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REVIEW PAPER

Unlocking the potential of chitosan-based polymeric nanoparticles for the treatment of neurological disorders

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ABSTRACT

Neurological disorders are the diseases associated with the central and peripheral nervous system. They are among the most serious and prevalent diseases nowadays. However, most of the pharmacological agents used to treat neurological disorders demonstrate severe toxicities and side effects, along with failure to achieve the desired outcomes due to their inability to cross the blood-brain barrier (BBB). Therefore, efforts have been made to develop potential drug carriers that can enhance the penetration of various therapeutic agents across the BBB. Due to the remarkable selectivity of nanoparticles and their ability to penetrate the BBB, they have attracted enormous interest as a viable solution to overcome these challenges. Polymeric nanoparticles used as drug delivery systems, in particular, demonstrated multiple advantages over traditional drug delivery systems in the treatment of neurological and psychological disorders due to several beneficial properties. This minireview article discusses the current literature on the use of chitosan nanoparticles in particular as promising carriers for delivering therapeutic agents to the brain for the treatment of different neurological diseases. The article emphasizes the advantages of using chitosan over other natural and synthetic polymers, and illustrates the methods of preparation of chitosan nanoparticles, in addition to the characterization of chitosan-based nanoparticles. The article also discusses the specific application of chitosan-based nanoparticles for brain targeting with the aim of the treatment of neurological disorders. Furthermore, challenges and future prospects were also discussed.

Keywords: *Chitosan, Drug delivery systems, Nanocapsules, Neurological disorders, Polymer*

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Neurological disorders

Neurological disorders are the diseases associated with the central and peripheral nervous system [1]. Some neurological disorders are characterized by progressive and irreversible degeneration of the neurons, resulting in a reduction in the patients' quality of life, and are referred to as neurodegenerative disorders [2]. They are considered one of the most serious diseases nowadays. Neurological disorders remain increasingly prevalent, especially among the elderly population [3, 4]. Indeed, neurological disorders have a significant impact on the society due to their high prevalence and associated morbidity and mortality [4]. According to the Global Burden of Diseases, Injuries, and Risk Factors Study, neurological disorders are one of the major causes of death and disability worldwide [5]. In addition, neurological disorders account for 12% of total deaths globally [4]. Among the most common neurodegenerative diseases are Alzheimer's disease (AD) and Parkinson's disease (PD), which are characterized by progressive and irreversible degeneration of the neurons [6, 7], resulting in a reduction in the patients' quality of life [6].

Most pharmacological agents used to treat neurological disorders demonstrate severe toxicities and side-effects, along with failure to achieve the desired outcomes due to their inability to cross the blood-brain barrier (BBB) [3]. The BBB is a unique microvasculature structure

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composed of endothelial cells that are closely held together by tight junctions (TJs) [5]. Moreover, the BBB is considered both a physical and a metabolic barrier that protects the brain and regulates the entry of nutrients and drugs into the brain. It also contains a number of enzymes that are responsible for breaking down neuropeptides [6, 8]. In addition, the BBB encounters efflux pumps that expel harmful agents as well as therapeutic agents. Therefore, the BBB is considered the main obstacle that limits the effectiveness of most substances. In general, macromolecules such as antimicrobial and anti-tumor agents are unable to cross the BBB, while only 2% of small molecules such as opiates are able to cross this physiological barrier [4]. Due to the high prevalence of CNS disorders, efforts have been made to develop potential drug carriers that can enhance the penetration of therapeutic agents across the BBB. In this context, nanoparticles designed for drug delivery have gained immense interest as possible means to overcome these limitations [3, 6]. This is due to the high selectivity of nanoparticles, which enables them to maintain the optimum therapeutic index of the drug with minimal side effects [9]. This review paper discusses the specific application of chitosan-based nanoparticles for brain targeting with the aim of treatment of neurological disorders.

Drug delivery pathways for neurological disorders

Only small lipid-soluble molecules with a molecular weight less than 400 Da can cross the BBB [10]. Therefore, the delivery of therapeutic agents to the brain for the management of neurological disorders is quite challenging. Other than the conventional methods, a number of drug-delivery pathways have been developed in order to overcome these obstacles and deliver the drug to the brain in a safe and effective manner. For instance, the intranasal route is recognized as an effective means of administration to deliver drugs to the brain for the management of neurological disorders [11, 12]. The intranasal route has shown great benefits over traditional systemic administration methods, for being non-invasive, fast, and associated with fewer side effects [11]. Intracerebroventricular (ICV) injection is another technique for delivering drugs directly into the brain by injecting them into the cerebral ventricles in order to bypass the BBB and minimize the systemic side effects [13]. Clinical studies have demonstrated the effectiveness of this technique in managing the symptoms of parkinsonism [14]. Convection-enhanced delivery is a new promising technique that delivers therapeutic agents via an infusion catheter to the CNS [15]. This technique is used for various neurological disorders such as Alzheimer's and Parkinson's diseases, and it also allows bypassing BBB, fast drug delivery and fewer systemic side effects [15].

