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INTRANASAL LIPOSOMES IN NOSE-TO-BRAIN DELIVERY: CURRENT INSIGHTS AND FUTURE DIRECTIONS

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ABSTRACT

Through direct transportation through the trigeminal and olfactory channels, Intra Nasal (IN) medication delivery has become a notable non-invasive technique in order to target the Central Nervous System (CNS) and avoid the Blood Brain Barrier (BBB). Because liposome-based nanocarriers may encapsulate hydrophilic and lipophilic drugs, improve stability, increase bioavailability, and prolong residence time, they provide significant advantages for IN administration. Optimized liposomal formulations can be created using a variety of preparation methods, including solvent injection, emulsification, thin-film hydration, and reverse-phase evaporation. Stability, muco-adhesion, and controlled release are offered by functional excipients such as phospholipids, cholesterol, chitosan, and PEG derivatives. To guarantee therapeutic efficacy, evaluation parameters such particle size, entrapment efficiency, zeta potential, and *in-vitro* drug release are crucial. Intranasal liposomal delivery has shown promise in treating glioblastoma, Parkinson's disease, Alzheimer's disease, and other conditions affecting the central nervous system. however, challenges like lysosomal trapping and restricted biodistribution in specific tumour microenvironments.

KEYWORDS: Intranasal drug delivery, Blood-brain barrier, Nose-to-brain delivery, Neuro-degenerative diseases.

INTRODUCTION

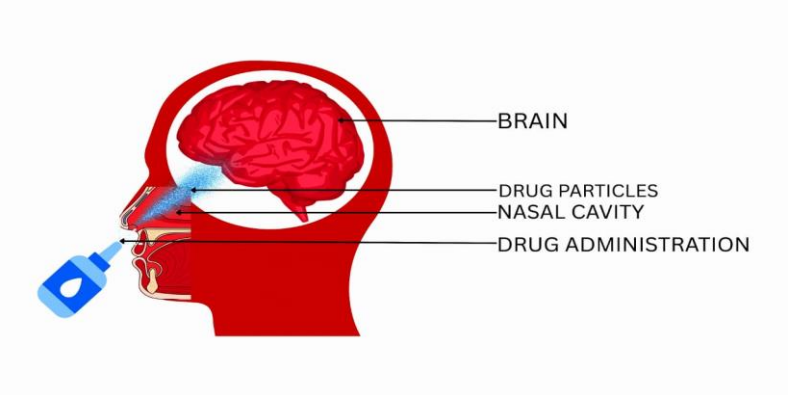
In recent years, Administration of Intra Nasal (IN) has become a non-invasive technique. To delivering drugs that can achieve either local or systemic effects by facilitating direct delivery from the nose to the brain. The nasal cavity has a direct physical relationship with the Central Nervous System (CNS), IN administration allows drugs to access the CNS effectively. In contrast to parenteral techniques, Intranasal administration can bypass the Blood Brain Barrier (BBB), deliver medications to the brain faster, and improve therapeutic targeting and bioavailability. Additionally, IN administration circumvents gastrointestinal and liver metabolism, reduces the buildup of drugs in organs that are not the target, and leads to fewer systemic side effects.[1] As the population ages, there has been a steady increase in the number of individuals with neurodegenerative illnesses and other abnormalities of the Central Nervous System (CNS) over the last ten years. Among the prominent disorders affecting the central nervous system are Alzheimer's Disease (AD), Parkinson's disease, schizophrenia, migraine, malignant glioma, vestibular schwannoma, meningitis, and multiple sclerosis. However, because of their intricate and multidimensional pathogenic pathways, most of these illnesses currently lack appropriate treatments.[2] The non-invasive technique of intranasal drug administration has garnered a lot of interest recently since it can bypass the brain barriers and send drugs directly to the brain through the trigeminal and olfactory nerve pathways. Furthermore, this route avoids first-pass metabolism and deterioration in the gastrointestinal tract while providing a rapid commencement of action.[3]

