SPIRONOLACTONE ORAL SUSPENSION (5 mg/mL): FORMULATION STRATEGIES AND PHYSICOCHEMICAL CHARACTERIZATION

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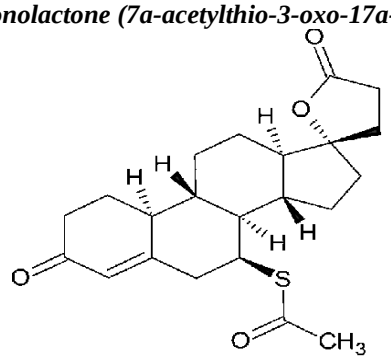
Abstract: Spironolactone is widely prescribed, but its conventional solid dosage forms are often unsuitable for pediatric, geriatric, or dysphagic patients. This study aimed to develop and evaluate a stable 5 mg/mL spironolactone oral suspension for individualized dosing and improved adherence. Micronized spironolactone was incorporated stepwise into an aqueous base containing xanthan gum, VIVA pur, and potassium sorbate, followed by comprehensive physicochemical characterization including particle size, viscosity, pH, redispersibility, and drug content uniformity via HPLC. The developed suspension was homogeneous, viscous, and readily redispersible, exhibiting excellent physical and chemical stability, uniform drug distribution, and meeting pharmacopoeial standards. This pharmaceutically acceptable and patient-friendly oral suspension offers a flexible alternative for individualized dosing, potentially enhancing therapeutic adherence and optimizing clinical outcomes in vulnerable populations.
Background: Spironolactone is a potassium-sparing diuretic widely used in cardiovascular and endocrine disorders. Conventional solid dosage forms are often unsuitable for pediatric, geriatric, or dysphagic patients.
The aim of this study is to develop and evaluate a spironolactone oral suspension (5 mg/mL) suitable for individualized dosing and clinical use.
Methods: Micronized spironolactone was incorporated stepwise into a base containing xanthan gum, VIVA pur, potassium sorbate, and purified water. Key physicochemical parameters, including particle size distribution, sedimentation, viscosity, pH, redispersibility, and drug content uniformity, were assessed. Amber glass and PET bottles with droppers were used for packaging.
Results: The suspension was homogeneous, viscous, and redispersible, with uniform drug distribution and adequate flow properties. HPLC analysis confirmed content uniformity.
Conclusion: The developed oral suspension is a pharmaceutically acceptable, patient-friendly formulation that facilitates individualized dosing and may improve therapeutic adherence in populations requiring alternative dosage forms.
Keywords: Spironolactone, Oral Suspension, Individualized Dosing, Pediatrics, Geriatrics, Dysphagia

1. INTRODUCTION

Spironolactone is a synthetic steroidal, potassium-sparing diuretic and mineralocorticoid receptor antagonist (MRA) widely used for cardiovascular, renal, and endocrine disorders like heart failure and hypertension [1,2]. It competitively blocks aldosterone at kidney receptors, inhibiting sodium/water reabsorption while reducing potassium excretion, offering mild diuretic action with potassium retention [1–3].
Beyond diuresis, spironolactone is crucial in cardiovascular medicine. It effectively treats heart failure with reduced ejection fraction (HFrEF), slowing progression and reducing morbidity/mortality (e.g., RALES trial) [4]. It also aids resistant hypertension and improves left ventricular diastolic function in heart failure with preserved ejection fraction (HFpEF) [5,6]. Antiarrhythmic effects may stem from HERG channel blockade [7]. However, anti-androgenic side effects (e.g., gynecomastia) can limit its use, sometimes favoring eplerenone, though spironolactone remains popular due to proven efficacy and lower cost [2,5].
Pharmacokinetically, spironolactone is extensively metabolized in the liver to active, long-acting metabolites, eliminated renally and biliary. Potassium and renal function monitoring is vital due to hyperkalemia risk, especially in renal impairment [8].

Recent efforts focus on oral suspension formulations for spironolactone, enabling flexible, individualized dosing for pediatric, geriatric, and dysphagic patients [9,10]. Studies confirm their stability, uniformity, and quality [9,10]. Chemically, it's a steroidal lactone (C24H32O4S, ~416.57 g/mol) related to progesterone, with a lactone ring and thioacetyl group defining its activity [1,3].

