FORMULATION AND EVALUATION OF A STABLE ORAL SUSPENSION OF SPIRONOLACTONE FOR PEDIATRIC AND GERIATRIC USE

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Abstract

The present study focused on the formulation and evaluation of a stable oral suspension of spironolactone to improve its dispersion, uniformity, and patient acceptability. Preformulation studies confirmed the drug's identity, purity, poor aqueous solubility, and lipophilic nature. Different formulations (F1–F10) were prepared using suitable suspending and wetting agents and evaluated for micromeritic properties, pH, viscosity, sedimentation volume, particle size, drug content, and in vitro drug release. Among all batches, formulation F10 showed the best performance with excellent homogeneity, optimum viscosity, high sedimentation volume, uniform drug content, and maximum drug release. Stability studies under ICH conditions demonstrated that the optimized formulation remained physically and chemically stable throughout the study period. Overall, the study confirmed that the developed spironolactone oral suspension is stable, effective, and suitable for further pharmaceutical development.

Keywords: *Spironolactone, Oral suspension, Preformulation studies, Micromeritic properties, Drug release, Stability studies.*

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Received: 05/05/2026
Revised: 25/05/2026
Accepted: 02/06/2026
DOI: http://doi.org/10.66204/GJPSR-858-2026-2-6-3

How to Cite

Yadav S, Parmar S. Formulation and evaluation of a stable oral suspension of spironolactone for pediatric and geriatric use. Global Journal of Pharmaceutical and Scientific Research. 2026, ISSN: 3108-0103. 2026;2(6):858-886. ISSN: 3108-0103. http://doi.org/10.66204/GJPSR-858-2026-2-6-3.

1. Introduction

Oral drug delivery remains the most preferred route of administration due to its convenience, cost-effectiveness, and high patient compliance. Among oral dosage forms, suspensions are particularly useful for drugs that exhibit poor aqueous solubility or instability in solution form. Suspensions are biphasic systems in which finely divided solid drug particles are dispersed in a liquid medium, and their performance depends on critical formulation parameters such as particle size distribution, wetting ability, viscosity, sedimentation rate, and redispersibility. Ensuring physical stability and uniform dose distribution is essential for therapeutic efficacy and patient safety, making preformulation studies a key step in suspension development (Aulton & Taylor, 2018; Sinko, 2021).

Spironolactone is a synthetic steroidal aldosterone antagonist widely used as a potassium-sparing diuretic in conditions such as hypertension, congestive heart failure, hepatic cirrhosis-associated ascites, and edema. It acts by competitively inhibiting aldosterone receptors in the distal renal tubules, thereby promoting sodium and water excretion while conserving potassium. However, spironolactone is characterized by poor aqueous solubility and high lipophilicity, which can lead to dissolution-limited absorption and variable bioavailability when administered orally in conventional solid dosage forms (Katzung, 2021; Brunton et al., 2018).

The Biopharmaceutics Classification System (BCS) categorizes spironolactone as a low-solubility drug, highlighting the need for formulation strategies that enhance its dissolution and dispersion. Liquid dosage forms such as oral suspensions offer a promising approach to overcome these limitations by improving drug wettability, enhancing surface area, and facilitating more uniform drug distribution. The success of suspension formulations depends on the careful selection of excipients including suspending agents, wetting agents, preservatives, sweeteners, and flavoring agents to ensure stability, palatability, and microbiological safety (Allen et al., 2020; Sinko, 2021).

Furthermore, evaluation of critical quality attributes such as micromeritic properties, rheological behavior, sedimentation volume, drug content uniformity, and in vitro drug release is essential to ensure product performance and reproducibility. Stability studies conducted under ICH guidelines further confirm the robustness and shelf-life of the developed formulation under varying environmental conditions (ICH, 2003).

Therefore, the present study aims to design, develop, and evaluate a stable spironolactone oral suspension by optimizing formulation variables and assessing its physicochemical,

rheological, and in vitro performance characteristics in comparison with a marketed product.

2. Collection and Authentication of Materials

Spironolactone was selected as the model drug for this study due to its clinical importance and suitability for development as an oral suspension, and was procured from a licensed supplier. Excipients including suspending agents, wetting agents, preservatives, sweeteners, and flavoring agents were chosen based on their functional role, compatibility with the drug, and suitability for oral liquid formulation. All materials were authenticated as per IP/USP standards. Drug authentication involved evaluation of organoleptic properties, melting point, and IR spectroscopy, while excipients were assessed for basic physicochemical properties such as appearance, solubility, and pH. Only materials complying with pharmacopeial specifications were used for formulation development.

3. Preformulation Studies of Drug

3.1 Organoleptic evaluation

Color

The color of spironolactone was evaluated as part of its organoleptic characterization to confirm its physical identity and purity. A small quantity of the drug was placed on a clean glass slide and visually examined under natural daylight. The observed color was compared with official pharmacopoeial descriptions to detect any signs of impurities, degradation, or improper storage. Color consistency was considered an important quality parameter indicating the stability and uniformity of the drug material. The observations were recorded for further preformulation and formulation studies.

Odor

The odor of spironolactone was evaluated during organoleptic characterization to confirm its identity and detect any signs of impurity or degradation. A small quantity of the drug sample was examined under ambient conditions by gently wafting the air above the sample toward the nose. The observed odor was compared with standard pharmacopeial descriptions and recorded for further preformulation studies.

Appearance

The appearance of spironolactone was evaluated to assess its physical characteristics and suitability for formulation development. A small quantity of the drug sample was observed on a clean glass surface under proper lighting for its nature, uniformity, and presence of any visible impurities or foreign particles. The observed appearance was compared with standard

pharmacopeial descriptions, and the findings were recorded for further preformulation studies.

3.2 Melting point determination

The melting point of spironolactone was determined by the capillary method to confirm its identity and purity. A small quantity of finely powdered drug was filled into a sealed capillary tube and placed in a melting point apparatus. The temperature at which the sample started and completely finished melting was recorded. The observed melting point range was compared with standard pharmacopeial values, where a sharp and narrow range indicated purity, while any deviation suggested possible impurities or degradation. The results were recorded for further preformulation studies.

3.3 Solubility studies in various solvents

The solubility of spironolactone was evaluated in various solvents during preformulation studies to understand its dissolution behavior and support excipient selection. An excess amount of drug was added to solvents such as distilled water, ethanol, and methanol, followed by continuous shaking to reach equilibrium. The solutions were then filtered, and solubility was determined qualitatively and/or quantitatively. The results were interpreted using standard pharmacopeial descriptors, providing essential information for selecting suitable formulation components for the oral suspension.

3.4 pH

The pH of spironolactone was determined to evaluate its physicochemical behavior and compatibility with formulation excipients. A suitable dispersion of the drug was prepared in distilled water, and the pH was measured using a calibrated digital pH meter standardized with buffer solutions of pH 4.0, 7.0, and 9.2. The electrode was immersed in the sample, and the stable pH reading was recorded at room temperature. The observed pH was used to assess the drug's stability and suitability for oral suspension formulation.

3.5 Partition coefficient (Log P)

The partition coefficient (Log P) of spironolactone was determined using the shake-flask method to evaluate its lipophilicity and distribution behavior between aqueous and organic phases. A biphasic system of n-octanol and distilled water was prepared, and a known quantity of the drug was added and shaken until equilibrium was achieved. After phase separation, the drug concentration in each layer was analyzed using UV-visible spectrophotometry. The partition coefficient was calculated as the ratio of drug concentration in the organic phase to the aqueous phase, and the Log P value was determined. The study

provided information about the drug's hydrophilic-lipophilic balance and aided in formulation design for the oral suspension.

