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Intranasal Liposomes: An Approach for Drug Delivery to Brain

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ABSTRACT

Targeting drug molecules to brain is one of the most challenging research areas in pharmaceutical sciences. Drugs that are effective against diseases in the CNS and reach the brain via the blood compartment must pass the BBB. The blood-brain barrier (BBB) represents an insurmountable obstacle for a large number of drugs, including antibiotics, anti-neoplastic agents, and a variety of central nervous system (CNS)-active drugs. Therefore, various strategies have been proposed to improve the delivery of different drugs to this tissue which includes liposomes, colloidal drug carriers, micelles, chimeric peptide technology, intranasal and olfactory route of administration and nano technology. The discovery of liposome or lipid vesicle emerged from self forming enclosed lipid bi-layer upon hydration; liposome drug delivery systems have played a significant role in formulation of potent drug to improve therapeutics Liposomes have been investigated as carriers of various pharmacologically active agents such as antineoplastic, antimicrobial drugs, chelating agents, steroids, vaccines, and genetic materials. Liposomes provide an efficient drug delivery system because they can alter the pharmacokinetics and pharmacodynamics of the entrapped drugs. Liposomes have been widely used for brain delivery *in vivo*. Nowadays, the nasal route for systemic drug delivery has gained great interest. It provides several advantages over other routes of drug administrations, which includes rapid absorption, avoids intestinal and hepatic presystemic disposition and high potential for drug transfer to the CSF. Moreover, the nasal route is a potential alternative route for systemic availability of drugs restricted to intravenous administration, viz. peptide and protein drugs and vaccines. As well, intranasal route has also been successfully exploited for bypassing the blood brain barrier [BBB] and subsequently delivering drug molecules to central nervous system [CNS].

KEYWORDS

Nasal route, olfactory region, blood brain barrier, liposomes

INTRODUCTION

The brain is a delicate organ, and nature has very efficiently protected it. The brain is shielded against potentially toxic substances by the presence of two barrier systems: the blood brain barrier (BBB) and the blood cerebrospinal fluid barrier (BCSFB)[1]. These barriers have distinct morphological and physiological characteristics, according to their different tasks[3]. Compared to other tissues, brain endothelia have the most intimate cell-to-cell connections: endothelial cells adhere strongly to each other, forming structures specific to the CNS called "tight junctions" or zonula occludens. These tight junctions prevent cell migration or cell movement across endothelial cells. Tight epithelium, similar in nature to this barrier, is also found in other organs (skin, bladder, colon, and lung).This permeability barrier, comprising, the brain capillary endothelium, is known as the BBB[4]. Owing to its stringent permeability, it allows only restricted entry of promising drugs to the target brain tissues and is presumed to be the key hurdle in developing CNS drugs [2].

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BLOOD BRAIN BARRIER

The brain is unique as a target organ for drug delivery: while it ranks amongst organs with the greatest blood supply. The brain receives about 20% of the cardiac output in humans, access to the tissue is highly restricted by a tight vascular barrier, the blood–brain barrier (BBB)[3]. It is now well established that the BBB is a unique membranous barrier that tightly segregates the brain from circulating blood[4].

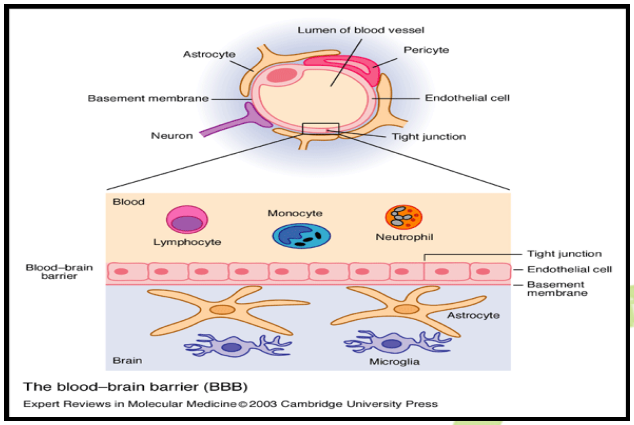


Figure 1: Anatomical features of the blood-brain barrier (www.expertreviews.org, 2003) [52]

Due to the existence of the BBB, the transport of potentially neuroactive drugs from blood into brain is rarely blood-flow limited (for example for highly diffusible drugs like diazepam), but is in many cases extraction-limited. Therefore, drug delivery/targeting to the brain has primarily a permeability problem. The structure of the BBB is subdivided into two components: the endothelial or capillary barrier and the ependymal barrier[2]. The CNS consist blood capillaries which are structurally different from the blood capillaries in other tissues; these structural differences result in a permeability barrier between the blood within brain capillaries and the extracellular fluid in brain tissue. Capillaries of the vertebrate brain and spinal cord lack the small pores that allow rapid movement of solutes from circulation into other organs; these capillaries are lined with a layer of special endothelial cells that lack fenestrations and are sealed with tight junctions [4]. The BBB is considered to be the major route for the uptake of serum ligands since its surface area is approximately 5000-fold greater than that of BCSFB[2].

