GALGOTIAS UNIVERSITY

A PROJECT ON

" Treatment of Alzheimer's disease for blood brain delivery system"

IN

BACHELOR OF PHARMACY

Submitted By

Rahul Saini

B. PHARMA 4TH YEAR

ENROLLMENT NO. 1712102065

Under the Supervision of

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GALGOTIAS UNIVERSITY

Greater Noida

MAY,2021

TABLE OF CONTENT

DEPARTMENT OF PHARMACY

GALGOTIAS UNIVERSITY, GREATER NOIDA, G.B. NAGAR (U.P)

CERTIFICATE

This is to certify that the Project work entitled "**Treatment of Alzheimer disease for blood brain delivery system"** is a bonafide research work done by **Rahul Saini** at Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University, Greater Noida, under the supervision and guidance of Ms. Swati Verma, Assistant Professor, School of Medical and Allied Sciences, Greater Noida. The work is completed and ready for evaluation in partial fulfilment for the award of Bachelor of Pharmacy under Galgotias University, Greater Noida during the academic year 2020-2021.

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DEPARTMENT OF PHARMACY

GALGOTIAS UNIVERSITY, GREATER NOIDA, G.B. NAGAR (U.P)

CERTIFICATE

This is to certify that the project work entitled **"Treatment of Alzheimer disease for blood brain delivery system"** by Rahul Saini for the award of "Bachelor of Pharmacy" degree, comprises of the bonafide research work done by him at Department of Pharmacy, School of Medical & Allied Sciences, Galgotias University, Greater Noida under my guidance and supervision and to my full satisfaction.

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DECLARATION

The project report entitled **"Treatment of Alzheimer disease for blood brain delivery system"** is the compilation work of **Mr. Rahul Saini** under supervision of **Ms. Swati Verma** Assistant Professor **Department of Pharmacy, GALGOTIAS UNIVERSITY Greater Noida U.P India**. All pictures, Figures and information used in project are taken from various sources are true and best of my knowledge.

Date:

Place:

Rahul Saini

ENROLLMENT No.1712102065

GALGOTIAS UNIVERSITY

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Praise to be almighty God who made me able to carry out the present study successful. I feel high privileged while starting my dissertation work with acknowledge of the genuine help and support received from others who made this research and project possible for me.

I deem it a great pleasure record my heartfelt gratitude to my supervisor, for her valuable guidance.

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Last but not the least I wish to express my gratitude to my lovely parents for their patience and constant support. They provided me with every opportunity to succeed.

RAHUL SAINI

Treatment of Alzheimer disease for blood brain delivery system

Abstrect

Brain pathologies such as brain cancer, Alzheimer's disease, Parkinson's disease, stroke, and multiple sclerosis are among the most common, because they are currently undertreated due to drug development, administration, and targeting to the brain challenges. The blood-brain barrier is a significant barrier to therapeutic drug delivery to the brain. It is a selective permeability network that acts as a local gateway against circulating foreign drugs. The creation of brain delivery methods based on nanotechnology, such as nanoparticles, liposomes, dendrimers, micelles, and carbon nanotubes, may be the response.

Introduction

Brain diseases, including brain cancer, Alzheimer’s disease, Parkinson’s disease, stroke and multiple sclerosis, are some of the most prevalent diseases, which are becoming a great concern due to the increase in elderly population [1]. These disorders may be caused by genetic and environmental factors, pathologies in processes involving protein aggregation which lead to neurodegeneration or disregulation of the immune process, or abnormalities regarding the development and function ofthe brain [2]. However, compared to other areas of an organism, the treatment for brain diseases is presently unsuccessful mostly due to the complexity of the brain. Additionally, drug development for brain diseases requires longer periods of time and more complex clinical trials. Since the number of cases are expected to increase over the following years, the discovery of novel and improved strategies is crucial [3]. The pathways for the delivery of therapeutic agents to the brain can either be invasive or non-invasive. The invasive route involves the surgical administration of drugs directly inside the brain, thus providing a sufficient dosage without causing systemic toxicity. However, the intra-cerebral injection relies on the cerebral diffusion, thus being concentration-dependent and decreasing from the administration site. The non-invasive administration strategies are based on the anatomical structureof the brain capillaries, cells, and extracellular environment, and on the directional transfer of fluids across the brain, the main routes including the nasal and the

systemic administration [4]. The nasal route is preferred over the systemic drug delivery as the drug is directly delivered into the brain through the olfactory bulb, which increases the bioavailability and reduces the degradation of the drug.

Nevertheless, limitations such as poor drug permeations through the nasal mucosa and mucociliaryclearance might be encountered [5]. Considering the systemic route, the circulating drugs must enter the parenchyma and the cerebrospinal fluid and further diffuse through the brain extracellular space to the targeted site [4]. The brain is one of the most complex and important organs of living organisms. Therefore, it is necessary to protect it against the contamination with environmental and foreign substances which could lead to changes in the inner and outer concentrations of neuronal cells and subsequently to impairments in nerve conduction and dysfunctions in the body control processes [6]. The blood-brain barrier is the structure responsible for the protection of the brain, acting as a local gateway against thecirculating toxins and cells [7] through a selective permeability system. Hence, the delivery systemsfor the treatment of brain diseases should have the capacity to cross the blood-brain barrier without causing immune responses. However, the physiological function of the blood-brain barrier is the key challenge for the delivery of pharmaceutical drugs to the brain, which represents the main reason for complications in the existing treatment strategies and for the numerous research studies focusing on the development of novel drug delivery systems for the treatment of brain-associated diseases [8].

The principal pathways for crossing the blood-brain barrier are through paracellular transport, between endothelial cells, and through trans cellular transport, involving passive or active mechanisms, across the luminal side of the endothelial cells, through the cytoplasm, and subsequently across the albuminalside, into the brain interstitium [9]. Although there are multiple crossing pathways, approximately 98% of small molecules and most large molecules are unable to reach the brain through the blood-brain barrier [10].

