Mousa and Mohammad
Egypt J Neurol Psychiatry Neurosurg (2022) 58:68
https://doi.org/10.1186/s41983-022-00503-8

The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

REVIEW

Open Access

Potential role of chitosan, PLGA and iron oxide nanoparticles in Parkinson's disease therapy

Ahmed Hafez Mousa[1,2*] and Salwa Agha Mohammad[1,2]

Abstract

Background: Parkinson's disease (PD) is a debilitating disease that alters an individual's functionality. Parkinsonism is a complex symptom consisting of numerous motor and non-motor features, and although several disorders are responsible, PD remains the most important. Several theories have been proposed for the characteristic pathological changes, the most important of which is the loss of dopaminergic neurons associated with a reduced ability to perform voluntary movements. Many drugs have been developed over the years to treat the condition and prevent its progression, but drug delivery is still a challenge due to the blood–brain barrier, which prevents the passage of drugs into the central nervous system. However, with the advances in nanotechnology in the medical field, there is growing hope of overcoming this challenge.

Summary: Our review highlights the potential role of three commonly studied nanoparticles in laboratory-induced animal models of PD: chitosan, PLGA, and iron oxide nanoparticles as potential PD therapy in humans.

Keywords: Parkinson's disease, Nanotechnology, Nanoparticles, Chitosan, PLGA, Iron oxide, SPION

Key messages

Although our review shows good potential for these nanoparticles in PD animal models, prospective and human patient studies are needed to further develop this technology for future widespread application.

Introduction

Parkinson's disease (PD) was first described as a "shaking palsy" by Dr. James Parkinson. It affects 1–2 per 1000 of the population at any time, with its prevalence increasing with age, and 1% of the population above the age of 60 suffering from it [1]. The term Parkinsonism is a complex symptom describing the typical motor features of PD attributed to the loss of striatal dopaminergic neurons which include resting tremors, bradykinesia, and muscular rigidity [2]. Parkinsonism may also occur secondary to other causes such as medication side effects, normal pressure hydrocephalus, and vascular encephalopathy, all of which can be identified and eliminated [3]. Additionally, there are many atypical parkinsonian syndromes resulting from neurodegenerative disorders with intracellular deposition of amyloidogenic proteins, such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD) [3]. These syndromes are characterized by prominent non-motor features such as autonomic dysfunction, gastrointestinal symptoms, sleep dysfunction, and pain, resulting from neuronal loss in nondopaminergic areas [2, 4]. Evidence suggests that the pathophysiological changes associated with PD may start before the onset of motor features and include several non-motor presentations, such as sleep disorders, depression, and cognitive changes [2]. Although many effective drugs have been developed for treating PD, failure of their administration remains a significant challenge as they cannot cross the

*Correspondence: drahmedhafezmousa@gmail.com

[1] College of Medicine, Batterjee Medical College, Jeddah, Saudi Arabia
Full list of author information is available at the end of the article

blood–brain barrier [5]. Nanotechnology will play a key role in developing new diagnostic and therapeutic tools using engineered materials modified to the finest units on the nanometer scale [6]. At present, the formulation of nanoparticles (NPs) as drug delivery systems has represented several advantages over conventional treatments due to improved stability and solubility of the encapsulated drugs, enhanced transport across membranes, and prolonged circulation time [7]. Furthermore, the NP formulation ferumoxytol has been approved for use as a contrast agent for MRI and several superparamagnetic iron oxide NPs are currently undergoing clinical trials to pave a path for future diagnostic methods [8]. Our review aims to shed light on the potential role of three commonly studied NPs in laboratory models of PD: chitosan, poly(lactic-co-glycolic acid), and iron oxide NPs as potential PD therapy in human subjects.

Chitosan

Properties

Chitosan is a linear polysaccharide composed of *N*-acetyl-D-glucosamine and D-glucosamine linked by 1-4-β-glycosidic bonds. It is a deacetylated derivative of the naturally occurring polysaccharide chitin found in the shells of Crustaceans [9].

Chitosan NPs can range in size between 30 and 2500 nm [10, 11], and the deacetylated structure allows its interaction with the negative charge of cell membranes, therefore it is classified as a mucoadhesive compound, allowing its passage through the otherwise impermeable blood–brain barrier [12].

It is water-insoluble under physiologic conditions, as a result, chitosan derivatives such as quaternized chitosan may be used to produce potential injectable formulas like hydrogels for localized drug delivery in PD [13].

Chitosan NPs are nontoxic, biocompatible, biodegradable, and have antimicrobial activity with potential antioxidant properties [12, 14]. Other important properties are high drug entrapment efficiency and sustained drug release [14, 15].

Uses and potential routes of administration in PD

Intranasal administration

In a rotenone-induced neurodegeneration model of PD with intranasal administration of pramipexole dihydrochloride-loaded chitosan NPs [16], and two other similar studies using the drug selegiline-loaded chitosan NPs [17, 18], significantly increased dopamine and glutathione (GSH) levels, and catalase activity in the brain, and demonstrated improved locomotor activity compared to the groups treated with the intranasal and oral non-NP formulated counterpart solutions.

The use of *N,N,N*-trimethyl chitosan (TMC) for surface modification of tristearin-based nanostructured-lipid carriers (NLCs) increases the latter's mucoadhesive potential by 13.3 times compared to non-surface-modified NPs. This bioadhesive strength at the nasal mucosa permits sustained release of the drug and transport to the brain via olfactory and/or trigeminal pathways, increasing target drug concentrations in the brain. This allows us to benefit from lower doses of drugs with high systemic adverse effects to achieve effective results [19]. In the same study, the NPs were also administered intravenously. While the brain–blood ratio of the chitosan-modified drug ROPI-DS was higher than the non-surface-modified NP, it did not surpass or equal the value in the intranasal route. Similarly, TMC-modified ROPI-DS nanoplex-loaded flaxseed oil-based neuro-nanoemulsions produced results that support the earlier study, the only difference being the mucoadhesive strength, which was increased by 6.6 times [20].