Several drug delivery systems have also been emerged for brain delivery. These drug-delivery systems include viral vectors, exosomes, active transporters, brain permeability enhancers, and nanoparticles [10]. Viral vectors, such as adeno-associated viruses, are used for gene delivery to the brains of patients with neurological disorders through passive transport across the BBB [16]. However, the use of viral vectors is limited due to the high cost of production and concerns about their safety and immunogenicity [16]. Exosomes have been used as a non-immunogenic alternative to deliver small molecules to the brain, such as, nucleic acids [17]. The use of active transporters, such as amino acids, has also been investigated for drug delivery to the brain via active transport across the BBB [10]. For instance, an attempt was made to enhance the uptake of dopamine by the brain using an amino acid carrier transporter [18]. In addition, some molecules act as brain-delivery enhancers through their ability to open the BBB and allow the passage of higher concentrations of drugs to the brain [19]. Nanoparticle-based drug delivery systems improve drug stability, promote drug passage across the BBB, and improve their efficacy while minimizing their side effects [20]. In the next section, the advantages of using nanoparticle-based drug delivery systems is discussed thoroughly.

Nanotechnology targeting BBB penetration

The BBB is the major physiological barrier that protects the brain and regulates the transport of molecules to the brain [21]. Drug delivery to the brain requires a strong understanding of the physiology and anatomy of the BBB [3]. Briefly, The BBB is composed of tightly connected microvascular endothelial cells, pericytes, and astrocytes [22]. The endothelial cells are connected by tight junctions (TJs) and adherence junctions (AJs) [22]. This complex structure of the brain is the reason for the selective permeability of molecules. Consequently, it is responsible for

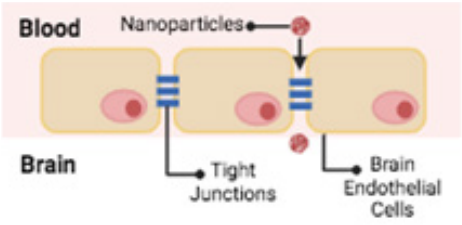

Fig. 1. Schematic illustration of nanoparticle penetration of the BBB (Created in Biorender.com)

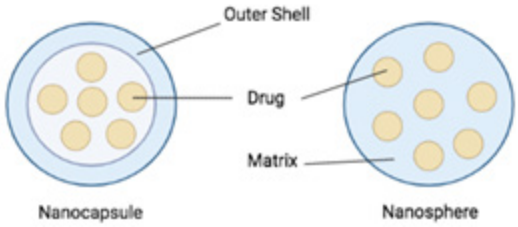

Fig. 2. Schematic illustration of nanocapsules and nanospheres (Created in Biorender.com)

the limited efficacy and increased side effects of neurological medications given in conventional drug dosage forms [6]. For instance, the most effective intravenous formulations are only able to deliver 5% of the initial dose to the brain [23].

In order to overcome the obstacle of the BBB hindering the delivery of therapeutic agents to the brain, several nano-drug delivery systems have been designed to deliver a therapeutic agent to specific sites in the body [6]. A graphical illustration demonstrating the penetration of nanoparticles through the BBB is presented in Fig. 1. According to Saraiva et al. (2016), these nanopreparations demonstrated promising findings in the management of neurodegenerative diseases [23].

Nanoparticles are commonly sized between 1 and 1000 nm, enabling them to easily penetrate the BBB and enhance the therapeutic efficacy of the drug, while minimizing its side effects [23]. Upon increasing the bioavailability of the drug at the target sites, nanoparticles are capable of reducing the required doses [23]. In addition, nanoparticles demonstrate sustained, slow, and controlled release profiles, which help to overcome toxicities while also protecting the drugs against enzymatic degradation in the gastrointestinal tract [3]. Polymeric nanocapsules, in particular, are found to be effective in transporting bioactive agents across the BBB in several *in vitro* and *in vivo* models.

