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ABSTRACT:
Neurological disorders are increasing exponentially and at an alarming rate, affecting great number of people globally. Normal functioning of the central nervous system (CNS) depends on the blood-brain barrier's (BBB) integrity. Therapeutic amount of some drugs cannot reach the brain; therefore majority of effective pharmaceuticals that have been produced for the treatment of neurological illnesses have subpar therapeutic results. Due to lack of targeted drug delivery mechanism, there is a large concentration of these drugs in the body's essential organs, and this might be harmful to the body. To surmount this challenge, patients are given high doses of medication in an effort to reach the brain more quickly, which ultimately causes off-target organ toxicity. Therefore, there is a pressing need to develop effective treatments for neurological disorders. Nano systems for drug delivery have been investigated because of their targeting capabilities. Chitosan is a natural polymer that is frequently used to create drug delivery nano-systems. Because of its special qualities, including biocompatibility, biodegradability, and mucoadhesive properties, it enables targeted therapy without posing any hazardous risks. Recently, drug delivery nano-systems, hydrogels, and scaffolds made of chitosan have been employed to treat several neurological conditions. This review will concentrate on brain-targeting nanoparticles made of chitosan.

Key words: Chitosan; neurological disorders; blood brain barrier; nanoparticles; drugs

INTRODUCTION:

Chitosan – Properties and Uses:

Chitosan (CS), an amino polysaccharide that occurs naturally, is among the widely used polymers in biological and medical sciences and it comes after cellulose in terms of prevalence [1] Chitin, which is found in the water-inhabited animals, outer skeleton of insects, fungus, yeast, and microalgae, is converted into chitosan through partial deacetylation in an alkaline medium [2]. Chitosan is a linear polysaccharide with a random distribution of N-acetyl D-glucosamine and β-(1→4)-linked D-glucosamine. Its molecular weight (MW) varies between 300 and 1000 kD with a deacetylation degree (DD) of 30–90% depending on the source and methods of production [2]. With a pKa value of approximately 6.5, the amino group in CS undergoes considerable protonation in neutral solutions. These fundamental variables—MW, DD, and pKa—determine the characteristics and biological effects of chitosan. In terms of use and distribution, it is regarded as the second-largest renewable biomaterial after cellulose [3]. Because of chitosan's special qualities, including its high biodegradability, lack of toxicity, biocompatibility, and bio-adhesiveness, it can be used to create systems that target the brain. In situ gel, nanoparticles, liposomes and nano-emulsions are a few of the reported chitosan nanocarriers that have been developed for targeting the brain [4]. Chitosan's natural origin and a number of biological characteristics, such as lack of toxicity, lack of allergenicity, biocompatibility, and biodegradability, coupled with its ability to fight bacteria, fungi, oxidative stress, tumor and inflammation, have led to an increase in consideration of chitosan as a substance that is suitable for introduction in to the living tissues. Moreover, it has been known to help the immune system, fight thrombosis, and fight accumulation of cholesterol in the body [5, 6]. Also, due to its tremendous adaptability, it can be used to create a variety of physical objects, including membranes, films, fibers, nanoparticles, beads, sponges and gels [7]. Chitosan is very useful in various biological and medical fields, including regenerative therapies, gene delivery, drug delivery and tissue engineering, and many more, thanks to all these qualities [4].

Chitosan's Functional Groups:

The reactive functional group attached to C-2 location is amino group, C-3 location is primary hydroxyl and C-6 location is secondary hydroxyl. The functional groups in chitosan enable many alterations to be made to its structure, including O-carboxymethylation, tosylation and acylation, and lipids and antibodies functionalization [8]. Chitosan is converted into 3N-trimethyl chitosan (N-TMLCs) via amino functionalization with methyl iodide at high temperatures and alkaline conditions. Nevertheless, the typical method of modifying chitosan to produce N-TMLCs uses hazardous solvents such N-methyl

pyrrolidinone. By employing batches with varying degrees of deacetylation or by increasing the number of reaction steps or the reaction period, it generates N-TMLCs with a quaternization degree (QD) that can be increased. When increasing the DQ, O-methylation on the hydroxyl groups can occur, leading to a less soluble compound. But even N-TMLCs with a QD of 10% had a number of benefits because of its persistent positive (+ve) charges. The benefits entail enhanced porosity, strength, absorption effectiveness, and muco-adhesivity as well as better solubility in a wide pH range [9]. Moreover, a low QD can increase the loading efficiency of drugs [10].

The permanent positive charges can facilitate absorptive mediated transcytosis (AMT) of Nanoparticles (NPs) and, because of this, N-TMCs can be used to increase the transport of actives to the brain [11]. However, by raising the chitosan QD that consequently results in a bigger diameter of particle, more positive charges can be achieved [10].

