoluble:** Ethylcellulose(EC)	-Prolong the residence time of drug in nasal cavity. -Sustain the release of drug due to high viscosity. -Act as absorption enhancer. -Effectively increase intranasal bioavailability.

Microcrystalline cellulose(MCC)	
Polyacrylates Carbomers Polycarbophils	-Excellent mucoadhesive and gel forming capability. -Capable of attaching to mucosal surfaces hence ensure intimate contact between the formulation and membrane surface.
Starch Maize starch Degradable starch microspheres (DSM)	-Effectively improve absorption of both small hydrophobic and hydrophilic macromolecular drugs. -Mostly used in mucoadhesive microparticulate nasal delivery system.
Chitosan	-Insoluble at neutral and alkaline pH. -It can form water soluble salts with inorganic and organic acids. -Low cost, Biodegradable and Biocompatible.

Evaluation of nasal insitu gel [18, 19]

A) Preformulation studies

a) UV-Visible spectroscopy (Determination of λmax)
b) FTIR study (for Drug polymer interaction study/ compatibility study)
c) DSC study (evaluate thermal behavior of pure drug

B) Post formulation studies

a) Clarity
b) pH and Viscosity of the gel
c) Drug content
d) Gel strength
e) Sol-gel transition temperature and gelling time
f) Mucoadhesive Strength
g) Stability study

C) *In-vitro* study

a) *In-vitro* drug release study
b) *In-vitro* diffusion study
c) *In-vitro* Permeation study

Intranasal Route for Brain Targeting [20]

- Blood brain barrier limits the entry of drugs and this makes the CNS treatment ineffective. Nose to brain drug delivery can revolutionize the treatment of brain disorders.
- The olfactory region, next to respiratory region is the foremost site from where drug can be absorbed directly into the brain by different mechanisms including transcellular, paracellular, olfactory (front of the brain) and trigeminal (back of the brain) neural pathways. The nerve cells of the olfactory epithelium project into the olfactory bulb of the brain, which provide a direct connection between brain and external environment.
- Intranasal delivery avoids gut and liver first pass metabolism so the drugs which get metabolized in GIT can be easily given by this route. The major challenges to this delivery are to achieve maximum absorption by efficiently targeting and retaining the formulation in the olfactory region.
- Drug can be targeted with the help of nanostructured lipid carrier, pressurized olfactory device, mucoadhesive microemulsions. Intranasal delivery seems to be the most promising application form to improve CNS disorders including brain injuries. Route from nasal cavity to brain,

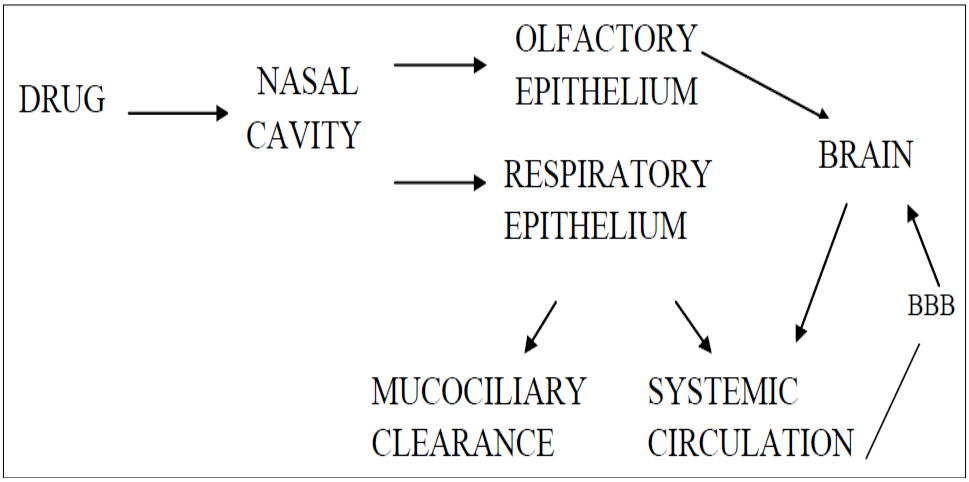

Fig 3: Route to Brain Pathway from Nasal Cavity

Olfactory region [21]

- The olfactory region is located in the roof of the nasal cavity and extends a short way down the septum and lateral wall it is of about 10 cm^2 in surface area and it plays a vital role in transportation of drugs to the brain and the CSF.
- When the drug is administered intranasally, it can enter into the brain via three different paths. The first one is the systemic pathway by which the drug is absorbed into the systemic circulation and subsequently reaches the brain by crossing BBB [especially lipophilic drug]. The others are the olfactory region and the trigeminal neural pathway by which drug is transported directly from the nasal cavity to CNS [cerebrospinal fluid and brain tissue]. There are different mechanism by which the drugs across the olfactory membrane to reach CNS. The first mechanism involves direct transfer of the drug to primary neurons of the olfactory epithelium and transport to the olfactory bulb by intracellular axonal transport with subsequent possible distribution into more distant brain tissues.
- The second mechanism depends on the drug permeation across the olfactory sustentacular epithelial cells, either by transcellular or paracellular mechanisms followed by uptake into CNS. The last one employs pinocytosis by olfactory neurons.

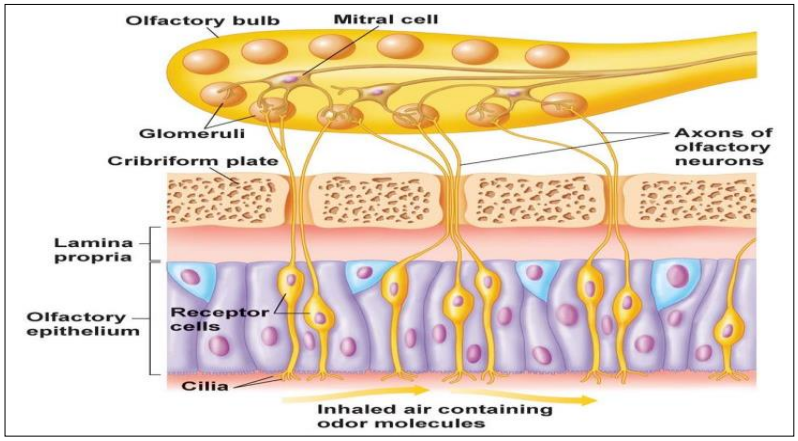

Fig 4: Representation of Olfactory Region

Application of Nasal Delivery

Intranasal administration confers a simple, economic, convenient and noninvasive route for rapid drug delivery to systemic circulation.

- Treatment of epilepsy and schizophrenia
- Treatment of migraine
- As an antidepressant
- Treatment of angina pectoris and neurological deficit
- Treatment of amnesia
- Intranasal delivery of peptides

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