Physiological barriers such the blood-brain barrier, enzymatic breakdown, hepatic metabolism, and systemic clearance make it crucial to get medications to the brain.[4] Anti-Retroviral Therapy (ART) drugs that can cross the Blood Brain Barrier (BBB) can help lower viral loads, prevent viruses from spreading into the brain parenchyma, and improve neurocognition. Currently, a variety of nanoparticle formulations are being created to directly target the central nervous system.[5] A systemic delivery approach called nasal administration lowers the

risk of adverse side effects while facilitating rapid drug absorption and enhanced bioavailability. Due to these benefits and the ease of administration, intranasal drug delivery methods are becoming more and more popular.[6] By encasing medications in a matrix and preventing P-glycoprotein efflux proteins from transporting them outside the cell, nanoparticles improve drug stability.[7] Regarding patents, it is important to recognize William H. Frey II, the inventor of nose-to-brain delivery, who in 1989 found that the non-invasive method was the Intra Nasal (IN) route means of passing through the Blood Brain Barrier (BBB) and delivering drugs (like insulin) directly to the brain for conditions like stroke, Alzheimer's disease, and Parkinson's disease.[8] More surface area, enhanced stability, better absorption, and increased drug solubility are just a few advantages of these nanoscale systems, which are usually made up of particles smaller than 1000 nm. Common nano carriers for drug delivery include Solid Lipid Nanoparticles (SLNs), polymeric nanoparticles (NPs), liposomes, nano-emulsions, micelles, and Nanostructured Lipid Carriers (NLCs).[9] According to medical data, the number of CNS illnesses is rapidly increasing worldwide, which is driving up healthcare costs.[10] Liposomes can improve medicine delivery from the nose to the brain, according to recent research. One or more phospholipid bilayers encircle the water core of these spherical liposomes. Because liposomes may encapsulate both hydrophilic and lipophilic compounds, they have been demonstrated to protect pharmaceuticals against premature breakdown and elimination when utilized for nose-to-brain medication delivery.[11]

Direct medication administration is made possible by the nasal cavity's, the olfactory and trigeminal nerves establish direct connections to the Central Nervous System (CNS), linking to the brain and the Cerebrospinal Fluid (CSF). Bypassing the first-pass effect and gastrointestinal breakdown, In addition to achieving high medication absorption and minimizing side effects, the nasal route offers other benefits for better drug delivery. However, this approach has some disadvantages as well, such as the mucociliary clearance mechanism's quick drug removal.[12] It is possible to create an intranasal formulation that includes temperature-sensitive polymers such as Poloxamer 407 and chitosan-based in situ gel. The formulation strength and biocompatibility are improved while toxicity is reduced by the combination of natural and synthetic polymers. The mucoadhesive qualities of chitosan allow this thermosensitive formulation that adhere to the mucus, which reduces the possibility of mucociliary removal. It’s prevents the medication from being broken down by enzymes and allows for a regulated release of the drug, which eventually boosts its bioavailability in the brain.[13]

2. ROUTE OF DRUG ADMINISTRATION



“Fig. 1: Route of Drug Administration”

To enter the brain, drug molecules must meet certain requirements: They should be non-ionized and lipophilic, possess a molecular weight of under 400 Da, and have the capacity to form no more than eight hydrogen bonds. Although intrathecal, intraparenchymal, and intracerebroventricular injections or infusions are Invasive and unsuitable for medications that must be taken continuously, they could be used to deliver therapies reaches the central nervous system directly (CNS).[14] A large absorption area (~160 cm^2), the rapid action of the medications, and the large number of blood arteries in the nasal cavity make it possible to achieve efficient therapeutic effects when drugs are administered through the nasal route.[15] The anatomy and physiology of the nose cavity must be considered while developing intranasal formulations. The least permeable areas are represented by the transepithelial portion of the atrium, which is the thinnest segment, and the vibrissae located in the nasal vestibule. The respiratory area's superior, middle, and inferior turbinates, on the other hand, are more permeable, and the olfactory area's specialized ciliated olfactory nerve cells have a direct route to the Cerebro Spinal Fluid (CSF) (Fig. 1).[16]