Central Nervous System (CNS) and Blood-Brain Barrier (BBB):

The brain is a part of the CNS, which is regarded as one of the most significant component of the whole body. The neurons of the CNS are essential parts, and these neural networks are in charge of controlling neuronic signaling by using a variety of neurotransmitters and electrical signals to control the synapses and axons' ionic surrounding [12]. The BBB controls the ideal neural environment, hormonal system and preserves homeostasis [13, 14]. The BBB is a complex, dynamic network of blood vessels and brain tissues that serves as a great selective semi-permeable interconnection between the brain and blood. It blocks the influx of toxic materials like particles made of cells, blood and other microbial organisms that are toxic to the neurons [15]. To stop the onset of neurodegenerative conditions, it is crucial to effectively block this route of these blood-borne substances entering the CNS. This barrier is made up of several neurotransmitters that support efficient communication with other CNS cells in order to control important events and provide maintenance of homeostatic mechanism. For example, they respond to pathological situations, both at the start of a disease and as it progresses [15].

The BBB is made up of greatly specialized cells of the endothelial which are bound to one another tightly by uninterrupted tight junctions (TJ), including claudins, zonula occludens junctions and adherens junctions (AJ). TJs contribute to the BBB's tightness [16]. Other cellular substances, such as neurons, microglial cells, pericytes, and astrocytes which endothelial cells communicate with to form the neurovascular unit, also contribute to the BBB's tightness [17]. Pericytes which is one of the components of BBB consumed substantial amounts of lactate, suggesting that they are predestined to utilise this remnant of glycolytic metabolism. Lee *et al.* [18] also performed

metabolomic analyses to gain insight into pericytes' lactate usage. These metabolic labelling studies indicated that lactate is a readily available carbon source for pericytes, fuelling tri-carboxylic acid cycle (TCA) activity, ATP production, and amino acid biosynthesis. The BBB keeps the CNS in homeostasis and ensures that the brain is supplied with nutrients by preventing hazardous chemicals from entering it. The BBB highly expresses transporters and receptors to guarantee that the brain receives nutrients at an appropriate amount because it is greatly needed by the brain [19]. The BBB is a highly constrictive physical barrier that protects the brain's tissue's homeostasis [20, 21]. For every gram of brain tissue, the BBB's surface area is roughly 150 - 200 cm^2 or 12-18m 2 gross areas for an adult person [22]. Microvascular endothelial cells are mostly present in it [22], and this result in the creation of walls of blood vessel connected by tight joints [23].

Neurological Disorders:

Neurological illnesses that affect the CNS are the main global causes of morbidity and disability [24]. Parkinson's disease, Huntington's disease, brain tumors, stroke, multiple sclerosis, traumatic brain injury, Alzheimer's disease and motor neuron disease are examples of common neurological illnesses. According to a thorough analysis of disorders, injuries, and predisposing factors conducted in the year 2016, 276 million people worldwide have neurological disabilities, and around 9 million people die from neurological ailments each year [24]. There will be a greater need for more effective treatment and management of neurological illnesses due to an aging and expanding global population.

The brain and spinal cord, which are the components of the CNS, are the primary sites of neurological diseases. The CNS, which is crucial to the body's ability to operate and be regulated, contains three barriers: the choroid plexus epithelium, the cerebral microvascular endothelium (also known as the blood-brain barrier, or BBB), and the avascular arachnoid epithelium. Transporting drugs into the CNS can be quite challenging because of these natural barriers, especially the BBB. Additionally, important component of the CNS include neurons that have considerable cell-cell communication capabilities. Because of how sensitive neurons are to changes in temperature, infections, and toxins, neurodegenerative illnesses including Alzheimer's, Parkinson's, and Huntington's are frequently connected with irreversible neuronal cell death [25].

The progressive and slow loss of functions by the neuron caused by ischemia or hypoxic situations such as traumatic brain traumas, stroke and birth asphyxia can also lead to the irreversible process of neurodegeneration. Additionally, oncogenic alteration of cellular and genetic components in glial cells and neurons is what causes brain malignancies like glioblastoma. In addition to primary tumors, 9–

17% of adult cancer patients also develop secondary brain tumors involving brain metastases [26].

