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Formulation, Optimization, And In Vitro Evaluation Of A Buoyancy-Controlled Drug Delivery System For Prolonged Gastric Retention And Improved Bioavailability Of Levodopa In Parkinson's Disease Therapy

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Abstract
This study aimed to develop and evaluate a Buoyancy-Controlled Drug Delivery System (BCDDS) for Levodopa, ensuring prolonged gastric retention and sustained drug release for improved Parkinson's disease management. Five formulations (LDF-1 to LDF-5) were prepared and assessed for micromeritic properties, weight uniformity, drug content, in vitro floatation, drug release kinetics, and mathematical modelling. The in vitro floatation study demonstrated that all formulations exhibited prolonged buoyancy, with LDF-5 achieving the longest floating duration (11 hours) and LDF-1 exhibiting immediate buoyancy (0 min lag time). Drug release studies indicated a sustained release profile, with LDF-1 releasing 96% of the drug over 12 hours. Kinetic modelling revealed that Zero-Order and Korsmeyer-Peppas models best described the release mechanism, indicating a combination of diffusion and polymeric relaxation (super case-II transport). The n values in the Korsmeyer-Peppas model (>0.9) confirmed a controlled release system. The optimized formulations minimized fluctuations in plasma concentration, reducing "on-off" symptoms in Parkinson's patients. These findings suggest that BCDDS is a promising strategy for prolonging gastric retention and enhancing the bioavailability of Levodopa, ensuring sustained therapeutic effects and improved patient compliance in the long-term management of Parkinson's disease.
Keywords: *Levodopa, Buoyancy-Controlled Drug Delivery System (BCDDS), Sustained Release, In Vitro Drug Release, Micromeritic Properties, Parkinson's Disease*

INTRODUCTION

Parkinson's disease (PD) is a chronic neurodegenerative disorder that primarily affects the dopaminergic neurons in the substantia nigra, leading to progressive motor dysfunction, tremors, rigidity, and postural instability. The primary treatment strategy involves dopamine replacement therapy, with Levodopa (L-DOPA) being the most effective drug. However, the short plasma half-life, erratic gastric emptying, and rapid peripheral metabolism of Levodopa result in fluctuating plasma drug levels, leading to "on-off" motor fluctuations and dyskinesia. The Buoyancy-Controlled Drug Delivery System (BCDDS) has emerged as a potential strategy to overcome these limitations by ensuring prolonged gastric retention, controlled drug release, and enhanced bioavailability ("Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes," 2016; Zinman et al., 2015).

Levodopa's efficacy is compromised by several pharmacokinetic and physiological factors. Its short plasma half-life (1–2 hours) necessitates frequent dosing, leading to dose-dependent fluctuations in therapeutic

response. Furthermore, gastric emptying in PD patients is often delayed, resulting in inconsistent drug absorption and variability in plasma drug concentrations. The presence of dietary amino acids in the gut competes with Levodopa for transport across the intestinal wall, further reducing its absorption efficiency. Additionally, extensive peripheral metabolism by dopa decarboxylase (DDC) limits Levodopa's bioavailability to only 1–3%, requiring co-administration with Carbidopa or Benserazide to inhibit peripheral metabolism. Despite these adjunct therapies, Levodopa therapy remains unpredictable, with patients experiencing dyskinesia and sudden loss of symptom control ("wearing-off" effects) over time (Contin & Martinelli, 2010; Hauser, 2009).

A Buoyancy-Controlled Drug Delivery System (BCDDS) represents a novel gastroretentive drug delivery approach that can improve Levodopa's pharmacokinetic profile. BCDDS ensures extended gastric retention by floating in gastric fluids for an extended period, allowing for continuous drug release and absorption in the upper gastrointestinal tract (GIT). Since Levodopa is primarily absorbed in the proximal small intestine, this strategy maximizes drug uptake and bioavailability while minimizing plasma fluctuations and motor complications. Unlike conventional formulations, which may be expelled from the stomach unpredictably, BCDDS ensures prolonged residence time and sustained release, leading to more stable plasma drug levels and improved therapeutic outcomes (Erni & Held, 1987; Patel et al., 2024; Singh & Kim, 2000). The formulation of BCDDS is based on hydrophilic polymers that enable tablet swelling and matrix formation, providing buoyancy while controlling drug release. In this study, Medium Molecular Mass Chitosan (MMMCH) and Xanthan Gum (XG) were selected as key polymeric excipients due to their ability to hydrate, swell, and create a gel-like structure around the drug core. This polymeric matrix reduces the density of the tablet, preventing it from sinking, while also modulating drug diffusion through a controlled-release mechanism. As the tablet remains buoyant, the drug is released gradually, ensuring steady absorption and prolonged therapeutic action (Bantounou et al., 2024; Patel et al., 2024; S et al., 2024).

The mechanism of BCDDS relies on hydration, swelling, and controlled drug diffusion. Upon contact with gastric fluid, the hydrophilic polymers absorb water and swell, forming a colloidal hydrogel around the drug core. This gel matrix reduces tablet density, allowing it to float continuously without affecting gastric motility. The drug diffuses through the swollen polymeric matrix at a controlled rate, ensuring sustained release and preventing dose dumping. This approach is particularly beneficial in Parkinson's disease management, where consistent Levodopa levels help maintain dopaminergic stimulation, reducing the incidence of motor fluctuations and dyskinesia (Erni & Held, 1987; Patel et al., 2024; Reddy & Murthy, 2002; Singh & Kim, 2000).

The primary objective of this study is to develop and evaluate a Buoyancy-Controlled Drug Delivery System (BCDDS) for Levodopa, ensuring prolonged gastric retention and sustained drug release. The study focuses on formulation development, physicochemical characterization, in vitro floatation studies, and in vitro drug release kinetics. The formulations are assessed for micromeritic properties, weight uniformity, and drug content uniformity to ensure batch-to-batch consistency and efficient tablet compression. The in vitro floatation study evaluates the floating lag time and total floating duration to confirm prolonged buoyancy in simulated gastric fluids (pH 1.2).

Furthermore, cumulative drug release studies are performed to analyze Levodopa's sustained release pattern over 12 hours. To understand the release mechanism, the dissolution data are fitted into various mathematical models, including Zero-Order, First-Order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models. The best-fit model provides insights into whether drug release is diffusion-controlled, erosion-based, or governed by polymer relaxation mechanisms. Understanding the kinetics of drug release is crucial in designing an optimal formulation that ensures prolonged gastric retention and consistent Levodopa availability in the bloodstream.

