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Levodopa delivery systems: advancements in delivery of the gold standard

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Importance of the field: Despite the fact that Parkinson's disease (PD) was discovered almost 200 years ago, its treatment and management remain immense challenges because progressive loss of dopaminergic nigral neurons, motor complications experienced by the patients as the disease progresses and drawbacks of pharmacotherapeutic management still persist. Various therapeutic agents have been used in the management of PD, including levodopa (L-DOPA), selegiline, amantadine, bromocriptine, entacapone, pramipexole dihydrochloride and more recently istradefylline and rasagiline. Of all agents, L-DOPA although the oldest, remains the most effective. L-DOPA is easier to administer, better tolerated, less expensive and is required by almost all PD patients. However, L-DOPA's efficacy in advanced PD is significantly reduced due to metabolism, subsequent low bioavailability and irregular fluctuations in its plasma levels. Significant strides have been made to improve the delivery of L-DOPA in order to enhance its bioavailability and reduce plasma fluctuations as well as motor complications experienced by patients purportedly resulting from pulsatile stimulation of the striatal dopamine receptors.

Areas covered in this review: Drug delivery systems that have been instituted for the delivery of L-DOPA include immediate release formulations, liquid formulations, dispersible tablets, controlled release formulations, dual-release formulations, microspheres, infusion and transdermal delivery, among others. In this review, the L-DOPA-loaded drug delivery systems developed over the past three decades are elaborated.

What the reader will gain: The ultimate aim was to assess critically the attempts made thus far directed at improving L-DOPA absorption, bioavailability and maintenance of constant plasma concentrations, including the drug delivery technologies implicated.

Take home message: This review highlights the fact that neuropharmaceutics is at a precipice, which is expected to spur investigators to take that leap to enable the generation of innovative delivery systems for the effective management of PD.

Keywords: bioavailability, conventional dosage forms, drug delivery systems, levodopa, microspheres, motor complications, nanotechnology, neuropharmaceutics, Parkinson's disease, pulmonary delivery, transdermal delivery

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1. Introduction

So far, the successful management and treatment of Parkinson's disease (PD) has remained elusive despite the disease being discovered many years ago. James Parkinson was first to describe the disease in 1817, in his article 'An essay on

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Article highlights.

- This review considers the pros and cons of levodopa (L-DOPA)-loaded drug delivery systems developed over the past three decades with a focused assessment of the attempts to improve absorption, subsequent bioavailability and maintenance of constant plasma concentration of L-DOPA, as well as the technological basis of the delivery systems.
- The first immediate release drug delivery systems for L-DOPA were tablets composed of L-DOPA in combination with carbidopa, a peripheral dopa decarboxylase inhibitor, in order to control the concentration of dopamine at appropriate levels with reduced side effects.
- Controlled release formulations were developed with the intention of delivering L-DOPA to the brain in such a manner that little or no fluctuations in L-DOPA concentrations would occur.
- Liquid L-DOPA formulations were introduced to facilitate rapid onset of action, even though their effects were observed to last for a very short period.
- Dispersible tablets for L-DOPA were developed with the aim of achieving quick onset of action and accurate dosing, as was the case with liquid L-DOPA.
- To compensate for the reduced duration of clinical response experienced by immediate release drug delivery systems, oral disintegrating tablets were introduced.
- To overcome the delayed action of conventional controlled release systems, dual-release formulations were introduced.
- Infusions for the delivery of L-DOPA were introduced with the intention of achieving constant plasma concentrations, which would in turn produce continuous dopaminergic stimulation of the dopamine receptors.
- The use of microspheres as a drug delivery system for L-DOPA allows for a decrease in the dosage size, frequency of administration, systemic side effects and dose-dumping, while providing continuous drug release. The use of microspheres as drug delivery agents for L-DOPA and carbidopa is another approach for improving the bioavailability and subsequent clinical response of L-DOPA.
- Prolonging the residence time of drug delivery systems in the upper region of the intestine enhances absorption and subsequent bioavailability of drugs with a narrow absorption window such as L-DOPA. Gastroretentive dosage forms are time-controlled oral drug delivery systems that can enable prolonged and continuous delivery of drugs to the upper region of the gastrointestinal tract (duodenum and jejunum).
- Hydrodynamically balanced systems are single-unit delivery systems designed and formulated to be less dense than the gastric content to enable them float on the surface of gastric content, prolonging gastric residence time, thereby improving absorption of L-DOPA.
- Multiple-unit dosage forms such as pellets and minitablets are more advantageous when compared with single-unit dosage forms in that they have more reproducible gastric residence time, less inter-subject variability in absorption and dose-dumping and better dispersion through the gastrointestinal tract with less chance of localized mucosal damage.
- Long-term implantable levodopa-controlled release matrix: these systems are aimed at achieving continuous delivery of L-DOPA with fewer or no plasma fluctuations, which in turn may eliminate the 'on and off' syndrome.
- Pulmonary delivery of levodopa: investigators have aimed to improve the bioavailability of L-DOPA by developing pulmonary formulations for L-DOPA, which are anticipated to achieve a rapid onset of action and maintain the effective therapeutic level of L-DOPA.
- Nasal delivery of levodopa: the nasal route has been explored for drug delivery because of its large surface area enhanced by the presence of microvilli that cover the epithelial cells, which in turn are highly vascularized. Other important aspects are that it is easily accessible and avoids first-pass metabolism. The nasal drug delivery system is an immediate release system and thus would not provide constant and sustained delivery of L-DOPA for the achievement of continuous dopaminergic stimulation.
- Transdermal delivery of L-DOPA has been envisaged to be an alternative route for delivery of L-DOPA, which could overcome the adverse effects and complications encountered with the oral route. It may also be preferred over infusion and implantation because of its non-invasiveness and therefore enhanced patient adherence.
- In an attempt to improve the solubility and subsequent pharmacokinetic profile of L-DOPA, prodrugs that include various esters of L-DOPA have been developed.
- Thus far, L-DOPA has been administered through the rectal route in the form of tablets, suppositories and insufflations of powdered tablets, but its absorption into the systemic circulation of Parkinson's disease patients is not yet adequate.
- The need for effective delivery of L-DOPA for the therapeutic management of PD is imperative and should be the focus of extensive research. Nanotechnology does offer one avenue for the achievement of neuropharmaceutical innovations to enhance the delivery of L-DOPA, and thus PD management.

This box summarises key points contained in the article.

the shaking palsy'. This was written after observing the symptoms by examining three patients and watching three patients on the streets of London [1]. It was only later in the nineteenth century that Charcot named the disease 'maladie de Parkinson', or Parkinson's disease, after adding to Parkinson's description of what he called 'non-tremulous forms of the disease' [2]. The commonality and severity of the debilitation of this disease make it a significant concern [3].

Anticholinergic drugs were the first drugs to be used in the symptomatic treatment of PD [4,5]. The trigger for PD was not identified until 1919, when it was recognized that PD patients lose neuronal cells in the substantia nigra [6]. Thirty-eight years

later, Carlsson and co-workers [7] identified dopamine as a neurotransmitter in the brain and suggested the effects of its deficiency in PD [6,8-10]. In 1960, Ehringer and Hornykiewicz [11] discovered that dopamine is depleted from the striatum of PD patients [6,12,13]. The discovery of dopamine's inability to cross the blood–brain barrier (BBB) [14-19] led to the trial studies of levodopa (L-DOPA), a dopamine precursor (**Figure 1A**), which was injected into PD patients for the first time in 1961 [14].

A study conducted by Cotzias and co-workers in 1967 utilizing high doses of L-DOPA emphasized its significance for symptomatic treatment of PD [12,20]. However, the bioavailability and consequently the therapeutic efficacy were found to be significantly reduced by extensive metabolism of L-DOPA, principally through decarboxylation, O-methylation, transamination and oxidation (**Figure 1B**) [21,22]. The metabolic products of L-DOPA (**Figure 1B**) were also observed to generate side effects such as nausea, vomiting and cardiac arrhythmias (i.e., dopamine), as well as inhibit further absorption of L-DOPA in the gastrointestinal tract (GIT) (i.e., 3-*O*-methyldopa, which competes with L-DOPA for the same transport system – a saturable-facilitated large neutral amino acid transport system) [22,23]. In general, > 95% of L-DOPA is metabolized in the GIT, liver and plasma, whereas only 1% of the ingested dose of L-DOPA penetrates the central nervous system (CNS) for the treatment of PD [22,24,25].

It has been observed that L-DOPA absorption is highly affected by irregular gastric emptying time, metabolism and competition with aromatic and branched chain amino acids for absorption and transport. Also, its half-life is relatively short (50 min) and it possesses a T_{max} of 1.4 h [26]. Owing to poor bioavailability of L-DOPA (33%), further attempts were made to improve the efficacy of oral formulations by increasing the dose of L-DOPA and the frequency of dosing [27,28]. However, these did not reduce the side effects emanating from the extensive metabolism of L-DOPA [29]. The product formed by combining aromatic L-amino acid decarboxylase inhibitor with L-DOPA was shown to reduce the side effects of L-DOPA by decreasing either the metabolism or the dose [9]. Decarboxylase inhibitors (which do not cross the BBB) can increase the plasma level and half-life of L-DOPA (from 50 min to 1.5 h) and also reduce the L-DOPA dose by 75%, thereby allowing 10% of the ingested L-DOPA to reach the CNS [24,30]. Studies have shown that although PD is initiated by loss of dopaminergic nigral neurons, there are still sufficient neurons to maintain constant striatal dopamine concentrations and a continuous activation of the striatal dopamine receptors for normal or close to normal basal ganglia function in the early stage of the disease [31,32]. The dopaminergic neurons convert the administered L-DOPA to dopamine and can still store, release, re-uptake, recycle or autoregulate large amounts of dopamine to maintain constant dopamine concentrations. Furthermore, it has been proposed that dopaminergic neurons are able to buffer the fluctuation of the plasma levels by masking the pulsatile stimulation of the striatal dopamine receptors [33]. However, the pulsatile stimulation becomes magnified as the loss of dopaminergic neurons progresses because the buffering and autoregulation capacity lessens, leading to motor complications such as dyskinesias and motor fluctuations [31-35]. The conversion of administered L-DOPA then takes place at the non-dopaminergic sites such as glial cells, serotonergic neurons and non-aminergic interneurons [36]. These sites do not store dopamine, but rather convert L-DOPA to dopamine and release it to the striatum (**Figure 1A**). Lack of storage capacity forces the striatal dopamine receptors to depend almost entirely on the peripheral availability of L-DOPA, which in turn is limited by its short half-life [33]. Hence constant striatal dopamine concentration and continuous activation of the striatal dopamine receptors are impaired and replaced by pulsatile stimulation determined by the pharmacokinetics of L-DOPA, leading to motor complications (dyskinesias and motor fluctuations) experienced by PD patients. Motor fluctuations consist of 'on' periods in which therapeutic response and good antiparkinsonian effect are experienced, and 'off' periods during which patients experience crippling Parkinsonism resulting from the absence of or low L-DOPA concentrations in the plasma [33].