3.6 Flow Properties of Drug Powder

3.6.1 Bulk density

The bulk density of spironolactone powder was determined to evaluate its packing behavior and flow properties important for formulation development. A known quantity of the powder was carefully transferred into a clean graduated cylinder without tapping, and the initial volume occupied by the powder was recorded as the bulk volume. Bulk density was then calculated using the formula:

$$\textbf{Bulk Density } (\boldsymbol{\rho b}) = \frac{\textbf{Mass of Powder}}{\textbf{Bulk Volume}}$$

The determination was performed in triplicate, and the mean value was recorded. The obtained data provided information about the powder's porosity, packing efficiency, and flow characteristics, and were further used for calculating Carr's index and Hausner's ratio.

3.6.2 Tapped density

The tapped density of spironolactone powder was determined to evaluate its packing ability, compressibility, and flow properties. A known quantity of powder was transferred into a graduated cylinder, and the initial bulk volume was recorded. The cylinder was then subjected to repeated tapping using a tapped density apparatus until a constant volume was obtained. The final tapped volume was noted, and tapped density was calculated using the formula:

$$\textbf{Tapped Density } (\boldsymbol{\rho t}) = \frac{\textbf{Mass of Powder}}{\textbf{Tapped Volume}}$$

The determination was carried out in triplicate, and the average value was recorded. The tapped density data provided information about the powder's packing efficiency and compressibility and were further used to calculate Carr's index and Hausner's ratio.

3.6.3 Carr's index (%)

Carr's compressibility index was determined to evaluate the flowability and compressibility of spironolactone powder. The calculation was based on the experimentally determined bulk density and tapped density values. Carr's index was calculated using the following formula:

$$\textbf{Carr's Index } (\%) = \frac{\textbf{Tapped Density} - \textbf{Bulk Density}}{\textbf{Tapped Density}} * \textbf{100}$$

The determination was performed in triplicate, and the average value was recorded. Lower Carr's index values indicated good flow properties, while higher values suggested poor flow

due to increased particle cohesiveness. The results were used to assess the suitability of spironolactone powder for formulation development.

3.6.4 Hausner's ratio

Hausner's ratio was determined to evaluate the cohesiveness and flow properties of spironolactone powder. The ratio was calculated using the experimentally determined bulk density and tapped density values according to the following equation:

$$\textbf{Hausner's Ratio} = \frac{\textbf{Tapped Density}}{\textbf{Bulk Density}}$$

The determination was carried out in triplicate, and the average value was recorded. A Hausner's ratio close to 1 indicated good flowability and low cohesiveness, whereas higher values suggested poor flow properties due to increased interparticle friction. The results were used to assess the suitability of spironolactone powder for formulation development.

3.6.5 Angle of repose

The angle of repose of spironolactone powder was determined to evaluate its flowability and frictional properties. The fixed funnel method was used, in which the powder was allowed to flow freely through a funnel to form a conical heap on a horizontal surface. The height (h) and radius (r) of the powder heap were measured, and the angle of repose was calculated using the following equation:

$$\tan\theta = \frac{h}{r}$$

The determination was performed in triplicate, and the average value was recorded. Lower angle values indicated good flow properties, while higher values suggested poor flow due to increased interparticle friction. The results helped assess the suitability of spironolactone powder for formulation development.

4. Preparation of Spironolactone Oral Suspension

The spironolactone oral suspension was prepared using a systematic method to obtain a stable and uniformly dispersed formulation. Suitable suspending agents were optimized to improve viscosity, reduce sedimentation, and enhance redispersibility. Wetting agents were incorporated due to the poor aqueous solubility of spironolactone, and the drug was first levigated to form a smooth paste before gradual addition of the aqueous phase under continuous stirring. Sweetening and flavoring agents were added to improve palatability, while preservatives ensured microbiological stability. Various trial batches were prepared with different excipient concentrations and evaluated for homogeneity, viscosity,

sedimentation volume, redispersibility, and physical stability. The optimized formulation with the best overall performance was selected for further evaluation and stability studies.

Table 1: Composition of Spironolactone Oral Suspension

S. No.	Ingredients	Function	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Spironolactone	Active Drug	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
2.	Xanthan Gum	Suspending Agent	0.2	0.4	0.6	0.4	0.3	0.5	0.6	0.3	0.4	0.5
3.	Sodium CMC	Suspending Agent	0.3	0.3	0.3	0.5	0.4	0.4	0.3	0.5	0.4	0.3
4.	Tween 80	Wetting Agent	0.2	0.2	0.2	0.3	0.25	0.3	0.25	0.2	0.3	0.25
5.	Glycerin	Wetting Agent / Humectant	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
6.	Sucrose	Sweetening Agent	20	20	20	25	25	20	25	20	25	20
7.	Sodium Saccharin	Sweetener	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
8.	Methyl Paraben	Preservative	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
9.	Propyl Paraben	Preservative	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
10.	Flavor (Orange)	Flavoring Agent	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
11.	Purified Water	Vehicle	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL

5. Evaluation of Oral Suspension

5.1 Physical appearance and homogeneity

Physical appearance and homogeneity of the optimized spironolactone oral suspension were evaluated during stability studies by visually inspecting samples at predetermined intervals for changes in color, sedimentation, caking, phase separation, and particle aggregation. The suspension was gently shaken to assess redispersibility and uniformity. A stable formulation was expected to retain its original appearance and show easy redispersion without significant physical changes.

5.2 pH determination

The pH of the optimized spironolactone oral suspension was monitored during stability studies to evaluate its chemical stability and compatibility with excipients. Samples were

withdrawn at predetermined intervals, and the pH was measured using a calibrated digital pH meter standardized with buffer solutions of pH 4.0, 7.0, and 9.2. The measurements were performed in triplicate at room temperature after gentle stirring of the suspension. The observed pH values were compared with the initial pH of the formulation, where minimal variation indicated good stability, while significant changes suggested possible drug degradation or incompatibility.

5.3 Viscosity measurement

The viscosity of the optimized spironolactone oral suspension was measured during stability studies to evaluate changes in flow behavior and physical stability over time. Samples were withdrawn at predetermined intervals, gently shaken, and analyzed using a Brookfield viscometer fitted with a suitable spindle at controlled temperature and rotational speed. The measurements were performed in triplicate after obtaining stable readings. The observed viscosity values were compared with the initial viscosity of the formulation, where minimal changes indicated good physical stability, while significant increases or decreases suggested aggregation or breakdown of the suspending system.

5.4 Sedimentation volume

The sedimentation volume of the optimized spironolactone oral suspension was determined during stability studies to evaluate its physical stability and settling behavior. Samples were transferred into graduated cylinders, and the initial suspension volume (H_0) and sediment height (H_u) at predetermined intervals were recorded. Sedimentation volume was calculated using the formula:

$$F = \frac{Hu}{H0}$$

The study was performed in triplicate, and the values were compared with the initial observations. A stable suspension was expected to show minimal changes in sedimentation volume, indicating good dispersibility and physical stability.

5.5 Particle size analysis

Particle size analysis of the optimized spironolactone oral suspension was carried out using optical microscopy to evaluate the dispersion and physical stability of the formulation. The suspension was gently shaken, suitably diluted, and a drop of the sample was placed on a glass slide under a cover slip. After calibration of the eyepiece micrometer with a stage micrometer, the particle diameters were measured under an optical microscope by randomly selecting particles from different regions of the slide. Approximately 50–100 particles were analyzed, and the average particle size was calculated. The study was performed in triplicate

to ensure accuracy and reproducibility. Smaller and uniformly distributed particles indicated better stability and dispersion of the suspension.

5.6 Drug content uniformity

Drug content of the optimized spironolactone oral suspension was determined using UV–Visible spectrophotometry to evaluate uniformity and dosage accuracy. The suspension was thoroughly shaken, and an accurately measured quantity equivalent to a known amount of drug was diluted with a suitable solvent to ensure complete dissolution. The solution was filtered, suitably diluted, and analyzed at the predetermined λmax of spironolactone using a UV–Visible spectrophotometer. Drug concentration was determined using a calibration curve, and the drug content was expressed as a percentage of the labeled claim. The analysis was performed in triplicate to ensure accuracy and reproducibility. Drug content values close to 100% indicated uniform drug distribution and good formulation quality.