Polymeric nanoparticles

Siddiqi et al. (2018), defined polymeric nanoparticles as solid colloidal particles that are able to attach, adsorb, dissolve, and encapsulate bioactive compounds [1]. As shown in Fig. 2, polymeric nanoparticles can act as a "reservoir system" called a nanocapsule where the drug is surrounded by a polymeric shell that controls the release of the drug, or a "matrix system" called a nanosphere where the drug is adsorbed on the surface of the matrix [1, 24].

The most compelling advantages of using polymeric nanocapsules include the enhancement of the drug solubility and permeability, as well as improving its bioavailability [25]. Siddiqi et al, (2018) and Sahni et. Al, (2011) mentioned that polymeric nanoparticles are capable of opening TJs of the BBB [1, 26], which qualifies them to be the most commonly used drug delivery systems in neurological disorders [1]. In addition, they protect the drug from degrading factors in the surrounding biological environment and control the release of the drug [1, 24]. Polymeric nanoparticles are also considered to be safe for human beings [24]. Therefore, they are considered one of the most innovative and non-invasive approaches for drug delivery [6].

Several biodegradable polymers can be used for the fabrication of polymeric nanoparticles. A biodegradable polymer is a polymer that can undergo spontaneous degradation within the body [6]. Biodegradable polymers can be synthetic or natural. Synthetic biodegradable polymers include polyethylene glycol (PEG), poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(lactic-co-glycolide) (PLGA) [6]. Natural polymers include albumin, gelatin, alginate, collagen, dextran, and chitosan [6]. Among the previously mentioned natural polymers, chitosan is the most widely used for brain targeting chitosan due to its superior bioadhesive and biocompatible properties [27]. In this paper, more focus will be given to natural and biodegradable chitosan polymeric nanocapsules and their role in the management of neurodegenerative disorders.

Chitosan biopolymer crossing the BBB

Chitosan is a cationic polysaccharide and a natural polymer obtained by the extraction and subsequent deacetylation of chitin produced by crustaceans or mushrooms [5, 9]. This process results in a linear and unbranched polymer composed of β-(1,4)-linked N-acetyl-glucosamine

units [5, 9]. The structure of Chitosan is presented in Fig. 3, demonstrating the presence of two free hydroxyl groups and one amino group on each C6 structure unit [28], which undergoes protonation at low pH to increase the solubility of chitosan in acidic media [29]. Chitosan has a cellulose-like structure with chelating properties [3]. Among the advantages of chitosan are its non-toxic, non-allergenic, biodegradable, biocompatible, low-priced, and mucoadhesive properties [5,9]. Besides, the functional groups in chitosan aid in the grafting of molecules, giving the modified chitosan its distinct properties by enhancing its solubility and therapeutic value [30]. These qualities make chitosan a good material to be used for medical purposes [31, 32]. In addition, the hydrophilic nature of chitosan makes it a good candidate for biomedical applications [33]. As stated by Pacheco et al. (2020), chitosan is a positively charged polymer that can readily interact with negatively charged surfaces through various chemical reactions such as carboxylation and hydroxylation [9].

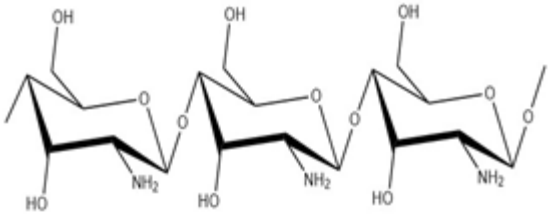

Fig. 3. The structure of chitosan (Created by Chemdraw)

Chitosan-coated nanoparticles have shown great potential for brain targeting, enhancing the therapeutic effect of CNS drugs [31]. Chitosan is known for its ability to transiently open the epithelial TJs, as a result, the drug permeation rate across the BBB and its bioavailability in the brain are augmented [9, 32]. Gholizadeh et al. (2019) developed a chitosan-based hydrogel that increased the bioavailability of ibuprofen for the treatment of neurological disorders, indicating the transient modulation of epithelial TJs by chitosan [32]. In addition, the opposite charges of chitosan allow the internalization of chitosan nanoparticles via transcytosis adsorptive-mediated mechanism through the endothelium [34]. In a previous study, it was found that the internalization mechanisms of chitosan nanoparticles occur through receptor-mediated transport as well as the macropinocytic route [35].