Nanotechnology, the emerging field that encompasses knowledge from multiple disciplines including chemistry, physics, engineering, and biology, implicates the development and modification of materials within the size range of 1–100 nm in at least one dimension [11–13]. Additionally, nanotechnology represents the capacity to understand, manipulate, and control the matter at the level of individual atoms and molecules [14]. Therefore, the implication of nanotechnology for the development of non-invasive drug delivery strategies

could lead to the design of novel and improved formulations to enhance the delivery of therapeutic agents across the blood-brain barrier [3,15–18].

Numerous research studies have focused on the exploration of nanotechnology-based drug delivery systems, including nanoparticles, liposomes, dendrimers, carbon nanotubes, and micelles, **The Blood-Brain Barrier**which have the potential to deliver the desired quantity of the drug to the brain [10].

Study of the literature

During the study of the proposed work, an extensive literature review on repurposing for the treatment of Alzheimer's disease for blood brain belivery system operation was conducted.

Daniel Mihai Teleanu 1, Cristina Chircov 2,3, Alexandru Mihai Grumezescu 3,4, Adrian Volceanov 3,*, and Raluca Ioana Teleanu 1 1 Emergency University Hospital, Bucharest, Romania, “Carol Davila” University of Medicine and Pharmacy, 050474 Bucharest, Romania; telepapa@hotmail.com (D.M.T.); raluca.t@gmail.com (R.I.T.) 2 Politehnica University of Bucharest, Faculty of Engineering in Foreign Languages, 060042 Bucures, ti, Romania; cristina.chircov@yahoo.com.

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Hongzhuan Chen1, Xiao Gu1 The 11th of December, 2018.

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The Blood-Brain Barrier

The central nervous system compartment, consisting of the brain and the spinal cord, is protectedby two main barriers: the blood-brain barrier, formed by the brain micro vascular endothelial cells, and the blood-cerebrospinal fluid barrier, comprised of the epithelial layer of choroid plexus, the cerebral ventricles, and the arachnoid mater covering the outer brain surface [19]. As the subject of this review, the blood-brain barrier is characterized by its unique structure and the highly controlled interactions between its cellular and acellular components. The main function of the blood-brain barrier is to ensure an optimal environment for the proper functionality of the neuronal network, by maintaining brain homeostasis, regulating the influx and efflux of fluids, and protecting thebrain against pathogenic agents [20] through a dynamic combination of cellular, vascular, molecular, and ionic factors. Additionally, it contributes to the neuronal functionality by allowing the glucose transport [21].

The Anatomical Structure of the Blood-Brain Barrier

The main component of the blood-brain barrier is the continuous layer of endothelial cells connected through tight junctions composed of claudin-5, occludin, and other molecules [22], which represents the luminal surface of more than 99% of the capillaries of the brain and spinal

cord [23]. Additionally, the blood-brain barrier is composed of specialized cells, including the pericytes, the astrocytes, and the adjacent neurons (Figure 1) [24]. The functions associated to the mainblood-brain barrier components are summarized in Table 1.

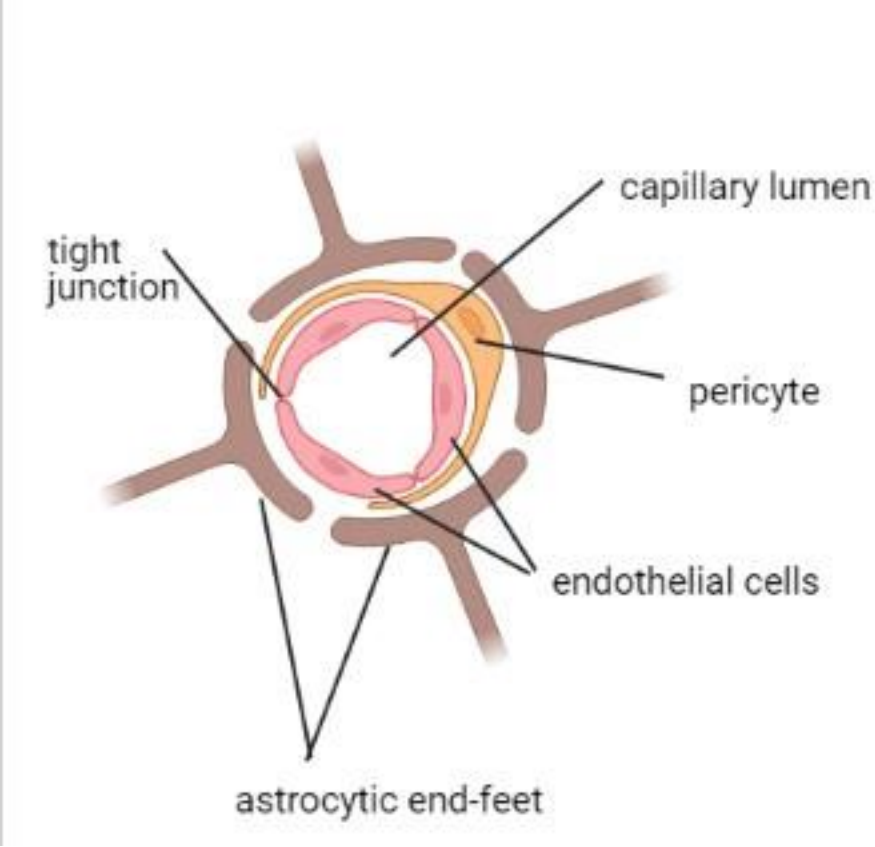


Figure 1. The main structural components of the blood-brain barrier.

