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Chapter 6

Liposomes and Vesicular Systems for Nose-to-Brain Transport

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1. Introduction

1.1. Challenges of CNS Drug Delivery

The transport of therapeutic agents to the central nervous system (CNS) is one of the most difficult tasks in the modern pharmaceutical sciences and clinical medicine. Although there have been spectacular improvements in drug discovery and development, there is a drastic low conversion of promising neurotherapeutic candidates into effective treatment due to their inability to effectively deliver these molecules across biological barriers to the location of action in the brain [1,2]. Neurological disorders such as Alzheimer disease, Parkinson disease, multiple sclerosis, brain tumors, epilepsy, stroke, and other psychiatric disorders, pose a tremendous socioeconomic burden to health care systems throughout the world [3]. World Health Organization approximates that 6.3% of the world disease burden is attributed to neurological disorders and that the figure will increase significantly due to the ageing populations [4]. However, even though an enormous amount of research has been conducted, and considerable resources have been allocated to the development of neuro pharmaceuticals, the therapeutic choice in most of these devastating conditions has been a huge disappointment. The major hurdle has been to overcome. Cle does not always pose a barrier to the development of CNS drugs; the difficulty is not always how to get this agent to its intended target within the brain at therapeutically significant concentrations [5]. Traditional pathways of drugs administration such as oral, intravenous, intramuscular, and subcutaneous all pose severe constraints when administering drugs to the therapeutic target in the CNS. The drugs taken orally have to survive the poor GI conditions, not undergo excessive first-pass hepatic metabolism, get sufficient systemic absorption, and then face the blood-brain barrier [6]. Parenteral routes circumvent gastrointestinal and hepatic obstacles, but must also overcome the extremely limiting nature of the blood-brain barrier. Moreover, most promising routes circumvent gastrointestinal and hepatic barriers yet still have to struggle with such a limiting nature of the blood-brain barrier. Neurotherapeutic drugs, especially biologics, including proteins, peptides, antibodies, and nucleic acids, are poorly absorbed orally, rapidly degraded by the system, and cannot cross cellular barriers, making the orthodox methods of delivery virtually ineffective [7]. Even in small molecules that may theoretically traverse the blood-brain barrier, selectivity, off-target effects and systemic toxicity often become limiting drug delivery in practice [8].

1.2. Blood-Brain Barrier: Structure and Limitations

The blood-brain interface is a highly specialized and exceptionally selective barrier between the systemic circulation and the brain parenchyma, originally described in the first half of the twentieth century, which has critically important protective roles, including homeostasis of the CNS, regulation of entry of nutrients and signaling molecules, and isolation of potentially neurotoxic substances and pathogens [9, 10]. Structure it is a unique physiological interface with both critical protective roles: maintaining CNS homeostasis, regulation of entry of nutrients and signaling molecules, naturally, blood-brain barrier is a special endothelial cells of the brain capillaries that are significantly dissimilar to peripheral endothelium. The existence of a large quantity of tight junctions created by transmembrane proteins such as claudins, occluding, as well as junctional adhesion molecules characterizes such cells and practically excludes the possibility of paracellular transport pathways [11]. In contrast to peripheral capillaries where there are fenestrations and intercellular gaps where the passage of molecules is practically free, the brain capillary endothelial cells create a continuous, non-fenestrated barrier with electrical resistance [12]. Minimal pinocytic activity is expressed by the endothelial cells thereby limiting transcellular transport. The blood brain barrier is also lined with a number of efflux pumps, most notably, the P-glycoprotein and other members of the ATP-binding cassade (ABC) transporter family, which actively pump out a variety of substances directly into the bloodstream, thus preventing their concentration in the brain [13, 14]. This efflux system is also a secondary barrier to drug delivery, since many drug molecules are themselves substrates of the transporters also contains other cellular components which are helpful in its effect as a barrier and regulatory activity. Pericytes embedded into the basement membrane are structural support providers that are also involved in barrier regulation and astrocytic end-feet processes closely opposed to the endothelium release factors that stimulate and sustain barrier phenotypes [15]. In total, these elements form what is commonly

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known as the neurovascular unit a complex, dynamic mechanism that strictly controls the movement of molecules both between blood and brain. In perspective of drug delivery. Only a very limited number of molecules are allowed to enter the blood-brain barrier. Smaller lipophilic molecules whose molecular weights are less than 400-500 Daltons and whose physicochemical properties (most especially lipid solubility) suit via passive diffusion, though even these are restricted by efflux transporter [16]. Some vital nutrients are absorbed through designated carrier-mediated transport processes, whereas some larger molecules can use receptor-mediated transcytosis pathways [17]. But nearly all other therapeutic molecules such as 98% of small molecule drugs and virtually 100% of large molecule therapeutics do not reach therapeutically-relevant levels in the brain after systemic delivery [1]. It has significant implications on CNS drug development. Many drug candidates that have shown great efficacy in preclinical in vitro studies do not make the leap to in vivo therapeutic effects simply due to the inability to reach their target within the brain [18]. Even in cases where drugs actually gain some level of entry into the brain, the concentrations possibly may be too low to be therapeutically effective, or it may only be possible to achieve therapeutic concentrations of the brain by systemic exposures which cause unacceptable peripheral toxicity [19].

1.3. Alternative Routes for Brain Targeting

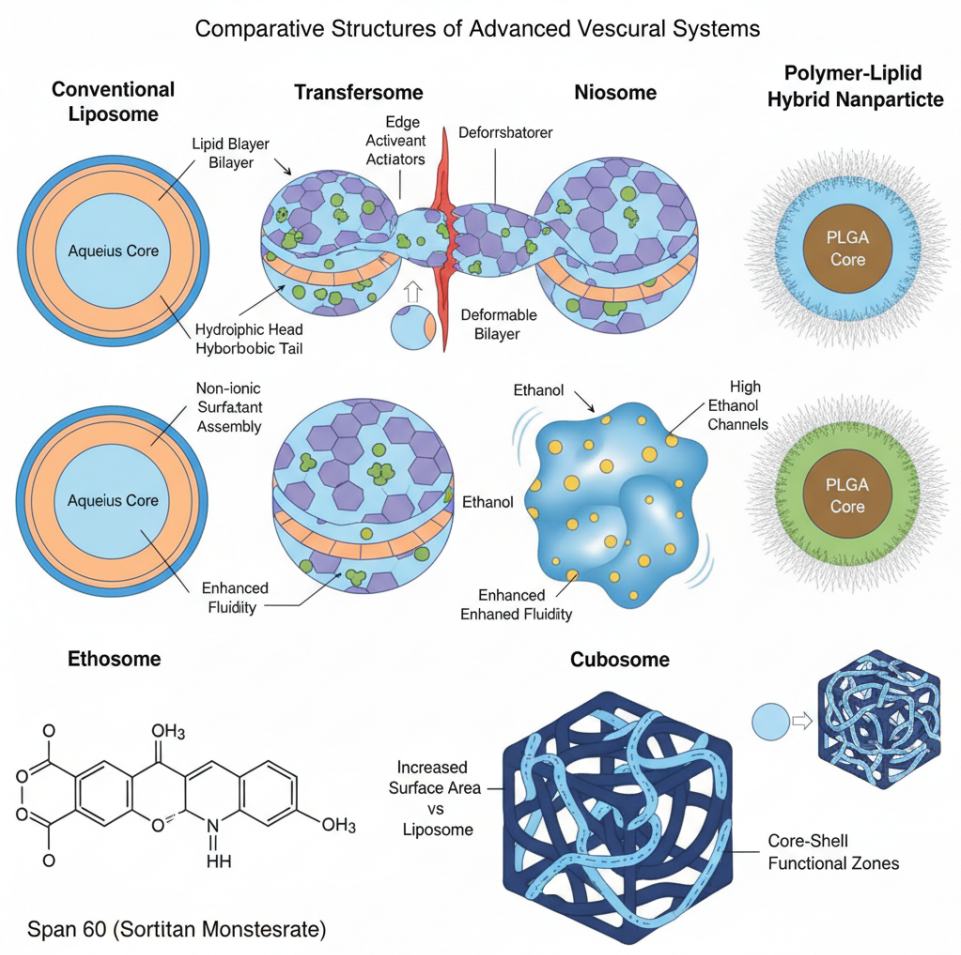

Figure 1: Comparative structure of advanced vascular systems

With such a high level of restrictions that is set by the blood-brain barrier, scientists have been trying to come up with alternative methods of improving brain drug delivery. These strategies can be classified into general groups as barrier disruption strategies, endogenous transport systems exploitation strategies and other anatomical pathways to avoid the barrier completely [20]. disruption Strategies: Osmotic opening the blood-brain barrier with hypertonic solutions e.g. mannitol has been considered in clinical practice, especially to deliver chemotherapeutic agents to brain tumor. This method temporarily destabilizes tight junctions, making it possible to cross paracellular drug [21]. But this technique is invasive, it involves the introduction of intra-arterial catheters, has a risk of neurotoxicity due to accidental access to blood-borne substances, and is only capable of temporary and non-selective opening of barriers [22]. Image-guided Focused ultrasound and microbubbles Focused ultrasound using microbubbles is a more recent and possibly safer barrier disruption technology, which allows localizing barrier disruption in a transient manner [23].