Despite all these drawbacks and the fact that there are several therapeutic agents for the management of PD, L-DOPA remains the gold standard and most effective agent for the initial treatment of PD [33]. Compared with other therapeutic agents, L-DOPA is more effective, better tolerated, easier and quicker to titrate, and less expensive [37]. This review considers the pros and cons of L-DOPA-loaded drug delivery systems developed over the past three decades with a focused assessment of the attempts to improve absorption, subsequent bioavailability, and maintenance of constant plasma concentration of L-DOPA, as well as the technological basis of the delivery systems, with ultimate elucidation of an informed critique of these systems. This critical analysis underlines the fact that neuropharmaceutics is at a precipice, and investigators need to be encouraged to take that leap to enable the generation of innovative delivery systems for the effective management of PD.

2. Immediate release oral drug delivery systems for the administration of levodopa

The first immediate release drug delivery systems for L-DOPA were tablets composed of L-DOPA in combination with carbidopa (Sinemet®, Merck & Co., Inc., Whitehouse Station, NJ, USA) [38]. Carbidopa is a peripheral dopa decarboxylase (DDC) inhibitor. Administration of L-DOPA with carbidopa controlled the concentration of dopamine at appropriate levels with reduced side effects [39]. This was proposedly achieved through the diminished conversion of L-DOPA to dopamine in the peripheral tissues, which also permitted lower effective doses of L-DOPA for the

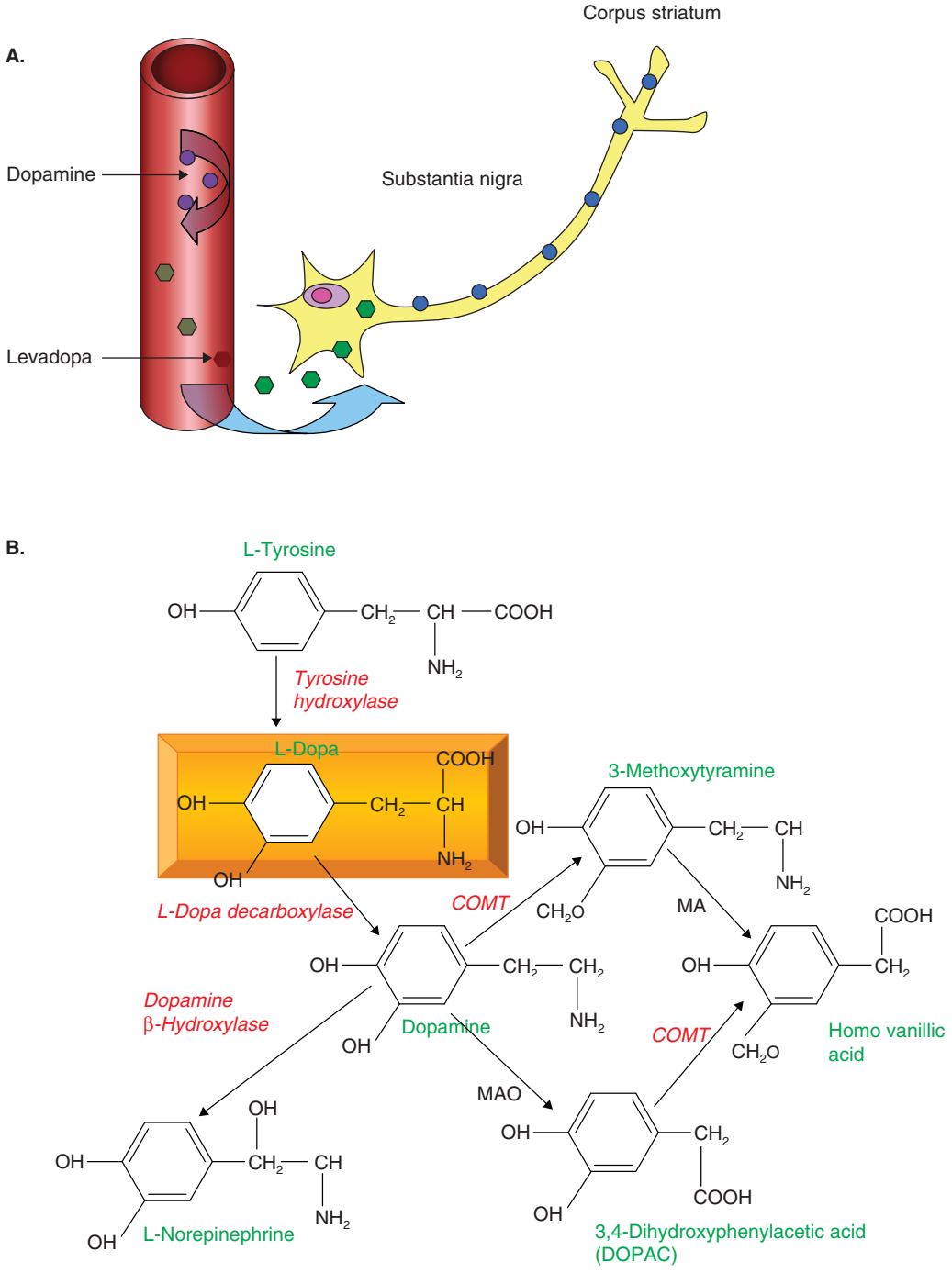

Figure 1. Schematics showing (A) the mechanism of action of l-DOPA, the 'gold standard' in the brain (adapted from [140]) and (B) synthesis and catabolism of dopamine – l-DOPA and dopamine are precursors to norepinephrine, which in turn could be metabolized further to epinephrine (not shown). Catechol-*O*-methyltransferase (COMT) catalyzes the 3-*O*-methylation of levodopa (not shown) as well as dopamine (and other catechols). Monoamine oxidase (MAO) deaminates and oxidizes the monoamines, dopamine, norepinephrine, epinephrine and serotonin (only the dopamine pathway is shown).
Adapted from [141].

treatment of PD [39]. Benserazide is another decarboxylase inhibitor that is used in combination with L-DOPA as Madopar® (F. Hoffmann-La Roche Ltd, Basel, Switzerland). These combinations, namely Sinemet and Madopar, could reduce the peripheral metabolism of L-DOPA and side effects such as nausea and vomiting but were ineffective in controlling dyskinesias and motor fluctuations associated with long-term use of L-DOPA [33]. Generally, Sinemet and Madopar produce fluctuations of L-DOPA plasma levels that either exceed safe therapeutic concentrations or fall below the minimum effective concentrations [39]. However, the plasma fluctuations depend not only on L-DOPA's biological half-life, but also on frequency of administration and release rate from the drug delivery systems, the latter of which can be modulated [39].

Catechol-*O*-methyl transferase (COMT) inhibitors such as entacapone and tolcapone have been added to L-DOPA/carbidopa to block the second metabolic pathway (O-methylation) – there is thus the possibility of associating tolcapone or entacapone as a unique formulation to the conventional L-DOPA/DDC inhibitors. An example of a triple combination of L-DOPA, carbidopa and entacapone as a single tablet is Stalevo® (Orion Pharma, Espoo, Finland), which was approved by the Food and Drug Administration (FDA) in 2003. The main function of Stalevo is to replace L-DOPA/carbidopa in PD patients who experience 'off' periods [40]. Entacapone is a highly potent peripherally acting COMT inhibitor. It increases the bioavailability of L-DOPA by reducing its peripheral conversion to 3-methoxytyramine (**Figure 1B**) [41]. It also enhances the clinical efficacy of both standard and controlled release L-DOPA/carbidopa. It has been demonstrated that entacapone increases the plasma level of L-DOPA by 35% and the half-life from 1.5 to 2.4 h [30]. However, it has also been observed that entacapone increases dopaminergic side effects such as dyskinesias, therefore necessitating L-DOPA dose reduction [42].

In preparing Stalevo, the conventional wet granulation method, which involves combining the active ingredients, retarded the release of carbidopa with decreased absorption and subsequent poor bioavailability. To increase the bioavailability of carbidopa from the solid composition, entacapone and L-DOPA were granulated together, adding carbidopa separately in the form of granules before compression. Furthermore, microcrystalline cellulose, which is an excipient used mostly in L-DOPA/carbidopa and entacapone formulations, was found to be incompatible owing to poor stability on long-term storage when the three active ingredients are combined [43].

Koller *et al.* [40] were the first group of scientists to conduct a study on Stalevo as a single tablet. They carried out a multicentered open-label single-arm 4-week study on 169 PD patients who experienced 'off' periods. The results of their study are illustrated in **Figure 2** and indicated that the incidence of dyskinesias as a result of enhanced dopaminergic activity was ameliorated with a reduction in Stalevo dose or returned to baseline levels without a change of dose. Thus, Stalevo could reduce 'off' periods principally by enhancing the pharmacokinetic profile of L-DOPA [40]. However, this observation was countered in a large prospective double-blind placebo-controlled trial; Stalevo could not improve dyskinesias and motor fluctuations mainly because of its inability to provide constant therapeutic plasma concentrations [44]. Benefits were seen only in several quality of life measures. Smith and co-workers [45] suggested that the frequency of dosing be increased to four times daily. They conducted their study in primates with the aim of providing continuous activation of the striatal dopamine receptors so as to reduce the incidence of dyskinesias [45]. However, frequency of dosing could certainly instigate patient non-compliance, which in return would not achieve the aim of increased dosing.

Subsequently, Hauser *et al.* [46] performed a 39-week, randomized, double-blind, multi-center study for comparison of the efficacy, safety and tolerability of levodopa/carbidopa/entacapone (LCE, Stalevo) with levodopa/carbidopa (LC, Sinemet IR) in patients with early PD. Four hundred and twenty-three patients with early PD warranting levodopa were randomly assigned to treatment with LCE 100/25/200 or LC 100/25 three times daily. The adjusted mean difference in total unified Parkinson's disease rating scale (UPDRS) Parts II and III between groups using the analysis of covariance model (prespecified primary outcome measure) was 1.7 (standard error = 0.84) points, favoring LCE. Significantly greater improvement with LCE compared with LC was also observed in UPDRS Part II scores. There was no significant difference in UPDRS Part III scores. Wearing-off was observed in 29 (13.9%) subjects in the LCE group and 43 (20.0%) in the LC group. Dyskinesia was observed in 5.3% subjects in the LCE group and 7.4% in the LC group. Nausea and diarrhea were reported more frequently in the LCE group. LCE provided greater symptomatic benefit than LC and did not increase motor complications.