Practically all drugs currently used for disorders of the brain are lipid-soluble and can readily cross the BBB following oral administration.

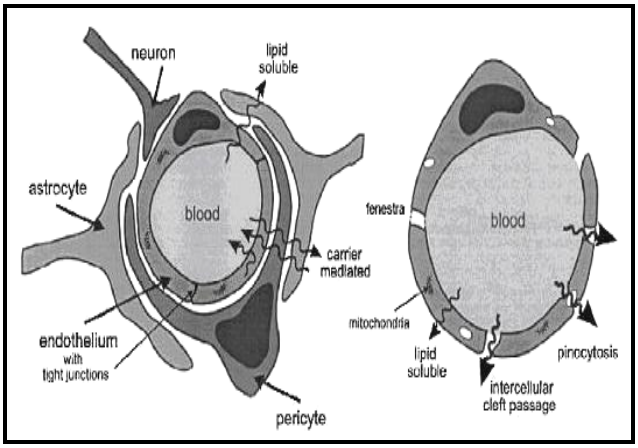


Figure 2: Schematic comparison between general (right) and brain (left) capillaries[4]

The pericytes embedded in the basal lamina entangle the capillaries with claw-like appendices. They have important functional properties: they mediate inflammatory processes, regulate the activity of the brain endothelial cells, and induce capillary-like structures to which they rapidly associate [5, 6].

Astrocytes of the grey matter are characterized by many thick cytoplasmic appendices and large nuclei. The endings of these appendices form cap-like structures, known as endfeet[5].

Antibiotics, when administered intravenously or orally, do not cause CNS side effect because their limited transport across BBB. Further, in spite of being well distributed into various tissues, a lipophilic quinolone antimicrobial agent, grepafloxacin, cannot enter the brain, resulting in the avoidance of CNS side effects such as headache and dizziness. On the other hand, benzodiazepines such as diazepam have been used as sedative-hypnotic agents, because these lipophilic drugs readily cross the BBB. However, the BBB transport of an immunosuppressive agent, cyclosporin A, which is more lipophilic than diazepam, is highly restricted. Similarly, almost all of the lipophilic anticancer agents such as doxorubicin,

epipodophylotoxin and vinca alkaloids hardly enter the brain, causing difficulty in the treatment of brain tumors. Although levodopa, which is useful for treatment of Parkinson's disease, is very hydrophilic, it can readily penetrate the BBB[4].

Despite aggressive research, patients suffering from fatal and/or debilitating central nervous system (CNS) diseases, such as brain tumors, HIV encephalopathy, epilepsy, cerebrovascular diseases and neurodegenerative disorders, far outnumber those dying of all types of systemic cancer or heart disease. The clinical failure of much potentially effective therapeutics is often not due to a lack of drug potency but rather to shortcomings in the method by which the drug is delivered[4].

What mechanisms underlie these diverse BBB transport characteristics of drugs which are apparently structurally and pharmacologically unrelated? The BBB also has an additional enzymatic aspect. Solutes crossing the cell membrane are subsequently exposed to degrading enzymes present in large numbers inside the endothelial cells that contain large densities of mitochondria. Finally, the BBB is further reinforced by a high concentration of P-glycoprotein, active –drug-efflux-transporter protein in the luminal membranes of the cerebral capillary endothelium. This efflux transporter actively removes a broad range of drug molecules from the endothelial cell cytoplasm before they cross into the brain parenchyma [7].

BLOOD-CEREBROSPINAL FLUID BARRIER

The second barrier that a systemically administered drug encounters before entering the CNS is known as the blood-cerebrospinal fluid barrier (BCSFB)[4].

INTRANASAL DRUG DELIVERY

The history of nasal drug delivery dates back to earlier topical applications of drugs intended for local effects[8]. The early 1980s saw the introduction of nasal route as a promising systemic delivery alternative to other conventional drug delivery routes. Intranasal drug delivery has many advantages over other routes of drug administration.