Figure 1. Chemical structure of spironolactone (7a-acetylthio-3-oxo-17a-pregn4-ene-21,17-carbolactone) (14)



Source: Authors research

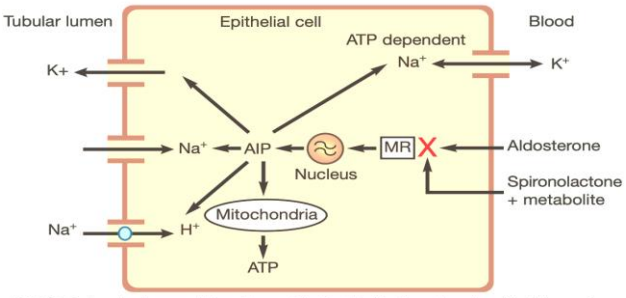
Oral Pharmaceutical Formulation of Spironolactone Spironolactone, a practically water-insoluble crystalline powder, faces significant challenges in liquid dosage form development, potentially compromising dispersion, dose uniformity, and bioavailability . While solid forms are common, liquid suspensions offer a valuable alternative for patients with swallowing difficulties, providing easier administration and flexible dosing [8,10].

Suspensions are biphasic systems where insoluble drug particles are dispersed in a liquid. Sedimentation requires careful formulation to ensure physical stability, uniform distribution, and accurate dosing. They are ideal for poorly soluble drugs, maintaining chemical stability and efficacy in liquid form [7,8].

Successful suspension formulation depends on controlling physicochemical parameters. Optimal particle size distribution is critical to improve dispersion and reduce sedimentation without causing aggregation [8]. Suspending agents (e.g., xanthan gum) increase viscosity, slowing sedimentatio. Wetting agents (e.g., polysorbates) aid hydrophobic particle dispersion [9]. Preservatives, sweeteners, flavorings, and buffering systems enhance stability, pH control, and palatability, especially for pediatric use [9].

Formulating spironolactone as an oral suspension is challenging due to its poor aqueous solubility, leading to potential wettability issues, aggregation, and rapid sedimentation. Thus, meticulous selection and optimization of excipients—including suspending, wetting, and viscosity modifiers—are crucial for product quality [9,10].

Figure 2. Mechanism of action of spironolactone (9)



NOTES. Spironolactone and its active metabolite bind to the mineralocorticoid receptor (MR) in the renal tubules blocking the synthesis of aldosterone induced proteins (AIP). This reduces Na^+ reabsorption and K^+ and H^+ secretion by various mechanisms illustrated, resulting in a diuresis and the potential for hyperkalaemia. (ATP = adenosine triphosphate.)

Source: Authors research

Evaluating spironolactone suspensions involves characterizing particle size, sedimentation, viscosity, pH, redispersibility, and drug content uniformity. Stability studies and quality control ensure physicochemical integrity and microbiological quality over its shelf life, confirming safety and efficacy [10].

Given spironolactone's importance and the need for flexible dosage forms, developing a stable oral suspension is a key research area. This study aims to develop and evaluate a spironolactone oral suspension, focusing on excipient

selection and physicochemical properties, to create a stable, pharmaceutically acceptable, and patient-friendly formulation for clinical and compounding use.

Aim of the Study This study aimed to develop and evaluate an oral spironolactone suspension, addressing the need for flexible liquid dosing in specific patient groups (pediatric, geriatric, dysphagic). We focused on selecting suitable excipients and characterizing key physicochemical parameters (e.g., particle size, sedimentation, viscosity, pH, redispersibility, drug content uniformity) to achieve a stable, pharmaceutically acceptable liquid formulation for clinical use.

2. MATERIALS AND METHODS

Formulation of Spironolactone Oral Suspension (5 mg/mL) The spironolactone oral suspension (5 mg/mL) was formulated following NRF 26.5 specifications and European Pharmacopoeia 11.3 [EP]. Each milliliter contains 5 mg spironolactone API, along with VIVA pur, xanthan gum, potassium sorbate, and purified water. The final product is intended for oral administration via dropper.