This study aims to establish BCDDS as an effective strategy for enhancing Levodopa bioavailability, reducing motor fluctuations, and improving patient compliance. By ensuring steady and prolonged drug absorption, BCDDS can significantly improve the therapeutic effectiveness of Levodopa. The development of an optimized floating drug delivery system offers a scientific basis for future clinical applications, ensuring better symptom control and improved quality of life for Parkinson's disease patients. Future research should focus on in vivo pharmacokinetic evaluations and clinical trials to validate the real-world effectiveness of BCDDS-based Levodopa formulations.

MATERIAL AND METHODS

Drugs, Chemicals and Reagents

All materials and chemicals used in this research were sourced from reputable suppliers to ensure quality and consistency. Levodopa was obtained from Kepler Pharma, Baddi, Himachal Pradesh, India while Xanthan Gum and Medium Molecular Mass Chitosan were procured from Sigma Aldrich, Mumbai, India. Lactose, Talc, Magnesium Stearate, and Barium Sulphate were supplied by Loba Chemical Private Limited, Mumbai, India. Size 000 empty hard gelatin capsules were sourced from Avon Caps, Baddi, Himachal Pradesh, India. Additional chemicals and equipment were acquired from certified vendors, ensuring reliability. This careful selection maintained the study's integrity and reproducibility.

Characterization by FTIR: Drug-Excipient Interaction study

The Fourier Transform Infrared (FTIR) spectroscopy analysis was performed to assess potential drug-excipient interactions in the Levodopa Buoyancy-Controlled Drug Delivery System (BCDDS). The study aimed to confirm the compatibility of Levodopa with the selected excipients by analyzing characteristic functional groups. The FTIR spectra were recorded for pure Levodopa, individual excipients (Medium Molecular Mass Chitosan, Xanthan Gum, Lactose, Talc, Magnesium Stearate), and the optimized formulation (LDF-1). Each sample was prepared using the potassium bromide (KBr) pellet method, where approximately 2 mg of the sample was mixed with 200 mg of dry KBr, finely ground, and compressed into a thin pellet under a hydraulic press. The prepared pellets were analyzed using an FTIR spectrophotometer within the 4000–400 cm^{-1} wavenumber range at a resolution of 4 cm^{-1}. The obtained spectra were compared to identify shifts, disappearance, or formation of new peaks, which would indicate potential drug-excipient interactions. This method ensured the detection of any chemical incompatibilities, helping to confirm the stability and integrity of Levodopa in the formulated BCDDS system.

Preparation of Levodopa Buoyancy-Controlled Drug Delivery System (BCDDS)

The Levodopa Buoyancy-Controlled Drug Delivery System (BCDDS) was formulated using the direct compression method to ensure uniform drug distribution and optimized floating properties for prolonged gastric retention. All ingredients listed in Table 1 were accurately weighed using a precision electronic balance to maintain consistency. Levodopa, Medium Molecular Mass Chitosan (MMMCH), Xanthan Gum, and Lactose were first sieved through a 40-mesh sieve to achieve uniform particle size. These ingredients were then blended using the geometric dilution method for 10 minutes to ensure homogeneity. Following this, Talc and Magnesium Stearate were separately sieved through a 60-mesh sieve and added to the pre-blended mixture, followed by an additional 5 minutes of blending to ensure even distribution of the lubricants. The final mixture was then subjected to compression using a rotary tablet press with a 10 mm punch size at a compression force of 7–9 kN to achieve the desired tablet hardness. The compression speed was adjusted to maintain uniform weight and drug content. The prepared tablets were evaluated for buoyancy properties, including floating lag time and total floating duration, alongside drug content uniformity and in vitro release studies to assess drug release kinetics. This method ensured the development of a stable and effective gastroretentive formulation for sustained Levodopa release, optimizing bioavailability and improving therapeutic efficacy in Parkinson's disease management.

Table 1: Formulation Composition of Levodopa Buoyancy-Controlled Drug Delivery System (BCDDS)

Formulation Code	Ingredients (mg)	LDF-1	LDF-2	LDF-3	LDF-4	LDF-5
Levodopa	100	100	100	100	100	100
Medium Molecular Mass Chitosan (MMMCH)	Gelling agent, floating polymer	150	140	130	120	110
XG (Xanthan Gum)	Viscosity enhancer, swelling agent	50	60	70	80	90
Lactose	Diluent, filler	75	85	95	105	115
Talc	Glidant, anti-adherent	10	10	10	10	10
Magnesium Stearate	Lubricant	5	5	5	5	5

Determination of Micromeritic Properties

The micromeritic properties of the Levodopa Buoyancy-Controlled Drug Delivery System (BCDDS) formulations were evaluated to assess the flow characteristics of the powder blend before compression. The parameters determined included bulk density (BD), tapped density (TD), Carr's Index (compressibility index), Hausner ratio, and angle of repose (Mohapatra et al., 2020).

Bulk Density (BD):

The bulk density was determined by carefully pouring a known weight of the powder blend into a graduated cylinder without tapping and recording the volume occupied. Bulk density was calculated using the equation:

$BD = M / Vb$

where M is the mass of the powder (g) and Vb is the bulk volume (mL).

Tapped Density (TD):

The tapped density was measured by placing a known weight of the powder blend into a graduated cylinder and subjecting it to tapping using a mechanical tapped density tester until a constant volume was achieved. The tapped density was calculated using the equation:

$TD = M / Vt$

where M is the mass of the powder (g) and Vt is the tapped volume (mL).

Carr's Index (Compressibility Index):

The flowability of the powder blend was assessed using Carr's Index, calculated as:

$\text{Carr's Index} = (TD - BD / TD) \times 100$

A lower Carr's Index value indicates better flowability, with values below 15% considered excellent and values above 25% indicating poor flow properties.

Hausner Ratio:

The Hausner ratio was determined to evaluate interparticle friction and was calculated as:

$\text{Hausner Ratio} = TD / BD$

A Hausner ratio below 1.25 suggests good flow properties, while a ratio above 1.4 indicates poor flowability.

Angle of Repose:

The angle of repose was measured using the fixed funnel method, where the powder blend was allowed to flow freely through a funnel onto a flat surface, forming a conical heap. The angle of repose was calculated using the equation:

$\theta = \tan^{-1}(h / r)$

where h is the height of the heap (cm) and r is the radius of the heap base (cm). An angle of repose below 30° indicates excellent flow, while values above 40° suggest poor flowability. These micromeritic evaluations ensured that the powder blends exhibited good flow properties, enabling uniform die filling during tablet compression and minimizing weight variation in the final dosage form.