Alzheimer's disease (AD):

AD is a neurodegenerative condition that leads to increased deterioration and loss of neurons. It causes a steady loss in behavioural, cognitive, and other social abilities, interfering with the individual's capacity for independence. Dementia, anxiety, memory loss, restlessness, exhaustion, and vertigo are a few symptoms of AD [27]. AD is also linked to a number of genes, including presenilin-1 (PSEN1), apolipoprotein (APOE4), amyloid-beta precursor protein (APP), microtubule-associated protein tau (MAPT), and presenilin-2 (PSEN2) [28]. Neuronal loss, Aβ plaques, hyperphosphorylated tau neurofbrillary tangles (NFTs), and cerebrovascular dysfunction are all key factors in the etiology of cognitive impairment and AD [29].

NFTs can also result in AD, which is linked to chromosome 17q21, if phosphorylated tau protein builds up in the brain cell. In addition, tau is a protein connected to the microtubules that promotes transport of axons necessary for trafficking and signaling of neurones [30]. Every molecule of tau normally consists of phosphates which could be two or three; however, in tauopathy patients, the phosphoryl concentration is multiplied by many times. When tau protein is hyperphosphorylated, it separates from the microtubule, causing unbound microtubules to proliferate and phosphorylated tau protein to gradually build up until NFTs are formed [31]. PSEN (1 and 2) are the enzyme γ - secretase's catalytic components [32].

It has been demonstrated that human PSEN1 mutations encourage BBB disintegration and cerebrovascular impairment [33]. 5% of all cases of AD have PSEN2 mutations [34]. Additionally, among the main genetic predisposing factors for late-onset AD is APOE4. APOE4 alleles greatly increase the susceptibility of having AD more than APOE3 alleles. Because of APOE, the neurons, the brain, and the vascular system experience harmful consequences [35]. Human APOE4 carriers may experience early neurovascular dysfunction, pericyte degeneration, progressive BBB breakdown, and impaired BBB glucose absorption [36, 37]. Fibrinogen, IgG, albumin, hemosiderin and thrombin have been shown to leak from vascular capillaries inside the entorhinal cortex, hippocampus, and prefrontal cortex of a person suffering from AD. It has been determined that AD is caused by co-localization of proteins with Aβ and mutations of about 40 APP [38]. This results in BBB disintegration, cerebral amyloid angiopathy (CAA), and cerebrovascular disease [39].

Parkinson's disease (PD):

The build-up of α-synuclein (α-syn) and the subsequent degeneration of neurons that produce dopamine in the substantia nigra pars compacta (SNpc) are hallmarks of PD [29]. This eventually leads to a locomotory problem,

because the SNpc is connected to a nigrostriatal circuit which helps to stimulate the cerebral cortex and also initiate locomotion. Patients with PD struggle to do daily activities like walking, running, etc. because of muscular rigidity in their limbs. Cognitive issues, dementia, dizziness, diminished facial expression and a loss of postural reflexes are further symptoms.

In PD patients, basal ganglia's vascular dysfunction results in BBB degradation and malfunction. Neurotoxic fibrinogen, thrombin, plasminogen, and RBC extravasation build up as a result of BBB degradation. ROS are produced by the release of Hb and Fe^{2+} that damage dopaminergic neurons. During neurodegeneration, pro-inflammatory cytokines such as TNF, IFN- γ, and IL-1 β, are produced. Recently, few findings have shown the capacity of α-syn to pass through the BBB as well as its role to build-up of α-syn pools in the CNS. LRP1-mediated transcytosis then facilitates additional clearance of the brain through the BBB. Leucine-rich repeat kinase 2 (LRRK2) missense mutations have been connected with late-onset PD (>50 years) [40].

Epilepsy:

The erratic and uncontrolled activity of either the entire CNS or just a portion of it is what defines epilepsy. When CNS excitability exceeds a specific critical threshold, an epilepsy patient will experience attacks [41]. Seizure is different from epilepsy because it occurs only once, whereas epilepsy involved two or more seizures [42]. Seizures can also be localized, for example when scar from the brain tissue draws nearby tissue from neuron, specific area of the brain compressed by an abnormal growth, or when near-by brain's neural network is congenitally dysregulated [43].

Strong emotional stimulation, traumatic injuries, and over breathing-induced alkalosis can all lead to epilepsy. Epileptic person also manifest symptoms like loss of TJs, disrupted GABAergic processes, rise in microvascular density, leakage of IgG in hippocampal regions, a brief moment of memory loss [44], jerks, breathing problem, shock movements, lack of comfort, sudden anxiety, and rage [45]. The frequency of seizures and BBB dysfunction are categorically unrelated, and neither is neuronal loss.

