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Formulation- and Manufacturing-Dependent Pharmacokinetic Behavior and Clinical Outcomes of Immediate- and Extended-Release Sinemet® Dosage Forms

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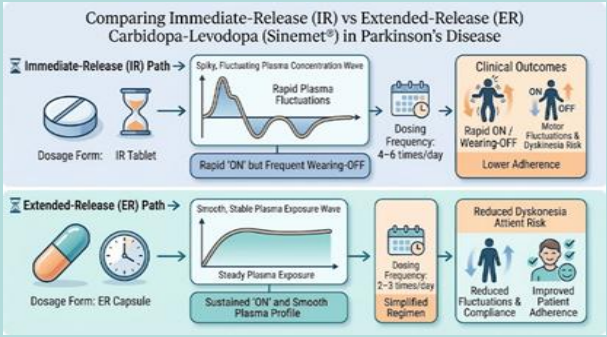
Abstract: Parkinson's disease (PD) is considered a neurodegenerative disorder of the nigrostriatal system. It is characterized by progressive motor dysfunction and treatment-related complications. Levodopa combined with carbidopa remains the cornerstone of therapy. Extended-release formulations may improve treatment stability and adherence. **Objective:** This study was conducted to compare immediate-release (IR) and extended-release (ER) carbidopa-levodopa formulations with respect to pharmacokinetics, clinical outcomes, and treatment adherence. **Methodology:** This observational study included 120 patients with idiopathic PD (65-75 years), who were assigned to two groups (n=60 each) receiving IR or ER formulations. Dose-normalized pharmacokinetic parameters (AUCT/Dose, C_{max}/Dose, C_{avg}/Dose, and T_{max}) were analyzed. Clinical outcomes, including motor fluctuations, dyskinesia, and adherence, were examined over a 6-month follow-up period. Statistical comparisons were performed between the two groups. **Key Findings:** The IR formulation showed a higher C_{max}/Dose (1.2 vs. 0.85, $p < 0.001$) and a shorter T_{max} (1.0 vs. 2.5 h, $p < 0.001$), indicating a faster absorption profile. The ER formulation showed a slightly higher AUCT/Dose (3.2 vs. 3.0, $p = 0.28$) and a lower C_{avg}/Dose (0.4 vs. 0.5, $p = 0.01$), reflecting a more sustained plasma profile. No statistically significant differences were found in motor fluctuations (17% vs. 12%) or dyskinesia (20% vs. 13%). However, treatment adherence was higher in the ER group. **Conclusions:** Although IR and ER formulations demonstrated similar clinical outcomes, the ER formulation was associated with a more stable pharmacokinetic profile and improved patient adherence. **Recommendations:** ER carbidopa-levodopa may be considered when simplified dosing and improved adherence are desired. Larger, long-term studies are needed to confirm its clinical advantages.



Keywords: idiopathic Parkinson's disease, carbidopa-levodopa, pharmacokinetic profile, motor fluctuations, treatment adherence.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder involving progressive loss of dopaminergic neurons in the nigrostriatal pathway of the basal ganglia. It presents with extrapyramidal motor dysfunction, including postural instability, tremor, bradykinesia and rigidity. It is the second most common neurodegenerative disorder after Alzheimer's disease. The primary objective of treating PD is to restore dopaminergic transmission. All medical and minimally invasive neurosurgical treatments are supplementary procedures that replace dopamine in the brain. Levodopa (LD) is the most effective pharmacological treatment for PD. It has been used since the 1960s and is considered the primary medication for PD [1,2]. Studies have found that 60–80% of dopaminergic neurons in the substantia nigra are lost by the advanced or final stages of PD. Dopaminergic neuronal loss at the time of disease onset ranges from 30 to 70% [3]. The treatment with dopamine is complicated by motor fluctuations, including "off time" symptoms, which occur when the medication effects wear off. These fluctuations can also include dyskinesia, which are involuntary movements caused by the medication. Progressive degeneration of dopaminergic neurons and dopamine depletion in late stages of PD lead to the need for higher doses of levodopa [4,5]. Levodopa (LD) can cross the blood-brain barrier (BBB) and is locally converted to dopamine by DOPA decarboxylase. To prevent the conversion of LD to dopamine before it crosses the BBB, LD is typically administered with carbidopa (CD), a peripheral inhibitor that cannot cross the BBB. Since the 1960s, alternative methods have been introduced to release the LD gradually after intake than standard IR tablets. These methods are called extended-release. They reduce dopamine fluctuations, but provide slower