Recent developments in nasal drug delivery have suggested intranasal administration as a safe and acceptable route for brain targeting, especially for drugs with biological effects on the central nerves system (CNS) and limited blood– brain permeability (BBB)[9].

Currently, many nasal drug products on the market are indicated for the treatment of local disease such as allergic rhinitis, pain and for centrally acting drugs where the direct pathway from the nose to brain might offer a quicker and further specific therapeutic effect[10].

ANATOMY AND PHYSIOLOGY

The total surface area of the nasal cavity in human adult is about 150 cm^2 and total volume is about 15 ml[11].

The nasal cavity is subdivided along the centre into two halves by the nasal septum. The two cavities open to the facial side through the anterior nasal apertures and to the rhinopharynx via the posterior nasal apertures and each of two nasal cavities can be subdivided into different regions: nasal vestibule, inferior turbinate, middle turbinate, superior turbinate, olfactory region, frontal sinus, sphenoidal sinus, and cribriform plate of ethmoid bone. The nasal cavity also contains the nasal associated lymphoid tissue (NALT), which is mainly situated in the nasopharynx[12].

The respiratory region contains three nasal turbinates: superior, middle, and inferior which project from the lateral wall of each half of the nasal cavity. The respiratory region is considered as the major site for drug absorption into systemic circulation.

The olfactory region in men covers an area of about 10 cm^2 and is positioned on superior turbinate on opposite septum[11], and plays a vital role in transportation of drugs to the brain and the CSF. The olfactory receptor cells are bipolar neurons with a single dendritic and extending from the cell body to the free apical surface

where it ends in an olfactory knob carrying non-motile cilia, which extend above the epithelium[10].

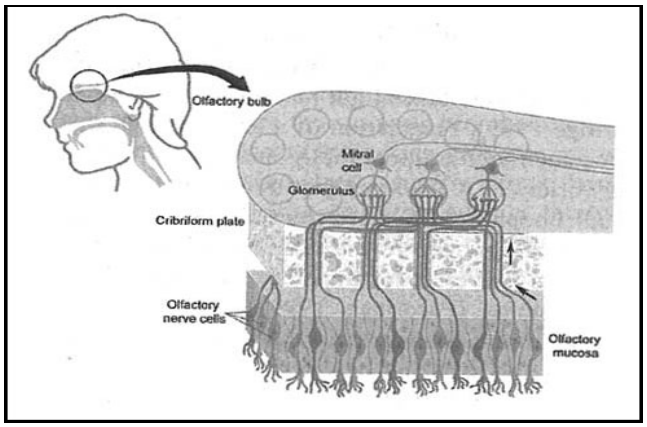


Figure 3: The olfactory bulb, olfactory mucosa, and olfactory nerve cells in humans. Modified picture from the Nobel Prize official homepage (NobelPrize.org)

The pH of the mucosal secretions ranges from 5.5 to 6.5 in adults and 5.0 to 6.7 in children. The mucus moves through the nose at an approximate rate of 5 to 6 mm/min resulting in particle clearance within the nose every 15 to 20 minutes. Numerous enzymes for instance, cytochromeP450 enzymes, carboxylesterases and glutathione S-transferases are found in nasal cavity[13, 14].

The olfactory region is situated between the nasal septum and the lateral walls of each of the two nasal cavities and just below the cribriform plate of the ethmoid bone separating the cranial cavity from nasal cavity. The olfactory epithelium is a pseudostratified epithelium, comprising olfactory sensory neurons and two types of cells; basal cells that are able to differentiate into neuronal receptor cells and supporting cell that provide mechanical support by neuronal receptor cells and maintain the normal extracellular potassium level for neuronal activity. The Olfactory region is of considerable interest in drug delivery because it bypasses the BBB, delivering therapeutic drugs to CNS[15].

Nasal delivery is considered to be a promising technique for the following reasons[16, 17]:

- The nose has a large surface area available for drug absorption due to the coverage of the epithelial surface by numerous microvilli.
- The sub epithelial layer is highly vascularized, the venous blood from the nose passes directly into the systemic circulation and therefore avoids the loss of drug by first pass metabolism in the liver,
- It offers lower doses, more rapid attainment of therapeutic blood levels, quicker onset of pharmacological activity fewer side effects, high total blood flow per cm^3,
- Porous endothelial membrane is easily accessible, and drug is delivered directly to the brain along the olfactory nerves.
- Non – invasive, rapid, Self-administration thus improved convenience and compliance.
- Bypasses the BBB and targets the CNS, reducing systemic exposure and thus systemic exposure and thus systemic side effects.
- Minimal aftertaste
- Does not require any modification of the therapeutic agent being delivered neurological and psychiatric disorders.

