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Nose to Brain Drug Delivery: New Perspectives for Old Problems -An Enlightening Review

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ABSTRACT

Intranasal route of administration is one of the best routes for delivery of drug to brain. For the delivery of drugs from nose to brain, the low dose is required. This route of administration avoids first pass effect, onset of action is rapid, bioavailability is more and it has no degradation in GIT or toxicity in lungs and it does not cause pain. The capability of the drugs to target through the BBB and possibility of nasal delivery of drug is higher. In the recent years the intranasal route is considered as the superior delivery route for many drugs because of following factors like high permeability, high vascularity, low enzymatic activity, manageable surface area and it avoid first pass metabolism of lungs. Drug delivery systems, such as liposomes, microspheres, microemulsion, nanoemulsion and hydrogels have been shown that it has good bioadhesive to biological system and are briefly discussed in present review. An enormous range of neurotherapeutics, both macromolecules and low molecular weight drugs, can be delivered to the central nervous system (CNS) via this route.

Keywords: Drug delivery; Mucociliary clearance; Nanotherapeutics; Nose to brain targeting; Toxicity

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INTRODUCTION

Nasal delivery of drug is taken as the convenient route of administration for delivery of drugs which is used for curing nasal congestion, nasal allergy and nasal infection. The drug has to be delivered to the brain for treating CNS diseases like Alzheimer's, Meningitis, Schizophrenia, Migraine and Parkinson's diseases. The concentration and onset of action of drug through the intranasal route is similar to that of intravenous administration [1]. Over 36 million people in the world have CNS related diseases and disorders, by 2030 about 66 million the numbers will continue to rise to about 66 million by 2030 and projected to be around 115 million by 2050 [2]. The study conducting experiments on animal through nasal drug delivery route shows that 35-40 substances reach the central nervous system e.g., carbamazepine, dopamine, neurotoxic metals, local anaesthetics, carboxylic acids and the nerve growth factor [3]. The nasal cavity and brain are connected from peripheral circulation by olfactory or trigeminal or respiratory pathway [4,5]. The drug is administered for the treatment of CNS issues for treating CNS disorders and systemic administration for sedatives, analgesics, corticosteroid hormones, hormones, vaccines and cardiovascular drugs through the nasal mucosa [6]. The choroid plexus epithelium, cerebral capillary endothelium and the arachnoid membranes consists of layers of cell called blood brain barrier. These epithelium membranes are connected by tight junctions. The blood separates the cerebrospinal fluid and brain. These endothelium tight junctions are 100 times tighter compare to other capillary endothelium junction. The quercetin liposomes are delivered through intranasal route, a non-invasive delivery system has high bioavailability than oral route owing to decreased hepatic metabolism. The distance from nasal to brain is shorter, penetration through brain is easy. quercetin liposomes improve memory impairment [7,8]. The formulation like solid lipid nanoparticles has been

developed to improve drug absorption through nasal mucosa. The nasal drug delivery route was non-invasive because it avoids degradation of drugs in GI tract and also helps in the sufficient transport across the epithelial cells.

Different Routes for Intranasal Delivery of Drug to Reach Brain

The most direct pathway to the brain are olfactory and the trigeminal nerve pathway [9]. The three various routes for effective passage of drug to the brain.

- Taken up by the epithelium of respiratory system directing the drug to systemic circulation which is further delivered to the brain through BBB.
- Taken up by the nasal epithelium and is transferred to the brain parenchyma through olfactory bulb.
- Taken up by the trigeminal network and transferred to the cerebrospinal fluid and the brain. As depicted in the (Figure 1).

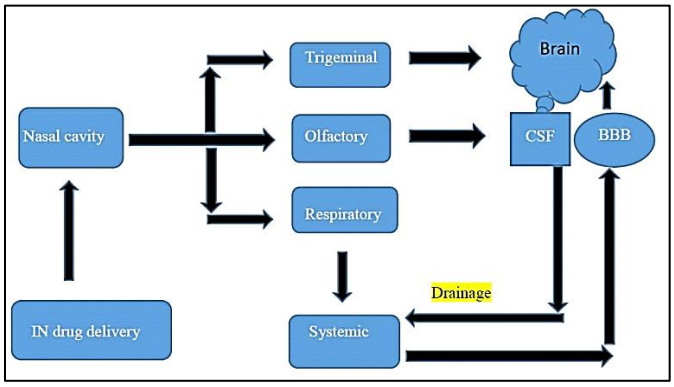

Figure 1: Different routes for intranasal delivery of drug to reach brain [10]