Another strategy to bypass BBB is the administration of the nano-encapsulated drug via the intranasal route [3, 7]. Chitosan has mucoadhesive properties due to the electrostatic attraction forces between the positively charged polychationic amino groups on chitosan and the negatively charged anions on mucosal surfaces [28, 36]. This mucoadhesive property of chitosan increases the time of attachment to the target site, thereby enhancing the membrane absorption [36]. A study showed that olanzapine-loaded chitosan nanoparticles exhibited no toxicity when tested on goat nasal mucosa, indicating the suitability of chitosan nanoparticles for delivering drugs to the brain via the nasal route [37]. Chitosan-coated rosmarinic acid nanoparticles were optimized as a neuroprotective therapy and demonstrated suitability for nasal drug delivery due to the mucoadhesive and permeation-enhancing properties of chitosan [7].

Altogether, the aforementioned chitosan's physicochemical and biological properties make chitosan an ideal polymer to be used in drug delivery systems for the treatment of neurological disorders. Therefore, chitosan-based polymeric nanocapsules can be considered promising candidates for transporting therapeutic agents across the BBB. Chitosan was widely used in polymeric nanocapsules targeting brain delivery [31].

Methods for fabrication of chitosan nanocapsules

Ionic Gelation method

The ionic gelation method is widely used in the fabrication of chitosan nanoparticles because it can be carried out under mild conditions. It depends on the formation of electrostatic interactions between the positively charged protonated amino groups on chitosan and a negatively charged, non-toxic cross-linker, such as sodium tripolyphosphate (TPP) under constant stirring conditions, which leads to the formation of a hydrogel [38]. TPP is the most common agent capable of crosslinking chitosan with hydrophilic or hydrophobic drugs [35]. The ratio between chitosan and polyphosphate ions affects the size of the formed particles [38]. A schematic diagram is presented in Fig. 4.

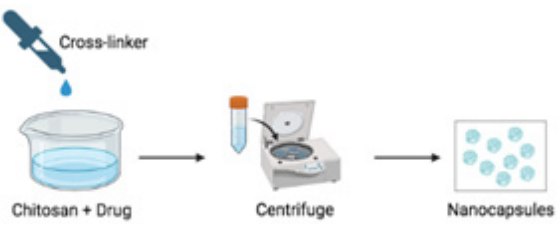

Fig. 4. Schematic illustration of polymeric nanocapsule synthesis using the ionic gelation method (Created in Biorender.com)

Salting-out method

In the salting-out method, the drug and the polymer are dissolved in water-miscible solvent, such as acetone or metanol. This solvent is then added to an aqueous solution containing a salting-out agent such as magnesium chloride ($MgCl_2$) or calcium chloride ($CaCl_2$) and a colloidal stabilizer. The excess solvent and salting-out agent are removed by filtration [24]. The method is graphically illustrated in Fig. 5.

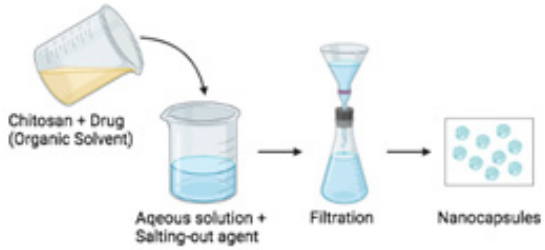

Fig. 5. Schematic illustration of polymeric nanocapsule synthesis using the salting-out method (Created in Biorender.com)

Emulsification/ Double emulsion method

Double emulsions are formed when a hydrophilic substance is dissolved in water and then dispersed into an oily phase to form a primary emulsion which is then emulsified into an aqueous phase containing a surfactant, resulting in water-in-oil-in water (w/o/w) emulsion [39, 40]. After evaporation of the solvent, the nanocarriers can be collected and lyophilized [39, 40]. Fig. 6 represents a graphical illustration of this method.

Fig. 6. Schematic illustration of polymeric nanocapsule synthesis using the double emulsion method (Created in Biorender.com)

Nanoprecipitation

This method is also known as solvent-displacement or interfacial deposition method. In this method, the polymer is dissolved in a water-miscible organic solvent, which is then added to an aqueous phase that may contain one or more surfactants to improve the stability of the nanocapsules [6, 24]. The nanocarriers are obtained when the polymer diffuses into the organic solvent and precipitates at the interface between oil and water [6, 24]. The fabricated nanocapsules can then be collected after the organic solvent is removed through evaporation or diffusion. The method is illustrated in Fig. 7.