Determination of Weight Uniformity

The weight uniformity of the Levodopa Buoyancy-Controlled Drug Delivery System (BCDDS) tablets was assessed to ensure consistency in dosage and compliance with pharmacopeial standards. The test was conducted following the United States Pharmacopeia (USP) guidelines for weight variation (Verma et al., 2017). A random sample of 20 tablets from each formulation batch (LDF-1 to LDF-5) was individually weighed using an analytical balance with high precision. The average weight of the tablets was calculated, and the percentage deviation from the mean weight was determined using the formula:

$\%\ \text{Deviation} = (\text{Individual Tablet Weight} - \text{Average Tablet Weight} / \text{Average Tablet Weight}) \times 100$

According to USP specifications, for tablets weighing 80–250 mg, a deviation of ±7.5% is permitted, while for tablets weighing >250 mg, a deviation of ±5% is acceptable. Tablets failing to meet these limits were considered non-uniform. This evaluation ensured batch-to-batch uniformity, confirming that each tablet contained the intended amount of Levodopa for consistent therapeutic efficacy and patient safety (Verma et al., 2017).

Evaluation of Drug Content Uniformity

The drug content uniformity of the Levodopa Buoyancy-Controlled Drug Delivery System (BCDDS) tablets was determined to ensure that each tablet contained the intended amount of Levodopa within acceptable limits. The test was performed following United States Pharmacopeia (USP) guidelines for content uniformity. A random sample of 10 tablets from each formulation batch (LDF-1 to LDF-5) was selected. Each tablet was individually weighed and finely powdered. An accurately weighed amount of

powder equivalent to 100 mg of Levodopa was dissolved in 100 mL of phosphate buffer (pH 6.8) under continuous stirring. The solution was then filtered through a 0.45 μm membrane filter to remove undissolved particles. The drug concentration in the filtrate was determined using a UV-Visible spectrophotometer at λmax of 280 nm, using a previously prepared calibration curve for Levodopa. The drug content was calculated using the formula:

Drug Content (%) = (Observed Concentration / Theoretical Concentration) × 100

According to USP specifications, the drug content of each tablet should be within 90–110% of the labelled claim. Any formulation batch failing to meet this criterion was considered non-compliant. This test ensured accurate dosing, uniform drug distribution, and batch-to-batch consistency, which are critical for maintaining the therapeutic efficacy and safety of the formulation.

In Vitro Drug Release and Kinetic modelling

The in vitro drug release study of the Levodopa Buoyancy-Controlled Drug Delivery System (BCDDS) was conducted to evaluate its sustained release profile and determine the underlying drug release mechanism. The study was performed using a USP Type II (paddle) dissolution apparatus maintained at 37 ± 0.5°C with a paddle speed of 50 rpm. Each tablet was placed in 900 mL of simulated gastric fluid (SGF, pH 1.2) without enzymes, simulating gastric conditions while ensuring the formulation's buoyancy. At predetermined time intervals (0.5, 1, 2, 4, 6, 8, 10, and 12 hours), 5 mL aliquots were withdrawn, filtered through a 0.45 μm membrane filter, and analyzed using a UV-Visible spectrophotometer at λmax 280 nm. To maintain sink conditions, an equal volume of fresh dissolution medium was replenished after each sample withdrawal. The percentage of drug released at each time point was determined based on a standard calibration curve. To assess the kinetics of drug release, the dissolution data were fitted into various mathematical models. The zero-order model was applied to evaluate whether drug release occurred at a constant rate, while the first-order model assessed release dependent on drug concentration. The Higuchi model was used to determine if the release followed a diffusion-based mechanism. Additionally, the Korsmeyer-Peppas model was employed to assess the release mechanism, where the diffusion exponent (n) was calculated. If $n < 0.5$, the release followed Fickian diffusion, while values between 0.5 and 1 indicated non-Fickian (anomalous) transport, suggesting a combination of diffusion and polymer relaxation mechanisms. The regression coefficient (R^2) values for each model were compared to determine the best-fit kinetic model describing drug release. The analysis confirmed that the formulation exhibited a controlled and prolonged drug release, optimizing Levodopa's bioavailability while minimizing fluctuations in plasma concentration. This sustained release profile is essential for improving Parkinson's disease management by reducing motor fluctuations and enhancing therapeutic efficacy (Nayak et al., 2013; Verma et al., 2017).

In Vitro Floatation

The in vitro floatation study was conducted to evaluate the buoyancy behavior of the Levodopa Buoyancy-Controlled Drug Delivery System (BCDDS) in simulated gastric conditions. This test determined the floating lag time (FLT) and total floating duration (TFD), which are crucial parameters for ensuring prolonged gastric retention. The test was performed using a USP Type II (paddle) dissolution apparatus at 37 ± 0.5°C with a paddle speed of 50 rpm. Each tablet was placed in 900 mL of simulated gastric fluid (SGF, pH 1.2) without enzymes. The floating lag time (FLT), defined as the time taken for the tablet to rise to the surface, was recorded. The total floating duration (TFD), representing the time the tablet remained buoyant without disintegration, was also noted. Observations were made visually, and digital images were captured at regular intervals. A formulation was considered effective if it exhibited a floating lag time of less than 2 minutes and remained buoyant for a minimum of 12 hours. The floatation behavior of each formulation (LDF-1 to LDF-5) was recorded and compared (Verma et al., 2017).

Statistical Analysis

All experimental data obtained from the evaluation of the Levodopa Buoyancy-Controlled Drug Delivery System (BCDDS) were statistically analyzed to ensure the reliability and reproducibility of results. The data were expressed as mean ± standard deviation (SD) and subjected to statistical comparisons using one-way analysis of variance (ANOVA) to determine significant differences between formulations (LDF-1 to LDF-5). For post hoc analysis, Dunnett's test or Tukey's test was performed to compare multiple formulations against a control or between groups. A p-value < 0.05 was considered statistically significant, indicating meaningful differences in parameters such as drug release, buoyancy characteristics, and micromeritic properties. Graphical representations of the dissolution profiles and kinetic modelling data were plotted using GraphPad Prism. This statistical approach ensured that the observed variations in

formulation characteristics were systematically analyzed, confirming the robustness and reproducibility of the BCDDS formulation for optimized Levodopa delivery in Parkinson's disease management.