Exploitation of Endogenous Transport Systems: Strategies to hijack receptor-mediated transcytosis systems have been of interest. Transferrin receptor-targeted delivery systems, such as, are based on the natural role of the transferrin receptor in iron transport and are used to deliver drugs [24]. Equally, there is investigation on insulin receptor and the low-density lipoprotein receptor-related protein pathways. The Trojan horse approaches, in which therapeutic cargo has a conjugation to antibodies or peptides that cross by receptor-mediated transcytosis have progressed to clinical trials [25]. Nonetheless, such methods are associated with such limitations as lack of transport capacity, possible

disruption of normal receptor activity and immunogenicity. Inhibition of Efflux Transporters: Strategist block P-glycoprotein and other efflux transporters in a attempt to reduce brain endothelium drug extrusion. Although attractive conceptually, toxicity issues have inhibited clinical use of these transporters, because they have important protective roles, and by compensatory upregulation of other efflux systems [26].

Intracerebral Delivery: Injection into brain parenchyma or cerebrospinal fluid avoids using the blood-brain barrier altogether. The intrathecal and intracerebroventricular routes inject drugs into the cerebrospinal fluid, where they could diffuse into brain tissue [27]. Convection-enhanced delivery involves the continuous infusion with under positive pressure in order to obtain wider parenchymal distribution. Although these methods are potentially effective they are extremely invasive, involve serious risks such as infection and hemorrhage, and they generally demand special neurosurgical skills and equipment [28].

1.4. Rationale for Nose-to-Brain Delivery

Direct nose-to-brain drug delivery through the intranasal route has been of great interest as a non-invasive method of bypassing limitations of the blood-brain barrier. The rationale behind this is the fact that there are already established anatomical and physiological principles that show that there are direct relationships between the nasal cavity and the central nervous system [31, 32]. Of the upper nasal cavity has factory epithelium, which contains bipolar olfactory sensory neurons, the dendrites of which are in contact with the nasal lumen, detecting odorants, and their unmyelinated axons run through the cribriform directly to the olfactory bulb the only site where neurons are directly exposed to the outside environment and CNS tissue [33]. This unusual anatomy offers a direct route of drug transport between nasal cavity and the brain without passing through the blood-brain barrier either. Transport may be intracellular (through axonal transport within neurons) or extracellular (via bulk flow and diffusion along perineural and perivascular channels surrounding the olfactory nerve bundles) [34, 35]. The etrigeminal nerve that innervates a large part of the nasal respiratory epithelium on top of olfactory regions offers alternative neural routes of the brainstem and other parts of CNS [36]. The vascularized nasal mucosa is also highly vascularized, which also provides the possibility of systemic uptake, but to some extent reduces the benefit of avoiding the blood-brain barrier. The nose-to-brain route has a number of strong points, such as (1) non-invasive delivery improving patient compliance, (2) bypassing hepatic first-pass metabolism, (3) direct access to the CNS bypassing blood-brain barrier, (4) rapid action because of close proximity to the brain, (5) reduced systemic exposure and peripheral toxicity, and (6) ease of delivery to both small molecules and biologics which do not cross the blood-brain barrier [37, 38]. Nonetheless, there are a few strong points of also has problems, such as limited dose caused by small volume of the nasal cavity, fast mucociliary clearance, which shortens absorption time, inter-subject variation in nasal anatomy and physiology, which may cause for enzyme breakdown, and inability to address the small olfactory area where direct neural pathways are dominant [39, 40]. It is these challenges that have led to the emergence of new sophisticated formulation approaches, including lipid-based nanocarrier-based systems (liposomes) which can be used to maximize nose-to-brain drug delivery.

2. Anatomical and Physiological Foundations

2.1. Nasal Cavity Architecture

Structural Organization

The human nasal cavity is a complicated anatomical system that expands between the nostrils in front to the nasopharynx behind and a total of 12-14 cm in length with a total volume of 15-20 mL [4, 45]. Nares divided into two equal chambers by nasal septum with three nasal turbinate's (superior, middle, and inferior conchae) that protrude on the lateral walls forming four corresponding passages [26]. This complex structure has several physiological purposes such as air conditioning, humidifying, screening out particles, and smelling. The nasal this large area of the surface is covered by mucosa, which is about 150-180 cm^2 and in two functionally and histologically separate areas, the respiratory epithelial area and the olfactory epithelial area [27]. The large portion (about 95-97) of the nasal cavity surface is covered with a type of pseudostratified columnar ciliated epithelium interspersed with goblet cells producing mucus; this is termed the respiratory region [28]. This area is very vascular and has a dense capillary network of fenestrated capillaries directly underneath the epithelial layer and therefore makes this an excellent site of systemic drug absorption but not direct brain targeting [7]. It has its source mainly in the branches of internal and external carotid arteries forming a rich vascular plexus allowing quick absorption of drugs and aiding in the body in temperature regulation of the inspired air [29]. Venous drainage usage entails several courses such as connection to the cavernous sinu plexus, and pterygoid plexus, which might further offer other routes to the distribution of drugs to the cranial structures [10].

Olfactory Region Characteristics

The olfactory area is found in the superior-posterior area of the nasal cavity which incorporates the superior turbinate, the roof of the nasal cavity underneath the cribriform plate, and the upper end of the nasal septum which is the most important entry point of a nose-to-brain drug delivery [8, 21]. Although this specialized area comprises 3-5 percent of the overall nasal surface area in humans (around 2-10 cm^2), it has special anatomical characteristics, which allow the direct access of the CNS [12]. A pseudostratified columnar neuroepithelium that is approximately 60 mm thick and contains three major cell types: olfactory sensory neurons (bipolar neurons that detect odor), supporting sustentacular cells and basal cells (which are also the progenitors of neuronal replacement) [23, 23]. In comparison to the respiratory epithelium, the olfactory region has a yellowish-brown coloration because of the cytochrome pigments of olfactory neurons present in the olfactory area. Most notably, the olfactory epithelium contains real bipolar neurons that extend to the surface of the epithelium and have specialized cilia that detect odorant molecules, but the axons (unmyelinated 0.1-0.2 mm diameter) of these neurons (olfactory neurons) bundle up to form the olfactory nerve (cranial nerve I) [24]. Their unmyelinated axons (0.1-0.2 mm diameters) pass through the cribriform plate through about 20- mm is lined by a fine sheet of mucus (in 10-40 mm thick) which is produced by the glands of Bowman in the underlying lamina propria [15]. Odorants are detected by this mucus layer which also forms the initial point of drug delivery. The perineuronal and perivascular spaces that enclose olfactory nerve bundles and blood vessels form the possible pathways of bulk flow of fluids and dissolved

substances of the nasal cavity to the brain [24, 36].

2.2. Neural Pathways from Nose to Brain

Olfactory Pathway

Intracellular Transport: Olfactory neurons can internalize drugs or nanocarriers by different forms such as endocytosis, receptor-mediated uptake, or by direct membrane penetration [27]. Substances may be taxed by axonal transport once internalized in anterograde (towards the olfactory bulb via kinesin motor proteins) or retrograde (towards the cell body via dynein motors) along networks of microtubules located within axons [28]. The rate of axonal transport will depend on the mechanism; fast axonal transport occurs at about 200-400 mm/day, whereas slow axonal transport occurs at 0.1-3 mm/day [39]. Drugs may travel to the related brain centers such as olfactory cortex, hippocampus, amygdala and other limbic systems via synaptic connections as a result of the olfactory bulb.