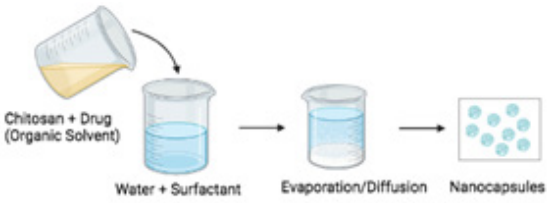

Fig. 7. Schematic illustration of polymeric nanocapsule synthesis using the nanoprecipitation method (Created in Biorender.com)

Characterization of chitosan nanoparticles

There are several parameters that affect the passage of nanoparticles across the BBB. Therefore, it is important to characterize chitosan nanoparticles, which involves assessing their physical properties that have impact on their efficacy and toxicity. The characterization of chitosan nanoparticles can be done using various methods:

Particle size (PS), polydispersity index (PdI) and Zeta Potential (ZP)

The most commonly used technique to determine the particle size, the polydispersity index (PdI) and zeta potential (ZP) is the dynamic light scattering (DLS) technique [24, 41]. It is worth mentioning that in order to cross the BBB, the size of the nanoparticles should be less than 200 nm and the ZP should be a positive value [42].

The most fundamental parameter in the characterization of nanoparticles is the particle size because it influences their cellular uptake [43]. Smaller nanoparticles have a greater surface area and bioavailability [43]. A study that investigated the association between the size of chitosan nanoparticle the crosslinking degree found that moderate crosslinking degree results in smaller nanoparticle size [44]. On the other hand, Agarwal et al. (2018) found that by increasing the concentration of chitosan, the dense arrangement of chitosan molecules results in increasing particle size [45]. Therefore, smaller particle size can be obtained by reducing the concentration of chitosan due to decreased viscosity during preparation via ionic gelation [45]. It is worth to mention that the particle size determined using DLS where the nanoparticles pass through a liquid medium, is found to be greater than the particle size measured using the Scanning Electron Microscope (SEM) in the absence of hydration medium due to the high

swelling capacity of chitosan nanoparticles [45]. In particular, most of the studies conducted so far against neurological disorders have used chitosan nanoparticles with diameters up to 250 nm [46].

The PDI value, which defines size distribution and ranges between 0.01 which indicates a narrow size distribution and 0.7 which indicates a wide size distribution [41]. PDI values closer to zero reflect highly homogeneous nano-emulsions [47].

Zeta potential indicates the nature and intensity of the surface charge which greatly influences particle stability in suspension through the electronic repulsion between nanoparticles [48]. Nanoparticles surface can be either positively or negatively charged. The surface charge is affected by the functional groups of the shell material, or by the adsorption of ions that are present in the dispersion medium. A higher zeta potential is important for the stability of the nanoemulsion, as greater repulsion prevents the aggregation of particles [24]. The amino groups in chitosan nanoparticles are responsible for the positive and high value of the zeta potential [29], which accordingly helps to maintain the stability of chitosan nanoparticles.

Morphology

The scanning and transmission electron microscopy (SEM and TEM) have been used to determine the shape and size of chitosan nanoparticles [24]. Most commonly, chitosan nanoparticles are prepared using ionic gelation method are usually spherical in shape as demonstrated in Table 1.

Encapsulation efficiency

In order to determine the amount of the encapsulated drug, the amount of the free drug present in the supernatant after centrifugation is determined spectrophotometrically, and the difference between the total and the free drug is calculated. The result indicates the amount of the encapsulated drug [24]. Increasing the amount of the encapsulated drug is likely to increase the encapsulation efficiency [49]. The drug can be effectively incorporated in the polymeric nanocapsules when the drug-polymer interactions outweigh the drug-drug interactions [50]. However, drug crystallization occurs if the drug-drug interaction exceeds the drug-polymer interactions [50].

In-vitro release assay

The release of the drug from the nanocapsule depends on several factors, including the polymeric matrix and drug diffusion. Among the methods used to determine the drug release, the dialysis bag method is most commonly used [24]. The amount of the released drug over time is determined spectrophotometrically. It has been reported that the drug release from the nanocapsules follows the first-order kinetics and forms an exponential [24].

FTIR (Fourrier-transform infrared)

FTIR method determines the functional groups present in a molecule and reveals the intermolecular interactions. The FTIR of chitosan nanoparticles reveals the presence of hydroxyl (OH), carbonyl (C=O) and amino (NH2) groups [51]. Moreover, FTIR is used to confirm the interaction between the drug and the polymer, which can be identified if any of the characteristic FTIR peaks of the drug are reduced or disappeared [41].

In-vitro toxicological studies

The toxicity of the nanocapsules can be tested *in vitro* by assessing the viability of selected normal cell lines using colorimetric assays, such as, Alamar blue and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) [24]. The nanoparticles are considered safe if the cell viability is above 70% [35].