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relief from PD symptoms [5,6]. The concomitant administration of aromatic L-amino acid decarboxylase inhibitors (AADCIs) increases the systemic bioavailability of LD by about three times, which reduces the required therapeutic dose. In late stage of PD, the dopamine release is poorly regulated and lacks efficient reuptake, resulting in more significant fluctuations in plasma dopamine levels after each LD dose. This increases the risk of dyskinesia and OFF-phase [5]. A high-protein diet increases amino acid concentrations, consequently reducing levodopa absorption; therefore, the intake of levodopa should be adapted with the mealtime to increase its therapeutic effect [7]. LD is often combined with CD to increase its effectiveness and reduce side effects. Dyskinesia and motor "on/off" fluctuations are common side effects, as conventional immediate-release oral formulations produce rapid peaks and troughs in plasma levodopa concentrations. The extended-release Sinemet® tablet formulation provides sustained levodopa plasma exposure with reduced concentration variability. This results in fewer daily administrations, fewer motor fluctuations, and less dyskinesia [8,9]. The cornerstone of PD management is maintaining stable dopamine levels in the brain. Despite the various dosage forms of levodopa, oral administration remains the mainstay of clinical practice [10]. The design of oral tablet formulations is critical for controlling drug absorption and systemic concentration profiles. The release characteristics of these formulations play a central role in shaping LD pharmacokinetics and overall therapeutic performance. These profiles are characterized by pharmacokinetic parameters, including C_{max}, T_{max}, and AUC. Thus, these parameters are key indicators for comparing the performance, clinical efficacy, and adverse effects of pharmaceutical dosage forms [11].

Materials and Methods

This is an observational study performed between March 2025 and August 2025, on the patients of idiopathic Parkinson's disease (PD) with duration of diagnosis less than 3 years in the clinic of the professor of neurology Dr. Raad A. Hussein in Baghdad. Patients were consecutively recruited according to the treating physician's clinical decision, reflecting the real-world clinical population without selection based on gender. The aim of the study was to compare IR and ER CD-LD by dividing the 120 patients into 2 groups, 60 patients in each one, the first treated with the IR CD-LD and the second with the ER CD-LD by comparing the plasma LD levels, the motor fluctuation with dyskinesia and the other adverse effects, as well as patient compliance.

In this study, we initially started with 150 patients aged 65-75 years with Parkinson's disease who were treated with CD-LD (Sinemet®) therapy only. Patients receiving antiparkinsonian therapy other than LD/CD, such as dopamine agonists or MAO inhibitors, were not included in this study. Of the included 150 patients, 30 patients were excluded. The exclusions were due to loss of follow-up or the presence of comorbid conditions such as cerebrovascular disease that might affect the study results. The disease duration for all the patients was 3 years and below, therefore, patients with idiopathic PD for more than 3 years were excluded. The gender distribution was 85 males and 35 females. All patients were treated with carbidopa/levodopa (Sinemet®). Baseline demographic and clinical characteristics were recorded for all included patients.

Study Groups and Treatment Protocol: Patients in each group were followed up for 6 months and were divided into two groups (60 patients in each one):

Group I: IR CD-LD: Patients received IR CD-LD at a total daily dose ranged 800–1200 mg divided 4–6 doses/day.

Group II: ER CD-LD: Patients received ER CD-LD at a daily dose of 1000–1200 mg divided into 2–3 doses/day.

The selected CD-LD dose ranges in our study were based on those typically used in moderately advanced Parkinson's disease. These dose ranges were found to provide adequate symptom control with fewer side effects, such as motor fluctuations. This approach balanced clinical realism, safety, and the ability to meaningfully compare ER and IR levodopa formulations. The IR and ER formulations differ in their drug-release mechanisms, with IR providing rapid release and ER formulations designed to sustain drug release over an extended period. To account for differences in dosing between groups, pharmacokinetic parameters were normalized to the administered dose.

Patients were evaluated clinically every month throughout the 6-month study period and biochemically by blood analysis every 3 months. Patients were instructed to take levodopa one hour before meals to minimize the effect of food on drug absorption. Clinical assessments included motor fluctuations, dyskinesia, treatment compliance, and the occurrence of other adverse effects. Regarding plasma LD levels, the two groups were compared on the basis of dose-normalized exposure by calculating pharmacokinetic (PK) endpoints and normalizing them to dose: AUCт/Dose, C_{max}/Dose, C_{avg}/Dose.

Steady-state sampling approach: Plasma concentration profiles were evaluated for IR Sinemet® administered 4–6 times daily and ER Sinemet® administered every 8 hours. We used plasma collection with an EDTA anticoagulant. Samples were then centrifuged and stored at −80 °C. Levodopa (LD) and carbidopa (CD) concentrations were quantified using a validated LC–MS/MS method with calibration curves then non-compartmental analysis (NCA) for dense sampling. All patients were receiving stable doses of levodopa prior to sampling, ensuring steady-state conditions during pharmacokinetic analysis. At steady state, AUCт, C_{max}, C_{min}, fluctuation index, and peak-to-trough ratio were measured. Dose-normalized AUC and C_{max} values were compared (e.g., AUC/dose, C_{max}/dose) and included the dose as a covariate in a PopPK or ANCOVA model. Plasma samples were collected at: 0 (pre-dose), 0.5, 1, 2, 4, 6, and 8 for IR Sinemet®, and 10 h for ER Sinemet®. The difference in sampling time points between IR and ER formulations was based on their distinct pharmacokinetic profiles and dosing intervals. Levodopa concentrations were quantified using LC–MS/MS (±3-OMD/carbidopa) and NCA was performed for each

patient; we compared AUC and C_{max} using log-scale models; and reported fluctuation and trough coverage. Statistical comparisons between IR and ER groups were performed using independent-samples t-test for normally distributed variables and Mann–Whitney U test for non-normally distributed variables (T_{max}). Normality of the data distribution was assessed using appropriate methods. Statistical analysis was performed using SPSS software (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