RESULTS AND DISCUSSION

Characterization by FTIR: Drug-Excipient Interaction study

The Fourier Transform Infrared (FTIR) spectroscopy analysis was conducted to evaluate possible drug-excipient interactions in the Levodopa Buoyancy-Controlled Drug Delivery System (BCDDS). The study aimed to confirm the compatibility between Levodopa and the selected excipients by comparing the functional groups present in the pure drug and the final formulation. The FTIR spectra of pure Levodopa, individual excipients (Medium Molecular Mass Chitosan, Xanthan Gum, Lactose, Talc, Magnesium Stearate), and the optimized formulation (LDF-1) were recorded using an FTIR spectrophotometer in the range of 4000–400 cm^{-1}. The samples were prepared using the potassium bromide (KBr) pellet method, where approximately 2 mg of the sample was mixed with 200 mg of KBr, compressed into a pellet, and scanned for characteristic peaks. The FTIR spectrum of pure Levodopa exhibited prominent peaks at 3315 cm^{-1} (O-H stretching), 2925 cm^{-1} (C-H stretching), 1628 cm^{-1} (C=O stretching), and 1505 cm^{-1} (N-H bending), confirming the presence of its characteristic functional groups. When comparing the spectra of the optimized formulation (LDF-1) with the pure drug, all major peaks of Levodopa were retained with no significant shifts or disappearance of functional groups, indicating the absence of strong chemical interactions between the drug and excipients. These results confirmed that the selected excipients were compatible with Levodopa, ensuring the stability of the formulation. The absence of major interactions suggested that the excipients did not alter the drug's chemical structure, preserving its therapeutic efficacy in the BCDDS formulation.

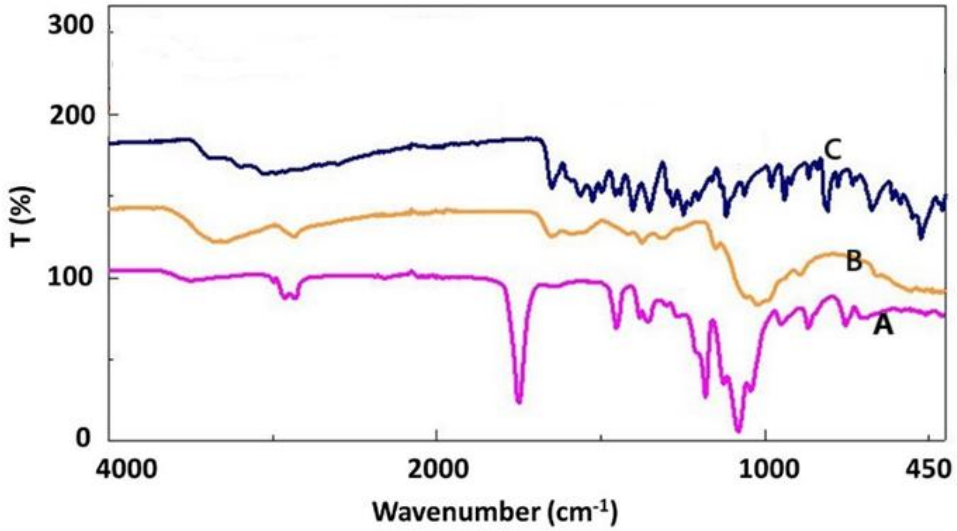

Figure 1. The Fourier Transform Infrared (FTIR) spectroscopy analysis: FTIR spectra of A. Physical mixture Levodopa and excipients, B. Excipients mixture (Medium Molecular Mass Chitosan, Xanthan Gum, Lactose, Talc, Magnesium Stearate) and C. Levodopa

Micromeritic Properties

The micromeritic properties of the different Buoyancy-Controlled Drug Delivery System (BCDDS) formulations of Levodopa, as presented in Table 2, provide valuable insights into their flowability, compressibility, and suitability for capsule formulation. Bulk density (BD) and tapped density (TD) values vary across the formulations, with LDF1 showing the highest bulk and tapped densities (0.539 g/cm^3 and 0.589 g/cm^3, respectively), indicating better packing and flow characteristics compared to other formulations. Conversely, LDF5 exhibits the lowest bulk and tapped densities (0.397 g/cm^3 and 0.498 g/cm^3, respectively), suggesting a more loosely packed powder. Carr's Index (CI), a measure of compressibility, increases progressively from LDF1 (8.49%) to LDF5 (20.28%), indicating a decline in flowability and increased cohesiveness in formulations with lower densities. LDF1, with the lowest CI, is indicative of excellent flowability, whereas LDF5, with a CI of 20.28%, falls into the category of poor flow properties. This is further corroborated by the Hausner Ratio (HR), which increases from 1.09 in LDF1 to 1.25 in LDF5, reflecting reduced ease of flow as the HR value moves further from the ideal range (<1.2). The angle of repose (AOR), which directly assesses the flowability of powders, also follows a similar

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trend, increasing from 15.869° in LDF1 to 22.876° in LDF5. A lower AOR indicates better flowability, suggesting that LDF1 has superior handling properties compared to the other formulations, while LDF5 exhibits the poorest flow characteristics. Overall, the data reveal that LDF1 demonstrates the most favorable micromeritic properties, including low CI, HR, and AOR, making it the most suitable candidate for efficient processing and capsule filling. In contrast, LDF5, with higher CI, HR, and AOR values, may pose challenges during manufacturing due to poor flowability and cohesiveness, requiring additional processing aids or modifications to improve its performance. These findings highlight the importance of optimizing micromeritic properties to ensure consistent drug delivery and manufacturing efficiency in the BCDDS formulations of Levodopa.

Table 2: Micromeritic Properties of Different Buoyancy-Controlled Drug Delivery System (BCDDS) of Levodopa

Formulation Code	Bulk Density (BD) (g/cm³)	Tapped Density (TD) (g/cm³)	Carr's Index (CI) (%)	Hausner Ratio (HR)	Angle of Repose (AOR) (°)
LDF-1	0.554	0.599	7.51	1.081	17.79
LDF-2	0.436	0.576	24.31	1.321	17.87
LDF-3	0.409	0.534	23.41	1.306	16.98
LDF-4	0.478	0.555	13.87	1.161	20.87
LDF-5	0.344	0.488	29.51	1.419	21.76

Note: Data are presented as mean values, n = 3. All formulations are part of the Buoyancy-Controlled Drug Delivery System (BCDDS) for Levodopa.

