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## Nose to brain drug delivery of nanoformulations in the treatment of migraine

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### Abstract

Migraine is among most prevalent neurological disorders. Effective drug delivery to brain is first preference to treat neurological disorders. Most of the antimigraine drug used presently suffered with poor bioavailability and slow onset of action by oral route. Various approaches are utilized for drug delivery to brain and among all, nose to brain drug delivery is evolved as effective method to circumvent blood brain barrier. Novel intranasal nanoformulations can be a promising approach for direct drug delivery to the brain to treat migraine headache. Recently different types of nanoformulations are developed to improve the brain targeting efficacy by improving drug retention and permeation over the nasal mucosal epithelium. Nanoformulations are designed to avoid different problems, including low solubility, poor bioavailability, slow onset of action, and enzymatic degradation. The present review summarizes the various applications and benefits of nanoformulations used for nose to brain drug delivery of antimigraine drugs.

**Keywords:** Migraine, intranasal, nanoformulations, drug delivery, brain targeting

### 1. Introduction

Migraine primary headache disorder mainly characterized by an intense throbbing and pulsating pain around the head and its secondary most common symptoms are nausea, vomiting, and photophobia<sup>[1, 2]</sup>. According to WHO, migraine is currently the third most common disease with an estimated global prevalence of 15% and most often begins at puberty and most affects those aged between 35 and 45 years. For the migraine treatment various routes are explored such as oral, systemic and nasal route and among the entire nasal route significantly beneficial for fast delivery and brain targeting drug delivery<sup>[3]</sup>. Oral and systemic routes are the most commonly used for all types of treatments but in case of brain drug delivery, blood brain barrier (BBB) is a major hurdle as most of the drug can't cross this barrier to reach the brain<sup>[4]</sup>. To bypass the BBB and deliver drug directly to brain, nasal drug delivery approach is widely explored. Some other benefits of intranasal delivery are such as avoiding extensive first pass metabolism, gastrointestinal degradation, better patient compliance due to ease of administration and non-invasiveness. The distinctive linkage provided by the olfactory and/or trigeminal nerve system present between the olfactory epithelium and the brain, skip the BBB and deliver drugs directly to brain. From last few years, nanoparticles based drug delivery systems are investigated, through different routes and found beneficial. Intranasal delivery of nanoformulations are highly explored for brain targeting as they provide high drug encapsulation efficiency, improved absorption and high permeability through mucosal epithelium<sup>[5]</sup>. Furthermore, surface modification of nanoparticles with mucoadhesive polymers, improves the drug permeation by increasing olfactory contact and reducing the mucociliary clearance in the nasal cavity<sup>[6, 7]</sup>. Different types of nanoparticles are investigated for nose to brain transport for the treatment of migraine such as polymeric nanoparticles, solid lipid nanoparticles, nanoemulsions, micellar nanocarriers etc. This review summarizes the mechanism of nanoparticles mediated transport in nose to brain drug delivery and different types of nanoparticles used in treatment of migraine with their possible advantages.

### 2. Nanoparticles mediated nose to brain drug transport mechanism

The nasal route has gained a big attention as a convenient and reliable approach for the brain targeting of various therapeutics. The nasal cavity is mainly divided into respiratory area and the olfactory area, form where drug transport directly from nose to brain. Absorption of molecules mainly takes place at the olfactory and respiratory epithelia<sup>[8]</sup>.

