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New non-oral drug delivery systems for Parkinson's disease treatment

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Introduction: Parkinson's disease (PD) remains the only neurodegenerative disorder for which there are highly effective symptomatic therapies, but still unmet needs regarding its long-term management. Levodopa (LD) remains the most effective treatment; however, chronic use is associated with potentially disabling motor complications.

Areas covered: This review highlights a variety of new non-oral drug delivery strategies for non-invasive and invasive routes of drug administration for the treatment of PD. It also includes current and future trends of liposomes, solid lipid nanoparticles and biocompatible microparticles as new non-oral drug delivery systems.

Expert opinion: The long-term complications and limitations of LD treatment might be improved by changing therapy from the present pulsatile stimulation to a more constant stimulation of central dopamine receptors. Stimulation of these receptors may be possible with a new non-oral drug delivery system, with the aim of achieving long-lasting and less fluctuating drug levels, minimization of peak levels and thereby reduction of side effects.

Keywords: inhalational delivery, levodopa, non-oral, Parkinson's disease, transdermal delivery

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1. Introduction

The total share of the CNS therapeutics market in 2008 was ~ $99 billion and is going to be driven by an increase in incidence rates of CNS complications and an increasingly ageing population. This market is expected to grow to $121 billion with a compound annual growth rate (CAGR) of 2.8% by the year 2015 [1]. The total revenues generated by CNS therapies are next only to the cardiovascular disease therapy markets in revenues. At present, ~ 4.1 million people worldwide are suffering from Parkinson's disease (PD), which makes it the second most common neurological disorder after Alzheimer's disease (AD) [2,3]. As the occurrence rate of PD is set to rise significantly in the coming years, clinical involvement will play a major role in fighting broad clinical needs associated with the disease. In 2008, the global sales of PD therapeutics were $3.22 billion, up by 23% from $2.5 billion in 2005. The total share of approved PD drugs across the major markets, that is, Germany, US, France, Japan, Italy, Spain and the UK, was estimated as ~ $2.2 billion in 2006, which is expected to increase by $4.6 billion by 2012 [4]. In the near future some of the important PD drugs are going to lose their patents, thus allowing for the entry of new products, but which products will be successful and how much profit they will generate remains a challenge. Oral levodopa (LD) represents the most clinically useful drug in the treatment of PD. The magnitude of improvement in parkinsonism with LD therapy cannot be surpassed by any other available antiparkinsonian agent [5]. Unfortunately, the clinical response to

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Article highlights.

- New non-oral drug delivery systems, for example, non-invasive and invasive routes, have been accepted as a potential route of drug administration for PD.
- Intranasal, sublingual, inhalational and transdermal routes are the most promising non-invasive non-oral delivery options.
- The invasive routes of drug delivery for PD include direct drug delivery to the CNS, intravenous drug delivery, enteral infusion drug delivery and subcutaneous drug delivery.
- Gene therapy is a new paradigm for treatment of PD.
- Nano-enabled devices are now being invented for site-specific targeting in PD.
- New non-oral drug delivery strategies have immense potential for the treatment of PD.

This box summarizes key points contained in the article.

oral LD is variable and unreliable because of its erratic oral absorption and fluctuations in plasma concentrations. Fluctuations in motor performance and the development of drug-induced involuntary movements (dyskinesias) constitute a difficult challenge in the treatment of PD. Increasing interest has been addressed to the introduction of new therapeutic approaches to obtain continuous dopaminergic stimulation (CDS). The goal of these therapeutic strategies is to reduce the occurrence and severity of LD-associated motor fluctuations and dyskinesia, and provide good long-term safety and tolerability [6]. Controversy over whether the treatment of PD should start with LD or with a dopamine receptor agonist has been continuing for several years. After comparing LD and dopamine receptor agonists, it was shown that LD provides better symptom control but at the cost of an increased incidence of dyskinesias. However, the CDS concept favors long-acting dopamine receptor agonists in order to prevent or treat motor fluctuations. CDS can be achieved by the administration of oral dopamine agonists with a new non-oral drug delivery system [7-9]. Many of these new non-oral drug delivery systems have been evaluated during the last few decades to find a better solution for continuous drug delivery. These non-oral treatment modes include non-invasive and invasive routes of drug delivery. The advantages of the non-oral, more continuous dopaminergic treatment of PD need to be established in clinical trials and long-term clinical practice, after which they can be considered to outperform standard oral therapy. Stefano and co-workers have described extensively controlled oral drug delivery strategies and a co-drug approach as new delivery strategies for the treatment of PD [10]. This review highlights a variety of experimental non-oral new drug delivery strategies for non-invasive and invasive routes of drug administration. This review also includes current and future trends of liposomes, solid lipid nanoparticles and biocompatible microparticles as a new non-oral drug delivery system.

2. Parkinson's disease

Parkinson's disease is a common progressive neurodegenerative disorder characterized by massive depletion of striatal dopamine (DA) as a result of degeneration of dopaminergic (DAergic) neurons in the substantia nigra. Clinically, the disease is manifested by both motor and non-motor symptoms. The cardinal motor symptoms include bradykinesia, resting tremor, rigidity and disturbance of posture and gait, and non-motor symptoms are diminished sense of smell, depression and sleep disturbance [11,12]. So far, the etiopathogenesis of nigral DAergic neuron loss in PD is unclear. However, the presence of continuing oxidative stress as a result of inefficacious antioxidant defense mechanisms and generation of radical oxygen species in the substantia nigra pars compacta (SNpc) of the parkinsonian brain is an important pathogenic mechanism [13-15].

At present, several treatment regimens are available for PD that can reduce signs and symptoms of the disease, lessen physical disability and improve overall quality of life [16,17]. The current treatment options include carbidopa/LD, dopamine agonists, monoamine oxidase type B (MAO-B) inhibitors, catechol-*O*-methyltransferase (COMT) inhibitors, amantadine and anticholinergics [18].