Another study using rotigotine-loaded chitosan NPs on Sprague–Dawley rats also supports the use of intranasal route in comparison to intravenous [21], in addition to the superior anti-inflammatory, neuroprotective and antioxidant properties, indicated by the decrease in reactive oxygen species (ROS) levels and neuronal changes in chitosan-loaded drug compared to the drug alone [14, 21, 22].

Chitosan-coated-PLGA NP preparations loaded with the drug rasagiline have also been studied on Wistar rats in both intranasal and intravenous pathways in comparison to plain rasagiline solution. In the in vitro release tests, the results showed that chitosan-coated NPs enhanced drug release by increasing the hydrophilicity of the PLGA NPs compared to their non-coated PLGA counterparts. This study also reports an increased bioavailability and direct targeting to the brain through olfactory neurons by various endocytic pathways of neuronal cells in the olfactory membrane. The study, however, still requires further pre-clinical and clinical studies to evaluate its efficacy in humans based on risk/benefit ratio [23].

In another paper, the neuroprotective and neurorestorative effect of intranasal administration of glial cell line-derived neurotrophic factor (GDNF)-loaded NLCs coated with chitosan was studied in a 6-hydroxydopamine (6-OHDA) hemiparkinsonian rat model. The in vitro experiment took place on the PC-12 cell line of dopaminergic neurons, where the neuroprotective effect of the coated NPs was studied against the 6-OHDA neurotoxin. However, the results showed a very slight increase in the neuroprotective value of the encapsulated GDNF compared to the non-encapsulated GDNF based on behavioral tests performed on the Sprague–Dawley rats [24].

Resveratrol-loaded chitosan glutamate NPs were also administered intranasally in MPTP-induced parkinsonism C57BL/6 mice. Results indicated significantly higher brain levels of resveratrol in the chitosan NP group than the plain resveratrol solution [25].

In a study, conductive hydrogels based on chitosan were evaluated as potential cell carriers for transplanting human olfactory ecto-mesenchymal stem cells (OE-MSCs) in future cell therapy for the treatment of PD via nasal injection. These hydrogels can potentially be used as a medium to differentiate OE-MSCs into dopaminergic neuron-like cells and function as a substrate for functional synapses between cultured cells [26].

Intravenous administration

If we flip the coin, chitosan NPs can also be surface-coated by other compounds. An example of this includes using polysorbate 80-coated ropinirole hydrochloride (R-HCL)-loaded chitosan NPs for treating PD. In in vitro drug release tests, polysorbate 80-coated NPs showed sustained release of R-HCl compared to the non-coated preparations, besides prolonging the storage life of the NPs. Meanwhile, in in vivo models, the concentration of R-HCl was measured in the highly perfused organs: brain, liver, spleen, and kidney of Wistar rats, 1 h after intravenously administering the drug. Concentration in the brain was higher with the polysorbate 80-coated NPs, followed by the uncoated chitosan NP, while minimum concentration was associated with the pure drug. This data suggests the ability of polysorbate coating to bypass the blood–brain barrier. Conversely, drug concentration in the other three organs showed the opposite pattern [27].

Potential oral route

Procedures performed on adult male Sprague–Dawley rats with a unilateral 6-OHDA-lesion model of PD revealed a significant decrease in the scores of abnormal involuntary movements, FosB/ΔFosB, phospho-ERK1/2, and phospho-Thr34 DARPP-32 expression in the chitosan-coated levodopa nanoliposome group, compared to the levodopa group by intragastric administration [28]. These results may suggest a potential oral route of administration in humans.

Potential pulmonary route

A study published in 2016 nods towards the possibility of developing L-Dopa-loaded chitosan-based dry powder NPs for inhalation, however, this alternative method is yet to be evaluated, and the success of brain delivery via this route is unknown [29].

Other uses

On the other hand, developing chitosan NPs as a gene delivery system for PD is still in progress. In one study, chitosan PEG-PLGA NPs conjugated with NGF, ACT, and pDNA (called APPDNs) demonstrated the ability to reverse dopaminergic (DA) neuron loss in the substantia nigra and striatum of sick mice [30]. In another study, chitosan-mangafodipir NPs carrying anti-eGFP siRNA or dsDNA were evaluated in cell cultures of an eGFP-expressing cell line of mouse fibroblasts (NIH3T3) [31].

A study evaluated the efficacy of chitosan and gold NPs as a sensing platform for the detecting and differentiation of α-synuclein monomer and fibril, which is known to aggregate and is a critical component in the pathogenesis of PD. The developed assay is label-free, robust, requiring minimal sample pre-processing, and can be a promising alternative to dye-based techniques, with better sensitivity, fast response time without the need for bulky instruments [32].

Poly(lactic-co-glycolic acid) (PLGA)

Properties

Poly(lactic-co-glycolic acid) (PLGA) is a copolymer of lactide and glycolide whose ester chain spontaneously hydrolyzes, producing lactic acid and glycolic acid [33, 34].

It inherits the intrinsic properties of poly(glycolic acid) which is a crystalline, hydrophilic polymer with a fast degradation rate under physiological conditions, and poly(lactic acid) which is a stiff, hydrophobic polymer with low mechanical strength [35]. As a result, its degradation rate is affected by its lactic acid-to-glycolic acid ratio [34].

