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REVIEW ARTICLE

# Lamotrigine Lipid Nanoparticles for Effective Treatment of Epilepsy: a Focus on Brain Targeting via Nasal Route

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## Abstract

**Background** Pharmaceutical research in the field of medicine aims to improve the quality of life of a patient. Epilepsy is a neurological disorder affecting a number of patients worldwide because of poor penetration of antiepileptic drugs across the blood brain barrier. Therefore, there is a need to find an alternative drug delivery technology to overcome problems associated with conventional therapy.

**Objective** The aim of this review is to introduce and understand the importance of targeting lamotrigine to the brain via the nasal route. Mechanism of drug transport via nasal cavity to brain and various strategies to improve drug absorption through nasal cavity.

**Methods** Existing route of drug administration of lamotrigine is oral route. The route that has been rarely explored for lamotrigine targeting to the brain such as nasal route of drug administration is focused in this article.

**Results** Nanomedicine has gained a lot of importance in the recent past. Many studies have been taken up to deliver drugs to the brain as nanoparticles. In most of the approaches, efforts were made to deliver the nanoparticles either by the oral route or intravenous route of administration. In the present review, we have discussed the current outlook on advances in brain targeting by administration of drug via the nasal route.

**Conclusion** Targeting lamotrigine via the nasal route to the brain is a promising delivery system and would be advantageous in the treatment of other poorly bioavailable drugs to treat disorders of the brain.

**Keywords** Epilepsy · Nasal drug delivery · Brain targeting · Lamotrigine · Lipid nanoparticles · Solid lipid nanoparticles · Factors affecting nasal absorption

## Introduction

Epilepsy is a chronic neurological condition which results from transient abnormal electrical activity affecting the nervous system. Epileptic seizures are a result of disturbance in the normal electrical activity of the brain [1]. Practically, epilepsy is defined as having at least two unprovoked seizures occurring in less than 24 h [2]. Epilepsy can result in general seizure or partial seizure. Generalized seizures are widespread, as they affect both hemispheres of the brain. Unlike the generalized seizure, partial seizure originates at a focus and is specific to a certain area in the brain. Figure 1 shows the classification of epileptic seizures [3]. There are various causes of epilepsy. Some of the causes include traumatic brain injury, stroke, tumor, central nervous system (CNS) infection such as viral and bacterial meningoencephalitis, inflammation or autoimmune diseases, genetic causes such as SCN1A mutation in Dravet syndrome, and structural brain abnormalities including hippocampal sclerosis, cortical dysplasia, and vascular malformation [4]. Since multiple causes can lead to an epileptic attack, it is necessary to keep a check on the symptoms of epilepsy. Seizure is one of the noticeable epileptic symptoms. Other symptoms include short attention blackouts, repeated and unusual movements such as head nodding or rapid blinking, staring spell, loss of consciousness or awareness, stiffening of the body, and psychic symptoms such as fear, anxiety, and anger.

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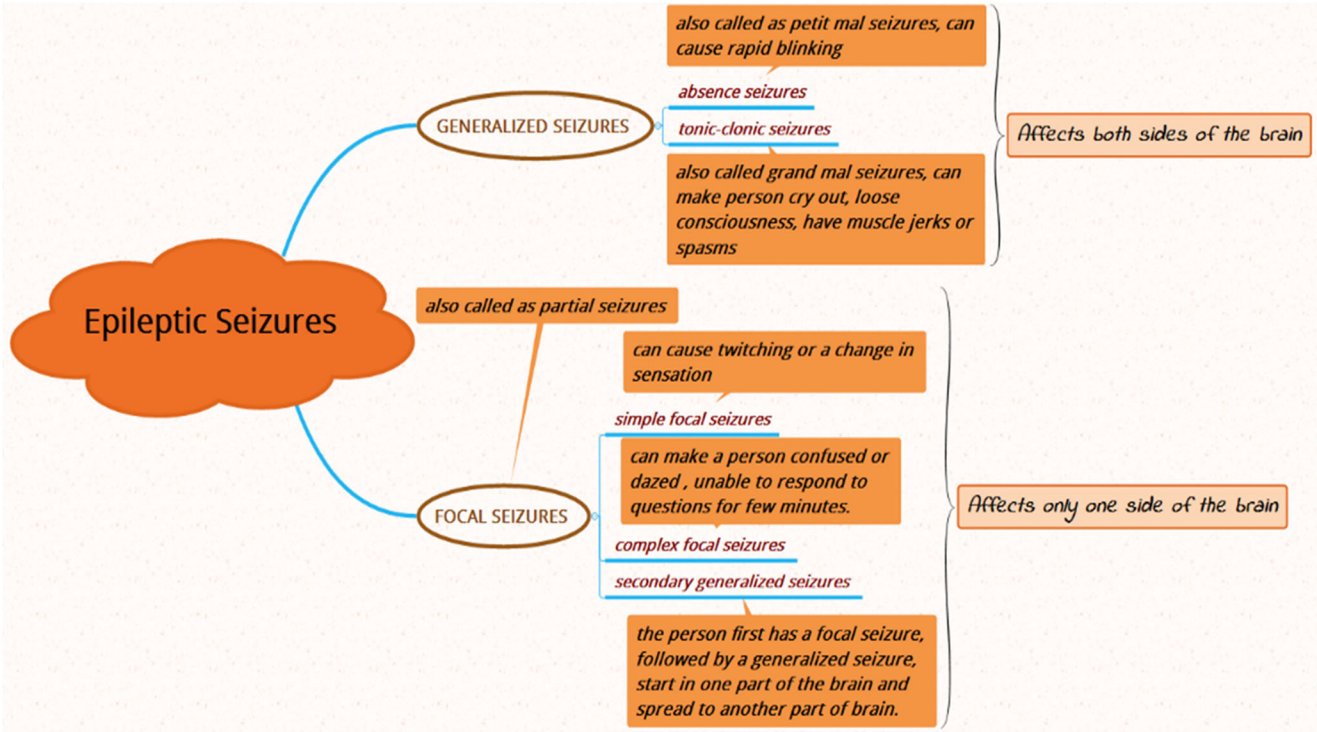


**Fig. 1** Classification of epileptic seizures [3]

## Epidemiology

The incidence rate of epilepsy is highest in young patients, newborn children, and in geriatric patients [5, 6]. Over 65 million people around the world are affected by epilepsy, which accounts for approximately 80% of population in developing countries. According to the Indian Epilepsy Centre, New Delhi, India, prevalence of epilepsy in India is estimated to be 5.59 to 10 per 1000 population [7]. In the United States, approximately 150,000 new cases of epilepsy are reported each year [8]. Epilepsy affects at least one in every 26 people worldwide [8].

## Diagnosis and Treatment

One-third of patients suffering from epilepsy have uncontrollable seizures [9] due to unavailability of proper diagnosis and treatment. With the arrival of modernization, numerous diagnostic tools and methods are available to find and categorize the type of epilepsy and study the localization pattern of seizures. Diagnostic tools such as electroencephalogram (EEG), positron emission tomography (PET), magnetic resonance imaging (MRI), magnetoencephalogram (MEG), single photon emission computed tomography (SPECT), and neuropsychiatric testing are few of the commonly used instruments. Once epilepsy is diagnosed, a patient is prescribed with anti-epileptic drugs. An ideal anti-epileptic drug should prevent the occurrence of seizures without causing its own side effects. Unfortunately, currently available anti-epileptic agents fail to control seizure activity in some patients and are also responsible for causing adverse effects. Examples of few drugs used for the treatment of epilepsy are represented in Table 1. As there are many drugs approved for the treatment of epilepsy, it has been classified into different categories based on their mechanism of action (MOA). Figure 2 depicts the classification of antiepileptic drugs according to their MOA.

## Invasive and Non-invasive Routes for Delivery of Antiepileptic Drugs

The route of administration of drugs is very important with respect to the bioavailability, adverse effects, and site specific delivery of drugs. As shown in Fig. 3, antiepileptic drugs can be delivered by invasive (intravenous, intramuscular, intracerebroventricular, intra-parenchymal) and non-invasive routes (such as oral and intranasal).

