

Designing nanocarriers to overcome the limitations in conventional drug administration for Parkinson's disease

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Neurodegenerative diseases (NDs) have become one of the leading causes of death and disability worldwide, and cause enormous pain and suffering for both patients and their families. Some of the most common NDs include Alzheimer's disease, Parkinson's disease (PD) and Huntington's disease, among others (Feng, 2020). PD is a widespread neurodegenerative disease that affects more than 10 million people worldwide (No author listed, 2021). The direct cause of the disease is unknown, but it is characterized by the selective degeneration of dopaminergic neurons in the midbrain in the substantia nigra. This leads to the depletion of dopamine (3,4-dihydroxyphenethylamine, DA) in the striatum of patients, in addition to the existence of abnormal α -synuclein in nerve cells and the development of toxic protein aggregates in neurons called Lewy bodies, which causes muscle stiffness, slowness of movements and tremors. It is believed that a combination of genetic and environmental factors may be the cause of PD, but the exact reason for the disease is not yet fully understood.

There is no standard treatment for PD since treatment for each person is based on his or her symptoms and can include medication and surgical therapy. Current drugs mainly relieve symptoms and do not inhibit the continued degeneration of dopaminergic neurons. Unfortunately, DA does not cross the blood-brain barrier (BBB), which prevents its oral use for the treatment of PD, and hence alternative therapies are the most common forms of PD treatment. Among them is the DA precursor levodopa (L-3,4-dihydroxyphenylalanine, L-dopa), which is widely considered to be the most useful drug for treating PD. However, its long-term administration, coupled with the non-continuous mode of administration, results in fluctuations with sawtooth-like profiles of L-dopa in plasma concentration over time, which is associated with the appearance of dyskinesia and motor complications. Other therapies that have shown great promise in the treatment of PD include: Neurotrophic factors consisting of the administration of proteins that favor the development, survival, and plasticity of neurons; antioxidants to combat the oxidative stress as one of the most relevant mechanisms involved in PD, and RNA molecules controlled delivery into the brain. However, major drawbacks associated with short *in vivo* half-lives, poor pharmacokinetic properties, and restricted access through the BBB remain a challenge to deliver these moieties into the brain (Bondarenko, 2021; Torres-Ortega, 2019). Therefore, the development of alternative approaches to overcome these limitations and biological barriers is crucial to combat PD.

From the exciting talk of the outstanding physicist Richard Feynman in 1959 who questioned "why cannot we write the entire 24 volumes of the *Encyclopedia Britannica* on the head of a pin?", exploring the immense possibilities afforded by miniaturization, to the Nobel Prize in Chemistry 2016 being awarded to Sauvage, Stoddart and Feringa "for the design and synthesis of molecular machines" – the development of the nanoscience and nanotechnology disciplines have been one of the most exciting and fastest moving areas of science and technology. Nanoscience and nanotechnology cover the fields of science that design, obtain, make, and/or manipulate in a controlled way, materials, substances and devices or machines in the size range 1–1000 nanometres (1 nanometre is a millionth part of a millimetre). In recent years, the nanoparticle term is even more restricted to materials with mean size ranging from 1–100 nm. Specifically, in medicine, nanoparticles (NPs) of this size have emerged as suitable nanovehicles or nanocarriers for overcoming limitations associated with conventional drug formulations. These nanoparticles can be engineered to synthetically control their size, morphology, roughness, surface chemistry, etc.

In the treatment of neurological diseases, particularly in PD, NPs can play a remarkable role mainly due to their distinctive thermal, magnetic, and physicochemical properties, such as shape, small size, large specific surface area, hydrophobicity, high loading capacity of different moieties and drugs, chemistry and surface charge, and coating and easy functionalization. The latter allows modifying the NPs surface area with various functional molecules, and therefore introducing the capability that NPs reach target sites by means of active targeting strategies for enhanced uptake in specific cells. Therefore, NPs can help DA or alternative therapies to ensure that they: are not metabolized with uncontrolled effects, do not interfere with other organ function, have lasting effects as a consequence of the slow release in a continuous and sustained way, and are even able to cross the BBB to reach the target sites and escape the reticuloendothelial system, thus reducing drug administration and, therefore, reducing side effects (both adverse and otherwise).