Olfactory Pathway

In human the nasal cavity encompasses less than 10% of olfactory region and olfactory pathway is significant for the delivery of drug to brain through nose [11]. The extension of CNS is characterized by the sensory fibres of the olfactory bulb. From the olfactory mucosa, the olfactory pathway begins in the neuronal olfactory receptor. The neurons from the olfactory system venture from the nasal mucosa via the cribriform plate were the nasal cavity parts off the cranial cavity to the mitral cells inside the bulbus olfactorius. The various regions of brain that include the olfactory tract, the anterior olfactory nucleus, the piriform cortex, the entorhinal cortex, the amygdale and are connected by the sensory fibres of the olfactory bulb [12]. The basal cells, microvillar cells and supporting cells are surrounded around the olfactory receptor through tight juctions. The olfactory receptor neurons can be replaced by the basal cells which act as neural progenitors cells [13,14]. The drug is taken up by the nasal epithelium and the arachnoid membrane which is surrounding the arachnoid space in a route via nose to the brain parenchyma as shown in Figure 2. The three mechanisms involved in the drug uptake by nasal epithelium are:

- The drug is uptaken by endocytosis which is a transcellular pathway for hydrophillic drugs and by passive diffusion for hydrophobic drugs.
- For drugs which are lipophobic paracellular mechanism is involved.
- Intracellular pathway is taken for the uptake of drugs via olfactory nerve pathway by phagocytosis and pinocytosis [15].

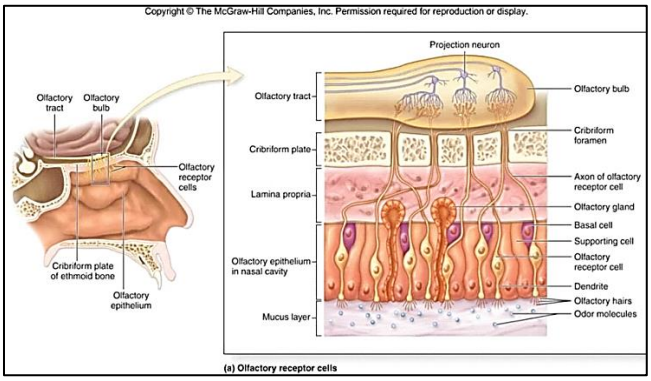

Figure 2: Olfactory region pathway

Trigeminal Pathway / Respiratory Region

In humans nasal cavity up to 80%-90% of the area was covered by the respiratory region. The epithelium layer of the nasal mucosa consists of ciliary and non-ciliary cells, goblet cells and basal cells, non- ciliated and ciliated columnar cells, basal cells and goblet cells [16]. The goblet secretes mucus which is provoked by the ciliary cells towards the nasopharynx. There are 3 main twigs in the trigeminal nerve/V cranial nerve:

- Ophthalmic nerve (V1)
- Maxillary nerve (V2)
- Mandiblar nerve (V3)

The ethmoidal, nasopalatine and nasal branch are innervated by V1 and V2 nasal passages.

The two sites through which these passages enter into brain are:

- The lacerated foramen
- The cribriform plate

The two regions like caudal and rostral brain regions are created by these branches [17]. When an infrared dye applied intranasally, the dye reaches within 10 min to the brain and the dye distribution is significantly stable which is transported through the trigeminal nerve as shown in Figure 3 [18].

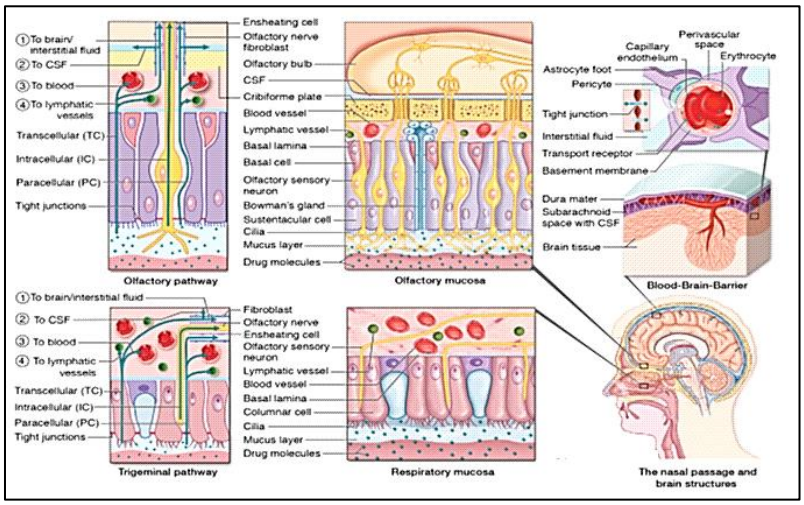

Figure 3: The forthcoming route of transport of drugs from blood to brain through BBB and along the nasal and trigeminal [19]