3. New non-oral approaches to enhance drug delivery for parkinsonism

To circumvent the multitude of barriers inhibiting CNS penetration by potential therapeutic agents to treat parkinsonism, numerous drug delivery systems or approaches have been developed and patented [19]. These strategies generally fall into the following three categories: i) manipulating drugs for various deliveries, such as lipophilic analogue, prodrugs, chemical method, carrier-mediated drug delivery and colloidal drug delivery; ii) blood–brain barrier (BBB) disruption; and iii) finding alternative or non-oral routes for drug delivery [20-29]. The third class of strategy, which aims to enhance CNS penetration of drug molecules, is composed of delivery methodologies by the non-oral route. As most of the above-mentioned techniques aim to enhance the CNS penetration of drugs by increasing the systemic concentration, the result is higher drug penetration throughout the entire body and frequently uninvited systemic side effects. Also, systemically administered agents must penetrate the BBB to enter the brain, which is a difficult task. The benefits of a non-oral route of drug delivery are consistency of drug delivery, avoidance of the first-pass effect, rapid drug delivery for emergency use, lesser toxicity, rate-controlled delivery, targeting to the CNS, avoidance of the BBB and good patient acceptability. These non-oral routes of drug delivery are mainly classified in two categories, that is, non-invasive and invasive routes. The non-invasive approaches are transdermal drug delivery, intranasal, inhalational, sublingual/buccal and rectal drug delivery, and the invasive

approaches are intravenous, subcutaneous direct drug delivery, enteral (duodenal, jejunal) and the recently introduced gene therapy [30].

4. Non-invasive non-oral routes of drug delivery

In recent years non-invasive routes of administration have gained significant momentum and consideration to complement approved drug products or to enable those that are delivered by the parenteral or oral route. The transdermal, intranasal, inhalational and buccal/sublingual routes are the most promising non-invasive non-oral delivery options. Considering non-invasive routes of administration early in the development process may be useful to enable new chemical entities (NCE) that have deficiencies of (extensive first-pass metabolism, unfavorable physicochemical properties, gastrointestinal adverse effects) or suboptimal pharmacokinetic profiles to be identified and can be useful for the above reason. Thus, the non-invasive routes are considered to be the preferred mode of drug delivery as compared with invasive therapies.

4.1 Transdermal drug delivery system

The transdermal drug delivery system (TDS) is an innovative approach to treat PD by delivery of drugs through the skin for therapeutic use as an alternative to the oral, intravascular, subcutaneous and transmucosal routes. The transdermal delivery system is also an advantage when non-oral administration is desired. In this system, 24 h continuous, non-fluctuating drug levels can improve early morning and nocturnal symptoms of PD. The skin patch is the most common approach for transdermal delivery of drugs. The patch has been an effective adjunct to oral therapies as its affords smoother continuous plasma levels and reduces gastrointestinal variation, such as reduced motility, variable or low bioavailability, and first-pass effects that lead to fluctuation in efficacy and treatment response [31,32].

Rotigotine is a highly lipophilic dopamine-receptor agonist and undergoes extensive gut and hepatic first-pass metabolism by the oral route, but this is not observed in the TDS products [33]. Rotigotine is the first antiparkinson drug to be successfully delivered by TDS. The silicon-based transdermal patches of rotigotine are safe, well tolerated and effective as monotherapy for patients in the early stages of PD and as an add-on therapy in LD-treated patients in advanced PD to reduce 'off' hours with sufficient efficacy and safety [34]. It also reduces the side effects of LD in advanced PD. The reduction in side effects of LD is owing to a lower dose being used in combination therapy. It is available on the market under the brand name Neupro® (UCB, Brussels, Belgium) [35,36]. Recently, the rotigotine transdermal patch has been recalled in the US owing to the formation of snowflake-like rotigotine crystals on the patch surface. The rotigotine TDS manufacturer has modified the storage conditions (temperature between 2 and 8°C) to reduce the occurrence of crystallization of the active substance [37]. Thus, the development of a transdermal drug delivery system requires extensive study on stability issues as compared with therapeutic benefits.

Lisuride, a potent dopamine agonist having short half-life (2 h) and low bioavailability after oral administration, has been available for almost 20 years for the treatment of PD. The oral administration of lisuride in doses of 1.5 – 4.5 mg three times a day provides pulsatile stimulation and causes psychiatric complications. The lisuride transdermal patch (Nenad®, Axxonis Pharma, Berlin, Germany) was developed to provide a constant release rate (2 – 5μg lisuride base/(cm^2 h)) and continuous dopaminergic stimulation for over 2 days at lower doses as compared with oral therapy of lisuride. Thus, a lower dose of lisuride transdermal patch and CDS helped in minimizing psychiatric complications usually noticed during long-term oral administration and is indicated as add-on therapy for PD [38,39]. Thus, the transdermal approach of lisuride provides high benefit to low risk ratio as compared with low benefit to high risk ratio when compared with conventional therapy.

Apomorphine, which is indicated in the treatment of PD, suffers from the drawback of extensive inactivation during hepatic first-pass metabolism. To overcome this drawback, microemulsion was prepared to be delivered by TDS. The feasibility of apomorphine by a transdermal delivery system was investigated by *in vitro* transdermal absorption using the skin of the hairless mouse as a membrane. The two microemulsion preparations, each containing 3.9% of apomorphine hydrochloride, were used. The fluxes of the drug from the microemulsions through hairless mouse skin were increased by the formation of apomorphine–octanoic acid ion pairs. The microemulsion formulation of apomorphine protected it from light and degradation for up to 6 months. This proves that apomorphine can be delivered by a transdermal delivery system [40]. The propriety passport™ system (Altea therapeutics, GA, USA) is developing a transdermal skin patch to provide continuous delivery of apomorphine for the prevention of an off period and to provide an improved option for the symptomatic management of PD, and is at the preclinical study stage [41].

Degim and associates developed a transdermal formulation of bromocriptine (BRC). They prepared three gel formulations of different polymers (Carbopol-934, chitosan and Gantrez-SP215) and compared the effectiveness and bioavailability of the formulations in rabbits. They found that chitosan gel formulation was the best formulation and blood BRC concentrations were obtained when applied to the rabbit skin. The administration of BRC by the transdermal route bypasses the first-pass effect. It was confirmed that transdermal delivery of BRC could be an alternative route to the oral route for the treatment of PD [42]. Some scientists disclosed that the transdermal administration of dopamine D_2 agonists, that is, ropinirole and pergolide, which help in the treatment of PD with reduced incidence of side effects,

improved patient compliance and maintained therapeutic drug plasma levels [43,44].

Forlando and co-workers disclosed a monolithic device for transdermal administration of an active pharmaceutical ingredient such as selegiline and rivastigmine in an acrylic polymer pressure-sensitive adhesive without crosslinking agent. The system provides a low level of skin irritation and good release of the drug [45]. Kushnir and Eliahu disclosed a new route of administration of LD-ethyl-ester (LDEE), dissolved in a non-degradative solvent that is designed to maintain the stability of drug in solution and make continuous penetration of drug through the skin for treatment of Parkinson's disease [46]. Thus, the system provided efficient drug delivery and at the same time stability of the system was also maintained. Dipierro and Steven disclosed a new system called the biosynchronous transdermal drug delivery system utilizing a pressurized reservoir, a pump for removing depleted carrier solution and a dispensing actuator. This active preprogrammed transdermal system is used to provide pulsed doses of medication for the treatment of PD [47]. The pulsed doses of medication would release the drug at the right time for treatment.