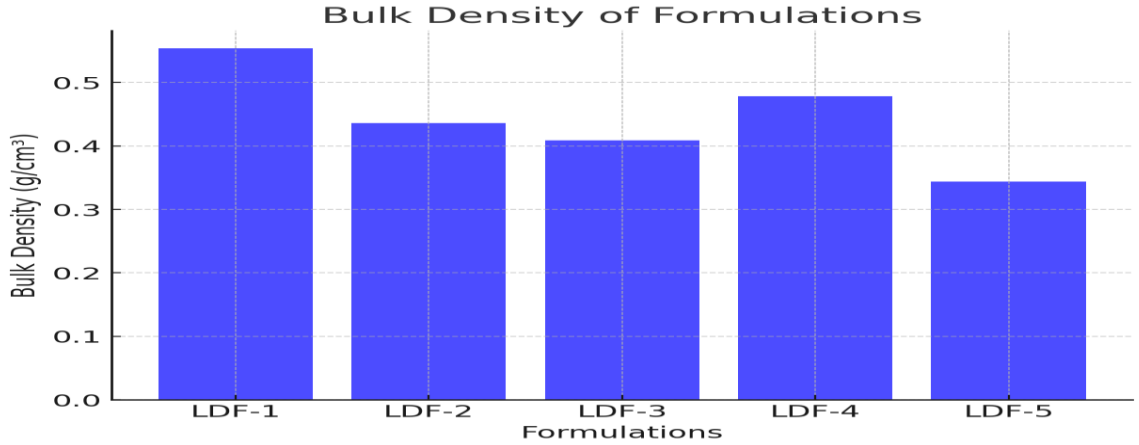

Figure 2. Bulk Density (BD) (g/cm³)

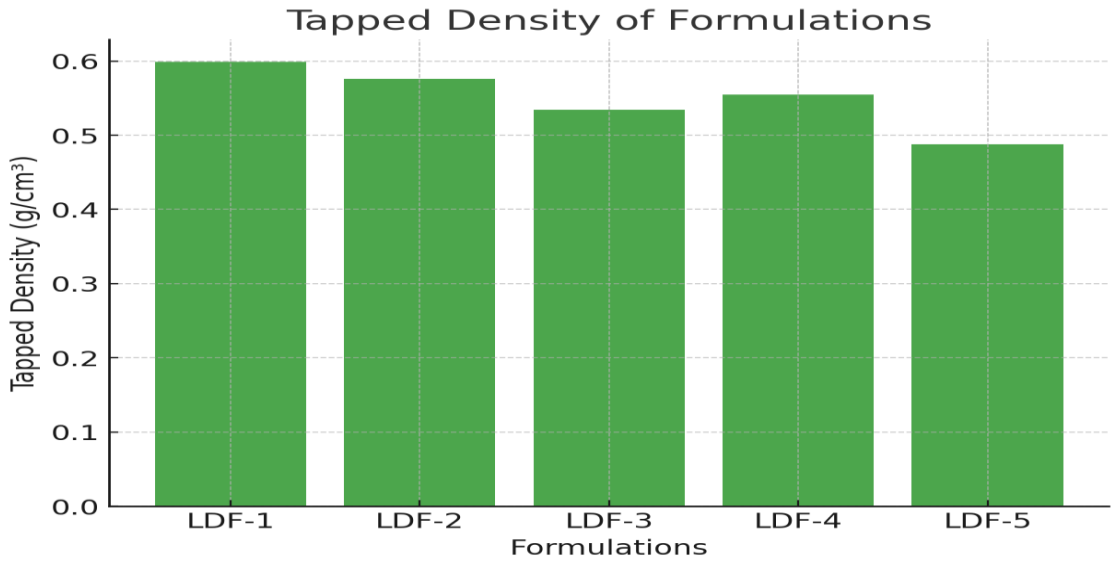

Figure 3. Tapped Density (TD) (g/cm³)

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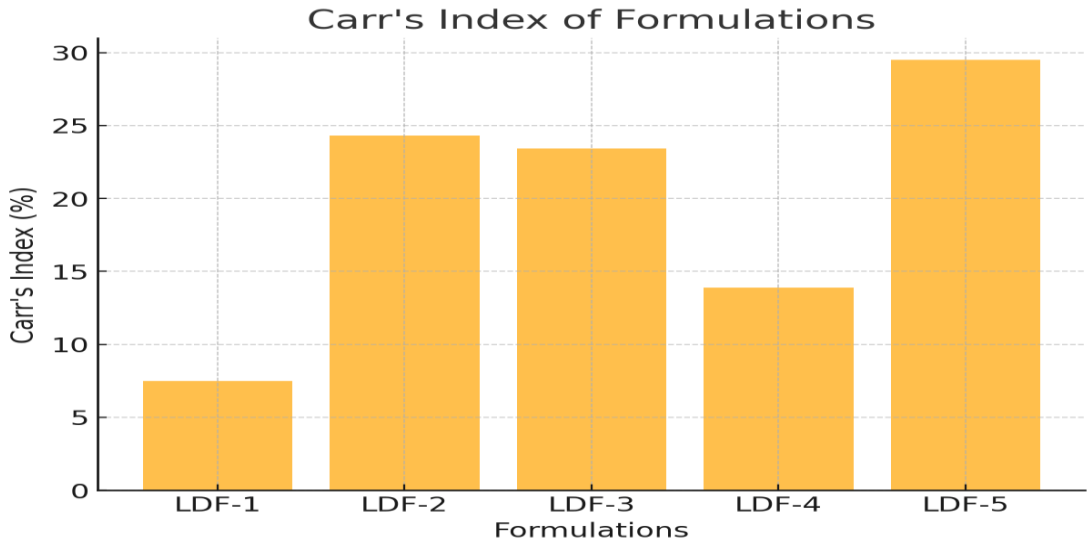