Other Possible Pathways

In nose to brain pathway the perineural transport laterally with the nasal and trigeminal nerves are the foremost concluding factors [20]. The olfactory region's vascularization initiates and the pulmonary system obtains the supply of blood from the maxillary artery from the trivial branches of ophthalmic artery [21-23]. The mucus layer was the first barrier through which the drug comes across the intranasal administration by casing the nasal and the pulmonary mucosa. The cells like goblet cells that are complex in nature secrete mucous in the nasal mucosa. The mixtures contains 95% of water, 1% of salt, 2% of mucin, 1% of albumin, lactoferrin, lysozymes, Ig(immunoglobulins) and fats [24,25]. The mucus of the nasal cavity has a pH which is nearly neutral or weakly acidic (pH 5-6). The cilium has a frequency of 1000 beats/min and can push the mucus at a rate of 5 mm/min [26].

Transport by paracellular mechanism:

Here the drug needs to move in between the epithelial cells and also some barriers. The paracellular transport is regulated by intactness of tight junction [27]. Certain formulations can promote the drug from nose-to-brain through tight junction rapidly occurs within 30 min after administration.

Transport by transcellular mechanism:

The mechanisms of transcellular pathway depend on the size of the particles (i.e., <20 nm is travelled) and nature of the substances like:

- Clathrin-reliant or independent,
- Caveolae- reliant or independent,
- Macropinocytosis or phagocytosis [28].

The particle size less than 200 nm prefers caveolae mediated endocytosis and the particle size ranging from 300-1,100 nm desires clathrin mediated endocytosis. Transport by transcellular mechanism takes more time from several hours to days.

Organization nerves/filia olfactoria:

There are several olfactory neurons which are joined together and covered by Schwann cells in the lamina propria under the nasal mucosa; this organization is called the filia olfactoria where 20 axons are put together in the form of fascicles. 5-10 fascicles can be covered with a single Schwann cell and hence contain axons less than 100 in number. Perineuronal channels having a diameter of 10-15 nm help in transporting ions and transneuronal transport takes place with drug having 100-700 nm in diameter in human. Perineuronal channels of 10-15 nm act as ionic reservoirs[29]. Mesaxons are present within the filia olfactoria and extracellular fluids are passed through the pores.

Intranasal Delivery of Cancer Drugs

Many therapeutic agents, having particle size ranging from small and macromolecules are used a targeted drug delivery to the nasal system, e.g. intranasal erythropoietin is used as a protective in animal models against stroke. Nerve protective peptide (NAP) is used to treat neuro-degeneration similarly for the improvement of memory and functioning in patients having Alzheimers disease intranasal insulin is given [30,31]. Intranasal delivery of genes, stem cells and other components to the brain [32,33]. It is been demonstrated that there is no increase in the plasma absorptions after drug delivery through nasal route showing that the drug delivery has occurred directly from nose to brain [34]. Overall, the drug delivery through the nasal route has been extensively studied in the background of general brain function and neuro degeneration, this mode of drug delivery has achieved less interest with respect to the intracranial tumor growth [35]. In the observation of intracranial tumor chemotherapy, anti-neoplastic agent 5-fluorouracil in rats show transport of drug through nasal route to the brain which results in brain being exposed in a greater way than with intravenous [36,37].

Factors Affecting Nose to Brain Drug Delivery

The factors which affect absorption of drug through intranasal route are the physical as well as the chemical properties of the drug substance, the environment of the nose and dosage form characteristics. These factors have a significant role in penetration of the drug to reach the desired plasma concentration through intranasal delivery of drug [38,39].