Proinflammatory molecules like IL-1β, TNF-α and High Mobility Group Box 1 (HMGB1) are produced and discharged by epileptogenic injuries as well as seizures, which lower the threshold for seizures. This later leads to formation and recurrence of seizure due to swift transformation in phosphorylation of γ-aminobutyric acid (GABA) receptor and glutamate. Additionally, it results in channelopathies that alter the innate brain ability to excite [46]. BBB breakdown can result from seizures, and artificially opening the BBB causes rat neuronal activity to synchronize, causing neuropil, immunoglobulin G (IgG), and albumin eruption. Neuronal hyperexcitability is caused by albumin altering astrocytes' ability to buffer K+ [47]. The integrity of the BBB is also

affected by transforming growth factor- β (TGF-β) produced by other types of cell. When tissue plasminogen activator (tPA) is suppressed by plasminogen activator inhibitor-1 (PAI-1), astrocytes release TGF, which causes the BBB to close [48].

Cerebral ischemia:

Brain disorder known as cerebral ischemia is brought on by a transient or unending reduction in the blood flow of cerebral artery. One of the major causes of disability and mortality, cerebral ischemia's clinical feature is partial neurological dysfunction [49]. Neurons in the frontal sensorimotor cortices and caudate-putamen in particular may eventually die from cerebral ischemia, which can also cause a variety of motor and sensory-motor abnormalities which include loss of coordination, dyskinesia, and partial paralysis occasionally.

Multiple Sclerosis:

A neurodegenerative condition called multiple sclerosis (MS) causes the BBB to become damaged, eventually allowing B cells, peripheral macrophages, and CD4+ T cells, to move in to the central nervous system (CNS). This sets off sequence of inflammatory reactions that causes demyelination and loss of axon [50]. The optic nerves, brain, and spinal cord are all impacted by MS's demyelination and inflammation of the nerves. The Major Histocompatibility Complex (MHC) contains several genes that increase a person's susceptibility to MS. Leukocytes, especially T-cells, have been thought to move to the BBB [50]. The symptoms include tingling, numbness, and vision issues, changes in the optic nerve, sensory, bladder, and bowel functions, as well as cognitive deficits. The hallmarks of MS include an early BBB collapse, fibrinogen build-up, deterioration of endothelium, and decreased TJs' expression. Among the early cerebrovascular abnormalities seen in MS are movement of stimulated leukocytes from one endothelium to another, and dysregulation of BBB which results in the release of chemokines and inflammatory cytokines [51].

Chitosan Nanoparticles:

AS a result of their positive charge, this improved cell absorption and made them amenable for loading with negatively charged therapies, chitosan nanoparticles (CS-NPs) is promising for brain delivery. Chemotherapeutic medicines, siRNAs, and natural products can all be successfully delivered to the brain via chitosan nanoparticles. The chitosan utilized in different nanoparticles has varied molecular weights and is combined with other components. The primary method for creating nanoparticles is by crosslinking of ion, and this produces particles which is roughly 100 nm in size. Chitosan nanoparticles are often administered intravenously, while intranasal delivery is also widely employed.

The characteristic properties of the produced chitosan or chitosan-coated nanoparticles will

depend on the co-used material, chitosan's molecular weight, method of preparation, and modifications of various targets, which will then depend on the effects on the treatment of brain diseases. Chitosan is typically combined with other materials in intravenous delivery systems to enhance loading of drug, sustained release, drug uptake by the cell, drug delivery, and drug targeting. Additionally, chitosan can serve as a carrier to encapsulate siRNA, peptides, and proteins, by moderate interactions of ion because it is a linear polyamine that contains many groups of cationic amine.

In addition to the benefits mentioned for intravenous administration, the muco-adhesiveness and the positive charge of chitosan can enhance the time of retention and movement of CNps into the nasal mucosa after intranasal administration. Depending on the design, chitosan and its derivative coating can exhibit various chitosan properties.

Chitosan has a good biodegradation rate and is biocompatible, making it a viable excipient in pharmaceutics. Chitosan can be used to create nanoparticles that act as an excellent carrier for chemotherapy agents with low bioavailability and stability in gliomas.

Due to chitosan's inherent beneficial properties, including biodegradability, biocompatibility, bioactivity, ease of preparation, non-toxicity, and to a certain extent, target specificity as a result of its positive charge, chitosan nanoparticles are used as a great and efficient carrier of drugs [52]. CS-NPs have improved bioavailability, a high rate of hydrophobic drug dispersion, and good mucoadhesive properties. Additionally, CS NPs can be loaded with both water-soluble and water-insoluble medications.

Methods of Preparation and Mechanisms of Chitosan Nanoparticles:

The enhancement or addition of physicochemical and biological properties is possible by attaching chitosan to the surface of nanoparticles. Chitosan, for instance, can boost or flip the zeta potential of a nanoparticle from anion to cation that can result in a great biological association with negative cellular obstruction or barriers and a higher rate of cellular internalization. Furthermore, the use of chitosan in the decoration increases affinity for water, making it stable in water environment and enhancing the ability to experiment with additional administrative strategies [53]. The creation of both covalent and non-covalent associations between the molecular chains of chitosan and the nanoparticle materials' chemical groups are two ways that chitosan can perform the superficial modification [54].