Different types of nanoplateforms have been used to achieve some of these different goals (Figure 1), including liposomes, micelles, hydrogels, polymeric materials, such as poly(ethylenimine), poly(alkylcyanoacrylates), poly(lactic-co-glycolic acid), polyesters (poly(lactic acid), and inorganic materials, such as carbon nanotubes, gold, silicon dioxide, iron oxide (Pahuja, 2015; Morales, 2016, 2021;

García-Pardo, 2021).

In conventional PD therapy, the drugs are ingested or injected, and thus freely diffuse and distribute throughout the bloodstream resulting in sharp fluctuations in blood concentration. This causes the drugs to be exposed to enzymes and metabolites that can modify them before reaching the target site, giving rise to potentially toxic products, and even undesirable side effects in unwanted organs. Moreover, recent observations have shown that continuous dopaminergic stimulation in PD has some advantages over pulsatile, non-continuous modes of administration, and conclude that continuous administration of dopaminergic receptors induces fewer complications, such as dyskinesia, compared to pulsatile stimulation (van Wamelen, 2018). Therefore, a better control of the amount, time of exposure and place of action of the drugs would be desirable.

The use of NPs has shown some promise in overcoming this issue. We recently reported the sustained and controlled pH-responsive release of L-dopa from inorganic mesoporous silica nanoparticles (MSNs). MSNs were synthesized based on a new concept first developed by our group, using drug-structure-directing agents (DSDAs), a concept with a global nature that has been successfully used for the technological development and innovative design of MSNs and their use as nanocarriers for drug delivery (Morales, 2016). The DSDA plays a dual role, first as a surfactant that forms the micellar structure that is responsible for generating the porous structure of MSNs conforming the silica framework, and second being the active pharmacological substance to be released from MSNs. Pharmacologically active DSDAs are obtained by chemical modification of different model drugs to promote the formation of micelles, around which the inorganic silica species hydrolyse and condense to form MSNs. Thus, the DSDA of L-dopa was obtained by its amidation with fatty acids of different length, such as decanoic, palmitic and mainly oleic acid that allowed the formation of micelles of DSDA, around which the inorganic species self-assembled to build MSNs. Subsequently the DSDA *in vitro* release was stimulated in two different media: simulated gastric fluid, or stomach acid, at pH 1.2 and simulated small intestinal fluid at pH 7.4, and therefore mimicking the response to diverse biological stimuli in the gastrointestinal tract. When L-dopa is usually administered (typically orally), L-dopa is fully absorbed in the duodenum and first portions of the jejunum, and therefore enters into the bloodstream from the intestine mediated by active transport (Figure 1). Our results showed hardly any release in the simulated acid conditions at pH 1.2, and therefore avoiding the premature release in the stomach, while for intestinal conditions of pH 7.4, the release of L-Dopa occurred in a continuous and sustained manner, which is well suited to the drug's application and biochemical delivery route. After release from MSN, the cleavage of the DSDA is promoted by the body's enzymatic activity and results in the gradual delivery of both, oleic acid and L-dopa separately, in equimolar quantities, i.e. the active drug and a lipid moiety with nutraceutical properties. We hypothesized that the L-Dopa

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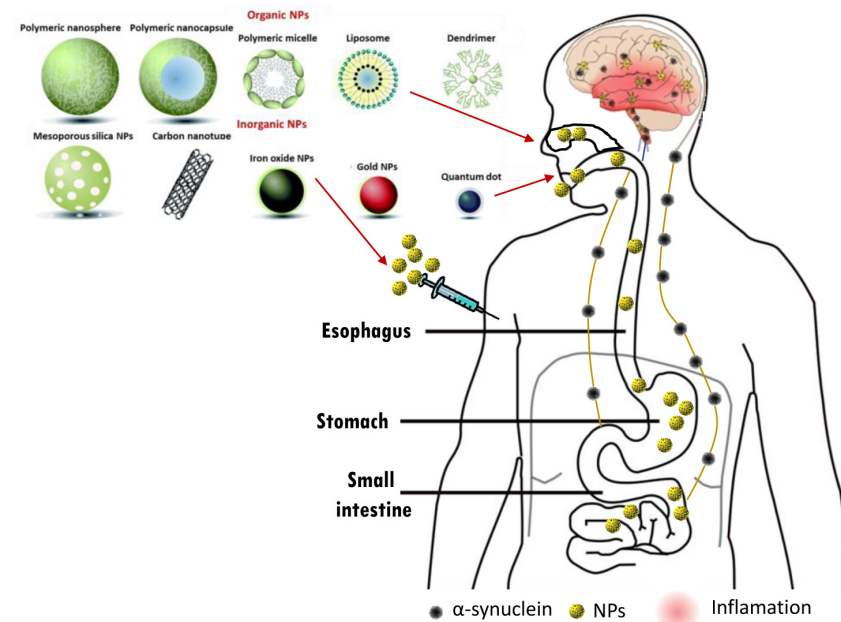


