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Liposomes: a drug delivery carrier for the management of Parkinson's disease

Palash Das[1], Rajana James[2], Jitakshara Das[3], Karishma Sultana[4], Mirza Mahmuda Yasmin[5]

[1,2] *Department of Pharmacology, Girijananda Chowdhury University, Azara, Guwahati, Assam-781017, India*
[3,4,5] *Department of Pharmaceutics, Girijananda Chowdhury University, Azara, Guwahati, Assam-781017, India*

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ABSTRACT

Delivering medications across the blood-brain barrier (BBB) is a significant obstacle in the treatment of neurogenerative illnesses. The development of a liposome-based drug delivery system with improved BBB penetration for effective brain medication delivery is summarised in this article. Due to the fact that Parkinson's disease is the second most prevalent form of adult chronic neurodegenerative condition, we concentrated on liposome-based treatments that target it. A number of liposomes have been developed with surface modifications of BBB-targeting ligands to enable the therapeutic efficacy of Parkinson's disease medications to cross the BBB via transcytosis. Recent developments in liposome technology are offering solutions to go around the BBB for a more effective treatment approach. We must fully comprehend the pathophysiological alterations at the BBB in order to increase liposome BBB penetration. This review covers an overview of Parkinson's disease and its pathophysiology, details about the blood-brain barrier, a summary about liposomes and their types, and about their effectiveness in crossing the blood-brain barrier.

KEYWORDS: Parkinson's disease, Blood-brain Barrier, Liposomes, Pathophysiology of PD.

I. INTRODUCTION

Parkinson's disease (PD) is a chronic, deteriorating neurological condition that results in the loss of dopamine due to the degradation of dopaminergic neurons in the substantia nigra par compacta (SNpc)(Kalia & Lang, 2015; Mhyre et al., 2012). Dopamine deficiency in the basal ganglia causes a movement disease characterized by bradykinesia, muscle stiffness, rest tremor, postural and gait difficulties, and other characteristic Parkinsonian motor symptoms(Kalia & Lang, 2015; Mhyre et al., 2012). PD is also known to be a multi-system condition outside of the nigrostriatal system that is connected to non-motor symptoms including cognitive decline, depression, and constipation in addition to impairments in smell, sleep, and mood(Kalia & Lang, 2015).

The BBB has a very low permeability, which restricts the delivery of medications to the central nervous system (CNS), and is made up of polarised endothelial cells joined by tight junctions of the cerebral capillary endothelium (Hawkins & Davis, 2005; Pardridge, 2007). An assortment of diverse cell types, including astrocytes, pericytes, and neurons, work together to dynamically control BBB activity(Abbott et al., 2006, 2010; Ballabh et al., 2004). A layer of tissue called the basal lamina surrounds endothelial cells and is often rich in laminin, fibronectin, type IV collagen, and heparin sulphate(Abbott et al., 2006, 2010; Ballabh et al., 2004; Hawkins & Davis, 2005). These substances may be attractive targets for drug delivery and offer a negatively charged interface(Scherrmann, 2002; Vorbrodt, 1989).

Drug carriers, including erythrocytes, immunoglobulins(Cao et al., 2020), lipid and lipidoid nanoparticles (NPs)(Li et al., 2020; Liu et al., 2020), liposomes, polymer-based particles(Fu et al., 2020), drug particles, and inorganic particles(Zhang et al., 2020), among others, are now the best options for delivering desired medications with selective action on selected organs or tissues(Hua & Wu, 2013; Li et al., 2021; Yu et al., 2020). Among these carriers, liposomes have limitless potential for effective medication delivery to the target region. It is well known that liposomes have a number of benefits, including increasing stability through encapsulation, increasing drug efficacy and therapeutic index, improving pharmacokinetic effects (i.e., reducing elimination and lengthening circulation lifetime), and lowering the toxicity of encapsulated agents(Shi et al., 2020; Zhou et al., 2018). Additionally, employing liposomes as drug carriers has made it possible to

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transport drugs across membranes, to selectively target tumour tissues passively, and to combine site-specific ligands for active targeting (Nikam et al., 2020). In addition, liposomes are preferable to other carriers due to their simplicity, ease of manufacture, biodegradability, repeatability, variety of clinical uses, and safety(Alanazi et al., 2020; Deshpande et al., 2013; Kabilova et al., 2018; Vitor et al., 2013).