Applications of chitosan-based nanocapsules in neurological disorders

Due to several advantages, research has focused on designing chitosan-based polymeric nanoparticles due to their unique properties, such as biodegradability, biocompatibility, and cationic nature that enable them to cross the BBB. This makes them suitable for the management or treatment of neurologic disorders. Numerous studies have evaluated drug-loaded chitosan nanoparticles administered in animals via several routes of administration, as well as *in vitro*.

For instance, naringen-encapsulated chitosan nanoparticles enhanced the neuroprotective and antioxidant effects against 6-OHDA-induced neurotoxicity in SH-SY5Y cells *in-vitro* [52]. In another in-vitro study performed by De Giglio et al. (2011), dopamine-loaded chitosan nanoparticles were synthesized and characterized with the aim of improving the bioavailability of the dopamine neurotransmitter in the brain, and is therefore seen as a promising means to manage and treat parkinsonism [53]. On the other hand, Trapani et

Table 1. Application of chitosan nanoparticles to a number of CNS disorders-related studies

Study	Method	Drug	*PS (nm), *PdI	Morph.	*EE (%)	Route of Admin.	Findings
[52]	Ionic Gelation	Naringenin	96.87, 0.322	Spherical/smooth	*NS	-	Enhanced neuroprotective and antioxidant effect
[53]	Ionic Gelation	Dopamine	NS	NS	NS	-	Increased dopamine bioavailability
[34]	Modified Ionic Gelation	Dopamine	148, 0.41	Spherical	81	Intra-peritoneal	Increased dopamine level in the brain
[54]	Ionic Gelation	Rivastigmine	185.4, 0.39	Spherical and sub-spherical	85.3	Intranasal	Increased rivastigmine level in the brain
[55]	Modified Ionic gelation	Rivastigmine	154.06, NS	Spherical	96.36	Oral	Significant reversal of amnesia
[56]	Ionic Gelation	Bromocriptine	161.3, 0.44	spherical or ellipsoidal/ smooth	84.2	Intranasal	Increased bromocriptine in brain and plasma and increased concentration of dopamine
[49]	Ionic Gelation	Ropinirole	156.5, 0.41	Spherical / rough	52.2 to 69.6	Intranasal	Increased ropinirole bioavailability
[46]	Ionic Gelation	Piperine	248.5, 0.24	Spherical	81.7	Intranasal	Increased piperine bioavailability and improved behavioral symptoms
[37]	Ionic Gelation	Olanzapine	183.1. 0.122	Spherical	72.4	Intranasal	Olanzapine loaded chitosan nanoparticles are suitable for brain targeting via intranasal route
[57]	Ionic Gelation	Piperine	30, NS	NS	53	Intraperitoneal	Inhibition of seizures in (PTZ)-induced epilepsy
[58]	Ionic Gelation	Sitagliptin	188.4	Spherical	NS	Intranasal	Increased levels of sitagliptin in the brain
[59]	Ionic Gelation	Risperidone	86, 0.287	Spherical /Rough	77.9	Intranasal	Increased risperidone delivery to the brain.
[60]	Ionic Gelation	Gallic acid	173, 0.106	Spherical/smooth	83.5	Oral	Enhanced anti-ischemic effect of Gallic acid.

*PS = Particle Size, PDI = Polydispersity Index, EE = Encapsulation Efficiency, NS = Not Specified

al. (2011) evaluated the ability of dopamine-loaded chitosan nanoparticles to deliver dopamine to the brains of rats [34]. Trapani et al. (2011) concluded that the loaded nanoparticles were able to increase the level of dopamine in the brain, thus ameliorating Parkinson's disease [34]. It was also evident from another study that encapsulating rivastigmine in chitosan nanoparticles enhanced the brain uptake of the rivastigmine when administered intranasally in Wistar rats [54]. Also, Rivastigmine-loaded chitosan nanoparticles were successfully able to reverse scopolamine-induced amnesia in Swiss male albino mice [55]. In order to compare the effects of Bromocriptine-loaded chitosan nanoparticles and a Bromocriptine solution, both preparations were administered intranasally, and the results showed that levels of bromocriptine in the brain and blood plasma significantly increased when using the nano-encapsulated Bromocriptine [56]. In addition, Bromocriptine-loaded chitosan nanoparticles showed a remarkable increase in dopamine levels compared to Haloperidol-treated mice [56]. Furthermore, there was less degeneration observed in dopaminergic neurons [56]. Similarly, another nose-to-brain drug delivery carrier using ropinirole-loaded chitosan nanoparticles demonstrated increased bioavailability compared to free ropinirole [49]. Likewise, the nano-encapsulation of piperine in chitosan nanoparticles improved its bioavailability when administered via the intranasal route and reduced the dose by 20 folds as compared to the oral route [46]. In addition, piperine-loaded nanoparticles improved the cognitive and behavioral functions in rats, suggesting their potential ability in the treatment of Alzheimer disease [46]. For the treatment of depression, Ruby and Pandey (2016) fabricated olanzapine—loaded chitosan nanoparticles and evaluated them in an ex-vivo histopathological study using excised goat nasal mucosa [37]. The results suggest that olanzapine-loaded chitosan nanoparticles can be considered for the treatment of depression when administered via the nasal pathway to the brain [37]. In a pentylentetrazol (PTZ)-induced kindling model, epileptic seizures were reduced in response to Piperine loaded in chitosan-sodium tripolyphosphate nanoparticles [57]. The nanoencapsulation of the anti-alzheimer