3. Conventional controlled release formulations for levodopa administration

Reducing the interval between L-DOPA doses through the administration of controlled release formulations was one of the approaches utilized to solve the 'wearing off' problem encountered with L-DOPA [47]. Thus, controlled release formulations (CRF) were developed with the intention of delivering L-DOPA to the brain in such a manner that little or no fluctuations in L-DOPA concentrations would occur. Unfortunately the intention was not fulfilled, as patients still experienced motor complications as a result of plasma fluctuations [47]. However, these formulations were established to be useful for patients experiencing sleep disturbances [48]. Controlled release formulations are often associated with the problem of variable bioavailability and consequently unpredictable efficacy [49]. Peak plasma levels are reached ~ 2 – 4 h after administration and peak concentration may

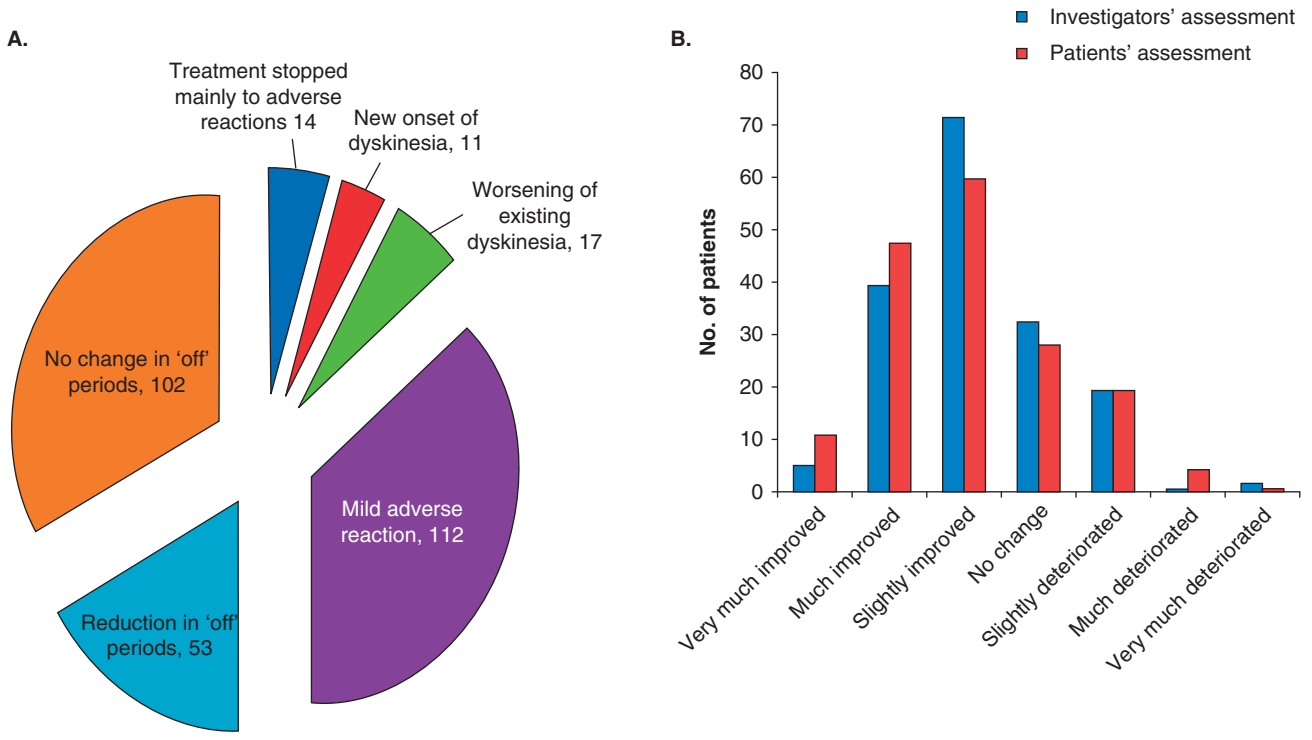

Figure 2. A. Summary of the study results on Stalevo® in patients experiencing 'off' periods. **B.** Assessment of efficacy of Stalevo®. Data extracted from [40].

be lower than those obtained with immediate release formulations (IRF). This may necessitate the patients taking an IRF in the morning and a CRF or combination of an IRF and a CRF during the day in order to achieve a rapid onset of action [49].

Advanced PD patients have been observed to be more sensitive to minor changes in plasma and brain L-DOPA levels as the disease progresses owing to more dependence on peripheral availability of L-DOPA [50]. Therefore, IRFs may be preferred to CRFs in advanced PD patients because gastrointestinal absorption can be irregular and unpredictable with controlled release formulations as a result of the gastrointestinal changes such as delayed gastric emptying and constipation that occur as the disease progresses [50]. Furthermore, CRFs have no significant advantage over IRFs in 'time to onset' of motor fluctuations [47].

Sinemet CR (L-DOPA/carbidopa) is a conventional CRF now available on the market. Sinemet CR is a sustained release polymer-based drug delivery system that releases L-DOPA/carbidopa as it slowly erodes [51]. Principally, L-DOPA, carbidopa and carrier agents such as hydroxypropyl cellulose and polyvinylacetate-crotonic acid copolymer are blended and compressed into tablets. Koller *et al.* [38] conducted a 5-year blinded randomized parallel study using a total of 618 patients in 36 centers worldwide to compare the effects of IRFs and CRFs. Their study showed that there was no significant difference between the IRF group and the CRF group. However, compared with the IRF, Sinemet CR provided a slight but statistically significant improvement in the quality of life of the individuals evaluated. This might have been due to the less dramatic change to the 'off' effect with Sinemet CR [38].

4. Administration of levodopa as a liquid formulation

Liquid L-DOPA formulations were introduced to facilitate rapid onset of action, even though their effects were observed to last for a very short period. Patients were observed to benefit from liquid L-DOPA formulation within 5 min, with the duration of the effect persisting for 1 – 2 h [52]. L-DOPA liquid formulations are therefore given to reduce the delay in the 'on' effect, which has been observed to be augmented by CRFs [53]. Unlike conventional formulations, the pharmacokinetic profiles of liquid L-DOPA formulations are not affected by the gastric emptying rate. Liquid formulations allow for a rapid gastric transit as the gastric emptying interval does not affect their absorption [54]. Thus, L-DOPA liquid formulations may allow more precise dose titration throughout the day and may therefore prove to be useful particularly in patients with prolonged gastric transit time, difficulties in swallowing, advanced motor fluctuations and also during the 'off' effect period [55-58].

Woitalla and his team [54] conducted a study that involved 50 PD patients who were randomly selected at various stages of the disease, fasted overnight and then given a single dose of dissolved L-DOPA/benserazide formulation in 100 ml of water. Blood samples were withdrawn at predetermined intervals between 0 and 180 min while the patients were scored on the UPDRS and Hoehn and Yahr Scale. The results depicted that there was an increased plasma availability of L-DOPA compared with the conventional formulations [54,59].

The conventional method for preparing liquid L-DOPA involved the crushing of a tablet of L-DOPA/carbidopa and then incorporating it into a fluid such as orange juice [60]. However, Remenar and co-workers [61] formulated stable compositions of liquid L-DOPA/carbidopa in various forms such as dispersible tablets, dry powders and stable liquids. These allowed for the incorporation of an acid (e.g., citric acid), metal chelator (e.g., EDTA), sweetener (e.g., aspartame or sugar) or a preservative (e.g., sodium benzoate). One of the liquid compositions was found to be stable for ~ 1 year with < 5% degradation of carbidopa at 40°C.

It has been observed that although L-DOPA liquid formulations may be independent of the gastric emptying rate, pulsatile delivery is often obtained instead of the desired constant delivery [57]. Furthermore, liquid formulations are cumbersome as their therapeutic effects are short-lived, thus requiring patients to take an hourly or bihourly dose, which makes them considerably prone to non-compliance. Thus, patients cannot rely entirely on liquid L-DOPA because the frequent dosing does not consistently reduce motor fluctuations [57].

5. Dispersible tablets for delivery of levodopa

Mathur and co-workers [62] formulated dispersible tablets of L-DOPA/carbidopa using wet granulation with the aim of achieving quick onset of action and accurate dosing, as was the case with liquid L-DOPA. The formulation comprised L-DOPA, carbidopa, filler and a coloring agent. The intragranular portion of a superdisintegrant such as croscarmellose sodium was granulated with a dispersion of a binder such as pregelatinized starch in a granulating fluid. The granules were blended with sweetener and flavoring agent and the extragranular portion consisted of a superdisintegrant and a lubricant/glidant, which was then compressed into tablets. The tablet dispersed completely in water in 3 min or less to form a solution that presented as a non-gritty suspension or slurry with a smooth feeling to the patient [62].

6. Oral disintegrating levodopa tablets

To compensate for the reduced duration of clinical response experienced by immediate release drug delivery systems, oral disintegrating tablets were introduced in 2004 [63]. L-DOPA oral disintegrating tablets (ODTs) enable the patient to take smaller and more frequent doses, which made it possible to tailor dosages to individual patient needs [30]. ODTs do not need to be administered with water, which makes it easy for elderly patients who may have difficulty swallowing. ODTs dissolve quickly once placed on the tongue. The solubilized L-DOPA/carbidopa is then swallowed with saliva [50]. ODTs permit reliable and rapid absorption of L-DOPA. However, the absorption occurs in the proximal intestine (duodenum) in the same manner as the IRFs and its time-to-peak is not shortened significantly when compared with IRFs [50]. Thus, if a patient has a bowel malfunction such as paralytic ileus, ODTs are not superior to IRFs [63]. Clinically, ODTs are preferred for naive and late stage PD patients as well as patients maintained at low doses or patients requiring dose titration [63]. The results obtained from a multi-centered, open-label, sequential study that compared preferences for ODTs and conventional tablets in PD subjects suggested that ODTs may be of value in certain patients with PD depending on their personal preferences, disease status and willingness to alter an aspect of their use of medication [64]. The attributes of ODTs that influenced subjects' preference included accessibility to medication to treat 'off' times, ease of activities of daily living, reduced concern about swallowing, applicability for night time dosing, ease of compliance with the dosing schedule, and lowered self-consciousness regarding medication use [64]. Parcopa® (Schwarz Pharma, Inc., Milwaukee, WI, USA), a commercially available ODT approved by the FDA in 2004, was used in the study. It was manufactured based on RapiTab™ (Schwarz Pharma, Inc., Milwaukee, WI, USA), technology, which formulates drugs into ODTs that dissolve rapidly on the tongue. Results from the study are depicted in **Figure 3**.

