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PREPARATION AND STABILITY EVALUATION OF MESNA ORAL SOLUTION FROM COMMERCIALLY AVAILABLE TABLETS FOR PEDIATRIC PATIENTS

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Abstract: This study focused on the formulation and evaluation of a pediatric oral solution of mesna, a chemoprotective agent used to mitigate urotoxicity associated with chemotherapy drugs, such as ifosfamide and cyclophosphamide. Given the challenges faced by pediatric patients in swallowing tablets, an extemporaneous oral solution was developed to improve accessibility and compliance. The formulation process involved adjusting the pH to approximately 3 using citric acid, which not only enhanced mesna's water solubility but also acted as an antioxidant and flavor enhancer. The study assessed the physicochemical stability of the mesna solution over a 90-day period and evaluated parameters such as color stability, pH consistency, and drug content. The results demonstrated that the oral solution maintained its physicochemical properties with minimal changes in pH and drug concentration, indicating good stability under refrigerated conditions. Additionally, microbiological evaluations confirmed the safety of the formulation. This study highlights the potential of an extemporaneous mesna oral solution as a viable alternative for pediatric patients, ensuring effective treatment while addressing the challenges related to medication administration or shortages.

Keywords: mesna, extemporaneous preparations, oral solution, and pediatric patients.

Pediatric oncology has undergone a remarkable transformation in recent decades, with chemotherapy playing a pivotal role in improving patient outcomes. This advancement has instilled a renewed sense of hope for a cure among young patients and their families [1]. The dramatic progress in survival statistics can be largely attributed to the incorporation of more aggressive and refined chemotherapy protocols, which have become the cornerstone of modern pediatric cancer treatment [2]. Nonetheless, chemotherapy medications can lead to significant side effects, including nephrotoxicity, myelosuppression, and symptoms such as nausea and vomiting [3]. One of the commonly used chemotherapeutic agents in pediatric solid tumors is ifosfamide (IFOS) and cyclophosphamide (CYLO), two oxazaphosphorine antineoplastic agents that pose a high risk for developing hemorrhagic cystitis (HC), a condition in which the bladder lining becomes inflamed leading to hematuria. HC can be severe if no prophylactic mesna is used [4].

Mesna, sodium 2-sulfanylethanesulfonate, is a thiol-containing substance that is a vital pharmacological agent commonly used to prevent and manage urotoxicity associated with some chemo agents, particularly with IFOS and CYCLO [10]. This uroprotective effect of mesna is attributed to its ability to neutralize and detoxify acrolein, a toxic metabolite produced during the metabolism of these chemotherapeutic medications within the urinary tract. Mesna's clinical use in pediatrics is off-label, with dosing typically following 60-100% of the ifosfamide dose split into 3-4 daily administrations. For example, a child receiving ifosfamide 1.2 g/m² would require mesna 240 mg/m² IV at 0 hours, followed by 480 mg/m² orally at 2 and 6 hours. Although IV mesna is used in pediatrics at 20% of the ifosfamide dose (e.g., 240 mg/m² every 4 hours), its benzyl alcohol

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content poses risks such as gasping syndrome in neonates, limiting its use [5]. Mesna is absorbed from the intestine and quickly oxidized during absorption to its disulfide dimesna once it enters the bloodstream, and is subsequently eliminated by the kidneys [6]. Glutathione reductase reduces between 30% and 50% of glomerularly filtered dimesna back to mesna in the renal tubular epithelium. The resultant sulfhydryl can react with toxic oxazaphosphorine metabolites in the bladder, including acrolein and 4-hydroxy-ifosfamide [7].

Mesna is available in various dosage forms, including parenteral and solid tablet formulations. The availability of oral mesna formulations, such as Uromitexan® tablets (400-600 mg) and Mesnex® tablets (400 mg), has been widely examined, as these are commonly accessible worldwide. Although intravenous mesna remains the primary choice in clinical settings, oral formulations are often favored for outpatient care because of their convenience [8]. On the other hand, pediatric-specific oral mesna solutions are not commercially available, often requiring healthcare providers to prepare extemporaneous formulations using tablets or intravenous products during supply shortages. Additionally, the safety and efficacy of parenteral mesna in pediatric patients remain unestablished due to its benzyl alcohol content (10.4 mg/mL), which has been linked to severe adverse effects such as gasping syndrome, neurological deterioration, seizures, intracranial hemorrhage, and death. These risks underscore the need for alternative approaches, including the preparation of oral solutions from mesna tablets in clinical practice [9].