II. PATHOPHYSIOLOGY OF PARKINSON'S DISEASE

The biological reasons for neurodegeneration are not yet known but there are some factors that might relate to degeneration of neurons. The development of this condition is influenced by aging, high acetylcholinesterase activity, a correspondingly low level of acetylcholine, oxidative stress, inflammatory factors, glutamate-dependent neurotoxicity, and a number of environmental variables(Pan et al., 2021).

The loss of dopaminergic neurons, which leads to the SNpc's eventual depigmentation, and the existence of LBs are the primary pathological characteristics of PD. Alpha-synuclein and ubiquitin are the two main proteins that make up LBs, which are intraneuronal, round, eosinophilic inclusions with a hyaline core and a pale peripheral halo that contains almost 90 proteins or more(Wakabayashi et al., 2013). Alpha-synuclein has a propensity to misfold, become insoluble, and form beta sheet-rich amyloid aggregates that accumulate and form intracellular inclusions(Spillantini et al., 1997). The hazardous oligomeric and proto-fibrillar stages in this aggregation process disrupt biological membranes(Danzer et al., 2007) and the cytoskeleton(Alim et al., 2004), impair mitochondrial(Hsu et al., 2000), lysosomal, and proteasomal function(Snyder et al., 2003), change synaptic function(Scott et al., 2010) and result in neuronal degeneration. According to estimates, up to 60% of dopaminergic neurons may already have died by the time of the diagnosis(Marsden, 1990).

Another factor for neurodegeneration can be genetic factors. Early onset autosomal recessive PD is brought on by mutations in the PARKIN(Kitada et al., 1998) and PINK1 (Valente et al., 2004) genes. Both PARKIN and PINK1 have been connected to a cellular mechanism that preferentially degrades damaged mitochondria in lysosomes by macroautophagy, often known as "mitophagy." These genes' loss of function impairs mitophagy, which causes a buildup of defective mitochondria.

Blood brain barrier:

Blood-brain barrier (BBB) is present in all creatures with fully developed CNS. The endothelial cells that make up the capillary walls generate the BBB in the brain and spinal cord of animals, including humans. The total surface area of these microvessels makes up by far the greatest blood-brain barrier. Depending on the anatomical location, this surface area ranges from 150 to 200 cm^2 g^{-1} tissue, resulting in a total area for exchange in the average adult human brain of 12 to 18 m^2(Nag & Begley, 2005).

The blood-cerebrospinal fluid barrier (BCSFB), which is made up of the choroid plexus' epithelial cells that front the cerebrospinal fluid, creates a second interface. The remaining brain extracellular fluid, the interstitial fluid (ISF), is obtained, at least in part, by secretion through the capillary endothelium of the BBB(Dolman et al., 2005). The CSF is released via the choroid plexus epithelial cells into the brain ventricular system(Brown et al., 2004). ISF and CSF are able to connect freely at a number of sites; according to several experimental investigations, ISF contributes between 10 and 60% of the CSF. The Na+, K+-ATPase, which is expressed in the apical membrane of the choroid plexus epithelium and the abluminal membrane of the BBB endothelium, is what drives the secretion of CSF and ISF, causing water movement and volume flow(Abbott et al., 2006).

The avascular arachnoid epithelium, which lies underneath the dura and completely encloses the CNS, serves as the third interface, completing the barrier between the extracellular fluids of the central nervous system and those of the rest of the body(Abbott et al., 2006). The arachnoid creates a barrier layer as well, but due to its tiny surface area and avascular character, it does not serve as a substantial surface for blood-to-CNS exchange(Kandel et al., 2000).

Physical barriers (tight junctions between cells reducing flux via the intercellular cleft or paracellular pathway), transport barriers (certain transport mechanisms mediating solute flux), and metabolic barriers (enzymes metabolising molecules in transit) combine to form barriers at all three interfaces. Both in physiology and in disease, the barrier function may be adjusted and controlled rather than being fixed(Abbott et al., 2006).

III. LIPOSOME

Liposomes are aqueous compartments surrounded by one or more lipid bilayers that are roughly nano- or microsized vesicles. Soon after

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their development in the early 1960s, the potential utility of these vesicles as a carrier system for therapeutically active chemicals was realised(Lai et al., 2013). Recently, liposomes have been investigated for use in the treatment and/or diagnosis of neurological illnesses as carriers of medicinal medicines, imaging agents, and genes. Therapeutic substances that are hydrophilic as well as lipophilic can be incorporated into liposomes because of their distinct physicochemical properties (Johnsen & Moos, 2016).