Physiochemical Properties

Molecular weight:

The molecular weight of the drug has a significant effect on the permeation and the availability of the drug in the system via nasal cavity. The molecular weight of the drug less than 300 Daltons can be easily penetrated through the nasal mucosa. Lipophilic drugs like proteins and peptide shows excellent absorption through nasal mucosa which has a molecular weight >1 K Daltons e.g., for proteins and peptides the bioavailability usually ranges from 0.5% to 5% with the drug having molecular weight around 1 K Daltons [40-42]. The drug having a particle size less than 5 microns inhaled directly into the lungs whereas the particle size having bigger than 10 microns administered through the nasal cavity whereas the permeation of water soluble drugs through the nasal cavity does not depends on the molecular weight of the drugs [43,44]. The having molecular weight more than 1000 Daltons can be administered through the nasal pathway with permeation enhancer. The drug remains in the lungs having the particle size 2 to 10 μm, whereas the particle size less than 1 μm are exhaled [45]. The bioavailability can be enhanced up to 6000 Daltons by permeation enhancers [46,47]. The molecules less than 1,000 absorbs better [48,49]. Drug penetration is established by the molecular weight of the drug, hydrophobicity and lipophobicity of the drug [50].

Solubility:

The water soluble drugs are required for better drug absorption. Through nasal membrane, it should dissolve in the aqueous fluids of nasal cavity before drug absorption. The nasal cavity smaller in size hence for drug dissolution the availability of fluid is less hence suitable water soluble drug is needed for enhanced nasal absorption [29]. After dissolution the diffused particles of the drug may cross the bio membranes at the site of absorption. Since the nasal cavity is very small a less amount of drug is required for administration through nasal route [51]. Drug absorption may not be observed if particles deposit or removed from the nasal cavity. If drug is not suitably soluble in the preferred vehicle it limits both drug absorption, formulator's ability to formulate a product. It is necessary to know concerning the link among the solubility, absorption and saturation of the drug from the point of mechanistic and thermodynamic view. The absorption is affected by the solubility of the drug broadly discovered especially with the GIT and the skin [52,53]. Lipophilic drugs less soluble in the aqueous secretions. Based on their solubility the drugs

are absorbed by passive diffusion if the drugs are soluble in aqueous medium and lipid soluble drugs via active transport [54].

Lipophilic and hydrophilic balance:
The drug should have balance between two factors like lipophilicity and hydrophilicity is essential for enhanced nasal absorption the membrane of nasal cavity is lipophilic in nature. So lipophilic drugs are absorbed well and bioavailability through this route is near to 100%. Compared to lypophyllic drugs Polar drugs not transported easily across nasal membrane [55]. Various lipophilic drugs which are absorbed completely are naloxone, buprenorphine, testosterone and estradiol when administered through the nasal membrane [56,57]. However when lipophilicity is too high, the penetration of drug through the walls get reduced due to insufficient solubility of drug in the nasal fluid [58]. Lipid soluble drugs can easily traverse through the cell membrane hence reach the cells cytoplasm [59].

Pka and partition coefficient:
According to the theory of pH partition, ionized molecules are less absorbed in comparison to the unionized molecules as in case of intranasal route. Concentration of the drug in biological tissues increases as the lipid solubility of the drugs [60]. Normally, permeation of lyphophylic drugs increases through nasal mucosa. Lipophilic drugs with less molecular weight efficiently absorbed across the nasal membrane, and hydrophilic drugs with more molecular weight, like peptides have low molecular weight because the drug is not permeated easily through nasal membrane which enhances mucociliary clearance [61]. A quantitative relationship between the nasal absorption and the partition coefficient is constant. Similarly, ionised classes of drugs also infuses through the nasal route e.g., in benzoic acid it is found that 10% of drug absorbed at pH 7. In general, the quantity of uncharged class of drugs and lipophilicity/hydrophilicity affects the passage of drug through the biomembrane. By this, it was concluded that, the major factor which influences the passage of drug through nasal mucosa for polar drugs is partition coefficient [62].

Osmolarity:
In generally isotonic Formulation significantly effects absorption through the nasal mucosa [63]. It is observed that. Epithelial cells shrinks in the presence of hypertonic solutions. Ciliary activity is inhibited by hypertonic solutions. The hypertonic solution matches the low pH. The osmolarity factor influences that the drug is absorbed in animals through nasal secretion [64]. In the preparation the concentration of the sodium chloride affects the absorption rate and it reaches up to 0.45 M sodium chloride. The higher amount of salt solution not only increased bioavailability it also causes the nasal epithelial toxicity [65]. It is observed that by using sorbitol as an osmoregulatory agent and from structural changes drug permeation can be enhanced. Isotonic solutions are preferred for administration due to decreased infusion of secretin [66,67]. Hence, to get best results an isotonic solution is preferred [68].

