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NEUROLOGICAL UPDATE

Nanoparticles for drug delivery in Parkinson's disease

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Abstract
Although effective symptomatic treatments for Parkinson's disease (PD) have been available for some time, efficient and well-controlled drug delivery to the brain has proven to be challenging. The emergence of nanotechnology has created new opportunities not only for improving the pharmacokinetics of conventional therapies but also for developing novel treatment approaches and disease modifying therapies. Several exciting strategies including drug carrier nanoparticles targeting specific intracellular pathways and structural reconformation of tangled proteins as well as introducing reprogramming genes have already shown promise and are likely to deliver more tailored approaches to the treatment of PD in the future. This paper reviews the role of nanoparticles in PD including a discussion of both their composition and functional capacity as well as their potential to deliver better therapeutic agents.

Keywords Nanoparticles · Parkinson's disease · Blood–brain barrier · Targeted delivery · Polymeric nanoparticles · Lipid-based nanoparticles · Inorganic nanoparticles

Introduction

Current treatment strategies for Parkinson's disease (PD) largely focus on relieving motor symptoms by increasing dopamine levels within the central nervous system (CNS) or by stimulating dopamine receptors. The most effective treatment is levodopa but its benefits are impacted by unpredictable absorption and extensive peripheral metabolism, leading to motor fluctuations [1].

Nanotechnology-based drug-delivery systems provide a promising avenue to overcome the pharmacokinetic limitations of conventional therapies, but also provide distinct benefits by virtue of their small size (1–100 nm). Nanoparticles can act as drug-delivery vehicles with the potential to directly manipulate biological targets (e.g. DNA, RNA, proteins) [2]. In particular, they can protect drug from degradation, provide sustained release, facilitate entry into the CNS and also deliver drug to specific cells to target particular intracellular pathways [3, 4].

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In this review, we will focus on nanoparticles that may impact on future PD therapies. We will first describe the composition and structure of the various subtypes of nanoparticles that have been developed for PD, highlighting polymer-based, lipid-based and inorganic agents. We will then outline how nanoparticles may be applied in the future treatment of PD from a functional perspective.

Nanoparticle composition

Nanoparticles are classically divided by their structural composition. The advantages and disadvantages of each type are described in Table 1.

Polymeric nanoparticles

Polymeric nanoparticles can be composed of synthetic or naturally occurring polymers and are organised into a variety of structures, which have been shown to be biocompatible, biodegradable, and non-toxic [5]. The two most basic types are nanocapsules, where the drug is encapsulated in a polymeric vesicle, and nanospheres, where the drug is entrapped in a matrix of polymer or adsorbed onto its surface (Fig. 1). In either case, the drug is released as the polymer is

Table 1 Advantages and disadvantages of various nanoparticle formulations

Class	Structure	Composition	Advantages	Disadvantages	Citations
Polymer-based	Polymeric Nanosphere / Nanocapsules	*Synthetic polymers:* PLGA, PLA, PEG *Natural polymers:* chitosan	Customisable size, degradation rate and functionalisation. High drug loading Biocompatible, biodegradable, FDA-approved PEG: hydrophilic, reduced protein adsorption, reduced immunogenicity, improved circulation time Polymeric Micelles: able to solubilise water insoluble drugs, hydrophilic shell may prevent RES uptake	Phagocytosis may accelerate degradation. PLGA/PLA are hydrophobic with poor encapsulation of hydrophilic drugs Possibly toxic degradation products Use of solvents during production Natural polymers have less chemical stability, and increased batch to batch variability Difficulties with scaling	[5, 57]
	Polymeric Micelles	Amphiphilic polymers			[7]
	Dendrimers	Poly(amidoamine) (PAMAM), Carbosilane, PEG polyethylenimine	Small, stable, easy surface modification, water-soluble, well-defined controllable structure, inherent anti-aggregation properties	'Generation' dependent cytotoxicity Small dendrimers rapidly cleared	[8, 11]
Lipid-based	Solid Lipid Nanocarriers (SLN)	Biodegradable solid fats	Stable, easier manufacturing, high-scale production. Biocompatible, biodegradable Reduced first-pass metabolism via lymphatic route Reduced surfactant use Sustained release capability Higher surface area particles have more rapid dissolution rate and accelerate onset of action of drug NLC's have improved drug loading over SLN	SLN's have low loading capacity and leakage of drug during storage. Variable release profile Possibility of oxidation Increased organ penetration as lipophilic	[15, 16, 116]
	Nanostructured Lipid Carriers (NLC)	Mixture of solid fats and oil			
	Nanoemulsions	Emulsified oil and water droplets, surfactants			[23, 24]
	Liposomes/ micelles	Aliphatic phospholipids	Allow encapsulation of hydrophobic and hydrophilic drugs with high efficiency in liposomes, provide sustained release, enhanced intracellular transport, low toxicity, wide clinical use	Costly production, poor scalability, possibility of oxidation and hydrolysis, leakage of drugs and structural instability with prolonged storage, clearance by RES	[17, 117, 118]
	Exosomes	Cell-derived	Utilise natural cell-specific targeting mechanisms, less immunogenicity, good biocompatibility, low toxicity, cross BBB, high drug loading efficiency	Large scale production issues, purification and quality control require optimisation	[19, 20]

Table 1 (continued)

Class	Structure	Composition	Advantages	Disadvantages	Citations
Other	Metal nanoparticles	Gold, iron oxide, silver	Inert, non-immunogenic, easy to synthesise in variety of shapes, easy surface modification, size-dependent electrochemistry with gold, good penetration, theranostic use, super-paramagnetic properties of iron	Possible toxicity with smaller gold nanoparticles. Surface ligands and charge may cause toxicity	[28, 29, 119]
	Carbon nanotubes Fullerene Graphene	Allotropes of carbon	Versatile size and shape, large surface area which can be functionalised	Toxicity dependent on shape (e.g. nanotubes), toxicities due to impurities or surface ligands	[28, 31, 32, 34]

degraded allowing flexibility in the rate of delivery, which can range from weeks to months [6].