Pharmaceutics 2018, 10, x FOR PEER REVIEW 3 of 16 represents the luminal surface of more than 99% of the capillaries of the brain and spinal cord [23]. Additionally, the blood-brain barrier is composed of specialized cells, including the pericytes, the astrocytes, and the adjacent neurons (Figure 1) [24].

The endothelium of the brain provides a surface area of 20 m2 for the blood-brain exchange, while the tight junctions direct the molecular trafficking across the blood-brain barrier through the transcellular route [25]. The influx of necessary substances and the efflux of waste are enabled by the structural and functional unit of the central nervous system, which is the neurovascular unit [24]. This structure is formed at the contact sites between small blood vessels, such as arterioles, precapillary arterioles, capillaries, and postcapillary venules, and the parenchymal cells of the brain. The wall of the blood vessels consists of three different types of layers. The inner layer of endothelial cells is separated from the middle layer of contractile cells through the basement membrane. Subsequently, the outer layer differs depending on the size of the vessel: in arteries and arterioles it consists of smooth muscle cells, in capillaries, the smooth muscle cells are replaced by pericytes, and larger

vessels are surrounded by an adventitial layer, which contains perivascular nerve endings of extracerebral origin for the pial vasculature and intrinsic nerves originating from subcortical areas or local interneurons for the intraparenchymal vasculature, and are separated from the parenchyma by the Virchow-Robin space [26]. The paracellular space between endothelial cells is eliminated through the tight junctions, which appear as continuous, anastomosing, intramembranous networks of strands and interact with the tight junction proteins on the adjacent endothelial cells. Therefore, the transfer of solutes and ions between the brain and the blood is blocked by the fusion of tight junctions [27] Pericytes, spatially isolated contractile cells found in the perivascular space, are involved in angiogenesis, maintenance of the blood-brain barrier, regulation of immune cell entry to the brain, control of the cerebral blood flow, and constriction of capillaries in stroke [28]. Astrocytes, also known as astrogliathe most abundant cells of the human brain [29], are responsible for theregulation of metabolism, the modulation of neuronal transmission, and brain development andrepair. The astrocytic end-feet processes that surround the endothelial cells, over the basal lamina,termed glia limitans, forms a highly restrictive second barrier [22]. barrier [22]. Neurons are actively involved through the nervous terminations that reach all the cells that form the blood-brain barrier
[30]

The Physiology of the Blood-Brain Barrier

Each of the three main CNS interface layers: the BBB, choroid plexus epithelium and the epithelium of the arachnoid mater, functions as a physical, transport, metabolic, and immunologic barrier. The barrier functions are dynamic and respond to regulatory signals from both blood and brain. Tight junctions between adjacent cells restrict diffusion of polar solutes through the intercellular cleft (paracellular pathway). The barriers are permeable to O_2 and CO_2 and other gaseous molecules such as helium, xenon, N_2 and many gaseous anesthetics. The permeability to xenon may provide a high resolution magnetic resonance imaging tool by which small morphological alteration may be detectable within the living tissue and also permit the analysis of binding sites using molecular probing techniques. Lipid soluble substances can pass the barrier by diffusion. Principally, the BBB is also permeable to water, however solute carriers on the apical and basal membranes together with ectoenzymes and endoenzymes regulate small solute entry and efflux. Transfer of some molecules is regulated

by multidrug transporters that can limit their concentrations within the central nervous system. Multidrug transporters are ubiquitous transport proteins that exploit ATP hydrolysis to funnel molecules across lipid membranes; they facilitate transport of molecules into cells but may also prevent accumulation of molecules within the brain interstitial space. Multidrug transporters and Pgp-like proteins are expressed at the BBB and limit access of drugs to brain tissue but also other lipophilic molecules, including (for example) bilirubin, the degradation product of hemoglobin, which - if entering the central nervous system – is neurotoxic and can cause significant damage [31]. Recent studies suggest that upregulation of transporter molecules in pathological conditions may reduce drug levels within the brain, and explain treatment failures (pharmacoresistant) in neurological and psychiatric disorders [32].

Large molecules (e.g. peptides and proteins) with particular growth and signaling roles within the CNS enter the brain in a restricted and regulated manner by adsorptive and receptor-mediated transcytosis (ART and RMT, respectively). Smaller peptides may cross the BBB by either nonspecific fluid-phase endocytosis or RMT mechanisms. Similarly, 98% of all small molecules are not freely transported across the BBB [33]. The barriers also regulate the recruitment and entry of leukocytes and innate immune elements and involve in both the reactive and surveillance functions of CNS immunity. Leukocyte migration involves a complex set of adhesion molecules at the surface of leukocytes and vascular endothelial cells. Tethering and rolling of leukocytes is achieved via integrins VLA-4 (α4β1) and α4β7 [34] and adhesion molecules such as ICAM-1, VCAM-1 and PECAM-1, contribute to the adhesion and/or migration of distinct subsets of leukocytes to the CNS through cytokine-activated brain endothelium [35]. Transport systems across the blood-brain barrier are illustrated in Figure 1.