4.2 Iontophoretic drug delivery system

Iontophoresis is the introduction of various ions into the skin by means of electricity. Iontophoresis provides several advantages that are useful in the treatment of PD over traditional transdermal drug delivery. It allows programming of flux at the required therapeutic rate by adjusting the current, which permits rapid start and termination of the medication administered when desired. As the iontophoretic flux is influenced by several parameters, it is crucial for achieving an optimum flux to optimize separately these parameters. It was found that using the composition comprising rotigotine and its facilitator chloride salt in a donor compartment of the iontophoretic devices, fluxes within the therapeutic range could be administered [48]. Li and co-workers disclosed the composition comprising rotigotine and at least one chloride salt in an iontophoretic device for the treatment of PD. They found that the rotigotine flux across the human stratum corneum was higher than the rotigotine flux obtained previously with conventional passive transdermal therapeutic diffusion systems [49].

Van Laar and co-workers investigated the feasibility of transdermal iontophoretic delivery of apomorphine in patients with PD. The authors also determined the transdermal transport rates of the dopamine agonist R-apomorphine in patients with idiopathic PD. The investigation showed that *in vitro* iontophoretic delivery of apomorphine could be controlled and manipulated accurately by the applied current, and current-dependent delivery of apomorphine was possible *in vivo* at acceptable levels of skin irritation. Excellent correlation was found between the calculated *in vivo* transport rates and the rates that were obtained previously *in vitro* [50].

4.3 Intranasal drug delivery

Diseases of the CNS such as Parkinson's disease, schizophrenia, meningitis, migraine and Alzheimer's disease require delivery of the drug to the brain for treatment. However, the intranasal drug delivery system is inefficient for hydrophilic and high-molecular-mass drugs, owing to the impermeability of the endothelial membrane forming the blood–brain barrier [51]. Many therapeutic agents may have been cast off because sufficient drug levels in the brain cannot be achieved by means of the systemic circulation. A non-invasive mode of therapy would be desirable for patient compliance, and particularly for diseases that require chronic dosing such as in PD. The intranasal route has great potential for bypassing the BBB owing to the unique connection between the olfactory or trigeminal nerve systems initiating in the brain and terminating in the nasal cavity at the olfactory neuroepithelium or respiratory epithelium, respectively [52]. They are the only externally exposed portions of the CNS and therefore represent the most direct method of non-invasive entry into the brain. However, the amounts of drug administered nasally are very low, normally < 0.1%, and hence the system is not used therapeutically at present and no product is licensed specifically for this route [53]. The intranasal administration of apomorphine for the treatment of PD has been reported previously [54]. The efficacy of intranasal apomorphine was assessed in patients with PD and severe LD-related 'off-period' disabilities. The apomorphine in aqueous solution was absorbed well from the nasal route in PD patients, at rates comparable to subcutaneous injection reported by Laar and co-workers [54]. However, the low intranasal bioavailability may have been a result of drainage of the solution from the nose, as this study was not confirmed by the Van Laar group, but it was reported by Sam and co-workers [55]. The time to onset of therapeutic action was fast (within 8.9 min), but the duration of drug effect was very short (mean of 44 min) [56]. A mucoadhesive and sustained release powder dosage form will no doubt improve on some of the disadvantages associated with the solution, given that intranasal solution as the mucocilliary clearance will be decreased by enhancing the retention in the nasal cavity.

Ugwoke and associates formulated sustained-release lyophilized polyacrylic acid powders loaded with antiparkinsonian drug apomorphine HCL to accomplish the delivery of drug to the brain by means of the nasal mucoadhesive system. Their results showed that increasing the drug loading influenced the *in vitro* release rate and release mechanism but did not increase to a large extent the rate of release and absorption *in vivo* in rabbits [57]. The apomorphine hydrochloride dry powders were developed for intranasal delivery (Apomorphine nasal, Lyonase technology, Britannia Pharmaceuticals, Surrey, UK). The results of a clinical trial Phase III suggested that the prepared formulation had a clinical effect equivalent to subcutaneously administered apomorphine [58].

Brime and co-workers developed a method of administrating LD following the intranasal route. They prepared and *in vitro*

characterized gelatin microspheres of LD for nasal administration, which has been recognized as an interesting alternative to the more conventional routes of administration of LD for PD [59].

With the aim of overcoming the low oral bioavailability of oral LD formulation, several water-soluble alkyl ester of LD have been synthesized as prodrug candidates for intranasal administration. The prodrug of butyl ester administered intranasally in rats improved CNS bioavailability compared with the same substance in an equimolar intravenous (i.v.) dose without producing any significant quantities of dopamine in peripheral circulation [60].

In coming years, intranasal delivery of drugs will demand more complex and automated delivery devices to ensure accurate and repeatable dosing. Thus, new efforts are needed to make this non-invasive route of delivery more efficient and popular, and it is also predicted that in future a range of intranasal products will be used in the treatment of PD.

4.4 Inhalation drug delivery

The inhalation route allows the delivery of small doses of drug directly to the alveoli, attaining a high concentration of drug in the local area, which minimizes systemic side effects, resulting in a high therapeutic ratio of drugs compared with that of systemic delivery administered by either the oral or the parenteral routes. Inhalational delivery offers effective therapy with minimum adverse effects by using small doses of drugs through inhalation and allows substantially greater bioavailability of polypeptides [61].

At present, delivery of drugs for the management of neurological disorders, especially PD and AD, is done by oral, parenteral and transdermal routes. Deep-lung delivery of LD particles for treating a patient with PD has been reported [62]; however, no further data are available for the readers. Drugs for pulmonary delivery for the management of PD have not been approved at present; however, only one formulation containing LD has been investigated [63]. The data for inhalation delivery of L-DOPA showed at least twofold lower doses compared with that of oral dose [64]. In another study, aerosol delivery of LD dry powder formulation in a rat model and pulmonary administered LD showed rapid and higher plasma levels (C_{max} = 4.8 ± 1.10 mg/ml at 2 min) compared with that of oral administration where the drug produced delayed and lower plasma level (C_{max} = 1.8 ± 0.40 mg/ml at 30 min) [65].