Extracellular Transport: The extracellular pathway is a bulk flow and diffusion across the perineural spaces (channels between the bundles of axons and their surrounding unsheathing cells) and perivascular spaces around blood vessels [34, 20]. These fluid-filled pathways offer a more immediate and possibly quicker pathway than axonal conveyance, as things flow along concentration gradients and are possibly aided by cerebral spinal fluid contractions and alterations in respiratory pressure [21]. Large molecules and nanoparticles which cannot be carried into the cell via intracellular uptake are transportable via the perineural pathway, and thus it is of particular interest to liposomal delivery systems [26] transport. The speed of the action via the olfactory route is comparatively fast and some of the studies have revealed the appearance of drugs in the brain tissue within 5-30 minutes after intranasal delivery of the drugs [22]. The main distribution center is the olfactory bulb where the drugs may be dispersed to other parts of the brain in neural connections or diffusion through interstitial fluid and cerebrospinal fluid pathways.

Trigeminal Pathway

There is an alternative neural route that for nose-to-brain through the trigeminal nerve (cranial nerve V) [36, 13]. Their axon, in contrast to that of the olfactory nerve that is pure sensory and conveying information of olfaction, projects somatosensory information of the nasal mucosa, which perceives irritants, temperature, and mechanical stimuli. The trigeminal nerve has its thalamic (V1) and maxillary (V2) divisions that broadly serve the nasal respiratory epithelium besides some parts of the olfactory region [24]. The nerve endings invade the epithelium, which might permit drug absorption like olfactory neurons. The trigeminal nerve enters the brainstem (pons and medulla) and offers access to CNS regions that have no direct connection with the olfactory system [12, 36]. Trigeminal pathways probably take place by accompanying intracellular and extracellular means as olfactory transport. Trigeminal pathway could be of particular relevance to the drugs given to the anterior and middle nasal cavity where the olfactory epithelium is sparse or non-existent [15]. Also, the communications between trigeminal nuclei and other parts of the brain as thalamus, hypothalamus, and cerebral cortex could enable more extensive dissemination of drugs throughout the CNS [33].

Vascular and Lymphatic Routes

Vascular Route: The respiratory epithelium is highly vascularized and allows rapid systemic absorption of drugs, which can in turn circulate and find their way to the brain via traditional blood-brain barrier routes [13]. Although this route has the same BBB limitation as other pathways of systemic drug delivery, the route also adds to the overall pharmacological activity and could be important to drugs with limited BBB permeability [27]. The large nasal capillary system interrelates with intracranial venous systems, which may be more direct access to the cranial area than peripheral delivery [30].

Lymphatic Route: New evidence suggests that the nasal mucosa has lymphatic drainage pathways which can lead to cervical lymph nodes and possibly to newly discovered meningeal lymphatic vessels which drain cerebrospinal fluid [14, 28]. These pathways can be used to deliver drugs and nanoparticles into perivascular and peri meningeal spaces, and provide an indirect route to brain parenchyma [19]. Lymphatic role in nose-to-brain delivery is still being actively pursued and more and more may play an important role than we previously appreciated [30].

2.3. Physiological Barriers

Mucus Layer and Mucociliary Clearance

The nasal mucus layer is the initial and one of the major obstacles to successful intranasal drug delivery [15, 11]. This layer of viscoelastic gel, about 515 mm thick in the respiratory area and 1040 mm in the olfactory area consists of about 95% water with the rest of the constituents being mucin glycoproteins (243 percent), lipids, proteins, enzymes, antibodies and cell debris [12]. Mucins 1. submucosal glands goblet cells and submucosal secretions in particular, secret secretions of the high-molecular-weight glycoproteins (0.5-20 million Da) MUC5AC and MUC5B form a size-selective barrier particles and molecules smaller than the mesh pore size (usually 100-500 nm) may pass, whereas larger ones are trapped [33]. Mucus has a net negative charge as a result of sulfate and sialic acid on mucin glycoproteins to form an electrostatic interaction between the mucin and positively charged molecules or particles, thereby slowing down their diffusion [25]. Mucus has the is clastic properties that physically impede the movement of particles and formulations must be developed to either traverse or stick to the mucus layer. It mediated by a synchronized lashing of cilia with a frequency of 12-15 Hz, the layer of mucus is constantly swept towards the nasopharynx at a rate of about 5-6 mm/minute [16]. This defense mechanism which is vital in the removal of pathogens and particulates poses a significant problem to drug delivery by reducing the duration of time in which drugs can be absorbed to about 15-30 minutes prior to clearance [39]. Formulations should either be rapid absorbing within this window, have an extended residence by adhesion to the mucus, or

Figure 1: Anatonical Pathways for Nose-to-Brain Drug Delivery

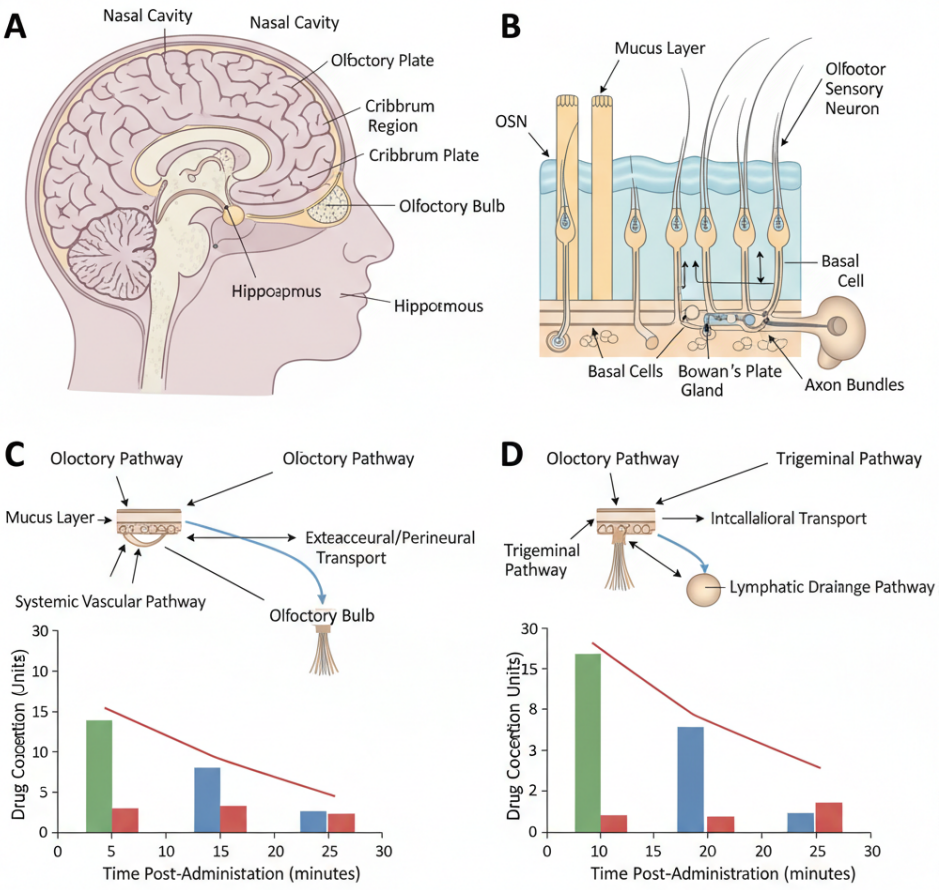

Figure 2: Anatomical Pathway for nose to Braine Drug delivery

have a rapid permeation into the underlying epithelium via the mucus.