Non-compartmental pharmacokinetic analysis (NCA) is used to compute PK endpoints such as AUC_{τ}, C_{max}, and C_{avg}. Dose normalization is then applied by dividing each PK endpoint by the administered dose (AUC_{τ}/Dose, C_{max}/Dose). CD-LD plasma levels were measured every 3 months to assess drug bioavailability for both formulations. Blood samples were analyzed using liquid chromatography tandem mass spectrometry. The pharmacokinetic parameters evaluated included AUC, C_{max}, and t_{max}. AUC was studied and interpreted using the linear or logarithmic trapezoidal methods when concentrations were increasing or decreasing, respectively.

To assess motor dysfunction and dyskinesia, the Unified Dyskinesia Rating Scale and the Disability Scale (Part 4) were considered.

Results

The present study included 120 patients who completed the study. 30 patients were excluded due to loss of contact or follow-up or due to other comorbidities, such as cerebrovascular accidents. The 120 included patients were divided into two groups. The patients were distributed into 60 patients in each group, 85 were male and 35 were female. The male-to-female ratio is 2.4:1. The male-to-female ratio in each group was based on the treating physician's clinical decision. The patients were between 65 and 75 years old. The body weight ranged from 70–105 kg, and the mean BMI was 25.1 kg/m^2 (range, 20.0–31.2 kg/m^2). IR CD-LD was administered at doses ranging from 800–1200 mg/day in 4–6 divided doses. ER CD-LD was administered at doses ranging from 1000–1200 mg/day in 2–3 divided doses. Plasma carbidopa-levodopa levels were evaluated every three months in both groups throughout the study. Motor fluctuation and dyskinesia were assessed according to the Unified Dyskinesia Rating Scale and Disability Scale (Part 4). The baseline demographic and clinical characteristics of the study participants are presented in Table 1.

IR Sinemet® was rapidly absorbed, with T_{max} around 1 h. LD plasma concentrations decreased, dropping to less than 10% of the peak level within 5 h. With ER Sinemet®, plasma concentrations reached an initial plateau at around 1 h, with a T_{max} noted at around 2.5 h. Plasma levels were below 10% of the peak level after 10 h. The Dose-normalized C_{max} (C_{max}/D) for IR Sinemet® was 1.2 compared to 0.85 for ER CD-LD. The AUC_{τ}/dose was 3 and the C_{avg}/dose was 0.5 for the IR CD LD, while the AUC_{τ}/dose was 3.20 and the C_{avg}/dose was 0.4 for the ER CD LD. These findings demonstrate that ER CD-LD exhibits a slightly higher dose-normalized exposure (AUC_{τ}/Dose) and a lower dose-normalized peak (C_{max}/Dose) than IR CD-LD. In addition, ER CD-LD remained above its dose-normalized average concentration (C_{avg}/Dose) for a longer duration (~4 h) than IR CD-LD (~2.5 h). This finding suggests that the ER formulation provides a more stable LD plasma profile and reduced peak-to-trough fluctuations than the IR formulation (Fig. 1; Tables 2–4). A statistical comparison of dose-normalized pharmacokinetic parameters between the IR and ER groups is presented in Table 5.

Table 6 shows the pharmacokinetic and clinical comparisons between Sinemet® IR and Sinemet® ER for Parkinson's patients taking 200 mg and 400 mg of levodopa, respectively.

After 6 months, the incidence of motor fluctuations in the immediate-release group was approximately 17% and dyskinesia occurred in 20% of patients. In the extended-release group, motor fluctuation occurred in 12% and dyskinesia occurred in 13% as shown in Table 7.

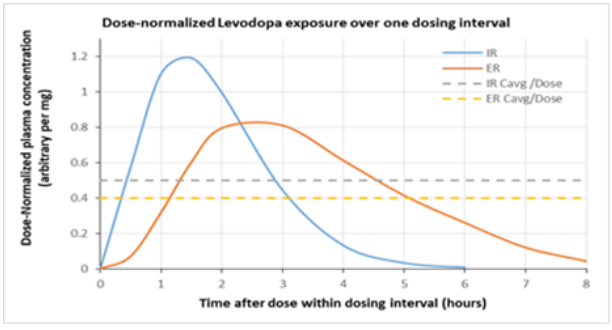

Figure (1): Comparison of C_{max}, T_{max} and AUC for IR CD-LD and ER CD-LD. (AUC = AUC_{τ}/Dose). (Immediate Release (IR), τ=6 h, C_{max}/Dose=1.2, T_{max}=~1.2, AUC_{τ}/Dose=3.0, C_{avg}/Dose=0.5). (Extended Release (ER), τ=8 h, C_{max}/Dose=0.85, T_{max}= ~2.5, AUC_{τ}/Dose=3.2, C_{avg}/Dose=0.4).

Table (1): Baseline demographic and clinical characteristics of the study participants.