Using metered-dose inhaler (MDI) delivery of a DA agonist to the airways has been demonstrated, and the authors indicated that the inhalation route provided effective delivery of the drug to the receptor. Inhalational administration of a drug (ABT-431, a selective D1 receptor agonist) was found to be significantly greater than that of oral administration [66]. The future of the inhalational route does include non-invasive and efficient delivery of large molecules for systemic conditions with improved patient compliance. Therefore, inhalational drug delivery can herald a new era of drug delivery research, which can eventually extend the life of drugs, increase patient compliance and reduce the total cost of treatment of neurodegenerative disorders.

4.5 Sublingual/buccal drug delivery

The sublingual route of administration proved to be a rational, effective and advantageous route of drug delivery as it ensures more rapid and reliable absorption than from the gastrointestinal tract, bypasses hepatic metabolism and provides for the possibility of being used in a gastroresected subject or in patients with impaired absorption. Buccal drug delivery using bioadhesive/mucoadhesive polymers also provides the suitable advantages of adhering to oral mucosa, releasing the amount of drugs in constant time, assuring steady plasmatic levels and consequently avoiding fluctuating clinical responses [67]. In 1991, Montastruc and associates performed two long-term studies involving 15 patients, and showed that sublingual apomorphine reduced the daily off period by 56 and 68%. Most of the patients complained of adverse reactions, such as stomatitis with ulcer, a burning tongue and an unpleasant bitter taste of the drug; so apomorphine is not a good choice as a sublingual tablet for rapid action in emergency situations [68]. Recently, a sublingual formulation of apomorphine (Amarin Corp., London, UK) was formulated. This new sublingual formulation provides rapid absorption of apomorphine directly into the bloodstream after administration. This new formulation would offer patients an improved alternative to the injectable formulation of apomorphine that is available at present [69].

Clarke and associates did comparative studies of a new formulation designed for buccal absorption, 'Zydis Selegiline' (1.25 – 10 mg) with 'conventional selegiline tablets' (10 mg), in 156 healthy volunteers. They proved that the new formulation imparted more efficient and less variable absorption as well as lower plasma concentration of metabolites and reduced risk of stomatitis at the same time [70]. Zelapar (selegiline HCl, Valeant Pharmaceuticals, CA, USA) is a selective monoamine oxidase inhibitor (MAO-B), which was approved by the US FDA in 2006 as a once-daily adjunct therapy for PD patients being treated with LD/carbidopa. The new sublingual drug delivery system called Zydis® Technology (Zydis, Cardinal Health, OH, Dublin) allows the tablets to dissolve within seconds in the mouth and deliver more active drug at a lower dose [71,72].

4.6 Rectal drug delivery

Rectal administration is another non-invasive technique that may be used to deliver LD to PD patients. Unfortunately, when LD was given rectally alone, there was no rise in plasma level and no clinical benefit [73]. This lack of absorption was attributed to the relative alkalinity of the rectal secretions. Clinical improvement following rectal administration of a strongly acidic suspension of LD-CD in a hospitalized PD patient supported this hypothesis [74] that the acidification of the rectal secretions improved the overall therapy which was not the case in the earlier study.

In 2004, Laar and associates described the pharmacokinetics and clinical efficacy of rectal apomorphine in patients with PD. Different formulations for rectal administration of apomorphine were investigated, with wide differences in t_{max}, where the formulation with the longest t_{max} could possibly be clinically useful for rectal sustained release of drug. The three different pharmaceutical formulations were a rectal solution, a gelatin suppository and a Witepsol-H15 suppository of apomorphine. The mean bioavailability of the formulation varied between 14.7 and 40.2%, until the end of clinical benefit. These results showed that rectal administration of apomorphine presented as an alternative to subcutaneous administration. The Witepsol-H15 suppositories were of special interest in the treatment of on-off fluctuations in PD owing to their sustained release characteristic [75].

5. Invasive non-oral routes of drug delivery

Drugs such as peptide and protein, antibody, vaccine and gene-based drugs in general may not be delivered using non-invasive routes because they are vulnerable to enzymatic degradation and cannot be efficiently absorbed into the systemic circulation owing to their molecular size and charge. For this reason many protein and peptide drugs have to be delivered by an invasive route if a non-invasive route is not feasible. The invasive routes of drug delivery for PD are direct drug delivery to the CNS, intravenous drug delivery, enteral infusion drug delivery, subcutaneous drug delivery and gene therapy.

5.1 Direct drug delivery

A large number of drugs are unable to reach the brain owing to the negligible permeability of the brain capillary endothelial wall, which makes up the BBB *in vivo*. The BBB can be bypassed by directly injecting a drug either into the brain parenchyma or intraventricularly or intrathecally into cerebrospinal fluid (CSF), or with an implant into the brain. Directly targeting the BBB theoretically has several advantages in comparison with vascular and other delivery routes [76,77]. This route bypasses the BBB and the drugs encounter minimal protein binding in the CSF, leading to longer drug half-life in the CSF owing to a decrease in enzymatic activity in plasma, thus resulting in an immediate high drug concentration in CSF to provide better CNS effects and effectively minimize systemic toxicity [78]. Direct injection into the brain has some disadvantages, such as the requirement of surgical intervention, and for drugs relying mainly on diffusion for penetration, insufficient concentration of drug may reach the desired site. Besides this the microvessels of the brain secrete interstitial fluid at a low but finite rate, generating a flow towards the CSF spaces, which also works against diffusive drug penetration, and the drug may not reach in proper concentrations the desired site in the CNS owing to dilution and flushing out of the brain because of the continuous production of new CSF by the brain. A slow rate of drug distribution within the CSF and increase in intracranial pressure associated with fluid injection or infusion into small ventricular volumes results in a high clinical incidence of hemorrhage, CSF leaks, neurotoxicity and CNS infections [79,80].

An implantable polymeric vector for controlled drug release in the CNS has been developed. Different polymeric devices composed primarily of synthetic biocompatible and biodegradable polymers have been investigated for this purpose. The macroscopic implants (monolithic device) were the first polymeric devices to be developed that required open surgery for implantation. However, microparticles or nanoparticles loaded with neuroactive drugs can be produced by the microencapsulation technique. These micro- or nanoparticles may be easily implanted precisely by stereotaxy in discrete and functional areas of the brain without causing damage to the surrounding tissue owing to their small size. The method is mostly applied in the fields of neuro-oncology and neurodegenerative diseases such as PD and AD [81-83]. Implantation of dopamine or norepinephrine-loaded PLGA microspheres into the striatum has been reported to stimulate regrowth of dopaminergic fibers accompanied by an 80% decrease in apomorphine-induced rotational behavior for up to 4 weeks [84,85]. Recently, a mixture of L-DOPA/CD-loaded microspheres in the intrastriatal implants was found to reduce apomorphine-induced rotational motor asymmetry in hemiparkinsonian rats. This type of research could provide hope of treatment in PD, and such therapy with biodegradable microspheres is a promising approach for the purposes of future clinical application [86].