DEMERITS OF INTRANASAL DRUG DELIVERY[10]

- Delivery is expected to decrease with increasing molecular weight of drug.
- Some therapeutic agents may be susceptible to partial degradation in the nasal mucosa or may cause irritation to the mucosa.
- Nasal congestion due to cold or allergies may interfere with this method of delivery.
- Frequent use of this route may result in mucosal damage.

FACTORS INFLUENCING THE ABSORPTION OF DRUGS ACROSS THE NASAL EPITHELIUM

The factors influencing nasal absorption are related to nasal physiology, the physicochemical

characteristics of the drug, and the properties of specific drug formulation[8].

1. Physiological Barrier
    a. Mucociliary Clearance
    b. Enzymes
2. Physicochemical Characteristics of the Drug
    a. Molecular weight
    b. Solubility
    c. Dissolution rate
    d. Charge
    e. Partition coefficient
    f. pka
    g. Particle size
    h. Presence of polymorphism

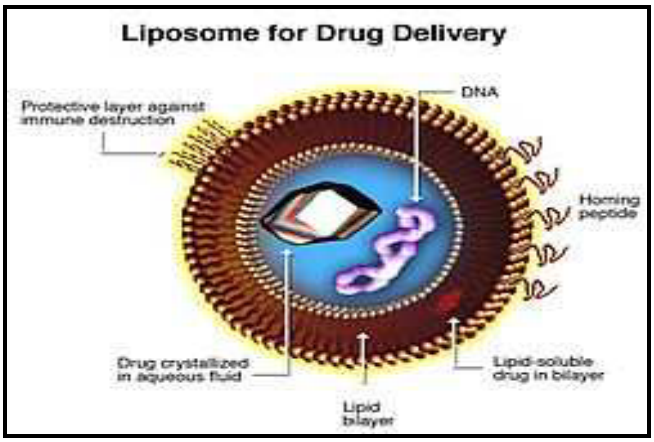
LIPOSOMES

The aim of using colloidal carriers is generally, to increase the specificity towards cells or tissues, to improve the bioavailability of drugs by increasing their diffusion through biological membranes and/or to protect them against enzyme inactivation[2].

Colloidal drug carriers include micelles, emulsions, liposomes and nanoparticles (nanospheres and nanocapsules), have been largely exploited for brain drug delivery because the methods of preparation are generally simple and easy to scale-up.

Liposomes are self assembling colloidal structures consisting of lipid bilayers surrounding an aqueous compartment, and are able to encapsulate a wide variety of hydrophilic drugs within this compartment[2]. Liposomes are spherical vesicle structures composed of a uni- or multilamellar lipid bilayer surrounding internal aqueous compartments and a relatively impermeable outer lipophilic phospholipid bilayer [18].

Liposomes have been shown to provide stable encapsulation for various drugs and offer distinct advantages over unencapsulated agents; thus, liposomes have been proposed for use in a variety of applications in research, industry, and medicine, particularly for the use as carriers of diagnostic and therapeutic compounds [19].



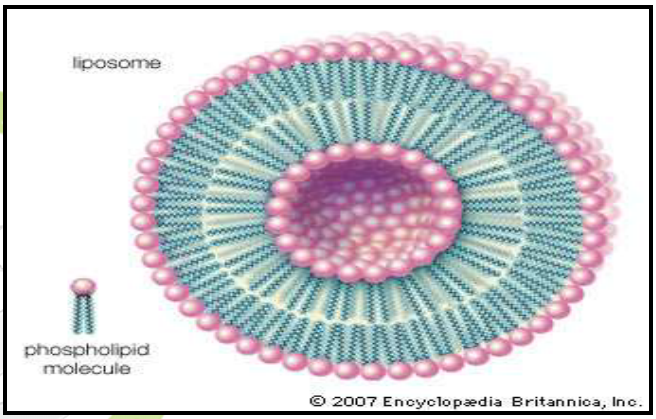
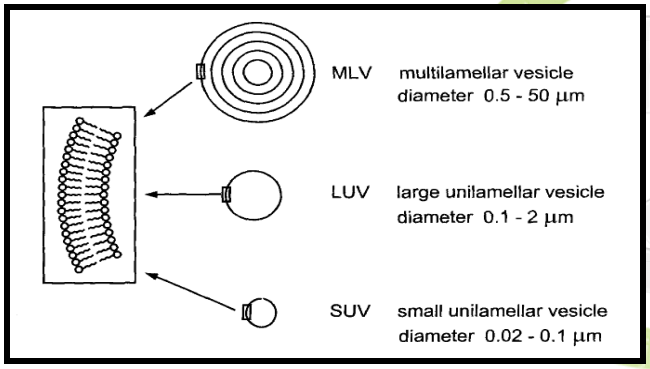