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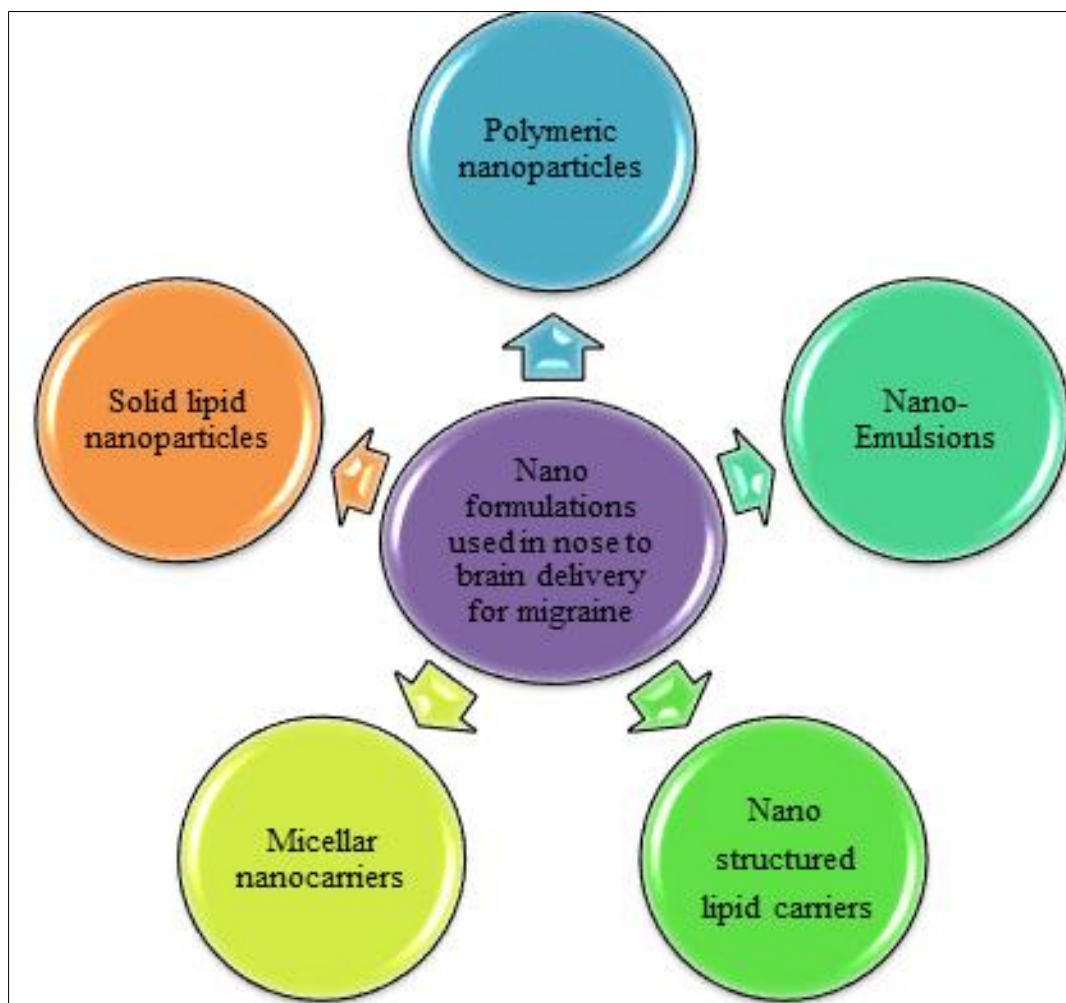
Within the olfactory area, olfactory neurons are exposed, enabling the transport of drug compounds directly into the brain via the olfactory neurons [9]. Olfactory mucosal cell consists of mainly bipolar neurons, supporting (sustentacular) cells, basal cells, and Bowman's glands. The mucous layer is produced by the Bowman's glands which reside in the olfactory epithelium [10]. Intranasal drug administered rapidly passes extracellularly along the olfactory nerve pathways initially from the upper part of the nasal cavity to brain directly [8, 11]. This pathway delivers significant amount of drug in the olfactory bulbs which is highest among the all nose to CNS passages [12, 13]. The olfactory epithelium enclosed another sensory nerve known as trigeminal nerve. Axons of the bipolar neurons connects the trigeminal nerve (cranial nerve V) to the pons and the cribriformplate, which allows paravascular transport to the cadual brain regions and the spinal cord [8, 14]. Transport to other brain areas after entry to the brain (e.g., to the mid brain from the olfactory bulb or to the brain stem from the trigeminal nerve) is thought to be mainly either by extracellular convective bulk flow or via perivascular routes [8]. Drug transport across the nasal epithelium occurs either by transcellular (inside the epithelial cell) or paracellular (between the epithelial cells) mechanisms.

Transcellular transport occurs by endocytic uptake by the olfactory sensory neurons (OSN) to the olfactory bulb. Endocytosis transport occurs by the number of different molecular mechanisms including macropinocytosis, clathrin mediated, clathrin-independent, caveolin-mediated, caveolin-

independent and phagocytosis [15]. Paracellular or extracellular transport occurs across the sustentacular cells to the lamina propria. The paracellular pathway consists of hydrophilic channels with tight junctional complexes connecting the epithelial cells and allows only small drug molecules to pass through it. Due to extra small size the nanoformulations, represent promising formulations to deliver drugs directly into the brain through the intranasal route [16]. Therefore, they can be used as a possible alternative to oral administration, avoiding problems such as low solubility in water, poor bioavailability, enzymatic degradation and slow onset of action [17].