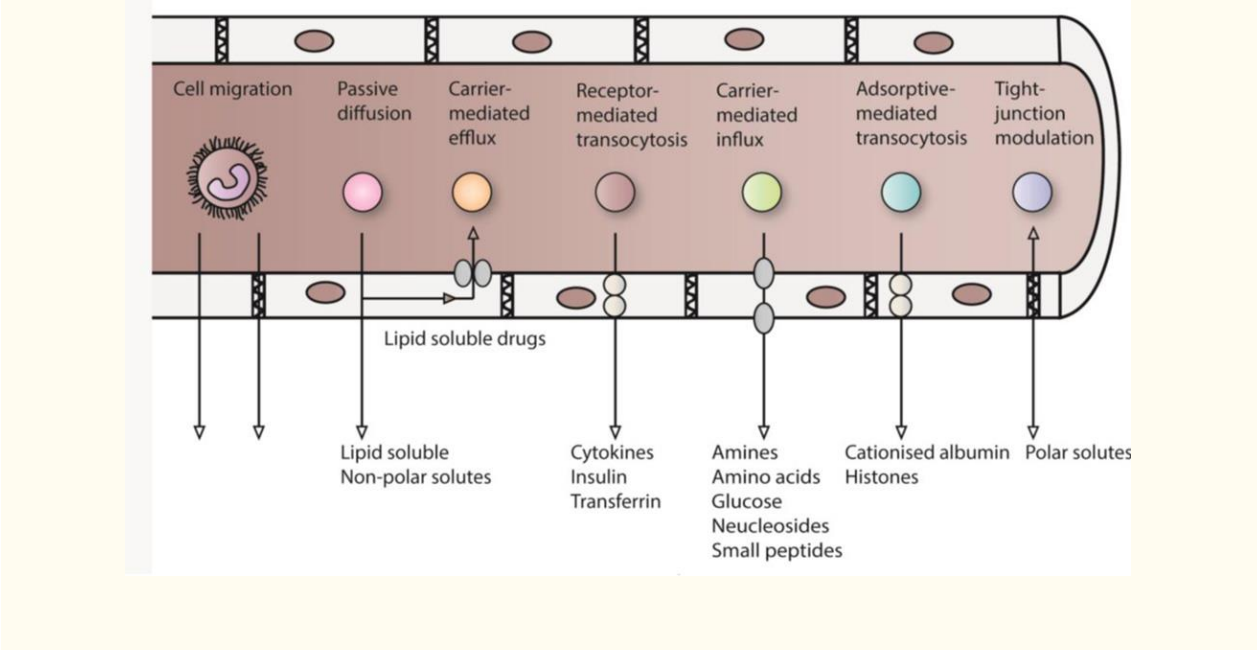


Figure 2. Nano-carrier delivery pathways across the blood-brain barrier.

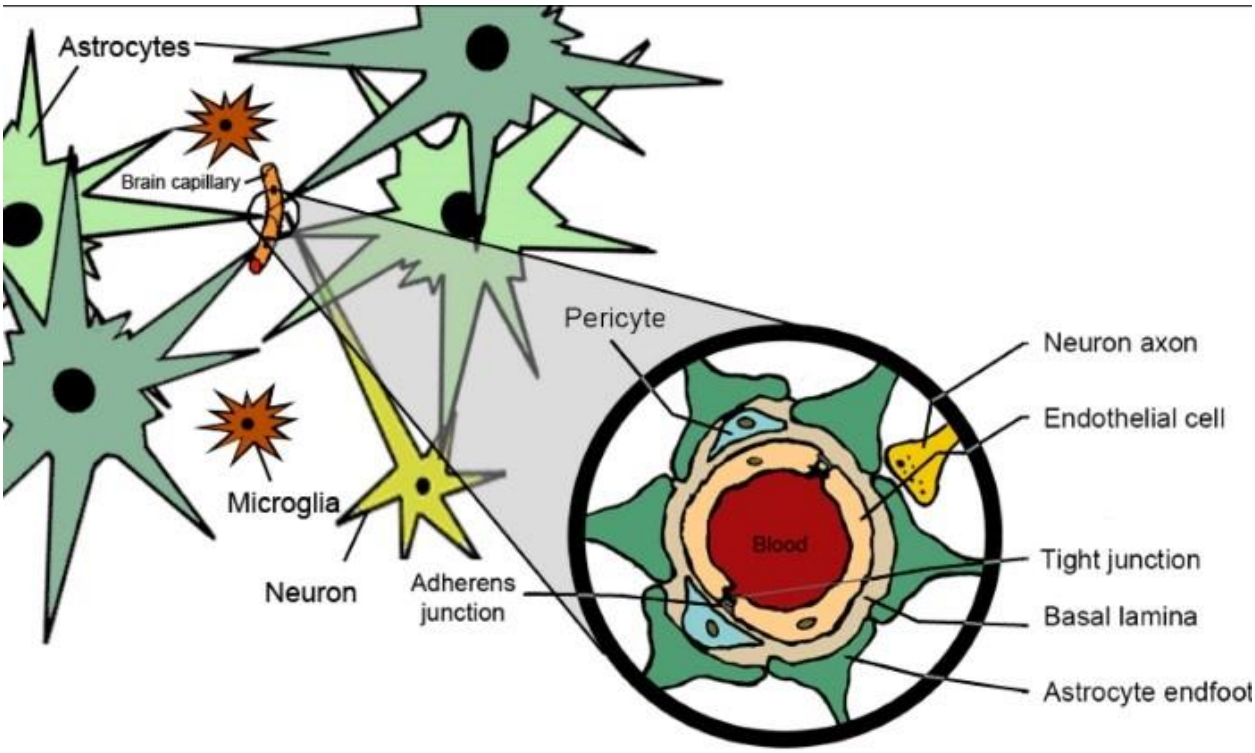


Figure 3. Schematic diagram of diseased and healthy BBB.

Nanotechnology Approaches for Crossing the Blood-Brain Barrier

The development of nanotechnology through integrated multidisciplinary efforts will result in novel insights into the functions of neural circuits and approaches for of brain diseases [38]. This is especially necessary due to the limitations of current strategies to deliver drugs into The specific properties nanomaterials, such as reduced size, biocompatibility, prolonged blood circulation, and non-toxicity, have been exploited for the creation of an emerging delivery platform that can easily transport therapeutic agents to the brain [39]. The nanotechnology-mediated drug delivery systems are based on both specific and non-specific mechanisms for targeting brain sites [40]. Recent studies have focused on the development of drug delivery nano-vehicles, including nanoparticles, liposomes, dendrimers, micelles, and carbon nanotubes, for the delivery of pharmaceutical agents, peptides, proteins, vaccines, or nucleic acids. The parameters of the main nano-carriers used for drug delivery across the blood-brain barrier are summarized in.