Nasal Environmental Factors
Blood Flow:
Nasal mucosa is provided by rich vascularisation and large surface area is present for drug absorption. The rate of flow of Blood determines the drug absorption rate by diffusion is done by maintaining the concentration gradient throughout the membrane is necessary. The absorption of the vasoconstrictor drugs reduces the rate of flow of drug and absorption is reduced considerably [69]. The blood flow rate considerably influences nasal absorption of drugs, as it increases more drug crosses through nasal tissue and come in contact with blood circulation. In the nasal mucosa blood vessels are bounded through adrenergic nerves that perform as alpha adreno receptors. Flow of blood and blood content in the nasal membrane in animals and humans is decreased by the Stimulation of these receptors [70]. Various external factors which affect nasal blood flow are ambient temperature; vasoactive drugs are present, humidity, inflammation, trauma [71]. This shows that nasal flow is very sensitive to locally or systemically acting drug [72,73].

Nasal enzymes causing degradation of drugs:
The peptides and proteins have low bioavailabilitythrough the nasal cavity. So these drugs may undergo enzymatic degradation of the drug molecule in the lumen of the nasal cavity or during passage through the epithelial barrier. These sites contain exo-peptidases and endo-peptidases. Exo-peptidases are mono-aminopeptidases and di-aminopeptidases [74]. In nasal epithelial cells enzymes such as carboxyl esterases, aldehyde dehydrogenases, epoxide hydrolases and glutathione S-transferases are present. Cocaine, nicotine, progesterone and some decongestants are degraded by isoenzymes Cytochrome P450. Peptide drugs such as insulin and calcitonin are degraded by proteolytic enzymes such as aminopeptidases. For designing nasal drug delivery system the degradation of drug by nasal enzymes must be taken into consideration [27].

Mucociliary clearance:
MCC is a self-clearing protective mechanism for the upper respiratory tract (bronchi) which plays important role in preventing the reaching of noxious substances to lungs. The inhaled air contains foreign particles, pathogens which adhere to sticky fluidic mucous lining of the nasal openings and are passes to nasopharynx and finally to gastrointestinal tract and prevented to reach lungs. It also affects drug absorption. Mucociliary clearance is altered under various pathological conditions [75,76]. Normal mucociliary passage is about 11-14 min. The impaired mucuciliary clearance was indicated by measuring the transit time less than 30 min. The nasal mucus was cleared at the range of 8 mm/min, i.e., less than 1 and more than 20 mm/min. Mucociliary clearance (MCC) decreases and ciliary beating which provides increased contact time of drug and mucus membrane which increases the permeation of drug, the MCC increases as decreases with the permeation of drug by providing less time of contact [77,78].

Pathological conditions:
Mucociliary clearance is altered by Common cold, rhinitis and other pathological conditions which affects drug absorbed through the nasal pathway. The drug permeation is also influenced by the hypo secretion and hyper secretion of nasal mucosa [26]. For nasal drug absorption the state of nasal mucosa is important. The several diseases that people are suffering like sanities, rhinitis, nasal allergy and nasal infection which cleared the formulation before the drug absorbed through the nasal mucosa [43].

Nasal secretion:
From the anterior serous and sero mucus glands the nasal secretions are produced. About 1.4-2.2 mi/day the mucus is produced. The mucus layer occur as a double layer.periciliary sol phase is present in it by which cilia helps in the forward movement of gel viscosity of nasal secretion also affects drug permeability across the nasal mucosa. If mucus is thin it inhibits ciliary clearance. Drug should be dissolved before permeation. In such cases chronokinetics will order the pattern and permeation rate [40].

Formulation Factors

Viscosity:
In nasal mucosa the contact time of the drug increases with the use of viscosity increasing agent in the formulation which increases the nasal permeation of the drugs. The mucociliary clearance and ciliary beating is reduced by high viscosity agents [79,80].

pH of formulation:
The pH of the preparation and nasal surface affects a drug permeation. Nasal irritation is avoided by using nasal preparations of pH ranges from 4.5-6.5. Under acidic pH lysozyme present in nasal secretions destroys certain bacteria. The lysozymes are inactivated if alkaline pH is low and the microbial infection affects the tissue. By it shows that by maintaining pH of the formulation nasal irritation can be avoided and also, prevents bacterial growth and can obtain effective drug permeation [26]. The volume of dosage depends on the area of the nasal cavity. It has an upper limit of 25 mg/dose and 0.1-0.2 ml/nostrils [42].
The importance of maintaining the pH of the nasal formulations are as follows:-
a) It prevents the irritation in nasal mucosa.
b) It permits the absorption of drug in unionized form.
c) It prevents bacterial growth in the nasal passage.
d) It bears normal physiological ciliary movement [38].