Figure 4: 3D view of liposomes[53, 54]

Lipophilic drugs are generally entrapped almost completely in the lipid bilayers of liposomes, and, since they are poorly water soluble, problems like loss of an entrapped drug on storage are rarely encountered. Hydrophilic drugs may either be entrapped inside the aqueous cores of liposomes or be located in the external water phase. Noteworthy is that the encapsulation percentage of hydrophilic drugs by liposomes depends on the bilayer composition and preparation procedure of the liposomes[20].

The similarity between liposome and natural membranes can be increased by extensive chemical modification of liposome membrane, and may be exploited in areas such as drug targeting or immune modulation, both in vivo and in vitro, where the ability to improve or mimic the behaviour of natural membranes [51].

Liposomes can enhance drug delivery to the brain across the BBB. Phospholipids play an important role in both plant and animal cells, and are used in formulation of very many foodstuffs (of soya lecithin). Phospholipids are esters of glycerin with two different fatty acids and a phosphoric acid derivative. The diversity of phospholipids means that they and their mixtures have a wide range of colloidal properties. With water, these amphiphiles are able to form different lyotropic mesophases such as lamellar, cubic, and hexagonal phases, as well as vesicles and liposomes. Vesicles are a special case of the lamellar phase in which the bilayer membranes make closed uni- or multilamellar spherical or ellipsoidal structures. Vesicles based on amphiphilic lipids made from biological substances are known as liposornes[21]. Such vesicles are classified according to structure and size by the scheme shown here.



PREPARATION[21]

There are various techniques for the production of vesicles. Some are only suited to the laboratory scale, others can also be used for large-scale manufacture.

MLV- Agitation of lipid films or lyophilized foams

- Size fractionation by filter extrusion

LUV- Reverse-phase evaporation

SUV - Ultrasound

- High-pressure homogenizer

- Chelate dialysis ("Lipoprep", laboratory apparatus)

- Injection of alcohol

- Injection of ether

- Spontaneous formation on the addition of certain lipids.

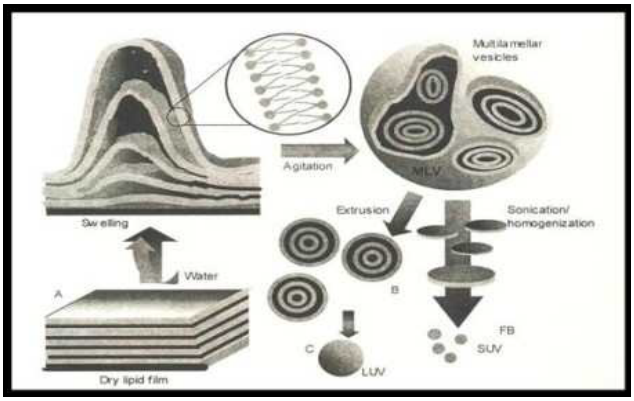


Figure 5: Mechanism and processing steps to generate various types of vesicles[55]

Liposomes have been widely used for brain delivery *in vivo*. The unique ability of liposomes to entrap drugs both in an aqueous and a lipid phase make such delivery systems attractive for hydrophilic and hydrophobic drugs, such encapsulation has been shown to reduce drug toxicity while retaining or improving the therapeutic efficacy.

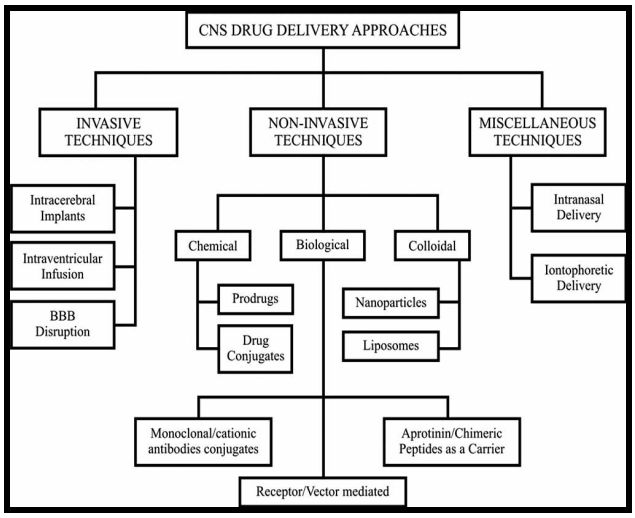
LIPOSOMES: A NOVEL CARRIER SYSTEM FOR BRAIN TARGETING THROUGH INTRANASAL ROUTE

Brain drug delivery[2, 22]