Packaging Materials Amber glass or polyethylene terephthalate (PET) bottles with screw-cap droppers were used. Child-resistant dosing devices may be considered based on risk assessment.

Table 1. Composition per 100 mL:

Ingredient	Quantity (g)
Spironolactone (micronized powder)	0.50
Xanthan gum	1.00
VIVA pur	2.00
Potassium sorbate	0.05
Purified water	q.s. to 100 mL

Source: Authors research

Packaging Materials

- Amber glass bottles with screw-cap droppers
- Amber polyethylene terephthalate (PET) bottles with screw-cap droppers
- Child-resistant dosing devices may be used depending on risk assessment

Preparation Procedure

1. ***Pre-dispersion of excipients:*** High-dispersibility silicon dioxide (if used) was triturated using a glass or stainless-steel mortar to achieve a fine, lump-free powder.
2. ***Initial wetting of API:*** The measured spironolactone powder was incorporated into approximately ten times its weight of base (1:10 ratio) and mixed thoroughly.
3. ***Incremental incorporation:*** The mixture was gradually combined with approximately five times the base (1:5 ratio) and further with additional portions of the base until approximately 20% of the total formulation volume was reached. The mixture was continuously checked to ensure a viscous suspension without coarse aggregates.
4. ***Weighing accuracy:*** The API was weighed on a calibrated balance with a maximum deviation of ±1.0% relative to the intended mass.
5. ***Progressive mixing:*** Spironolactone was blended with 1.5 times the base (1:1.5 ratio) and subsequently incorporated in successive 1:1 portions of the base to ensure uniform dispersion.
6. ***Combination with pre-prepared base:*** The active mixture was gradually added to the pre-prepared base and mixed using scraping and folding techniques to ensure homogeneity.
7. ***Final incorporation:*** The remaining base was added in two approximately equal portions with continuous mixing until a uniform, white, viscous, and translucent suspension was obtained.

Filling and Labeling

- The suspension was filled immediately after preparation.
- Labels included the NRF registration number and essential information according to pharmacy regulations:
  - "1 mL contains 5 mg spironolactone"
  - Administration instructions (e.g., "___ times/day, ___ mL")
  - "Shake well before use"
  - Expiration date.

Shelf-life: The oral suspension may be stored in amber glass or PET bottles for up to six months.

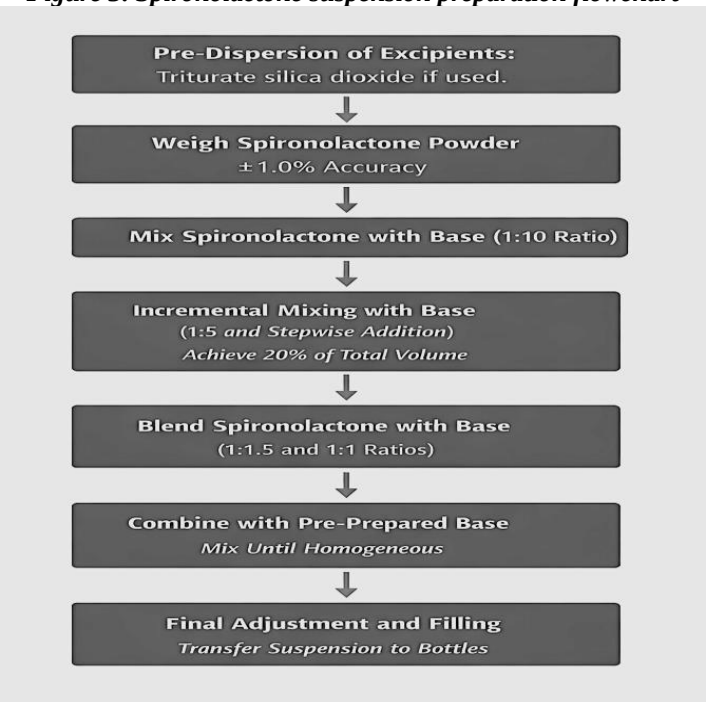
Important notes

- Weight adjustment of spironolactone may be necessary to comply with pharmacopoeial specifications.