In several PD models glial cell line-derived neurotrophic factor (GDNF) was considered to be a highly promising growth factor for PD treatment. Two open-label trials involving continuous GDNF infusion into the putamen of 5 PD patients in Bristol, UK [87,88], and 10 PD patients in Lexington, Kentucky, showed that the growth factor could also improve motor symptoms that stayed on during the 1-month washout period [89]. However, a double-blind placebo-controlled study on GDNF infusion into PD patients presented by the biotechnology corporation AMGEN reduced the interest because the results were negative [90,91]. Essentially there were no beneficial effects in the patients, and in non-human primate safety studies AMGEN reported unwanted side effects. As a result, all clinical research of GDNF treatment in PD was discontinued. However, GDNF may still be an interesting candidate for the future. The problems in the AMGEN trials could be related to dose and mode of delivery of the growth factor and therefore polymer-based drug delivery systems could be valuable in this respect.

Positive results were also obtained when GDNF was delivered using biodegradable microparticles. Microparticles prepared by the Total Recirculation One-Machine System (TROMS) and loaded with glycosylated GDNF showed excellent *in vivo* efficacy and safety with a consistent improvement in behavior, significantly different from both controls and non-loaded microparticles 6 weeks after implantation. Furthermore, 60% of the animals treated with GDNF-loaded microparticles recovered fully from their rotational asymmetry

8 weeks after treatment and 20% showed < 2 turns/min at the same time. The motor behavior restoration was accompanied with a higher fiber density in the GDNF-treated striatum, as Garbayo and co-workers described previously [92,93], making this strategy effective for delivering GDNF in the striatum of hemiparkinsonian rats.

Jenkins and Jackson investigated the intraperitoneal (i.p.) administration of bromocriptine in rats to study dose-dependent, long-lasting stereotyped behavior in rats. Apomorphine administered subcutaneously (s.c.) in both immature and catecholamine-depleted rats produced stereotyped behavior significantly enhanced by previous treatment with bromocriptine (i.p.). The bilateral application of bromocriptine (2.5 – 40 μg/side in either 0.5% tartaric acid or 50% propylene glycol aqueous vehicles) to the nucleus accumbens (NAC) of rats had no effect on locomotion over a 12 h period after injection. Being inactive after direct application to the nucleus accumbens, bromocriptine (10 – 160 μg/side) did not induce stereotyped behavior after bilateral injection into the caudate nucleus. However, the local application of bromocriptine (10 μg/side) to the nucleus accumbens, although itself inactive, significantly enhanced the locomotor stimulant effect of DA using a dose of 5 μg/side applied to the same nucleus. The data suggested that bromocriptine was able to enhance the effects of agonists such as dopamine and apomorphine at DA receptors, even under conditions where bromocriptine itself was inactive [94].

The movement disorder is a group of neurological disturbances that involves one or more muscles or muscle groups. The movement disorders are common in PD, especially the resting tremors. Donovan and Beach invented methods for effectively treating a movement disorder of PD by intracranial administration of a neurotoxin (biologically active molecule with a specific affinity for a neuronal cell surface receptor) that has the characteristics of long duration of activity, low rates of diffusion out of an intracranial site where administered and insignificant systemic effects at therapeutic dose level [95].

5.2 Intravenous drug delivery

Innovative drug delivery in PD has the potential to surpass many side effects of current treatment, such as dyskinesia, wearing-off type fluctuations, on-off phenomena or bouts of motor freezing. The various delivery techniques are used for clinical application of dopamine agonists as antiparkinson drugs. For example, apomorphine, which is delivered conventionally by parenteral administration for maximum bioavailability, may be delivered by means of intranasal, rectal, sublingual and subcutaneous routes, for example, apomorphine hydrochloride (Apokyn, Mylan Bertek Pharmaceuticals, Sugar Land, USA). Some studies have shown the clinical benefits of parenteral administration of antiparkinson drugs. Patients with PD on long-term LD with or without peripheral decarboxylase inhibitors commonly develop fluctuations in clinical response to the drug [96]. However, continuous i.v. infusion has shown that symptom control can be restored by maintaining a constant plasma concentration. The authors studied the clinical effects and pharmacokinetics of LD infusions and oral therapy in patients with PD. They showed on-off fluctuations while receiving long-term treatment with LD in combination with a peripheral decarboxylase inhibitor. Intravenous infusion at a constant rate for up to 16 h resulted in a smoother clinical response and maintained plasma LD concentrations within narrower limits compared with conventional oral therapy. Following infusion rates of 32 – 80 mg/h (0.5 – 1.3 mg/(kg h)), the plasma concentration associated with optimum therapeutic response lay between 0.3 and 1.6 mg/h [97].

The causes of response fluctuations in patients with PD treated chronically with LD were unknown. Quinn and associates worked on complicated response fluctuations in PD, and continuous i.v. infusion of LD in three patients with replacement of oral treatment by continuous i.v. infusion of LD, with oral administration of decarboxylase inhibitor, produced a prolonged and stable clinical response. This response was maintained not only in one subject showing predictable fluctuations, but also in two subjects with unpredictable response to oral treatment. The addition of i.v. LD infusion to the usual oral regimen of the patient when experiencing prolonged 'off' periods despite generous doses of oral LD with decarboxylase inhibitor also produced stable clinical benefit. These results suggested that, even in patients with complicated response swings, central dopamine receptors remained available for stimulation providing LD that can be delivered at a constant rate and in an adequate quantity to the brain. Thus, the use of continuous i.v. infusion of LD is to reduce the occurrence and severity of LD-associated motor fluctuation and dyskinesia, and provides good long-term safety and tolerability. However, the unfavorable physicochemical properties of continuous i.v. infusion of LD resulted in a cumbersome system and showed patient non-compliance [98].

In 1987, Juncos and co-workers described the administration of methyl and ethyl ester of LD, which is more soluble than LD by the i.v. route. The LD methyl ester (LDME) infusions resulted in marked reductions of both plasma LD variations and motor response fluctuations in patients with either wearing-off or on-off phenomena when compared with oral LD [99].