6. In Vitro Drug Release Studies

In vitro drug release studies of the optimized spironolactone oral suspension were carried out using a USP dissolution apparatus (Type II – paddle method) to evaluate the rate and extent of drug release under simulated physiological conditions. An accurately measured quantity of the suspension was added to the dissolution medium maintained at 37 ± 0.5°C and stirred at a predetermined rpm. Samples were withdrawn at specific time intervals, filtered, and analyzed using a UV–Visible spectrophotometer at the λmax of spironolactone, with fresh medium replaced after each sampling. The cumulative percentage drug release was calculated using a calibration curve and plotted against time. The study was performed in triplicate, and a consistent, complete drug release profile indicated good formulation performance.

7. Stability Studies as per ICH guidlines

Stability studies of the optimized spironolactone oral suspension were carried out according to ICH guidelines to evaluate the effect of temperature and humidity on the formulation over time. The suspension was stored in well-closed containers under accelerated (40 ± 2°C/75 ± 5% RH) and long-term (25 ± 2°C/60 ± 5% RH) conditions. Samples were withdrawn at predetermined intervals and evaluated for physical appearance, pH, viscosity, sedimentation volume, redispersibility, drug content, and in vitro drug release. All studies were performed in triplicate to ensure reproducibility. A stable formulation was expected to show minimal changes in these parameters throughout the study, indicating good stability and suitable shelf life.

8. Results

8.1 Preformulation Studies of Drug

8.1.1 Organoleptic evaluation

The organoleptic evaluation of spironolactone revealed that the drug was a white to off-white, odorless crystalline powder, consistent with official pharmacopeial standards. The sample was free from visible impurities, aggregates, or foreign particles, confirming its acceptable quality and physical identity. These observations indicated that the drug was suitable for further preformulation and formulation development studies.

Table 2: Organoleptic Evaluation of Spironolactone

S. No.	Parameter	Observation
1.	Color	White to off-white crystalline powder
2.	Odor	Odorless
3.	Appearance	Fine, crystalline powder; free from visible impurities

8.1.2 Melting point determination

The melting point of spironolactone was found to be in the range of 205–208°C using the capillary method. The sharp and narrow melting range indicated the purity of the drug sample and closely matched the standard pharmacopeial values, confirming the identity of spironolactone. The results also suggested the absence of significant impurities or degradation products, supporting its suitability for further formulation studies.

Table 3: Melting Point Determination of Spironolactone

S. No.	Parameter	observation
1.	Melting Point Range	205–208°C
2.	Nature of Melting	Sharp melting range

8.1.3 Solubility studies in various solvents

The solubility study of spironolactone showed very low solubility in distilled water (0.008 ± 0.002 mg/mL) and phosphate buffer pH 6.8 (0.012 ± 0.003 mg/mL), confirming its poor

aqueous solubility and hydrophobic nature. The drug exhibited higher solubility in organic solvents such as ethanol (2.15 ± 0.06 mg/mL), methanol (1.92 ± 0.05 mg/mL), and acetone (3.48 ± 0.08 mg/mL), indicating its lipophilic character. These findings supported the use of suitable wetting agents and suspending systems for developing a stable oral suspension with improved dispersion and bioavailability.

Table 4: Solubility Profile of Spironolactone in Various Solvents

S. No.	Solvent	Solubility (mg/mL)	Observed Solubility Category
1.	Distilled Water	0.008 ± 0.002	Practically insoluble
2.	Ethanol	2.15 ± 0.06	Slightly soluble
3.	Methanol	1.92 ± 0.05	Slightly soluble
4.	Acetone	3.48 ± 0.08	Moderately soluble
5.	Phosphate buffer pH 6.8	0.012 ± 0.003	Practically insoluble

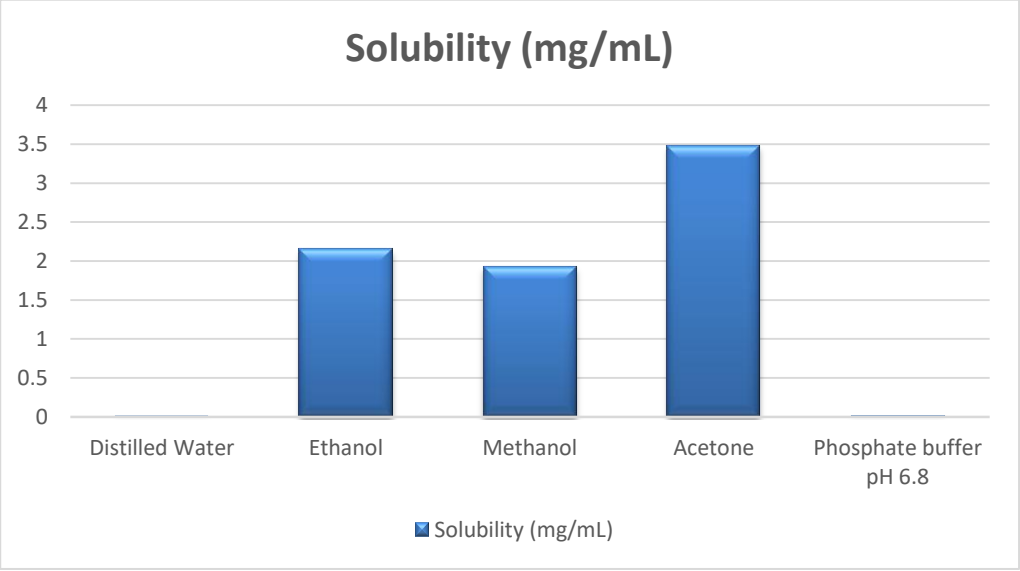

Fig 1: Solubility

8.1.4 pH

The pH of spironolactone dispersion was measured using a calibrated digital pH meter and found to be 6.42 ± 0.03, indicating a slightly acidic to near-neutral nature. This pH range is

considered suitable for oral administration and showed good compatibility with commonly used excipients such as suspending agents, preservatives, and sweeteners. The observed pH also suggested favorable conditions for maintaining drug stability in the oral suspension formulation, confirming the suitability of spironolactone for suspension development without major pH adjustment.

Table 5: pH of Spironolactone Dispersion

Sample Preparation	pH (Mean ± SD, n=3)
Spironolactone dispersion in distilled water	6.42 ± 0.03

8.1.5 Partition coefficient (Log P)

The partition coefficient study of spironolactone using the shake-flask method showed a significantly higher drug concentration in the n-octanol phase (4.82 ± 0.10 mg/mL) compared to the aqueous phase (0.18 ± 0.02 mg/mL), indicating its lipophilic nature. The partition coefficient (P) was found to be 26.77 ± 1.20 with a Log P value of 1.43 ± 0.02. These results confirmed the moderate lipophilicity and limited aqueous solubility of spironolactone, supporting the need for suitable formulation strategies such as wetting agents and suspending systems to improve its dispersion and bioavailability in oral suspension dosage form.

Table 6: Partition Coefficient (Log P) of Spironolactone

S. No.	Phase System (n-octanol : water)	Drug Conc. in Octanol (mg/mL)	Drug Conc. in Aqueous Phase (mg/mL)	Partition Coefficient (P)	Log P
1.	1:1	4.82 ± 0.10	0.18 ± 0.02	26.77 ± 1.20	1.43 ± 0.02

8.2 Flow Properties of Drug Powder

8.2.1 Bulk density

The bulk density of the prepared spironolactone formulations (F1–F10) ranged from 0.424 ± 0.004 g/mL to 0.484 ± 0.003 g/mL, showing a gradual increase across the batches due to variations in excipient concentration and particle packing behavior. The marketed formulation exhibited a bulk density of 0.462 ± 0.002 g/mL, which was comparable to formulations F6–F8. Among all batches, F7 (0.463 ± 0.004 g/mL) showed the closest similarity to the marketed product, indicating comparable packing and handling properties. These results confirmed that the developed formulations possessed acceptable bulk density characteristics suitable for further formulation development.