drug, sitagliptin, increased its bioavailability in the brain [58]. In another study, Risperidone-loaded chitosan nanoparticles administered intranasally demonstrated successful delivery of the drug to the brain against amphetamine-induced schizophrenia [59]. Likewise, Gallic acid-chitosan nanocapsules promoted the anti-ischemic effect of free Gallic acid [60]. The applications of chitosan nanoparticles in CNS diseases are presented in Table 1.

Chitosan was also used in combination with other polymers and were investigated against a number of neurological disorders, as presented in Table 2. Carbamazepine-loaded chitosan nanoparticles, combined with carboxymethyl cellulose, were developed and administered intranasally, and the findings revealed enhanced delivery of the drug to the brain [61]. Another study showed that the coating of rivastigmine-loaded chitosan nanoparticles with polysorbate 80 improved the rivastigmine bioavailability [62]. Similarly, Jain and Jain (2018) developed galantamine-loaded chitosan nanoparticles coated with polysorbate 80, and a high concentration of galantamine was successfully delivered to the brain [63]. Another natural and biocompatible anionic polysaccharide is Alginate which was used in combination with chitosan to prepare drug delivery systems [25]. For instance, curcumin-loaded chitosan-alginate-sodium triphosphate nanoparticles were found to ameliorate memory impairment and attenuate the level of activated glial cells in PTZ-induced epilepsy in mice [64]. In another application, a combination of sodium alginate/chitosan was used to encapsulate Quercetin in polymeric nanocapsules [65]. This encapsulation technique improved the neuroprotective effect of Quercetin on human neuroblastoma cells [65]. Also, Chitosan/PLGA nanoparticles enhanced the delivery of NP-355 and NP-647 TRH analogues to the brain, thereby inhibiting seizures in a PTZ-induced epilepsy model [66]. Likewise, Eugenol-loaded polycaprolactone nanoparticles coated with chitosan demonstrated increased bioavailability of Eugenol in the rat brain when administered intranasally, and can therefore be considered a potential treatment for cerebral ischemia [67]. Bovine serum albumin (BSA) is also used in combination with chitosan to encapsulate curcumin for treatment of Alzheimer's disease and it was found that CS-BSA NPs promoted the penetration of the drug through the BBB [68]. A recent study by Bashir et al. (2022) evaluated the antioxidant activity of magnoflorine alkaloid encapsulated in chitosan/collagen nanocapsules in-vitro, and reported potentiation of its antioxidant activity in order to be considered as

Table 2. Application of chitosan/co-polymer nanoparticles to a number of CNS disorders

Study	Co-polymer	Method	Drug	*PS (nm), *PdI	Morph.	*EE (%)	Route of Admin.	Findings
[61]	Carboxymethyl cellulose	Emulsification	Carbamazepine	218.7, 0.27	NS	79	Intranasal	Enhanced the bioavailability of carbamazepine to the brain
[62]	Polysorbate 80	Emulsification	Rivastigmine	47, NS	NS	NS	Intravenous	Improved biodistribution of the anti-Alzheimer drug rivastigmine
[63]	Polysorbate 80	Emulsification	Galantamine	62, not specified	Spherical	68.2	-	Increased the delivery of galantamine to the brain
[64]	Sodium alginate	Not specified	Curcumin	50, NS	Spherical	NS	Intraperitoneal	Improved memory impairment
[65]	Sodium alginate	Ionic Gelation	Quercetin	NS	NS	NS	-	Improved the neuroprotective activity of quercetin *in vitro*
[66]	poly-lactide-co-glycolide	W/O/W double emulsion method	Thyrotropin releasing hormone analogues. (i) NP335 (ii) NP647	(i) 91.9, 0.11 (ii) 96.5, 0.25	Spherical/ smooth	(i) 47.9 (ii) 52.5	Intranasal	Improved delivery of TRH analogues to the brain
[67]	Poly ε-caprolactone	W/O/W double emulsion method	Eugenol	224.5, 0.216	Spherical/ smooth	68.1	Intranasal	Increased bioavailability of Eugenol in the brain
[68]	Bovine Serum Albumin	NS	Curcumin	143.5, 0.021	Spherical	95.4	-	Increased drug penetration of the BBB
[69]	Collagen	NS	Magnoflorine	10.59, 0.19	Spherical	76	-	Potentiated antioxidant effect