Liposomes may be made in a variety of ways for medication delivery. However, there are four fundamental steps in each approach utilised to create liposomes. These include removing lipids from organic solvents, distributing them in water, cleaning the resulting liposomes, and analysing the finished product. Both passive and active loading methods are employed when loading a medication into a liposome. The three methods that make up the passive loading approach are detergent removal, solvent dispersion, and mechanical dispersion (i.e., removal of free drugs)(Samad et al., 2007).

Several liposome-mediated formulations that are now commercially available and permitted for use in clinical trials reflect the success of liposomes as drug carriers(Zylberberg & Matosevic, 2016). Numerous more anti-cancer drugs, including Depocyt®, DaunoXome®, OnivydeTM, and Myocet(Layek et al., 2020), have been successfully produced since the first liposome formulation (Doxil®) was created(Barenholz, 2012). A liposome can also be used to deliver nucleic acids (NAs), antibacterial (Ampicillin), antiviral (e.g., Epaxal®, Inflexal®), anti-fungal (e.g., Ambisome®, Abelcet®, Amphotec®), anti-fungal (e.g., Abelcet®, Amphotec®), and pain relief (DepoDurTM, Exparel®) agents (Bulbake et al., 2017; Stoicea et al., 2017; Alam & Hartrick, 2005; Cuddihy et al., 2019; Stone et al., 2016; Voak et al., 2021).

Types of liposomes:

The different types of liposomes are based on three parameters (1) Based on their composition and application, (2) based on their structural parameters in terms of size, charge lamellarity, and (3) on the basis of liposomal preparations. The types based on the first paramets are conventional liposomes, long circulating liposomes, pH-sensitive liposomes, temperature-sensitive liposomes(Lu et al., 2020), magnetic-response liposomes, enzyme-sensitive liposomes, and immunoliposomes (ILs). Multilamellar, oligolamellar, aramellar vesicles are based on structural parameters. The types of techniques that comes under third category are extrusion techniques, reverse phase evaporation method, sonication, and dehydration method, etc(Wadhwa et al., 2019). A liposome can range in size from extremely tiny to big vesicles, or 0.025 µm to 2.5 µm, respectively. Additionally, liposomes might have a single membrane or two bilayer membranes. A key factor in influencing the circulatory half-life of a liposome is the size of its vesicle. The quantity and size of bilayers have an impact on a liposome's capacity to encapsulate medicines. Liposomes are divided into three types based on the quantity and size of their bilayers: unilamellar vesicles (ULV), multilamellar vesicles (MLV), and multivesicular vesicles (MVV) (Akbarzadeh et al., 2013; Wadhwa et al., 2019). Giant unilamellar vesicles (GULV), size range >1 µm; large unilamellar vesicles (LUV), size range 100-1000 nm; and small unilamellar vesicles (SUV), size range 100 nm, are further classifications for unilamellar vesicles. A single spherical phospholipid bilayer encloses the aqueous solution in a unilamellar liposome, whereas the vesicles in multilamellar liposomes have an onion-like shape. In a multilamellar structure of concentric phospholipid spheres separated by layers of water, many unilamellar vesicles of lower sizes will often join together and form inside of one another (Shaheen et al., 2006). While MVV is primarily used for parenteral administration, LUV, SUV, and MLV are acceptable for a range of routes, including oral delivery(He et al., 2019).

IV. LIPOSOMES FACILITATING BBB CROSSING

Due to their physiochemical characteristics and simplicity of surface functionalization, nanoparticles (NPs), which are therapeutic carriers on a scale between 1 and 1000 nm, provide potential techniques for the transport of drugs to the brain. Liposomes are thought to be the most effective NPs in the clinic because they are very flexible and biocompatible(Beltrán-Gracia et al., 2019). They may readily be functionalized to engage with specific molecular targets(Beltrán-Gracia et al., 2019) and can contain hydrophilic pharmaceuticals in the aqueous core or hydrophobic chemicals in the lipid layers(Agrawal et al., 2017).

A number of liposomes with surface modifications of BBB-targeting ligands have been developed to cross the BBB via transcytosis thanks to the amazing developments in nanotechnology. Through a "Trojan horse strategy," it makes it easier

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for cargo to go from the apical to the basolateral plasma membrane of the BBB. Carrier-mediated transcytosis (CMT), receptor-mediated transcytosis (RMT), and adsorptive-mediated transcytosis (AMT) are all components of the Trojan horse method. Molecular transporters like the large neutral amino acid transporter (LAT1) and the glucose transporter (GLUT1), which are found at BBB membranes, are essential for CMT. For instance, when glucose binds to GLUT1, the transporter changes its conformation, allowing glucose to be transported along a high-to-low concentration gradient. When ligands like lactoferrin (Lf), transferrin (Tf), and insulin are bound to the specific receptors expressed on the BBB, RMT offers selective transport of relatively big molecules by vesicular transport through the cells, as opposed to CMT, which typically transports tiny molecules(Chen et al., 2017; Zheng et al., 2015). RMT has therefore been regarded as a cutting-edge method of transferring liposomes across the BBB(Piazzini et al., 2018). Although it is not specific to the BBB, liposomes can also use AMT based on electrostatic interactions between the positively charged surface and the negatively charged plasma membrane.