PLGA NPs size can range between 100 and 5000 nm [36]. However, the average for effective intracellular delivery varies between 107.7 nm and 245.7 nm [37].

Due to PLGA's hydrophobic nature, surface modification using polymers such as polyethylene glycol (PEG), polyvinyl alcohol (PVA), and D-α-tocopheryl PEG 1000 succinate (TPGS) plays a crucial role in the targeting strategy, biocompatibility, and blood half-life [38].

Although PLGA NPs are nontoxic, biocompatible, biodegradable, and produce a minimal inflammatory response in the body [34, 35], some recent studies have demonstrated acute inflammatory responses due to intracellular rise in reactive oxygen species associated with the size, shape, surface charge, and concentration of the NPs exposed to the cells. However, most PLGA NPs formulated as drug delivery systems are on the safer side of the spectrum [39, 40].

Uses and potential routes of administration in PD

Intranasal administration

PEG-PLGA-maleimide and methoxyPEG-PLGA were used in the preparation of rotigotine-loaded lactoferrin-modified PEG-PLGA NPs. Following intranasal administration, the effects of lactoferrin modification were studied comparatively to its non-modified counterpart in 16HBE and SH-SY5Y cells in vitro and male Kunming mice in vivo [41]. In an almost identical study, PEG-PLGA-maleimide and methoxyPEG-PLGA were also used in the preparation of dopamine-loaded borneol and lactoferrin co-modified NPs which were then intranasally administered to 6-OHDA-treated Sprague–Dawley rat parkinsonian model [42]. The drug release rates of dopamine from Lf-BNPs were comparatively lower than lactoferrin-modified NPs, which in turn were lower than the unmodified NPs, and there was relatively low toxicity when assessing all NP formulations with plain dopamine [41, 42]. Furthermore, lactoferrin modification promoted the uptake of dopamine-loaded NPs and rotigotine-loaded NPs by both 16HBE and SH-SY5Y cells. However, borneol modification promoted the uptake of dopamine-loaded NPs by 16HBE cells mainly [42]. Additionally, the contralateral rotation behavior test conducted on the rats revealed gradual improvement in all NP-treated rat groups, with the best results seen with the Lf-BNPs. These studies strongly suggested that the mentioned modification enables the targeted delivery of drugs for PD treatment.

Oral administration

Another new study synthesized a six-armed star-shaped PLGA (6-s-PLGA) polymer loaded with the neuroprotective drug Puerarin (PU). PU-loaded linear PLGA NPs were also formulated for the sake of comparison. PU-NPs incubated in simulated physiological conditions were found to be stable, suggesting their suitability for oral administration. In vitro drug release tests showed that drug release of PU-loaded linear PLGA NPs was faster and more complete compared to the 6-s-PLGA polymer NP, a feature that would make PU release more durable. PU transport across cell monolayers was also better with the use of PU-NPs compared to the drug alone. In in vivo studies on male Sprague–Dawley, improvement in oral drug bioavailability when using NPs supported the results obtained in vitro for the gradual release of the drug, and there was also better drug distribution in the brain, thought to be due to higher amounts of drug absorption in the plasma, beside the small size of the NPs permitting them to cross the BBB. In addition, no associated toxicity was seen in vitro and in vivo. Instead, these NPs seem to be able to protect against MPP+-mediated cytotoxicity in vitro and MPTP-induced behavioral deficits and neurotoxicity in vivo [43]. Another similar study using PU for oral administration supported the data [44].

Transdermal administration

Furthermore, upon a survey of the available literature that revealed the availability of selegiline transdermal patch for the treatment of major depressive disorder in the market, two studies tried to investigate the possibility of developing transdermal films with brain-targeting properties for PD using nanotechnology. In the first study, selegiline-loaded PLGA NPs were embedded in ethylene–vinyl acetate (EVA) transdermal film [45], while in the other one, PLGA-coated rasagiline mesylate NPs were embedded in a gellan gum transdermal film [46]. The transdermal route of administration of these two drugs was then compared to other modes of administration. Both studies concluded that transdermal administration of PLGA NPs helps in effective brain targeting and sustaining drug release for prolonged durations, opening the possibility of long-term, non-invasive, self-administration of drugs in patients with PD [45, 46].

Other uses

Several published studies investigate the in vitro and in vivo effects of using PLGA NPs as drug delivery vehicles for Parkinson's disease, and the results compared to using the plain drugs favor the NPs formulations, be it the nasal [47–49], intraperitoneal [50], intravenous or intracranial route [51, 52].

Based on recent studies that demonstrate the role of the autophagy–lysosome pathway in the pathogenesis of PD, two studies employed the use of PLGA NPs to investigate their neuroprotectivity, the first one using MPP+-treated PC-12 cells (MPP+is a mitochondrial parkinsonian neurotoxin) [53], and the other study using cultured fibroblasts from a PD patient harboring the ATP13A2 mutation [54]. As discussed before, upon degradation of PLGA, lactic and glycolic acids are released. This degradation inside the cells can lower the pH, restoring lysosomal acidity and autophagic flux inhibition [53]. Overall, the results obtained from these studies revealed that PLGA NPs could protect PC-12 cells against MPP+-induced mitochondrial dysfunction, as well as rescue lysosomal dysfunction related to ATP13A2 due to a loss of function [53, 54].

Furthermore, PLGA NPs may be used to encapsulate contrast agents and superparamagnetic NPs for enhancing their delivery into target areas in the body, and to be used in conjunction with available imaging modalities. As a result, they have become a new hotspot for cancer diagnosis and treatment and can potentially serve as a better diagnostic tool for PD [55].