- Bottles should have a minimum volume at least twice the contents to allow effective shaking prior to dosing.
- Release testing should be performed according to pharmacopoeial guidelines (Section 1.2.10).

3. RESULTS The preparation of a pharmaceutically acceptable spironolactone oral suspension requires careful consideration of both formulation and process parameters to ensure uniformity, redispersibility, and ease of administration. The poor aqueous solubility of spironolactone and its tendency to aggregate present significant challenges for the development of liquid dosage forms, particularly for pediatric, geriatric, or dysphagic patients. To overcome these challenges, a stepwise incorporation and progressive mixing strategy was employed, combining hydrophilic excipients such as xanthan gum and VIVA pur with potassium sorbate as a preservative.
The process flowchart presented in Figure 3 visually outlines the sequential steps necessary to produce a homogeneous suspension with consistent particle size distribution, viscosity, and drug content uniformity. Critical stages include pre-dispersion of excipients, gradual incorporation of micronized spironolactone into the base, progressive blending with the pre-prepared suspension, and final packaging into amber glass or PET bottles equipped with screw caps or child-resistant droppers. The flowchart also highlights essential quality control checkpoints, including particle size monitoring, viscosity assessment, and redispersibility verification, ensuring that the final formulation complies with pharmacopoeial standards and is suitable for clinical application.

Figure 3. Spironolactone suspension preparation flowchart



Source: Authors research

The figure 4 shows the prepared spironolactone suspension formulation stored in a pharmaceutical bottle. The formulation was compounded to obtain a uniform oral liquid dosage form suitable for accurate dosing. The suspension was packaged in an appropriate container to ensure stability, protection from environmental factors, and ease of administration.

Figure 4. Spironolactone suspension formulation in a bottle

Source: Authors research

The following tables 2, 3 and 4 presents the results of a seven-day, fourteen day and twenty-one-day points stability study for Spironolactone suspension (5 mg/ml) and the content of the preservative (Potassium Sorbate). The contents are expressed in milligrams (mg) and as a percentage (%) of the nominal value. The table shows individual measurements, average values for each series (content 1 and content 2), as well as the overall average from both series.

Table 2. Stability of Spironolactone Suspension 5 mg/ml of a seven day-point stability study and Preservative Content

Active substance content			**Preservative content**		
Seven point stability Spironolactone susp. 5mg/ml			**Seven point stability Spironolactone susp. 5mg/ml**		
Spironolactone Rf- 1.001			***Potassium sorbate Rf- 0.997***		
content 1	mg	%	content 1	mg	%
Spironolactone co 1 st.	5.00	99.98	Potassium sorbate co 1 st.	0.54	90.56
Spironolactone co 2 st.	5.03	100.56	Potassium sorbate co 2 st.	0.54	90.76
co Spironolactone average value	5.01	100.27	co Potassium sorbateaverage value	0.54	90.66
content 2			content 2		
Spironolactone 1 st.	4.99	99.72	Potassium sorbate 1 st.	0.55	91.38
Spironolactone 2 st.	5.01	100.29	Potassium sorbate 2 st.	0.55	91.59
co Spironolactone average value	5.00	100.00	co Potassium sorbate average value	0.55	91.48
Average of the two contents	**5.01mg**	**100.14%**	**Average of the two contents**	**0.55mg**	**91.07%**

Source: Authors research

Table 3. Stability of Spironolactone Suspension 5 mg/ml of a fourteen day-point stability study and Preservative Content

Active substance content			**Preservative content**		
Fourteen-day suspension of spironolactone 5 mg/ml stability point			**Fourteen-day suspension of spironolactone 5 mg/ml stability point**		
Spironolactone Rf-1.006			***Potassium sorbate Rf-1.002***		
content 1	mg	%	content 1	mg	%
Spironolactone co 1 st.	5.03	100.69	Potassium sorbate co 1 st.	0.54	90.56
Spironolactone co 2 st.	5.04	100.79	Potassium sorbate co 2 st.	0.54	90.76
co Spironolactone average value	5.04	100.74	co Potassium sorbateaverage value	0.54	90.66
content 2			content 2		
Spironolactone 1 st.	5.01	100.13	Potassium sorbate 1 st.	0.55	91.38
Spironolactone 2 st.	5.01	100.24	Potassium sorbate 2 st.	0,55	91.59
co Spironolactone average value	5.01	100,19	co Potassium sorbate average value	0.55	91.48
Average of the two contents	**5.01mg**	**100.14%**	**Average of the two contents**	**0.55mg**	**91.07%**