Variable	IR group (n=60)	ER group (n=60)	Total (n=120)
Number of patients	60	60	120
Age (years)	65-75	65-75	65-75
Male, n (%)	43 (71.67)	42 (70)	85 (70.8%)
Female, n (%)	17 (28.33)	18 (30)	35 (29.2%)
Disease duration (years)	≤3	≤3	≤3
Body weight (kg)	70–105	70–105	70–105
BMI (kg/m²)	25.1	25.1	25.1

Table (2): Comparative Pharmacokinetics of LD Following ER and IR CD-LD.

Parameter	IR CD-LD	ER CD-LD
Levodopa dose (mg)	200	400
T_{max} (h)	~1.0	~2.5
Time to <10% of C_{max} (h)	~5	~10
Dose-normalized C_{max} (C_{max}/Dose)	1.2	0.85
Terminal half-life, $t_{½}$ (h)	1.6–1.9	1.6–1.9
C_{max}/C6h ratio	Higher	Lower

Table (3): Compare AUC, C_{max} and C_{avg} for both IR CD-LD and ER CD-LD.

Form.	Daily frequency	Dose (mg/day)	(mg/dose)	τ(h)	AUCτ/Dose (ng·h/mL/mg)	C_{max}/Dose (ng/mL /mg)	C_{avg}/Dose (ng/mL/mg)
LD IR	4-6×/day	800–1200	200	6	3.0	1.2	0.5
LD ER	2-3×/day	1000–1200	400	8	3.2	0.85	0.4

Table (4): Pharmacokinetic properties comparison of IR CD-LD vs ER CD-LD.

Parameter (dose-normalized)	IR LD	ER LD
Typical daily dose (mg/day)	800–1200	1000–1200
Dosing frequency	4–6× daily	~3× daily
Relative bioavailability	Higher (consider as reference 1)	Lower (1.07)
$AUC_{0–τ}$ per 100 mg dose	Lower (300)	Slightly Higher (320)
C_{max} per 100 mg dose	Higher (120)	Lower (85) (↓ ~25–35%)
T_{max}	Rapid (~1 h)	Delayed, broadened (~2.5 h)
C_{min} per dosing interval (Cτ)	Lower	Higher
Peak-to-trough fluctuation index, (Cmax−Cτ)/Cavg	High (~2.34)	Low (~1.88)
Time >50% of C_{max} (per dose)	~1.5–2 h	~3.0–3.5 h
Plasma concentration profile	Spiky	Flattened

Table (5): Statistical comparison of dose-normalized pharmacokinetic parameters between IR and ER groups.

Parameter	IR LD	ER LD	p-value
AUCτ/Dose	3.0 ± 0.8	3.2 ± 0.9	0.28
C_{max}/Dose	1.2 ± 0.3	0.85 ± 0.2	< 0.001
C_{avg}/Dose	0.5 ± 0.1	0.4 ± 0.08	0.01
T_{max} (h)	1.0 (1.0-1.5)	2.5 (2-3)	< 0.001

Table (6): Demonstrated pharmacokinetic and clinical comparison of Sinemet® IR versus Sinemet® ER for a Parkinson patient taking 200 mg vs 400 mg of levodopa, respectively.

Category	Parameter	Sinemet® IR (25/200 mg)	Sinemet® ER (100/400 mg)
Formulation	Levodopa dose Carbidopa dose	200 mg 25 mg	400 mg 100 mg
LD Bioavailability	Absolute bioavailability Systemic LD exposure (AUC) Dose for equal exposure	~95-100% (reference) ~200 mg IR-equivalent 1x	~70-75% of IR ~280-300 mg IR-equivalent ~ 1.3-1.5x IR
Plasma LD Levels	T_{max} C_{max} Fluctuation Duration above threshold	~1 h Higher Marked Peak-trough ~3-4 h	~2.5 h ~30-50% lower Smoother, flatter ~6-8 h
Clinical Effects	Onset of action Peak effect Duration Dyskinesia risk Wearing-off	Fast Strong Short Higher More likely	Slow Moderate Long Lower Less likely
Overall	Dose equivalence	Reference	~1.4X IR

Table (7): Clinical Outcomes and Complications Comparison (IR vs. ER Levodopa)

Parameter / Clinical Outcome	IR Levodopa (n = 60)	ER Levodopa (n = 60)	Chi-square (χ^2)	p-value
Daily Dosage Range	800–1200 mg/day	1000–1200 mg/day	—	—
Dyskinesia Status (Grade 3–4)			0.54	0.46 (NS)
• Present	12 (20.0%)	8 (13.3%)		
• Absent	48 (80.0%)	52 (86.7%)		
Disability Status (Grade 3–4)			0.27	0.60 (NS)
• Present	10 (16.7%)	7 (11.7%)		
• Absent	50 (83.3%)	53 (88.3%)		

NS: Not Statistically Significant (p > 0.05).

Clinical outcomes and complications are summarized in Table 7. No statistically significant differences were observed between IR and ER levodopa regarding dyskinesia (20.0% vs. 13.3%, $X^2 = 0.54$, $p = 0.46$) or disability status (16.7% vs. 11.7%, $X^2 = 0.27$, $p = 0.60$).