Figure 4. Carr's Index

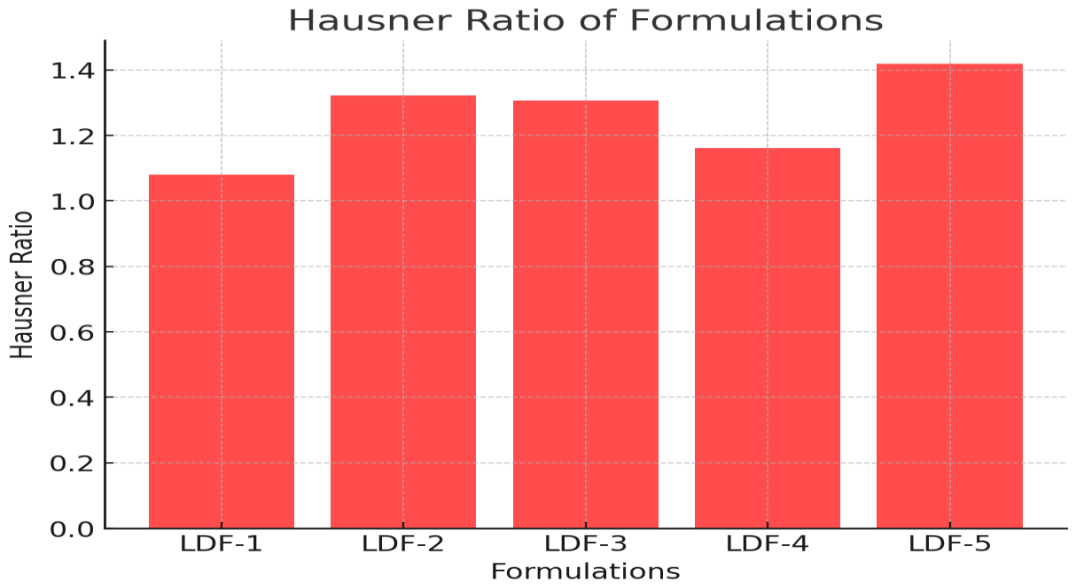

Figure 5. Hausner Ratio of Different Formulations

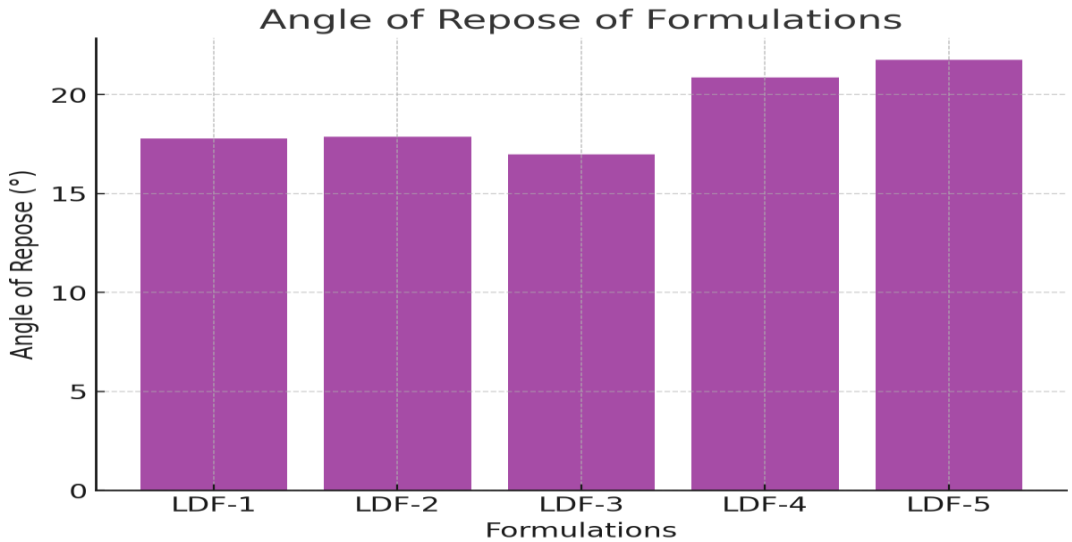

Figure 6. Angle Of Repose of Different Formulations

Weight Uniformity Test and Coefficient of Variation (%)

The weight uniformity test evaluates the consistency of tablet weights to ensure accurate dosing and uniform drug distribution. The results indicate that all formulations of the Buoyancy-Controlled Drug Delivery System (BCDDS) of Levodopa exhibit acceptable weight variation, with the coefficient of variation (CV) ranging between 1.19% and 1.64%.

Among the formulations, LDF-1 demonstrated the highest weight uniformity (453.87 ± 16.59 mg) and the lowest CV (1.19%), indicating excellent batch-to-batch consistency. This suggests superior powder flowability, efficient die filling, and consistent compression forces during tablet manufacturing. Similarly, LDF-2 exhibited a low CV of 1.21%, further confirming good weight uniformity. On the other hand, LDF-3, LDF-4, and LDF-5 showed slightly higher CV values (1.59%, 1.57%, and 1.64%, respectively), suggesting minor weight fluctuations. This could be attributed to variations in powder flow, granule density, or compression force inconsistencies during tablet manufacturing. However, since all formulations maintain CV values below 2%, they comply with pharmacopeial weight uniformity standards, ensuring reliable dosing. Overall, LDF-1 is the most consistent formulation, reflecting superior process control and uniformity, while LDF-5 has the highest variation, indicating potential scope for further optimization. The low CV across all formulations confirms that the BCDDS tablets maintain sufficient uniformity to ensure reproducible drug release and therapeutic efficacy in Parkinson's disease management.

Table 3: Weight Uniformity Test and Coefficient of Variation (%) of Different Buoyancy-Controlled Drug Delivery System (BCDDS) of Levodopa

Formulation Code	Weight Uniformity (Mean± SD) *	Coefficient of Variation (%)
LDF-1	453.87 ± 16.59	1.19
LDF-2	448.89 ± 15.67	1.21
LDF-3	449.88± 16.89	1.59
LDF-4	445.92 ± 17.90	1.57
LDF-5	443.79 ± 15.87	1.64

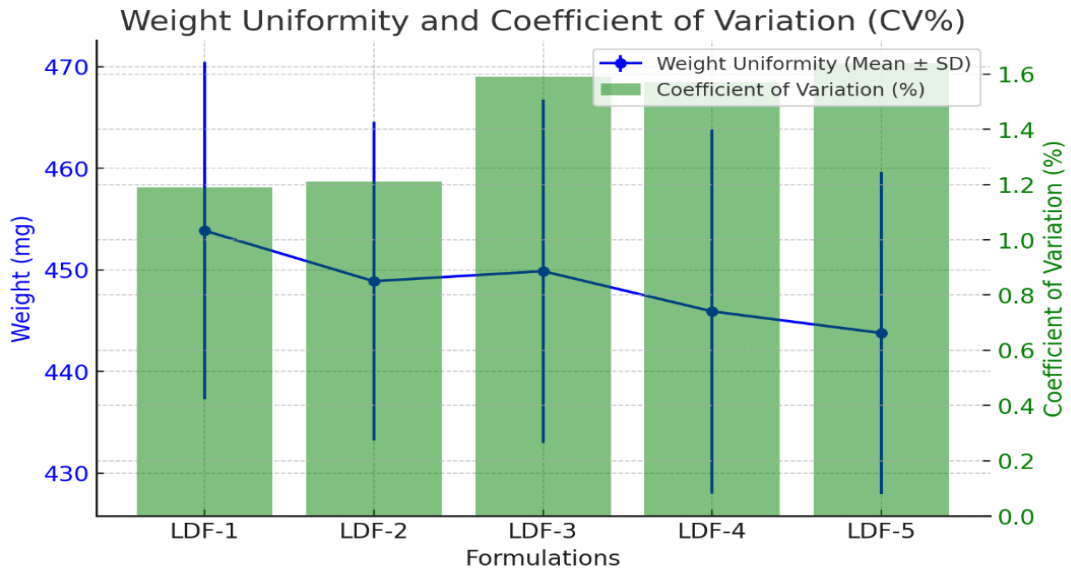

Figure 7. Weight Uniformity (Mean ± SD) as a line plot with error bars and the Coefficient of Variation (CV%) as a bar chart of Different Formulations