More sophisticated polymeric structures exist in the form of polymeric micelles and dendrites (Fig. 1). Polymeric micelles are formed by amphiphilic polymers that self-assemble typically into a sphere with a hydrophobic core and hydrophilic shell [7]. They are particularly beneficial for encapsulating hydrophobic drugs. Dendrimers, on the other hand, are highly branched macromolecules formed by radially branched polymers in repeating units called 'generations.' Due to their well-defined chemical structure, they are uniform in size and can be very small (< 20 nm) [8]. Multiple binding sites on the terminal branches of these dendrimers provide additional functions and it has been shown that they can prevent α-synuclein fibrillation and potentially remove fibrils in vitro [9–11].

The most common FDA-approved polymers to prepare nanoparticles are poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA) and polyethylene glycol (PEG). Of the clinically approved nanoparticles, PEG is the most widely used polymer as it is used to coat nanoparticles as well as to stabilise proteins in more conventional therapies [12]. The earliest example of pegylation was used in Adagen® in 1990, which is PEG-adenosine deaminase for the treatment of severe combined immunodeficiency disease. Furthermore, Eligard®, a PLGA-encapsulated leuprorelin (a testosterone inhibiting drug), is commonly used for the controlled release of hormone therapy for the treatment of prostate cancer, allowing for subcutaneous injection every six months [13]. Unfortunately, there are few other examples of polymeric nanoparticles in clinical use with the majority of current trials being conducted in cancer therapies [14]. Despite the proof of concept in these clinical trials, polymeric nanoparticles have not progressed beyond preclinical studies in Parkinson's disease.

Lipid-based nanoparticles

Lipid-based nanoparticles are biocompatible and due to their lipid nature and size can penetrate the CNS without any modification [15]. They may circumvent first-pass metabolism when absorbed via the lymphatic system [16]. Lipid vesicles made from a single layer of phospholipids (micelles) or a bilayer (liposomes) can encapsulate drugs and provide sustained protection from degradation in the circulation (Fig. 2) [17]. Endogenous extracellular vesicles (exosomes) naturally composed of phospholipid bilayers have been harvested and loaded with PD drugs with lower immunogenicity utilising natural cell-specific targeting mechanisms [18–20]. Other lipid-based nanostructures can also be made of solid lipid, liquid lipid (Nanoemulsions) or a mixture of the two (Nanostructured Lipid Carriers)

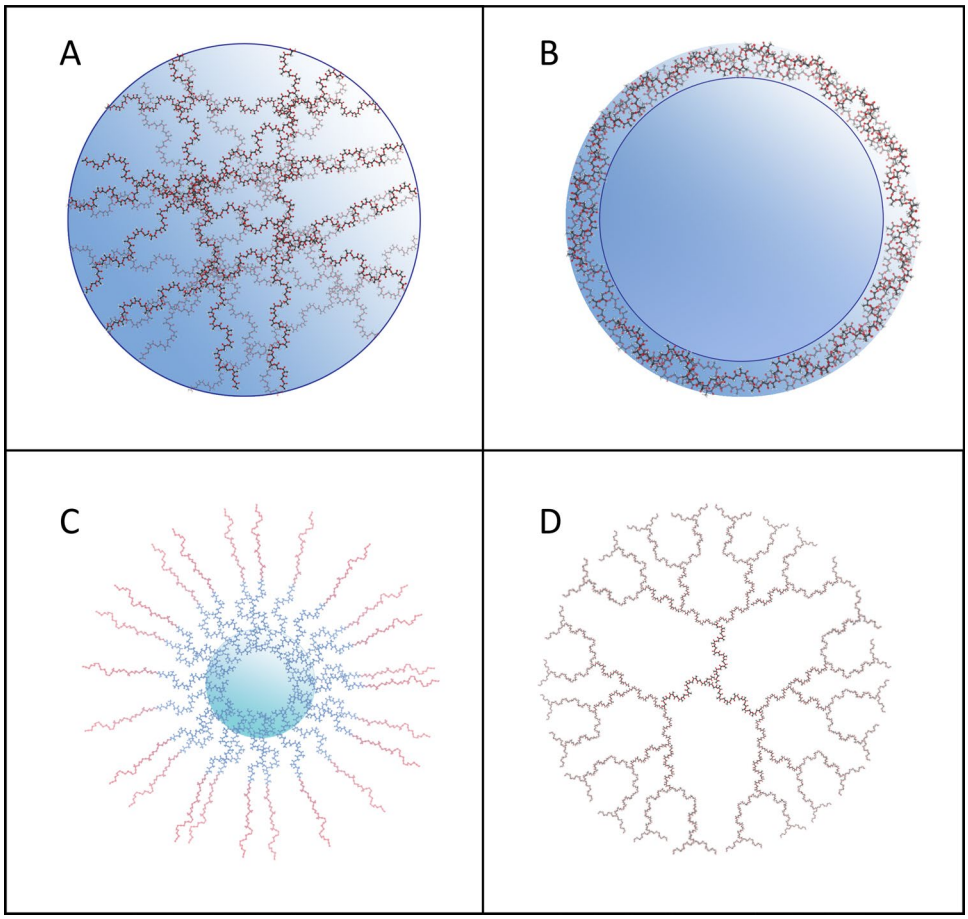

Fig. 1 Polymer-based nanoparticles. **a** Polymeric Nanosphere **b** Polymeric nanocapsule, **c** Polymeric micelle, **d** Dendrimer

[21–24]. These are shown in Fig. 2, with advantages and disadvantages listed in Table 1.