Enzymatic Degradation

Nasal cavity is full of enzymes which have the potential to degrade therapeutic molecules, especially proteins, and peptides as well as nucleic acids [17, 27]. A variety of peptidases are found in the nasal secretions and in epithelial cells and can present a significant challenge to biologics stability [38]. Although the hromeP450 enzymes are not as abundant as those in liver or intestine, they have the ability to metabolize some small molecules [19]. Also, esterase's, proteins, and other degradation enzymes are added to the enzymatic barrier. Another reason why this region should be targeted in drug delivery is that the olfactory region has a little lower enzymatic activity than the respiratory epithelium [20]. On Liposomal or other Nanocarrier protection against enzymatic degradation protection via physical shielding of drug molecules of enzyme contact until cellular uptake takes place [28, 31]. This is important especially when it comes to peptide and protein therapeutics which would otherwise be destroyed so easily in the nasal site.

pH and Temperature Considerations

Normal values of the nasal pH lie between 5.5 and 6.5 but pathologic conditions like rhinitis or sinusitis could change these values [18, 22]. This is a slightly acidic environment that may have an impact on drug stability, especially on pH sensitive molecules, on the ionization state of drugs and excipients, which can influence solubility, permeability and mucus interaction [13]. The nasal cavity temperature is kept at around 30-34degC which is a little bit less than core body temperature [34]. This temperature influences drug dissolution, degradation kinetics, fluidity of membrane, and the physical state of lipid-based formulations. Liposomal formulations should be developed with phase transition temperatures that are favorable in nasal cavity to guarantee optimum stability and drug release properties [25]. Also, physiological changes such as circadian rhythms, disease conditions, age and environmental conditions may affect nasal pH, temperature, mucus composition, and clearance rates, which may be critical to the development of strong liposomal formulations in nose-to-brain delivery.

Table 1: Anatomical and Physiological Foundations of Nose-to-Brain Delivery

Aspect	Key Features	Dimensions/ Characteristics	Relevance for Drug Delivery
NASAL CAVITY ARCHITECTURE			
Overall Structure	Divided by nasal septum; Contains 3 turbinates per side; Creates 4 meati passages	Length: 12-14 cm; Volume: 15-20 mL; Surface area: 150-180 cm^2	Large surface area for absorption; Limited volume restricts dose
Respiratory Epithelium	Pseudostratified columnar ciliated; Contains goblet cells; Highly vascularized; Fenestrated capillaries	Covers approximately 95-97% of nasal cavity; Rich blood supply from carotid arteries	Excellent for systemic absorption; Not optimal for direct brain targeting
Olfactory Epithelium	Specialized neuroepithelium; Contains bipolar neurons; Yellowish-brown pigmentation; Located in superior-posterior region	Surface area: 2-10 cm^2 (3-5% of total); Thickness: approximately 60 μm; Mucus layer: 10-40 μm	Critical gateway for direct brain delivery; Direct CNS connection without BBB
Olfactory Cell Types	Olfactory sensory neurons; Sustentacular (support) cells; Basal (progenitor) cells	Bipolar neurons with cilia; Axon diameter: 0.1-0.2 μm; 20-30 nerve bundles through cribriform plate	Neurons provide direct pathway to brain; Perineuronal spaces allow extracellular transport
NEURAL PATHWAYS TO BRAIN			
Olfactory Pathway - Intracellular Route	Endocytic uptake by neurons; Axonal transport (anterograde/retrogra de); Kinesin and dynein motors	Fast transport: 200-400 mm/day; Slow transport: 0.1-3 mm/day; Drug appears in brain: 5-30 min	Suitable for small molecules and nanocarriers; Direct neuronal delivery to olfactory bulb
Olfactory - Pathway Extracellular Route	Bulk flow through perineuronal spaces; Diffusion along concentration gradients; Facilitated by CSF pulsations	Channels between axon bundles; Perivascular spaces around vessels; Faster than intracellular for some drugs	Preferred route for liposomes; Accommodates larger particles
Olfactory - Pathway Distribution	Primary: Olfactory bulb; Secondary: Limbic structures	Hippocampus; Amygdala; Olfactory cortex	Access to regions affected in AD and PD; Limited to connected areas
Trigeminal Pathway - Innervation	Ophthalmic (V1) division; Maxillary (V2) division; Terminals penetrate epithelium	Innervates respiratory and olfactory regions; Projects to brainstem (pons, medulla)	Alternative pathway when olfactory limited; Access to different brain regions
Trigeminal Pathway - Transport	Similar to olfactory (intra/extracellular); Connections to thalamus and hypothalamus	Wider CNS distribution potential	Important for anterior/middle nasal delivery
Vascular Route	Fenestrated capillaries; Systemic absorption; Connections to intracranial vessels	Dense vascular plexus; Rapid absorption; Links to cavernous sinus	Contributes to systemic exposure; Still faces BBB restrictions
Lymphatic Route	Cervical lymph node drainage; Meningeal lymphatic connections; Perivascular/perimeni ngeal spaces	Emerging area of research; Connection to recently discovered meningeal lymphatics	May provide indirect brain access; Role still being elucidated
PHYSIOLOGICAL BARRIERS			
Mucus Layer - Composition	Water: approximately 95%; Mucins (MUC5AC, MUC5B): 2-3%; Lipids, proteins, enzymes; Antibodies and cellular debris	Thickness (respiratory): 5-15 μm; Thickness (olfactory): 10-40 μm; Mucin MW: 0.5-20 million Da	Primary physical barrier; Size-selective mesh traps particles; Electrostatic interactions affect penetration

Table 1 continuous

Aspect	Key Features	Dimensions/ Characteristics	Relevance for Drug Delivery
Mucus Layer - Mesh Properties	Pore size: 100-500 nm (variable); Net negative charge (sialic acid, sulfate); Viscoelastic gel network	pH-dependent properties; Rheological resistance to particle movement	Particles below 100 nm penetrate better; Neutral or PEGylated surfaces preferred
Mucociliary Clearance	Coordinated ciliary beating; Moves mucus toward nasopharynx; Protective defense mechanism	Ciliary beat frequency: 12-15 Hz; Clearance rate: 5-6 mm/min; Absorption window: 15-30 min	Major limitation on residence time; Requires rapid absorption or mucoadhesion
Enzymatic Degradation - Enzyme Types	Peptidases (amino-, carboxy-, endo-); Cytochrome P450; Esterases and proteases	Higher in respiratory vs. olfactory region; Present in secretions and cells	Critical for biologics stability; Liposomal encapsulation provides protection
Enzymatic Degradation - Regional Variation	Lower enzymatic activity in olfactory region	Favors olfactory targeting for peptides and proteins	Additional rationale for olfactory delivery
pH Conditions	Slightly acidic environment; Altered in pathological states	Normal range: 5.5-6.5; Affects ionization and stability	Formulations must be pH-compatible; Buffering may be needed
Temperature Conditions	Cooler than core body temperature; Affects drug and formulation properties	Typical range: 30-34°C; Influences lipid phase transitions	Liposomes must be stable at nasal temperature; Phase transition considerations important
Physiological Variability	Circadian rhythms; Disease states; Age and environmental factors	Variable mucus composition; Altered clearance rates; pH fluctuations	Source of inter/intra-individual variability; Robust formulations needed

3. Liposomes: Fundamentals and Classification

3.1. Historical Perspective and Definition

Liposomes represent one of the greatest inventions in drug delivery technology because they were accidentally discovered by the British hematologist, Alec Bangham, in1965 [19]. As Bangham studied phospholipid dispersions, using electron microscopy, he discovered that closed structures formed spontaneously in the form of spherical vesicles of one or more concentric layers of phospholipid bi-layers around an aqueous compartment [37]. The phrase liposome was coined by combining the words lipos (fat) and soma (body) in Greek, which were used to describe these spherical vesicles constituted by one or more concentric phospholipid bilayers surrounding aqueous compartments [18]. Lip are self-assembled colloidal particles made of amphiphilic lipid molecules in form of bilayer membranes enclosing internal aqueous spaces [20, 39]. Ever since their discovery, liposomes have grown out of provocative lab curiosities to become commercially approved nanomedical vectors, with numerous liposomal formulations currently available in the market to treat cancer, fungal infection and as analgesics [20].