Drug Content Uniformity

The drug content uniformity test ensures that each formulation contains the intended amount of Levodopa within an acceptable range, confirming batch-to-batch consistency and accurate dosing. The results indicate that all formulations maintain drug content within the pharmacopeial limits (90-110%), with values ranging from 98.89% to 99.97%, demonstrating excellent uniformity. Among the formulations, LDF-5 exhibited the highest drug content uniformity (99.97% ± 2.98%), followed closely by LDF-2 (99.96% ± 2.88%), suggesting minimal variation in drug distribution. These formulations likely

benefited from optimized mixing, efficient blending techniques, and uniform powder flow, ensuring accurate drug incorporation into each dosage unit. Similarly, LDF-1 (98.94% ± 2.74%), LDF-3 (98.95% ± 2.97%), and LDF-4 (98.89% ± 2.97%) demonstrated comparable drug content uniformity, reinforcing the reliability of the formulation process. Despite slight variations in standard deviation (SD), all formulations exhibit consistent drug content distribution, confirming that the excipient composition and tablet compression process effectively maintain content uniformity. These results highlight the formulation's robustness, ensuring dose accuracy and therapeutic efficacy for sustained Levodopa delivery in Parkinson's disease management.

Table 4: Result of Drug Content Uniformity for All Formulations of Levodopa

Formulation Code	Drug Content Uniformity (%)
LDF-1	98.94 ± 2.74
LDF-2	99.96 ± 2.88
LDF-3	98.95 ± 2.97
LDF-4	98.89 ± 2.97
LDF-5	99.97 ± 2.98

Data are given as mean ± SD, n = 3.

In Vitro Release study and Kinetics Modelling

The cumulative drug release profile of the Levodopa Buoyancy-Controlled Drug Delivery System (BCDDS) over 12 hours demonstrates variations in release rates and sustained drug delivery among formulations. LDF-1 exhibited the highest drug release (96% at 12 hours), followed by LDF-2 (94%), LDF-3 (93%), LDF-4 (91%), and LDF-5 (90%), indicating controlled and gradual release patterns in all formulations. In the initial phase (0–4 hours), drug release was relatively slow across all formulations, with LDF-1 showing a slightly higher release rate (21% at 2 hours, 34% at 4 hours) compared to LDF-5 (17% and 29%, respectively). This controlled release suggests effective polymer swelling and matrix formation, which regulates drug diffusion and prevents burst release. By 6–8 hours, a steady increase in drug release was observed, with LDF-1 reaching 47% and 61%, whereas LDF-5 achieved 41% and 55%, confirming sustained release kinetics. The extended drug release over 10–12 hours indicates effective polymeric matrix integrity, allowing for continuous and prolonged Levodopa delivery. LDF-1 showed the most optimized release (96%), ensuring higher bioavailability and prolonged therapeutic effect, which is critical in Parkinson's disease management. The slightly slower release in LDF-5 (90%) suggests a denser matrix or higher polymer concentration, which may further delay drug diffusion. Overall, LDF-1 demonstrated the most effective sustained release profile, ensuring maximum drug availability while preventing dose fluctuations. The results confirm that all formulations follow a controlled-release pattern, supporting prolonged gastric retention and improved therapeutic efficacy in Levodopa delivery.

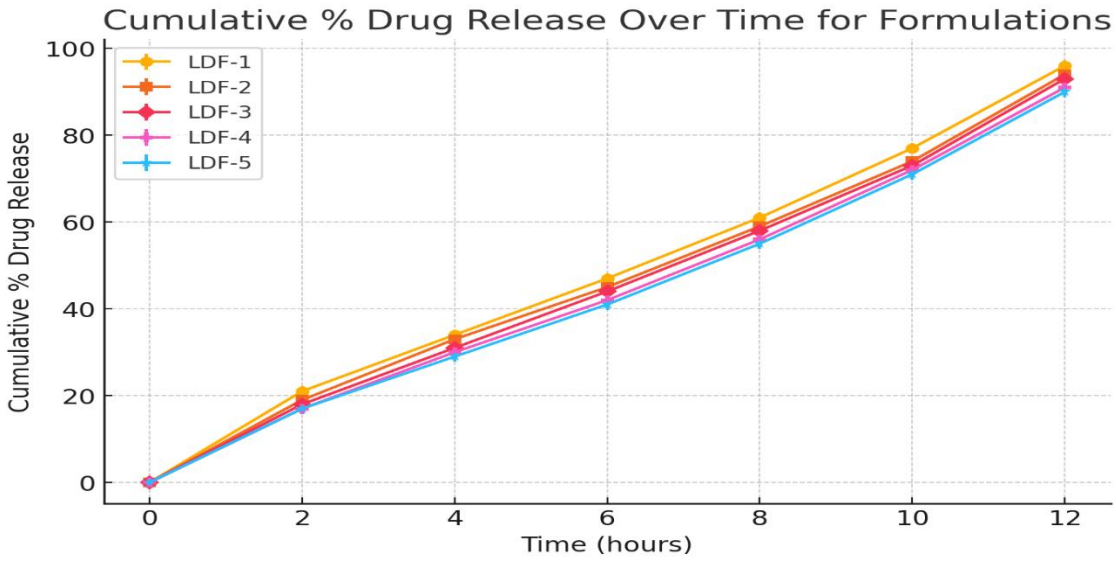

Figure 8. In vitro release of Levodopa from the BCDDS.