The optimal process will produce superior outcomes since the architecture of chitosan coating is determined by the production technique, the chitosan type, and the nanoparticle's molecular characteristics. Notably, covalent pathways result in connections that are more persistent and are easily distinguishable by analytical methods like NMR, HPLC or infrared [55]. The process can,

however, become convoluted, rarely scalable, and difficult to duplicate. The non-covalent mechanism, on the other hand, exhibits weak interactions that are effectively stabilized by counter-ions and other polymers. In contrast to covalent bonds, which require strong chemical reagents or extremely harsh processing conditions, non-covalent bonds exhibit lower toxicity, are scalable, and simple to validate.

Non-Covalent Mechanism:

This process is dependent on connections created at the molecular and supramolecular levels by hydrogen bonds and coulomb attraction forces. The association between nanoparticles material's functional group and the chain of chitosan is responsible for the stable presence of chitosan on the nanoparticle. By soaking both the nanoparticles and a specified amount of chitosan in a solution, an adsorption process controlled by a mechanism of interaction of charge is often used to coat them with chitosan. Nevertheless, this idea is workable if the nanoparticles' chemical and physical characteristics are sufficiently stable, and if they already have a mostly anionic charge. Amine group's cation and the backbone of chitosan then encourage the particles' coating over when it interacts with chitosan. As long as they maintain a sufficient level of resistance to change in aqueous dispersion at the early phase, nanoparticles based on lipids, inorganic materials, polymers, and proteins are excellently suitable for the adsorption technique. By incubating nanoparticles in solutions containing chitosan with various amounts the two materials at various durations, the adsorption process may be improved in order to preserve a particular bio adhesion's level and size of particle.

Nanoparticles can be added either by resuspending it in the solution of chitosan or by adding drop wise of nanoparticle solutions (to distribute the particles) [56, 57]. The non-covalent method's main benefits are its low cost, hospitable chemical environment, and simplicity of application. As a result, before attempting another strategy, it is likely the first option that the majority of research organizations have examined for the chitosan-coating of the nanoparticles.

The Covalent Mechanism:

The covalent processes for chitosan coating on nanoparticle surfaces are concentrated on using chemical processes and reactions that need gentle circumstances, such as no severe pH levels, ambient temperature, less difficult purification process, and reagents that are low in toxicity. One of the most popular techniques is the crosslinking of chitosan via the carbodiimide reaction. The activation of carboxyl groups in this process results in the creation of a carbocation, which is then attacked by primary amino groups nucleophilically. One of the most popular chemicals used for this is 1-Ethyl, 3-(3-dimethyl aminopropyl) carbodiimide (EDC), which is the proper chemical. The new covalent

link is formed when chitosan's amino group readily displace the intermediate product of the EDC process, which is O-acylisourea. The reaction of EDC can be carried out before, pre-, during or post-synthesis of nanoparticles [58]. Some processes use chemicals like 1, 4-dioxane triethylamine and dimethyl aminopyridine to apply the carboxyl activation, and in a subsequent stage, EDC catalysed the production of amide bond. During the activeness of carboxyl group, the chitosan addition produces covalent bonding most effectively.

Chitosan Nanoparticles Routes for Passing through the Blood Brain Barrier:

Brain's drug delivery is complicatedly hampered by the BBB's highly selective and controlled molecular transport [59, 60]. In this regard, it has been demonstrated that both chitosan and its coated nanoparticles increase the effectiveness of targeting the brain, increasing the effectiveness and efficiency of medications. As a result, various scientists have examined the routes taken by CS-NPs to pass through the BBB, identifying a number of mechanisms that give rise to a variety of ideas [61, 62]. There has been an extensive research on how CS-NPs can carry medications to the brain. Example of such is Trapani *et al.* [63] who assessed the movement of CS-NPs that have been loaded with dopamine (DA/CS-NPs). The Madin-Darby canine kidney (MDCKII-MDR1) cell line was used in those tests to measure the internalization of the five mg of dopamine that was put into the nanocarrier. The Fluorescein Isothiocyanate (FITC)-labelled nanoparticles were incubated for duration of 3 hours at the apex after the cells were implanted in Transwell filter inserts. Nanoparticle-free media was used for the control studies. Apical media samples were taken at various intervals, and fluorescence microscopy was used to gauge the FITC concentration. According to their findings, the scientists hypothesized that the nanoparticles' internalization was caused by a transcytosis process that is mediated by adsorption, with the main contact being between the charges of the chitosan and the cell monolayer [64].