3.2. Structure and Self-Assembly

Liposomal fundamental structure is determined by the amphiphilicity of phospholipids molecules which have hydrophilic polar head and two hydrophobic fatty acid tail chains [12]. In aqueous media, these molecules spontaneously form structures to limit the undesirable thermodynamic interactions between the hydrophobic areas and the water a process that is powered by the hydrophobic effect [23]. lf-assembly leads to bilayer structures in which hydrophobic tails are concentrated into the interior of the membrane, which is water-shielded, and hydrophilic headgroups are exposed to water on the outer and inner surfaces [24]. The bilayer is capable of closing and creating sealed vesicular structures that eliminate exposed hydrophobic edges and are thermodynamically stable [21]. The resultant liposomes vary in sophistication between simple single-bilayer uniflagellar vesicles and complicated multilamellar structures of onion-like arrangements [21]. It has a length of 4-5 nm, which varies by the composition of lipids and length of hydrocarbon chains [25]. The core diameter of the aqueous is tensor nanometers to a few micrometers, which defines the drug loading capacity of the vesicle, and biological behavior [96]. The biomimetic structure, which is highly similar to biological cell membranes, is able to provide high biocompatibility, and is able to interact with biological membranes through fusion, endocytosis, and lipid exchange mechanisms [30, 37].

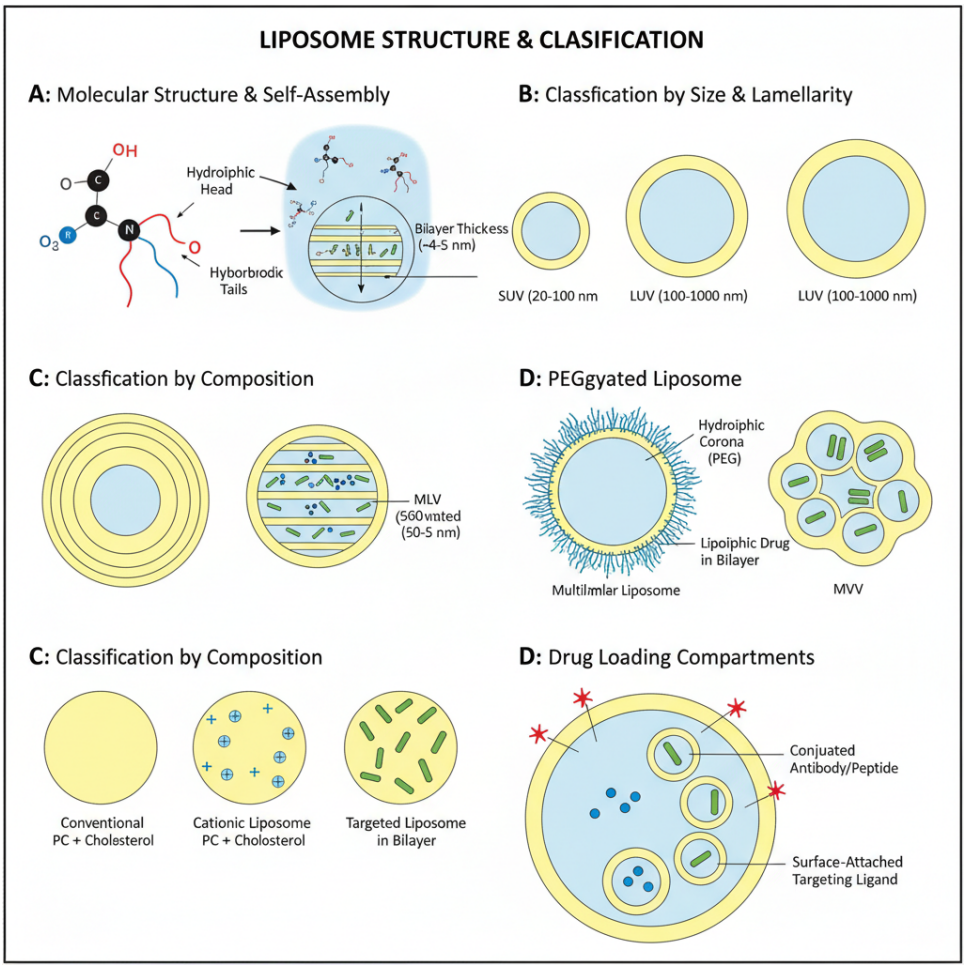

Figure 3: Liposomes Structure and Classification

3.3. Key Components and Their Roles

Phospholipids

Liposomes are structurally built on phospholipids and are selected depending on the fatty acid chain length, level of saturation, and head group chemistry [23,11]. The most commonly utilized phosphatidylcholine (PC) is that of egg or soybean source with good biocompatibility, proper phase transition temperature and commercial availability [12]. Phosphatidylethanolamine (PE) can offer greater membrane stability and tumorgenicity [13]. Phosphatidylglycerol (PG) and phosphatidylserine (PS) provide negative charges, and sphingomyelin provides increased stability but decreased permeability [14]. Saturated phospholipids (e.g., DSPC, DPPC) are more stable but have higher phase transition temperatures, whereas unsaturated ones (e.g., DOPC, egg PC) are able to confer membrane fluidity at physiological temperatures but can be destroyed by oxidative degradation [15]. In nasal preparations, the phospholipids used must contain lower transition temperature than that of the nasal cavity (30-34degC) this way, they are guaranteed the correct fluidity [5].

Cholesterol

The presence of cholesterol, which is normally added at 30-50 mol, has a significant effect on the liposomal properties [24, 16]. It binds between phospholipid molecules, sealing the gaps and decreasing permeability of the membrane to water-soluble molecules, and thus eliminating the leakage of drugs into the bloodstream in time [17]. The sharp phase transition is removed by cholesterol, which forms a more uniform state of the membrane over the ranges of temperatures [18]. It also minimizes mechanical instability, hence minimizing the exposure to disturbance by plasma proteins and biological membranes [19]. But too much cholesterol may lead to a decrease in the fluidity of membranes and prevent fusion with target cells [10].

Surface Modifiers

Surface modification modifies the behavior of liposomes to particular delivery difficulties [11]. PEG constitutes steric stabilization with molecular weights between 2000-5000 Da that inhibits aggregation and protein adsorption and promotes mucus penetration [25, 10]. Chitosan is a cationic polysaccharide, which offers mucoadhesive properties due to the electrostatic binding with negatively charged mucins, which increases the nasal residence time [10, 12]. Hyaluronic acid can also be used as a cohesion and targeting agent by recognizing CD [24] receptors [12]. The surface modifier depends on the type of mucus penetration or cohesion required in a given application [7].

Targeting Ligands

Conjugation of targeting ligands facilitates active delivery to target cells or tissues [26,12]. Transferrin binds to brain endothelial cell transferrin receptors that are overexpressed on some brain neurons in addition to brain endothelial cells [33]. Lactoferrin identifies lactoferrin receptors located on olfactory epithelium and brain endothelium [12]. Cell-penetrating peptides (TAT, penetrating) are used to increase cellular internalization by membrane interaction and receptor-mediated pathways [4]. The antibodies to particular neuronal markers or disease-related proteins offer high levels of specific targeting [16]. PEG spacers are typically used to conjugate ligands with terminal functional groups (maleimide, NHS ester) to retain biological activity and achieve stable covalent conjugation [17].

4. Rationale for Liposomal Nose-to-Brain Delivery

4.1. Advantages Over Conventional Formulations

The use of liposomal technology in the delivery of intranasal to the brain would have significant benefits compared to the traditional nasal solutions, suspensions, or powders [28, 18]. Besides, freely suspended drugs in solution are completely subjected to enzyme destruction, mucus trapping, as well as, dilution by nasal secretions, and bioavailability is greatly reduced [17, 7]. Liposomal The basic principle of encapsulation changes the kinetics and biodistribution of drugs. The lipid vesicles are protection carriers which protect the therapeutic molecules against the harsh environment of the nose and enable them to pass through biological barriers [1, 19]. Comparisons between liposomal and free drug formulations have always been found to result in 2-5-fold increases in brain bioavailability of drugs encapsulated in appropriately designed liposomes [13]. This increased delivery corresponds to less dosage required, reduced systemic exposure and better indices of therapy. Liposomal systems allow the delivery of a wide range of therapeutic agents of small hydrophobic molecules to large hydrophilic biologics using a single platform technology [90, 13]. Hydrophilic drugs are trapped in the aqueous core; lipophilic drugs are trapped in the bilayer and amphiphilic drugs are trapped in both of the compartments, which offer flexibility not available to conventional formulations [11]. Further, liposomes can be be surface-functionalized with targeting ligands, mucoadhesive polymers or penetration enhancers to overcome certain delivery obstacles and the development of truly multifunctional delivery systems [21, 13].