For drugs that do not easily penetrate the BBB, many attempts have been made to facilitate brain entry. The CNS drug delivery tree encompassing the various possible strategies is given in the chart**.**

DELIVERY BY INVASIVE METHODS

Traditional methods to get drugs into the brain completely circumvent the BBB or its associated endogenous transport pathways. These methods include intracerebroventricular (icv) injection, intracerebral (ic) injection, and permeability enhancement. These methods are much more invasive than oral or intravenous administration.



DELIVERY BY NON INVASIVE METHODS

A variety of non-invasive brain drug delivery methods have been investigated, that make use of the brain blood vessel network to gain widespread drug distribution. Noninvasive techniques of delivery may be of a chemical or biological nature. Such methods usually rely upon drug manipulations which may includealterations as prodrugs, lipophilic analogues, chemical drug delivery, carrier-mediated drug delivery, receptor/vector mediated drug delivery etc [23].

TRANSPORT ACROSS THE BBB

There are several transport pathways for molecules to enter the brain. They include transcellular lipophilic diffusion, paracellular hydrophilic diffusion, carrier mediated transcytosis, adsorptive mediated endocytosis, and receptor mediated endocytosis [24].

Lipid soluble molecules with molecular weights below 400 D are able to cross by transcellular lipophilic diffusion, provided that they are less plasma protein bound, or form a substrate for a transport system at the BBB [25].

For a variety of molecules that are essential for brain function, such as amino acids, glucose, peptides, and proteins, specific endogenous BBB transporters exist. These transporters can be either defined as carriers or receptors [26].

Carriers are membrane-restricted systems. They are generally responsible for the transport of small molecules with a fixed size and mass smaller than 600 D. Endocytosis at the BBB is effectuated through adsorption or receptor binding. Adsorptive-mediated endocytosis is initiated by the binding of polycationic substances to negative charges on the plasma membrane.

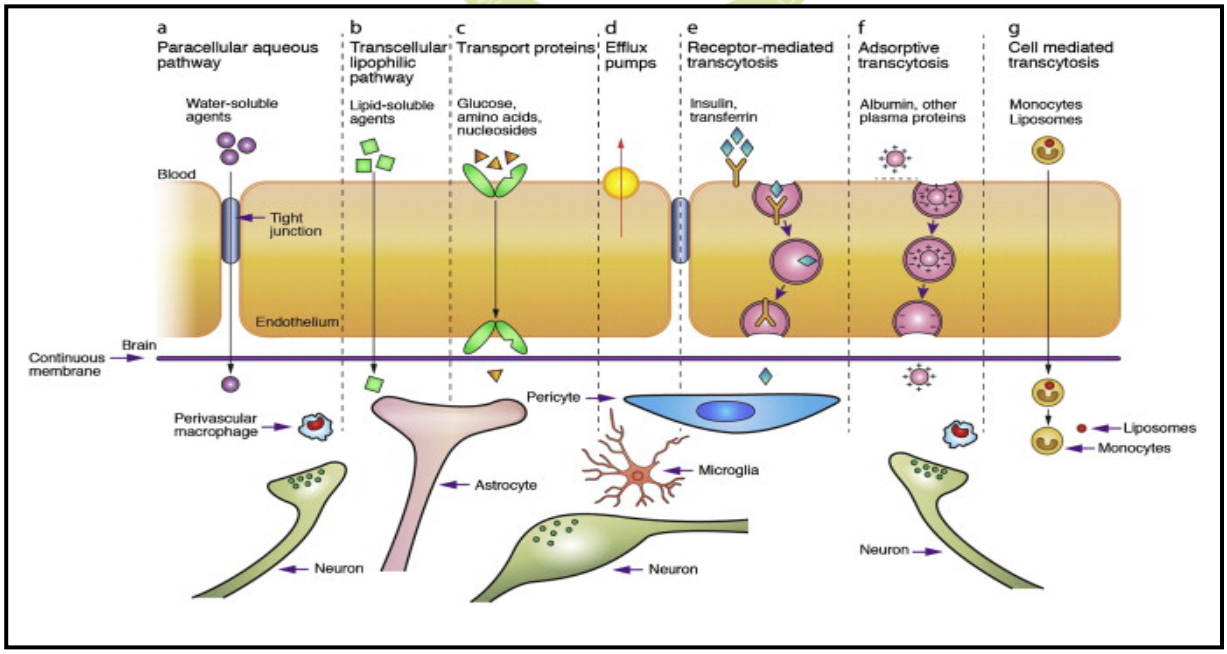


Figure 6: Pathways across the blood-brain barrier[56]

Receptor-mediated endocytosis is initiated by the binding of a receptor specific ligand. Following adsorption or binding, the substance is internalized and transported via the early endosome to the lysosome, or transcytosed to the plasma membrane. Next to these influx systems, many efflux mechanisms exist at the BBB as well. These include P-glycoprotein, MDR-related protein, ABC transporters, and several others [27, 28].