Few invasive routes such as intracerebroventricular and intraparenechymal are considered to be more effective for their quick response and site-specific delivery [61]. But these routes need expertise and safety issues are always involved with these routes of drug administration. Few invasive routes such as intravascular and intramuscular routes are safe compared to intracerebroventricular and intraparenechymal routes,

**Table 1** List of drugs used for treatment of epilepsy

| S. no. | Name of drug | Daily adult dose | Available dosage forms | ROA | Indications | MOA | BCS class | BA (%) | Ref |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Acetazolamide | Initial dose given is 8 to 30 mg/kg orally/IV; initial dose for patient on anticonvulsant treatment 250 mg orally/IV (OD) | Tablets, capsules, powder for solution | Oral, IV | Edema due to CHF, centrencephalic epilepsies | CAi | IV | 98 | [10–12] |
| 2 | Carbamazepine | Start with 100 and 200 mg (OD/BD) increase slowly to 400 mg to 1.2 g in divided doses. If required from 1.6 to 2 g | Tablets, capsules, syrups | Oral | Partial seizures with or without secondary generation; trigeminal neuralgia; bipolar disorder | iNa; BST | II | 89 | [13, 14] |
| 3 | Clobazam | 0.3 to 2.9 mg/kg (OD/BD) | Tablets, suspensions | Oral | Refractory partial, complex and generalized seizures, myoclonic epilepsy, absence seizures | +GABA, cGAB, CP2Di | II | 80–90 | [15] |
| 4 | Clorazepate | Initial dose: 7.5 mg orally (TDS), MAX. 90 mg | Tablets, Capsules | Oral | Adjunctive therapy in management of partial seizures and can also be used for management of anxiety disorder | BNZ1, cGABA | – | 91 | [16, 17] |
| 5 | Clonazepam | 0.5 to 5 mg (TDS), starting dose < 1.5 mg, maintenance dose 4 to 8 mg | Tablets | Oral | Absence seizures, myoclonic seizures, akinetic seizures, panic disorder, subcortical myoclonus, refractory epilepsy | eGABA | III | 90 | [18, 19] |
| 6 | Diazepam | 10 mg at the rate of 5 mg/mL/min. It can be repeated if required after 10 min | Tablets, capsules, suspension, injection, gel, emulsion | Oral, IV, R-C, IM | Status epilepsy, emergency management of recurrent seizures, febrile convulsions, anxiety | cGABA, BNZ1 | II | 93 | [20] |
| 7 | Eslicarbazepine acetate | 400 mg, maintenance dose: 800 to 1600 mg | Tablets, suspension | Oral | Treatment of partial-onset seizure epilepsy which are not controlled by conventional therapy | vNa, iCa | II | 100 | [21, 22] |
| 8 | Ethosuximide | 500 mg | Capsules, syrup, solution | Oral | Treatment of absence seizures | tvNa | 3 | 93 | [23] |
| 9 | Ezogabine | 100 mg (TDS). Max. dose: 400 mg (TDS) | Film coated tablets | Oral | Treatment of partial onset seizures in adult patients with refractory epilepsy | NAK, STP | II | 60 | [24, 25] |
| 10 | Fosphenytoin | 15 mg/kg IV infusion at a rate of 100–150 mg/min | Injection | IM, IV | Generalized tonic-clonic status epilepsy | FVNa | I | 100 | [26, 27] |
| 11 | Felbamate | 1200 mg | Tablets, suspension | Oral | Treat partial seizures in adults and partial and generalized seizures associated with Lennox-Gastaut syndrome in children | ANMDA, iGABA | II | > 90 | [28, 29] |
| 12 | Gabapentin | Start with 10 mg/kg and increase 10 mg/kg to maintain dose 30 to 100 mg/kg in 3 divided doses | Film coated tablets, capsules | Oral | Partial seizure, first line in epilepsy patients with hepatic disease | sGABA | III | 60 | [30, 31] |
| 13 | Lacosamide | Monotherapy: 100 mg (BD). Adjunctive therapy: 50 mg (BD) | Film coated tablets, injection, solution | Oral, IV | Partial-onset seizures, diabetic neuropathic pain | iNa | I | 100 | [32] |
| 14 | Lamotrigine | Over 12 yrs. of age: 25 mg (OD) for 2 weeks followed by 50 mg (OD) for 2 weeks, then increase by 50 to 100 mg every 1 to 2 weeks | Tablets | Oral | Partial seizures and secondary generalized tonic-clonic seizures | iNaCa | II | 98 | [33, 34] |

**Table 1** (continued)

| S. no. | Name of drug | Daily adult dose | Available dosage forms | ROA | Indications | MOA | BCS class | BA (%) | Ref |
|---|---|---|---|---|---|---|---|---|---|
| | | to maintenance dose of 100 to 200 mg | | | | | | | |
| 15 | Levetiracetam | Oral: Start with 10 to 20 mg/kg and increase by 10 mg/kg every week up to 40 to 60 mg/kg in 2 divided doses.<br>IV: 20 to 30 mg/kg at the rate of 5 mg/kg/min | Film coated tablets, extended release syrups, injection | Oral, IV | Photosensitivity and myoclonus—generalized epilepsy with photosensitivity, myoclonic epilepsy, epileptic encephalopathies, severe myoclonic epilepsy, absence seizure, rolandic epilepsy | HS | I | 99 | [35] |
| 16 | Lorazpeam | 3 to 4 mg<br>IV dose: 0.1 mg/kg.<br>Max. dose: 8 mg | Tablets, injection | Oral, IV, I-M, SB | Treatment of status epilepticus | baGABA | II | 90 | [36, 37] |
| 17 | Magnesium Sulphate | IV (with conc. less than 20%)—start with 4 g over 5 to 15 min, followed by infusion 1 g/h for at least 24 h after last seizure and can be given additional dose of 2 g/70 kg to 4 g/70 kg, if seizure reappears | Injection | IV, IM | Prevention of recurrent seizures in eclampsia, prevention of seizure in pre-eclampsia, acute nephritis in children | PNTVC | – | 30 | [38, 39] |
| 18 | Oxcarbamazepine | Start with 8 to 10 mg/kg, increase by 8 to 10 mg/kg as tolerated at the interval of 3 to 7 days. Max. 30 mg/kg can be given in 2 divided doses | Tablets, suspension | Oral | Treatment of partial seizures, secondary generalized seizure | iNa | II | 100 | [40] |
| 19 | Phenobarbitone | Oral: 60 to 200 mg Parenteral: 20 to 320 mg IM or IV every 6 h | Tablets, solution | Oral, IV, I-M. | Partial seizures, generalized seizure | iGABA, iGiD | II | > 95 | [41, 42] |
| 20 | Phenytoin | 300 mg | Tablets, capsules, suspension, Liquid | Oral, I-M, IV | Generalized tonic-clonic seizures, partial seizures and seizures occur during neurosurgery | iNa | II | 70–100 | [43, 44] |
| 21 | Pregabalin | 75 mg (BD)<br>Max. dose: 600 mg | Capsules | Oral | Used for partial onset seizures | ICaNT | I | 90 | [44, 45] |
| 22 | Primidone | 100 to 250 mg. Max. dose: 500 mg | Tablets | Oral | Generalized tonic-clonic seizures, focal seizures, temporal lobe epilepsy | GABAra | II | 90–100 | [46] |
| 23 | Perampanel | 2 mg. Max. dose: 8 to 12 mg | Film coated tablets | Oral | Treatment of partial-onset seizures and primary generalized clonic tonic seizures | AMPA | II | 100 | [47, 48] |
| 24 | Rufinamide | 400 to 800 mg | Film coated tablets, suspension | Oral | Treatment of seizures associated with Lennox-Gastaut syndrome | vNa | III | 70–85 | [49, 50] |
| 25 | Sodium valproate | 1 to 2 g | Tablets, capsules | Oral | Epilepsy, bipolar disorders | IncGABA | II | 90 | [51, 52] |
| 26 | Tiagabine | 4 mg. Max. dose: 56 mg | Film coated tablets, tablets | Oral | Partial onset seizures | sGABAri | I | > 95 | [53] |
| 27 | Topiramate | Epilepsy: 400mg. Lennox-Gastaut Syndrome: 200–400 mg | Tablets, extended release capsules | Oral | Partial seizures, severe generalized tonic-clonic seizures and seizures associate with Lennox-Gastaut syndrome | iNa, eGABA | I | 80 | [54] |
| 28 | Valproic acid | 10 to 15 mg | | | | incGABA | II | > 90 | [55] |

**Table 1** (continued)

| S. no. | Name of drug | Daily adult dose | Available dosage forms | ROA | Indications | MOA | BCS class | BA (%) | Ref |
|---|---|---|---|---|---|---|---|---|---|
| | | | Extended release tablets, liquid filled capsules, injection | Oral, IV | To control absence seizures, tonic-clonic seizures, complex partial seizures, and seizures associated with Lennox-Gastaut syndrome | | | | |
| 29 | Vigabatrin | 500 mg | Film coated tablets, powder for solution | Oral | Refractory complex partial seizures, and secondary generalized seizures also used for treatment of resistant epilepsy | irABT, catGABA | I | 100 | [56] |
| 30 | Zonisamide | 100 mg. Max. dose: 600 mg | Orally disintegrating tablets, capsules | Oral | Partial-onset seizures | CAi, iNa | I | 100 | [57, 58] |