3. MECHANISM OF NOSE TO BRAIN DRUG DELIVERY

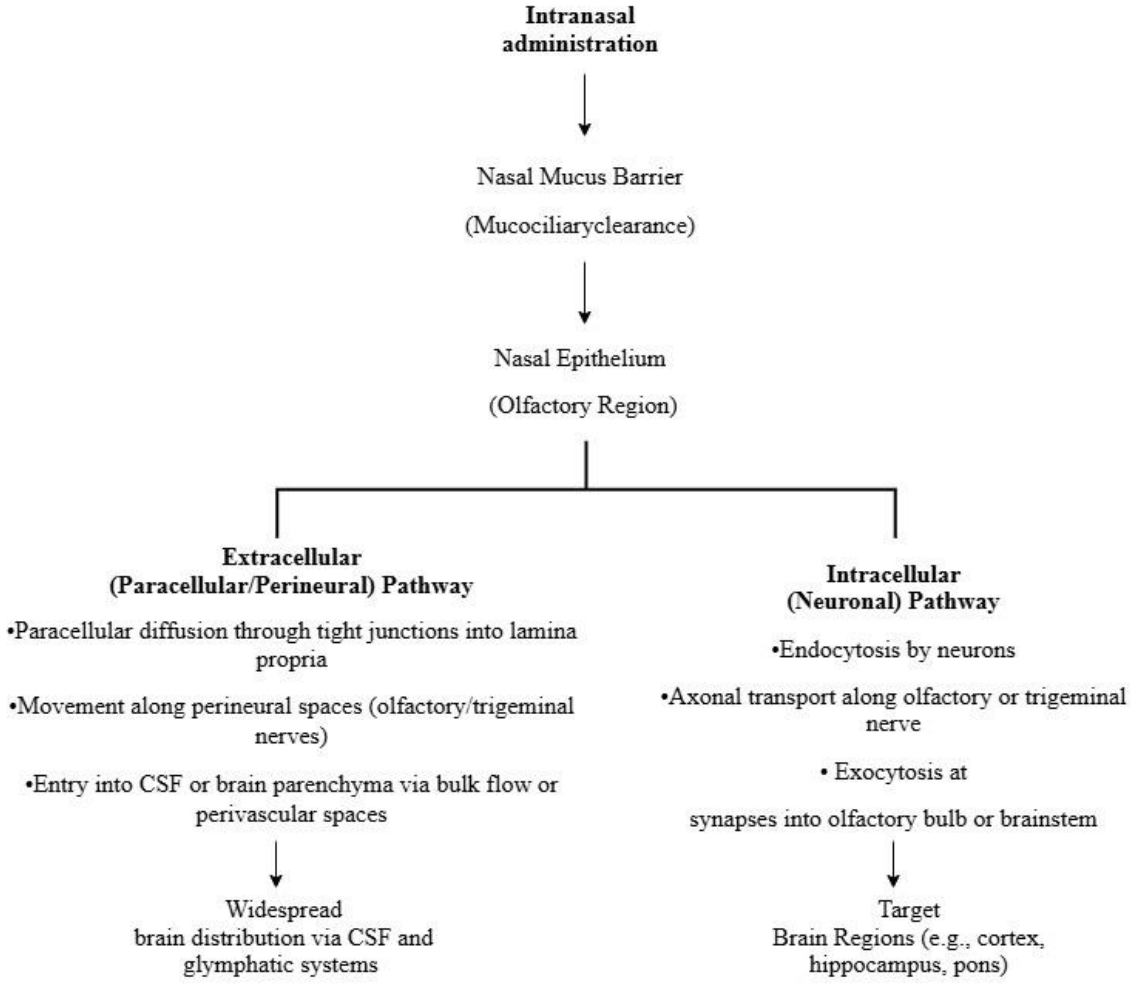
Medications administered through the nose initially pass through the mucus layer to access the olfactory region of the nasal epithelium, allowing them to bypass the blood-brain barrier and interact with the brain.

Extracellular pathway

Drug substances enter the lamina propria, which is situated beneath the nasal epithelium, via the extracellular route by passing through the tight connections between epithelial cells. From this location, they travel through the perineural and perivascular areas connected to the olfactory and trigeminal nerves, entering the CSF or brain tissue before spreading widely via the glymphatic system and CSF flow.

Intracellular pathway

The medication is taken up by nerve cells in the trigeminal and olfactory systems at their terminals in the nasal mucosa via endocytosis in the intracellular pathway. The medication is then carried by axons to the brainstem or olfactory bulb, where it is released through exocytosis at synapses and distributed to particular brain regions, such as the hippocampus and cortex (Fig. 2).[17,18,19,20]



"Fig. 2: Mechanism of Nose to Brain Drug Delivery"

4. MATERIALS USED FOR PREPARATION OF LIPOSOMES

4.1. Rivastigmine

Another cholinesterase inhibitor that the FDA has approved for the treatment of Alzheimer's disease is rivastigmine. Its oral bioavailability is minimal due to considerable first-pass metabolism and limited penetration across the blood-brain barrier (BBB). Furthermore, oral treatment frequently leads to uncertain systemic exposure and a high frequency of systemic side effects. Consequently, intranasal (IN) liposomes have been produced to increase the transport of the medicine to the brain. The IN liposomes revealed better distribution of rivastigmine in the hippocampus and cortex, combined with a considerable suppression of acetylcholinesterase and butyrylcholinesterase activity in rat models. Researchers used di-decyl dimethyl ammonium bromide, a positive charge inducer, to improve the stability of electrostatic stealth rivastigmine-loaded liposomes. The area under the curve (AUC) for the IN liposomes' plasma and brain concentrations in rabbits was found to be 4.2 and 4.9 times higher, respectively, than the AUC of the IN-free drug solution. The increased drug accumulation in the brain after intranasal administration of rivastigmine-loaded liposomes has not yet been verified, which is a shortcoming of our study.[21]