Table 7: Bulk Density of Spironolactone Formulations

Formulation	Bulk Density (g/mL)
F1	0.424 ± 0.004
F2	0.431 ± 0.003
F3	0.439 ± 0.005
F4	0.444 ± 0.003
F5	0.450 ± 0.004
F6	0.457 ± 0.003
F7	0.463 ± 0.004
F8	0.470 ± 0.003
F9	0.476 ± 0.004
F10	0.484 ± 0.003
Marketed formulation	0.462 ± 0.002

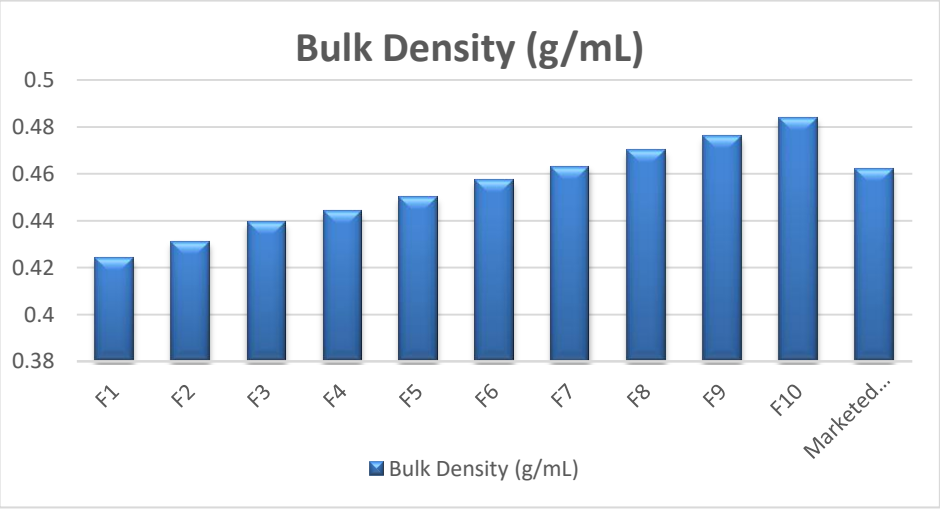

Fig 2: Bulk Density (g/mL)

8.2.2 Tapped density

The tapped density of the developed spironolactone formulations (F1–F10) ranged from 0.492 ± 0.005 g/mL to 0.565 ± 0.004 g/mL, indicating progressive improvement in particle packing and compressibility across the batches. The marketed formulation showed a tapped density of 0.540 ± 0.003 g/mL, which was comparable to formulations F6–F8. Among all formulations, F7 (0.538 ± 0.003 g/mL) exhibited the closest similarity to the marketed product, suggesting comparable packing behavior and consolidation properties. The results indicated acceptable compressibility and flow characteristics, supporting the suitability of the developed formulations for stable and uniform oral suspension preparation.

Table 8: Tapped Density of Spironolactone Formulations (F1–F10) and Marketed Product

Formulation	Tapped Density (g/mL)
F1	0.492 ± 0.005
F2	0.498 ± 0.004
F3	0.506 ± 0.003
F4	0.513 ± 0.004
F5	0.521 ± 0.005
F6	0.529 ± 0.004
F7	0.538 ± 0.003
F8	0.547 ± 0.004
F9	0.556 ± 0.005
F10	0.565 ± 0.004
Marketed formulation	0.540 ± 0.003

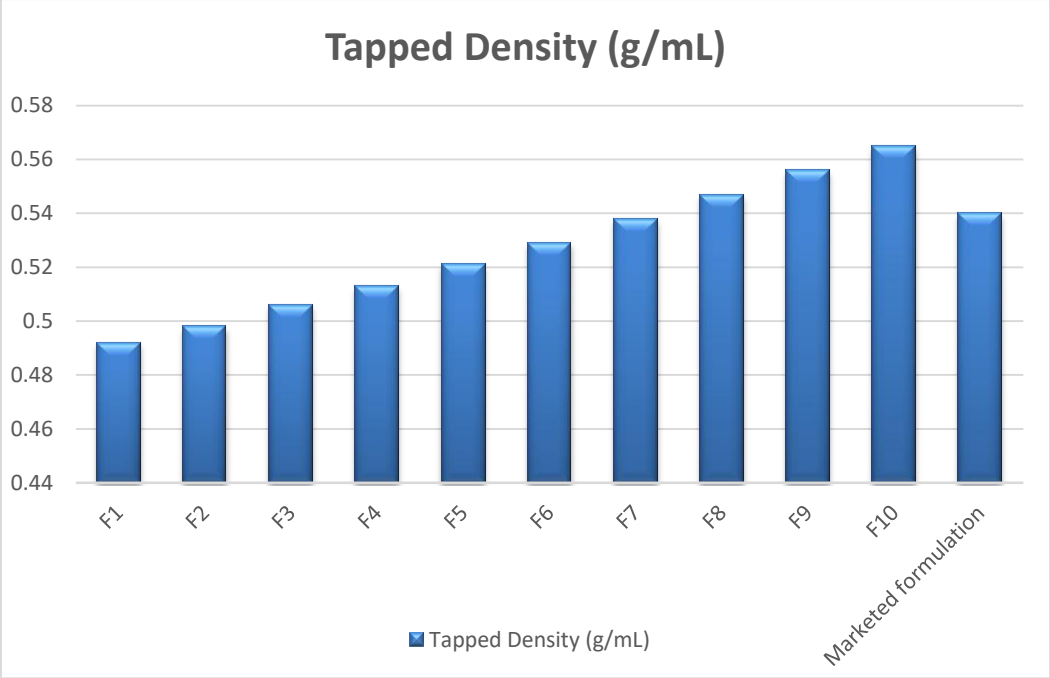

Fig 3: Tapped Density (g/mL)

8.2.3 Carr's index (%)

The Carr's index of the developed spironolactone formulations (F1–F10) ranged from 13.27 ± 0.22% to 14.39 ± 0.23%, indicating good flow properties according to pharmacopeial standards. The marketed formulation showed a Carr's index of 14.44 ± 0.18%, which was comparable to the developed batches, particularly F9 and F10. Formulation F3 exhibited the lowest Carr's index (13.27 ± 0.22%), suggesting slightly better flowability and lower interparticle friction. Overall, the low Carr's index values confirmed efficient packing, reduced cohesiveness, and acceptable flow behavior of the formulations, supporting their suitability for further formulation development and processing.

Table 9: Carr's Index (%) of Spironolactone Formulations

Formulation	Carr's Index (%)	Flow Property
F1	13.82 ± 0.21	Good
F2	13.45 ± 0.19	Good
F3	13.27 ± 0.22	Good
F4	13.50 ± 0.20	Good
F5	13.64 ± 0.23	Good
F6	13.60 ± 0.21	Good

F7	13.93 ± 0.24	Good
F8	13.93 ± 0.22	Good
F9	14.39 ± 0.23	Good
F10	14.35 ± 0.24	Good
Marketed formulation	14.44 ± 0.18	Good