*Abbreviations*: *+GABA* binds to the interface of α and $\gamma_2$-subunit of the GABA-A receptor, *ADF* available dosage forms, *AMPA* noncompetitive AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) glutamate receptor antagonist, *ANMDA* antagonist of NMDA receptor, *BA* bioavailability, *baGABA* binds to an allosteric site on GABA-A receptor and increases the effects of the inhibitory neurotransmitter GABA, *BCS* biopharmaceutics classification system, *BD* twice in a day, *BNZ1* binds non-specifically to benzodiazepine receptor, *BST* blocks synaptic transmission, *CAi* carbonic anhydrase inhibitor, *catGABA* enzyme responsible for the catabolism of GABA, *cGAB* clobazam is partial agonist to the GABA receptor, *cGABA* coupled to GABA receptors and leads to GABA affinity to GABA receptor, *CHF* congestive heart failure, *conc* concentration, *CP2Di* cytochrome P450 2D6 inhibitor, *eGABA* enhances effect of GABA receptor, *FVNa* blocks frequency and voltage dependent neuronal sodium channels, *GABAra* GABA receptor agonist, *HS* hypersynchronization of epileptiform burst firing and propagation of seizure activity, *iCa* inhibits T-type calcium channels leading to stabilization of neuronal membrane, *iCaNT* blocks voltage-gated calcium channels and modulates the release of many excitatory neurotransmitters, *iGABA* inhibitory effects on GABA-receptor, *iGiD* inhibits glutamate-induced depolarization, *IM* intramuscular, *iNa* sodium channel blocker, *iNaCa* inhibits voltage-sensitive sodium and calcium channels, *incGABA* increases GABA levels in brain by altering voltage-dependent sodium channels, *irABT* irreversible inhibitor of 4-aminbutyrate transaminase, *IV* intravenous, *LQ* liquids, *max.* maximum, *MOA* mechanism of action, *NAK* opens neuronal voltage-activated potassium channels which enables the generation of M-current, *OD* once in a day, *PNTVC* blocks peripheral neuromuscular transmission by reducing acetylcholine release at the myoneural junction and it also inhibits voltage-dependent channels, *RC* rectal, *Ref* reference, *ROA* route of administration, *SB* sublingual, *sGABA* increases synaptic concentration of GABA and reduces the release of mono-amine neurotransmitters leading to reduction in axon excitability, *sGABAri* selective GABA reuptake inhibitor, *STP* a sub-threshold potassium current that serves to stabilize the neuronal membrane, *TDS* thrice in a day, *tvNa* binds to T-type voltage-sensitive calcium channels and suppresses the cell activities, *vNa* inhibits voltage-gated sodium channels

but at the same time less effective because of restricted entry of drugs to the brain due to the blood brain barrier (BBB) (especially oral route). Orally administered drugs first go to the systemic circulation before entering the brain via crossing the BBB. Hence, the drugs given by this route should have high dose to maintain the sufficient concentration in the brain as some of the drug may get wasted due to first-pass metabolism, P-glycoproteins (P-gp) efflux, less permeability due to tight junction (BBB), non-targeting, etc. The side effects proportionally increase with increase in the dose of the drugs. This proves that the oral route of drug administration cannot solve the problems of poor bioavailability of drugs in the brain [62]. Furthermore, intravascular and intramuscular routes are responsible for build-up of higher concentration of

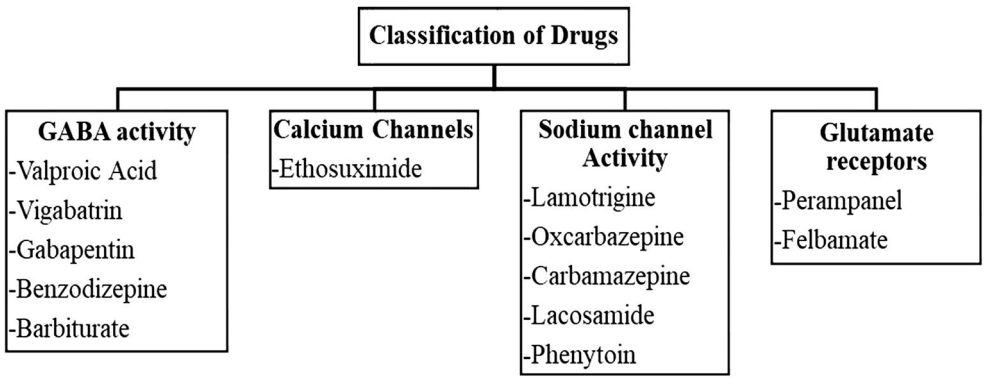


**Fig. 2** Antiepileptic drug classification according to their mechanism of action [59]

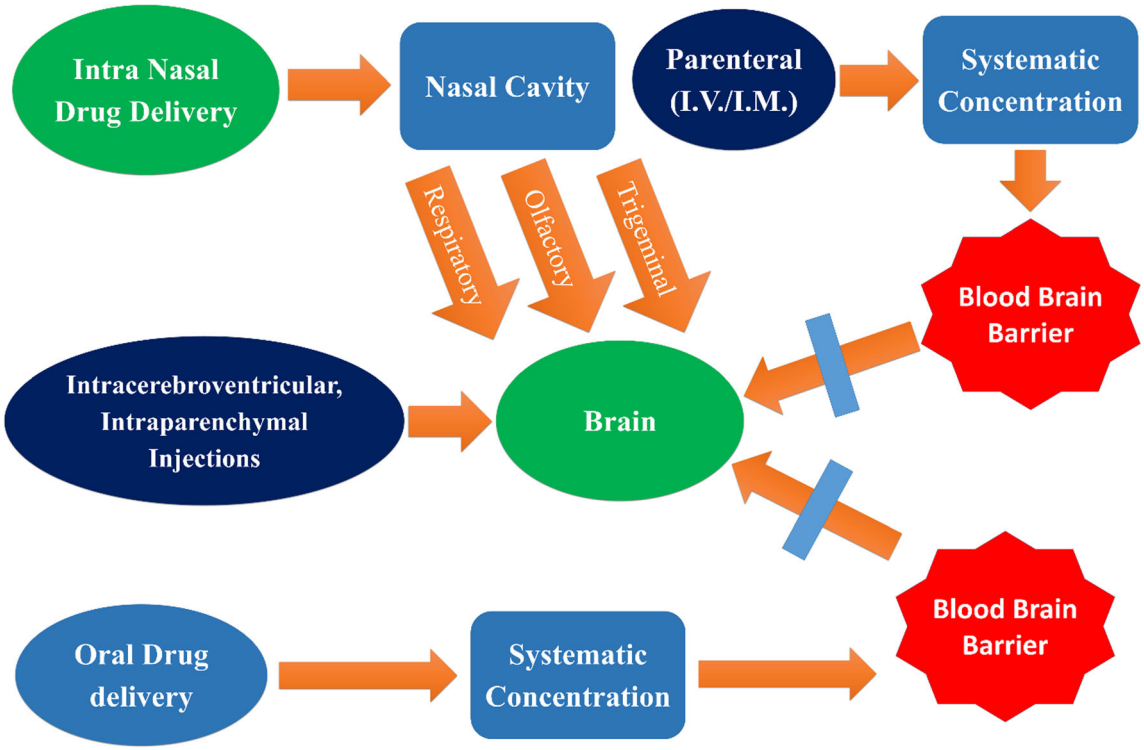


**Fig. 3** Entry of antiepileptic drugs to the brain through different routes of administration [60, 61]

antiepileptic drugs in the blood which causes more side effects.

Non-invasive routes are more preferable over the invasive routes due to more advantages such as self-administration, privacy, safety, and economic. But the drugs administered by these routes have limited entry to the brain as the BBB restricts the same and the oral route of drug administration is having more side effects as it is responsible to increase the systemic concentration of drugs.

## Lamotrigine

Lamotrigine is a good candidate for monotherapy in patients who suffer from adverse side effects with other antiepileptic drugs. It was approved by FDA in 1994 for the treatment for epilepsy [63]. Lamotrigine can be sold only under the prescriptions written by the physicians. Lamotrigine exhibits broad spectrum efficacy as it is widely used for the treatment of partial seizures, secondary generalized tonic-clonic seizures, and Lennox-Gastaut syndrome [64]. It is also used for maintenance treatment of bipolar I disorder to delay the time of occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy [65]. By using lamotrigine, 13 to 67% of patients experienced a decline of greater than 50% in seizure frequency [66]. Kaminow et al. reported that lamotrigine monotherapy is more effective than carbamazepine, phenytoin, and valproate to reduce the seizure frequency [66]. Lamotrigine is a phenyl triazine derivative with chemical name 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine. It has a molecular weight of 256.09 g/mol and pKa value of 5.7 [67]. It shows some of the adverse effects like hepatotoxicity, leukopenia, thrombocytopenia, hallucination, skin eruption, toxic epidermal necrosis, nausea, vomiting, headache, and confusion [64].