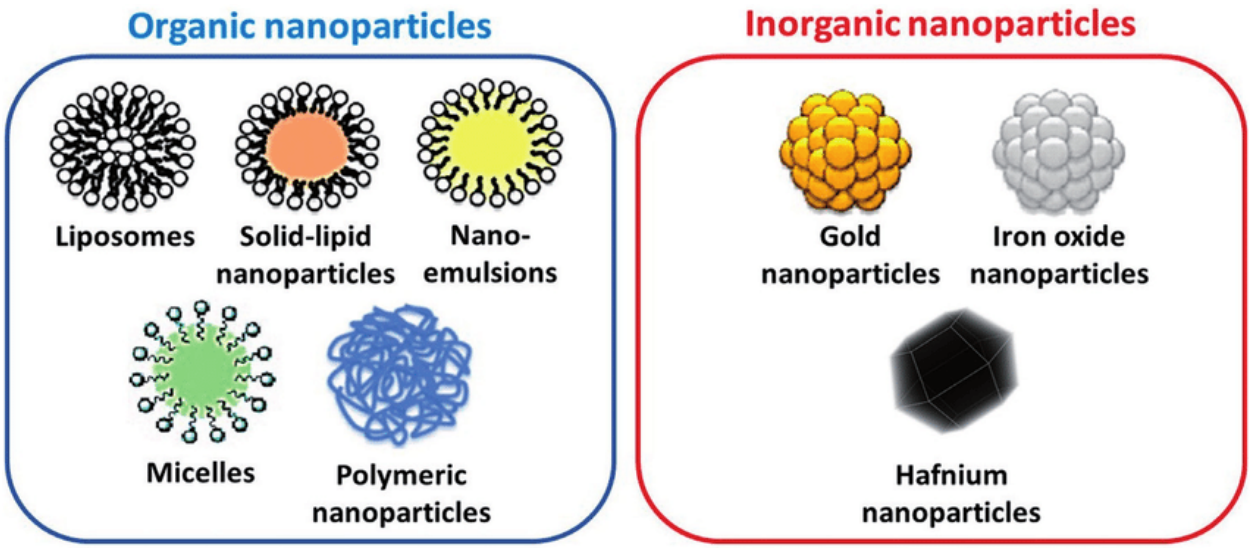
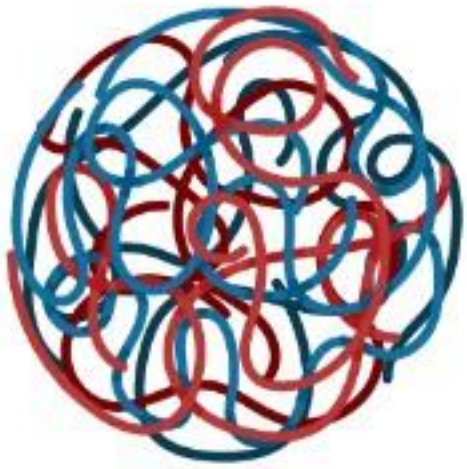


Fig – types of nanoparticles

Organic nanoparticles

Polymeric Nanoparticles



As nanoparticles possess suitable properties for drug delivery, such as controlled drug releaseand targeting efficiency, they have been widely used for the development of drug delivery carriers to cross the blood-brain barrier. Moreover, they can avoid phagocytosis by the reticuloendothelial system, thus improving the concentration of drugs in the brain [41]. Several types of nanoparticles have been studied for the efficient blood-brain barrier crossing, including polymeric and inorganic nanoparticles. Recent studies have focused on the use of poly(lactide-co-glycolic) acid as a material for the synthesis of nanoparticles to encapsulate therapeutic agents for the treatment of Alzheimer's disease [42] and brain cancer [43,44]. In vitro studies showed that the use of polymeric nanoparticles enhanced drug delivery to the brain, with reduced oxidative stress, inflammation and plaque load through the improved delivery of curcumin for treating Alzheimer's disease [42], and efficient internalization of doxorubicin into the human glioma cells, resulting in cytotoxic effect on cancer cells [43]. Additionally, the in vivo experiment regarding the co-delivery of cisplatin and boldine, an antioxidant agent, using the poly(lactide-co-glycolic) nanocarriers resulted in an effective

target-specific delivery for therapeutic use in brain cancer therapy [44]. Furthermore, the use of a positively charged polymer, poly(ethylene imine) [45], and of the poly(ethylene imine)-poly(L-lysine) copolymer [46] as gene delivery vehicles has been reported. To improve the cytocompatibilityof poly(ethylene imine), L-glutathione was attached to the backbone of the polymer, which also enhanced the passage through the blood-brain barrier in vitro [45]. Thus, it has been demonstrated the potential of poly(ethylene imine)-based nanoparticles for the delivery of genes for gene therapy in brain cancer [45,46]. Another polymer used for the synthesis of nanoparticles for brain delivery is poly(allylamine) hydrochloride. The encapsulation of kynurenic acid into the core-shell structures has indicated neuroprotective properties and therapeutic potential for neurological disorders, in both in vitro and in vivo experiments [47]. Other studies have focused on the use of andrographolideloaded into human serum albumin-based nanoparticles and polyethylcyanoacrylate nanoparticles for the treatment of inflammation related to neurodegenerative diseases. Results showed a slightly increased permeability for the human serum albumin nanoparticles, while the polyethylcyanoacrylatenanoparticles reversibly disrupted the integrity of the cell monolayer utilized for the in vitro experiment [61]. The delivery of docetaxel for the treatment of brain metastasis has been achieved through the development of penetrating amphiphilic polymer-lipid nanoparticles system. The in vivo tests indicated the accumulation of the nanoparticles at the tumor site, with effectively inhibited tumor growth, and increased median survival compared to an equivalent dose of clinically used docetaxelsolution formulation [48]. Chitosan conjugated with L-valine has been utilized as vehicle to deliver saxagliptin, a hydrophilic therapeutic agent, for the therapy of Alzheimer's disease. In the in vivo studies, the nanoparticles showed plasma stability, thus preventing premature release, and enhanced brain delivery compared to the suspension of saxagliptin [62].