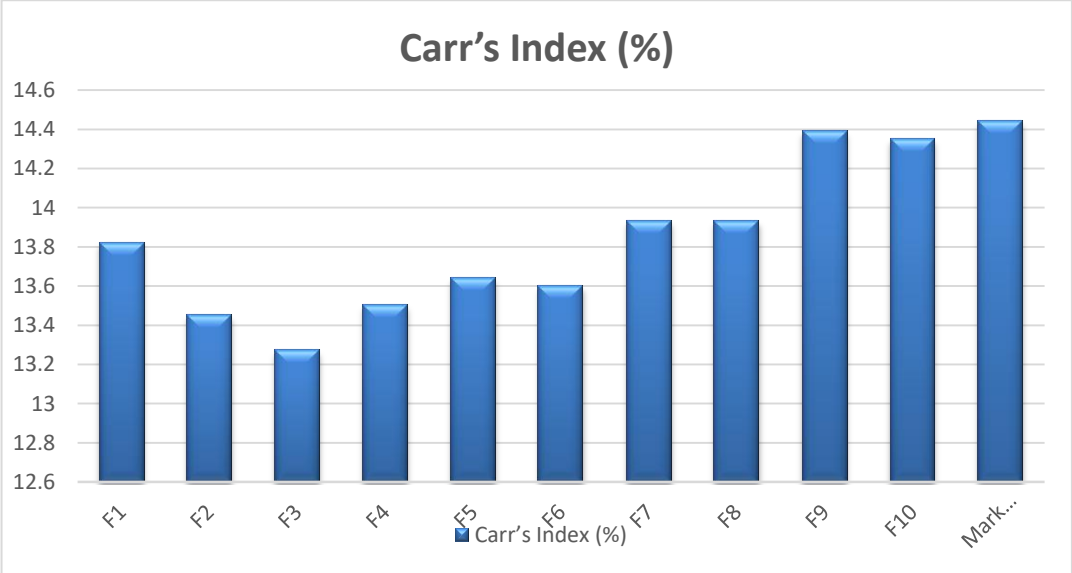

Fig 4: Carr's Index (%)

8.2.4 Hausner's ratio

The Hausner's ratio of the developed spironolactone formulations (F1–F10) ranged from 1.15 ± 0.01 to 1.18 ± 0.01, indicating good flow properties according to pharmacopeial standards. The marketed formulation showed a Hausner's ratio of 1.17 ± 0.01, which was comparable to most developed formulations, particularly F7 and F8. Among all batches, F3 exhibited the lowest value (1.15 ± 0.01), suggesting lower interparticle friction and better flowability. Overall, the results confirmed low cohesiveness, efficient particle packing, and acceptable flow behavior of the formulations, supporting their suitability for further processing and formulation development.

Table 10: Hausner's Ratio of Spironolactone Formulations

Formulation	Hausner's Ratio	Flow Property
F1	1.16 ± 0.01	Good

F2	1.16 ± 0.01	Good
F3	1.15 ± 0.01	Good
F4	1.16 ± 0.01	Good
F5	1.16 ± 0.01	Good
F6	1.16 ± 0.01	Good
F7	1.17 ± 0.01	Good
F8	1.17 ± 0.01	Good
F9	1.18 ± 0.01	Good
F10	1.18 ± 0.01	Good
Marketed formulation	1.17 ± 0.01	Good

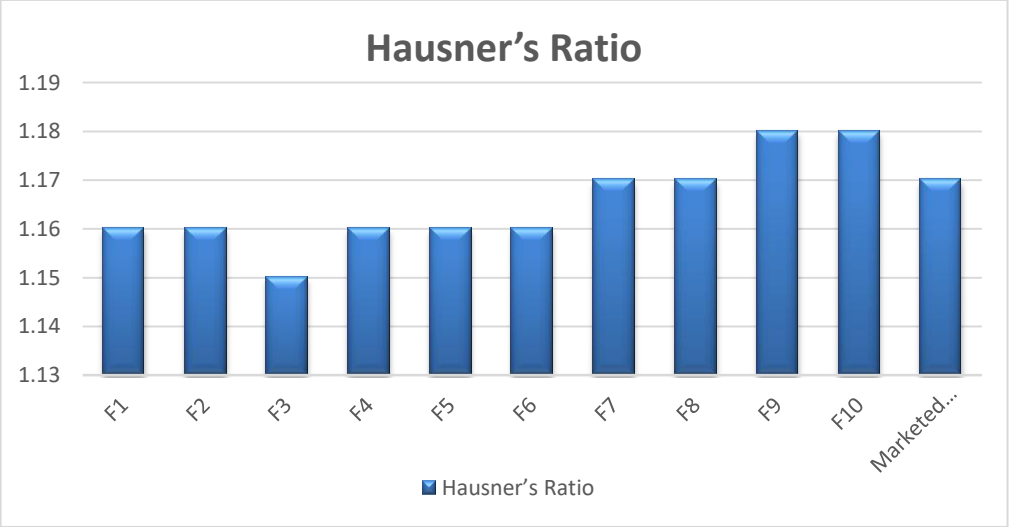

Fig 5: Hausner's Ratio

8.2.5 Angle of repose

The angle of repose of the developed spironolactone formulations (F1–F10) ranged from 27.8 ± 0.4° to 32.8 ± 0.4°, indicating good to excellent flow properties according to pharmacopeial standards. Formulations F1–F4 showed lower values below 29°, suggesting superior flowability with minimal interparticle friction, while F8–F10 exhibited slightly higher values above 31°, indicating comparatively greater cohesiveness but still acceptable flow behavior. The marketed formulation showed an angle of repose of 30.5 ± 0.3°, which was comparable to formulations F6 and F7. Overall, the results confirmed good micromeritic properties and

suitable flow characteristics of the developed formulations for further processing and formulation development.

Table 11: Angle of Repose of Spironolactone Formulations

Formulation	Angle of Repose (°)
F1	27.8 ± 0.4
F2	28.1 ± 0.3
F3	28.5 ± 0.5
F4	29.0 ± 0.4
F5	29.6 ± 0.3
F6	30.2 ± 0.4
F7	30.8 ± 0.5
F8	31.5 ± 0.4
F9	32.1 ± 0.3
F10	32.8 ± 0.4
Marketed formulation	30.5 ± 0.3

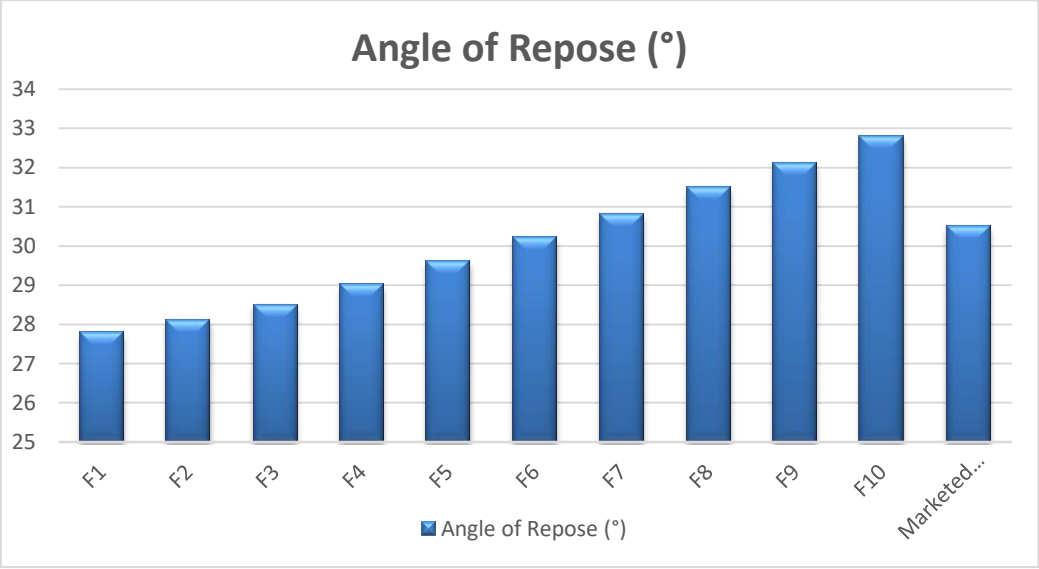

Fig 6: Angle of Repose (°)

8.3 Evaluation of Oral Suspension

8.3.1 Physical appearance and homogeneity

The spironolactone oral suspension formulations (F1–F10) were evaluated for physical appearance and homogeneity and compared with the marketed formulation. Initial batches (F1–F2) showed slight phase separation, coarse texture, and poor uniformity, indicating inadequate dispersion. Formulations F3–F5 exhibited improved uniformity, while F6–F10 showed smooth appearance, excellent homogeneity, and easy redispersibility without phase separation. The marketed formulation displayed a smooth, off-white, and uniform appearance comparable to formulations F7–F10. Among all batches, F8–F10 demonstrated the best physical stability and homogeneity, with F10 identified as the optimized formulation.