Liposomes comprise the majority of clinically available nanoparticles [14] with over 20 years of clinical use including agents such as liposomal amphotericin (AmBisome®) and doxorubicin (Doxil® or Caelyx®). Liposomal amphotericin improves the half-life of the drug as well as reducing nephrotoxicity by preventing the active drug from interacting with the renal distal tubules [25]. Liposomal doxorubicin, whilst improving the pharmacokinetic profile of doxorubicin, also reduces cardiotoxicity, myelosuppression and nausea and vomiting. This is because the liposome favours distribution away from sites that have tight capillary junctions, such as the heart and gastrointestinal tract, and into areas with fenestrated capillaries such as sites of inflammation or tumour growth [26]. Newer liposomal drugs are available, but there is limited clinical availability of the other types of lipid nanoparticles. Drug-loaded exosomes have made it has far as completing phase II studies in cancer therapeutics [27]. Despite the emerging clinical use of exosomes and the wide clinical usage of liposomes, research into lipid-based nanoparticles for PD is currently limited to preclinical studies.

Inorganic nanoparticles

Inorganic nanoparticles have attracted considerable attention as drug-delivery systems, as well as potential disease modifiers [28]. Current developments have evaluated gold [29], magnetic iron oxide [30], as well as the synthetic allotropes of carbon [31, 32], such as fullerene, graphene and carbon nanotubes for use in PD (Fig. 3). These structures are very small (< 25 nm) and have electrochemical properties that are size and shape dependent [33]. Importantly, some concerns have been raised about the use of carbon nanotubes due to some asbestos-like toxicity whereby they can induce the secretion of proinflammatory cytokines such as IL-1β from macrophages [34].

Iron oxide nanoparticles are the most widely FDA-approved inorganic nanoparticles, with examples such as iron carboxymaltose (Ferrinject®) for anaemia and others being used as imaging agents [14]. However, gold nanoparticles are emerging with Phase II clinical trials underway for multiple sclerosis, amyotrophic lateral sclerosis, and Parkinson's disease, which will be discussed below [35–37].

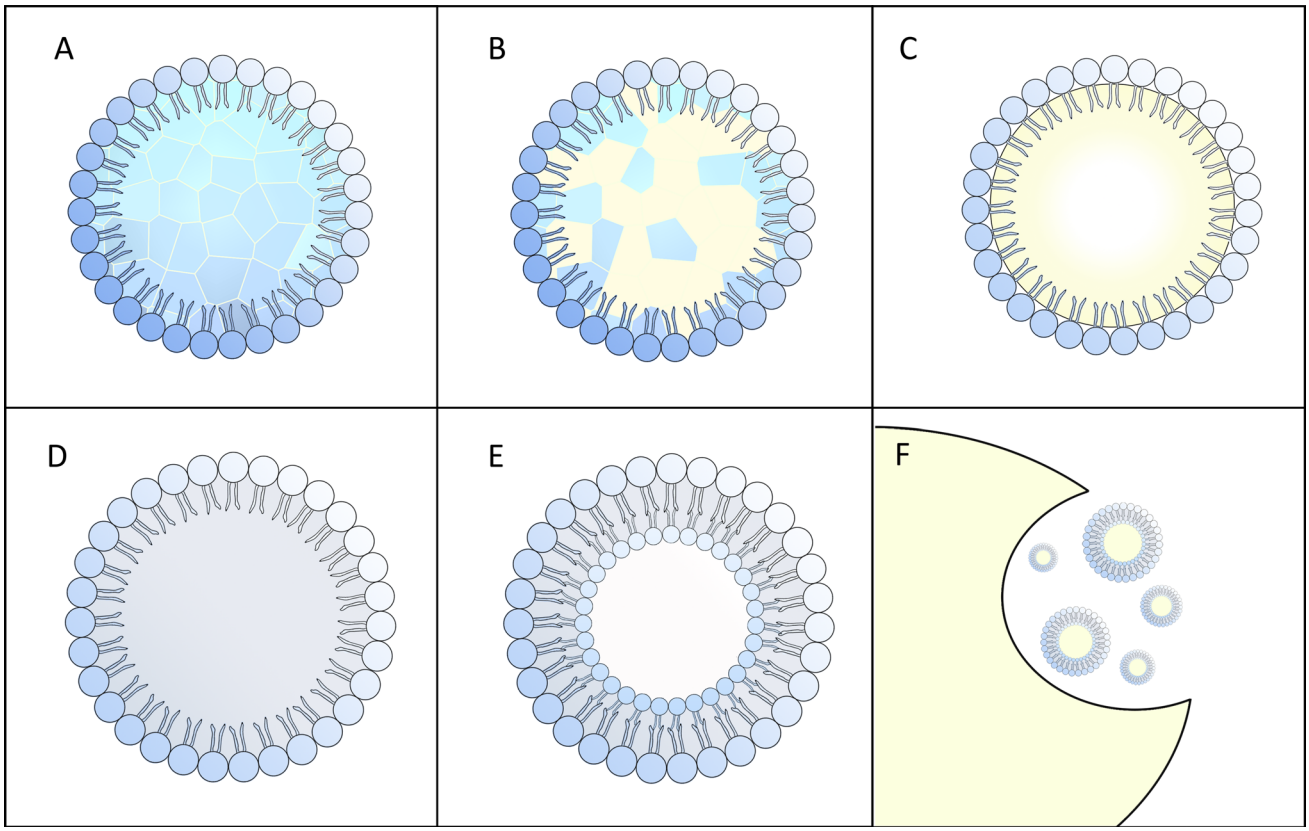

Fig. 2 Lipid-based nanoparticles. **a** Solid lipid nanoparticle, **b** Nanostructured lipid carrier, **c** Nanoemulsion, **d** Micelle, **e** Liposome, **f** Exosome

Application to Parkinson's Disease

To date, nanoparticles have been trialled around a number of different rationales including providing the sustained release of conventional PD therapies, evading the immune system and facilitating entry into the CNS [4]. They have also been modified with functional elements to further enhance entry across mucosal surfaces, to target particular cell types (e.g. dopaminergic neurons) or to only release the active drug in particular circumstances, such as within acidic intracellular organelle compartments (e.g. lysosomes) (Fig. 4; Table 2) [38]. Therefore, potential benefits of nanotherapies extend beyond simply improving the pharmacokinetic properties of conventional treatments to the delivery of novel therapies that could target particular intracellular pathways (e.g. oxidative stress, inflammation) or even specific genes [39].