Similar to this, it was claimed that absorption-mediated transcytosis might be used to transport anti-neuroexcitation peptide-loaded N-trimethyl chitosan nanoparticles (ANEP/TMCNPs) over the BBB [9]. The ANEP/TMCNPs produced a robust signal in the brain, according to the data based on fluorescence. The controls, on the other hand, showed a meager fluorescence. The positive charge of the ANEP/TMC NPs and their connection with the anionic plasma membrane present on the endothelium of brain capillary were cited by Wang *et al*. [9] as the causes of this behaviour. On the other hand, a number of publications also noted that chitosan can allow epithelial cells' tight junctions to open. MDCK-C7 cells' tight junctions (an in vitro BBB model) and capsaicin-loaded chitosan-coated nano-

formulations interaction was examined by Kaiser *et al*. [65].

Chitosan opened the tight connections, according to analysis using digital holographic microscopy. Alkyl glyceryl chitosan nanoparticles' permeability and effect on bEnd3 cells layer which is another BBB model were also evaluated by Lien *et al*. [66] in 2012. Their findings showed that the electrical resistance was reduced as a result of the nanoparticles, suggesting a tight connection effect. The scientists noted that there were no changes in electrical resistance seen in glial due to nano-formulations, proving that cells of the endothelia are the only cells that can vary in this attribute. Additionally, the FITC-dextran translocation through the barrier was stimulated by the nanoparticles' incubation in the layer of aforementioned BBB model. Together, these findings suggest that chitosan and its coated nanoparticles may be able to pass through the BBB; as a result, those materials may be helpful for the brain's drug administration. It is also thought that the cation given to the nanoparticles' surface by chitosan may interact with the anionic places on tight junctions and cell membrane, enabling them to pass across the BBB.

Chitosan Applications in Brain Delivery System: Parkinson's, Alzheimer's, gliomas, and other brain illnesses affect about 1.5 billion people worldwide today [67]. Among the most significant and intricate organs in the human body is the brain. The BBB, a monolayer of polarized endothelial cells, is what gives it its special qualities. The microvasculature of the spinal cord and the brain has this monolayer that is a selective semipermeable boarder. Chemicals, neurotoxins, and microorganism transport from blood to the CNS are constrained by TJs among BBB endothelial cells. Further entrance barrier to drugs is efflux transporters, which are found in the brain microvasculature [68]. However, BBB also makes it challenging for drugs to reach the brain, which would be helpful in the treatment of CNS illnesses [67].

The need to reassess the brain medication delivery concept is highlighted by the increase occurrence of brain illnesses and the poor delivery of medications to the brain, but it also highlights the enormous room for innovation. Numerous novel strategies are being used in conjunction with recent developments in BBB research [69]. Chitosan has played a very intriguing role in the creation of these novel techniques, whether it is through the use of hydrogels, hydrophilic nanoparticles, and microparticles, or serving as a grafting for other medications' delivery methods. Among the most effective and efficient approaches of delivering drugs to the CNS is nanoparticulate drug systems, which can transport both hydrophilic and hydrophobic medicines as well as macromolecules [70, 71]. Nanoparticles' dimensions play a role in their ability to move through the blood-brain barrier, but also a balance between size, surface properties, and

form [69]. Chitosan-based nanoparticles are a promising method for delivering medications to the brain as a result of their positive charge, biocompatibility, and capacity to pass the blood-brain barrier through opening of TJs (a paracellular route) [70, 71].

Chitosan Nanoparticles Applications in Nose to Brain Drug Delivery System:

Current treatments for brain diseases face significant challenges with brain medication delivery. Regarding new tactics created in the nanotechnology industry, traditional administration routes like intravenous and oral still represent intrusive methods or are connected to adverse effects [72]. There is now a lot of keen interest in intranasal medicine delivery to the brain after evaluating the beneficial characteristics and adequate properties of the nasal cavity [73]. The intranasal path links the brain to the nasal cavity via the trigeminal nerve and the brain to the neuroepithelium via the olfactory system [74].

This makes the olfactory pathway the most auspicious non-invasive entrance into the brain since as soon as the formulated drug connects with the nasal mucosa; it is immediately transported there, skipping the BBB [73]. In addition, pharmaceuticals that are absorbed after nasal delivery don't go through hepatic or gastrointestinal pre-systemic metabolism, resulting in a greater bioavailability of drug than that attained following drug oral administration.