Table 12: Physical Appearance and Homogeneity of Spironolactone Oral Suspension Formulations

Formulation	Color & Appearance	Homogeneity	Phase Separation	Redispersibility
F1	White, slightly coarse	Non-uniform	Slight	Requires vigorous shaking
F2	White, slightly coarse	Moderately uniform	Slight	Requires moderate shaking
F3	White, slightly smooth	Moderately uniform	Absent	Redispersible with shaking
F4	White, smooth	Uniform	Absent	Easily redispersible
F5	White, smooth	Uniform	Absent	Easily redispersible
F6	White, smooth	Uniform	Absent	Easily redispersible
F7	White, smooth and elegant	Highly uniform	Absent	Easily redispersible
F8	White, elegant	Highly uniform	Absent	Easily redispersible
F9	White, elegant	Highly uniform	Absent	Easily redispersible
F10	White, elegant	Highly uniform	Absent	Easily redispersible
Marketed formulation	Off-white, smooth	Highly uniform	Absent	Easily redispersible

8.3.2 pH determination

The pH of spironolactone formulations (F1–F10) ranged from 6.38 ± 0.03 to 6.57 ± 0.02, indicating a slightly acidic to near-neutral nature suitable for oral administration. Among all formulations, F7 showed a pH of 6.52 ± 0.03, which was very close to the marketed formulation (6.49 ± 0.02), suggesting good compatibility and stability. Minor variations in pH were attributed to differences in excipient composition; however, all formulations remained within an acceptable physiological range. Overall, the results confirmed stable pH characteristics, with F7 showing the closest similarity to the marketed product and considered suitable for further evaluation.

Table 13: pH of Optimized Spironolactone Formulation

S. No.	Formulation	pH (Mean ± SD, n=3)
1.	F1	6.38 ± 0.03
2.	F2	6.41 ± 0.02
3.	F3	6.44 ± 0.03
4.	F4	6.46 ± 0.02
5.	F5	6.48 ± 0.03
6.	F6	6.50 ± 0.02
7.	F7	6.52 ± 0.03
8.	F8	6.53 ± 0.02
9.	F9	6.55 ± 0.03
10.	F10	6.57 ± 0.02
11.	Marketed Product	**6.49 ± 0.02**

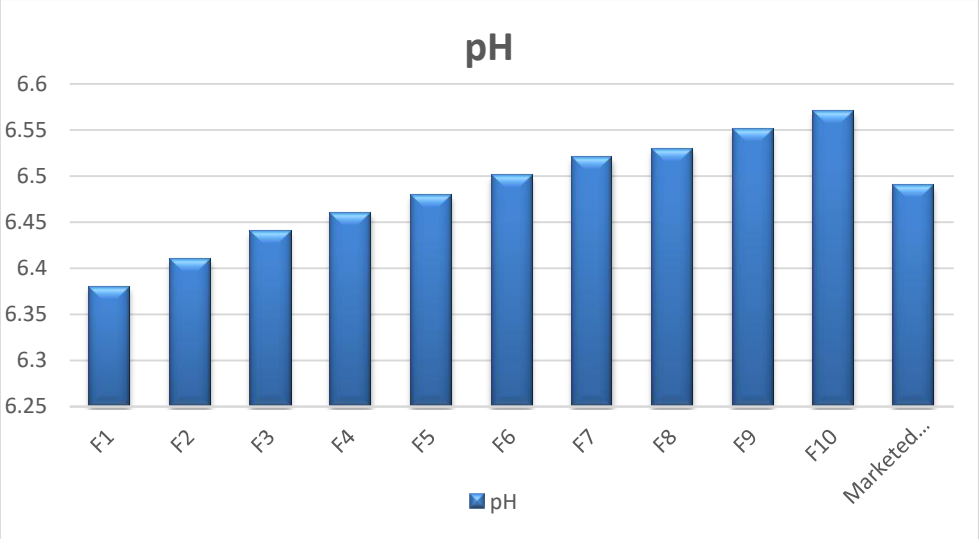

Fig 7: pH

8.3.3 Viscosity measurement

The viscosity of spironolactone oral suspension formulations (F1–F10) ranged from 1025 ± 10 cP to 1580 ± 16 cP, showing a gradual increase with higher concentrations of suspending agents. Formulations F1–F3 exhibited lower viscosity, which may lead to faster sedimentation, while F8–F10 showed higher viscosity, indicating improved suspension stability but comparatively lower pourability. The marketed formulation had a viscosity of 1345 ± 12 cP, which was comparable to formulations F6 and F7, suggesting similar rheological behavior. Overall, formulations F6–F7 demonstrated an optimal balance between viscosity, stability, and pourability, making them suitable for further formulation development.

Table 14: Viscosity of Spironolactone Oral Suspension Formulations

Formulation	Viscosity (cP) Mean ± SD
F1	1025 ± 10
F2	1085 ± 12
F3	1150 ± 11
F4	1210 ± 13
F5	1265 ± 12
F6	1320 ± 14
F7	1385 ± 13
F8	1450 ± 15
F9	1510 ± 14
F10	1580 ± 16

Marketed formulation	1345 ± 12

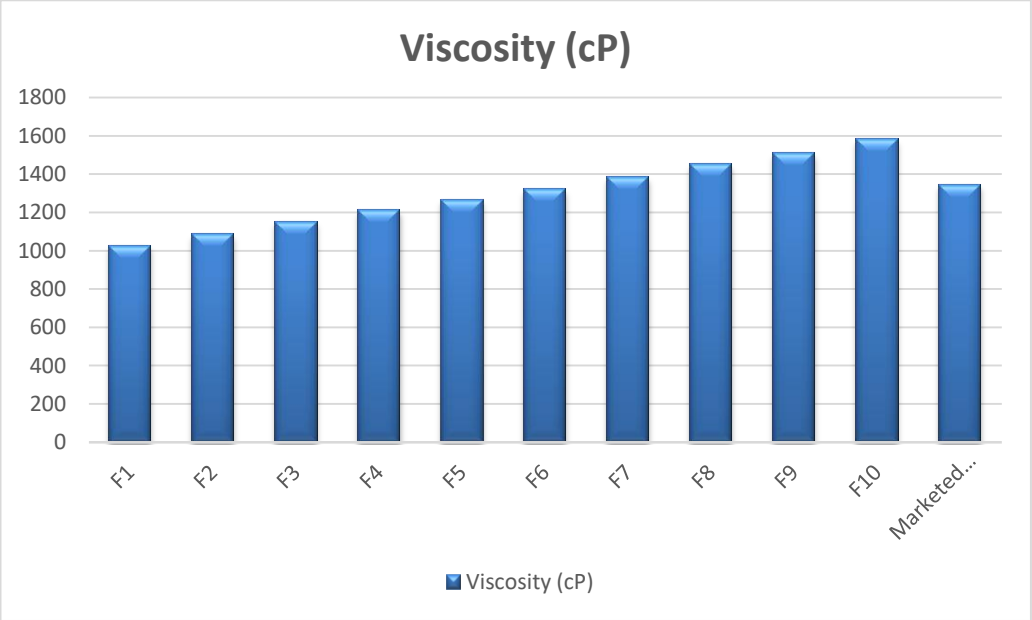

Fig 8: Viscosity (cP)

8.3.4 Sedimentation volume

The sedimentation volume of spironolactone oral suspension formulations (F1–F10) ranged from 0.78 ± 0.02 to 0.95 ± 0.01, indicating progressive improvement in physical stability with formulation optimization. Lower values observed in F1–F2 suggested faster sedimentation and weaker suspension stability, while higher values in F8–F10 indicated better particle dispersion and resistance to settling. Formulations F6–F10 showed sedimentation volumes above 0.90, reflecting good flocculation behavior and improved physical stability. The marketed formulation exhibited a sedimentation volume of 0.91 ± 0.01, which was comparable to formulations F6 and F7. Among all batches, F10 showed the highest sedimentation volume, indicating excellent suspension stability and redispersibility suitable for oral administration.