Table 8 shows the observed clinical correlation between plasma LD profiles and motor response (ON/OFF time) for the IR and ER levodopa groups.

Table (8): Clinical correlation of plasma LD profiles and motor response (ON/OFF time) for IR- and ER levodopa groups.

Clinical parameter	IR LD	ER LD
Daily ON time (without troublesome dyskinesia)	Reduced	Increased
OFF time	Increased	Reduced
Wearing-off between doses	Common	Less frequent
Morning akinesia control	Often insufficient	Improved
Dyskinesia risk	Higher peak-related risk	Lower peak-related risk
Motor response predictability	Variable	High
Need for rescue dosing	More frequent	Less frequent
Patient adherence	Reduced (high pill burden)	Improved

The most common adverse effects (AEs) were nausea, vomiting, headache and hallucination. There were no significant differences in adverse effects between the two groups (Table 9).

Table (9): Incidence of systemic adverse effects in the IR vs ER group.

(%) Adverse effect	(%) IR LD	(%) ER LD
Nausea and vomiting	25%	12%
Orthostatic hypotension	12%	8%
Hallucinations	9%	5%

Nausea and Vomiting: Chi-square (χ^2) = 3.56, Chi-square p-value = 0.059, Fisher's exact p-value = 0.097 Trend toward higher incidence in IR, but not statistically significant at $\alpha = 0.05$. Orthostatic Hypotension: Chi-square (χ^2) = 0.37, Chi-square p-value = 0.543, Fisher's exact p-value = 0.762. No significant difference between ER and IR. Hallucinations: Chi-square (χ^2) = 1.08, Chi-square p-value = 0.298, Fisher's exact p-value = 0.491. No statistically significant difference (Table 10).

Table (10): Statistical analysis of adverse effects in the IR and ER groups.

Adverse Effect	χ^2	Chi-square p	Fisher p
Nausea/Vomiting	3.56	0.059	0.097
Orthostatic Hypotension	0.37	0.543	0.762
Hallucinations	1.08	0.298	0.491

Medication adherence was higher in the ER group throughout the study. The difference was statistically significant ($p < 0.001$) and correlated with reduced daily dosing frequency.

ER group: 90% of patients demonstrated good adherence.

IR group: 65% of patients demonstrated good adherence.

Discussion

In the present study, IR CD-LD was administered to patients with idiopathic PD at a dose of 200 mg 4–6 times daily, whereas ER Sinemet® was administered at a dose of 400 mg 2–3 times daily. Plasma level analysis showed that IR CD-LD was rapidly absorbed with T_{max} at around 1 h compared to around 2.5 h for ER CD-LD (time to < 10% of C_{max} was around 5 h for IR CD-LD compared to 10 h for ER CD-LD. The C_{max} of plasma LD after 400 mg ER Sinemet® was lower than the mean C_{max} observed after 200 mg IR Sinemet®. Clinically, IR CD-LD demonstrated a faster onset and stronger peak effect compared with ER CD-LD. However, it was associated with a shorter duration of action, a higher risk of dyskinesia, and a higher incidence of wearing off motor complication. ER CD-LD doses should be approximately 1.3 to 1.5 times higher than IR doses to achieve an equivalent exposure. ER CD-LD doses are most effective in reducing wearing-off and dyskinesia. The effect of CD plateaus at approximately 70–100 mg/day, so the extra CD in ER formulation does not proportionally increase benefit, but helps ensure full peripheral decarboxylase inhibition.

The IR CD-LD 200 mg: produces pulsatile dopaminergic stimulation, characterized by rapid absorption and a rapid increase in plasma LD levels until reaching the maximum concentration (C_{max}) at a maximum concentration time (T_{max}) of approximately 1 h after administration, thereby increasing the risk of LD-induced dyskinesia. This peak is followed by a rapid decline in concentration, leading to a motor "off" state within 3-4 h. Conversely, IR CD-LD provides rapid symptom relief but is associated with a shorter duration of action and greater fluctuation-related complications.

The ER CD-LD 400 mg: produces continuous dopaminergic stimulation with a slower gradual rise, lower peak, and broader curve, resulting in sustained levels for around 10 h, with fewer wearing-off complications and dyskinesia-related side effects compared to IR formulations. The systemic bioavailability of ER CD-LD is approximately 70-75% of that of IR CD-LD. Therefore, despite prolonged exposure, higher ER doses are required to achieve comparable systemic LD exposure due to reduced bioavailability and lower peak plasma concentrations. Consequently, a 400 mg dose of ER CD-LD yields LD exposure equivalent to approximately 280–300 mg of IR CD-LD. Despite the lower peak concentration, ER CD-LD produces prolonged plasma levels and, in some cases, yields 40–50% greater total exposure than IR CD-LD 200 mg. Clinically, ER CD-LD formulations are useful for nighttime dosing and managing early-morning akinesia due to their sustained plasma concentrations and reduced wearing-off effects. The area under the curve (AUC) for ER CD-LD showed a significant reduction in intra-day plasma variability. From a pharmacokinetic perspective, the reduced fluctuation observed with ER CD-LD linked to improved motor stability. The IR group demonstrated significantly greater peak–trough fluctuation compared with the ER group ($p < 0.001$). With IR CD-LD given 4-6×/day (total 800–1200 mg/day), the plasma curve shows rapid rise to a peak (C_{max}) after each dose, followed by a relatively fast decline because LD has a short effective half-life when given orally. The repeated dosing creates multiple high peaks and deep troughs across the day, this contributes to motor "on/off" fluctuations in advanced disease. The ER CD-LD given 3×/day (total 1000–1200 mg/day), the concentration–time profile is less "spiky", it reaches therapeutic levels relatively quickly, and maintains concentrations for longer, so the curve is broader with smaller peak-to-trough swings.