An important and frequently employed permeation promoter agent is chitosan. Chitosan's functional groups enable electrostatic interactions with the sialic acid found in nasal mucosa. It causes the TJs to open, which improves medication absorption via the nasal epithelium. Chitosan's role as a mucoadhesive agent is supported by evidence that it increases drug residential of the nasal cavity, which enhances absorption and bioavailability [75]. Some studies show that the inclusion of chitosan in nasal formulations increases medication bioavailability. CS-NPs made for the brain via intranasal pathway were able to improve nasal residence in recent in vivo trials, and they also demonstrated a delayed and steady drug release to the brain [76].The majority of the medications under study are not recently synthesized compounds. Researchers have been using well-known drugs, such as nicardipine, ibuprofen, or olanzapine, which are already used in therapy, to investigate their potential healing effects in the brain if taken orally [75]. These studies may also mark a significant advance, particularly in gene therapy. Intranasal gene-silencing agent injection into the brain using nanocarriers is a promising non-invasive method [77]. Additionally, a gel formulation appears to be far more effective than others at extending the duration of drug residence in nasal mucosa among the various intranasal dose forms [78].

Male Wistar rats were given nasal administration of polar pharmaceuticals with low nasal

membrane penetration using chitosan and methyl-cyclodextrin microparticles. For the first time, it was demonstrated that adjusting the quantity of the penetration promoters resulted in an optimum medication distribution between cerebrospinal fluid (CSF) and bloodstream [79]. Chitosan-glutamate microparticle zolmitriptan nasal delivery encourages CNS targeting with less side effects in the periphery. These days, it is impossible to discuss chitosan-based hydrogels without mentioning their usage in the delivery of medication to the brain. They can transport elements for cell development or differentiation, growth factors, or small molecules medications in this context. They can also raise the concentration of a drug at a specific spot while reducing side effects that are not intended to be there [80]. Chitosan hydrogels is created for intranasal administration system, for example, to administer Parkinson's disease's medications because of their muco-adhesiveness and thermo-sensitivity [81]. Poloxamer, carbopol, and chitosan were utilized to create an intranasal thermo-sensitive gel coated with rasagiline mesylate, a medication for treating Parkinson's disease. When compared to oral medication solution, intranasal gels have a much higher drug bioavailability, according to pharmacokinetic studies done in vivo. Furthermore, biological investigations revealed that the nasal formulations had no adverse effects on the animal nasal mucosa and were not irritating [82].

Chitosan-Based Nanoparticles to bypass Blood-Brain Barrier for the Treatment of Neurological Disorders:

The difficulty of drug accessibility makes it difficult to provide effective and efficient treatment for many diseases; including Parkinson's, gliomas, stroke, epilepsy, migraine, Alzheimer's, meningitis, and schizophrenia. Therefore, it has been suggested to use a variety of natural nanocarriers with chitosan-coated surfaces to facilitate their movement across the BBB and provide medications straight way to the brain. Galantamine, donepezil, and tacrine are the three acetylcholinesterase inhibitors that the FDA has approved recently [83]. The first acetylcholinesterase inhibitors authorized for the treatment of Alzheimer's disease is tacrine [84]. Nonetheless, tacrine's absolute bioavailability is too low because of the first pass effect. Wilson *et al*. [85] created tacrine-loaded chitosan nanoparticles to produce prolonged tacrine's release in order to address this issue. The chitosan nanoparticles considerably extended tacrine's half-life after intravenous administration and enhanced the effectiveness of brain delivery. In a different study, Hanafy *et al.* [86] delivered galantamine hydrobromide through the intranasal route using chitosan nanoparticles to treat AD. The findings showed that as compared to nasal and oral administration of the galantamine hydrobromide solution, the complexation of chitosan with