Table 15: Sedimentation Volume of Spironolactone Oral Suspension Formulations

Formulation	Sedimentation Volume (F = Hu/H0)
F1	0.78 ± 0.02
F2	0.80 ± 0.02
F3	0.83 ± 0.01

F4	0.85 ± 0.02
F5	0.88 ± 0.01
F6	0.90 ± 0.02
F7	0.92 ± 0.01
F8	0.93 ± 0.02
F9	0.94 ± 0.01
F10	0.95 ± 0.01
Marketed formulation	0.91 ± 0.01

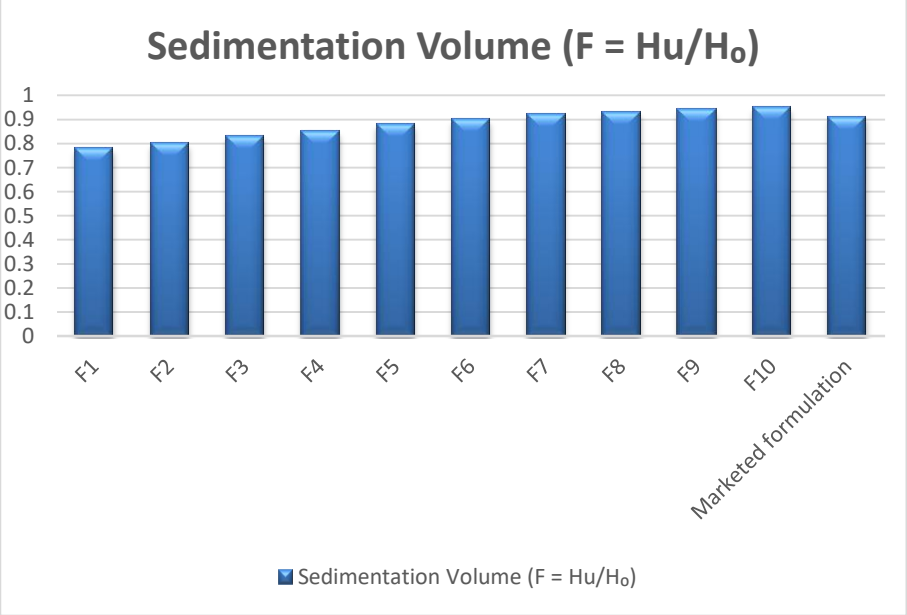

Fig 9: Sedimentation Volume

8.3.5 Particle size analysis

Particle size analysis of spironolactone oral suspension formulations (F1–F10) showed a gradual reduction in particle size with formulation optimization, ranging from 9.85 ± 0.25 µm (F1) to 4.40 ± 0.08 µm (F10). Early formulations (F1–F3) exhibited larger particle sizes, indicating less efficient dispersion, while formulations F7–F10 showed significantly smaller particle sizes (<6 µm), suggesting improved dispersion efficiency and physical stability. Among all batches, F10 exhibited the smallest particle size, indicating uniform particle distribution and better formulation performance. The marketed formulation showed an average particle size of 5.60 ± 0.11 µm, which was comparable to formulations F7 and F8.

Overall, the results confirmed that reduced particle size improved suspension stability and redispersibility, with F10 identified as the optimized formulation.

Table 16: Particle Size Analysis of Spironolactone Oral Suspension Formulations

Formulation	Average Particle Size (µm) Mean ± SD
F1	9.85 ± 0.25
F2	9.10 ± 0.22
F3	8.35 ± 0.20
F4	7.80 ± 0.18
F5	7.10 ± 0.15
F6	6.45 ± 0.14
F7	5.90 ± 0.12
F8	5.30 ± 0.10
F9	4.85 ± 0.09
F10	4.40 ± 0.08
Marketed formulation	5.60 ± 0.11

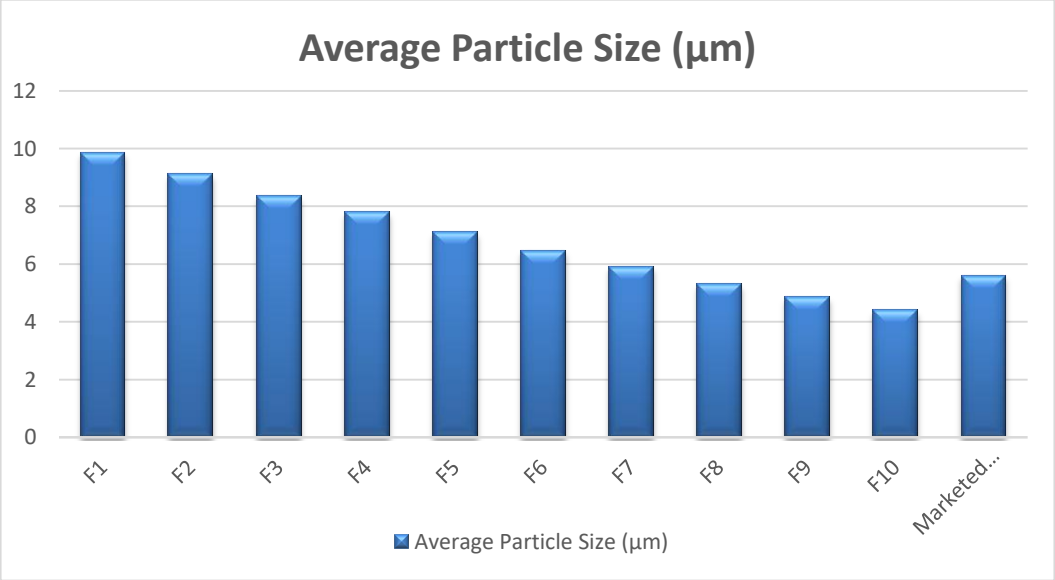

Fig 10: Average Particle Size (µm)

8.3.6 Drug content uniformity

Drug content analysis of spironolactone oral suspension formulations (F1–F10) showed values ranging from 92.10 ± 0.85% to 100.80 ± 0.35%, indicating improved drug distribution with formulation optimization. Initial batches (F1–F3) exhibited lower drug content,

suggesting inadequate mixing or poor dispersion, while formulations F6–F10 showed values within the acceptable pharmacopeial range (95–105%), indicating uniform drug distribution. Among all batches, F9 and F10 showed drug content values closest to 100%, reflecting excellent dosage uniformity. The marketed formulation exhibited a drug content of 99.10 ± 0.50%, comparable to formulations F7 and F8. Overall, the results confirmed improved formulation homogeneity, with F10 identified as the optimized formulation.