Table 5: In Vitro Release Kinetics Data of All Formulations of Levodopa

Formulation Code	R^2 Value (Zero Order)	R^2 Value (First Order)	R^2 Value (Higuchi)	R^2 Value (Korsmeyer-Peppas)	n value (Korsmeyer-Peppas)
LDF-1	0.9934	0.9362	0.8984	0.9948	0.9382
LDF-2	0.9942	0.9361	0.8896	0.9946	0.9662
LDF-3	0.9955	0.9327	0.8797	0.9955	1.0007
LDF-4	0.9954	0.9312	0.8718	0.9956	1.0272
LDF-5	0.9945	0.9297	0.8676	0.9950	1.0406

In vitro floatation

The in vitro floatation study results indicate notable differences in the floating lag time, total floating duration, and matrix integrity duration among the formulations, which directly influence the efficiency of Levodopa delivery. Most formulations, including LDF-1, LDF-2, and LDF-5, exhibited a floating lag time of 2 minutes, ensuring rapid hydration and swelling of the polymeric matrix for quick buoyancy. However, LDF-3 required 3 minutes, while LDF-4 had the longest lag time of 5 minutes, suggesting slower hydration and delayed floatation, likely due to differences in polymer composition or tablet compactness. In terms of total floating duration, LDF-5 exhibited the longest floating time of 11 hours, followed by LDF-1, LDF-2, and LDF-3, all maintaining buoyancy for 10 hours. LDF-4, however, had the shortest floating duration of 9 hours, indicating weaker floatation stability. The matrix integrity duration, crucial for sustained drug release, was highest in LDF-5 (10 hours), while LDF-1, LDF-2, and LDF-3 remained stable for 9 hours. LDF-4 had the shortest matrix integrity of 8 hours, suggesting an increased risk of premature disintegration and potential dose dumping. Overall, LDF-5 emerged as the most promising formulation, with its prolonged floating duration, highest matrix integrity, and sustained drug release profile, making it ideal for Levodopa delivery in Parkinson's disease management. LDF-1 and LDF-2 also performed well, demonstrating effective buoyancy and prolonged drug retention. LDF-3, despite its slightly longer lag time, remains a viable alternative, while LDF-4 exhibited the weakest floatation performance and may require further optimization to enhance gastric retention and sustain drug release (Nayak et al., 2013; Verma et al., 2012; Verma et al., 2017).

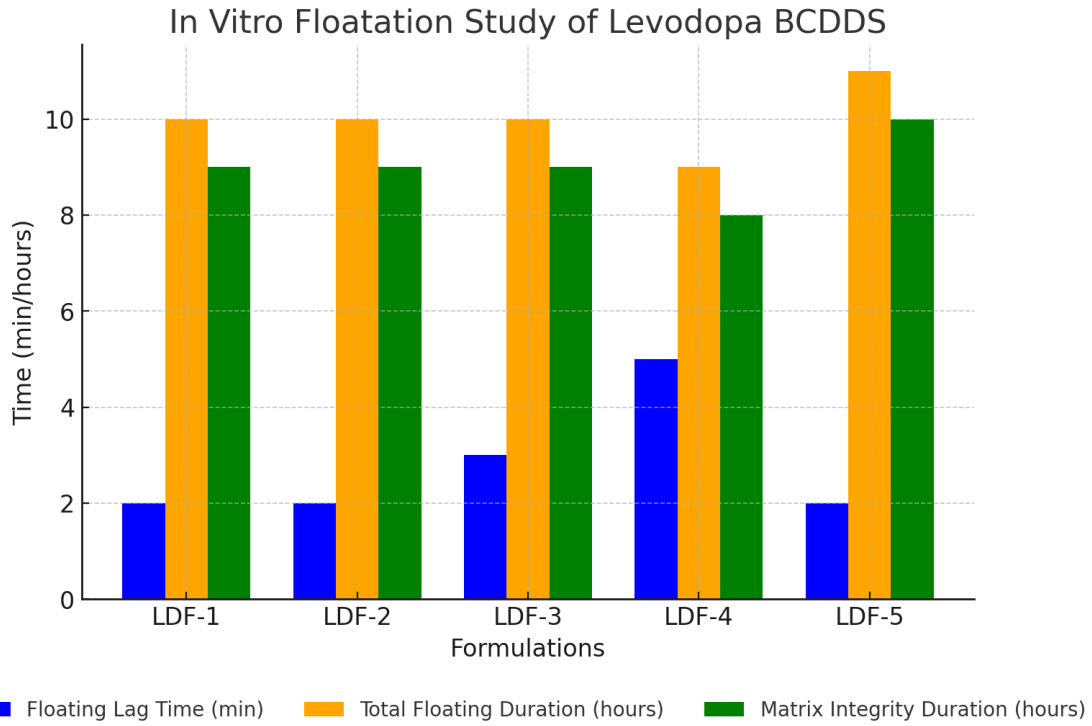

Figure 9. In vitro floatation study results indicate notable differences in the floating lag time, total floating duration, and matrix integrity duration among the BCDDS formulations.

CONCLUSION

The development of a Buoyancy-Controlled Drug Delivery System (BCDDS) for Levodopa demonstrated significant potential in overcoming the challenges of short plasma half-life and erratic gastric emptying, which are major limitations in conventional Levodopa therapy. The micromeritic analysis confirmed good flow properties and compressibility, ensuring efficient tablet formulation. The weight and drug content uniformity studies validated batch-to-batch consistency, an essential requirement for reproducible therapeutic efficacy.

The in vitro floatation study showed that all formulations exhibited prolonged gastric retention, with LDF-5 maintaining buoyancy for 11 hours and LDF-1 achieving instant flotation (0 min lag time). The prolonged floatation was attributed to hydrophilic polymers (Medium Molecular Mass Chitosan and Xanthan Gum), which facilitated hydration and swelling, forming a stable hydrogel matrix. This low-density matrix prevented tablet sinking, ensuring continuous drug release in the stomach. Drug release studies confirmed a controlled and sustained release profile, with LDF-1 demonstrating the highest release (96% in 12 hours). Kinetic modeling revealed that the Zero-Order and Korsmeyer-Peppas models provided the best fit, suggesting a combination of diffusion and polymeric relaxation mechanisms (super case-II transport). The high n values (>0.9) indicated a well-controlled release system, minimizing fluctuations in plasma drug levels, a critical factor in reducing "wearing-off" effects and motor fluctuations in Parkinson's disease patients. In conclusion, the study demonstrated that BCDDS formulations significantly improve Levodopa's bioavailability and therapeutic efficacy by prolonging gastric retention and ensuring sustained release. The optimized formulations reduce dose frequency, improve patient compliance, and enhance symptom control, making them a promising approach for Parkinson's disease management. Future research should focus on in vivo pharmacokinetic studies to further validate these findings and explore clinical applications of BCDDS in chronotherapeutic drug delivery.

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