In January 2010, lamotrigine-extended release tablets (administered once daily) received approval from FDA to use for the treatment of epilepsy [68]. Lamotrigine is currently available in the market as an oral tablet, but due to its non-targeted delivery, P-gp efflux, and high dose unwanted side effects are more common such as stomach pain, upset stomach, dry mouth, double vision, tremors, loss of coordination, back pain, changes in menstrual periods, sore throat, severe skin rashes, and insomnia, which further restrict its uses [69–71]. Intravenous administration is preferred in conditions of emergency, but it is not a suitable route of administration for long-term therapy. Anti-epileptic drugs face many challenges in achieving required therapeutic effects because of various physiological barriers such as the BBB, exhibition of ATP-binding cassette group of transporters, the ABCB-1 subtype, and p-glycoproteins (P-gp). The appearance of P-gp decreases drug concentration in the brain by active efflux transport of several lipophilic compounds [72]. As a result, numerous cases are reported with refractory epilepsy [73]. It is a condition which cannot be controlled with antiepileptic

medications. There are a number of different terms used to describe refractory epilepsy like uncontrolled, intractable epilepsy [73]. Over appearance of this P-gp in the BBB restricts the transport of antiepileptic drugs to the site of action. As a result, higher dose of drug is administered to achieve required therapeutic level in the brain. This leads to simultaneous increase in the blood concentration of lamotrigine causing its adverse effects. A study conducted by Rizzi et al. found that higher concentrations of topiramate, carbamazepine, lamotrigine, gabapentin, and phenytoin in the brain of MDR1a (multidrug-resistance) knockout mice, result to a deficient functional form of P-gp [74, 75]. The study justifies that enhanced appearance of P-gp in the BBB restricts the penetration of antiepileptic drugs. Lamotrigine is a P-gp substrate and hence P-gp expression in brain restricts its entry and leads to refractory epilepsy [75]. Volk et al. reported the difference in the exhibition of P-gp in normal and refractory cases of epilepsy in rats. Considerably, increased expression of P-gp was found in rats not responding to therapy [76]. Another report suggests that about 30% of the patients suffering from epilepsy undergoing treatment face the problem associated with drug resistance because of P-gp efflux activity [77]. It is evident that enhanced appearance of P-gp in the BBB restricts the penetration of antiepileptic drugs to the brain which is leading to refractory epilepsy. To overcome this problem, research was taken up to explore the nasal route for drug targeting the brain. Frey et al. studied that there are several methods to introduce therapeutics directly into the brain (mainly as intracerebroventricular junction, intraparenchymal junctions) [61]. These techniques are invasive, painful, require surgical expertise, and expensive; because of which they are less preferred. Drug delivery through the nasal route can overcome the disadvantages associated with the other techniques mentioned earlier and provide better results.

## Work Done So Far on Lamotrigine in the Area of Nanoparticulate Drug Delivery

Several investigators have developed lamotrigine nanoformulations to solve its low solubility problem [78], to improve its bioavailability [79], and to reduce its side effects by making its site-specific delivery [71, 80, 81]. The literature revealed that this concept of lamotrigine nanoformulations is suitable to increase the efficacy and to reduce side effects of this drug. Few studies among them are summarized herewith. Some researchers have developed nanoparticles of lamotrigine for the intravenous delivery to extend its drug release. Ammar et al. designed a depot preparation for releasing lamotrigine in the brain for a long period of time, i.e., 4 weeks. They formulated lamotrigine-loaded poly-ϵ-(D,L-lactide-co-caprolactone) (PLCL) nanoparticles for brain delivery and the intravenous route was used for administration. The size and polydispersity index of prepared nanoparticles were found to be less than 200 nm and less than 0.21, respectively. The developed formulation increased bioavailability and biodistribution of drug in the brain as compared to oral conventional tablet formulation. PLCL nanoparticles were formed by using spontaneous emulsification solvent diffusion method, as PLCL polymer is biodegradable and nontoxic in nature. Furthermore, PLCL is safe for depot preparations. This formulation was basically designed for targeted and sustained release of lamotrigine in the brain [78].

Investigators also developed lamotrigine nanosuspensions for non-invasive delivery to achieve the sustained release of lamotrigine. Mishra et al. developed nanosuspension of lamotrigine for oral delivery. The study shows that the formulation gives burst release profile during the first 1 h and gives extended-release for up to 24 h. It says that nanosuspension of lamotrigine can be used to obtain sustained drug delivery. In this study, nanosuspension was prepared by using emulsification-solvent diffusion method [81].

Few investigators have studied the effect of P-glycoprotein (P-gp) inhibitors also with lamotrigine to reduce the P-gp efflux which is responsible for most of the loss of drug; as a result, formulations cannot achieve the required therapeutic concentration in the brain. One research work was done by Yu and his co-workers for the developed methoxy poly(ethylene glycol)-poly (lactide) (mPEG-PLA)/D-α-tocopherol polyethylene glycol succinate (TPGS) mixed micelle drug delivery system to improve the bioavailability of lamotrigine in the brain. The researchers proposed this formulation, as the lamotrigine has restricted entry to the brain because of over appearance of P-gp. In this study, researchers prepared micelles with TPGS which inhibit the P-gp efflux effect and as a result increase drug permeation to the brain. They have also preferred the nasal route for delivery of this drug which helps in bypassing the BBB leading to increase in the absorption of lamotrigine in the brain. The study demonstrated that the absorption of nanoparticles with TPGS was nine times higher than the normal nanoparticles. Lamotrigine-mixed micelles were prepared by using solvent evaporation method. In the brain, bioavailability of micelles was four times higher than drug solution; this shows the effectiveness of the formulation [79].

Lamotrigine falls under BCS class II which means it has low solubility and high permeability [33, 34]. Hence, to increase its solubility and reduce its side-effects Gieszinger and his co-workers designed nasal powder containing nanonized lamotrigine. The nasal powder gave better adhesion and less mucociliary clearance as compared to nasal liquid formulations. Good dissolution and diffusion profiles were obtained from nanonized nasal powder as compared to a physical mixture of the drug [82].

Lamotrigine is also formulated as thermoreversible nasal gel. Thermoreversible gels are fluid at room temperature, but get chanced to gel with increase in temperature. This approach increases the MRT of drug in the nasal cavity. Serralheiro and his

co-workers developed thermoreversible nasal gel to study the effectiveness of intranasal route. Researchers found that thermoreversible lamotrigine nasal gel gives sustained release compared to the intravenous delivery of lamotrigine. Higher concentration of drug in the brain was found for a very long time; this can help in reducing the dose of lamotrigine as compared to the conventional dosage forms [71].

The work done by Alam and his co-workers designed sustained release nanostructured lipid carriers (NLCs) of lamotrigine for treatment of epilepsy. The route of administration used was the intranasal route which helps in bypassing the BBB and increasing the bioavailability of lamotrigine in the brain. NLCs were prepared by using solvent evaporation method. This study shows that the mean resistance time (MRT) of lamotrigine-loaded NLCs in the brain is much higher compared to oral and nasal administration of drug solution. The author has suggested that because of a higher concentration of drug in the brain we can reduce around one-fifth of the oral dose [80].

The literature above confirms that the nanoparticulate system of lamotrigine with intranasal administration can be a hopeful tactic to increase its efficacy and reduce its side effects with non-invasive and site-specific delivery with high patient compliance. Furthermore, the nanoparticulate drug delivery of lamotrigine can potentiate its activity and completely utilize the dose by maintaining its extended release, protecting the drug from P-gp efflux and enzymatic degradation [83]. This novel approach can help in reducing the daily dose of this drug.

## Intranasal Delivery

The rationale behind nasal drug delivery was brain drug targeting with the aim of bypassing their gastrointestinal degradation and avoidance of first-pass metabolism. Furthermore, the major purpose of nasal drug delivery in brain targeting was to help the drugs cross the BBB with ease in reaching the destination (or brain). Intranasal delivery can be a positive and hopeful substitute in brain targeting. Intranasal delivery may be considered as a beneficial and appreciated route of drug administration due to its non-invasive approach. Serralheiro et al. has reported that the bioavailability of lamotrigine was 116.5% after intranasal administration when compared to the intravenous administration in mice [71]. These results clearly indicate that intranasal route of administration is not only a non-invasive route of drug administration, but also have high bioavailability in comparison with the invasive routes of administration. Furthermore, this route of administration is safe and convenient for the patients as self-administration is also possible [84]. Anan et al. found the enhancement of bioavailability of lamotrigine in the hippocampus via intranasal administration as mPEG-PLA/TPGS mixed micelles [79].

### Merits and Demerits of Intranasal Drug Delivery

The advantage with the intranasal delivery system is direct delivery to the brain, reduction of drug dose compared to oral drug delivery to get the same therapeutic response, reduction in side effects experienced after other routes of drug delivery, and improvement in its pharmacokinetics. Table 2 represents the merits and demerits of the intranasal route of drug delivery.