V. LIPOSOME BASED THERAPY FOR PD

PD is a neurodegenerative illness that affects 1-3% of people over 65 years of age(Ball et al., 2019) and progresses over time. The primary characteristic of Parkinson's disease (PD) is the abnormal accumulation and aggregation of alpha-synuclein, which results in Lewy bodies and dysfunctions of the somatomotor system. This degeneration of the nigrostriatal dopaminergic pathway is accompanied by a significant loss of dopamine neurons in the substantia nigra(Ball et al., 2019). Therefore, a common PD treatment technique has been to give dopamine or dopamine derivatives to the brain.

Qu et al. created liposomes using the dopamine derivative N-3,4-bis(pivaloyloxy)-dopamine and a 29 amino acid peptide (RVG29) as a ligand(Qu et al., 2018). The RVG29, which binds nicotinic acetylcholine receptors expressed on BBB and neuron, is generated from the rabies virus glycoprotein(Qu et al., 2018). The liposomes demonstrated great absorption efficiency and RMT-based BBB penetration. And following intravenous administration, these carriers demonstrated preferential distribution to the brain, striatum, and substantia nigra in a mouse model of PD (6-OHDA), proving the RVG29 to be an effective target ligand for liposome transport into the brain (Qu et al., 2018).

Targeting the BBB's amyloid precursor protein receptors can also help receptor-mediated transcytosis (RMT) penetrate the BBB more effectively. According to Kahana et al., the dopamine- and APP-loaded liposomes were connected to a peptide of five amino acids (RERMS)(Kahana et al., 2021). In the PD mouse model, rats, and mini-pigs, intra-peritoneal injection of the APP-targeted liposomes caused a significant rise in striatal dopamine within 5 min (6.9-fold, p0.05). They also demonstrated how functionalizing the stratal circuit corrected the behavioural deficits (Kahana et al., 2021).

Recently, a magnetic liposomal delivery device has been investigated to increase the effectiveness of brain medication delivery(Ji et al., 2017). By combining the liposomal suspension with the PEG-coated Fe3O4 solution, the magnetic liposome (Fe3O4- nimodipine liposome (NMD)-liposome) was created. Under the influence of an external magnetic field, NMD retention in the brain was 2.5 times greater in the Fe3O4-NMD-liposomes treatment group in a PD rat model than it was in the NMD treatment group. They also demonstrated improved dopaminergic neuron protection in vivo by attenuating the PD neurotoxin via nimodipine integrated in liposomes. Given that Fe3O4-NMD-liposomes were effectively drawn to the brain, their therapeutic effect was clearly greater than that of the free NMD group. The Fe3O4-NMD-liposomes combined with Resveratrol, a natural product and neuroprotective medication, shown a potential therapeutic efficacy for the PD rat model in a subsequent investigation(Wang et al., 2018). These investigations suggest that a targeted liposome administration into the brain using a magnetic field may be a potential PD therapy method. But in order to transition from a lab setting to a clinical setting, various technological obstacles must be overcome, such as the quick loss of field strength in deep tissue and the requirement of driving a large number of magnetic objects to provide a therapeutic outcome.

VI. CONCLUSION

The Parkinson’s disease hampers the life style of individuals who are suffering from it and as it is uncurable disease makes it more difficult to live with it. However, symptomatic relief can be a big help for the patients and most of the present treatments are based on this. The BBB is the main impediment to the efficient transport of drugs to the

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brain. The creation of tailored liposomes that can cross the BBB and deliver therapeutic compounds solely to the illness location inside the brain has generated a lot of interest in this field. Liposomes as a carrier for targeted brain delivery help the treatment to reach the brain with increased bioavailability. Liposomes have demonstrated a strong capacity to compartmentalise and solubilize both hydrophilic and hydrophobic medicines due to their distinctive physicochemical features. Recent developments in liposome technology are offering possibilities to circumvent BBB for a more effective treatment approach. Future advances of liposomes that target BBB penetration mediated by RMT will present new chances to treat PD, in particular.

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