Hsu and Han [30] prepared ODTs by wet granulation. The ingredients included a binder (which could also function as a disintegrant) and an intragranular disintegrant, to disintegrate the granules, as well as an intergranular disintegrant, to disintegrate the tablet into granules. The ODT formulations contained a poorly water-soluble filler such as microcrystalline cellulose to improve compressibility and avail rapid dispersion characteristics. The ODTs were found to disintegrate rapidly (60 s or less) in an *in vitro* disintegrating apparatus [30].

7. Dual-release formulations for the delivery of levodopa

For the conventional controlled release delivery systems of L-DOPA, the onset of action is normally ~ 2 h, which is then followed by a prolonged release over a period of 4 – 6 h. To overcome the delayed action of these delivery systems, dual-release formulations (DRFs) were introduced [65]. A DRF is a two-compartment delivery system comprising a sustained release inner core and an immediate release outer layer. Rubin [65] developed three methods for preparing L-DOPA/carbidopa dual-release delivery systems. In the first method, the components for the inner core and the outer layer

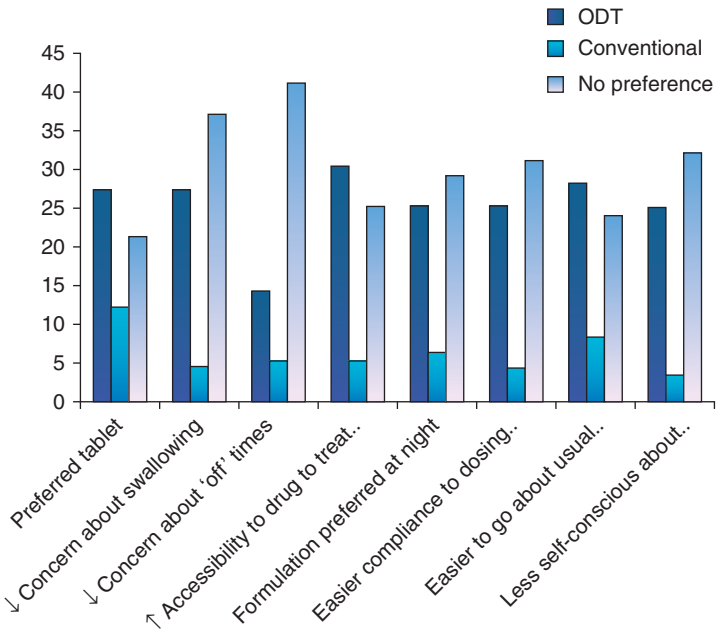

Figure 3. Preferences of patients undergoing treatment with carbidopa/l-DOPA ODT and conventional tablets.
Data extracted from [64].
ODT: Oral disintegrating tablet.

were blended separately, and subsequently the compressed inner core tablet was overcoated with the compressed outer layer blend with a suitable coating press. In the second method, a bilayer tablet was formed whereby the sustained layer blend and the immediate release blend were compressed adjacent to each other (or separated by an extra excipient layer) using a suitable layered press. In the third method, the uncoated pellets of immediate release L-DOPA/carbidopa and polymer-coated pellets of sustained release L-DOPA/carbidopa were included in an oral dosage form such as a capsule or compressed as a tablet in the desired ratio of immediate and sustained release L-DOPA/carbidopa. DRFs developed by Rubin showed that the L-DOPA-loaded immediate release compartment provided a rapid onset of antiparkinsonian effect, whereas the sustained release inner core, which was also loaded with L-DOPA, prolonged the therapeutic effect [65].

Madopar DR (SkyePharma, London, UK, for F. Hoffmann-La Roche Ltd, Basel, Switzerland) is a dual-release formulation containing L-DOPA and benserazide available in Switzerland and was developed in the ratio of 4:1 of L-DOPA/benserazide [49]. Madopar DR combines the advantages of a rapid onset of efficacy as well as a sustained effect. This delivery system consists of an IRF layer, a barrier and controlled release layer, which lead to early peak plasma levels at ~ 1 h, followed by sustained plasma levels [49].

An open-label, multiple-dose randomized two-way crossover clinical trial using this dual formulation was carried out on 18 subjects [49]. The assessment was at day 1 after a single dose (200 mg L-DOPA and 50 mg benserazide) and day 7 after a 5-day 3 times daily pretreatment with 100 mg L-DOPA and 25 mg benserazide in fasting state. Pharmacokinetic parameters such as bioavailability, accumulation and metabolism of L-DOPA were determined. On day 1, the results showed that there was rapid absorption, marked peak plasma concentration and an apparent elimination half-life with DRF when compared with the slow release formulation (SRF), as shown in **Table 1**. The marked difference was still apparent on day 7. After multiple dosing for 7 days, there was accumulation of 3-*O*-methyldopa for these formulations. It was further observed that there was no difference in accumulation of 3-*O*-methyldopa but plasma fluctuation was higher on day 7 with the DRF. However, bioavailability after single and multiple doses of the DRF was 40% higher than that of the SRF [49]. Furthermore, the study was conducted on healthy patients, therefore its impact on motor complications and 'on and off' effects could not be ascertained. Also, from the results shown in **Figure 4A, B**, it can be proposed that a continuous delivery of L-DOPA and stable plasma levels, which is envisaged to overcome the already existing problems, may not be obtainable. An ideal profile of a CRF with continuous drug delivery is depicted schematically in **Figure 4C**.

Descombes and co-workers [66] conducted a single-dose, crossover study on 16 PD patients utilizing a two-center randomized double-dummy (1 dual-release tablet of 200 mg L-DOPA, plus 50 mg benserazide or 2 slow-release capsules of 100 mg L-DOPA, plus 25 mg benserazide). The

Table 1. Comparative pharmacokinetic parameters of levodopa analysis obtained from dual-release formulation and controlled release formulation.

Formulation	C_{max} (μg/ml)	T_{max} (h)	$t_{½}$ (h)	AUC_{0-12} (μg × h/ml)	Comments
DRF day 1	1.7	1.1	1.2	4.3	Rapid absorption – DRF achieved ~ double the plasma concentration attained by CRF in approximately half the time it took CRF to attain its maximum concentration (37.0% on the first day and 34.3% on the seventh day, respectively)
DRF day 7	2.1	1.1	2.6	5.9	
CRF day 1	1.0	2.3	1.5	3.1	
CRF day 7	1.1	2.0	1.9	4.2	

Data extracted from Gasser *et al.* [49].
CRF: Controlled release formulation; DRF: Dual-release formulation.

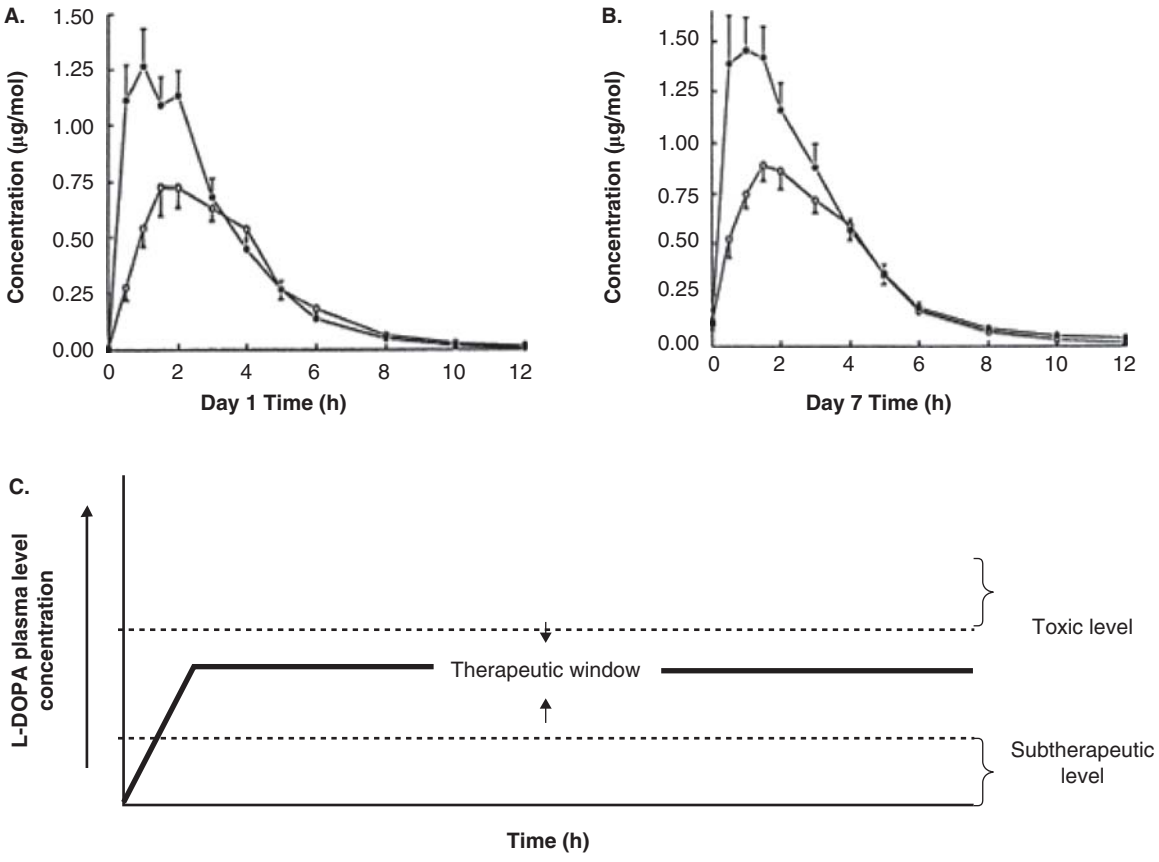

Figure 4. Mean l-DOPA plasma concentration–time curves of the DRF (filled symbols) and the SRF (open symbols) following (A) single-dose administration on day 1, (B) multiple-dose administration on day 7 (n = 18) (source: Gasser *et al.* [49]) and (C) an ideal controlled release profile.

efficacy parameters were time for onset of action ('on' effect relative to time of drug intake), duration of 'on' effect, time switch to 'off' effect relative to time of drug intake and motor performance (reduction in UPDRS III baseline score). The severity of dyskinesia was assessed with the Dyskinesia Rating Scale – maximum score, 28 [67]. Although the $t_{½}$ was similar for both DRF and SRF, the DRF had a significantly faster absorption, greater peak plasma concentration (by ~ 45%), and greater systemic bioavailability (~ 20%) [66]. The mean onset of the 'on' effect was more rapid with the DRF (43 ± 31 min) than with the SRF (81 ± 39 min). 'On' effect duration showed a trend for longer response with the DRF than the SRF (114 ± 92 min versus 80 ± 75 min), whereas the mean UPDRS baseline motor score was similar for both formulations (33.8 ± 10.6 versus 34.3 ± 11.6). However, maximum percentage reduction in UPDRS score was slightly

more pronounced (49 ± 32% versus 37 ± 34%) and occurred earlier (90 min versus 3 h) with the DRF. The results also showed that the mean Dyskinesia Rating Scale severity score was similar for both formulations (2.8 ± 2.5 versus 2.7 ± 3.1) [66].