The pharmaceutical formulations of the tablet of CD-LD explain the pharmacokinetic difference between the 2 dosage formula. Administering IR CD-LD tablets results in a higher C_{max}, reflecting the conventional tablet formulation designed for rapid

disintegration and immediate dissolution. The absence of release-retarding excipients enables rapid drug release through the quick disintegration of tablets in gastrointestinal fluids. This results in a higher effective absorption rate constant (k_a) and the sharp post-dose concentration increase that are characteristic of IR formulations [12,13]. In contrast, the controlled-release matrix system of ER CD-LD tablets modulates drug release through polymer swelling and diffusion-controlled release mechanisms. This results in a lower C_{max} per dose at steady state and a broader systemic exposure profile, despite the larger unit dose [12,14]. From a clinical perspective, this higher IR peak does not result in a better therapeutic response because controlling Parkinson's symptoms is primarily dependent on maintaining LD above its therapeutic threshold rather than achieving transient peak concentrations. Once plasma levels surpass this threshold, additional increases primarily lead to adverse effects related to the peak rather than improved efficacy [13,14]. Consequently, a lower but sustained ER peak is sufficient for a comparable clinical benefit. This explains why there are no meaningful differences in patient response, despite differences in C_{max} and fluctuation [12,14]. These results indicate that the observed differences in C_{max}, T_{max}, and plasma concentration profiles between IR and ER formulations are largely attributable to differences in their formulation design and drug release behavior.

The observed C_{max} values are closely linked to the corresponding T_{max} results. The short T_{max} of approximately 1 h after taking IR CD-LD tablets reflects the tablets' rapid disintegration and immediate dissolution of the drug, resulting in a high absorption rate constant (k_a) across dosing intervals. In contrast, the approximately 2.5 h delayed T_{max} observed with ER CD-LD results directly from the modified-release tablet architecture. In this architecture, drug molecules diffuse through hydrated polymer matrices or coated layers prior to systemic absorption, thereby slowing the effective absorption rate [12,13]. This prolonged-release process shifts peak plasma concentrations to later time points, demonstrating the sustained influence of formulation design on absorption kinetics. From a clinical perspective, differences in T_{max} primarily affect the timing of peak plasma levels rather than overall daily symptom control. Under steady-state conditions with repeated dosing, overlapping plasma concentration profiles are achieved throughout the day. This ensures that the delayed peak associated with ER CD-LD does not compromise therapeutic efficacy. These results are consistent with the comparable clinical outcomes reported between IR and ER formulations [14].

Regarding the dose-normalized area under the curve (AUC)-time profile (AUCт/dose), which reflects systemic exposure per administered dose and is related to the relationship AUC = F × Dose/CL, the ER CD-LD formulation exhibited a slightly higher exposure than the IR CD-LD tablets (3.2 *vs.* 3.0 ng•h/mL/mg). This indicates sustained LD availability over time despite the slower release kinetics of the ER system [12,13]. The extended-release matrix architecture likely supports continuous drug dissolution within the intestinal absorption window and reduces rapid loss associated with gastrointestinal transit and preserves the extent of absorption [13]. From a clinical perspective, the area under the curve (AUC) provides the strongest explanation for the comparable therapeutic outcomes observed between formulations because it reflects overall dopaminergic stimulation throughout the dosing interval. When systemic exposure is smoothly sustained or similar, symptom control remains equivalent despite differences in peak concentrations. This is consistent with reported clinical findings for ER versus IR Sinemet® [14]. The results are in agreement with those of previous pharmacokinetic studies, which showed higher C_{max} and shorter T_{max} for IR formulations and prolonged exposure (AUC) for ER formulations [12,14]. However, previous studies have primarily focused on specific aspects of carbidopa/levodopa formulations. For example, Hauser et al. studied short-term pharmacodynamic responses after single-dose administration under controlled conditions, without evaluating long-term clinical outcomes or treatment adherence [15]. Espay et al. gave expert recommendations about dose conversion and optimization of extended-release carbidopa/levodopa in clinical practice, rather than presenting original patient-based clinical data [14]. In addition, previous long-term studies between immediate-release and controlled-release formulations mostly focused on clinical efficacy without detailed pharmacokinetic evaluation [16].

In contrast, the present study provides an integrated assessment of dose-normalized pharmacokinetic parameters, clinical outcomes, and treatment adherence over a 6-month follow-up period in a real-world clinical setting.