In 2001, Manson and co-workers compared the intravenous and subcutaneous administration of apomorphine based on clinical and pharmacokinetics observations. Pharmacokinetic analysis demonstrated more reliable and smoother delivery of apomorphine by means of the i.v. route. However, severe thrombotic complications exclude the use of i.v. drug delivery at the moment [100].

5.3 Enteral infusion drug delivery

The term enteral infusion may sometimes involve gastric infusion besides duodenal/jejunal infusion. Intraduodenal

infusion was first studied in 1986 [101]. The motor response, so-called resistant on/off fluctuations, compared with conventional therapy improved dramatically, and was comparable to the effects of i.v. infusions. When comparing nasogastric, oral and nasoduodenal administration of LD, plasma variance did not decrease significantly with gastric infusion and decreased significantly in nasoduodenal infusions with corresponding reduction in motor fluctuation [102]. Nilsson and co-workers evaluated the effects of continuous duodenal infusion of LD over time on the disabling fluctuations in motor performance in advanced parkinsonian patients and showed that continuous duodenal infusion of LD is an alternative treatment strategy for patients with advanced PD when conventional therapy has failed [103].

The aim of enteral therapy was to ward off severity and prevalence of motor fluctuations associated with LD [104]. The relatively short serum half-life (90 min) of oral LD/carbidopa and its erratic absorption because of inconsistent and delayed gastric emptying (a non-motor feature of PD) are important factors in the development of motor fluctuations [105]. Levodopa/carbidopa continuous infusion directly into the small intestine of PD patients leads to reduction of motor fluctuations by reducing plasma LD variability, yielding a satisfactory therapeutic response. Nyholm in 2006 worked on enteral LD/carbidopa (20/5 mg/ml) suspensions utilizing a methylcellulose gel infusion (Duodopa®, Solvay Pharma, Brussels, Belgium) for the treatment of motor fluctuations and dyskinesias in advanced Parkinson's disease and showed that a gel formulation of LD/carbidopa had been developed for enteral (duodenal or jejunal) infusion by means of a portable pump. Continuous long-term enteric infusion of LD provided smooth plasma levels and more continuous dopaminergic stimulation, yielding a satisfactory therapeutic benefit in motor complications of PD [106,107]. A crossover trial comparing the LD infusion as monotherapy with 24 individually optimized conventional combination therapies showed significant improvements in motor performance and quality of life [108]. Antonini and co-workers in 2008 assessed prospectively the effectiveness of duodenal LD infusion on quality of life as well as motor features in patients with advanced PD [109].

5.4 Subcutaneous drug delivery

Subcutaneous administration of dopamine receptor agonists is an alternative when speedy onset of effect is desired in severe akinetic situations and when continuous infusion is needed to stabilize motor fluctuations. At present, apomorphine is used subcutaneously for the management of unexpected, sudden and refractory LD-induced 'off' states in fluctuating PD either as intermittent rescue injections or as continuous infusions. The subcutaneous apomorphine injection has conventionally been used as an add-on to LD therapy in advanced PD; however, apomorphine infusion has shown promising results as a monotherapy [110]. Continuous subcutaneous apomorphine infusions in monotherapy or as an add-on to LD therapy in advanced PD proved that subcutaneous apomorphine infusions are successful at aborting 'off' periods, reducing dyskinesias and improving PD motor scores, with the added benefit of a substantial LD-sparing effect [111]. The pharmacology, clinical efficacy and tolerability of intermittent subcutaneous apomorphine injections for the management of 'off' episodes in patients with PD was studied by Chen and Obering in 2005, and they concluded that the available clinical studies indicated that apomorphine is effective at providing prompt and consistent rescue from 'off' episodes in patients with PD [112].

In PD, response fluctuations may be a result of poor solubility of LD, which causes difficulties in its absorption. So a new rescue therapy for response fluctuation, that is, LDEE, a highly soluble prodrug of LD that has potential pharmacokinetic advantages over LD itself, was developed. LDEE infusion was administered to mice and rats subcutaneously and showed significant and beneficial effects owing to sustained elevations in plasma LD levels. The study suggested that subcutaneous infusion of LDEE may be advantageous as a new therapeutic strategy for response fluctuations. It may be particularly useful to rescue patients rapidly and predictably from a variety of disabling 'off' situations. The LDEE known as EtiLD TV-1203 (Teva Pharmaceutical, Petach Tikva, Israel), which is now in clinical Phase III, could be given as a subcutaneous infusion [113].

Lisuride is an ergot derivative that is almost completely absorbed from the gastrointestinal tract and its solubility is similar to that of apomorphine, and thus lisuride is a suitable candidate for subcutaneous infusion. Plasma levels of lisuride after subcutaneous infusion showed low interindividual variability in PD patients [114]. The lisuride formulation for subcutaneous infusion was compared with conventional oral therapy for safety and efficacy in a randomized 4-year trial. Subcutaneous infusion therapy provided a significant reduction in motor fluctuations and dyskinesia during the trial. Lisuride causes more common psychiatric adverse effects, owing to which it has limited use, but in this trial it did not show any severe complications; sometimes skin nodules were seen in some of the patients on s.c. infusion [115]. When s.c. infusion of lisuride was compared with s.c. apomorphine formulation both the formulations showed similar effects on motor fluctuations, but the improvement with apomorphine s.c. infusion was slightly better [116].

Recently, a continuous subcutaneous infusion of lisuride (Nenad® sc Axxonis Pharm, Berlin, Germany) delivered by a programmable minipump was formulated that helps to deliver the drug so that constant drug levels can be achieved; it is intended to treat late stage patients when standard combination therapy with LD and dopamine agonist proves no longer effective. It is in Phase III clinical trial. [117].

A research summary of trade names and phase of research of new non-oral drug delivery systems is given in **Table 1**.

Table 1. Research summary of trade names and phases of research of new non-oral drug delivery systems.