Cohen *et al.* [68] developed a dual-release tablet of L-DOPA ethyl ester with the aim of achieving an initial burst effect of L-DOPA for rapid onset of action followed by a sustained release period. L-DOPA ethyl ester was incorporated into a uniform blend of hydroxypropylmethyl cellulose, hydroxypropyl cellulose and carboxyl vinyl polymer in desired proportions with other excipients and compressed into a conventional tablet. However, *in vivo* results in healthy volunteers were the same as those obtained with Sinemet CR because the terminal half-life was only 2 h [69].

8. Delivery of levodopa by infusions

Infusions for the delivery of L-DOPA were introduced with the intention of achieving constant plasma concentrations, which would in turn produce continuous dopaminergic stimulation of the dopamine receptors. An intravenous infusion of L-DOPA was prepared by dissolving L-DOPA in normal saline to a final concentration of 2 mg/ml, while carbidopa was given orally ~ 1 h before providing the infusion [70]. Based on previous studies on intravenous and enteral infusions of water solutions of L-DOPA, which resulted in a reduction in fluctuations in L-DOPA plasma concentrations and milder side effects (though impractical), a more practical long-term intraduodenal infusion (Duodopa®, Solvay Pharmaceuticals GmbH, Hannover, Germany) was developed as L-DOPA/carbidopa enteral gel with a portable pump and intestinal tube [28,71]. Duodopa is an aqueous suspension containing 20 mg/ml L-DOPA and 5 mg/ml carbidopa as active ingredients in 2.92% carmellose sodium (carboxymethylcellulose). Twenty-five advanced PD patients were enrolled in a study that compared the intraduodenal infusion as monotherapy with individual combinations of conventional pharmacotherapy. There was significantly improved motor performance with the infusion in comparison with individual combinations of conventional therapy [71]. In another study, Nyholm *et al.* [72] stated that in addition to improvement of motor performance, a 24 h intraduodenal infusion improved sleep in advanced PD patients without clinically relevant tolerance or side effects. Hence, patients were found to have had improved quality of life when placed on intraduodenal infusion [71,73].

Thus far, L-DOPA duodenal infusion has been found to produce continuous plasma concentrations of L-DOPA, and reduced dyskinesias and 'off time' in clinical studies [74]. In a study that involved 7 patients, carbidopa/L-DOPA infusion (5/20 mg/ml) reduced daily motor fluctuations by 81% and dyskinesias by 70%. Most dyskinesias experienced by the patients were attributed to the bolus doses of L-DOPA taken in the mornings because the pump was turned off at night and the dyskinesias reportedly had a short duration. The administration of L-DOPA was controlled by a pump with an adjustable infusion rate allowing individual adaptation of the dose, which varied from 40 to 120 mg/h or more when required. Overall, the L-DOPA continuous infusion significantly increased the quality of life of the patients investigated [74].

9. Biodegradable microspheres as a drug delivery system for levodopa

Microspheres are controlled drug delivery systems for various applications, including hormone therapy, chemotherapy, cardiovascular diseases, neurological disorders, ocular drug delivery, and protein and vaccine deliveries [75-81]. Microspheres are known to modulate drug release and absorption characteristics [78]. It has been shown that with the use of microspheres as a drug delivery system for L-DOPA, the dosage size, frequency of administration, systemic side effects and dose-dumping decreased, while the drug could be released continuously [77]. This ultimately enhances patient compliance. Microspheres have been fabricated from a variety of biodegradable polymers, which include gelatin, albumin, polyanhydrides, polyorthoesters, polyesters and polysaccharides [76,82,83].

The use of microspheres as drug delivery agents for L-DOPA and carbidopa is another approach for improving the bioavailability and subsequent clinical response of L-DOPA [83]. Arica and co-workers [83] prepared L-DOPA and carbidopa microspheres by a solvent-evaporation technique using biodegradable polymers, namely poly(DL-lactide) and poly(DL-lactide-*co*-glycolide). Both *in vitro* and *in vivo* studies were performed. The *in vitro* results revealed that both L-DOPA- and carbidopa-loaded microspheres showed sustained profiles over 10 h (as depicted in **Figure 5**) whereas the *in vivo* results portrayed a sustained slow release in each rat [83]. The *in vitro* controlled drug release from the microspheres was attributed to the diffusion of L-DOPA or carbidopa through the pores or channels on and/or close to the surface of the microspheres, whereas the *in vivo* results showed that drug release was attributed to the degradation of the polymers. The microspheres were then stereotactically implanted into the brains of Parkinson-induced albino rats as an injectable dosage form. Reduced rotational behavior was observed, indicating that L-DOPA/carbidopa-loaded microspheres exerted functional effects on the striatal dopamine receptors [83]. The bioavailability of L-DOPA was improved because the L-DOPA/carbidopa was released directly on the striatal dopamine receptors, thereby reducing wide distribution of side effects [83]. However, the method is invasive and the improvement of motor complications can be clearly evaluated only in man.

In related studies, Arica and co-workers [83,84] fabricated L-DOPA-loaded chitosan microspheres using the emulsion-polymerization technique. They assessed

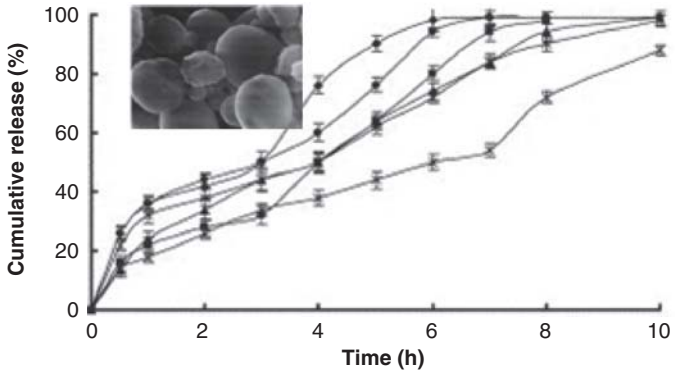

Figure 5. *In vitro* release profiles of l-DOPA from microspheres depicting a scanning electron micrograph of the l-DOPA-loaded microspheres (inset).
Adapted from Arica *et al.* [83].

the physicochemical characteristics of these microspheres with the intention of obtaining an optimal formulation for brain delivery of L-DOPA. They observed that on implanting these microspheres in the rats, the rotational behavior of rats became reduced [83,84].

10. Gastroretentive dosage forms as drug delivery systems for levodopa

It has been observed that the extent of absorption for drugs with maximal absorption at the proximal intestine (duodenum) is limited by the conventional immediate release and controlled release formulations [85-87]. Once emptied from the stomach, the passage of these formulations through the upper region of the intestine is rapid, limiting the bioavailability of drugs such as L-DOPA. Therefore, prolonging the residence time of drug delivery systems in the upper region of the intestine will enhance absorption and subsequent bioavailability of drugs with a narrow absorption window [87,88]. Gastroretentive dosage forms (GDFs) are time-controlled oral drug delivery systems that can enable prolonged and continuous delivery of drugs to the upper region of the GIT (duodenum and jejunum), improve absorption of drugs with a narrow absorption window, minimize erratic plasma concentrations of drugs, reduce the frequency of dosing, and reduce the total administered dose and associated side effects, thereby optimizing the therapeutic efficacy, which ultimately improves patient compliance [86-88]. However, continuous and sustained delivery of drugs in the upper region of the GIT may enhance the metabolic activity of the metabolic enzymes in the intestine wall, which will in turn reduce the bioavailability of drugs that have extensive metabolism [86,89]. Various approaches have been used to increase gastroretention of drug delivery systems. These include swelling or unfolding to a size that will prevent passage of GDFs through the pyloric sphincter, bioadhesion, buoyancy of gastric fluids and delaying of gastric emptying by the addition of lipid excipients and high-density delivery systems [86-89].

10.1 Single-unit sustained release floating systems for delivery of levodopa

Hydrodynamically balanced systems are single-unit delivery systems designed and formulated to prolong gastric residence time, thereby improving absorption. They are formulated to be less dense than the gastric content to enable them to float on the surface of gastric content. Madopar HBS (hydrodynamically balanced system) (L-DOPA/benserazide) is a single-unit floating system now available on the market that combines L-DOPA and benserazide. The system was designed with the aim of prolonging the residence time of drugs in the gastric region so as to enhance absorption [90]. The Madopar HBS is formulated as a capsule system. On oral administration, the capsule dissolves in the gastric fluid, forming a mucous body with a bulk density < 1 g/cm^3. L-DOPA/benserazide is then released as the system remains in the stomach for a prolonged period of time [90]. However, the gastric residence time of Madopar HBS was observed not to be significantly prolonged, which may explain the similar pharmacokinetic profile it shares with Sinemet CR [89].