Adamiak et al. demonstrated age/plasma concentration and Tmax correlation for LD. Such correlation between the age of the patients and plasma concentration of LD had not been interpreted and observed in our study [17]. Conti et al. demonstrated gender differences in LD pharmacokinetics in patients with PD who were not previously treated with LD. Specifically, they found that women had higher plasma concentrations of LD, a higher AUC, and a higher C_{max} than men. The researchers also found that dyskinesia was more common in female patients. The AUC for levodopa was 27% higher in females. Conti et al. study indicated that female patients required a 25% lower weight-normalized dose of levodopa to achieve the same plasma level as male patients [18]. In the present study, a higher proportion of male patients was observed. This finding is consistent with the known epidemiology of Parkinson's disease, which is more prevalent in males. Furthermore, patients were recruited consecutively from a real-world clinical setting without gender-based selection, which likely reflects the natural distribution of the disease in the studied population. Such gender difference in plasma LD concentration has not been interpreted or observed in the present study. LeWitt et al. and Poewe et al. demonstrated that the duration of plasma LD concentration above the therapeutic threshold depends on the dosage, and the peak concentrations of LD. However, decreased LD efficacy and a consequent threefold increase in the daily dose have been reported when ER preparations are compared with IR preparations [19,20]. Hauser et al. found that the oral ER CD-LD (IPX066) produces a therapeutic effect similar to that of IR Sinemet®, with a longer duration. These findings are consistent with the results of the present study [12]. Hiemke et al. and Rosebraugh et al. reported that, the reduced Fluctuation Index (FI) is driven by attenuation of C_{max} and sustained trough levels. Therefore, a low FI minimizes C_{max}-related adverse effects [21,22]. The study of Olanow et al. and Pirtošek et al. found that, the ER form of CD-LD IPX066 regimens provided a LD C_{max} similar to or lower than that provided by IR regimens [23,24]. In the present study, we found that plasma LD levels were affected by food and gastric emptying and that LD dose administration on empty stomach resulted in better absorption and therapeutic plasma concentrations. This result is consistent with the findings

of Turcano et al., who found that ingested proteins compete with the transport of LD in the gastrointestinal tract and the brain. Therefore, patients should avoid high-protein meals at the time of drug administration or take the medication before meals [25]. Milekovic et al. found that LD dose failures caused by poor LD absorption due to delayed gastric emptying or a prolonged "off" period caused by unresponsive striatal receptors. Therefore, protein should be avoided at the time of drug administration, or LD should be taken on an empty stomach [26].

In the present study, 17% of the patients in the IR group developed significant motor disability in the 6th month of the follow-up, compared to 12% of the patients who developed motor disability of those in the ER group. Regarding dyskinesia, 20% of the patients in the IR group developed dyskinesia grade 3-4 during the 6th month of the follow-up, compared with 13% of patients in the ER group who developed grade 3–4 dyskinesia. There was no statistically significant difference between IR and ER LD formulations in the incidence of grade 3–4 dyskinesia ($p = 0.46$) and also no statistically significant difference between the immediate release CD LD and the extended release CD LD groups in the motor disability ($p = 0.60$). Although fewer complications were observed in the ER group, these differences did not reach statistical significance. In addition, the relatively high attrition rate (20%) may have introduced potential bias, as patients who were lost to follow-up were not formally compared with those who completed the study. In the present study, patients with idiopathic Parkinson's disease within the first three years of diagnosis were intentionally selected. This period was chosen because patients are more likely to be managed with single-drug (monotherapy) regimens, carbidopa/levodopa, allowing a clearer evaluation of formulation-related effects without confounding from combination therapies. In addition, focusing on an early stage of the disease helps reduce variability associated with advanced disease progression. This approach aimed to minimize the variability associated with advanced disease stages, where differences in disease severity, dosing regimens, and motor complications are more evident. However, Parkinson's disease is inherently progressive, and some degree of clinical heterogeneity may still exist even within the first three years. Therefore, this factor should be considered a potential limitation of the study. The motor fluctuations are driven by oscillations in the plasma LD concentration. ER CD-LD provides more sustained plasma concentrations and improves motor stability primarily by reducing peak-to-trough fluctuation and consequently reducing the sub-therapeutic troughs and OFF periods, and also reducing the supratherapeutic peaks and consequently dyskinesia. The IR group showed higher peak–trough variability, fluctuated plasma concentrations and consequently more subtherapeutic troughs and OFF periods, and also more supratherapeutic peaks and dyskinesia.

Kelly et al. and Lieberman et al. stated that the risk factors for motor dysfunction in PD include younger age at the time of disease diagnosis, longer disease history, more severe non-motor symptoms, LD dose, responsiveness, and overall disease severity [27,28]. In comparison to our study result of 10-20% of motor complication in the first 3 years of PD, Turcano *et al.* and Prange *et al.* found that motor complications occurred in up to 30 to 40 percent of patients during the first five years of treatment and in 60 percent or more by 10 years [25,29]. Ahlskog *et al.* found that the incidence of motor dysfunction is approximately 3% after 1 year of treatment, 41% after 6 years, and 70% after 9 years [30].