Iron oxide

Properties

Generally, there are three iron oxide NPs available: magnetite (Fe3O4), hematite (α-Fe2O3), and maghemite (γ-Fe2O3). However, due to their superparamagnetic property in which no magnetism remains after removing the magnetic field, Fe3O4 NPs are used in clinical applications [56].

IONPs can range in size between 5 and 300 nm, but to avoid prompt spleen and liver filtration and prolong the blood circulation time, the size of the NPs should not exceed 200 nm [56].

IONPs can lose their magnetism due to rapid aggregation and oxidation under physiologic conditions because of their large surface area, chemical reactivity, and high surface energy. Consequently, surface modifications (most commonly coating) using organic or inorganic materials (such as chitosan) are necessary to enable their use and functionalization in the human body [57]. In support of this theory, a published study revealed that the distribution and diffusion of the IONPs at the tissue and subcellular levels in the brain could be adjusted by different surface modifications. The SPIONs in this work were coated using maleic anhydride, maleic anhydride and Arg-Gly-Asp (Mal-RGD) and maleic anhydride and bovine serum albumin (Mal-BSA). Results demonstrated that RGD/Mal-SPION was the best candidate among the three treatments since they accumulated in and on the cell membranes, mitochondria, and myelin sheath of axons, dendrites, and axon terminals [58].

Uses and potential routes of administration in PD

Intravenous administration

In addition to therapeutic uses, IONPs can be used to implement new MRI-based diagnostic approaches for PD. A study investigated the use of amyloid oligomer-specific scFv antibody (W20) conjugated with PEGylated SPIONs injected into the tail vein of A53T α-synuclein mice to identify amyloid oligomers in vivo by MRI. Pronounced MRI signals were observed in the brainstem of the mice with conjugated-SPIONs, but no such signal was seen in mice injected with unconjugated-SPIONs. These findings indicated that W20-SPIONs specifically labeled the toxic amyloid oligomers to help identify the area damaged [59]. In another similar study, "cell-addictive" NPs named B6ME-NPs were prepared by conjugating Mazindol (which has the same binding site as cocaine but 11-fold higher affinity than it) on the surface of the NPs which increased the affinity of the cells to them by dopamine transporter-induced internalization of NP, enabling easier uptake by cells. The accumulation of these NPs in the brain was made traceable via MRI following intravenous injection by incorporating superparamagnetic iron oxide nanocubes and suggested potential application in PD treatment [60].

Intracerebral administration

To evaluate the therapeutic effects of human mesenchymal stem cells on PD using dextran-coated IONPs, 6-OHDA was injected stereotactically into the left striatum of male Balb-c nude mice to induce Parkinsonism. Three weeks later, the mice were divided into groups and either transplanted intracerebrally or intravenously with dextran-coated IONP-labeled hMSCs and another with unlabeled hMSCs. Rotational behavior testing using apomorphine revealed the rotation numbers of the mice transplanted intracerebrally with labeled-hMSCs to be significantly less than those with unlabeled-hMSCs. However, there was no significant difference between labeled and unlabeled groups transplanted intravenously. Forelimb and hindlimb motor dysfunction were also measured using a rotarod test, and results obtained were like those of rotational behavior. Further investigations showed the enhanced migration of labeled-hMSCs toward damaged dopaminergic neurons, the ability to induce their transdifferentiation into DA-like neurons and promote their paracrine action to protect or regenerate compromised DA neurons in the PD recovery process [61].

In another bilateral 6-OHDA-induced PD rat model, the use of IONPs in conjunction with electromagnetic field (MF) exposure was investigated. IONPs were implanted into the striatum. Results revealed that the group treated with IONPs and MF attained presurgical values of food and water intake, gait, and postural stability compared to IONP or MF groups alone. Biochemical analysis for mitochondrial function and oxidative stress markers performed showed improvements. However, there was no significant difference between the IONP group and IONP + MF group [62].

Another study utilized electromagnetic fields to guide the migration of SPION-labeled adipose-derived stem cells transfected by GFP (ADSC/SPION) in male Sprague–Dawley rats. The lesion was produced by stereotactically injecting 6-HD solution into the right medial forebrain bundle, followed 2 weeks later by transplanting the ADSCs. The animal groups then wore an external magnet on their skull for 1 week. The comparison between experimental groups at week 6 for the rotational behavior test using apomorphine showed a significant decrease in rotations in the ADSC/SPION/EM group compared to the ADSC, ADSC/SPION, and PD groups. Two months post-transplantation, GFP-positive cells were counted, their highest numbers being in the substantia nigra and ventral tegmental area of the ADSC/

SPION/EM group compared to other groups. H&E staining also revealed the highest counted number of neural cells to be in the ADSC/SPION/EM group. This data concludes that the use of external magnets for the delivery and homing of stem cells in the target tissue can be promising in PD treatment [63].

Other uses

To understand the neuroprotective mechanism of action of IONPs, *Saccharomyces cerevisiae* yeast cells were treated with both 6-OHDA and IONPs, digital micrographs were taken and a gray level co-occurrence matrix (GLCM) algorithm was used to analyze the data. Results showed that IONPs antagonize the effects of 6-OHDA on some aspects of nuclear structure in *Saccharomyces cerevisiae* cells, and further research is necessary to understand the interactions between IONPs, PD-associated dopamine derivatives, and the cell nucleus [64].

One study modified the surface of IONPs with the highly stable protein streptavidin. These newly formed SA/PEI-SPIONs were adsorbed on the cell membrane of dopamine synthesizing PC-12 cells derived from male rat adrenal pheochromocytoma, followed by using transmission electron microscopy (TEM) to explore the biodistribution of SA/PEI-SPIONs on PC-12 cell membranes. Results revealed that the surface-modified SIONPs allowed more NPs to attach to the cell membranes, suggesting the possibility of their application in targeting cell membranes for drug delivery [65].