Type of dosage form:
The nasal route is simple in preparation and easy for administration. The most commonly used dosage form is nasal drops. The solutions and suspensions are used instead of dry nasal powders because dry nasal powder causes mucosal irritation. In nasal drops the exact amount of drug administered is not easily determined and results in overdose. The new type of dosage form is gel form of drug delivery is used for administration because of its low viscosity and it helps in reduction of anterior leakage, postnasal drip and formulation is fixed in nasal mucosa [25]. The gel type of dosage form increases the residence time reduces the mucociliary clearance and increases the nasal absorption. Liposomes, microspheres, lipid emulsions and films are developed for nasal drug delivery in last few years [60].

Biological Factors

Structural features:

The permeability of the drugs affected by type of cells, density of the cells, arrangement of cells and the number of cells present in that area. There is different type of cells present in nasal epithelium effects in nasal absorption. The presence of microvilli, cell density, surface area and number of cells. Because of large surface area the supply of blood to respiratory region is more and accepts the more amount of nasal secretion and it is suitable for drug permeation [40].

Biochemical changes:

Enzymes such as oxidative and conjugative enzymes, peptidases and proteases acts as enzymatic barrier on nasal mucosa for delivery of drugs and in nasal layer the degradation of drugs takes place and outcome as pseudo-first-pass effect is created which hinders the drug absorption. e.g., Nasal P450-dependent monoxygenase system is involved in nasal absorption of nasal decongestants, alcohols, nicotine and cocaine [81,82].

Formulations Approaches for Nose to Brain Drug Delivery

Nanoparticles:

Nanoparticles are colloidal systems with closed structure where the therapeutic agent is either trapped within colloidal matrix or covered the particle surface by conjugation or adsorption. They can offers sustained and controlled release of drug, and are made of polymer, lipid or combination of both as shown in Figures 4 and 5. The use nanoparticles increase the drug absorption in brain and the nanoparticles are also used in administration to conjugate biorecongnitive lectins to the surface of poly ethylene glycol through nasal route [83]. Lectin is a non-immunological biorecognitive ligand used to modify the surface. By this method nasal adsorption of nanoparticles can be increased. Lectins, specially identifies surface molecule [84]. The brain targeting Efficiency of nanoparticles is raised by conjugated Ulexcuropeus agglutinins I (UEAI). UAE-I altered nanoparticles shows higher attraction to nasal mucosa compared to the pulmonary mucosa. It becomes the potential drug carrier for brain. Odorranolectin shows less immunogenicity than other member of lectins family and is identified as smallest lecithin. Nano Odorranolectin macro-moleculacular drug could be potentially used as carrier for brain drug delivery in the treatment of CNS disorders. Polymeric nanoparticles are used for the develoent of nano drug delivery to treat CNS disorders e.g., nanospheres, nanosuspensions, nanoemulsions, nanogels, nano-micelles and nano-liposomes, carbon nanotubes, nanofibers and nanorobots, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC) and lipid drug conjugates (LDC). The correct mechanism of nanoparticles is not known exactly. But nanoparticles enter into the brain after administration by crossing the BBB by various endocytotic mechanisms. The polymeric nanoparticles made from albumin or poly (butylcyanoacrylate) enters into the brain by their reduced sized mediated endocytosis. These nanoparticles moves together and release the drug in brain microenvironment directly which is biodegraded at the end due to endocytotic uptake by BBB [85].

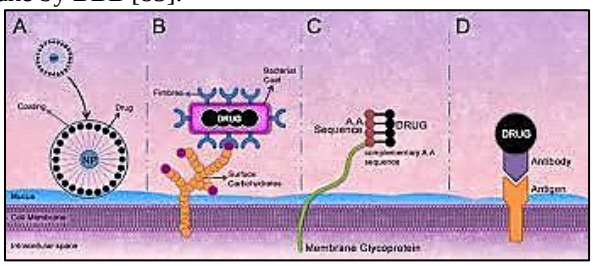

Figure 4: Nanoparticles for nose to brain drug delivery

Nasal drops;

The most convenient and simplest dosage form is nasal drops for nasal route. The amount of drug delivered is not known. The main drawback of this is the accuracy of the dosage. Hence nasal drops cannot be apt for prescription products. Nasal drops capably deposits serum albumin of human in the nostrils compared to nasal sprays [86,87].