Drug delivery system	Drug candidate	Trade name	Phase of research	Ref.
Transdermal delivery system	Rotigotine	Neupro® (UCB, Brussels, Belgium)	Marketed	[35,36]
	Lisuride	Nenad® (Axxonis, Berlin, Germany)	Clinical trial Phase III	[38,39]
	Apomorphine	passport™ system (Altea therapeutics, GA, USA)	Preclinical study	[41]
Intranasal delivery system	Apomorphine hydrochloride dry powders	Apomorphine nasal (Lyonase technology, Britannia Pharmaceuticals, Surrey, UK)	Clinical trial Phase III	[58]
	Rotigotine	Aderis Pharma (Mequon, Wisconsin, USA)	Clinical trial Phase II	[142]
Inhalational delivery system	Apomorphine	VR040 (Vectura group, London, UK)	Clinical trial Phase II	[143]
Sublingual delivery system	Apomorphine	Amarin Corp. (London, UK)	Clinical trial Phase I	[69]
	Selegiline HCl	Zelapar (Valeant Pharmaceuticals, CA, USA)	Clinical trial Phase IV	[71,72]
Intravenous delivery system	Apomorphine	APo-go-PFS(Britannia Pharmaceuticals, Surrey, UK)	Clinical trial Phase III	[140]
Subcutaneous delivery system	Apomorphine hydrochloride	Apokyn (Mylan Bertek Pharmaceuticals, Sugar Land, USA)	Marketed	[144]
	Apomorphine	APo-go-Ampoules (Britannia Pharmaceuticals, Surrey, UK)	Clinical trial Phase III	[145]
	Apomorphine	APo-go Pen (Britannia Pharmaceuticals, Surrey, UK)	Clinical trial Phase III	[145]
	Levodopa ethyl ester	Etilevodopa TV-1203 (Teva Pharmaceutical, Petach Tikva, Israel)	Clinical trial Phase III	[113]
Enteral delivery system	Levodopa/ carbidopa	Duodopa (Solvay Pharma, Brussels, Belgium)	Marketed	[106,107]

6. Gene therapy

Despite much recent progress in treating the symptoms of PD, there is still no therapy that has been demonstrated to alter the long-term course of the progressive neurodegenerative process. Gene therapy is a new paradigm for treatment, which holds the promise of fulfilling that role. Parkinson's disease is a particularly attractive target for gene therapy because surgical infusion is required at present for the delivery of viral vector into the brain, and PD is the only neurodegenerative disorder routinely treated with neurosurgery. Several animal models of PD are now available that accurately reflect the human disorder to test new therapies. These models display abnormal basal ganglia function resulting from loss of dopaminegric neurons found in the human disease [118]. Jarraya has used a non-human primate model of PD, which involves delivering multiple genes in one viral vector into the putamen to restore dopamine levels in a new gene therapy [119]. The latest finding about neurotrophic factors inhibiting neurodegenerative processes and neurotransmitter-synthesizing enzymes provides the basis for current gene therapy strategies for PD. For PD three different gene therapy approaches have been tested in humans. All three therapies use the adeno-associated virus (AAV) vector as the gene delivery agent. The glutamic acid decarboxylase gene was transferred into the subthalamic nucleus in the first approach, which is the preferred target at present for traditional deep brain stimulation surgery, in an attempt to restore normal physiological functioning to the basal ganglia circuitry [120]. In Phase I study remarkable clinical and radiographical improvements were observed in patients. In a second approach a growth factor similar to glial-derived neurotrophic factor, that is, neurturin, is expressed in the putamen. This Phase I trial has shown an improvement in PD symptoms by promoting development of the remaining dopaminergic neurons besides subsiding disease progression by reducing cell death [121]. Significant improvements in clinical rating were reported in patients in this study. At present, the aromatic L-amino acid decarboxylase (*AADC*) gene is transferred into the putamen in order to increase the conversion of LD to dopamine where the neurotransmitter is needed locally [122]. Muramatsu and associates introduced another vector called tricistronic lentiviral vector, which has the capacity to deliver all three genes necessary for dopamine synthesis, that is, tyrosine hydroxylase (*TH*), *AADC* and guanosine 5′-triphosphate cyclohydrolase 1 (*GCH1*) in a single vehicle. In primate models that received the vector, a significant improvement was observed in symptoms typically observed in human PD, including tremor and slow movements. In PD models that received the vector, a significant improvement was observed in symptoms typically observed in human PD, including tremor and slow movements [123,124]. In one study an adenovirus was injected, which was a modified version of the common cold virus, directly into the brains of rats whose dopamine-producing neurons were exposed to hydroxydopamine, a toxin, which gradually killed the neurons. The virus carried a gene that encoded glial cell-derived neurotrophic

factor in the brain and caused them to produce the substance directly. After 6 weeks of study it was found that neurons in untreated rats were three to four times more likely to die than neurons in the rats that received the *GDNF* gene. This experiment revealed that GDNF helped in relieving symptoms of PD [125]. Indeed, Jarraya has provided convincing preclinical evidence to suggest that the continuing human trial might help to advance further the field of PD gene therapy.

7. Current and future trends

Colloidal drug carriers such as microspheres, liposomes, polymeric micelles, microemulsion, nanoemulsion, as well as nanoparticle dispersions show great promise for drug delivery in PD. A large number of papers have highlighted the potential importance of colloidal drug delivery effectiveness for the treatment of PD. During and co-workers developed and characterized dopamine-containing liposomes that showed *in vitro* sustained release of dopamine for over 40 days, and stereotactically implanted these liposomes in the partially denervated corpus striatum of rats subjected to unilateral lesions of the substantia nigra, which showed *in vivo* levels of dopamine, which remained elevated for 25 days. These results suggested that dopamine-containing liposomes could partially ameliorate the deficits associated with a rodent model of PD and demonstrate the potential of this technology as a method for the controlled delivery of therapeutic agents into discrete areas of the brain. [126]. Pichandy and co-workers also showed that the surfactant-modified liposomal preparation could be an ideal lipophilic and BBB-targeted carrier for PD. The investigators performed psycopharmacological studies in Wistar rats to evaluate reduction of parkinsonism's extrapyramidal side effects using actophotometer and rotorod. They found that a surfactant-modified liposomal formulation was best at arresting the effect of haloperidol-induced parkinsonism [127].

Nanotechnologies use engineered materials with the smallest functional organization on the nanometer scale. Nanotechnology is being used in the development of biosensors, which are defined as devices giving information about the presence and quantity of a specific endogenous substance [128]. These biosensors detect the plasmatic levels of LD, which seems to be closely related to the striatal concentrations of dopamine and to the motor status of a given patient Adequate combination of a biosensor with a delivery system would make it possible to determine when a dose is needed and then deliver it automatically [129]. Nanoparticles such as solid lipid nanoparticles (SLN) have been utilized to prolong the duration of action of antiparkinson drugs having exclusive first-pass metabolism and short half-life. Esposito and associates prepared and characterized the SLN of BRC and evaluated the antiparkinsonian activities of free bromocriptine and BRC encapsulated in nanostructured lipid carriers in 6-hydroxydopamine hemilesioned rats. They found that tristearin/tricaprin nanostructured lipid carriers containing bromocriptine control release better in a prolonged fashion for 48 h and reduce the time spent on the blocks (i.e., attenuated akinesia) in the bar test with more rapid onset than BRC alone [130].