FACTORS AFFECTING DRUG TRANSPORT ACROSS BBB[4, 29]

Table 1: Factors affecting tansport across BBB[2]

Concentration gradient of drug/polymer	Molecular weight of the drug
Lipophilicity of the drug	Sequestration by other cells
Affinity for efflux proteins (e.g. Pgp)	Flexibility, conformation of drug/polymer
Molecular charge	Affinity for receptors or carriers
Cerebral blood flow	Systemic enzymatic stability
Metabolism by other tissues	Clearance rate of drug/polymer
Pathological status	Cellular enzymatic stability

INTRANASAL DRUG DELIVERY FOR BRAIN TARGETING

Strategy of delivering drug by intranasal route could be effective in the delivery of therapeutic proteins such as brain delivered neurotropic factor (BDNF) to the olfactory bulb as a treatment for Alzheimer's disease [30].

It is easily accessible, convenient, and a reliable method, with a porous endothelial membrane, and a highly vascularised epithelium that provides a rapid absorption of compound into the systemic circulation, avoiding the hepatic first pass elimination [31]. In addition, intranasal drug delivery enables dose reduction, rapid attainment of therapeutic blood levels, quicker onset of pharmacological activity, and fewer side effects [32, 33]. It was reported that lipophilic drugs are generally well absorbed from the nasal cavity with pharmacokinetic profiles, which are often identical to those obtained after an intravenous injection with a bioavailability approaching 100%. The unique characteristic of intranasal drug delivery is the high potential for drug transfer to the cerebrospinal fluid through the olfactory region which is situated in nasal cavity [34]. Recent developments in nasal drug delivery have suggested intranasal administration as a safe and acceptable route for brain targeting, especially for drugs with biological effects on the central nerves system (CNS) and limited blood– brain permeability (BBB) [9].

The major problems with nasal delivery are the mucociliary clearance, which reduces the residence time of nasally applied dosage forms and the poor nasal permeability of many drugs. Several alternative strategies have been employed to overcome these limitations [35]. Vesicular drug delivery systems provide promising alternatives with many advantages over the conventional systems. Various pharmaceutical approaches can be employed to render their final formulation more effective. Liposomes are preferred over other vesicular systems in nasal drug delivery. Liposomes are known to sustain the release of the entrapped drug and in the case of nasal administration are able to decrease mucociliary clearance due to their surface viscosity [36].

Liposomes have been delivered by various routes. Liposomes can be formulated as dry powder or a suspension, as an aerosol or in a semisolid form such as a gel or cream. In vivo, they can be administered topically or parenterally. In the systemic circulation, liposomes can be recognized as foreign particles and consequently endocytosed by

reticuloendothelial system reaching the liver and spleen [37].

The olfactory neural pathway provides both an intraneuronal and extraneuronal pathway into the brain [38]. The intraneuronal pathway involves axonal transport (olfactory nerve pathway) and it is considered a slow route where substance enters the olfactory neuron via endocytotic or pinocytotic mechanisms and diffuses to the olfactory bulb by utilizing the same mechanisms the cell uses to transport endogenous substances to the rest of the brain [39]. The extraneuronal pathway (epithelial pathway) is a faster route for direct nose-to-brain transfer as compounds pass paracellularly across the olfactory epithelium into the perineural space, which is continuous with the subarachnoid space before transport to basolatral side of the olfactory epithelium which delivers drugs directly to the brain parenchymal tissue and/or CSF[39].