Source: Authors research

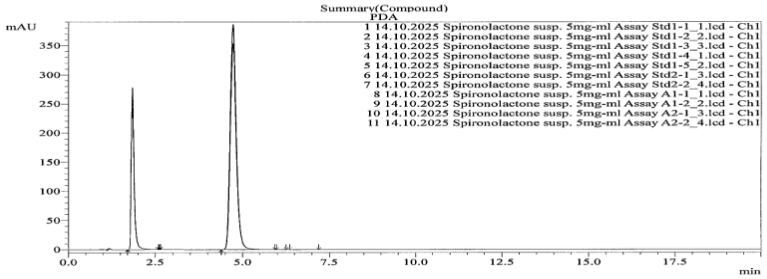
Table 4. Stability of Spironolactone Suspension 5 mg/ml of a twenty-one day-point stability study and Preservative Content

Active substance content			**Preservative content**		
Twenty-one suspension of spironolactone 5 mg/ml stability point			**Twenty-one suspension of spironolactone 5 mg/ml stability point**		
Spironolactone Rf-1.001			***Potassium sorbate Rf-1.001***		
content 1	mg	%	content 1	mg	%
Spironolactone co 1 st.	4.93	98.70	Potassium sorbate co 1 st.	0.51	84.84
Spironolactone co 2 st.	4.94	98.77	Potassium sorbate co 2 st.	0.51	84.91
co Spironolactone average value	4.94	98.74	co Potassium sorbateaverage value	0.51	84.87
content 2			content 2		
Spironolactone 1 st.	5.05	100.92	Potassium sorbate 1 st.	0.52	86.74
Spironolactone 2 st.	5.05	100.99	Potassium sorbate 2 st.	0.52	86.81
co Spironolactone average value	5.05	100.95	co Potassium sorbate average value	0.52	86.78
Average of the two contents	**4.99mg**	**99.85%**	**Average of the two contents**	**0.51mg**	**85.82%**

Source: Authors research

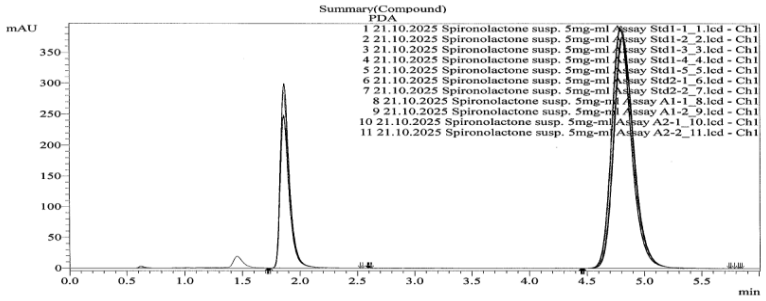
The quality control of the final formulation after the preparation and during the stability study was performed by High-Performance Liquid Chromatograph (HPLC). The figures 5, 6 and 7 shows a typical HPLC (y) chromatogram for Spironolactone suspension (5 mg/ml) during performed stability study (7, 14 and 21 day after the preparation). The x-axis represents retention time in minutes, while the y-axis represents detector response in milli-absorbance units (mAU). The chromatogram displays the separation of Spironolactone and other components, with peaks corresponding to individual assay standards and sample injections. The high-intensity peaks around 2.5 and 5.0 minutes indicate the presence of Spironolactone and the standard reference, confirming the assay accuracy and consistency across multiple injections.