Iron toxicity with prolonged use of SPIONs

SPIONs administered intravenously account for only 1.25–5% of the total body iron content. However, for maximal benefit, SPIONs must be magnetically targeted to a particular organ, resulting in high concentrations in a localized area. The accumulation of SPION, and in particular, free Fe ions in the exposed tissue, can have toxic implications as they can alter the homeostasis of the cells and cause aberrant cellular responses that include cytotoxicity, oxidative stress, inflammation, epigenetic events, and even initiate carcinogenesis [66].

Conclusions

In conclusion, there is revolutionary potential for PD therapy. The significant challenge of drug administration is gradually fading away with nanotechnology utilization. Further studies need to take place on human subjects to show the efficacy of these NPs, including in terminal PD patients, who otherwise have minimal chance of recovery with conventional methods. We also recommend studies to be conducted to identify physician perception, biases, and fears in the future implementation of nanotechnology in PD therapy.

Abbreviations

NP: Nanoparticle; PD: Parkinson's disease; GSH: Glutathione; ROS: Reactive oxygen species; GDNF: Glial cell line-derived neurotrophic factor; 6-OHDA: 6-Hydroxydopamine; R-HCL: Ropinirole hydrochloride; PLGA: Poly(lactic-co-glycolic acid); GLCM: Gray level co-occurrence matrix.

Acknowledgements

None.

Author contributions

The authors confirm contribution to the paper as follows: study conception and design: AHM, SAM; data collection: AHM, SAM; analysis and interpretation of results: AHM, SAM; draft manuscript preparation: AHM, SAM. All authors reviewed the results and approved the final version of the manuscript. All authors read and approved the final manuscript.

Funding

No funding was provided for this review.

Availability of data and materials

All articles used in this review have been cited in the article.

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing Interests

The authors declare that they have no competing interest.

Author details

[1]College of Medicine, Batterjee Medical College, Jeddah, Saudi Arabia. [2]Department of Medicine, Batterjee Medical College, 6231, Prince Abdullah Al-Faisal Street, North Obhur, Jeddah 21442, Saudi Arabia.

Received: 23 August 2021 Accepted: 23 May 2022
Published online: 03 June 2022

References

1. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. J Neural Transm. 2017;124(8):901–5. https://doi.org/10.1007/s00702-017-1686-y.
2. DeMaagd G, Philip A. Parkinson's disease and its management: part 1: disease entity, risk factors, pathophysiology, clinical presentation, and diagnosis. P T. 2015;40(8):504–32.
3. Levin J, Kurz A, Arzberger T, Giese A, Höglinger GU. The differential diagnosis and treatment of atypical Parkinsonism. Dtsch Arztebl Int. 2016;113(5):61–9. https://doi.org/10.3238/arztebl.2016.0061.
4. Bhatia KP, Stamelou M. Nonmotor features in atypical Parkinsonism. Int Rev Neurobiol. 2017. https://doi.org/10.1016/bs.irn.2017.06.001.
5. Sharma S, Rabbani SA, Agarwal T, Baboota S, Pottoo FH, Kadian R. Nanotechnology driven approaches for the management of Parkinson's disease: current status and future perspectives. Curr Drug Metab. 2021;22(4):287–98. https://doi.org/10.2174/1389200221666201124123405.
6. Linazasoro G, Nanotechnologies for Neurodegenerative Diseases Study Group of the Basque Country (NANEDIS). Potential applications of nanotechnologies to Parkinson's disease therapy. Parkinsonism Relat Disord. 2008;14(5):383–92. https://doi.org/10.1016/j.parkreldis.2007.11.012.
7. Mitchell MJ, Billingsley M, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov. 2021;20:101–24. https://doi.org/10.1038/s41573-020-0090-8.
8. Vallabani NVS, Singh S, Karakoti AS. Magnetic nanoparticles: current trends and future aspects in diagnostics and nanomedicine. Curr Drug