Sustained release

The earliest research into nanoparticles for PD involved improving the release profile of dopamine and then other dopaminergic medications, such as levodopa, dopamine agonists and monoamine oxidase B inhibitors. The first formulations involved stereotactically implanting dopamine-loaded liposomes directly into the striatum of a rat model of PD [40]. These liposomes released dopamine for 40 days with levels that remained elevated for 25 days following implantation. Similarly, formulations of levodopa have been able to achieve sustained levels via peripheral administration of liposomes [41, 42], as well as polymer-based nanoparticles [43–47]. A progression of studies resulted in a PLGA-PLA nanosphere being developed in 2012 that allowed for a once weekly administration of subcutaneous levodopa, resulting in elevated plasma dopamine levels that were sustained for 20 days in 6-OHDA lesioned rats. This approach not only improved bradykinesia but also ameliorated dyskinesias [43]. In an effort to avoid subcutaneous administration, more recent research has focused on intranasal formulations of levodopa-loaded PLGA nanoparticles, which appear to offer motor benefits that can persist for at least a week following administration [44]. In the last few years, studies have also demonstrated lower neuronal cytotoxicity from nanoparticles compared with free levodopa forming a stepping stone into first in human clinical studies [47].

Most of the recent research into extending the release of conventional PD therapies has been with polymeric nanoparticles rather than liposomes, which make up the

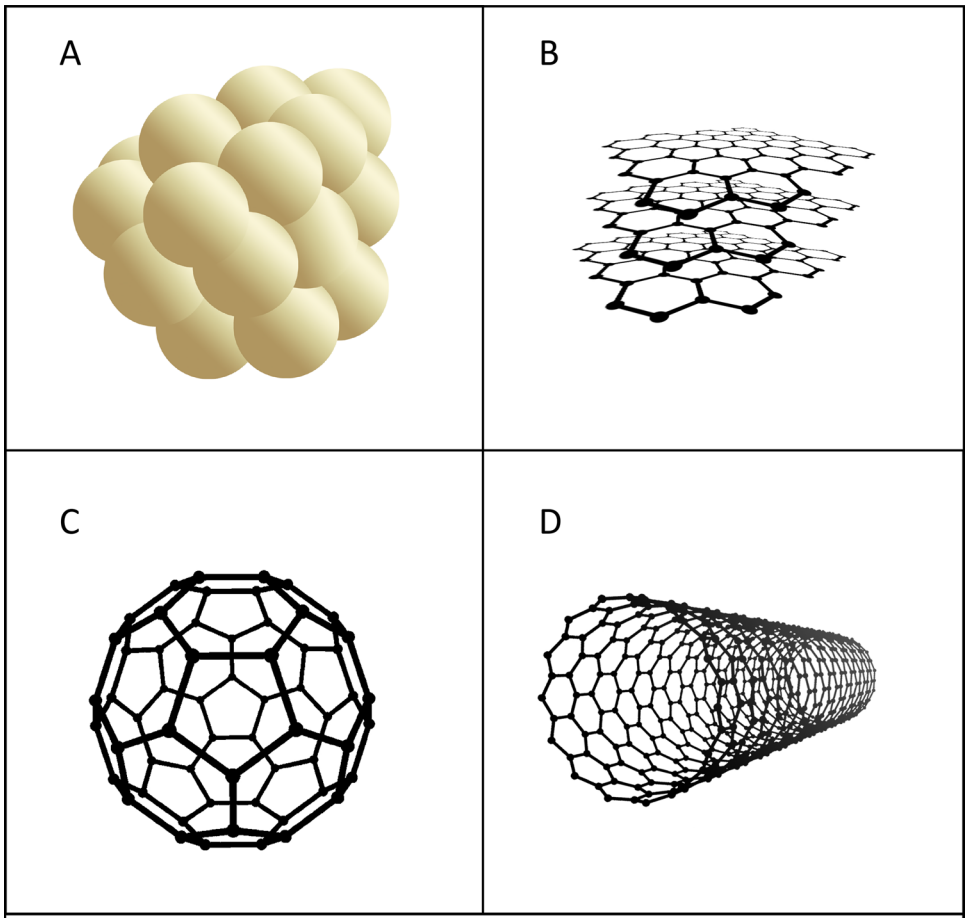

Fig. 3 Miscellaneous nanoparticles. **a** Gold nanoparticles, **b** Graphene, **c** Fullerene, **d** Carbon nanotube