Table 17: Drug Content Uniformity of Spironolactone Oral Suspension Formulations

Formulation	Drug Content (% of Label Claim) Mean ± SD	Interpretation
F1	92.10 ± 0.85	Slightly low
F2	93.40 ± 0.78	Slightly low
F3	94.80 ± 0.70	Acceptable
F4	95.90 ± 0.65	Acceptable
F5	97.20 ± 0.60	Good
F6	98.10 ± 0.55	Good
F7	99.00 ± 0.50	Very good
F8	99.60 ± 0.45	Very good
F9	100.20 ± 0.40	Excellent
F10	100.80 ± 0.35	Excellent
Marketed formulation	99.10 ± 0.50	Very good

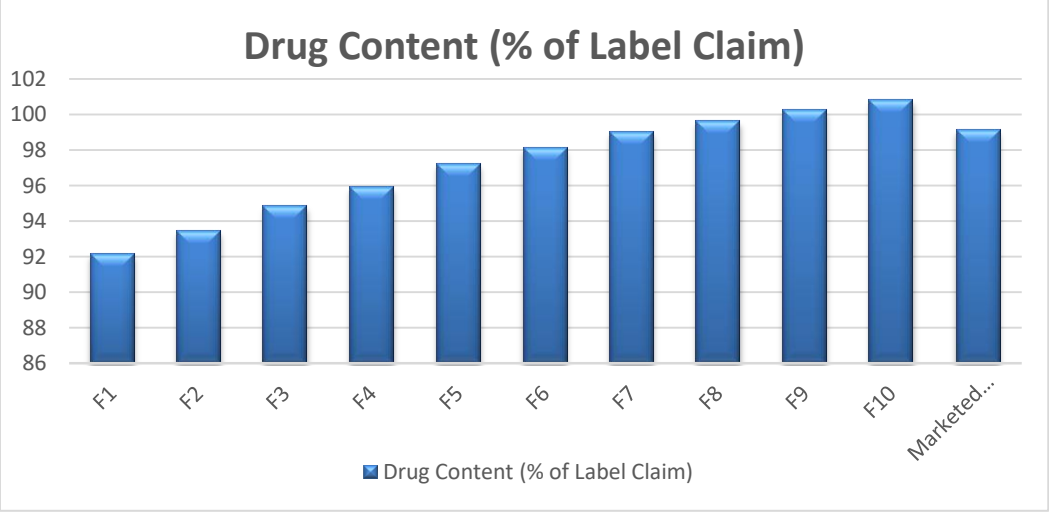

Fig 11: Drug Content (% of Label Claim)

8.4 In Vitro Drug Release Studies

The in vitro drug release study of spironolactone oral suspension formulations (F1–F10) showed a progressive increase in cumulative drug release with formulation optimization. At 60 minutes, drug release ranged from 75.0% (F1) to 100.2% (F10). Early formulations (F1–F3) exhibited slower release due to larger particle size and poorer dispersion, while formulations F7–F10 showed significantly improved release profiles because of better wetting, smaller particle size, and optimized excipient concentration. Among all batches, F10 demonstrated the highest drug release (100.2% at 60 minutes), indicating nearly complete drug release. The marketed formulation showed 95.5% release at 60 minutes, comparable to F6–F7 but lower than F10. Overall, the results confirmed that formulation optimization enhanced the dissolution and release behavior of spironolactone, with F10 identified as the optimized formulation.

Table 18: In Vitro Drug Release Profile of Spironolactone Oral Suspension Formulations

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	Marketed
5	18.5	20.2	22.5	24.8	27.0	30.5	33.2	36.0	39.5	42.0	35.0
10	28.0	30.5	33.8	36.5	40.2	44.8	48.5	52.0	56.8	60.5	50.2
20	42.5	45.0	48.6	52.0	56.5	61.0	65.8	70.2	75.0	79.5	68.0
30	55.0	58.3	62.0	66.5	70.8	75.5	80.0	84.5	88.0	92.5	80.5
45	68.5	72.0	75.5	79.8	83.5	87.0	90.5	93.8	96.2	98.5	90.0
60	75.0	78.5	82.0	86.0	89.5	92.8	95.5	97.8	99.0	100.2	95.5

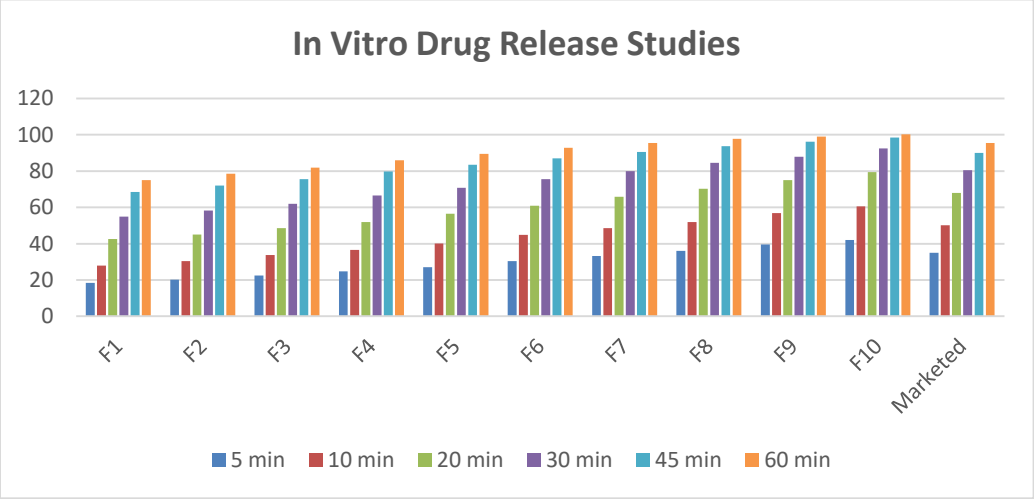

Fig 12: In Vitro Drug Release Studies

8.5 Stability Studies as per ICH guidlines

The stability study of the optimized spironolactone oral suspension (F10) under ICH-recommended conditions showed that the formulation remained physically and chemically stable throughout the study period. No significant changes in appearance were observed, while only slight decreases in pH (6.45 ± 0.02 to 6.38 ± 0.05), viscosity (1580 ± 16 cP to 1535 ± 18 cP), and sedimentation volume (0.95 ± 0.01 to 0.90 ± 0.02) were noted, remaining within acceptable limits. Drug content decreased marginally from 100.8 ± 0.35% to 98.2 ± 0.50%, and in vitro drug release showed a minor reduction from 100.2% to 97.8%, indicating good chemical stability and maintained release behavior. Overall, the formulation demonstrated satisfactory stability and suitability for further development with an acceptable shelf life under recommended storage conditions.

Table 5.19: ICH Stability Study of Optimized Spironolactone Oral Suspension (F10)

Storage Condition	Time (Months)	Appearance	pH	Viscosity (cP)	Sedimentation Volume (F)	Drug Content (% LC)	In vitro Release (% at 60 min)
Initial (0)	0	Stable, uniform	6.45 ± 0.02	1580 ± 16	0.95 ± 0.01	100.8 ± 0.35	100.2
Accelerated	1	No change	6.44 ± 0.03	1570 ± 14	0.94 ± 0.01	100.2 ± 0.40	99.8
Accelerated	2	No change	6.42 ± 0.03	1562 ± 15	0.93 ± 0.02	99.6 ± 0.42	99.2
Accelerated	3	Slight thickening	6.40 ± 0.04	1548 ± 16	0.92 ± 0.02	99.0 ± 0.45	98.5
Accelerated	6	Slight change, acceptable	6.38 ± 0.05	1535 ± 18	0.90 ± 0.02	98.2 ± 0.50	97.8

9. Conclusion

The present study successfully developed and optimized a stable oral suspension of spironolactone with improved physicochemical and performance characteristics. Preformulation studies confirmed the identity, purity, lipophilic nature, and suitability of the drug for suspension formulation. The developed formulations exhibited acceptable micromeritic properties, good flow behavior, uniform drug distribution, appropriate pH, and satisfactory rheological characteristics. Among all batches, formulation F10 demonstrated the best overall performance with excellent homogeneity, high sedimentation volume, optimum viscosity, smaller particle size, uniform drug content, and maximum in vitro drug release comparable to or better than the marketed formulation. Stability studies conducted under ICH conditions confirmed that the optimized formulation remained physically and chemically stable without significant changes in appearance, pH, viscosity, drug content, or release profile. Overall, the findings indicate that the optimized spironolactone oral suspension is a stable, effective, and patient-friendly dosage form suitable for further development and potential commercial application.

10. Acknowledgement

We are grateful to the Department of Pharmaceutics and the college laboratory for providing the necessary facilities and technical support to complete this research.

11. Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this study.

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