4.2. Overcoming Nasal Barriers

Mucus Penetration Strategy: PEG coated near-neutral surface charge small liposomes (less than 100 nm) can penetrate the mucus mesh network [27, 10]. The hydrophilic PEG chain forms a stealth surface that reduces adhesive contacts with mucin glycoproteins enabling complete diffusion to the underlying epithelium [38]. Particle-tracking micro rheology has shown that Pegylated liposomes less than 100 nm can diffuse through nasal mucus at a rate comparable to that of their theoretical maximum in water which effectively circumvents the mucus barrier [16].

Mucoadhesion Strategy: Otherwise, cationic polymers such as chitosan-coated larger liposomes have a high degree of mucoadhesive characteristic due to electrostatic interactions with negatively charged mucins [4, 12]. This sticking effect extends stay time in the nasal cavity and increases the absorption period by a factor of 30 minutes to a number of hours and allows longer release of drugs to happen [17]. Chitosan also promotes permeability through temporary opening of tight junctions between epithelia cells, promoting paracellular drug transport [4, 13]. Ucus interaction, liposomes breach epithelial barriers by using various mechanisms. Their lipophilic character facilitates close contact with cell membranes which may result in membrane fusion that directly deposits drug cargo into the cytoplasm [2, 7]. Although not fully fused, the liposomes temporarily fluidize and destabilize the membrane structure elevating the permeability of the encapsulated drugs [30]. Moreover, the transcellular transport is easily internalized via several endocytic routes including clathrinid-mediated, caveolin-mediated, and micropinocytosis pathways [3, 19]. Lipid bilayer has been used to protect sensitive therapeutics against enzymatic degradation which otherwise would cause a rapid inactivation of proteins, peptides and nucleic acids in the nasal milieu [28, 14]. This is especially important to biologics which are promising neurotherapeutics but horrifyingly unstable when delivered as free molecules [7].

4.3. Enhanced Drug Loading and Protection

An outstanding drug loading efficiency are attained by liposomal systems utilizing a combination of mechanisms depending upon drug physicochemical properties [14]. In the case of hydrophilic molecules, passive loading in the formation of vesicles is commonly approximately 5-30% encapsulation efficiency, whereas active loading in using transmembrane gradients can be over 95% efficient [12, 13]. It has been shown to load dopamine, doxorubicin among other drugs containing amine with almost complete encapsulation using the ammonium sulfate gradient method, e.g., [14]. Codrugs are removed into the bilayer, and they are frequently loaded with efficiencies more than 80% because of attractive lipid-drug interactions [14]. The high loading offered by the incorporation of drugs into the bilayer is also accompanied by the kinetics of release, where long-term release is observed between hours and days, depending on the lipid composition [13, 14]. This sustained release has the ability to sustain therapeutic levels in the brain following a single instillation in the nose, which improves patient compliance to chronic neurological conditions. The importance of the process of liposomal encapsulation cannot be overestimated, especially when it comes to biologics [14]. Brain-derived neurotrophic factor, nerve growth factor and other neurotrophic proteins are quickly broken down binasal peptidases when given as isolated molecules, and their half-lives are in the order of minutes [148]. Hours of stability is provided with liposomal encapsulation, maintaining therapeutic activity until cellular uptake is made [19]. Likewise, gene therapy vectors such as plasmid DNA and siRNA have the advantage of liposomal protection against nuclease degradation and increased colliers' delivery [15]. Lipid bilayer has the same advantage as well. Resists the degradation, oxidation, and aggregation caused by pH changes which affect the stability of drugs [15]. This shield is especially useful in the changing nasal environment when the pH is not constant (5.5- 6.5) and the activity of enzyme varies with disease conditions [18, 22].

4.4. Targeted and Sustained Delivery Potential

Surface of liposomes represents an excellent surface to conjugate targeting ligands that allow active delivery to target regions of the brain or cell type [26, 12]. Transferrin-conjugated liposomes use the transcytosis of transferrin receptor, which has preferred accumulation in high receptor expressing regions of the brain such as the olfactory bulb, hippocampus, and cortex [33, 34]. The rodent models' studies have indicated that there are 3-4-fold rises in the drug concentrations of the brain when comparisons are made between targeted and non-targeted liposomes when intranasally administered [15]. Conjugation attaches to lactoferrin receptors which are inherently present on olfactory epithelium, and may increase initial absorption at the absorption point preceding subsequent brain delivery [15]. Wheat germ agglutinin interacts with the N-acetylglucosamine residues that are highly expressed in the olfactory region and offer another targeting approach [15]. Here cell-penetrating peptide such as TAT and penetratin have been shown to increase neuronal uptake, enhance intracellular delivery, and potentially axonal delivery to deep brain regions [2, 15]. Sustained release, targeting is another important benefit [18]. Modulating lipid composition especially the cholesterol level and saturation of phospholipids drug release can be adjusted between rapid (minutes to hours) and protracted (days to weeks) by appropriate modulation [14, 19]. This long-term delivery presents therapeutic concentrations in the brain and additionally lowers dosing frequency which is most useful in chronic neurodegenerative diseases that need sustained neuroprotection [9]. Stimuli-responsively. Some are a new frontier, which use lipids or polymers that can react to particular stimuli such as changes in pH or temperature, or enzymatic activity typical of disease conditions [11]. The stability of these "smart liposomes is maintained during administration, but quickly induces the cargo release when exposed to pathological micro environments of the brain, such as the acidic environment of ischemic stroke or the inflammatory products of neurodegeneration [12].

4.5. Biocompatibility and Safety Aspects

The biocompatibility of liposomes is in part due to their nature or nature-identical phospholipids and cholesterol components that are already found in biological membranes [20, 13]. This is structural similarity to cell membranes which reduce foreign body recognition and inflammatory reactions that haunt most synthetic nanoparticle carriers [14]. Phospholipids can be broken down via standard lipid pathways and the products of breakdown are either degraded into lipid pools within the cell or they are transported out of the cell via well-known physiological processes [15]. *In vitro* cytotoxicity experiments with nasal epithelial cells, olfactory neuronal cells and brain-derived cell lines have shown that liposomes containing the right formula have very low toxicity at therapeutic doses [16,19]. Neutral or slightly anionic liposomes are generally safe in vivo, despite the fact that some surfactants or cationic polymers can result in the disruption and death of membranes [18]. In vivo safety rodent studies have demonstrated that intranasal liposomal formulations are not associated with significant nasal irritation, ciliotoxicity or histopathological effects at therapeutic doses [19, 22]. Extensive chronic toxicity studies of several months have not demonstrated any accumulation of lipid components in nasal tissue or brain with the use of intranasal liposomal formulations [11]. Notably, olfactory performance is not impaired after repeated liposomal injection, which shows that the olfactory epithelium and neurons are not impaired negatively [12]. moments must be selected carefully to make them safe. Although cationic lipids increase cellular uptake, they may be dose-dependently toxic and need to be used prudently [43, 18]. PEGylation is mostly well-tolerated, but it can induce the so-called accelerated blood clearance effects or a few cases of allergic reactions in sensitized people [13]. Preservatives, buffers and other excipients should be chosen as nasally acceptable ingredients with pre-existing safety profiles [14]. The accumulating preclinical s The availability of safety data and availability of clinically approved liposomal formulations of other routes should give confidence in the safety profile of liposomal nose-to-brain delivery systems, but strict clinical evaluation is necessary of each specific formulation [91, 15].