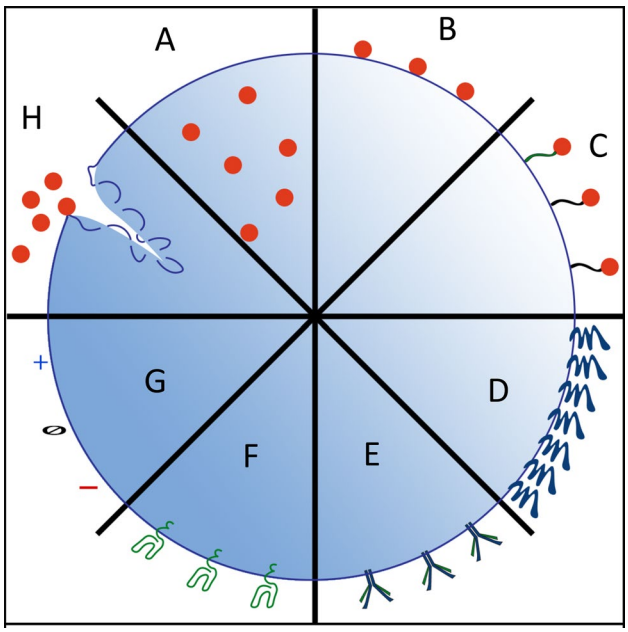

Fig. 4 Functional components of nanoparticles. **a** Drug encapsulation **b** Drug adsorption **c** Drug conjugation **d** PEGylation (or other coating) **e** Antibody-mediated targeting **f** Peptide-mediated targeting **g** Surface charge **h** Triggered release

majority of clinically approved nanoparticles in other diseases. Polymeric nanoparticles offering extended release have been successfully demonstrated in preclinical models with apomorphine [48, 49], bromocriptine [50], ropinirole [51], rotigotine [52–54] and selegeline [55]. Notably, one PLGA-based microsphere loaded with rotigotine has demonstrated stable plasma and striatal levels for 14 days, leading to reduced dyskinesias in 6-OHDA lesioned rats [54]. However, toxicity was not extensively investigated in any of these studies. Given that safety cannot be extrapolated from the composition of nanoparticles alone and thus the efficacy, safety, biodistribution and pharmacokinetics of each nanoparticle need to be evaluated more thoroughly prior to human studies [56].

Immunoevasion

Another important property of nanoparticles is the ability to manipulate their surface which allows them to avoid the immune system. Coating nanoparticles with polyethylene glycol (PEG) can bestow a 'stealth property', which prolongs peripheral circulation [14]. This is achieved by steric hindrance suppressing opsonisation, reducing activation of the

Table 2 Functional elements of nanoparticles investigated in preclinical trials of drug delivery in PD

Functional element	Mechanism	Citation
Polyethylene glycol (PEG)	Immunoevasion by steric hindrance	[59, 72, 80, 120]
Chitosan	Mucosal entry, BBB penetration	[50, 67, 69, 121–123]
Odorranalectin	Mucosal entry	[71]
Wheat germ agglutinin (WGA)	Mucosal entry	[72]
Lactoferrin	Mucosal entry, BBB entry	[52, 58, 64, 80, 81]
Transferrin	BBB entry	[59, 81, 124, 125]
OX26, transferrin-receptor antibody	BBB entry	[59]
Angiopep	BBB entry	[82]
Polysorbate-80	BBB entry by lipoprotein adsorption	[51, 102]
Microbubbles	BBB entry when combined with Focused Ultrasound (FUS)	[86–88, 102, 112]
RVG29	Dopaminergic neuron targeting, uptake, BBB entry	[60, 109, 111]
Nerve growth factor	Neuronal uptake	[30, 110]
Phenylboronic acid	Intracellular release (pH-sensitive)	[48, 96]
N-isopropylacrylamide	Intracellular release (pH-sensitive)	[30]

complement system and hence reducing clearance [57]. This approach has been used to improve the circulation times of dopamine [58–60], apomorphine [48, 61, 62], and rotigotine [52, 63, 64] in rodent models of PD only. PEG is used as an adjunct with other nanoparticles such as liposomes or as components of polymeric micelles rather than directly conjugated to PD drugs. Pegylated formulations of conventional PD therapies might be destined to follow the same fate as pegylated insulin, whose development was ceased despite completion of Phase III studies. This was reportedly due to the financial burden of investigating potential hepatotoxicity, which outweighed the potential financial returns in the context of competition from alternative basal insulins [65]. This does not mean that pegylation is not a viable strategy, as evidenced by the numerous pegylated therapies available in other conditions, but financial incentives might favour research into disease modifying therapies in PD rather than adding to the numerous symptomatic treatments that are currently available.

Mucosal entry

Intranasal drug delivery has the potential of circumventing first-pass metabolism and facilitating quick entry into the brain via olfactory and trigeminal nerve pathways [66]. Nanoparticles can optimise intranasal delivery via the use of mucoadhesive polymers, such as chitosan or by conjugating nanoparticles with ligands capable of binding to the nasoepithelial surface, such as lectins.

Chitosan is commonly used as the core polymer in nanoparticles [45] or as a coating [67] because it can easily adhere to mucous membranes for the purpose of enhancing absorption across the nasoepithelium. Chitosan has the added benefit that it can disrupt cellular tight junctions, allowing easier entry across the blood–brain barrier [68]. So far, chitosan nanoparticles have been used for intranasal formulations of bromocriptine [50], levodopa [45], pramipexole [69], selegeline [69], rotigotine [53] and ropinirole [67]. In general, these studies reported faster and increased absorption across the mucosa due to chitosan, which translated to clinical and biochemical benefits in rodent models of PD.

Conjugating nanoparticles with ligands capable of binding to the nasoepithelium can also enhance nasal absorption and have been used to deliver anti-PD drugs intranasally. For example, conjugation of the peptide odorranalectin has been utilised because it preferentially binds to L-fucose, a sugar moiety found on the olfactory epithelium [70]. In one study, fluorescence labelling was able to show that odorranalectin conjugation increased the uptake of urocortin-containing nanoparticles in the brain (sustained and continued to increase over 8 h) compared to those without odorranalectin [71]. Another similar approach has been through the use of wheat germ agglutinin (WGA), which binds to N-acetyl-D-glucosamine and sialic acid, molecules that are both abundant in the nasal cavity [72]. Indeed work in MPTP-lesioned mice demonstrated that WGA-grafted levodopa nanoparticles can cause a rapid and sustained improvement in locomotor activity following nasal delivery [47].