Figure 5. HPLC Chromatogram of Spironolactone Suspension 5 mg/ml of a seven day-point stability study



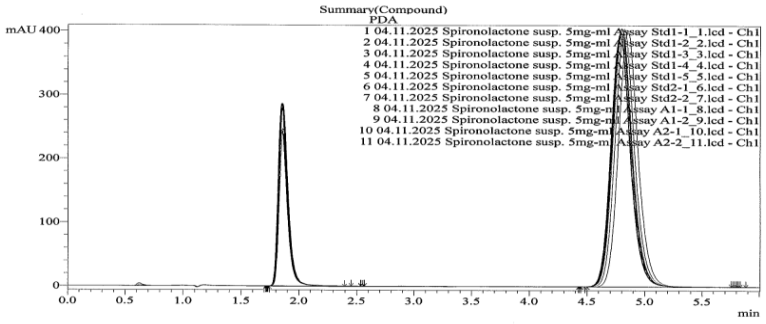
Source: Authors research

Figure 6. HPLC Chromatogram of Spironolactone Suspension 5 mg/ml of a fourteen day-point stability study



Source: Authors research

Figure 7. HPLC Chromatogram of Spironolactone Suspension 5 mg/ml of a twenty-one day-point stability study



Source: Authors research

The presented results provide a detailed interpretation of the experimental findings. HPLC profiles of spironolactone from the developed formulations were used to evaluate the drug's stability over 7, 14, and 21 days. The analysis considered retention times, peak areas, and the presence of any degradation products, enabling a comprehensive assessment of the formulations' physicochemical integrity. These observations reveal important aspects of stability behavior and potential degradation pathways, offering valuable insights into the overall suitability of the formulations for therapeutic use and their compliance with pharmaceutical development and quality control standards.

4. DISCUSSIONS

Our study successfully developed a 5 mg/mL spironolactone oral suspension, addressing the need for flexible dosing in pediatric, geriatric, and dysphagic patients where solid forms are problematic. Spironolactone's therapeutic importance in cardiovascular and endocrine disorders is well-established, making a liquid formulation crucial [1–3].

Overcoming challenges like spironolactone's poor aqueous solubility and instability [9], we used hydrophilic suspending agents (e.g., xanthan gum) and incremental API incorporation. This yielded a homogeneous, viscous, and redispersible suspension with consistent drug distribution, preventing aggregation and caking, in line with pharmaceutical principles [10,].

Rigorous process control and stepwise blending ensured a pharmaceutically acceptable suspension. The final product exhibited optimal particle size, sedimentation, viscosity, and redispersibility, allowing for easy dropper administration. Potassium sorbate provided microbiological safety, and VIVA pur with pH adjustment ensured good organoleptic properties. Validated HPLC confirmed consistent drug content and stability.

This patient-friendly oral suspension offers flexible, individualized dosing, likely enhancing adherence. Best practices were followed with amber glass/PET packaging and child-resistant closures. While beneficial, ensuring dose accuracy in compounded suspensions remains vital, stressing the need for standardized protocols. Future work should validate its utility through pharmacokinetic, bioavailability, and clinical outcome studies.

5. CONCLUSIONS

This study successfully developed a spironolactone oral suspension (5 mg/mL), providing a flexible, patient-friendly dosage form for pediatric, geriatric, and dysphagic populations. Through optimized excipient selection and controlled preparation, we achieved a homogeneous, viscous, and redispersible suspension with uniform drug distribution, accurate dosing, and acceptable organoleptic properties.

These findings align with studies emphasizing robust formulation strategies for compounded oral suspensions, highlighting the importance of galenic dispersion, dosing accuracy, and physicochemical evaluation for quality and stability [9,10].

In conclusion, the developed spironolactone oral suspension is a pharmaceutically acceptable and clinically relevant formulation. It facilitates individualized dosing, improves patient adherence, and broadens spironolactone's therapeutic reach in populations needing alternative dosage forms. Future research should investigate its pharmacokinetics, bioavailability, and long-term clinical outcomes to further validate its potential.

ACKNOWLEDGEMENTS

The author gratefully acknowledges **Pharmacy Higija Pharm, Bitola**, for their valuable support in the preparation of the formulation presented in this specialist work, and **Replek AD, Skopje**, for conducting the quality control analyses and ensuring the quality and reliability of the prepared product.

Their expertise, cooperation, and support were essential for the successful completion of this work.

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