Metab. 2019;20(6):457–72. https://doi.org/10.2174/1389200220666181122124458.
9. Ahmed TA, Aljaeid BM. Preparation, characterization, and potential application of chitosan, chitosan derivatives, and chitosan metal nanoparticles in pharmaceutical drug delivery. Drug Des Devel Ther. 2016;10:483–507. https://doi.org/10.2147/DDDT.S99651.
10. Khanmohammadi M, Elmizadeh H, Ghasemi K. Investigation of size and morphology of chitosan nanoparticles used in drug delivery system employing chemometric technique. Iran J Pharm Res. 2015;14(3):665–75.
11. Sreekumar S, Goycoolea FM, Moerschbacher BM, Rivera-Rodriguez GR. Parameters influencing the size of chitosan-TPP nano- and microparticles. Sci Rep. 2018;8(1):4695. https://doi.org/10.1038/s41598-018-23064-4.
12. Ways TM, Lau WM, Khutoryanskiy VV. Chitosan and its derivatives for application in mucoadhesive drug delivery systems. Polymers. 2018;10(3):267. https://doi.org/10.3390/polym10030267.
13. Ren Y, Zhao X, Liang X, Ma PX, Guo B. Injectable hydrogel based on quaternized chitosan, gelatin and dopamine as localized drug delivery system to treat Parkinson's disease. Int J Biol Macromol. 2017;105:1079–87. https://doi.org/10.1016/j.ijbiomac.2017.07.130.
14. Ahlawat J, Neupane R, Deemer E, Sreenivasan ST, Narayan M. Chitosan-ellagic acid nanohybrid for mitigating rotenone-induced oxidative stress. ACS Appl Mater Interfaces. 2020;12(16):18964–77. https://doi.org/10.1021/acsami.9b21215.
15. Ghamami S, Golzani M, Lashgari A. New inorganic-based nanohybrids of layered zinc hydroxide/Parkinson's disease drug and its chitosan biopolymer nanocarriers with controlled release rate. J Incl Phenom Macrocycl Chem. 2016;86(1–2):67–78. https://doi.org/10.1007/s10847-016-0642-z.
16. Raj R, Wairkar S, Sridhar V, Gaud R. Pramipexole dihydrochloride loaded chitosan nanoparticles for nose to brain delivery: development, characterization and in vivo anti-Parkinson activity. Int J Biol Macromol. 2018;109:27–35. https://doi.org/10.1016/j.ijbiomac.2017.12.056.
17. Sridhar V, Gaud R, Bajaj A, Wairkar S. Pharmacokinetics and pharmacodynamics of intranasally administered selegiline nanoparticles with improved brain delivery in Parkinson's disease. Nanomedicine. 2018;14(8):2609–18. https://doi.org/10.1016/j.nano.2018.08.004.
18. Rukmangathen R, Yallamalli IM, Yalavarthi PR. Biopharmaceutical potential of selegiline loaded chitosan nanoparticles in the management of Parkinson's disease. Curr Drug Discov Technol. 2019;16(4):417–25. https://doi.org/10.2174/1570163815666180418144019.
19. Pardeshi CV, Belgamwar VS. Improved brain pharmacokinetics following intranasal administration of *N*, *N*, *N*-trimethyl chitosan tailored mucoadhesive NLCs. Mater Technol. 2020;35(5):249–66. https://doi.org/10.1080/10667857.2019.1674522.
20. Pardeshi CV, Belgamwar VS. *N*, *N*, *N*-trimethyl chitosan modified flaxseed oil based mucoadhesive neuronanoemulsions for direct nose to brain drug delivery. Int J Biol Macromol. 2018;120(Pt B):2560–71. https://doi.org/10.1016/j.ijbiomac.2018.09.032.
21. Bhattamisra SK, Shak AT, Xi LW, Safian NH, Choudhury H, Lim WM, et al. Nose to brain delivery of rotigotine loaded chitosan nanoparticles in human SH-SY5Y neuroblastoma cells and animal model of Parkinson's disease. Int J Pharm. 2020;579: 119148. https://doi.org/10.1016/j.ijpharm.2020.119148.
22. Manigandan V, Nataraj J, Karthik R, Manivasagam T, Saravanan R, Thenmozhi AJ, et al. Low molecular weight sulfated chitosan: neuroprotective effect on rotenone-induced in vitro Parkinson's disease. Neurotox Res. 2019;35(3):505–15. https://doi.org/10.1007/s12640-018-9978-z.
23. Ahmad N. Rasagiline-encapsulated chitosan-coated PLGA nanoparticles targeted to the brain in the treatment of Parkinson's disease. J Liq Chromatogr Relat Technol. 2017;40(13):677–90. https://doi.org/10.1080/10826076.2017.1343735.
24. Gartziandia O, Herrán E, Ruiz-Ortega JA, Miguelez C, Igartua M, Lafuente JV, et al. Intranasal administration of chitosan-coated nanostructured lipid carriers loaded with GDNF improves behavioral and histological recovery in a partial lesion model of Parkinson's disease. J Biomed Nanotechnol. 2016;12(12):2220–30. https://doi.org/10.1166/jbn.2016.2313.
25. Rahman M, Kumar V. Improving neuroprotective effects of resveratrol by brain targeting through chitosan glutamate nanoparticles in MPTP induced Parkinsonism. J Neurol Sci. 2019;405:279–80.