### 3. Nanoformulations used in Nasal drug delivery for Migraine treatment

Nasal drug delivery is a promising alternative non-invasive approach due to fast absorption and rapid onset of drug action, avoiding degradation of labile drugs (such as peptides and proteins) in the GI tract and also minimizes the various GI related side effects [18]. In order to improve drug absorption through the nasal mucosa and brain targeting, different types of approaches such as novel drug delivery nanoformulations have been employed. Recently nanoparticulate systems such as polymeric NPs, solid lipid NPs, nanoemulsion, nanostructured lipid carriers, micellar nanocarriers etc. were explored for nose to brain delivery in treatment of migraine also were depicted in Fig. 1. Different types of nanoformulations explored in treatment of migraine are summarized with their research outcomes in table 1.



**Fig 1:** Different Nanoformulations used in nose to brain delivery for treatment of migraine

**Table 1:** Nose to brain drug delivery for migraine treatment by different nanoformulations

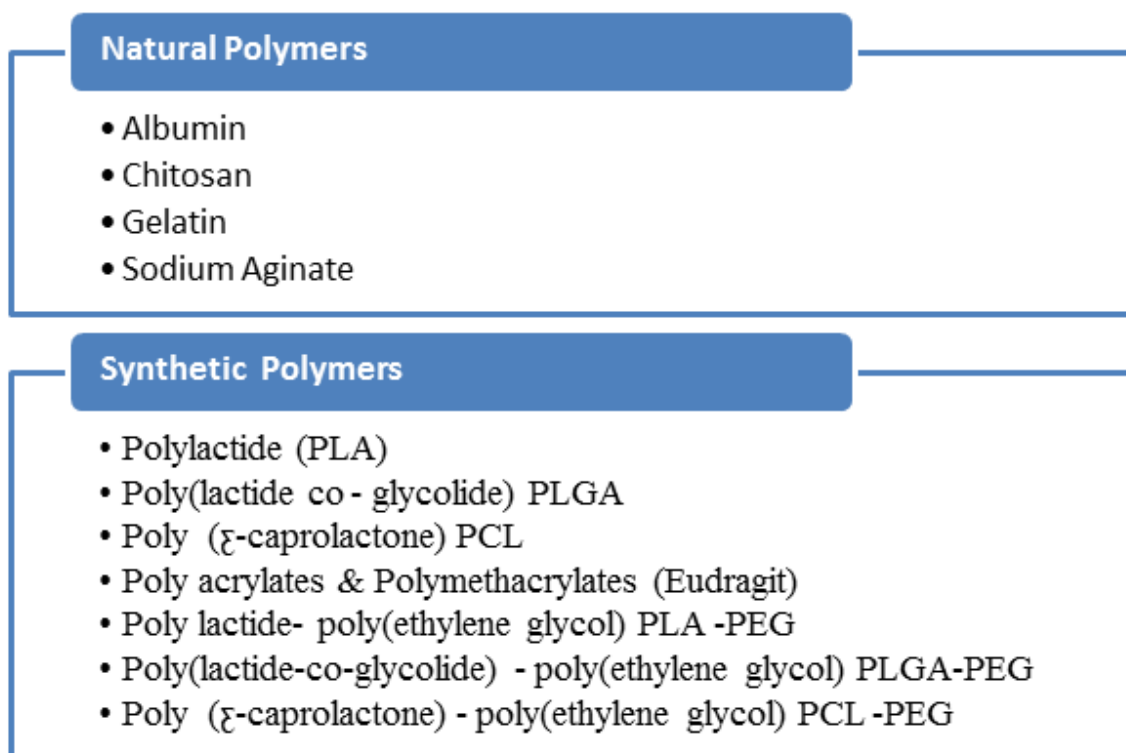
Drug	Formulation	Study outcomes	References
Sumatriptan	Polymeric Nanoparticles	Nanoparticles easily penetrate the nasal mucosa by virtue of particle size and formulation displayed sustained release up to 24 hours which may help to reduce multiple daily doses to once per day.	[19]
Zolmitriptan	Polymeric Nanoparticles	Ex vivo drug permeation studies reveals controlled drug release up to 24 hours and potential intranasal drug delivery tool for brain targeting in migraine.	[20]
Eletriptan Hydrobromide	Polymeric Nanoparticles	Reduce first pass metabolism and improves in bioavailability after nasal drug delivery in migraine therapy.	[21]
Rizatriptan Benzoate	Solid lipid nanoparticles (SLN)	Nasal SLN shows values of $C_{max}$ 473.56 ng/ml, $T_{max}$ 1hr, AUC 3706.95ng/ml and $T_{1/2}$ was 5.7hr and found more superior than marketed oral formulation and drug solutions given by iv route.	[22]
Almotriptan	Solid lipid nanoparticles (SLN)	Results revealed rapid drug brain delivery within 10mins and toxicological results confirmed the safety of the nanformulation for nasal administration.	[23]
Rizatriptan Benzoate	Nanoemulsion	Brain targeting of intranasal nanoemulsions (AUC=302.52 $\mu$ g min/g) was higher as compared to intranasal Gels (AUC=115 $\mu$ g min/g) and IV administration (AUC=109.63 $\mu$ g min/g) of the drug.	[24]
Flunarizine Dihydrochloride	Nanoemulsion	Nanoemulsion depicted lower droplet size, satisfactory zeta potential, and high drug loading reproducible drug release profile in nasal drug delivery for migraine treatment.	[25]
Flunarizine Dihydrochloride	Solid Lipid Nanoemulsion	Nanoemulsion provides improved the solubility and release of drug in a simulated nasal fluid. Overall preparation found suitable for nasal drug delivery.	[26]
Zolmitriptan	Micellar nanocarriers	<i>In vivo</i> biodistribution studies indicated the superiority of the developed nanocarrier for brain targeting when compared with the intravenous and nasal solutions of the drug. Brain localization studies revealed a possible nose-to-brain transport pathway for the labeled drug.	[27]
Sumatriptan	Nanostructured lipid carriers (NLCs)	Sufficient brain deposition of drug. DTE and DTP of intranasal-administered NLCs were calculated 258.02% and 61.23% respectively	[28]