Liposomes

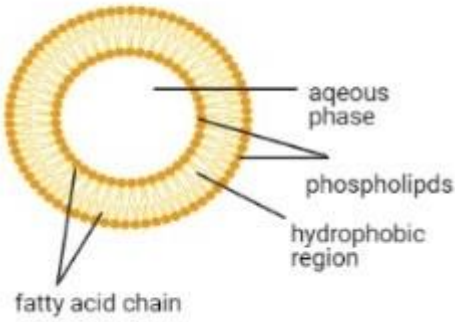


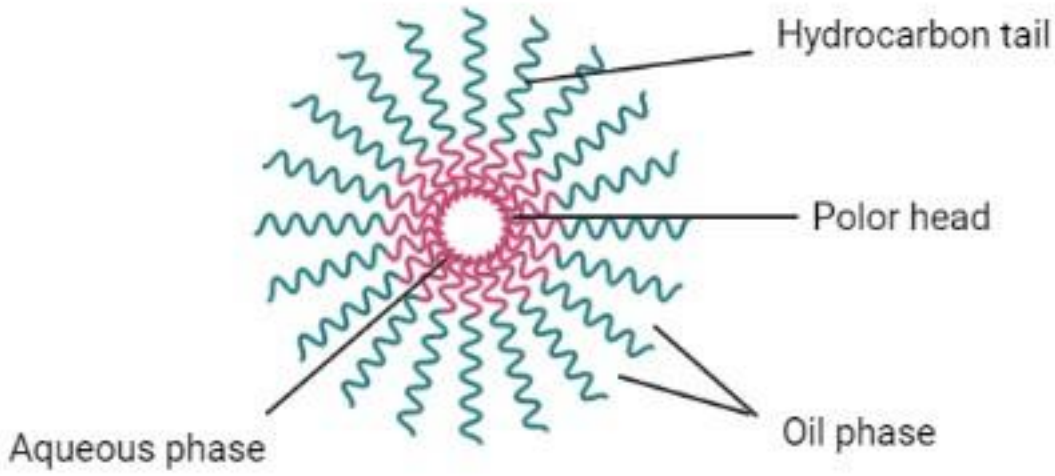
Fig- liposomes

Liposomes are synthetic and spherical cells, consisting of single amphiphilic lipid bilayers, which can entrap therapeutic molecules, including drugs, vaccines, nucleic acids, and proteins. Thus, they have been extensively used as drug delivery systems to enhance the safety and effectiveness of thetherapeutics [63].

The applications of liposomes mostly target brain cancer therapy, due to the capacity to cross the blood-brain barrier and deliver an appropriate quantity of drugs to the brain. Many studies havereported the use of liposomal formulations to deliver anti-cancer drugs, such as methotrexate [64],5-fluorouracil [65], paclitaxel [66], doxorubicin [49,50], and erlotinib [49]. In order to improve theefficiency of the blood-brain barrier passage of the liposomes, there are a few strategies that may beapplied to the formulations. Thus, liposomes can be coated with various molecules: poly(ethyleneglycol) has shown to extend the blood–circulation time of the formulations [64], transferrin for receptor targeting lead to enhanced translocation of the carriers across the brain [49,65], and the glucose-vitamin C complex has improved the accumulation of liposomes at the targeted site [66]. Additionally, in silicoexperiments demonstrated the capacity to facilitate a favorable hydraulic environment around the infusion site to enhance drug transport locally through convection enhanced delivery of liposomes [50]. Furthermore, the inhibition of _-amyloid-induced Alzheimer's disease using a drug carrier systemof apolipoprotein E-modified liposomes conjugated with phosphatidic acid designed to improveblood-brain barrier penetration and release quercetin and rosmarinic acid has been reported [51].Another treatment strategy involves the use of transferrin modified liposomes to

deliver _-mangostin,a potential candidate for neurodegenerative diseases therapy [67]. Both in vitro and in vivo studiesshowed enhanced blood-brain barrier permeation and efficient delivery of drugs.Liposomes have also been utilized as carriers for gene therapy. Research works have reportedthe delivery of oligonucleotides for brain cancer therapy using mannitol for blood-brain barrierdisruption [68] and the delivery of liposomes functionalized with transferrin receptor targeting andpenetratin for enhanced cell penetration for the efficient delivery of nucleic acids for brain diseasestreatment [52].

Micelles



Micelles are amphiphilic molecules, with a particle size within the range of 5–50 nm. Micelles formspontaneously under specific conditions of concentration and temperature of the aqueous solution [75].