Nasal inserts:

Nasal inserts are solid dosage forms which are unique and bioadhesive used for extended systemic delivery of drug through the nasal cavity. The principle involved in this is to absorb nasal secretion from the mucosa after administration and to avoid foreign body sense by forming gel in the nasal cavity [88].

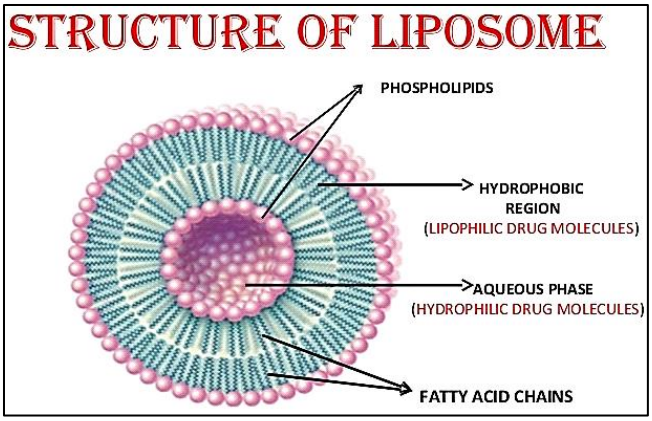

Figure 5: Structure of liposomes

Nasal sprays:

The nasal sprays are formulated as nasal solution and suspension. An exact dose can be delivered through nasal sprays by using metered dose pumps and actuators. About 25 to 200 μL are delivered through the nasal drug delivery. The dry powder sprays are replaced as nasal sprays because dry powder creates nasal irritation [89-91]. The new formulation called dripping method of formulation is used as nasal sprays for preparation of nasal mucus. The dripping method contains 1% Avicel to 3.5% Avicel [92-99].

Injections, catheters and pumps:

Many techniques are established for drugs delivery to brain interstitium directly. Ommaya reservoir or implantable pump technique is one of the methods which attain spontaneous drug delivery. But many implantable pumps that are developed recently are advantageous than Ommaya reservoir. This can be inserted subcutaneously and filled up by subcutaneous injection and are able to deliver drugs as a continuous infusion over a long period [100,101].

Solid lipid nanoparticles:

Solid lipid nanoparticles are colloidal substances. It composes biocompatible/biodegradable lipid medium which is solid in the body temperature and shows size ranges from 100 to 400 nm. It has many advantages like targeted delivery, controlled drug release, increased drug stability, smallest biotoxicity, and produced in large scale and easiness of sterilization [100]. SLN were introduced as submicron colloidal transporters (50-1000 nm) in 1991 as shown in Figure 6. SLN are used for hydrophilic and lipophilic drug(s) that are locked in biocompatible lipid core made by lipid or its combined form of lipids such as precirol ATO 5, Compritol 888 ATO, palmitic acid, glyceryl monostearate, stearic acid and stabilized by surfactant occur at the outer shell [101]. SLNs show an improvement to old drug delivery from nose to brain. As they are capable to guard the compressed drug from chemical or biological degradation and it also rises retention time of nasal because of an occlusive effect, adhesion and good application properties of the SLNs to mucous membranes [102].

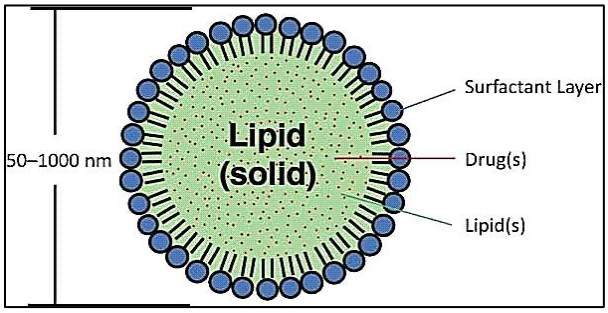

Figure 6: Structure of solid lipid nanoparticles

Micelles:

The micelles are prepared in aqueous solution and micelles are combined with the hydrophilic head region in connection with the nearby solvent, in micelle center the hydrophobic single tail region is assumed. The stuffing

behavior of single-tail lipids in a bilayer causes this phase. Micelles are roughly spherical in shape and other shapes are also present like cylinders, ellipsoids and double layer are also possible. The shape and size of micelles are important in molecular geometry of its surfactant particles and situations of solutions like temperature surfactant concentration, ionic strength and pH as shown in Figure 7. Polymeric micelles got from block copolymers as colloidal transporters for drug. Gene targeting receives more attention in the field of delivery of drug and targeting due to the greater drug-loading capacity [99].