Nano-enabled devices are being invented for site-specific targeting in PD. Pillay and associates designed an intracranial nano-enabled scaffold device (NESD) for the site-specific delivery of dopamine to reduce the peripheral side effects of conventional PD therapy. This innovative technique of coupling polymeric scaffold science and nanotechnology will enhance the site-specific delivery of dopamine from the NESD. Further research in optimization of the NESD with respect to ease of implantation, toxicity and bioadhesion needs to be undertaken to determine its efficacy as well as efficiency in humans [131]. Nanotechnology development can be very important in the field of neuroprotection [132]. Water-soluble derivatives of buckminsterfullerene (C60) derivatives (fullerenols) are the main achievement of nanotechnology for neuroprotection. Fullerenols not only have antioxidant properties but they also inhibit the activity of glutamate receptors and exert antiapoptotic effects *in vivo*. Studies on the malonic acid C60 derivatives (carboxyfullerenes) indicated that they are capable of saving mesencephalic dopamine neurons [133]. Bharali and associates provided evidence on the use of nanotechnology to stimulate the proliferation and migration of endogenous stem cells, which are converted to dopaminergic neurons once in the correct place and environment by way of receiving the appropriate signals [134].

Recently, a class of well-defined, monodisperse and tree-like polymers called dendrimers has attracted attention because of the flexibility they offer in terms of their size, shape, branching, length and surface functionality. A unique characteristic of dendrimers is that they can act as a particulate system while retaining the properties of a polymer [135]. Dan Luo and Yougen Li revealed dendrimers as multivalent and/or monodisperse structures that provide multiple sites for the addition of one or more molecules of interest, including bioactive agents, targeting agents, selection markers, antibiotics, detection signals/labels, drugs, or a combination thereof. The bioactive agents that can be incorporated can be, for example, analgesics, opioids, neurotoxins, hypnotics, tranquilizers, anti-convulsants, as well as antiparkinson agents [136]. These advances illustrate the direction of the future development of dendrimers in the treatment of various CNS disorders, including PD, by targeting the brain. [137,138].

Deep brain stimulation (DBS) is a new approach for the treatment of PD; it is actually a surgical procedure used to treat a variety of debilitating symptoms of PD, such as tremor, rigidity, stiffness, slowed movement and walking problems. At present, the procedure is used only for patients whose symptoms cannot be adequately controlled with medication. DBS uses a surgically implanted, battery-operated medical device called a neurostimulator, similar to a heart pacemaker and approximately the size of a stopwatch, to deliver electrical

stimulation to targeted areas in the brain that control movement, blocking the abnormal nerve signals that cause tremor and PD symptoms. Some surgeons may use microelectrode recording, which involves a small wire that monitors the activity of nerve cells in the target area to identify more specifically the precise brain target that will be stimulated [139]. Toselli and associates invented an implantable diode that emits red/near-infrared light onto the substantia nigra as a treatment for PD [140]. Xu and Zhong invented the use of androgens for the treatment of PD. In this study they found that oxidative stress associated with ageing is also one of the factors to cause PD, so androgen or androgen analogue help in reducing the oxidative stress, which indirectly helps in the treatment of PD [141].

8. Expert opinion

The neurodegeneration of PD has not been beneficially treated by classical oral therapy. Levodopa remains the gold standard for the therapy of PD. Nevertheless, there are still some problems linked to the LD therapy for PD. Levodopa suffers from an unfavorable pharmacokinetic profile, significant side effects and, more importantly, it is not able to arrest or delay the progression of the disease. For this reason, the design and development of an alternative patient-friendly route of administration for LD and other antiparkinson drugs represents an important task for improving the therapeutical approach to PD. Transdermal drug delivery provides a non-oral route and greater patient compliance because of the chronic therapy of this disease. Transdermal patches maintain fairly smooth drug levels in plasma as compared with oral drug delivery and reduce 'off hours' in patients. Iontophoresis has shown better results than conventional passive transdermal therapeutic diffusion systems in the delivery of antiparkinson drug such as rotigotine. This invention allows for a reasonable expectation that an effective treatment of PD can be provided.

Owing to high first-pass metabolism of antiparkinson drugs such as LD, selegiline, apomorphine and bromocriptine, subcutaneous, sublingual, intravenous and rectal formulations have been developed to surpass the first-pass metabolism of these drugs. Subcutaneous apomorphine is used at present for the management of sudden, unexpected and refractory LD-induced 'off' states in fluctuating PD, either as an intermittent rescue injection or as a continuous infusion.

The sublingual/buccal route provides the further advantages of more rapid and reliable absorption than gastrointestinal tract bypass, hepatic metabolism, and the possibility of being used in patients with impaired absorption. A fast-dissolving drug delivery system (FDDS, i.e., Zydis System) has even been developed for selegiline, Zydis selegiline (Zelapar, Valeant Pharmaceuticals, CA, USA). This has led to the development more such systems for already existing drugs.

In coming years, intranasal delivery of drugs will demand more complex and automated delivery devices to ensure accurate and repeatable dosing. Thus, new efforts are needed to make this non-invasive route of delivery more efficient and popular, and it is also predicted that in future a range of intranasal products will be used in the treatment of PD.

Direct brain delivery is an approach to bypass the BBB. Microspheres implanted directly into the brain tissue allow the possibility of high drug concentrations confined to the region of interest and reduced systemic toxicity compared with intravenous administration. *In vivo* studies have tested the use of microspheres containing neurological agents to treat different neurological disease. Such uses include delivery of steroids to control cerebral edema, nerve growth factor to the striatum to improve the survival of adrenal medullary tissue transplants, and dopamine to the striatum in experimental parkinsonisms. In several PD models, GDNF delivered using microspheres has been shown to protect mesencephalic dopaminergic neurons from 6-OHDA-induced degeneration if it is administered by means of direct brain targeting. This therapy is a promising approach for the purposes of future clinical application.

Hence, it is concluded that new non-oral drug delivery strategies have immense potential for the treatment of PD. The transdermal route has shown positive results; even the buccal/sublingual route is promising owing to their relative non-invasiveness and bioavailability enhancement. In coming years drug delivery through the intranasal route is going to play a pioneering role in the treatment of PD owing to its direct access to the brain and minimal side effects to the non-targeted sites.

Declaration of interest

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