Another method of improving intranasal drug absorption has been the incorporation of nanoparticles into thermosensitive gels, which improve the intranasal residence time of the drug due to increased viscosity and hence absorption. In one example, rotigotine, which is poorly water-soluble, was encapsulated in a polymeric micelle so that it could be dissolved into a water-based thermosensitive gel. Indeed, this method nearly doubled entry into the brain compared to intravenously administered rotigotine [63].

Blood–brain barrier entry

Clearly, one of the key obstacles in the treatment of PD lies with the blood–brain barrier (BBB), the tightly regulated interface between the CNS and the bloodstream. The BBB restricts passive transport to small and lipophilic drugs and almost no large molecules (> 1000 Daltons) and around 98% of all small molecules (< 500 Daltons) can get across it [73]. Furthermore, many molecules that are able to cross into the brain are quickly transported back to the bloodstream via efflux pumps [74]. Effective transport across the BBB may be facilitated by carriers (solute carriers), such as the large amino acid transporter (LAT1), receptor-mediated transport or adsorption-mediated transcytosis systems [75]. Importantly, nanoparticles can facilitate entry via each of these mechanisms.

Lipid-based vehicles can enter through the BBB unimpeded due to their small size and lipophilicity, as can some polymeric nanoparticles especially if they are under 100 nm. However, enhanced entry is usually achieved by functionalising the surface of nanoparticles with ligands known to target receptors on the BBB. For instance, lactoferrin (lf) is an iron-binding glycoprotein of the transferrin family reported to enhance transcytosis across the brain capillary endothelium through its interaction with lactoferrin-receptors, such as the low-density lipoprotein receptor-related protein (LRP) found on brain endothelial cells and neurons [76]. Lactoferrin-receptors appear to be increased in both dopaminergic neurons and respiratory epithelial cells [77, 78]. Thus, intranasally administered rotigotine-loaded nanoparticles conjugated with lactoferrin have shown increased concentration in the striatum over other areas in the brain such as the hippocampus [52, 64].

This approach has also been used to study a neuroprotective agent, urocortin, which is a corticotrophin-releasing factor-related peptide that has been shown to restore nigrostriatal function [79]. One study has demonstrated that urocortin-loaded Lf-conjugated PEG-PLGA nanoparticles were capable of increasing brain uptake by threefold, when compared to unconjugated nanoparticles [80]. Finally, it has also been demonstrated that lactoferrin conjugation can also improve the delivery of gene therapy to dopaminergic neurons, which are discussed in greater detail below [81].

An important synthetic peptide that is gaining clinical attention is angiopep, which is an efficient ligand to LRP and allows higher brain penetration than other brain-targeting peptides such as lactoferrin [82]. It has been used for the delivery of gene therapy to the CNS in preclinical studies of PD, but will be utilised in a Phase III study to delivery paclitaxel to brain or leptomeningeal metastases after successful open label Phase II study [83, 84].

Polysorbate-80 (PS80) is a surfactant that is well known for facilitating entry into the blood–brain barrier [85]. It is thought to act as an anchor for various lipoproteins that become attached to it in the circulation by adsorption. These lipoproteins, such as apolipoprotein B and/or E, then facilitate entry into the brain by receptor-mediated endocytosis. As an example, PS80-coated chitosan nanoparticles have been used to enhance the entry of ropinirole, which typically crosses the BBB poorly due to its hydrophilicity [51]. These PS80-coated nanoparticles exhibited higher concentrations in the brain and less accumulation in other organs, such as the liver, spleen, and kidney compared with uncoated nanoparticles. This suggests that PS80-coated nanoparticles not only improved CNS entry across the BBB but also reduced opsonisation by the mononuclear phagocytic system, allowing more effective drug delivery.

Another novel method of facilitating entry into the CNS has been by combining nanoparticles with MRI-guided focused ultrasound [86]. Nanoparticles can be complexed to microbubbles that when exposed to ultrasound are believed to exert a radial force on capillaries, leading to local openings of the blood–brain barrier. This approach has been used in two recent studies to deliver gene therapy encapsulated in liposomes specifically to striatal neurons [87, 88]. This will be discussed in greater detail in the section on gene therapy.

Cell-targeting

The conjugation of specific ligands on nanoparticles can be used to promote selective uptake into dopaminergic neurons. Indeed, the Rabies Virus Glycoprotein (RVG29) is thought to facilitate internalisation into neurons by specifically binding to the nicotinic acetylcholine receptor (nAchR), which is found on dopaminergic neurons, as well as the extracellular surface of the brain's microvascular endothelial cells. Using this approach, studies have demonstrated that RVG29 can be conjugated with liposomes to deliver a dopamine derivative to the substantia nigra and striatum in PD rodents with a higher specificity than other neurons and in greater concentrations than was achieved with non-conjugated liposomes [60]. This technique of conjugating nanoparticles with ligands capable of being internalised within specific neurons offers advantages when looking to target pathogenic intracellular processes (see below).

There are currently no clinically approved targeted nanoparticles available for any diseases. There are phase II studies for cancer therapies, with one active phase II trial exploring anti-EGFR-immunoliposomes loaded with doxorubicin in patients with advanced triple negative EGFR positive breast cancer [89]. These immunoliposomes are constructed by covalently linking liposomes to Fab fragments of the monoclonal antibody cetuximab, which recognises the

EGFR molecule on the tumour [90]. Clinical trials utilising targeted ligands have fallen short due to off-target toxicity, increased clearance by the increased immunological recognition of surface ligands, and because of the difficulties associated with upscaling product manufacture [91].