Table 2: Rationale for Liposomal Nose-to-Brain Delivery

Category	Challenge	Liposomal Solution	Key Benefits	Performance Data
ADVANTAGES OVER CONVENTIONAL FORMULATIONS				
Rapid clearance & degradation	Mucociliary clearance (15-30 min); Enzymatic degradation; Poor stability	Protective encapsulation; Mucoadhesion or penetration; Sustained release	Extended residence time; Protected cargo; Improved bioavailability	2-5 fold increase in brain levels vs. free drug
Limited drug versatility	Single formulation cannot carry diverse molecules	Dual-compartment structure (aqueous + lipid)	Encapsulates hydrophilic, lipophilic, and biologics	Universal platform for all drug classes
Non-selective distribution	Whole-body exposure; Off-target effects	Surface-conjugated targeting ligands	Brain-specific delivery; Reduced systemic exposure	3-4 fold higher brain accumulation with targeting
OVERCOMING NASAL BARRIERS				
Mucus barrier	Viscoelastic mucus traps particles; Negative charge; Size-selective mesh	Strategy 1: Small PEGylated liposomes (less than, 100 nm neutral charge) OR Str ategy 2: Chitosan-coated mucoadhesive liposomes	Penetration: Rapid diffusion to epithelium; Adhesion: Prolonged residence (hours vs. minutes)	PEGylated: 10-50× faster diffusion; Chitosan: 2-3× longer residence

Table 3: Rationale for Liposomal Nose-to-Brain Delivery

Category	Challenge	Liposomal Solution	Key Benefits	Performance Data
Epithelial impermeability	Tight junctions; Lipid membrane barrier; Limited uptake	Membrane fusion; Multiple endocytic pathways; Tight junction opening (chitosan)	Direct intracellular delivery; Enhanced transcellular transport; Paracellular pathway activation	Multiple mechanisms increase efficiency
Enzymatic degradation	Peptidases destroy proteins/pept ides in minutes	Physical shielding by lipid bilayer	Protected biologics maintain activity for hours	Protein half-life: minutes (free) → hours (liposomal)
DRUG LOADING & PROTECTION				
Low encapsulation efficiency	Passive loading: 5-30% for hydrophilic drugs	Active loading via gradients (ammonium sulfate, pH)	High efficiency encapsulation; Minimal drug waste	Encapsulation efficiency: greater than 95% (active); greater than 80% (lipophilic)
Drug instability	pH, oxidation, nucleases degrade sensitive molecules	Bilayer protection; Buffered core; Antioxidants	Stability across pH 5.5-6.5; Protection from enzymes and oxidation	Extended shelf-life; Maintained in vivo activity
Burst release	Rapid drug elimination; Need for frequent dosing	Controlled release from bilayer; Tunable composition	Sustained therapeutic levels; Reduced dosing frequency	Release kinetics: hours to days (composition-dependent)
TARGETED & SUSTAINED DELIVERY				
Poor brain specificity	Systemic distribution; BBB limitations	Transferrin, lactoferrin, WGA, CPP conjugation	Receptor-mediated brain targeting; Enhanced olfactory uptake	Region-specific accumulation (olfactory bulb, hippocampus)
Non-specific release	Drug released at wrong sites	Stimuli-responsive lipids (pH, temperature, enzyme)	Release triggered by disease microenviron ment	Selective release in ischemic/inflammatory/ tumor regions
BIOCOMPATIBI LITY & SAFETY				
Toxicity & immunogenicity	Foreign materials trigger immune response; Tissue damage	Natural phospholipids and cholesterol; Biodegradable components	Minimal immunogenicity; No tissue accumulation; Safe metabolism	No cytotoxicity, irritation, ciliotoxicity, or olfactory damage
Cationic toxicity concerns	High positive charges damage membranes	Limited cationic content (less than 20 mol%); Neutral alternatives	Reduced toxicity while maintaining uptake benefits	Dose-dependent safety; Optimal formulations safe
Regulatory uncertainty	No approved nasal brain delivery products	Existing approved liposomal drugs (Doxil, AmBisome)	Established regulatory pathway; Clinical precedent	Confidence in development and approval process

5. Advanced Vesicular Systems

5.1. Transfersomes and Elastic Vesicles

Transfer somes Represent a major improvement of the traditional liposomes, which are ultra-deformable, with a pore that can pass through pores substantially smaller in diameter than the liposomes [44, 16]. These elastic vesicles were developed in the 1990s and contain edge activators surfactants including Span 80, Tween 80 or sodium deoxycholate at 10-25% of total lipid content which destabilize the lipid bilayer and produce highly flexible membranes [17, 18]. With e activators, the membrane is made to enter into high curvature states, which permit drastic change in shape without rupturing the vesicles [19]. The deformability is measured by deformability index and transferosomes have large value of 5-10 times greater than the rigid liposomes [10]. In the case of nasal delivery, the flexibility can be translated to the advantage of mucus layers penetration and tight epithelial barrier passage [4, 11]. transpersonal rivastigmine and donepezil preparations of Alzheimer disease showed 3-5-fold rises in brain bioavailability relative to conventional liposomes after intranasal administration [12]. These vesicles are able to squeeze between cells and possibly travel along olfactory neural projections with greater efficiency than rigid structures due to the elastic nature [13]. Nonetheless, when surfactants are included, the risk of nasal irritation at high concentrations exists; this would have to be optimized [14].

5.2. Niosomes

The common surfactants are Span series (sorbitan esters) and Brij series (polyoxymethylene alkyl ethers), and Tween series (polysorbates), which are usually mixed with cholesterol with molar ratios of 1:1 to 7:3 [16, 17]. Vesicular systems have a number of benefits over phospholipid liposomes: it is less expensive because surfactants are cheap, more chemically stable (unsaturated chains are not oxidized), more stable at room temperature, and is easier to handle without cold chain logistics [7,18]. Noisome can be stored more than 12 months under refrigeration conditions than 3-6 months of liposomes in the conventional form [19]. Noisome formulations, brain delivery, noisome formulations have shown similar or better performance to liposomes when delivering a variety of neurotherapeutics [10]. A noisome version of sumatriptan to migraine reached brain concentrations 4.2 and 2.1 times higher than oral delivery and conventional nasal solution, respectively [11]. The antipsychotic effect of risperidone-impregnated intranasal noisome exhibited better efficaciousness in the treatment of animal models with low levels of catalepsy than the effects generated by orally administered risperidone, indicating better brain targeting with minimal extrapyramidal side effects [12]. Like liposomes, es of noisome can be decorated with charged surfactants (dicetyl phosphate to give the construct a negative charge, steary lamine to give the construct a positive charge) or coated with polymers such as chitosan or PEG [13, 14]. The synthetic surfactant composition, however, could provide a regulatory issue on the long-term biocompatibility aspect that natural phospholipids is not subjected to [15].