### 3.1 Polymeric nanoparticles

Polymers are widely used for the fabrication of nanoparticles and various types of natural and synthetic polymers are employed for nose to brain drug delivery are summarized in Fig. 2. Polymeric NPs interacts with mucosa and transports drug directly into the brain via olfactory and trigeminal sensory neurons [5, 29]. Bioadhesive /mucoadhesive nanoparticles are widely accepted as they decrease the mucocilliary clearance and prolong the residence time through their mucoadhesive interactions with nasal mucosa increases and thus improve bioavailability of the drugs at the

target site [30].

Some polymers act as permeation enhancer and facilitate nasal drug delivery by opening tight junctions and thus improves drug transport across transmucosal barriers e.g. chitosan [31, 32]. Intranasal administration of various anit migraine drugs such as sumatriptan, zolmitriptan etc suffers with poor bioavailability problem so their polymeric nanoformulations were exploited to produce high bioavailability and rapid absorption as compared to oral tablets in migraine attack [19, 20].

**Fig 2:** Different polymers used in nose to brain drug delivery

### 3.1.1 There are many benefits of using polymeric nanoparticles in nose to brain drug delivery

- Mostly polymers are biocompatible and biodegradable and thus non-toxic.
- Better drug targeting and thus minimize systemic side effects of drugs.
- Polymeric nanoparticles can encapsulate different types of hydrophilic, hydrophobic, and volatile drugs.
- High drug loading capacity and are easily fabricated in large quantities by various methods.
- Enhance the formulation retention time at the site of absorption and promote mucosal drug penetration.

### 3.2 Solid lipid Nanoparticles

Solid lipid nanoparticles (SLN) have been found significant and alternative system to emulsions, liposomes, microparticles and their polymeric counterparts for various drug delivery routes [33]. Their stability in body fluids is the major concern as SLN which are hydrophobic, are exposed to phagocytic uptake by macrophages [34]. Many studies reported improved stability by coating of particles with hydrophilic molecules such as poly(ethylene)glycol (PEG) derivatives. Modifying surface characteristics by coating SLN with hydrophilic polymers improves systemic stability and biodistribution, and subsequent bioavailability of drugs entrapped. SLN has been found useful in transmucosal delivery systems for various types of drug molecules and macromolecular therapeutic agents [35, 36]. Additionally, hydrophilic coating of SLN such as PEG will allow the interaction and transport of SLN through the nasal mucosa and therefore serves as promising nasal drug delivery carriers [37, 38, 39]. Various types of antimigraine drug such rizatriptan, almotriptan etc loaded solid lipid nanoparticles were found efficient in brain targeting and fast relief in migraine headache [22, 23]. Advantages of SLN in nose to brain drug delivery are:

- Enhancement of bioavailability of entrapped drugs via modification of dissolution rate
- Fast and Controlled drug delivery
- Improvement in tissue distribution and targeting of drugs
- Can be administered through various drug delivery routes such oral, systemic, topical, nasal etc.