26. Alizadeh R, Zarrintaj P, Kamrava SK, Bagher Z, Farhadi M, Heidari F, et al. Conductive hydrogels based on agarose/alginate/chitosan for neural disorder therapy. Carbohydr Polym. 2019;224: 115161. https://doi.org/10.1016/j.carbpol.2019.115161.
27. Ray S, Sinha P, Laha B, Maiti S, Bhattacharyya UK, Nayak AK. Polysorbate 80 coated crosslinked chitosan nanoparticles of ropinirole hydrochloride for brain targeting. J Drug Deliv Sci Technol. 2018;48:21–9. https://doi.org/10.1016/j.jddst.2018.08.016.
28. Cao X, Hou D, Wang L, Li S, Sun S, Ping Q, Xu Y. Effects and molecular mechanism of chitosan-coated levodopa nanoliposomes on behavior of dyskinesia rats. Biol Res. 2016;49(1):32. https://doi.org/10.1186/s40659-016-0093-4.
29. Yas AA. Preparation and characterization of L-Dopa loaded chitosan—based dry powder: rescue/continuous supplement in Parkinson's disease via inhalation. World J Pharm Res. 2016;4(1):23–36.
30. Xue Y, Wang N, Zeng Z, Huang J, Xiang Z, Guan Y-Q. Neuroprotective effect of chitosan nanoparticle gene delivery system grafted with acteoside (ACT) in Parkinson's disease models. J Mater Sci Technol. 2020;43:197–207. https://doi.org/10.1016/j.jmst.2019.10.013.
31. Sanchez-Ramos J, Song S, Kong X, Foroutan P, Martinez G, Dominguez-Viqueria W, et al. Chitosan-Mangafodipir nanoparticles designed for intranasal delivery of siRNA and DNA to brain. J Drug Deliv Sci Technol. 2018;43:453–60. https://doi.org/10.1016/j.jddst.2017.11.013.
32. Khatri A, Punjabi N, Ghosh D, Maji SK, Mukherji S. Detection and differentiation of α-Synuclein monomer and fibril by chitosan film coated nanogold array on optical sensor platform. Sens Actuators B Chem. 2018;255:692–700. https://doi.org/10.1016/j.snb.2017.08.051.
33. Bandelli D, Alex J, Weber C, Schubert US. Polyester stereocomplexes beyond PLA: could synthetic opportunities revolutionize established material blending? Macromol Rapid Commun. 2020;41(1): e1900560. https://doi.org/10.1002/marc.201900560.
34. Sadeghi-Avalshahr A, Nokhasteh S, Molavi AM, Khorsand-Ghayeni M, Mahdavi-Shahri M. Synthesis and characterization of collagen/PLGA biodegradable skin scaffold fibers. Regen Biomater. 2017;4(5):309–14. https://doi.org/10.1093/rb/rbx026.
35. Rezvantalab S, Keshavarz MM. Microfluidic assisted synthesis of PLGA drug delivery systems. RSC Adv. 2019;9(4):2055–72. https://doi.org/10.1039/C8RA08972H.
36. Huang W, Zhang C. Tuning the size of poly(lactic-co-glycolic Acid) (PLGA) nanoparticles fabricated by nanoprecipitation. Biotechnol J. 2018. https://doi.org/10.1002/biot.201700203.
37. Sahin A, Esendagli G, Yerlikaya F, Caban-Toktas S, Yoyen-Ermis D, Horzum U, et al. A small variation in average particle size of PLGA nanoparticles prepared by nanoprecipitation leads to considerable change in nanoparticles' characteristics and efficacy of intracellular delivery. Artif Cells Nanomed Biotechnol. 2017;45(8):1657–64. https://doi.org/10.1080/21691401.2016.1276924.
38. Rezvantalab S, Drude NI, Moraveji MK, Güvener N, Koons EK, Shi Y, et al. PLGA-based nanoparticles in cancer treatment. Front Pharmacol. 2018;9:1260. https://doi.org/10.3389/fphar.2018.01260.
39. Gomes dos Reis L, Lee W-H, Svolos M, Moir LM, Jaber R, Windhab N, et al. Nanotoxicologic effects of PLGA nanoparticles formulated with a cell-penetrating peptide: searching for a safe pDNA delivery system for the lungs. Pharmaceutics. 2019;11(1):12. https://doi.org/10.3390/pharmaceutics11010012.
40. Xiong S, George S, Yu H, Damoiseaux R, France B, Ng KW, et al. Size influences the cytotoxicity of poly (lactic-co-glycolic acid) (PLGA) and titanium dioxide (TiO2) nanoparticles. Arch Toxicol. 2012;87(6):1075–86. https://doi.org/10.1007/s00204-012-0938-8.
41. Bi C, Wang A, Chu Y, Liu S, Mu H, Liu W, et al. Intranasal delivery of rotigotine to the brain with lactoferrin-modified PEG-PLGA nanoparticles for Parkinson's disease treatment. Int J Nanomedicine. 2016;11:6547–59. https://doi.org/10.2147/IJN.S120939.
42. Tang S, Wang A, Yan X, Chu L, Yang X, Song Y, et al. Brain-targeted intranasal delivery of dopamine with borneol and lactoferrin co-modified nanoparticles for treating Parkinson's disease. Drug Deliv. 2019;26(1):700–7. https://doi.org/10.1080/10717544.2019.1636420.
43. Chen T, Liu W, Xiong S, Li D, Fang S, Wu Z, et al. Nanoparticles mediating the sustained puerarin release facilitate improved brain delivery to treat Parkinson's disease. ACS Appl Mater Interfaces. 2019;11(48):45276–89. https://doi.org/10.1021/acsami.9b16047.
44. Xiong S, Liu W, Li D, Chen X, Liu F, Yuan D, et al. Oral delivery of puerarin nanocrystals to improve brain accumulation and anti-parkinsonian