### Barriers in Targeting of Lamotrigine to Brain

Targeting drugs to the brain is challenging. The presence of the BBB acts as an impermeable barrier and selective sieve.

**Table 2** Advantages and disadvantages of nasal drug delivery system [84]

| Benefits | Limitations |
|---|---|
| ✓ The nasal cavity offers a hefty surface area with extensive vascularization | ✓ Concentration achieved after absorption in different areas of the brain and spinal cord differs with each drug |
| ✓ It is a non-invasive, quick, easy, safe, and convenient method of drug administration | ✓ There will be a fast clearance of drug from nasal cavity due to mucociliary action |
| ✓ Nasal cavity avoids first-pass metabolism and gut wall metabolism of drugs gives improved bioavailability | ✓ There will be decreased absorption of drugs with high molecular weight |
| ✓ Bypasses the BBB and gives central nervous system (CNS) targeted drug delivery, decreases systemic exposure and thus systemic side effects | ✓ Some drugs are susceptible to enzymes present in nasal mucosa and can cause irritation to the mucosa |
| ✓ Rich vascularization and vastly permeable structure of the nasal mucosa significantly improves the drug absorption and gives quick onset of action | ✓ Nasal congestion due to cold or allergies interferes with absorption through nasal cavity which leads to decrease in bioavailability |
| ✓ Did not require any changes in the therapeutic agent to be delivered | ✓ Recurrent use of nasal route causes mucosal impairment (especially because of absorption enhancers) |
| ✓ Nasal drug delivery eases the treatment of various neurologic and psychiatric disorders | |

The endothelial cells of capillary wall are permeable to ions, electrolytes, and small lipophilic molecules. It protects the brain from variations in blood composition and toxins. It also helps to avoid uncontrolled activity of the brain. BBB cells consist of tight junction, narrow intracellular gaps with continuous basement [85, 86]. The BBB prevents entry of many antiepileptic drugs including lamotrigine. It causes decrease in concentration of drug reaching to the brain. Hence, it does not show good pharmacological activity. To overcome this problem, drug delivery through nasal route can easily bypass the BBB and helps to increase drug effect in the brain.

## Intranasal Administration

In intranasal drug delivery system, drugs are administered through the nose. During the administration of the drug by the nasal route, preferably the formulation should be administered by the one nostril. As the surface area of the site is greater, the drug absorption is expected to be more and better which enhances the drug's effectiveness [87]. Administration of the drug via the nasal cavity is pain free and easy to access. Presence of mucosa along the nasal cavity provides a rich vasculature and helps in bypassing the first-pass metabolism [88]. These features of the nasal cavity help in better absorption and rapid onset of action [89].

## Mechanisms of Drug Transport

Intranasal delivery of drugs involves three mechanisms underlying the direct delivery of drug to the brain via the nasal route such as transfer of drug through olfactory mucosa, trigeminal nerve pathway, and respiratory pathway [90–92]. The mechanisms involved in transporting drugs to the CNS depend upon the characteristics of drug formulations and the device used for the drug delivery [93].

### Trigeminal Nerve Pathway

Drug bypasses the BBB by traveling along the trigeminal nerve and reaching the olfactory bulb. After reaching the olfactory bulb of the trigeminal region, drugs enter the different parts of the brain. It is an important pathway consisting of the trigeminal nerve. The trigeminal nerve is one of the biggest nerves of the cranial nerves. It innervates the respiratory and olfactory epithelium and transports the drug to the brain [94]. Three twigs of the trigeminal nerve combine at the trigeminal ganglion and further extend to enter the CNS. The trigeminal nerve enters the brain from the respiratory epithelium of the nasal passage at two sites: One is through the anterior lacerated foramen near the pons (the part of the brainstem that links the medulla oblongata and thalamus) [95]. Another is through the cribriform plate near the olfactory bulbs. Thorne et al. first demonstrated drug delivery through the trigeminal pathway by using 125I-IGI (radioactive isotope). Intense radioactivity was observed in the trigeminal nerve, ganglion, and olfactory bulbs [96]. Johnson et al. showed the intranasal administration of an infrared dye. The dye was detected in the brain within 10 min and transport of the dye was done via the trigeminal nerve pathway [97]. It has also been reported that the low molecular weight drugs can be easily delivered through the trigeminal nerve to the central nervous system [98].

### Olfactory Pathway

Most of the drugs delivered by nostrile are absorbed by olfactory pathway to the brain. Hence, this is considered as the major pathway for the drugs administered by this route. The olfactory pathway arises from the olfactory region in the nasal cavity (olfactory neuronal receptors within olfactory mucous). Olfactory drug delivery is done by the combination of two mechanisms: One mechanism is the extracellular transport [99]. It involves the fast movement of drug molecule to the brain. Luzzati et al. conducted the study by using X-ray scattering to observe the drug uptake by olfactory nerve pathway. Another mechanism is described by the intracellular transport [87, 100]. Intracellular axonal transport to olfactory bulb is a very slow mechanism of drug transport. It takes several hours to days. The drug enters the neurons by the mechanism of receptor-mediated endocytosis, pinocytosis, or passive diffusion. After drug enters into the neurons it travels along axon via nerve bundle and crosses the cribriform plate through perforations. There is a positive correlation between concentration in the olfactory epithelium and olfactory bulb [95]. A study conducted by Jansson et al. shows that fluorescein dextran (FD3) is mostly absorbed transcellularly through the olfactory epithelium [101]. This mechanism is also influenced by lipophilicity, particle size, and molecular weight of the drugs [98].

### Respiratory Pathway

It is a traditional way of drug delivery used to deliver the drug to the systemic circulation via absorption into the blood capillaries in the nasal mucosa. The drug is transported to the CNS by crossing the BBB. High-lipophilic and low-molecular-weight compounds can easily cross the BBB than hydrophilic molecules. This route of drug delivery delivers the drug through systemic circulation resulting in problems like first-pass metabolism and enzymatic degradation [102].

# Factors Influencing Nasal Drug Absorption

There are several factors influencing the absorption of drugs delivered by nasal route. Major factors affecting nasal drug absorption are listed in Fig. 4.