### 3.3 Nanoemulsion

Nanoemulsion consist of lipophilic system stabilized by one or more surfactants and eventually co-surfactants delivered in droplets of nano size range (100-300 nm) with high surface area [40]. For nasal drug delivery, mucoadhesive polymer such as chitosan can be added to the formulation to overcome rapid nasal clearance. Nanoemulsions represent promising systems to deliver drugs directly into the brain through the intranasal route [41]. Therefore, they can be used as a possible alternative to oral delivery by skipping obstacles such as low solubility in water, poor bioavailability, enzymatic degradation and slow onset of action [42]. Several nasal formulations, primarily of the o/w type, have been developed for nose-to-brain delivery and play significant role in the permeation of drugs through the nasal mucosa [43]. Thus Nasal nanoemulsions found to be very effective, non-invasive and safe drug delivery systems to achieve brain targeting for the treatment of migraine and provide fast relief in acute migraine headaches. Rizatriptan and Zolmitriptan are widely prescribed as antimigraine drugs suffer with a short half-life (2-3hrs) and poor oral bioavailability. They are commercially available as tablets

and orally disintegrating tablets. Though orally disintegrating tablets are suitable for administration during a migraine attack, it would not improve the poor bioavailability of the drug [44]. To increase the bioavailability and brain targeting of rizatriptan, its intranasal nanoemulsions delivery systems were investigated for antimigraine therapy [24].

### 3.4 Micellar nanocarriers

Micellar nanocarriers of the drug were developed to exploit their advantages, such as low particle size, enhanced permeability across nasal mucosa, suitable flow properties and ability to carry various drug molecules, which would allow targeting and higher retention effects at the target site [45]. Micelles, self-assembling nanosized colloidal particles with a hydrophobic core and hydrophilic shell are potentially used as pharmaceutical carriers for water-insoluble drugs and found efficient in drug delivery at target site [46]. Polymeric micelles possess high stability both *in vitro* and *in vivo* and good biocompatibility, and can solubilize a broad variety of poorly soluble, antimigraine drugs such as zolmitriptan and sumatriptan [27, 47, 48]. Micellar nanocarriers can also be used as targeted drug delivery systems via the enhanced permeability and retention (EPR) effect (into the areas with the compromised vasculature), by making micelles of stimuli-responsive amphiphilic block-copolymers, or by attaching specific targeting ligand molecules to the micelle surface.

### 3.5 Nanostructured lipid carriers

Nanostructured lipid carriers are found beneficial and used as an alternative to polymeric nanoparticles, liposomes and nanoemulsions. Nanostructured lipid carriers (NLCs) are drug-delivery systems composed of both solid and liquid lipids as a core matrix and thus utilized primarily for the delivery of lipophilic drugs and now their suitability for hydrophilic drugs is well proved [49]. It was shown that NLCs reveal some advantages for drug therapy over conventional carriers, including increased solubility, the ability to enhance storage stability, improved permeability and bioavailability, reduced adverse effect, prolonged half-life, and tissue-targeted delivery [50, 51]. The lipid nanoparticles are considered as good carriers for nose-to-brain drug delivery [28].

### 4. Challenges and Future potential

Despite of various advantages of nasal drug delivery, some important obstacles are also there such nasal mucocilliary clearance, which needs to be addressed. Mucoadhesive formulations can be a better solution to overcome the mucocilliary clearance. Other concerns of intranasal delivery are nasal irritation and damage of nasal mucosa on repeated administrations of nanoformulations. Studies have shown that surfactants are good permeation enhancers that may cause irreversible damage of the nasal mucosa [52]. More precise brain bioavailability assessment methods are also need to be developed for proper dose calculation and administration by intranasal drug delivery for brain targeting.

Furthermore, nanoformulations related neurotoxicity is also a major concern of future research should be more focused and evaluated wisely. Long term safety and stability parameters are also developed for better practical utilization of nanoformulations in future.

### 5. Conclusions

Nanoformulations are a promising approach for the nose-to-brain delivery of drugs to achieve the therapeutic



concentrations in a short duration. Most of the current antimigraine drugs suffer with poor bioavailability issues and required more effective drug delivery systems. Various studies have been reported the significance and effectiveness of nanoformulations over conventional nasal spray, for nose-to-brain targeting in migraine treatment. However, safety and toxicity-related issues of most the nanoformulations are still requires more deep research to fully exploit their clinical applications.

## 6. Declaration of interest

The authors address no conflicts of interest.

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