4.2. Chitosan

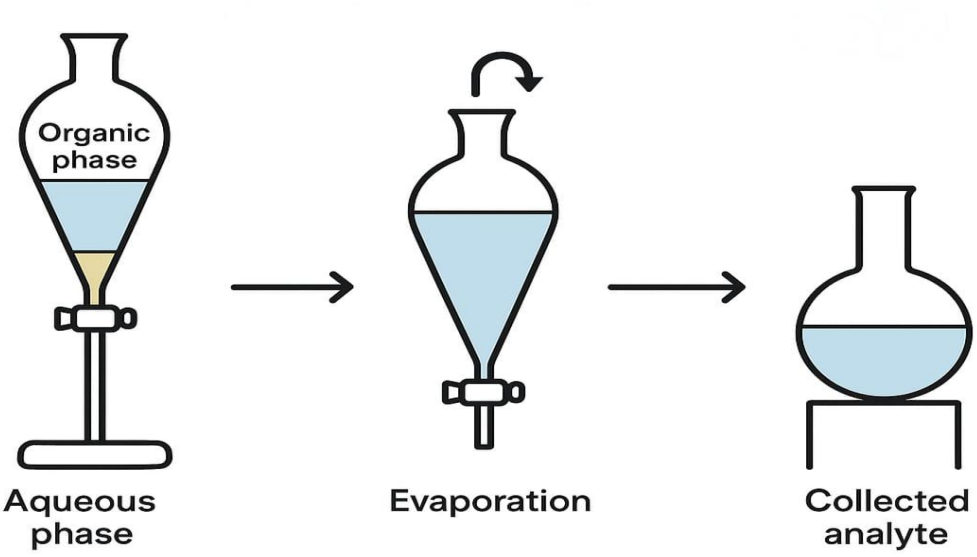
In medication delivery systems, chitosan, a naturally occurring cationic polymer obtained from the deacetylation of chitin, acts as a mucoadhesive agent by electrostatically interacting with the negatively charged mucin present in the nasal cavity. Consequently, the application of chitosan serves to improve the overall residence duration of liposomes, which ultimately enhances drug bioavailability and penetration.[22]

5. METHOD OF PREPARATION

Initially, lipid membranes must be prepared. Using membranes from human cancer cell lines or obtaining them from living cells are more complex methods. While the simplest techniques focus on the production of simple liposomes, other strategies involve creating them as tethered, planar, or different non-spherical lipid bilayers.[23] The process of producing liposomes involves the attainment of a narrow size distribution and the required degree of lamellarity to guarantee effective drug encapsulation and long-term colloidal product stability. Traditional techniques involve mixing an aqueous phase with liposomes that have been dissolved in a volatile organic solvent.[24]