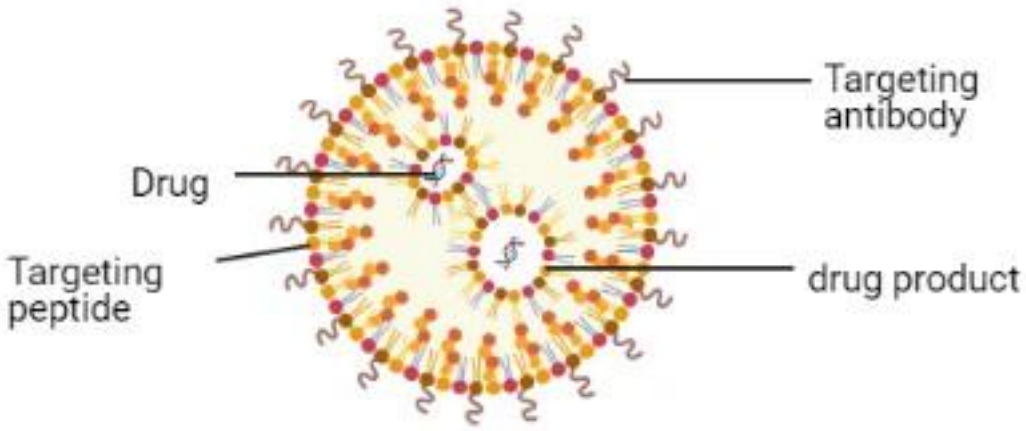
The mechanism involves the self-assembly of amphiphilic molecules, with the hydrophilic/polar

region, known as the head, facing the outside surface and the hydrophobic/non-polar region, known as the tail, forming the core. Micelles have attracted the attention for the delivery of poorly water-soluble molecules, providing sustained and controlled release, chemical and physical stability of the drugs, and improving drug bioavailability [76]. The potential of polymeric micelles has been evaluated for improving the blood-brain barrier passage of drugs for brain diseases therapy. Several block copolymers have been studied, including

poly(styrene)-poly(acrylic acid), poly(ethylene glycol)-b-poly(lactic acid), and distearyl-sn-glycero-3-phosphoethanolamine-N-methoxy poly(ethylene glycol), of which the latter provided enhanced cellular uptake, proving the potential of polymeric micelles to deliver encapsulated drugs to the specific brain sites [77]. Furthermore, the development of targeting and cellular uptake mediating lipopeptide derived from apolipoprotein E, that forms micelles and rapidly incorporates into liposomes have led to the conclusion that the size of the carriers and the surface density of

cationic peptides are key determinants for the development of target specific drug delivery systems to the brain [78]. Recent works have focused on the delivery of curcumin for targeting glioma [79] and treating Alzheimer's disease [55] using micelles as nanocarriers. Additionally, micelles carrying contrast agents might be applied for the magnetic resonance imaging of neuroinflammation [56] and ischemic stroke injuries [57].

Solid lipid nanoparticles



Lipid-based nano-carriers are another type of nanoparticulate systems that offer good drug loading capacities, protection against drug degradation, sustained and controlled drug release and low toxicity issues. Lipid NPs are colloidal particles that can cross the BBB via endocytosis due to their lipophilic nature, which would also have a beneficial effect on the ease of loading lipophilic drugs and surface functionalization [58]. Additionally, lipid carriers

havecomparatively enhanced drug loading efficacies compared to polymeric NPs, allowing them to have greater control over drug release [59]. Yet, they also express some limitations including poor in vivo stability and poor loading of hydrophilic agents [35]. Lipid NPs consist of solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), both of which have been used as drug delivery vehicles for AD treatment. SLNs are typically composed of a solid lipid core matrix, in which the therapeutic drugs can be dispersed or dissolved [60]. Their nano-size (40 nm – 200 nm) offer them the ability to elude the liver and the reticuloendothelial system, and thus penetrate through the endothelial cells of the BBB [61]. SLNs may be prepared from lipids, emulsifying agents, and water/solvent that are biocompatible for application in humans.Different preparation techniques can be utilized in their manufacture comprising ultra-sonication/high-shear technique, high pressure homogenization, solvent emulsification – diffusion, evaporation, double emulsion and spray drying techniques [62]. NLCs, on the other hand, are drug delivery vehicles with both solid and liquid lipid cores, that were developed to avoid some of the limitations of SLNs such as limited drug-loading capacity and expulsion during storage [63].

*Nano emulsion**Neurodegenerative disorders (NDDs) are characterized by the progressive loss of structure or neuron function, often associated with neuronal death. Treatments for neurodegenerative diseases only address symptoms without having any disease-modifying effect but serious side effects. Currently, there is no effective treatment for NDDs. This is due to the poor flow of drugs to the blood-barrier brain (BBB) which does not allow macromolecules like proteins and peptides to pass through it. Targeted drug delivery to the central nervous system (CNS) for the diagnosis and treatment of NDDs, such as Alzheimer's disease (AD), is restricted due to the limitations posed by the BBB as well as Opsonization by plasma proteins in the systemic circulation and peripheral side-effects. Nanotechnology thereby presents a broad approach for transporting molecules through the BBB, thus allowing the entry of substances acting directly on the site affected by the disease. The aim of this review is to outline current strategies in nanotechnology for treating Alzheimer's and Parkinson's diseases.*