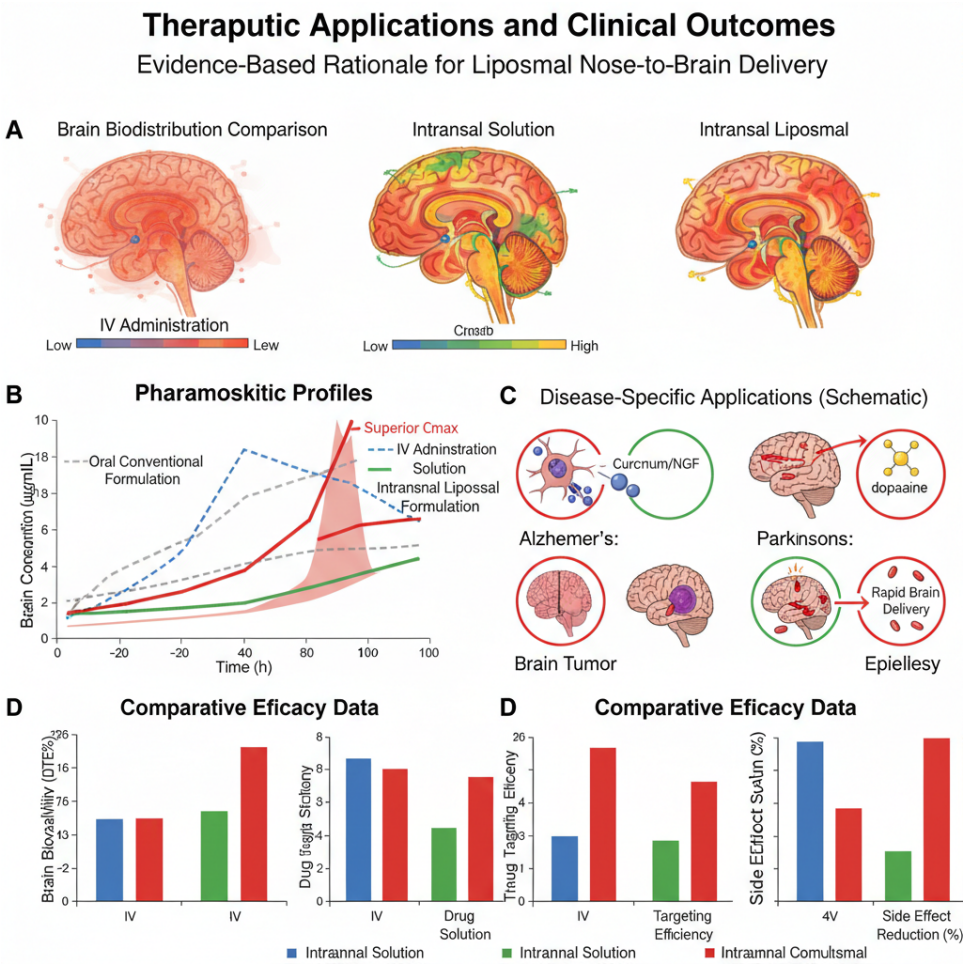

Figure 4: Liposomes Structure and Classification

5.3. Ethosomes and Transethosomes

Ethosomes are novel lipid vesicles with a large content of ethanol (20-45%w/w) giving them some distinct characteristics such as extreme softness, malleability and increased penetration [4, 16]. The ethanol has dual purposes: to increase the fluidity of the membranes forming highly deformable vesicles and to work as a permeability enhancer, by interacting and fluidizing biological membranes [17, 18]. Hethanol content allows ethosomes to attain vesicle sizes less than 100 nm with small size distributions without necessity of input methods of high energy [19]. Their easy passage through tissues due to softness and malleability helps to penetrate deep tissues and theethanol component increases the penetration of the drug across lipid barriers by 10-20 folds in comparison to using standard liposomes [20]. It has been shown that ethosomal formulations penetrate deep tissue 10-20 fold better than conventional liposomes, however, data remains limited in terms of nasal penetration [4, 21]. Combine has characteristics of transferosomes and ectosomes, whereupon a combination of edge activators and high ethanol are used to generate very deformable, penetration-promoting vesicles [22]. These hybrid systems have in principle the synergetic advantage of offering the clinical evidence is still at an early stage [23]. In delivery, the main issue when using ectosomes is the likelihood of nasal irritation caused by a high level of ethanol [24]. Although a 20-30% ethanol can be tolerated, when used above 35% it is often associated with burning sensations and irritation of the epithelium [25]. There is also the challenge of manufacturing and storage

ethanol presents, which is volatile and thus its properties change with evaporation [26]. Nevertheless, in spite of these constraints ethosomal tacrine in the case of Alzheimer disease performed well in preclinical trials, reaching therapeutic brain levels with less hepatotoxicity [27].

5.4. Cubosomes and Hexosomes

Cubosomes hexosomes are a paradigm shift of the classical vesicular geometry, consisting of complex internal liquid crystalline geometries containing surface areas that are enormous [28, 29]. Cubosomes are made of certain lipids (monooleinor phytantriol and so on) that present themselves into bicontinuous cubic phases containing complex three-dimensional networks of curved lipid bilayers with water channels permeating through the network [20, 21]. The internal cubic symmetry forms extraordinarily high interfacial spaces (400m2/g) which offer extraordinary loading capability of hydrophilic and lipophilic drugs [22]. The tortuosity arises due to the tortuous internal pathways which inherently offer diffusional barriers which serve as a natural means of sustained release without the need to participate extra modifications [23]. The hexosomes share identical characteristics that have hexagonal internal structure as opposed to cubic structures [24]. Cubosomes, which have several distinct benefits such as a high drug loading (in many cases, 2-3 times greater than liposomes), bioreserve properties because of their lipid content and days of release (versus hours), cubosomes are being researched as alternatives to liposomes [25, 26]. Cubosome-loaded olanzapine studies revealed that the controlled release of olanzapine was over 48 hours with sustained therapeutic brain levels after single dose of intranasal administration [27]. The major challenge was found to be over 48 hours. Gas contain complicated manufacture necessitating strict regulation of hydration and temperature, which could cause the inability to penetrate narrow biological obstacles owing to their comparatively big size (100-300 nm in smallest), and their lack of knowledge regarding their conduct inside biological settings [28, 29]. Besides, the monoolein component is biocompatible but, moreover, it enzymatically degrades faster than phospholipids [20].

5.5. Polymer-Lipid Hybrid Nanoparticles

Polymer-lipid hybrid nanoparticles combine strongly with the properties of polymeric nanoparticles (mechanical strength, controlled release, structural stability) and lipid systems (biocompatibility, membrane interaction, fusogenic properties) [21, 22]. Such systems are usually characterized by the presence of polymeric cores (PLGA, chitosan and other biodegradable polymers) in the center and lipid shells or lipid building blocks embedded within polymer matrices [23, 26]. Some component offers strong mechanical framework that is not susceptible to environmental influences, has a high degree of control over the rate of drug release through the degradation rate of polymers, and is topographically functionalized in a wide range of ways [25]. The lipid shell increases biocompatibility, decreases detection by immune cells, promotes cellular internalization by membrane fusion, and may be engineered with targeting ligands [26, 27]. Fortran's. Hybrid nanoparticles l brain delivery, when chitosan is the polymeric component, hybrid nanoparticles have shown excellent cohesion superiority when combined with increased cellular uptake associated with the lipid surface [28]. PLGA-lipid hybrid nanoparticles of curcumin have been shown to have 6.8-foldhigher brain bioavailability than either curcumin suspension or curcumin suspension and therapeutic levels were observed up to 24 hours [29]. Engineered by containing several functional layers e.g. a drug-containing PLGA core, intermediate lipid layer to interact with membranes, and outer PEG or chitosan coating to navigate mucus or adhere [20]. Nevertheless, multi-component systems are complex, which makes them difficult to manufacture, there is a possibility of batch-to-batch variation, and their characterization may become complicated [21].

5.6. Comparative Performance Analysis

Comparative studies of various vesicular systems to deliver drugs into the nose to the brain demonstrate that their optimal selection varies with particular therapeutic needs [23]. Transferosomes tend to be more bioavailable (1.5-2x higher) than a standard liposome because of better deformability, the Heleniuses have the same effect with increased stability [33, 23]. Ethosomes are most effective and have maximum tolerability issues [25]. Cubosomes excel in the sustained-release use where longer-term therapeutic concentrations are required, and the hybrid nanoparticles offer the most flexible platform solution in the application of multi- functional delivery systems that need targeting, imaging, and controlled release in the same case [26]. Small elastic vesicles or ethosomes can be the preferential choice in cases of rapid-onset applications (acute seizures, migraine), but sustained-release cubosomes or hybrid systems are useful in chronic neurodegenerative diseases [27].

6. Conclusion

Integration of the intranasal drug delivery with liposomal and vesicular technologies is a paradigm shift in getting rid of the blood-brain barrier problem that has plagued successful treatment of neurological disorders. This chapter has thoroughly discussed how lipid based nanocarriers can take advantage of the anatomical niche between the nasal and brain via olfactory and trigeminal neural pathways with direct access to the CNS bypassing the systemic circulation challenges. suffers superior benefits in nose-to-brain delivery of sensitive therapeutics of: preventing enzymatic breakdown, increased membrane permeation via fusion and endocytosis, and loading different molecules (hydrophilic and lipophilic) in a versatile manner. PEGylated surface modifications allow mucus penetration, whereas chitosan coating allows cohesion, widening the short 15-30 minutes absorption window of mucociliary clearance. Research continues to show 2-5-fold increments in brain bioavailability relative to the traditional nasal preparations. Advanced vesicular systems build on these capabilities. Transfer somes have achieved best penetration using ultra-deformability, niosomes have better stability and cost reduction, and cubosomes have excellent drug loading and days of sustained release. The future of therapeutic precision is a series of emerging technologies like stimuli-responsive liposomes, theragnostic systems, and personalized formulations that offer increased therapy precision. It is promises to provide historic advances in the treatment of devastating neurological diseases such as Alzheimer disease, Parkinson disease, brain tumors, and psychiatric diseases with better efficacy and fewer system side effects. These technologies have the potential to revolutionize neurotherapeutics and give hope to millions of patients across the globe as research continues to be translated into clinical use.

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