5.1. Reverse Phase Evaporation Method

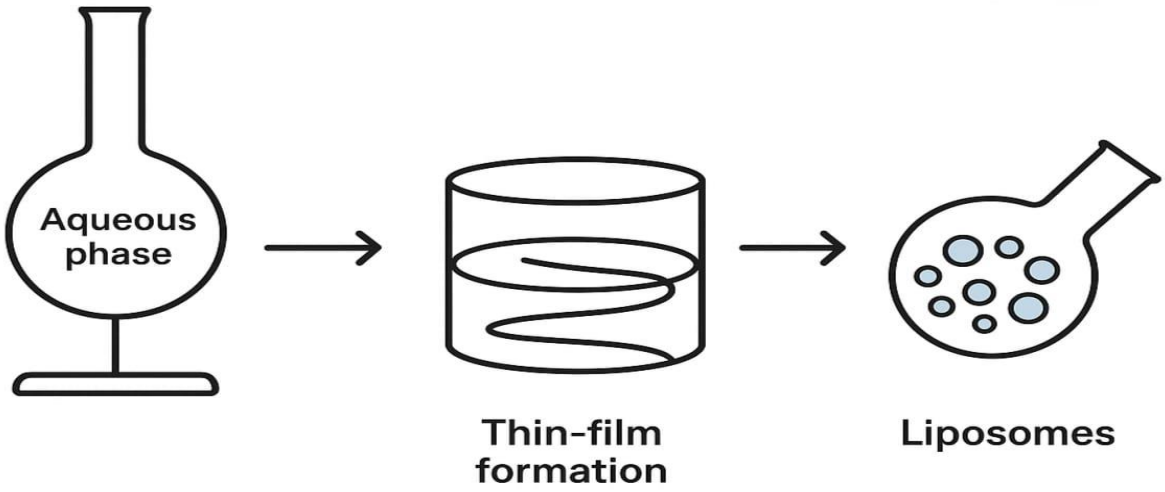
Lipids are solubilized utilizing the method in a non-aqueous solvent that causes inverted micelles to form, such as a 1:1 methanol and diethyl ether mixture, a 2:1 diethyl ether and isopropyl ether mixture, or a 1:1 diethyl ether and chloroform mixture. The combination is then combined with a specified volume of an aqueous phase (buffer). At the Water in Oil microemulsion interface between the organic and aqueous phases, the lipids subsequently rearrange. To produce a homogeneous dispersion, Water-in-Oil (W/O) microemulsion can undergo additional emulsification liposomal preparation form utilizing mechanical methods or sonication processes. To improve liposome performance, phosphate saline buffer is frequently added to the aqueous phase. Through constant rotation under low pressure, up to a thick gel form, the organic solvent is progressively evaporated. Slowly, the organic solvent is eliminated, which breaks up the inverted micelles and makes it easier for liposomes (LUVs) to form later. While the gel collapses once a critical threshold is achieved, the excess phospholipids in the surrounding solution engulf the inverted micelles, forming a lipid bilayer that encases the (remaining) water droplets and causes the production of liposomes (Fig. 3).[25]



"Fig. 3: Reverse Phase Evaporation Method"

5.2. Conventional Hydration Method

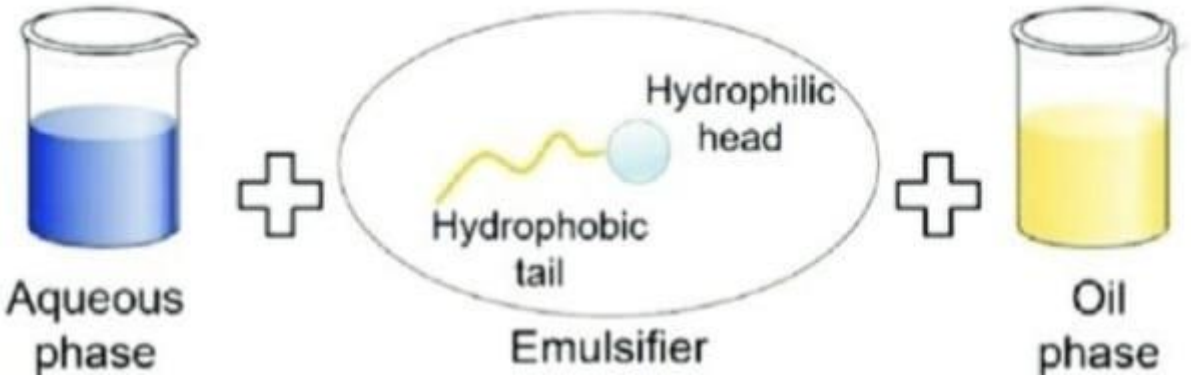
Multi Lamellar Vesicles (MLVs) are created in the conventional hydration method by applying too much water or buffer solution to thin lipid films. However, by using mechanical processes like extrusion and sonication, MLVs can be converted into Large Uni-lamellar Vesicles (LUVs) and Small Uni-lamellar Vesicles (SUVs). Additionally, a pH jumping technique can be used to create SUVs (20–60 nm) from MLVs. Beyond MLVs, lipid films can be progressively hydrated over a long period of time (1–48 hours) without agitation to generate Giant Uni-lamellar Vesicles (GUVs) as large as 10 mm. However, only when the ionic strength is low does the mild hydration method for generating GUVs work. Due to their insufficient entrapment efficiency, lack of scalability, and size variability (Fig. 4).[26]



"Fig. 4: Conventional Hydration Method"