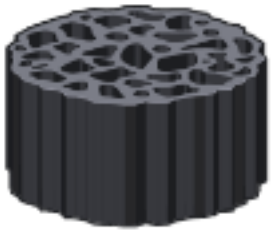
Inorganic nanoparticle

Gold nanoparticle

Gold nanoparticles have been commonly studied in the therapy of neurodegenerative diseasesthrough the functionalization with therapeutic macromolecules. The treatment of Alzheimer's disease by using gold nanoparticles functionalized with _-amyloid specific peptides [67] and the treatment of Parkinson's disease with L-DOPA functionalized multi-branched nanoflower-like gold nanoparticles [68] have been studied, showing enhanced blood-brain barrier permeability across in vitro models. Furthermore, the effect of insulin-coated gold nanoparticle size on the capacity to overcome the blood-brain barrier has been studied. Results showed that the smallest nanoparticles, with the diameter of 20 nm presented the most widespread biodistribution and accumulation within the brain [69]. Similarly, insulin-coated gold nanoparticles with 20 nm in diameter have been injected into the tail vein of mice. Microcomputed tomography images showed an accumulation in the mice brains, demonstrating the effectiveness of these nanosystems in imaging diagnosis of brain diseases and in the delivery of therapeutic agents [70]. Moreover, transactivator of transcription peptide-modified gold nanoparticles with a 5-nm core size containing doxorubicin, an anticancer drug, and gadolinium chelates as imaging contrast agents have been administered for theranostic applications in glioblastoma. In vitro and in vivo results proved the potential of these nano-carriers to penetrate the blood-brain barrier and efficiently deliver anticancer drugs and enhance brain tumor imaging [71]. nother research work focused on the use of citrate and polyethylene glycol-coated goldnanoparticles for visualizing cortical vasculature changes, which are associated with disruptions in the blood-brain barrier. Nanoparticles were administered to mouse models of stroke and the multi-photon luminescence imaging proved the capacity of the nanoplatforms for monitoring vascular morphology and physiology associated with brain diseases. Furthermore, nanoparticles with 5 nm or smaller diameters

could be useful for the diagnostics of early stages of blood-brain barrier dysfunctionsand for drug delivery [72].

Silica Nanoparticles



Surface modified fluorescent silica nanoparticle derivatives have shown potential for applying them as nano-vehicles for drug delivery to the brain considering the possibility of attaching various.

types of molecules to the core [73]. By attaching lactoferrin on the surface of the polyethylene glycol-coated silica nanoparticles, the process of receptor-mediated transcytosis of these nanosyste has been enhanced, with a maximum transport efficiency observed for nanoparticles with 25 nm.

in diameter. Thus, these nanosystems could be employed for drugs and imaging probes delivery

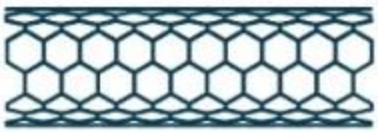
across the blood-brain barrier [74]. The application of silica nanoparticles to deliver nootropics, such as piracetam, pentoxifylline, and pyridoxine, that are designed to enhance the permeability of the blood-brain barrier has been reported. The efficiency of silica nanoparticles as nanocarriers for drugsin comparison to the unencapsulated drugs has been demonstrated, since the latter were not detectedin the brains of the mice [58].

A comparative study between spherical and rod-shaped bare mesoporous silica nanoparticles and

poly(ethylene glycol)-poly(ethylene imine)-coated mesoporous silica nanoparticles has been conducted.

Although the effect of the shape on the blood-brain barrier permeability, coating the nanoparticlesgreatly enhanced the cellular uptake for the in vitro models. However, the in vivo imaging experiments on mice showed no blood-brain barrier penetration, which could be associated to the large dimensionsof the particles, ranging from 50 to 240 nm [75]. Another study on zebrafish embryos demonstrated thatblood-brain barrier penetration is dependent on the surface charge and the size of the nanoparticles, with enhanced transport capacity related to negative charges and reduced sizes [Chen C-T, Chen Y-P, Wu S-H, Chang T-Y, Chou C-M. Negatively charged mesoporous silica nanoparticles penetrate through the Zebrafish larval blood-brain barrier. EuroSciCon Conference on Nanotech and NanobiotechnologyNano; Paris. Nano Research and Applications; 2018.] Polylactic acid-coated mesoporous silica nanoparticles conjugated with a ligand peptide of low-density lipoprotein receptor to enhance the transcytosis process across the blood-brain barrier have been employed in the delivery of resveratrol, a therapeutic agent for excess reactive oxygen species and reactive nitrogen species removal. The in vitro study showed the potential of the 200 nm nanoparticles in antioxidant-based therapy for neurodegenerative diseases and neural injuries treatment [76].

Carbon Nanotubes



Carbon nanotubes are a class of nanomaterials, consisting of graphite sheets tubes with nano-scaled diameters. Carbon nanotubes can be single-walled or multi-walled, with open ends or closed with fullerene caps [77]. Recently, they have gained a great interest as nanocarrier systems, due to the possibility of functionalization with specific chemical compounds, thus modifying their physical and biological properties. Additionally, carbon nanotubes can be applied cancer therapy through photothermal action [78].

Polymer-coated carbon nanodots [60] and chemically-functionalized multi-walled carbon nanotubes [59] have been applied for the delivery of drugs for brain cancer therapy. Both in vitro

and in vivo experiments indicated the penetration of the blood-brain barrier and enhanced uptake in tumors [59,60]. For the treatment of Alzheimer's disease, berberine, an isoquinoline alkaloid, used for the management of dementia and other neurological disorders, has been adsorbed onto the surface of multi-walled carbon nanotubes. Comparing to the administration of the pure drug, this drug delivery system significantly improved drug absorption in the brain, with potential in reducing _-amyloid induced Alzheimer's disease [79].

The permeation of amino-functionalized multi-walled carbon nanotubes through the blood-brain

barrier has been studied in vitro, using a co-culture model comprising primary porcine brain endothelial cells and primary rat astrocytes, and in vivo, through the systemic administration in

mice. The results of the study could pave the way for carbon nanotubes application in the delivery of drugs and biologics to the brain, causing no toxic effects on the cells [80]. .

Conclusions and Perspectives

Drug targeting and delivery to the brain represent key challenges due to presence of the blood-brain barrier, which is responsible for the protection of the brain against foreign substances. In order to progress in the effective treatment of brain cancer, neurodegenerative disease, and stroke,which are highly prevalent diseases, novel strategies for the enhanced passage of the blood-brainbarrier must be developed. Nanotechnology-based approaches are intensively studied at the moment,including nanoparticles, liposomes, dendrimers, micelles, and carbon nanotubes as nanocarriers toovercome the blood-brain barrier and deliver the appropriate amount of drug to the specific brain site.Further research is needed to understand and mediate the blood-brain barrier crossing mechanismsand to improve the efficiency of brain delivery

methods using nanotechnology.

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