In the study of Müller *et al.* dyskinesia occurred in 6.9% of patients [31]. These results compared to 20% in the IR group and 13% in the ER group who were developed dyskinesia in the present study. Zhang *et al.* found that the prevalence of dyskinesia within 10 years of onset was 59% in Europe and the United States, and 8.6% in a Chinese study [32]. Hechtner et al. found that dyskinesia was the same in the sustained release and IR groups [33]. They had been found that the motor fluctuations affect 50% of patients after 5 years and up to 90% after 10 years of LD therapy; dyskinesias occur in ~30–50% by 5 years and ~60–80% by 10 years, especially in younger patients [33].

The common systemic adverse effects other than motor dysfunction and dyskinesia are nausea and vomiting, headache and hallucination. Nausea and vomiting were reported in 25% in the IR group compared to 12% in the ER group. Chi-square (χ^2) = 3.56, Chi-square p-value = 0.059, Fisher's exact p-value = 0.097 trend toward higher incidence in IR, but not statistically significant at $\alpha = 0.05$. Headache and orthostatic hypotension are a cardiovascular adverse effect of excess dopamine therapy. They occurred in 12% in IR group and in 8% in ER group. Chi-square (χ^2) = 0.37, Chi-square p-value = 0.543, Fisher's exact p-value = 0.762. No significant difference between ER and IR. Hallucination were reported in 9% in IR group and in 5% in ER group. Chi-square (χ^2) = 1.08, Chi-square p-value = 0.298, Fisher's exact p-value = 0.491. No statistically significant difference. Although the statistical analysis of our results instituted that there was no statistically significant differences in adverse effects between the 2 groups, but we think that the smaller group numbers was a causative factor that lead to such insignificant statistical difference. As expected, compliance was higher in the ER group throughout the study, where 90% of patients in ER group demonstrated good adherence compared to 65% of patients in the IR group who demonstrated good adherence. The difference was statistically significant ($p < 0.001$) and correlated with reduced daily dosing frequency. In Hauser et al.'s study, the incidence of adverse events was as follows: insomnia (3% of ER CD-LD vs. 1% of IR CD-LD); nausea (3% on ER CD-LD vs. 2% on IR CD-LD); and falls (3% on ER Sinemet® vs. 2% on IR CD-LD) [12]. Hauser et al. found that the most commonly reported adverse events in the ER IPX203 group compared with the IR CD-LD group, were nausea (4.3% vs 0.8%) and anxiety (2.7% vs. 0%) [34]. Foltynie et al. stated that long-term administration of LD raises plasma homocysteine levels associated with stroke, heart attack, and dementia [35]. De Bie et al. found that increasing dopaminergic replacement therapy has orthostatic hypotension, impulsive behaviors, and visual hallucinations [36]. Navailles et al. said that stimulation of DA receptors throughout the parkinsonian brain may cause psychotic symptoms due to stimulation of dopamine receptors in mesolimbic and mesocortical brain regions [37].

Conclusion

In this study of patients with idiopathic PD, both IR and ER Sinemet® provided nearly the same control over six months. No statistically significant differences were observed in motor fluctuations or dyskinesia. The results were compared between the two dosage formulations. The 2–3-times-daily dosing regimen with ER Sinemet® offers advantages in simplifying dosing regimens, improving adherence, as well as better compliance and rather fewer side effects, particularly gastric upset symptoms. The tablet formulation design and manufacturing characteristics of IR and ER systems play a critical role in modulating drug release behavior and,

consequently, pharmacokinetic performance. ER Sinemet® was associated with better treatment adherence. Adherence and adverse effects were evaluated descriptively and dosing was individualized. We could not demonstrate a significant therapeutic advantage of ER over IR Levodopa regarding reduction in motor dysfunction and dyskinesia. The findings of the present study are limited by the small sample size and short follow-up period.

Recommendations:

Clinical practice: ER formulations may be considered when simplified dosing schedules and improved patient adherence are desired.

Future research: Larger, long-term studies are needed to confirm the clinical advantages of ER formulations and their impact on motor complications.

Disclosure Statements

Ethics approval and consent to participate

Ethical Considerations: The study protocol was reviewed and approved by the Institutional Ethics Committee of Aliraqia University. All procedures were conducted in accordance with relevant ethical standards. Written informed consent was obtained from all participants prior to inclusion in the study. Eligible participants were patients between 65-75 years diagnosed with idiopathic PD.
To assess the motor dysfunction and dyskinesia, the Unified Dyskinesia Rating Scale and the Disability Scale (Part 4) were considered.

Consent for publication

"Not applicable"

Availability of data and materials

"The raw data required to reproduce these findings are available in the body and illustrations of this manuscript."

Author's contribution

The authors confirm their contributions to the paper as follows: study conception and design: Al-Shaikh Hamed RHMA, Al Jumaily MHFH and Hussein RA; Data collection: Al Jumaily MHFH and Hussein RA; theoretical calculations and modeling: Al-Shaikh Hamed RHMA, Al Jumaily MHFH; data analysis and validation: Al-Shaikh Hamed RHMA, Al Jumaily MHFH; draft manuscript preparation: Al-Shaikh Hamed RHMA, Al Jumaily MHFH and Hussein RA. All authors reviewed the results and approved the final version of the manuscript.

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Conflicts of interest

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