10.2 Multiple-unit sustained release floating dosage forms for delivery of levodopa

It has been shown that multiple-unit dosage forms such as pellets and minitablets are more advantageous when compared with single-unit dosage forms in that they have more reproducible gastric residence time (GRT), less inter-subject variability in absorption and dose-dumping and better dispersion through the GIT with less chance of localized mucosal damage [91,92]. It has been postulated that most of the particles from floating multiple-unit dosage forms remain above stomach contents for an extended period of time [93]. Goole *et al.* [92] prepared L-DOPA sustained release floating minitablets by melt granulation and subsequent compression. Melt

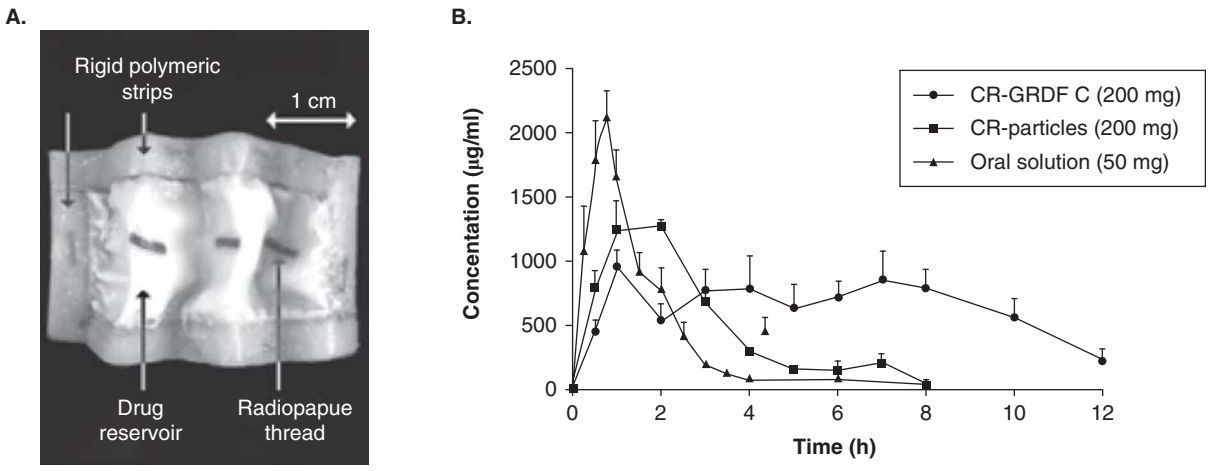

Figure 6. A. A picture of the gastroretentive dosage form (GRDF) drawn out of the dog stomach 15 min postadministration – the GRDF has unfolded almost completely to its original size. **B.** Effect of the mode of L-DOPA administration on the plasma concentrations in beagle dogs (n = 6) for CR-GRDF C in comparison with the two control modes of administration (oral solution and CR-particles).
Adapted from Klausner *et al.* [89].
CR-GRDF: Controlled release gastroretentive dosage form.

granulation exploits the melting or softening of a binder at a low melting point. The delivery system comprised L-DOPA, precirol ATO5 (glyceryl palmitostearate) as a meltable binder and drug release regulator, methocel K15M (HPMC) as swellable polymer, and lactose and Compritol® 888 (Glyceryl Behenate, Gattefossé, USA) as hydrophilic and lipophilic diluents, respectively, while sodium bicarbonate and calcium carbonate were gas-generating agents. L-DOPA and excipients were mixed in a laboratory-scale high-shear mixer at regulated revolutions and a temperature of 60°. The granules were cooled and then compressed into minitabs by direct compression. The *in vitro* results for one of the formulations indicated that minitabs floated after 12 min, remained buoyant for > 13 h and showed sustained release of L-DOPA with no 'burst' effect for > 8 h [92].

In other studies, Goole and his team [94,95] developed coated L-DOPA multiple-unit sustained release floating minitablets, developed with the overall aim of improving the floatability of such delivery systems. The procedure involved preparing sustained release granulates by melt granulation, compressing them into minitablets and then coating them with Eudragit® (Evonik Industries (previously Degussa), Essen, Germany) RL30D, a water-insoluble acrylic polymer. The resultant minitabs were found to be buoyant for > 13 h and provided sustained release of L-DOPA for > 20 h. However, an *in vivo* study that was carried out in 10 healthy humans depicted that the floating minitabs showed buoyancy on the surface of the gastric content for a period > 4 h. The floating minitabs were comparable to a marketed product, Prolopa® (Roche, Brazil) rHBS 125, with regards to AUC, T_{max} and C_{max}. The non-significant difference between formulations, however, was attributed to inter-subject variability and the small number of volunteers. In comparison with Prolopa and coated floating minitabs, the uncoated floating minitabs displayed more evenly distributed plasma levels of levodopa, whereas Prolopa did not have a floating lag time attributed to its low density [96]

Klausner *et al.* [89] developed a L-DOPA-loaded unfolding multilayer delivery system that comprised an inner layer of polymer–drug matrix (ethylcellulose:L-DOPA 1:1) framed with rigid polymeric strips (L-polylactic acid:ethylcellulose, 9:1) then covered on both sides with two layers comprising enzymatically hydrolyzed gelatin, methacrylic acid copolymer type B, glycerine and glutaraldehyde, in a ratio of 48:30:20:2. The exterior part of these layers was covered with a thin anti-adhesive layer of microcrystalline cellulose powder (**Figure 6A**). Three compositions of controlled release gastroretentive dosage forms (CR-GRDFs) were used in the study, which differed in the thickness of ethylcellulose–levodopa membrane and in the amount of ethylcellulose–levodopa incorporated: CR-GRDF A, 0.50 mm, 50 mg levodopa; CR-GRDF B, 0.31 mm, 125 mg levodopa; CR-GRDF C, 0.61 mm, 200 mg levodopa. Subsequently, CR-GRDFs were folded (6-mm-long folds) before insertion into gelatin capsules. *In vitro* analysis results indicated that the CR-GRDFs released L-DOPA in a controlled manner [88]. CR-GRDF C was found to exert controlled release of L-DOPA for > 12 h.

CR-GRDFs were administered to beagle dogs and the gastroscopy showed that it unfolded to its extended size 15 min after administration and maintained the extended size for at least 2 h [89]. CR-GRDF A resulted in a low plasma concentration of L-DOPA, whereas CR-GRDF C resulted in an elevated plasma concentration for > 10 h. The enhanced metabolic activity at the intestinal wall may explain the low bioavailability of CR-GRDF A in comparison with the oral

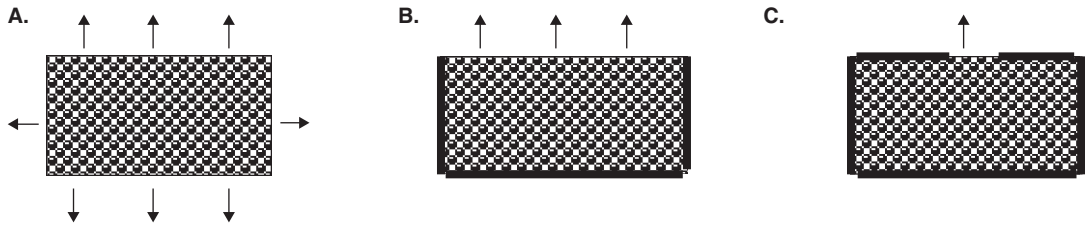

Figure 7. Rate of release modified by presence or absence of impermeable membrane for (A) uncoated polymer matrix, (B) one side uncoated and (C) an opening (pore)/coated.
Adapted from [102].

solution; hence the dose of L-DOPA in CR-GRDF B was increased, but a high concentration of L-DOPA was obtained only for a short period of time [89]. A further increase of L-DOPA dose coupled with modification of the release kinetics in CR-GRDF C produced prolonged and sustained release of L-DOPA, as visualized in **Figure 6B**, compared with two control modes of administration (non-gastroretentive CR particles and an oral solution). Overall, the study showed that the unfolding CR-GRDF can achieve prolonged absorption and sustained blood levels for L-DOPA [89]. It must be taken into account, however, that the dog was a poor representative model for the human's gastrointestinal tract [97-100] – an indication that the results may not translate well in humans [101]. Furthermore, the pylorus of dogs is smaller than that of human beings [89], therefore the gastric residence time for CR-GDRF in dogs may differ significantly from that of humans.

11. Long-term implantable levodopa controlled release matrix

Sabel *et al.* [102] fabricated a long-term controlled release matrix aimed at achieving continuous delivery of L-DOPA with fewer or no plasma fluctuations, which in turn may eliminate the 'on and off' syndrome. The fabricated matrices were able to deliver L-DOPA *in vitro* for > 600 days, and for 225 days in rats following subcutaneous implantation. To prepare the matrices, ethylene vinyl acetate (EVA) copolymer was dissolved in methylene chloride at 37°C for 24 h. L-DOPA was then added to the liquid polymer and mixed thoroughly. The blend was cast into a frozen rectangular glass mould at -60°C with subsequent evaporation at -20°C under vacuum. To ensure linear release of L-DOPA, the L-DOPA-loaded polymer matrices were coated with an impermeable barrier. Samples with dimensions of 15 × 30 × 2 mm were cut out of the polymer matrix and were variably coated to identify a configuration that created preferred release kinetics. Three types of sample were obtained. The first one was the uncoated polymer matrix, the second one coated polymer matrix on all sides except one face of the slab, whereas the third one was fully coated except for the presence of pore size diameters of 2, 4 and 6 mm such that the incubation medium could gain access to the loaded core (**Figure 7**) [102].

The results revealed that the uncoated polymer matrix released L-DOPA in all directions and for a short period of time. The one-side uncoated polymer matrix released L-DOPA in one direction thereby producing more linear release kinetics, whereas the polymer matrix with a pore diameter uncoated had linear release kinetics as well as a prolonged delivery period. In both cases, there was an initial 'burst' effect from all formulations followed by a sustained release of L-DOPA. The proposed mechanism of release was drug diffusion through the communicating channels and pores within the polymer matrix [102].

In a test that was undertaken using a rat model, the polymer matrix implants showed a continuous release of L-DOPA, which assured stable elevated plasma concentrations for ~ 1 year [102]. However, there might be a need to determine the potential of this delivery system for future applicability by assessing its ability to achieve stable levels of L-DOPA, thereby preventing the possibility of motor complications in human subjects.

12. Pulmonary delivery of levodopa

Jackson and co-workers [103] attempted to improve on the bioavailability of L-DOPA by developing pulmonary formulations for L-DOPA, which was anticipated to achieve a rapid onset of action and maintain the effective therapeutic level of L-DOPA. The formulation comprised an aqueous solution of L-DOPA with either sugars, such as trehalose, or phospholipids, such as dipalmitoyl phosphatidylcholine (*DPPC*), with salt (NaCl) as an option, which was then mixed with an organic solvent such as ethanol, passed through an atomizer and spray-dried [103]. Particles containing > 90% drug were delivered to the patient's pulmonary system (targeted at the alveoli or deep lung structures) utilizing inhalation devices such as dry powder inhalers, metered dose inhalers or nebulizers. This pulmonary formulation was compared with an oral liquid formulation in a PD-induced rat model. The pulmonary formulation furnished a rapid onset of action and elevation of plasma levels of L-DOPA, whereas the oral liquid formulation produced a delayed onset of action and lower

C_{max} [104]. Despite these promising results, pulmonary formulations have not yet been shown to provide continuous dopaminergic stimulation [105].