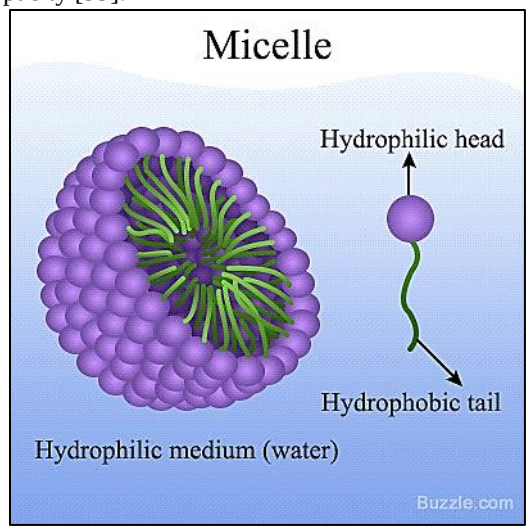

Figure 7: Structure of micelle

Chitosan loaded nanoparticles:

From cationic polysaccharides the nanoparticles are obtained, the chitosan shows favorable outcomes in delivery of drugs to brain through nose because the fundamental properties such as noxious substances are less; bio-compatibility of the substance is brilliant, the filling capacity and the entrapment efficiency. Nanoparticles that are obtained by that are gained from cationic polysaccharide chitosan (CS) shows favorable outcomes in brain through nasal drug delivery and it gives an outstanding essential properties such as less noxious, more bioavailability, greater filling and entrapment efficacy and capability of delivering hydrophilic particles. Bromocriptine loads chitosan nanoparticles by an ionic gelation with tri-polyphosphate as anion. Bio-distribution and pharmacokinetic studies shows the greater brain/blood ratios of intranasal BRC-CS NPs compared to intranasal BRC solution and intravenous BRC-CS NPs. This was confirmed by greater (DTI), drug targeting efficiency (DTE), drug targeting index and drug transport percentage (DTP) [98].

Chitosan hydrogels:

Chitosan, a kind of natural polysaccharide and is broadly used in the biomedical applications owing to its low immunogenicity, good biocompatibility, and specific biological activities. Chitosan-based in situ gelling systems considered as smart biomaterials in the expansion of several biomedical applications, for drug delivery systems and rejuvenation medicine. Hydrogels are the polymeric materials carriers for drugs, protein, cells, and others because of their good biocompatibility, solute permeability and tunable release characteristics [95]. The in situ forming hydrogels which usually show sol-to-gel transition at the in-situ site where they are administrated into the body, exhibit promising potentials for clinic applications. It is more practicable to apply in-situ forming hydrogels to tropical drug delivery, injectable implant, tissue engineering scaffold and so on [96,97]. Chitosan, the second most abundant natural polysaccharides next to cellulose, has many advantages over other polymers, like nontoxicity, biocompability and biodegradability chitosan-based hydrogels are proved to be very effective for delivery of biologically active particles such as growth factors and insulin for providing association of cells and tissues, due to the probability to create multilayered system [103].

CONCLUSION

The intranasal route of drug delivery system is an appropriate pathway for delivery of drugs to the brain directly and the passage of drugs to blood brain barrier through nasal pathway. Intranasal route has shown one very important advantage of delivering drug directly to brain by bypassing blood brain barrier. This route has shown great potential to directly target the brain with reduced systemic side effects. The nasal cavity is well suited for better absorption and patient compliance. The drugs should be evaluated for their safety and risk benefit ratio for targeting to brain. From the nasal cavity the drug is released from the carrier system and it is delivered to CNS and it is transported across the nasal or trigeminal nerve pathway to the CNS where the release of drug is achieved. Microemulsion based preparation with mucoadhesive agent addition can be administrated intranasally and exhibits greater advantages than another route to deliver the drug directly to the brain.

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