5.3. Emulsification Method

A popular approach for creating liposomes is emulsification using Water in Oil (W/O) techniques, which is proceeded by the gradual extraction of organic solvents. This method works especially well for hydrophilic drugs because it enables a large amount of water-based phases to be trapped inside the liposome's core. First, an organic solvent that doesn't mix with water is used to completely dissolve the lipid components. After gradually adding the aqueous phase, the mixture is sonicated to produce reverse micelles. The organic solvent is gradually removed, a thick gel phase emerges, which eventually changes into an aqueous suspension of Large Uni-lamellar Vesicles (LUVs) or Multi Lamellar Vesicles (MLVs). However, the complexity of the production process and the possibility of residual organic solvents in the finished product limit the technique's industrial use. Furthermore, because of the extended exposure of the material to the organic solvent, physiologically active substances, such as peptides, are not suited for encapsulating in liposomes using this technique. Although it requires the application of large shear forces for consistent liposome development in the absence of emulsifiers, other techniques called simple Oil in Water emulsification can also help to create liposomes. Phospholipid-stabilized Water Oil Water double emulsions can also produce Giant Uni-lamellar vesicles (GUVs) with advantageous encapsulation efficiencies when organic solvents are gradually removed (Fig. 5).[27]

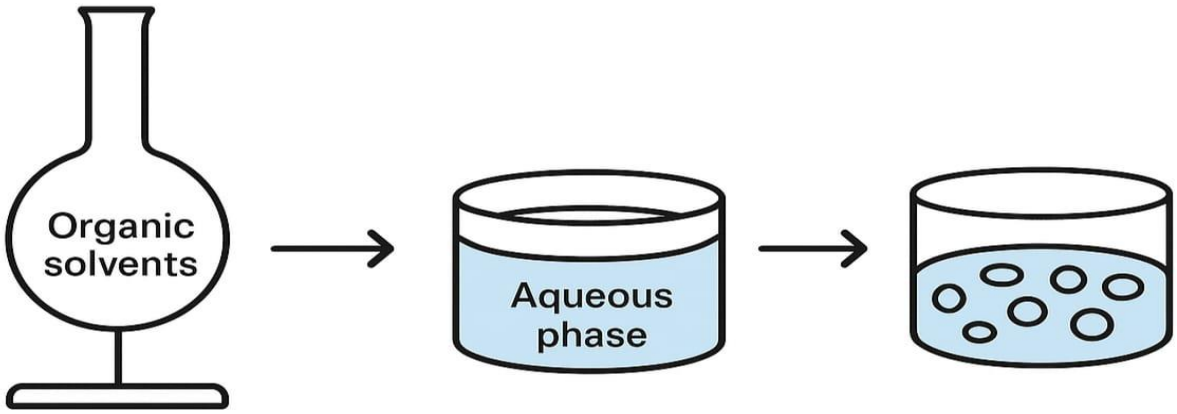


"Fig. 5: Emulsification Method"

5.4. Thin Film Method

The traditional method for successfully integrating lipophilic medications is the thin-film hydration technique. A lipid-solvent mixture is evaporated while the flask is rotated under vacuum to produce a thin layer. Aqueous solution is used to hydrate the lipid film, resulting in a suspension of Multi Lamellar Vesicles (MLVs). By further reducing the particle size, Small Uni-lamellar Vesicles (SUVs) can be created, and the medication can be added either actively during the liposome manufacturing process or passively after. The manufacturing process is used in commercial goods such as AmBisome, Visudyne, and Shingrix (Adjuvant system AS01B). To make Visudyne, for example, the components of dichloromethane are evaporated, then hydrated with a lactose solution, and finally the size is reduced by homogenization, filtration, and lyophilization. Shingrix comes in separate vials with a

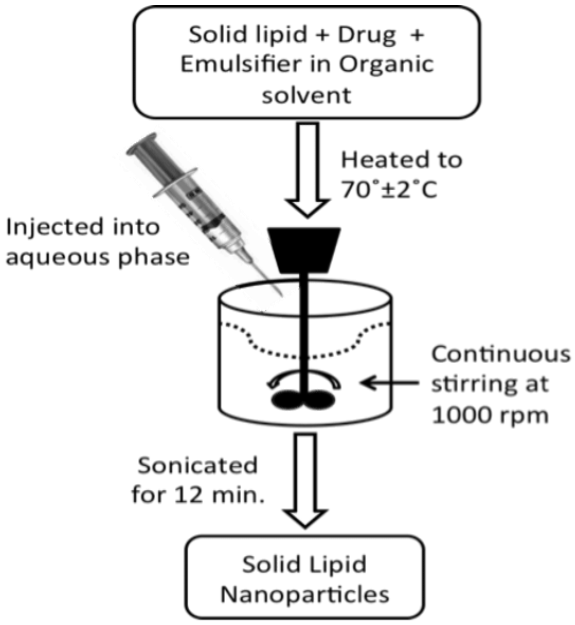
liposome-based adjuvant that contains two immune-boosting substances: MPL (Mono-Phosphoryl Lipid) and QS21, a triterpene glycoside that is gathered from the bark of the Quillajasaponaria Molina tree. After dissolving in an organic solvent, the MPL and other lipids are then evaporated. An aqueous solution of QS21 is added for the final formulation following hydration and size reduction (Fig. 6).[28]