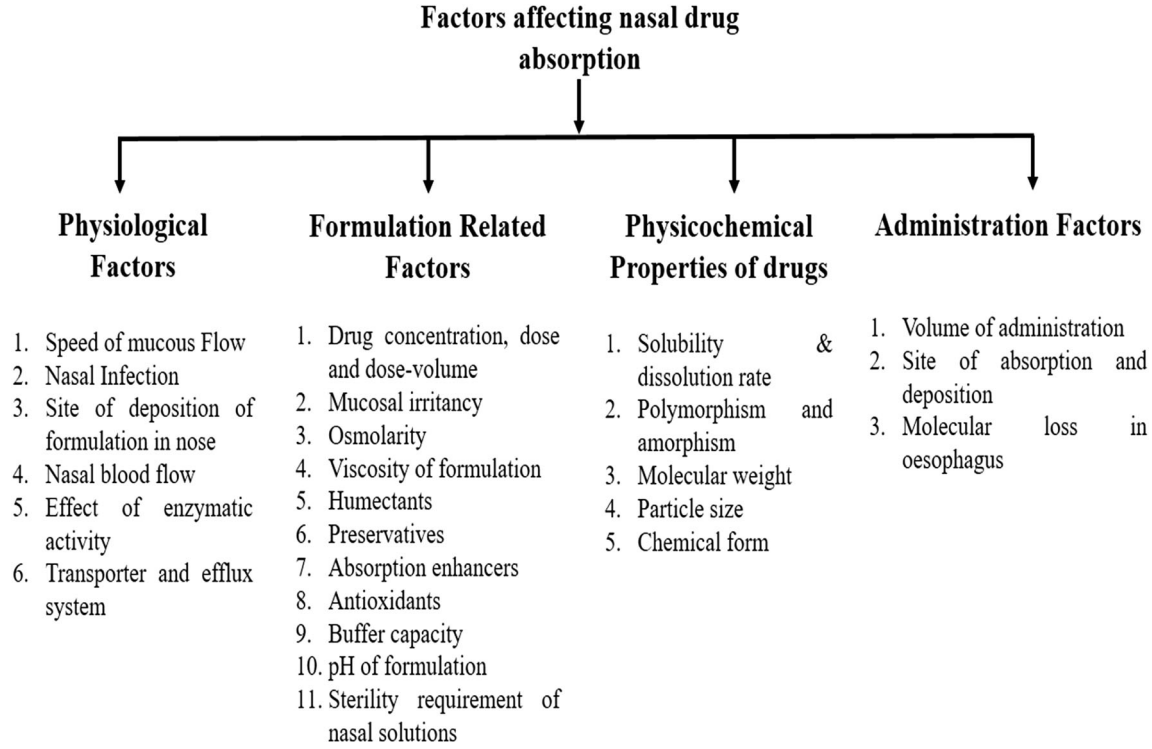


**Fig. 4** Gives list of factors affecting nasal drug absorption [60]

## Physiological Factors [103, 104]

### Speed of Mucous Flow

Respiratory epithelium and other parts of nasal cavity and airways are lined by superficial epithelium which is comprised of two kinds of cells, i.e., goblet cells (20%) and ciliated cells (80%). The goblet cells produce the mucus which traps the inhaled particulate and infectious debris and the propulsive force generated by ciliated cells help to transport the mucus towards the nasopharynx and gastrointestinal tract for elimination. This process is known as mucociliary clearance or speed of mucous flow [105, 106]. Nasal mucociliary clearance is one of the utmost key factors affecting the absorption of drug delivered via nasal route [107]. Mucociliary clearance usually affects the transit time of formulation in the nasal cavity. The average mucociliary clearance time in healthy human volunteers is around 20 min [106]. But, it has subject variability and also based upon the physiological control of ciliated cells and rheological properties of mucus layer. The more the transit time the more the absorption. The speed of mucous flow decreases the transit time resulting in decrease in the absorption [105]. There are several factors which affect the mucociliary clearance such as pH of the formulation, viscosity of the formulation, bioadhesive strength of the formulation, drugs used, excipients used, and environmental factors [107].

### Nasal Infection

There are several pathological disorders which are responsible for the interruption of nasal defense mechanism and for absorption of drugs. The most common conditions for the upset of nasal absorption are cold, rhinitis, asthma, etc.

The mucociliary clearance is based upon the working of cilia, goblet cells, and mucus covering. These are influenced by rhinitis [106]. The allergic rhinitis is also known as hay fever which may be due to acute, seasonal or chronic, and perennial [108]. Common cold is a disease of the nasal cavity which is initiated by viral infection [108, 109]. During the hypersecretory phase (rhinorrhea) of cold, the mucociliary clearance increases whereas retrieval after a cold promotes congestion which results to mucociliary clearance decreases [110–112]. These physiological conditions reduce the transit time of formulations in the nasal cavity which further reduces its nasal absorption. Asthma increases the inflammatory process and irritation [113].

### Site of Deposition of Formulation in Nose

Absorption of drugs not only depends upon the mucociliary clearance, but also depends upon disposition of drug [114]. The highest localized deposition occurs just beyond the nostril. In medical language, most of the drugs get deposited in the anterior region of the nose [115]. Discharge of

pharmaceutical formulations in the anterior part of the nose gives longer transit time but absorption of the drug from anterior part is less (because of low permeability) compared to the posterior part of the nose; although the deposition also depends upon the type of formulations, volume of formulations, excipients used for the formulations, delivery devices, particle size, shape of the nasal vestibule, etc. [114, 116, 117]. It has been reported in the literature that the spray takes more time for mucociliary clearance compared to the solutions [114].

Furthermore, there are several mechanisms involved for the deposition of drugs in the respiratory tract. These works on the basis of particle size present in the formulations. For the particles size 500 nm and above, the inertial impaction is the main deposition mechanism whereas for the particles less than 500 nm, the main deposition mechanism is Brownian diffusion [118–120]. For nanoformulations, the main deposition mechanism is Brownian diffusion [121]. It has been reported that only a small proportion of the diffusive particles can reach to the olfactory region. If the particles are larger than 200 nm, its deposition in the olfactory region further reduces [122–125]. The inertial particles do not show any deposition of particles in the olfactory region [122, 124, 125].

### Nasal Blood Flow

As nasal cavity is surrounded by a compact network of blood vessels which play a very significant role in drug absorption, drugs available in the nasal respiratory and olfactory regions have fate of absorption (in blood or in lymphatic vessels) or directly reach the brain through extravascular pathways linked to the trigeminal and/or olfactory nerves [126–130]. For targeting the drug to the brain through the nasal route, it should enter less into the systemic circulation which may help in increasing the concentration of the drug in the brain through the cranial-nerve-linked extravascular pathways [128, 130]. The low blood vessel density and restrictive capillary permeability may help the targeting of drug to the brain [130].

### Effect of Enzymatic Activity

There are numerous enzymes existing in the nasal cavity like cytochrome P-450 enzymes, steroid oxidoreductase, NADPH-cytochrome P-450 reductase, aromatase, aldehyde dehydrogenase, carboxylesterase, conjugative, exopeptidases, and endopeptidase enzymes [116, 128, 131]. Presence of these enzymes decreases the drug absorption. Proteins and peptide drugs undergo degradation because of presence of amino peptidase and proteases enzymes in the nasal mucosa [116]. Mucin present in the nasal cavity binds to solutes in the formulation that leads to decrease in absorption [132].

### Transporter and Efflux System

The presence of P-gp at the nose-brain interface diminishes drug uptake by the brain. P-gp also is expressed in normal human nasal mucosa [133]. The P-gp located at the olfactory epithelium and within the olfactory bulb restricts the uptake of drug into the brain [133, 134]. As efflux transporter (like P-gp) may affect the brain uptake of the drug from the nasal cavity, hence, if P-gp inhibitors are used with substrates this may help to increase the concentration of substrates in the brain. Graff and his co-worker studied the effect of rifampin on [$^3$H]-verapamil uptake in the brain after nasal delivery. [$^3$H]-verapamil uptake is very less in the brain which was increased with co-delivery of rifampin. It was also noticed that the extent of inhibition was dependent upon the dose and route of inhibitor and time after administration of inhibitor [133].

## Formulation Related Factors

### Drug Concentration, Dose, and Dose-Volume

Increase in nasal absorption was found when there is an increase in the concentration gradient. Nasal absorption of 1-tyrosyl-L-tyrosine was found to be increased with increasing concentration of the drug [135]. Although if a higher concentration of the drug is administered with higher volume then formulation will drain out from the nose that will lead to decrease in the drug absoption. Hence, the maximum amount of drug dissolved in small volume is preferred. Harris et al. conducted an experiment to study the effect of concentration and volume of desmopressin on nasal bioavailability. They found the increase in bioavailability of desmopressin after two 50-μL doses per day in comparison of both the single 50-μL dose per day and single 100-μL dose per day [136]. To control the dose and volume of the metered-dose pump sprays, multi-dose dry powder systems, pressurized multi-dose systems, multi-dose liquid nasal systems, etc. are preferred [120, 137].

### Mucosal Irritancy

Any of the excipients used in nasal formulation should not cause irritation to the nasal cavity. Generally, preservatives and some of the absorption enhancers can cause irritation to the nasal mucosa. Change in pH or tonicity of formulation can cause irritation. The uses of cosolvent beyond the certain limits in the preparations can cause mucosal irritation [138, 139]. It has also been reported that the sodium glycocholate used in concentration 1% *w*/*v* can enhance intranasal absorption, but causes slight irritation and morphological changes in nasal mucosa [138, 140, 141]. It has been reported that the percentage of water should be used more than 10% to reduce the nasal irritation caused by cosolvents in nasal formulations [138, 139].

Like surfactants and/or cosolvents, variations in pH also cause irritation to the nasal mucosa [142]. Quadir et al. prepared and evaluated a nasal formulation of ketorolac. They had studied the formulation at different pHs and found the increase in absorption of drug at low pH, i.e., 3.2 compared to the high pH, i.e., 6.0, but at pH 3.2 they also noticed slight irritation [142]. This finding revealed that the adjustment of pH is also very important in the nasal formulation development with respect to the absorption and irritation. Similarly, Ohwaki et al. also found structural changes in epithelial cells of nasal mucosa at pH 2.94 in their study [143]. In another study they also had reported that the absorption of secretin through the nasal mucosa increases as the pH decreases [143, 144].

### Osmolarity

Ohwaki et al. studied the effect of osmolarity on the absorption by using secretin as a model drug in rats. Maintenance of isotonicity is very important to avoid toxicity of nasal epithelial cells [144]. Maximum absorption of the drug was found in sodium chloride at the molarity of 0.462. Hypertonic saline solutions inhibit or reduce the ciliary activity and increase the absorption of drugs by increasing the transit time [145]. It has been reported in the literature that the bioavailability of sulfisoxazole decreases with the increase in osmotic pressure in an NaCl solution [146]. Similarly, in another study, it was revealed that the absorption of quinine was also decreased with increase in osmotic pressure. [147]. Ohwaki et al. reported in their findings that the nasal absorption of secretin decreases in proportion to the increase of molar concentration of sorbitol solution [143].