*PS = Particle Size, PDI = Polydispersity Index, EE = Encapsulation Efficiency, NS = Not Specified

a potential agent against neurodegenerative diseases [69].

Chitosan-coated nanoparticles were also explored as promising drug delivery systems for the treatment of central nervous system disorders. In a recent study, Tanshinone IIA was effectively delivered to the brain by chitosan-coated nanostructured lipid carriers for the treatment of Parkinson's disease [70]. Niosomes coated with chitosan were also used to transfer an anti-epileptic drug (clonazepam) to the brain via intranasal route [71]. Ferulic acid-based solid lipid nanoparticles coated with chitosan have been designed for efficient Alzheimer's disease treatment [72]. Another study also showed how the bioavailability of the orally administered hydrophilic doxycycline hydrochloride was improved when the drug was loaded in Tween 80-coated chitosan nanoparticles, making it a viable treatment option for psychotic symptoms [73].

Despite the benefits of chitosan and the wide-array of applications using chitosan nanoparticles for brain targeting, their use is still associated with some challenges and limitations.

Challenges and future prospects

Neurological disorders such as Alzheimer's disease and Parkinson's disease require lifelong treatment to maintain therapeutic levels of the medication in the blood. Unfortunately, repeated doses increase the risk of side effects and are inconvenient for patients. Therefore, proposing sustained-release chitosan nanoparticles formulations is recommended to overcome these challenges. In addition, it is worth to proposing novel chitosan/chitosan and co-polymer nanoparticles formulations for the administration of combinations of drugs with synergistic effects that can successfully penetrate the BBB.

The use of polymeric nanoparticles in drug delivery systems is evidently promising. Polymers of choice need to be safe and biocompatible to avoid an inflammatory response [6]. However, natural, biocompatible, and biodegradable polymers may possibly demonstrate potential toxicity when used as nanocarriers. This might be due to the use of organic solvent in their production. Therefore, safety studies *in vitro* and *in vivo* should be implemented. It is also recommended to assess the use of other natural biodegradable polymers with or without chitosan in fabricating nano-drug delivery systems targeting the CNS, including natural gums, gelatina, and lipids.

The particle size and the charge of NPs influence their brain delivery, since the ideal particle size for brain delivery is less than 200 nm, and the particles should be positively charged in order to interact with negatively charged cell membranes [74]. As a result, creating optimally sized and positively charged NPs is a difficult undertaking.

Scaling-up the manufacturing process of nanocarriers from laboratory to industry is a technological challenge [8]. Similarly, the pharmaceutical industry faces the obstacle of testing nano-based treatments in clinical settings due to high expanses, the long time, and the complicated process [8]. Thus, research attention should be directed towards the scaling-up process and clinical studies in order to implement them in practical applications. It is also anticipated that the development of nanoparticles that can specifically target certain cells of the brain might enhance the therapeutic outcome [23], and therefore require further investigation.

CONCLUSION

Neurological disorders have led to devastating effects on human's health and quality of life. CNS-targeting drugs administered using conventional dosage forms have been found to be associated with minimized efficacy and increased side effects due to their inability to cross the BBB. From this aspect, polymeric nanoparticles were recognized to provide the best approach to deliver drugs to the CNS while improving their efficacy and reducing their toxicities peripherally. Chitosan, a natural and biodegradable polymer, displayed a major advance as a drug delivery system in CNS disorders, and is widely being used as a drug carrier in the treatment of neurodegenerative diseases. Although chitosan nanoparticles are promising for the management of neurological disorders, safety studies are still needed. Scaling up the manufacturing process and testing nano-based treatments in clinical settings are other critical challenges. Therefore, further attempts and scientific efforts should be dedicated towards using chitosan and other safe and biodegradable polymers for encapsulating active constituents for the treatment of neurodegenerative diseases.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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