"Fig. 6: Thin Film Method"

5.5. Solvent Injection Method

Another technique for creating liposomes is the solvent injection approach. The technique produces liposomes by rapidly infusing lipids dissolved in a non-solvent like ethanol or ether into an aqueous solution. Due to its simplicity, uniformity, quick execution, easy scalability, and little danger of oxidative alterations or lipid degradation, solvent injection method is extensively used in the production of liposomes. Furthermore, according to the European Pharmacopoeia, ethanol is a good solvent for *in-vivo* drug delivery applications with lower concentrations. The lipid type, the concentration of it in ethanol, the ratio of lipid to drug, the size of the injection orifice, and the speed of injection are a few variables that can be adjusted to influence the particle size and encapsulation efficiency achieved through the solvent injection technique (Fig. 7).[29]



"Fig. 7: Solvent Injection Method"

6. EVALUATION OF LIPOSOMES

To test the effectiveness, safety, and targeting ability of liposomal formulations for distribution from the nose to the brain, numerous in vitro assessment procedures are performed. These procedures aid in comprehending Entrapment Efficiency, Particle dimensions and size distribution, Morphology and structure determination, Zeta potential, In-vitro medication release, Encapsulation Efficiency.[10]

6.1. Entrapment Efficiency (EE)

The percentage of medication that has been successfully integrated is known as entrapment efficiency. Once the unentrapped medication has been separated, the vesicles are broken down to evaluate it's efficiency. The ratio of the trapped drug concentration to the drug entire concentration.[30]

Entrapment efficiency = ED/TD x 100
ED= Quantity of medication entrapped
TD= Total quantity of drugs utilized

6.2. Particle dimensions and size distribution

In assessing the *in-vivo* release of liposomes containing drugs, the size of the vesicles is essential. The phospholipid composition and the manufacturing method have an impact on the average liposome size. The Particle dimensions and size distribution are measured using several methods**.**

- A variety of microscopic techniques are used, such as optical microscopy, SEM, TEM, and freeze-fracture TEM. Liposomes are imaged using SEM and TEM techniques, which also provide information on the thickness of the bilayers and the spacing between them. Atomic force microscopy is an advanced microscopic technique that provides high-resolution scanning probe microscopy. It generates three-dimensional micrographs and achieves resolution down to the nano-meter and angstrom levels, to assess the size, shape, stability, and dynamic behaviour of lipid nano-capsules and the shape of liposomes**.**
- Hydrodynamic methods like ultracentrifugation, flow fractionation, Gel exclusion chromatography, and analytical centrifugation are used to determine the molecular weight of substances and to evaluate the size distribution, elution properties, and homogeneity of liposomes.[31]

6.3. Morphology and structure determination

Using a variety of microscopy techniques, a thorough investigation of the morphological and structural characteristics of liposome formulations was undertaken. Using TEM, specific characteristics were highlighted. Glass-mounted HSPC and pH-sensitive liposomes may be thoroughly examined at the highest magnifications thanks to phase contrast microscopy. Photomicrographs were used to document these observations in a methodical manner, exposing the distinct visual traits of every formulation. Furthermore, a thorough TEM analysis was carried out, which included the formation of thin films on copper grids coated with carbon. At magnifications attained with an accelerating voltage of 200 kV, these grids, which included the liposome films, were meticulously air-dried and examined using TEM, providing important insights into their internal structure. A deeper comprehension of the liposomes' structural arrangement was made possible by the acquired photos.[32]

6.4. Zeta potential

The overall net charge of particles is typically represented by the surface or zeta potential. The capacity of liposomes to manage electrostatic interactions among suspended particles is considered an essential physical property. Key elements include the lipid composition, the lipid head group, and associated ligands that can either negatively, neutrally, or positively influence the net charge of liposomes. The ionic strength of the external environment can also affect the ζ-potential. Zeta-potential measurements are used to predict the stability of colloidal structures, such as liposomes, within their surrounding liquid.[33]