13. Nasal delivery of levodopa

The nasal route has been explored for drug delivery because of its large surface area enhanced by the presence of microvilli that cover the epithelial cells, which in turn are highly vascularized [82]. Other important aspects are that it is easily accessible and avoids first-pass metabolism. Brime *et al.* [82] fabricated L-DOPA-loaded gelatin microspheres by the w/o emulsification solvent extraction technique for delivery by means of the transnasal route. The bioadhesive properties of gelatin facilitated prolongation of the contact between the microspheres and the nasal mucosa, thereby enhancing absorption. However, *in vivo* release studies were not performed. The *in vitro* release profiles showed a dual-phase release for L-DOPA, which was characterized by an initial burst release followed by a slow release phase [82].

Kim and co-workers compared three routes of administration for L-DOPA: oral, intravenous and intranasal in a rat model [106]. L-DOPA without carbidopa given intranasally was rapidly absorbed, achieving the same peak plasma concentration (C_{max}, 0.55 ± 0.14 μg/ml) in 0.2 h as that given orally (T_{max}, 1.0 ± 0.5 h) and was rapidly eliminated ($t_{½}$, 0.23 ± 0.09 h). However, incorporation of carbidopa shifted the time courses by decreasing the T_{max} to 0.1 ± 0.0 h and increasing elimination half-life to 0.31 ± 0.09 h. The absolute bioavailabilities for the nasal and oral formulations with carbidopa were 45.4 and 17.7%, respectively [106]. The nasal drug delivery system is an immediate release system and thus would not provide constant and sustained delivery of L-DOPA for the achievement of continuous dopaminergic stimulation

14. Transdermal delivery systems for levodopa

Transdermal delivery of L-DOPA has been envisaged to be an alternative route for delivery of L-DOPA, which could overcome the adverse effects and complications encountered with the oral route [107,108]. It is also preferred to infusion and implantation because of its non-invasiveness and therefore enhanced patient adherence. It has been considered to be the optimum route for achieving constant plasma concentrations of L-DOPA, which therefore makes it possible to avoid akinesia and dyskinesia [107,108]. The transdermal route is recommended for the administration of drugs in geriatric PD patients who tend to have dementia and dysphagia [108,109]. However, one of the chief limitations that has been encountered with the transdermal route is the permeability barrier properties of skin resulting from the presence of a series of lipid multilayers made of ceramides, cholesterol and fatty acids [107,108]. Hence, the penetration of polar drugs such L-DOPA through the skin is inhibited and so would require the disruption of the lipid layers. Thus far, organic solvents such as ethanol and methanol have been used as cutaneous absorption enhancers to improve the penetration of L-DOPA through the skin [109].

Sudo and his team [109] prepared a hydrogel of L-DOPA using ethanol and methanol as absorption enhancers and assessed the transdermal L-DOPA absorption *in vitro* and *in vivo* using a rat model. The *in vitro* profiles of L-DOPA permeation indicated that ethanol and methanol in combination enhanced the penetration of L-DOPA through the skin while *in vivo* L-DOPA concentration continued to rise until 180 min. The cutaneous permeation rate *in vitro* was 1375 ng/(cm^2 min) and *in vivo* was 1236 ng/(cm^2 min). It was postulated that the death of some rats after 240 min may have been because of the adverse effects generated by the elevated levels of the L-DOPA metabolites. This is very likely considering the fact that carbidopa was not used in this study. With organic solvents it was observed that there was a rapid restoration of lipids, resulting in normalization of the permeability barrier function [109]. For example, the organic solvents' inhibitory effect of triglyceride was found to have waned after 5 h of treatment [109]. Babita and Tiwary [108] prepared adhesive transdermal patches consisting of a lipid synthetic inhibitor cerulenin, calcium chloride (optional in some patches), carbidopa (optional in some patches) and L-DOPA, which were applied to ethanol-perturbed shaved skins of rats. The presence of cerulenin produced 60% inhibition of triglyceride synthesis within 2 h of treatment and 20% of triglyceride synthesis remained inhibited after 48 h. Application of cerulenin and calcium chloride produced a significantly enhanced inhibitory effect compared with cerulenin alone. On normal skin, the plasma concentration of L-DOPA was negligible, but with carbidopa and cerulenin effective plasma concentrations were attained in 3 h and maintained up to 10 h, and further addition of calcium chloride increased the duration of activity to 24 h with a higher C_{max} and lower T_{max}.

In another study, Babita *et al.* [107] used three lipid synthesis inhibitors, atorvastatin, cerulenin and β-chloroalanine, for inhibition of cholesterol, triglycerides and sphingosine (a precursor of ceramide) syntheses, respectively. The combination of the three lipid synthesis inhibitors reduced lag time to 1 h compared with the individual applications (2, 4 and 6 h) and maintained the effective plasma concentration of L-DOPA for > 48 h in the rat model [107]. Thus far, transdermal studies seem to offer a non-invasive route for the delivery of L-DOPA. However, studies in human subjects would be a necessity to assess whether the dopaminergic stimulation is continuous and able to reduce motor complications.

15. Prodrugs as a delivery vehicle for levodopa

In an attempt to improve the solubility and subsequent pharmacokinetic profile of L-DOPA, prodrugs such as methyl, ethyl, isopropyl, butyl, cyclohexyl and 4-hydroxylbutyl esters

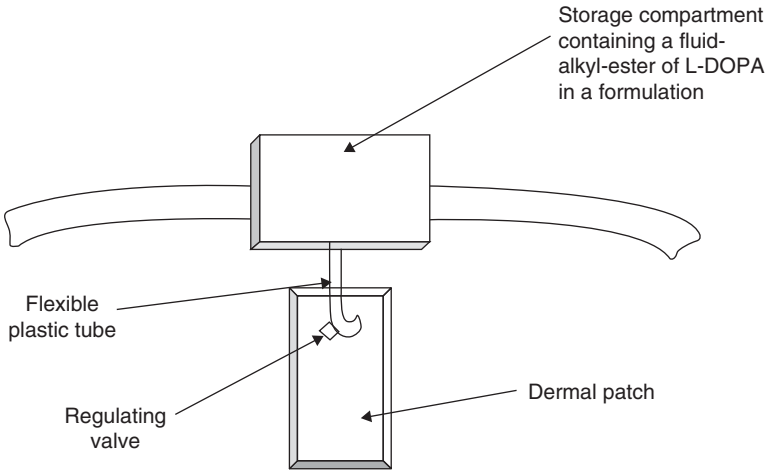

Figure 8. Transdermal apparatus for delivery of alkyl-esters of l-DOPA.
Adapted from [117].

of L-DOPA were developed [110-112]. It has been suggested that L-DOPA prodrugs are not absorbed through the neutral amino acids transport system as is the case with L-DOPA, but rather they are absorbed across the intestinal epithelium by active and/or passive transport [69,110].

Esters and alkyl esters of L-DOPA have been studied as solutions and tablets for transdermal, intranasal, subcutaneous, intramuscular and oral administration and also as microenemas for rectal application [68,111,113-118]. It has been demonstrated that Etilevodopa, which is an ethyl ester of L-DOPA, has greater gastric solubility compared with L-DOPA [26]. It is rapidly hydrolyzed to L-DOPA and possesses a shortened time to maximum L-DOPA concentration [26]. However, despite the aforementioned advantages, it has been noted that its clinical response is not superior to L-DOPA. In a double-blind, randomized, comparative clinical trial that was undertaken in 44 sites using a total number of 327 patients for the assessment of Etilevodopa's efficacy, safety and tolerability in PD patients with motor fluctuations, there was no improvement in the onset of drug benefit, response failure and 'off' periods compared with L-DOPA [118]. Dispersible tablets of Etilevodopa/carbidopa also had no advantage in 'on and off' effects experienced by PD patients when compared with L-DOPA/carbidopa tablets [26]. In another study it was observed that the alkyl esters of L-DOPA that were administered nasally in Sprague–Drawley rats showed rapid and complete absorption into the systemic circulation, whereas the butyl ester prodrug, specifically, did not result in significant formation of peripheral dopamine thereby enhancing the bioavailability to the CNS, which was comparable to an equivalent intravenous dose [116].

In 2004, Kushnir and Heldman [117] formulated an apparatus for the transdermal delivery of alkyl esters of L-DOPA. L-DOPA was dissolved in a non-aqueous solvent that also contained a transdermal enhancer and a detergent. The apparatus consisted of a storage compartment (compressible by mechanical pressure) containing a fluid for transdermal treatment of PD, a dermal patch connected to the storage compartment and a regulating valve to control flow of fluid from the storage compartment to the dermal patch, as depicted in **Figure 8**. Results obtained from an *in vivo* study in two human volunteers indicated that an effective concentration of 200 ng/ml was obtained.

In another trial, an oral controlled release system of L-DOPA methyl ester and carbidopa was developed by Bettini and co-workers [112] in 2002, who designed a three-layer matrix tablet with each layer possessing different release mechanisms. The first layer was swellable, the second layer was erodible and the last layer was disintegrating. Each layer incorporated several components (polymers and other excipients such as hydroxypropymethylcellulose, magnesium stearate, talc and polyvinylpyrrolidone) as well as L-DOPA methyl ester. The three-layer matrix was manufactured using a single punch machine. *In vitro* and *in vivo* studies showed that the drug release depended on the composition of the layers and their relative positions in the matrix [112]. The approach of including a swellable layer in the middle of the matrix can be exploited as a means of reducing morning 'on–off' fluctuations, whereas a disintegrating layer in the middle may be useful in preventing end of dose deterioration in the afternoon.

Maleic- and fumaric-diamides of (*O*,*O*-diacetyl)-L-DOPA-methylester-loaded liposomes have also been developed and administered intraperitoneally in rats [119]. The prodrug had the ability to induce sustained delivery of dopamine in the striatal dialysate of the rat with respect to intraperitoneal administration of equimolar concentrations of L-DOPA [119].