Figure 1 | Schematic showing nanoparticle (NP) types and routes of administration to treat Parkinson's disease: intravenous, oral and intranasal.

released from MSN materials is mediated by the size and solubility of the DSDAs, and the surface chemical interactions between the DSDAs and MSN hosts. Therefore, the L-dopa@MSNs drug delivery systems synthesized were proved to be responsive to biological pH stimuli (Morales, 2021).

Therefore, the development of nanoscale stimuli-responsive devices for alternative treatments of PD sensitive to specific endogenous stimuli, such as the pH, redox potential, or the concentrations of metabolites and enzymes that can trigger or slow down the release of the encapsulated drug, is a field of enormous interest to overcome the complications associated with the drug's conventional oral administration. Moreover, sustained and continuous drug release in PD could also be achieved by using exogenous stimuli, such as temperature changes, magnetic fields, ultrasound, light and electric field-sensitive NPs systems. Additionally, there is the possibility of selecting different routes of administration of the NPs such as intravenous, oral, or mucosal. This is another attractive area to be stimulated to combat PD (Figure 1).

Furthermore, one of the major challenges for successful therapy, not only for PD but for other NDs, is to promote the continuous, sustained and safe delivery of medicines across the physiological barrier that is the BBB (Furtado, 2018). This is required in order to deliver the drugs in the striatal region required for overcoming the functional deficits related to dopamine deficiency. Pahuja et al. (2015) were pioneering in making dopamine cross the BBB in the form of dopamine-loaded polymeric nanoparticles to reverse the functional deficit in Parkinsonian rats. Another interesting approach, based on the easy functionalization of the NPs surface, consists of anchoring them with targeting molecules that permit NPs to enter the brain through the BBB. Some NPs have been reported to inhibit α -synuclein fibrillation

and damage pre-formed fibers (Zaman et al., 2014). Nose-to-brain transport via intranasal administration (Figure 1) is a promising alternative to systemic administration since this method is able to bypass the BBB. This results in an efficient delivery in the nigrostriatal pathway attenuating motor alterations, improving the therapy's concentration in the brain, reducing side effects, and being minimally invasive to patients (García-Pardo, 2021; Corbin, 2021).

However, the complexity and diversity of brain tissue, together with the limited understanding of NPs-biological interactions and mechanisms, are major barriers for nanoscience and NPs applied to treat PD. Several physiological barriers including BBB, mononuclear phagocytic system, reticuloendothelial system, enzymatic degradation, hemorheological/blood vessel flow limitations, pressure gradients, endothelial permeability, and other factors such as the administration route (oral, intravenous, intranasal), and state of disease progression (early- versus late-stage PD) means the potential use of NPs to treat PD and other NDs is still under investigation, and we can say the technology is in its infancy. The path of NPs through the BBB has not been fully studied. Finally, another vital aspect in the use of NPs to treat NDs is related to NPs biodegradability and elimination from the brain. This will probably occur via the glymphatic system but currently limits therapeutic aspects of nanoscience applied to combat PD. Therefore, an enhanced understanding of biological processes and physiological barriers coupled with a new generation of nanomaterials and experimentation in bigger mammals than rodents are the prerequisite to translate NPs as drug delivery nanocarriers to treat PD from a promising and potential field to a clinical reality.

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