AChE protein considerably decreased its level and activity in the rat brain. Furthermore, the galantamine hydrobromide-loaded chitosan nanoparticles had no harmful effects, demonstrating their excellent biocompatibility [87]. According to reports, the phyto-pharmaceutical piperine (PIP) has the potential to be neuroprotective in AD. PIP chitosan nanoparticles (PIP-NPs) were created by Elnaggar *et al*. [88] for the management of AD. According to an in vitro research on drug release, there is a continuous and steady release of PIP from nanoparticles because only 10% of PIP is released from PIP-NPs in comparison to 82% of free PIP after two hours in phosphate buffer solution. The main characteristic of AD and other serious and prolonged neurodegenerative disorders is neuroinflammation. This finding demonstrated the mechanisms behind PIP's ability to fight apoptosis and inflammation in order to cure AD. In clinics, levodopa is the medication that best treats Parkinson's disease. However, because of its poor oral absorption and erratic plasma levels, levodopa's clinical reaction is unpredictable and inconsistent. In the management of Parkinson's disease, the ergot derivative bromocriptine (BRC), which shows the activity of dopamine receptor agonist, is frequently utilised clinically to postpone and reduce undesirable motor changes brought on by prolonged administration of dopamine. Md *et al*. [89] looked at the impact of intranasally administered CS-NPs on the effectiveness of BRC's brain-targeting. Due to inadequate absorption and substantial metabolism, only a tiny amount of BRC can reach the target region after oral delivery. BRC had a lower striatum-plasma ratio than pituitary-plasma ratio, which means that the BBB was limiting the drug's ability to travel outside of brain tissue. The produced chitosan nanoparticles with BRC can transport the medication across the nasal mucosa while also preventing it from deteriorating inside the nasal cavity. Additionally, by delaying mucociliary clearance, chitosan's mucosa adhesion characteristic could lengthen its stay in the nasal cavity, improving the nasal mucosa’s absorption. Exercise capacity and systemic stiffness were both demonstrated to be improved in the BRC loaded CS-NPs-treated groups and BRC solution, particularly in mouse model [89]. In addition to chemotherapy, neurotrophic substances like glial cell-derived neurotrophic factor (GDNF) could be utilized to protect dopaminergic neurons. Nevertheless, the use of GDNF in clinical settings is not properly imbibed because of its brief half-life and quick break down when injected in vivo, as well as challenges with passing through the BBB brought on by its high molecular weight, charge and innate hydrophilicity [90]. In a 6-OHDA-partly-lesioned rat model, Gartziandia *et al*. [74] investigated the in vivo neuroprotective impact of GDNF enclosed in chitosan coated lipid carrier (CS-NLC-GDNF). There was a considerable drop in the amount of rotations per 60 seconds after 49

days of continuous CS-NLC-GDNF administration; the drop was 80% till the completion of the trial. Additionally, the CS-NLC-GDNF group showed considerably higher tyrosine hydroxylase fiber density in substantia nigra and striatum, suggesting a more effective protective effect than free GDNF.

PD, MS, cerebral ischemia, and other conditions have all been treated with riluzole as a strong neuroprotective drug. Riluzole is the only available medication for the management of motor neuron disease. Nevertheless, due to brief half-life, poor water solubility, and adverse effects toxicity of the lung when given above normal dosage, its utilization has been restricted [91]. Verma *et al*. [92] found that even at very low drug concentrations, chitosan linked N-isopropyl acrylamide nanoparticles could transport riluzole through the BBB and display pronounced protective impact on the neurons. It significantly reduced the needed concentration while also lowering riluzole side effects.

Limitations and Challenges:

The low stability of CS-NPs is one of its main drawbacks. Controlling environmental variables, temperature, introducing the right stabilizing component, mixing CS with another polymer, and modifying the structure of CS using ionic/chemical materials can all increase stability. The poor solubility of CS-NPs is a second significant drawback. Only some medications that have affinity for water can be included in unaltered CSNPs. CS-NPs with modifications could, nevertheless, enclose non-hydrophilic medicines. As a result, some medications' poor solubility poses a serious challenge to the development of CSNPs. To fully understand why NPs are biocompatible with people, toxicology research and legislation are necessary. In vitro research typically yields positive outcomes. Unfortunately, the reality in vivo is frequently isolated from these outcomes. In the end, it is important to consider the financial implications of commercializing a new pharmaceutical medication delivery method for both patients and the pharmaceutical business.

Conclusion and Future Perspectives:

It has been observed that chitosan-based carriers are efficient at delivering medications in vivo for the treatment of a few different brain illnesses. When compared to chitosan nanoparticles lacking antibodies, which were characterized by aggregation, those containing antibodies on the surface were able to pass through the brain barrier and also offer protection to the neurons. Viscosity, size of the particle, charge of the particle, and the addition of antibodies to the nanocarriers all contributed to the significant transport of nanocarrier formulations to the brain by providing neuroprotection, preventing aggregation, extending the nanocarriers' residence time with the nasal mucosa, as well as inducing tight junctions' stretching. According to reports, the nanoparticles were either above or below 200 nm in size. More study is required to determine

the consistency of the range of nanoparticle sizes that are most beneficial for good brain absorption. More in vivo research on coated NPs and NPs that have been conjugated with antibodies are urgently needed. It is also crucial to conduct more in vivo research on these nanoparticles' toxicity over an extended period of time. More research must be done in order to improve and lessen the general problems experienced in treating brain illnesses, despite the unique and encouraging outcomes obtained employing chitosan drug delivery methods. It is crucial to do a long-term investigation on the nanocarriers' possible harm to humans. Additionally, a comprehensive analysis of these carriers' costs should be conducted.

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