6.5. *In-vitro* drug release

The main challenge in creating a test to assess the drug's *in-vitro* release from liposomes is simulating the release conditions observed in *in-vivo* studies. Even under *in-vitro* studies, capturing a release profile can be complex since slight changes in the physicochemical properties of the Liposomes have a significant impact on the drug's release. The forming ingredients' phase transition temperature usually defines the physicochemical characteristics, particularly phospholipids and cholesterol. The phase transition temperature, which emphasizes the change from densely packed hydrocarbons to a more disordered and fluid state, the temperature at which liposomes transition from an organized gel phase to a chaotic liquid crystalline phase. Therefore, the phase transition temperature is crucial in governing drug release from liposomes.[34]

6.6. Encapsulation Efficiency

Encapsulation efficiency is defined as the ratio of the amount of the encapsulated component in the liposome to the total weighted substance. To measure the encapsulation efficiency, the free medication is removed from the liposome encapsulated one by dialysis, gel filtration, or centrifugation.[35]

7. APPLICATIONS

- Because it frequently fails to distribute therapeutic medicines to the central nervous system in clinically appropriate concentrations, conventional oral drug delivery poses There are significant hurdles to treating neurological illnesses and diseases.
- The Blood brain barrier is made up of endothelial cells connected by adhesion and tight junctions, acts as the central nervous system's most important defense mechanism, keeping pathogens, infections, and neuro destructive substances from the brain's tissue.
- Only very particular molecules—small pharmaceutical compounds with a weight of less than 500 Da and strong lipophilicity—can naturally penetrate the blood-brain barrier. These molecules make up less than 1% of macromolecules and only 2% of small molecules.
- Specialized protein transporters actively pump (CNS) in addition to physical tight junctions, significantly limiting the systemic distribution of therapeutic medicines to brain tissue.
- Direct CNS access via the olfactory and trigeminal nerve pathways is made possible by intranasal drug

administration, a promising alternative route that skips first-pass hepatic metabolism and the blood-brain barrier.

- Drugs can travel by both intracellular and extracellular transport systems to the olfactory bulb in the forebrain thanks to the olfactory epithelium's special connected to the central nerve system physically.
- Drug molecules travel via the trigeminal and olfactory nerves fibers via transcellular, paracellular, and extracellular routes. From the olfactory bulb, they may diffuse extracellularly or undergo intracellular transport to higher brain areas.
- The significant lengths (millimeter-scale) that drugs must travel within brain tissue to reach their therapeutic targets make constant and focused distribution within the brain parenchyma challenging, even with effective BBB bypass.
- Regardless of the initial administration technique, the extracellular space, which makes up around 20% of the total brain volume, is essential for medication dispersion throughout the brain microenvironment.
- Through both intranasal and convection-enhanced delivery methods, advanced nanotherapeutics and nanomaterial systems dramatically improve medication biodistribution within brain tissue, exhibiting improved treatment efficacy for disorders like glioblastoma.[36]

8. LIMITATIONS

Liposomes transport to the nucleus is limited and their bioavailable concentrations are decreased when they become trapped inside cellular lysosomes.[37] The Enhanced Permeability and Retention (EPR) phenomenon linked to malignancies is the only source of energy for these liposomes. It is anticipated that the liposomes will passively enter the surrounding tumor tissue through the tumors permeable blood arteries. Nevertheless, the considerable variation in the EPR impact both within and across tumor types may limit this extravasation.[38] Due of the dense fibrous tissue, some tumor forms, such as pancreatic cancer, exhibit limited increased permeability and retention (EPR). Unlike in the primary tumor, the lymphatic outflow in the metastatic environment is still operational, preventing the liposome from becoming stuck in metastatic areas. This finding explains why PLD and non-PLD are ineffective in treating metastatic cancer.[39]

9. CURRENT CHALLANGES

Two major obstacles are maintaining uniformity in particle size and preventing liposome aggregation while being stored.[40] Formulations are quickly removed by mucociliary clearance in 15 to 20 minutes, limiting the amount of time they can stay in the nasal cavity.[2] Variability between batches and quality control problems make scaling up manufacturing challenging.[41] Nanotoxicity and possible long-term accumulation in the nasal epithelium raise safety concerns.[42]

10. FUTURE PROSPECTIVES

Liposomes have the ability to permeate the blood-brain barrier and access the brain after being absorbed into the systemic circulation through the nasal cavity. In some situations, more than 80% of medications enter the brain via this other route.[43] Liposomes can be changed using cholesterol–undecanoate–glucose conjugates to particularly target glucose transporter 1 at the blood-brain barrier (BBB), promoting their efficient transit from the bloodstream into the brain. Nevertheless, in certain situations, the bulk of medicines (over 90%) enter the brain through direct transport from the nose to the brain.[21]

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