efficacy. Mol Pharm. 2019;16(4):1444–55. https://doi.org/10.1021/acs.molpharmaceut.8b01012.
45. Bali NR, Salve PS. Selegiline nanoparticle embedded transdermal film: an alternative approach for brain targeting in Parkinson's disease. J Drug Deliv Sci Technol. 2019;54: 101299. https://doi.org/10.1016/j.jddst.2019.101299.
46. Bali NR, Salve PS. Impact of rasagiline nanoparticles on brain targeting efficiency via gellan gum based transdermal patch: a nanotheranostic perspective for Parkinsonism. Int J Biol Macromol. 2020;164:1006–24. https://doi.org/10.1016/j.ijbiomac.2020.06.261.
47. de Oliveira Junior ER, Truzzi E, Ferraro L, Fogagnolo M, Pavan B, Beggiato S, et al. Nasal administration of nanoencapsulated geraniol/ursodeoxycholic acid conjugate: towards a new approach for the management of Parkinson's disease. J Control Release. 2020;321:540–52. https://doi.org/10.1016/j.jconrel.2020.02.033.
48. Arisoy S, Sayiner O, Comoglu T, Onal D, Atalay O, Pehlivanoglu B. In vitro and in vivo evaluation of levodopa-loaded nanoparticles for nose to brain delivery. Pharm Dev Technol. 2020;25(6):735–47. https://doi.org/10.1080/10837450.2020.1740257.
49. Pavlov AN, Pyatigorskaya NV, Brkich GE, Shabalina MM, Beregovykh VV. Study of adhesive properties of new dosage forms for Nano-L-DOPA nasal delivery system based on PLGA nanoparticles. J Pharm Sci Res. 2018;10(3):668–71.
50. Barcia E, Boeva L, García-García L, Slowing K, Fernández-Carballido A, Casanova Y, et al. Nanotechnology-based drug delivery of ropinirole for Parkinson's disease. Drug Deliv. 2017;24(1):1112–23. https://doi.org/10.1080/10717544.2017.1359862.
51. Meng XY, Huang AQ, Khan A, Zhang L, Sun X-Q, Song H, et al. Vascular endothelial growth factor-loaded poly-lactic-co-glycolic acid nanoparticles with controlled release protect the dopaminergic neurons in Parkinson's rats. Chem Biol Drug Des. 2020;95(6):631–9. https://doi.org/10.1111/cbdd.13681.
52. You L, Wang J, Liu T, Zhang Y, Han X, Wang T, et al. Targeted brain delivery of rabies virus glycoprotein 29-modified deferoxamine-loaded nanoparticles reverses functional deficits in parkinsonian mice. ACS Nano. 2018;12(5):4123–39. https://doi.org/10.1021/acsnano.7b08172.
53. Zeng J, Martin A, Han X, Shirihai OS, Grinstaff MW. Biodegradable PLGA nanoparticles restore lysosomal acidity and protect neural PC-12 cells against mitochondrial toxicity. Ind Eng Chem Res. 2019;58(31):13910–7. https://doi.org/10.1021/acs.iecr.9b02003.
54. Bourdenx M, Daniel J, Genin E, Soria FN, Blanchard-Desce M, Bezard E, et al. Nanoparticles restore lysosomal acidification defects: Implications for Parkinson and other lysosomal-related diseases. Autophagy. 2016;12(3):472–83. https://doi.org/10.1080/15548627.2015.1136769.
55. Shen X, Li T, Xie X, Feng Y, Chen Z, Yang H, Wu C, Deng S, Liu Y. PLGA-based drug delivery systems for remotely triggered cancer therapeutic and diagnostic applications. Front Bioeng Biotechnol. 2020;8:381. https://doi.org/10.3389/fbioe.2020.00381.
56. Xie W, Guo Z, Gao F, Gao Q, Wang D, Liaw BS, et al. Shape-, size- and structure-controlled synthesis and biocompatibility of iron oxide nanoparticles for magnetic theranostics. Theranostics. 2018;8(12):3284–307. https://doi.org/10.7150/thno.25220.
57. Zhu N, Ji H, Yu P, Niu J, Farooq MU, Akram MW, et al. Surface modification of magnetic iron oxide nanoparticles. Nanomaterials. 2018;8(10):810. https://doi.org/10.3390/nano8100810.
58. Wang S, Zhang B, Su L, Nie W, Han D, Han G, et al. Subcellular distributions of iron oxide nanoparticles in rat brains affected by different surface modifications. J Biomed Mater Res A. 2019;107(9):1988–98. https://doi.org/10.1002/jbm.a.36711.
59. Liu XG, Lu S, Liu DQ, Zhang L, Zhang LX, Yu XL, et al. ScFv-conjugated superparamagnetic iron oxide nanoparticles for MRI-based diagnosis in transgenic mouse models of Parkinson's and Huntington's diseases. Brain Res. 2019;1707:141–53. https://doi.org/10.1016/j.brainres.2018.11.034.
60. Li Y, Chen Z, Lu Z, Yang Q, Liu L, Jiang Z, et al. "Cell-addictive" dual-target traceable nanodrug for Parkinson's disease treatment via flotillins pathway. Theranostics. 2018;8(19):5469–81. https://doi.org/10.7150/thno.28295.
61. Chung T-H, Hsu S-C, Wu S-H, Hsiao J-K, Lin C-P, Yao M, et al. Dextran-coated iron oxide nanoparticle-improved therapeutic effects of human mesenchymal stem cells in a mouse model of Parkinson's disease. Nanoscale. 2018;10(6):2998–3007. https://doi.org/10.1039/c7nr06976f.
62. Umarao P, Bose S, Bhattacharyya S, Kumar A, Jain S. Neuroprotective potential of superparamagnetic iron oxide nanoparticles along with exposure to electromagnetic field in 6-OHDA rat model of Parkinson's disease. J Nanosci Nanotechnol. 2016;16(1):261–9. https://doi.org/10.1166/jnn.2016.11103.
63. Moayeri A, Darvishi M, Amraei M. Homing of super paramagnetic iron oxide nanoparticles (SPIONs) labeled adipose-derived stem cells by magnetic attraction in a rat model of Parkinson's disease. Int J Nanomedicine. 2020;15:1297–308. https://doi.org/10.2147/IJN.S238266.
64. Nikolovski D, Cumic J, Pantic I. Application of gray level co-occurrence matrix algorithm for detection of discrete structural changes in cell nuclei after exposure to iron oxide nanoparticles and 6-hydroxydopamine. Microsc Microanal. 2019;25(4):982–8. https://doi.org/10.1017/S1431927619014594.
65. Han D, Zhang B, Su L, Yang B. Attachment of streptavidin-modified superparamagnetic iron oxide nanoparticles to the PC-12 cell membrane. Biomed Mater. 2020;15(4): 045014. https://doi.org/10.1088/1748-605X/ab7764.
66. Singh N, Jenkins GJ, Asadi R, Doak SH. Potential toxicity of superparamagnetic iron oxide nanoparticles (SPION). Nano Rev. 2010. https://doi.org/10.3402/nano.v1i0.5358.

Publisher's Note