### Viscosity of Formulation

High viscosity of the formulation increases the residence time of the formulation in the nasal cavity which results in increased drug absorption. The study conducted by Furubayashi et al. demonstrated that the moderate viscosity of dosing solution improves the in vivo nasal absorption of acyclovir whereas higher viscosity decreases the absorption [148]. This decrease in the absorption at high viscosity may be due to the decrease of drug release or hindering of regular functions such as mucociliary clearance and slow permeability of drug [113, 149]. In the conclusion, the nasal formulations should not have very low viscosity and at the same time should not have too high viscosity. The nasal formulations should have optimal viscosity to get the high absorption of the drug.

### Humectants

Humectants are not much likely to affect drug absorption but play a very important role in avoiding irritation due to dryness/dehydration of nasal cavity [150]. Commonly used humectants are PEG, glycerine, mannitol, etc. [151]. Some humectants also work as permeation enhancers such as PEG. This is most commonly used to increase the hydrophilicity of the molecules which helps in increasing the movement of the particles. It is expected that the polyethylene glycol (PEG) minimizes the contact with mucins and increases the mucus diffusivity thus enhancing the contact with underlying epithelium [152]. Vila et al. studied the effect of PLA-PEG particles across the nasal mucosa. They found from their research that the PEG-coated nanoparticles can easily cross the nasal mucosa [152, 153]. Of course, the permeability of the particles, along with the PEG coating is also based upon the particle size [153].

### Preservatives

Most of the nasal products are aqueous-based; hence, they required preservatives to avoid microbial growth [154]. The most important requirement of preservatives for nasal formulations is that they should not cause any kind of irritation to the nasal mucosa [155]. Benzalkonium chloride, ethyl alcohol, EDTA, parabens, and benzyl alcohol are commonly used preservatives. A study conducted by Graf suggests that benzalkonium chloride may produce an adverse effect on human nasal tissues. Batts et al. conducted a research to know the effect of preservatives on the mucociliary clearance and they found that methyl-p-hydroxybenzoate, propyl-p-hydroxybenzoate, and chlorbutol have reversible blocking effect on mucociliary clearance [112, 156].

### Absorption Enhancers

Absorption enhancers are used to increase the absorption of large molecules like proteins and peptide. Davis et al. reported the improved nasal delivery of vaccines by using chitosan as an absorption enhancer [157]. Cyclodextrins, glycols, and phospholipids are some of the commonly used absorption enhancers [158]. Permeability enhancers increase the paracellular absorption of the drugs [106].

### Antioxidants

A small quantity of antioxidants is preferable. There are chances of interaction between antioxidants with excipients, container used for packaging, etc. which can affect the absorption through the nasal cavity. Tocopherol, sodium metabisulfite, butylated hydroxyl toluene, and sodium bisulfite are some of the frequently used antioxidants for nasal formulations [150, 154].

### Buffer Capacity

Administration of nasal formulation may change the pH of the nasal cavity; this can change the concentration of unionized drug for absorption [112]. Change in the buffer capacity is very important as it may affect the solubility, absorption, and therapeutic response of the drug [159]. Because of this reason, a proper buffer capacity is required to avoid the changes in pH and hence absorption of the drug.

### pH of Formulation

The pH of the nasal cavity is 5.5–6.5. The control of pH in a given range is very important to avoid irritation of the nasal cavity. Lysozyme is a defensive enzyme present in nasal secretion which is responsible for destroying microorganisms at acidic pH, it gets deactivated in alkaline pH, which can cause infection in nasal cavity and hence can affect the nasal mucociliary clearance and bioavailability of nasal formulations [106, 108]. A pH lower than 5.5 or higher than 6.5 cannot match with the nasal epithelium buffer capacity which may cause toxicity and also affect the permeation of drugs [106].

### Sterility Requirement of Nasal Solutions

Nasal preparations (especially nasal inhalations) are required to be sterilized [160]. There are several methods for the sterilization such as filtration, dry heat sterilization, stream under pressure, gas sterilization, chemical sterilization, and radiations. Filtration (using a sterile membrane filter of 0.45 or 0.2 μ pore size) is most commonly preferred for the sterilization of nasal preparations [161]. Non-sterile nasal preparations may cause infection in the nasal cavity which may further affect the absorption of drug through the nasal cavity.

## Physicochemical Properties of Drugs

### Solubility & Dissolution Rate

Drug solubility and dissolution at mucosal level are very essential factors determining drug absorption. The drug particles deposited in the nasal cavity need to solubilize before absorption [150]. The higher the aqueous solubility of the drug, the higher will be the contact with the nasal mucosa which results to better posterior absorption of the drugs [162, 163]. Hydrophilic drugs are more soluble as compared to hydrophobic drugs and hence give good absorption, although the absorption is not always based upon the solubility of the drug. Horvãth et al. conducted an experiment with meloxicam and meloxicam potassium monohydrate to study the effect of solubility on nasal absorption. They found the same solubility of meloxicam and its salt at nasal mucosa pH (pH 5.6). But they found the fast dissolution and higher permeability through the synthetic membrane [164].

### Polymorphism and Amorphism

As polymorphs differ from each other with respect to solubility thus their absorption through nasal cavity also gets affected [150, 165]. Amorphous form has greater aqueous solubility than crystalline form which shows greater absorption.

### Molecular Weight

Drug absorption through nasal cavity is inversely proportional to the molecular weight of the drug. Most of the drugs with molecular weight of less than 300 Da easily get absorbed through nasal route [166]. High molecular weight drugs (> 1000 Da) have significantly decreased absorption in nasal cavity. Absorption can be increased by using absorption enhancers [150, 165, 167]. Fisher and his co-workers conducted an experiment to study the effect of molecular size on the nasal absorption of water-soluble compounds and they found that the absorption of drugs decreases with the increase in molecular weight. They also reported that the pore size should be large enough to all the passage of high molecular size molecules (such as inulin and dextran) whereas the nasal membrane has greater water flux because of more water channels of a smaller pore size which restrict the absorption of high molecular weight molecules [168].

### Particle Size

Particle size and surface area are related to each other, small particle size helps in increase of the surface area, results in increase in the solubility, and absorption. Particle size less than 0.5 μm get exhaled by nasal cavity. As the particle size increases, inhalability decreases [116, 121]. Particle size more than 7 μm gets deposited in the upper respiratory tract [116]. Deposition in respiratory tract is based upon the particle size. An olfactory deposition particle size less than 200 nm is preferable [122–125]. Smaller particle size also can help to enhance the permeability [106]. There are several ways to decrease the particle size such as increase in the concentration of surfactant, increase in stirring time, increase in stirring speed, pressure in high pressure homogenizer, number of cycles in high pressure homogenizer, increase in sonication time, increase in sonication amplitude, increase in sonication pulses, etc. [169–171].

### Chemical Form

The chemical form of drug plays a very significant role in drug absorption [154]. Absorption can be dependent upon lipophilicity, ionization, and hydrophobicity of the drug. Large hydrophilic peptide shows week mucosal permeability. Chemical modification can improve the drug absorption. If the molecule is hydrophobic in nature it can be turned into

hydrophilic compound by coating with hydrophilic diluents like polyethylene glycol, PVP, and dextrose. Formation of the salt form of drug is an easy way of increasing solubility which leads to increase in absorption. It has few examples such as sodium and potassium salt of barbiturate and sulphonamides [172].

### Administration Factors

#### Volume of Administration

An upper limit of 25 mg/dose and a volume of 25 to 200 μL/nostril have been suggested [116, 128, 154]. High volume results to faster mucociliary clearance which further reduces the absorption of the drugs [114]. Along with the volume, the surface area is also important [128]. Absorption will be faster and better, if the same volume covers the more surface. Surface area also increases the residence time of the formulation in the nostril. Harris et al. found from their research that the dose delivered as intranasal spray takes more time to clear from the nostril in comparison with the large drops which further affects the absorption and bioavailability of the drug [114]. Excess volume can also cause irritation of the nasal mucosa [173]. To reduce the volume of the dose solubility enhancement of drug is preferable [116].

#### Site of Absorption and Deposition

Deposition of the drug to the posterior nasal cavity gives good absorption because of high permeability [174]. The most likely sites for the absorption of nanoformulations administered intranasally are olfactory epithelium and respiratory epithelium with the highest surface area in all the four nasal epithelium [128]. In rats, the deposition efficiency of nanoparticles is greater than in human. This may be due to the greater olfactory epithelium surface area in the rats compared to the humans [175, 176]. The surface area of olfactory and respiratory epithelium in rats is 50 and 46%, respectively of the total nasal epithelium area [128, 175, 177] whereas the olfactory epithelium surface area in humans is only 5.5% of the total nasal epithelium area [128, 176]. But as discussed in the previous sections, deposition of the drug depends upon the pharmaceutical formulation types, delivery device, volume or concentration of dose, excipients used, shape of the nasal vestibule, etc. [114, 116, 117]. It has been reported in earlier studies that intranasal spray can help to deposit well-controlled doses into the nostril and can deliver the desired volume and concentration of the drug to the required site [114].