Triggered release

To combat off-target toxicity and adverse effects, nanoparticles can be modified to release drug in selective environments, such as inside intracellular organelles. This approach has been explored with apomorphine loaded into polymeric nanoparticles modified with phenylboronic acid. The boronate ester undergoes dynamic changes in acidic environments, so that the drug is protected from release in the circulation but is rapidly released when taken into the acidic environment of the endolysosomes within neurons [48]. This has been studied in animal models of PD, but not in human studies. A triggered release nanoparticle ThermoDox®, which is a thermosensitive liposome that releases doxorubicin in response to temperatures at 40 °C, is currently in a phase III study for the treatment of hepatocellular carcinoma in combination with radiofrequency ablation, which provides the external heat required for activation [91, 92].

Pathological targets

Anti-aggregation

Drugs that prevent α-synuclein misfolding and/or aggregation have been an appealing approach to disease modification [93]. For example, epigallocatechin gallate (EGCG) has demonstrated good in vitro evidence for the inhibition of α-synuclein aggregation but unfortunately failed in clinical trials of patients with Multiple System Atrophy due to a lack of efficacy and significant hepatoxicity [94]. Notwithstanding the in vivo evidence of anti-Parkinson's effect in rodent models, it has been suggested that some of the limitations of EGCG included difficulties crossing the blood–brain barrier and poor internalisation into dopaminergic neurons [95]. In order to combat these issues, EGCG has been incorporated in multi-functional lipid micelles that facilitate receptor-mediated transcytosis across the BBB (using B6, a peptide with high affinity for the transferrin receptor), as well as ligands that target entry into dopaminergic neurons via the dopamine transporter (using mazindol, a drug that binds to the dopamine transporter DAT and promotes its internalisation) [96]. EGCG was grafted onto the surface of these nanoparticles utilising the reversible boronate ester bond that was discussed in the previous section, allowing for the release of EGCG only after the nanoparticle had been taken into the acidic environment of the endolysosomes within dopaminergic neurons. In the same study, these nanoparticles were labelled with superparamagnetic iron oxide nanocubes, which traced accumulation via magnetic resonance imaging. Results showed not only favourable pharmacokinetics compared to free EGCG but also increased accumulation, specifically within the substantia nigra, which correlated with improvements in both behavioural and biochemical markers of dopaminergic neuronal loss in these murine models of PD.

Other examples of anti-α-synuclein aggregation are reasonably diverse but aggregates of several to hundreds of gold atoms called 'gold nanoclusters' have been reported to inhibit α-synuclein fibrillation, reverse dopaminergic neuronal loss and improve motor behaviour in MPTP-induced mice [97], whilst melatonin-loaded polymeric nanoparticles made from dopamine polymers (polydopamine) have demonstrated a cytoprotective effect and suppress α-synuclein phosphorylation in vitro [98]. Furthermore, dendrimers as a class of nanoparticles are thought to possess anti-fibrillation properties per se due to their highly branched structure, which has been supported using some in vitro models of PD [9, 10].

Oxidative stress

There is active research into the pathophysiological pathways in PD, including drugs that target mitochondrial dysfunction, oxidative stress and inflammation. Although there may be good in vitro evidence with some of these drugs, many of them have failed to demonstrate disease modification in clinical studies [99]. However, it is possible that some of these studies have been limited by the pharmacokinetic properties of these drugs and there may be an opportunity to re-evaluate their benefit if they were combined with nanoparticles to circumvent these issues [100]. Indeed, recent examples of antioxidants that have demonstrated motor improvements in rodent models of PD when delivered via nanoparticles have included coenzyme Q10 [101], curcumin [102], acteoside [103] and puerarin [104, 105].

Gold nanoparticles have been proposed as a means for protecting dopaminergic neurons against oxidative stress. Recent studies investigating the preclinical efficacy of the gold nanoparticle CNM-Au8 have reported the enhanced survival of dopaminergic neurons when subjected to MPP + and 6-OHDA lesions, as well as improvements in paw placement in 6-OHDA-lesioned rats [106]. These findings have prompted clinical trials of CNM-Au8, such as the REPAIR-PD study, a Phase II single-centre, open label pilot assessing this therapy in PD patients within three years of diagnosis [35]. The study proposes that these orally administered gold nanoparticles will act as redox catalysts, increasing the production of ATP and offering protection against

oxidative stress. The primary endpoint of this short clinical intervention will utilise magnetic resonance spectroscopy (^{31}P-MRS) to evaluate the ratio of oxidised to reduced nicotinamide adenine dinucleotide (NAD+/NADH) with a lower ratio indicating increased oxidative stress.

Intracellular iron

Excess intracellular iron is a common characteristic in PD patients and is thought to be a precipitating factor in the development of the disease, possibly through oxidative stress and consequent necrosis [107]. This insight has prompted a number of clinical trials, some of which have shown a trend towards motor benefits using iron chelators [108]. However, the most effective iron chelator, deferoxamine (or desferrioxamine) (DFO) has a short half with low bioavailability as it is hydrophilic with poor penetrance of the BBB. To overcome this, DFO has been encapsulated within a PEG-PLGA polymeric micelle, coated with RVG29 to facilitate entry across the BBB and promote internalisation within dopaminergic neurons. Early results in MPTP-induced mice have demonstrated a reduction in striatal iron, a reduction in α-synuclein levels, a reversal of dopaminergic neuronal loss and an improvement in motor deficits [109].