16. Delivery of levodopa by means of the rectal route

Thus far, L-DOPA has been administered through the rectal route in the form of tablets, suppositories and insufflations of

powdered tablets, but its absorption into the systemic circulation of PD patients has not been adequate [65,120]. This may possibly have been because of the alkalinity of rectal secretions, high bacterial content of the rectum, or perhaps because of the absence of a neutral amino acid transport system. Contrary to that, rectal absorption of simple alkyl esters of L-DOPA was found to be greater than that obtained with oral dosing in a study carried out in rats and dogs with the butyl ester prodrug, which showed bioavailabilities of 100 and 32% in rats and dogs, respectively [110].

17. Expert opinion

Much effort has been directed towards the management of PD but a large chasm is yet to be bridged in terms of ultimate efficacy, especially in advanced PD patients. Constant plasma levels of L-DOPA and subsequent continuous dopaminergic stimulation are greatly needed in PD patients. Although intraduodenal infusions have achieved constant plasma levels, their invasiveness limits their use in consideration of the fact that it is a chronic therapy. The transdermal route for L-DOPA is promising but studies have to be undertaken in humans to assess its ability to produce continuous dopaminergic stimulation. Furthermore, the oral route is the preferred route of administration for chronic therapy, thus an oral formulation that is able to achieve constant plasma concentration of L-DOPA will be a significant advancement in the management of PD. From these discussions, the described developments in L-DOPA systems can be summarily compared in terms of their relevant pros and cons, as depicted in **Figure 9**.

In considering the afore-described technologies, one of the sobering facts elicited when considering chronic suppressive maintenance therapy in neurodegenerative disorders such as PD is the often insurmountable presence of the BBB [121] and the considerable side effects of therapies prescribed at present [122]. The vascular endothelial cells, choroid plexus and arachnoid membrane act together to form the barrier between the blood and cerebrospinal fluid for efficient restriction of agents entering the brain [123]. An understanding of the intricacy of the BBB is imperative for the design of techniques to manipulate the barrier for transport of therapeutic agents to the brain for PD management.

An authority in the field, Prof. William Pardridge, wrote in *Drug Discovery Today*: 'Considering the potential size of the global CNS pharmaceutical market, and considering that so few drugs cross the BBB, one would expect that the development of BBB drug delivery technologies would be a high priority in the pharmaceutical industry and in the academic sciences. In fact, there is not a single medium or large pharmaceutical company in the world today that has a BBB-drug-targeting technology program. Even if big pharma wanted to change this situation, there would be no staff to hire because there are so few BBB scientists being trained in academia. In the USA, there is not a single academic neuroscience program that has any emphasis on BBB drug targeting technology ...' [124].

Consequently, in conceptualizing and developing a targeted system for PD management, the obstacle presented by the BBB must be tackled. Enhancement of drug lipophilicity through chemical modification, or drug conjugation with a BBB-specific transport vector have been considered [125]; however, these systems commonly implicate a 1:1 ratio of vector to drug, thus limiting their carrying capacity [126]. The carrying capacity could be vastly improved by incorporation of the drug into particulate systems such as liposomes or polymer nanoparticles. The design of antibody-coated liposomes [127] and mannosylated liposomes [128] has been attempted. Still, studies emanating from these approaches were not entirely convincing [126]. L-DOPA methylester-loaded liposomes formulated by Di Stefano *et al.* [119] have been discussed in this review. More concerted efforts are necessary.

A forward-thinking approach needs to be exercised. Nanotechnology does offer one avenue for the achievement of neuropharmaceutical innovations to enhance the delivery of L-DOPA, and thus PD management. Nanotechnology encompasses engineered materials or devices with the smallest functional organization on the nanometer scale (1 – 100 nm), and can instigate manipulation of complex biological systems such as the BBB with greater selectivity and responsiveness than conventional pharmacological approaches. Nanotechnology has a potentially revolutionary impact on the basic understanding and therapeutic approaches of neuroscience, and thus, pertinently, PD. The power of nanotechnology must be channelled towards the development of nano-enabled drug delivery systems for the treatment of PD, exploiting the nanoscale structures of neural cells. Nano-enabled systems, such as polymeric nanoparticles, are able to protect the drug from degradation in the GIT, bypassing the liver thereby avoiding first-pass metabolism, consequently improving bioavailability. In addition, polymeric nanoparticles are able to remain in the systemic circulation for extended periods, and therefore could target the delivery of L-DOPA to the CNS more effectively [129-131].

Di Stefano *et al.* [132] highlighted that a key challenge in PD therapy is targeted and localized delivery, which will purportedly limit severe side effects, such as psychiatric disturbances and dyskinesia deriving from the distribution of L-DOPA in healthy tissues. The concept of developing drug delivery systems able to target pharmacologically active molecules in close proximity to their site of action is receiving greater attention. Pertinently applicable systems capable of interacting with biological systems at the molecular level with a high degree of specificity for the provision of neuroprotection, and enabling the delivery of drugs and small molecules across the BBB, include liposomes, polymeric or lipidic micro- and nanoparticles, polymeric micelles and dendrimers [132]. In fact, scientists recently developed dendrimers for investigation of their effect on the fibrillation of α-synuclein [133]. The dendrimers redirected α-synuclein to an amorphous

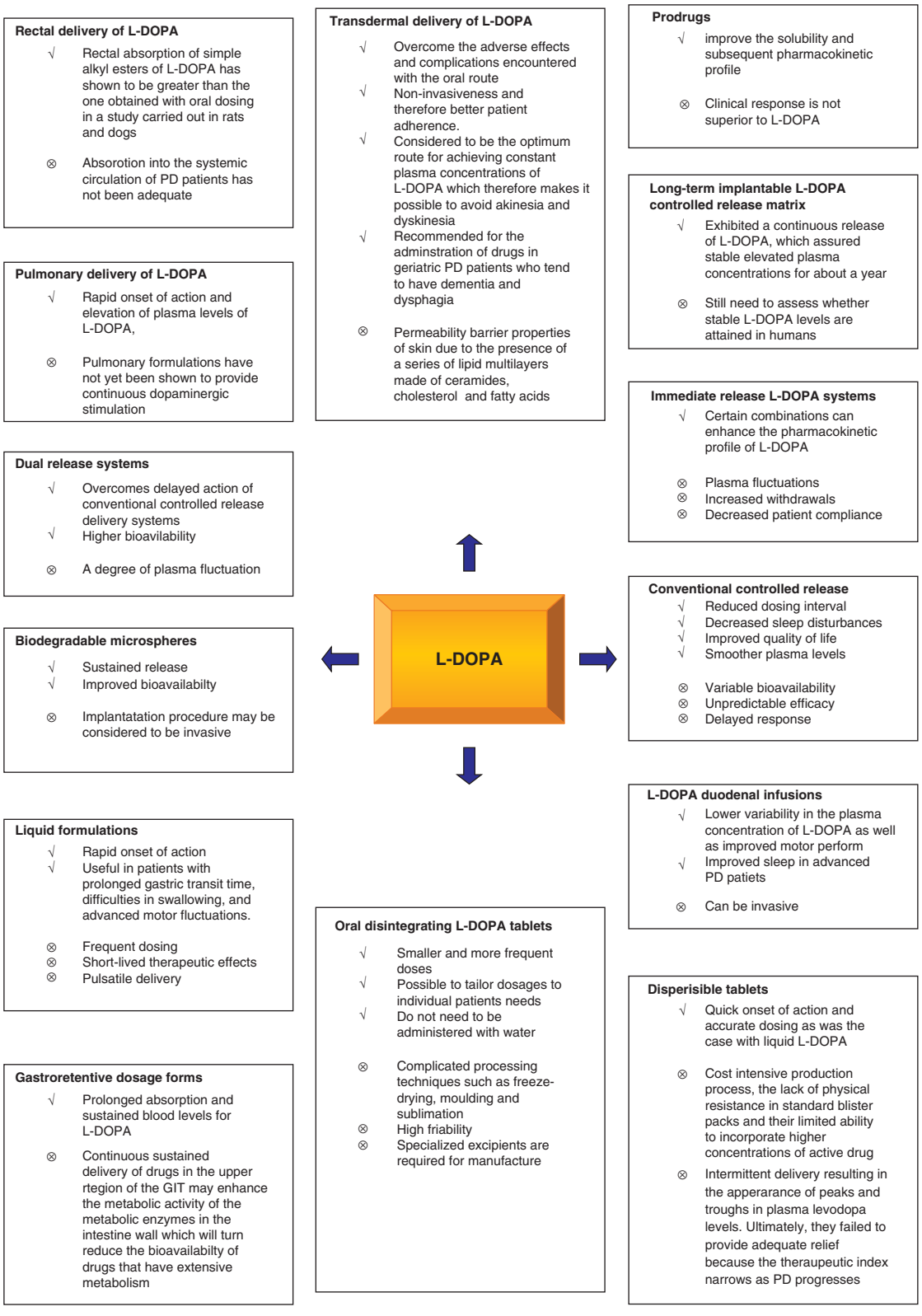

Figure 9. Overview of the pros and cons of the gamut of levodopa delivery systems.

aggregation pathway. It is these α-synuclein oligomers that are also believed to be the cytotoxic species associated with amyloidoses, and compounds such as dendrimers, which reduce the amount of prefibrillar oligomers by inducing amorphous aggregation, may be an attractive alternative preventive approach for PD. Furthermore, the rapid action of the dendrimers on pre-formed fibrils holds an extra therapeutic advantage of removing physiologically stable amyloid deposits already present in patients with PD [133]. The eventual impact of this research has yet to be fully realized through ensuing investigations.

To exploit the nanotechnological approach to its full potential for L-DOPA delivery in PD management, directed strategies are required to modify the bodily distribution of such entities [125]. Proposed properties that would be advantageous for targeted systems include: i) prolonged circulation, thus drug loading and release can be adjusted fairly independently of fluid circulation; ii) favorable tissue distribution, which will be largely lipid dose independent, such that therapeutic dose escalation produces increasing drug effects with minimal changes in pharmacokinetics; and iii) the facilitation of the addition of ligands (targeted to PD biomarkers, for example) or other functionalities to the polymer surface layer through chemical modifications. This will serve to intelligize devised nanosystems through the introduction of targeting capabilities.

Ultimately, the need for the effective delivery of existing agents, such as L-DOPA, for the therapeutic management of PD is thus imperative and should be the focus of extensive research [134-139]. From a pharmaceutical viewpoint, the vast challenges presented by PD must be tackled if we are to take a step forward in its management.

Declaration of interest

The authors state no conflict of interest and have received no payment in the preparation of this manuscript.

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