#### Mechanical Loss in Oesophagus

Loss of formulation can occur in case of breathing pattern. Excessive breathing leads to loss of the drug into lungs, in some cases it can cause irritation to the respiratory system [178].

## Future Strategies to Improve Nasal Drug Absorption

There are many strategies employed to improve nasal drug absorption including:

### Enzyme Inhibitors

Peptidase and protease inhibitors are commonly used to improve the bioavailability of protein and peptide molecules. Some of the absorption enhancers like bile salts and fusidic acid derivatives exert enzyme inhibition activity which results in increased absorption of the drug [179]. Bestatin, amastatin, boroleucine, borovalin, comostate amylase, puromycin, and bacitracin are some of the examples of enzyme inhibitors used in nasal formulations [163, 180].

### Absorption Enhancer

The absorption promoting effect of enhancers is due to following mechanisms like absorption enhancers which increases the membrane fluidity by extracting proteins from the nasal membrane and creating transient hydrophilic pores, they can decrease the viscosity of mucous membrane and can facilitate the leaking of tight junctions between epithelial cells [181]. EDTA and fatty acid salts increase the paracellular transport by removal of luminal calcium results in a subsequent increase in permeability of tight junctions. Cyclodextrins can be used as effective absorption enhancers and these are well-tolerated in humans. Bile salts can also be used effectively as absorption enhancer in nasal preparations [182, 183]. As reported in the literature, the bile salt enhances the transport of polar drugs through the paracellular routes and non-polar drugs through both paracellular and transcellular routes [184, 185]. Few studies presented that the bile salts are irritant to the nasal mucosa. To avoid the toxicity, the recommended concentration of bile salts for nasal preparations is 0.3% [184, 186]. Sodium deoxycholate is one of the bile salts which is considered as a potent permeation enhancer. This is also irritating if used in high concentrations. As reported in the literature, intranasal administration of 1% sodium deoxycholate has a severe irritating effect on nasal cilia [187]. Another study using the bile salts was conducted by Lee and his co-workers for intranasal delivery of powder containing insulin and permeation enhancer sodium tauro-24,25-dihydrofusidate (STDHF) in sheep model [188]. They reported that STDHF increases mucosal permeability and reduces the average molecular weight of the insulin species [188]. Few more examples of the commonly used bile salts are sodium glycocholate, sodium taurocholate, and sodium taurodeoxycholate [189].

## Mucoadhesive Polymers

As a mucociliary function of the nasal mucosa, it clears the applied material into the nasopharynx since there is a little contact time between drug and the nasal mucous membrane which can affect nasal absorption of the drug effectively. To avoid this there is a need of bioadhesive polymers. They can help to increase the MRT of formulation in the nasal cavity. Mechanism involves the multiple molecular interactions and non-covalent bond. Generally, a hydrophilic polymer containing carboxyl group gives the best bioadhesive properties. Suzuki and Makino found a significantly enhanced absorption of leuprolide and calcitonin which can be attained by using the combination of hydroxypropyl cellulose (HPC) and microcrystalline cellulose (MCC) in nasal powder. MCC acts as an absorption enhancer by creating a high concentration of drug in the area of mucosal surface, whereas HPC increases the retention time of drug through its gel forming property [190].

**Table 3** List of patents related to nasal administrations of antiepileptic drugs

| Publication date | Publication No. | Title | Description | Ref. no. |
|---|---|---|---|---|
| 17 Nov 2002 | WO2002089751 A1 | System and method for intranasal administration of lorazepam | Lorazepam spray for nasal administration was developed, which delivers predetermined volumetric unit dose avoiding chances of overdosing | [193] |
| 6 Jun 2004 | US20050002987 A1 | Transnasal microemulsions containing diazepam | Nasal administration of diazepam microemulsion yields a high plasma concentration of diazepam nearly as fast as intravenous administration. It is useful for the rapid and timely treatment of patients during acute induction seizures. Therapeutic dose of diazepam was achieved by intranasal spray which comprises about 250 to 500 μL of microemulsion | [194] |
| 6 Jun 2008 | US7390505B2 | Nanoparticulate topiramate formulations | Topiramate nanoparticles were designed having particle size of less than 2 μ. Invention claimed that this formulation can be effectively used for nasal delivery | [195] |
| 9 Oct 2008 | WO2009046444 A2 | Formulation for intranasal administration of diazepam | Aqueous suspension of diazepam was formulated. Formulation gives peak plasma concentrations in patients between 10 and 20 min after dosing. 150 μL to about 200 μL of nasal spray delivers 10–15 mg of drug. Formulation consists of particles having diameters from about 1 nm to about 1000 nm | [196] |
| 4 Oct 2012 | WO2012135536 A1 | Nasal formulations of benzodiazepine | The patent gives pharmaceutical composition for intranasal delivery of benzodiazepine with excellent bioavailability. Formulation can be given by a nasal spray bottle, metered dose inhaler (MDI), aerosols, and dry powder inhaler (DPI); it is very effective than intravenous and rectal formulations | [197] |
| 20 May 2014 | WO2012174158 A2 | Administration of benzodiazepine | Benzodiazepines were formulated for intranasal administration. Spray formulation having a volume from about 10 μL to about 200 μL was developed. Used for effective treatment of epilepsy than conventional route (oral, intravenous, rectal) | [198] |

### Lipid Nanoparticulate System for Nasal Drug Delivery

Use of lipid nanoparticulate system can be an effective strategy to enhance nasal drug absorption. Nowadays, tremendous importance is given to the nanoparticulate drug delivery system for bioavailability enhancement as well as for targeted drug delivery. In recent years, experiments on animal models have shown that nanoparticulate drug delivery systems can enhance nose-to-brain delivery through nasal mucosa in comparison to equivalent oral drug solutions (conventional) [60]. Nanoparticles protect the encapsulated drug from biological and chemical degradation. This can increase the effectiveness of the drug by increasing its central nervous system (CNS) availability. Nano size increases the surface area. Surface modification of nanoparticles can achieve brain targeted delivery of the drugs. There are various types of lipid nanoparticles like liposomes (1–100 nm), solid lipid nanoparticles (SLNs), and nanostructured lipid nanoparticles (NLCs).

Solid lipid nanoparticles (SLNs), amidst the various nanocarriers, are spherical particles with a solid core matrix in the range of 50 to 1000 nm which consists of biocompatible and biodegradable lipids that are solid at room temperature and dispersed in an aqueous solution containing a specific concentration of surfactants. Solid lipid core matrix can solubilize lipophilic drug. SLN presents unique properties such as small size, large surface area, and high drug loading of lipophilic drugs. This makes SLN an attractive carrier for their potential to improve the performance of pharmaceuticals [191]. Solid lipid nanoparticles are also preferred to protect the drugs from the enzymatic degradation [83]. Wissing et al. states that SLN are particles made from solid lipids and stabilized by surfactants. The lipids which can be used are complex glyceride mixtures, purified triglycerides, steroids (cholesterol), fatty acids (stearic acid), or even waxes (cetyl palmitate) with an average diameter in the nanometer range [192].

Some patents related to the nasal drug delivery of antiepileptic drugs are available (as shown in Table 3).

## Conclusion

Epilepsy is a condition affecting over 65 million people around the world. Targeting drug to the brain is a challenge due to the presence of the BBB. The difficulty in the administration of anti-epileptic drugs by the conventional routes (oral, intravenous, intramuscular) has prompted researchers to explore alternate routes of administration. Administration of antiepileptic drugs by conventional route leads to severe side effects like skin rashes, hepatotoxicity, and nephrolithiasis because of high systemic blood concentration. Delivery of drugs to the brain via the nasal route is considered to be promising, effective, and safe. Nasal delivery of drugs has shown optimistic results in animal models. Drug delivery via nasal cavity can be an effective strategy to overcome problems imposed by the BBB. Intranasal drug delivery may be helpful in reducing systemic side effects caused by antiepileptic drugs as it bypasses the BBB and helps to reduce the dose. Nasal drug delivery is safe and non-invasive. There are many barriers which can affect nasal drug absorption, can overcome by applying different strategies like use of enzyme inhibitors, permeation enhancers, mucoadhesive polymers, and lipid nanoparticulate system.

With on-going research in the field of lipid nanoparticles, it has been possible to overcome the major challenges observed with conventional dosage forms. Delivery of drugs by incorporating them into lipid nanocarriers such as liposomes, SLNs, and NLCs will help in making the formulation more lipophilic and suitable to cross over the BBB owing to its small size. SLNs overcome the disadvantages related to traditional colloidal systems like emulsion, liposomes, and polymeric nanoparticles. Site-specific delivery as well as sustained drug delivery can be achieved with SLNs. SLNs are effective for the treatment of epilepsy as they are easily taken up by the CNS.

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