Gene therapy

Gene therapy involves transferring nucleic acid-based therapeutic agents such as plasmid DNA, short interfering RNA (siRNA), microRNA or RNA into cells to repair, replace or regulate genes. In PD, gene therapy has been investigated to promote the expression of neuroprotective genes, such as glial cell line-derived neurotrophic factor (GDNF) [81, 82, 87, 88] or to downregulate the expression of α-synuclein [30, 110, 111]. Conventional viral vectors have faced challenges including some safety concerns, poor gene loading efficiency and immunogenicity with repeated administration. However, the biggest hurdle is that they require invasive intracranial administration due poor BBB penetration [112].

Nanoparticles can improve passage through the BBB via different methods, potentially allowing for the peripheral administration of gene therapy. Surface-modified dendrimers have been shown to improve penetration into the CNS by about fourfold compared with non-modified nanoparticles [81]. Peripheral intravenous administration of lactoferrin-modified dendrimers improved delivery of GDNF to the CNS over transferrin-modified and unmodified nanoparticles in PD rats. This resulted in improved locomotor activity, reduced dopaminergic neuronal loss and enhanced monoamine neurotransmitter levels [81]. The same group utilised a synthetic peptide called angiopep conjugated to a poly-L-lysine dendrimer to successfully deliver GDNF intravenously to the CNS of PD-induced rats resulting in improved locomotor activity and reduced dopaminergic neuronal loss [82]. A Phase III clinical trial is due to commence in 2021 studying the delivery of paclitaxel to brain and leptomeningeal metastases of brain cancer using angiopep-2 to target the CNS [84].

Another technique has been to combine nanoparticles with MRI-guided focused ultrasound (FUS) to achieve local disruption of the CNS. Intravenous administration of liposomes carrying GDNF has been shown improve penetration by fivefold when combined with FUS [87]. The combination of FUS with microbubbles complexed to liposomes carrying GDNF significantly improved behaviour of MPTP-induced mice and reduced dopaminergic neuronal loss when compared with liposomal delivery alone. In fact, liposomal delivery alone did not significantly improve behaviour over MPTP-induced controls [87]. Similar results were found when pegylated liposomes complexed with microbubbles were delivered intravenously to 6-OHDA lesioned rats. The combination increases the DNA-carrying capacity as well as BBB penetration, which would otherwise be traded off as increasing the size of the nanoparticle would reduce BBB penetration [88].

Inorganic nanoparticles present an alternative strategy to improve the loading efficiency of viral vectors due to their high surface area-to-volume ratio, and ability to be functionalised to target specific brain tissue [30, 110]. Examples have included gold nanoparticles and magnetic iron oxide nanoparticles, which both have been used to deploy plasmid DNA inhibiting SNCA to neurons with the aid of conjugating Nerve Growth Factor (NGF), which promotes neuronal uptake. In the study using magnetic iron oxide, nanoparticles also utilised a pH-sensitive and thermoresponsive polymer (N-isopropylacrylamide) to favour intracellular over extracellular release of the DNA [30]. This resulted in reduced α-synuclein expression, dopaminergic neuronal loss and improvements in behaviour in MPTP-induced mice. Gold nanoparticles with chitosan coating and NGF showed biochemical and histological improvements with no obvious toxicity [110]. Further studies and modifications are required to establish safety and improve efficacy, but these studies serve as starting point for the use of inorganic nanoparticles for gene therapy in PD.

Exosomes present an obvious solution to the immunoreactivity of traditional viral vectors in gene therapy. Exosomes have endogenous surface markers that are not recognised by the immune system and thus are less likely to generate immune responses even with repeated administration [20]. One recent study packaged DNA-targeting SNCA expression into exosomes, which were transfected with RV29 [111]. This ligand enabled passage through the BBB and internalisation into neurons so that the exosomes could be intravenously administered. The DNA was packed in efficient structures called ‘mini-circles’, which are essentially

bacterial plasmid DNA with excess DNA fragments removed to make them smaller, but still favouring transgene expression for long periods [113]. This method provided SNCA knockdown for at least 7 weeks after a single intravenous administration. Following a second dose, a behavioural improvement was demonstrated for up to 45 days in a synuclein mouse model. There were no increased inflammatory markers, but more studies are required to assess safety of these exosomes. The approach of using exosomes allowed for the more widespread knockdown of SNCA across the brain over more targeted delivery methods such as surgery or FUS [111]. However, exosomes are clearly at their infancy and require more research to improve harvesting, purification and scalability [19].

The possibilities of combining nanoparticles with gene therapy are growing. One suggested approach has been to implant exosome-secreting cells peripherally in situ and this has already been attempted subcutaneously in 6-OHDA-lesioned mice [114]. The cells automatically produced and packaged catalase mRNA into exosomes in vivo. The surface of these exosomes had ligands for BBB penetration and neuronal uptake where catalase could then be expressed by translation of the mRNA. The results of this study demonstrated that the implantation of designer cells could deliver mRNA-containing exosomes, resulting in the attenuation of neuroinflammation in 6-OHDA-induced mice opening up the potential for further studies and new therapeutic opportunities.

The Future

As our understanding of the pathogenic mechanisms of PD improves, nanoparticles could be designed to replace or repair specific pathological processes. This would involve multi-functionalised nanoparticles with the ability to protect drugs, proteins or nucleic acids from degradation in the peripheral circulation before providing targeted and triggered release in the brain. Various mechanisms of sensing the environment and triggered release are already being studied including using focused ultrasound, external heat or local pH. It is foreseeable that techniques to respond to local dopamine levels or deep brain stimulation cues are possible. However, despite the enormous potential demonstrated in preclinical studies, there is still a paucity of clinical translation for even the most basic applications of nanoparticles to PD therapy [14]. Obstacles have included limited scalability, cost and safety [56, 115]. Clearly, addressing these challenges is essential before the potential benefit of nanoparticles in the treatment of PD can be realised. Despite this, there are certainly many avenues that are worthy to pursue in order to bring these treatments from bench to bedside.

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Compliance with ethical standards

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