Table 2: Liposome-encapsulated drugs studied for nasal administration[8]

Drugs	Results
Diphenhydramine	Increased drug retention in the nose
HIV gp 160	HIV specific humoral and cellular immunity in mucosal and systemic sites
Meningococcal Opa-B and opa-J proteins	Induced highly significant anti-opa responses
Salmon calcitonin	Ultra flexible liposomes significantly enhanced the hypocalcemia then conventional liposomes
Ovalbumin in an archeal lipid mucosal vaccine adjuvant and delivery	Eliciting robust antigen specific mucosal and systemic immune response
Tetanus toxoid antigen	Effective mucosal immune responses and high mucosal secretory IgA titers
M. Tuberculosis vaccine	Effective protection against TB with a single dose vaccination

CONSIDERATIONS FOR BRAIN TARGETING OF INTRANASAL LIPOSOMES:

Poor liposomal stability is the major problem in liposome research. The instability problem arises from chemical degradation of the liposome components in addition to physical stability problems which are manifested as loss of entrapped drug and size change upon storage. Loss of entrapped material can be minimized by increasing the rigidity of the bilayer membrane or reducing the water content of liposome formulations producing the so-called proliposomes [40].

Depending on the substance administered, axonal transport rates range from 20–400 mm/day to a slower 0.1–4 mm/day [41]. Lipophilicity, molecular size, degree of dissociation, and route of administration are very important physicochemical factors must be considered when designing intranasal delivery for brain targeting [42]. Formulation factors are also to be considered while designing brain targeted nasal drug delivery systems. The liquid formulations, liquid spray, and drops are the most widely used preparations for intranasal drug delivery. The nasal spray deposits anteriorly in the nasal atrium provide greater residence time, while the drops are dispersed throughout the length of the nasal cavity. Nasal sprays deposit more anteriorly, having more potential for brain delivery. The permeability of the posterior nasal passage is generally higher than the anterior passage [43].

The potential adjuvant effect of liposomes on tetanus toxoid, when delivered via the nasal, oral and i.m. routes compared to delivery in simple solution in relation to the development of a non parenteral immunization procedure, which stimulates a strong systemic immunity. They found that tetanus toxoid entrapped in

Distearoylphospatidylcholine (DSPC) liposomes is stable and is taken up intact in the gut [17].

The permeability of liposome entrapping insulin through the nasal mucosa of rabbit has been studied and compared with the permeability of insulin solution with or without pre-treatment by sodium glycocholate (SGC). A comparison of the insulin solution and liposome suspension showed that the liposome had permeated more effectively after pre-treatment by SGC [44].

The loading and leakage characteristics of the desmopressin containing liposomes and the effect of liposomes on the nasal mucosa permeation and were investigated. The increase of permeability antidiuresis of desmopressin through the nasal mucosa occured in the order positively charged liposomes > negatively charged liposomes > solution [45].

The potential of liposomes as an intranasal dosage formulation for topical application of 5, 6- carboxyfluorescein (CF) was investigated in rats. CF was rapidly absorbed into the systemic circulation and no adhesion of CF to the nasal mucosa was observed [46].

Rivastigmine is an acetyl cholinesterase which can be rapidly absorbed after oral administration but extensively metabolized by cholinesterase-mediated hydrolysis. Liposomes my provide carrier system for this drug through nasal route to CNS. In a comparative study intranasal liposome was compared with the oral free drug and it was recorded that liposomal formulation can provide ten times higher Cmax, higher systemic AUC, and higher concentration in the brain compared to oral administration. The liposomal formulation provided better absorption into the brain following intranasal administration compared to the free drug. This might also be due to direct transfer of the drug from nasal mucosa to the brain via the olfactory route [47].

The intranasal administration of quercetin liposome to rats provided opportunity for the drug to enter the central nervous system and act on the central nervous system to promote anxiolytic activity and cognitive enhancing effect with high efficiency [48]. The anxiolytic activity of oral quercetin liposomes was compared with intranasal quercetin liposomes, both routes showed anxiolytic and cognitive-enhancing effects. A lower dose and a faster rate were observed with intranasal quercetin liposomes when compared with oral quercetin liposomes. The intranasal quercetin liposome was thus considered as effective in the delivery of quercetin to the central nervous system [49].

Nasal administration of acyclovir mucoadhesive liposomes has been demonstrated to have good permeability characteristics with enhanced nasal penetration of acyclovir in comparison to free drug suspended in gel [50].

CONCLUSION

From the discussion it was found that liposomes are the promising carriers to deliver drugs beyond the BBB for the scrutiny of the central nervous system. Most of the potentially available drugs for CNS therapies are large hydrophilic molecules, e.g., peptides, proteins and oligonucleotides that do not cross the BBB. Among all the applications of liposomal technology, the development of a suitable liposomal carrier to encapsulate neuroactive compounds is very promising. The nasal route of administration will probably have great potential for the future development of these hydrophilic preparations and other drugs that otherwise should be administered parenterally in the treatment of neurodegenerative diseases.

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