This extemporaneous preparation is exceptionally useful for patients who have difficulty swallowing tablets or when a supply chain issue prevents medication from being made available, as in the case of the coronavirus crisis [10]. Therefore, it is essential to ensure that extemporaneous preparations accurately maintain both efficacy and safety [11].

Mesna is freely soluble in water (1 g/2.5 mL), slightly soluble in methanol, and insoluble in organic solvents. It exhibits stability at a pH of approximately 3, but degrades under alkaline conditions. Upon oxidation, mesna decomposes into its disulfide form, dimesna. To prevent degradation, excipients such as citric acid, which is used as a pH adjuster, and vitamin C, which serves as an antioxidant, are compatible and effective stabilizers [12]. The mesna was formulated in a beverage or syrup and the stability study indicated that mesna 20 or 50 mg/mL in flavored syrup is stable at 24°C for up to seven days; while mesna 1, 10, or 50 mg/mL in carbonated beverages or apple or orange juice is stable at 5°C for at least 24 hours. The factors that may have jointly contributed to the stability of mesna include an acidic pH, a protein-free matrix, carbon dioxide saturation, and EDTA, as suggested by the smaller mesna concentration changes after 24 h in juices and acidic carbonated beverages compared with milk and by the loss of mesna in the control that did not contain EDTA. Minimizing the exposure of mesna to air during storage slowed its conversion to dimesna [13]. Moreover, in a stress stability study, mesna showed high resistance to acidic degradation, thermal degradation, and photodegradation and was more susceptible to alkaline and oxidative stress [14].

Preparing mesna oral solution from tablets addresses the specific needs of children who cannot swallow by providing a more accessible and age-appropriate administration method [15]. Furthermore, extemporaneous formulations provide patients and healthcare professionals with the option of continuing treatment without affecting outcomes due to common drug shortages. It may be possible to administer medicines on an outpatient basis, saving time and money by minimizing the requirement for inpatient care [10]. Although mesna is frequently used in clinical settings in IV or oral forms for adults, a proper pediatric formulation is limited to extemporaneous preparation from IV formulation only, based on the study conducted by Goren et al. [16]. Preservative-free pediatric formulations utilize citric acid to create an acidic pH environment that naturally inhibits microbial growth, eliminating the need for synthetic preservatives [10]. These formulations comply with European Pharmacopoeia standards, maintaining aerobic microbial counts below 10^2 CFU/mL and retaining at least 90% of their original potency over 90 days [17]. In addition, limited, yet conflicting data exist regarding its physical, chemical, and microbiological qualities during the dosing period. Consequently, the objective of this study was to formulate and thoroughly assess the quality and stability of an oral solution of mesna prepared from available oral tablets.

EXPERIMENTAL

Materials

Mesna (purity 99.8%) was purchased from Sigma-Aldrich, USA. Excipients such as citric acid and vitamin C were obtained from Astrix Pharma, Riyadh, Saudi Arabia. The simple syrup was received as a generous gift from the King

Faisal Medical Complex hospital (KFMC) Batch no. 1D022N (Patrin Pharma Skokie, USA). All other solvents were of analytical grade, and double-distilled water was used for all preparations.

Commercial mesna tablets (Uromitexan®, 400 mg; Temmler Pharma GmbH, Germany) were used for compounding. According to the product information and batch documentation, each tablet contains the following excipients: microcrystalline cellulose, crospovidone, lactose, calcium phosphate dibasic dihydrate, cornstarch, povidone, magnesium stearate, hydroxypropylmethylcellulose, polyethylene glycol, titanium dioxide, and simethicone.

Assay for Mesna

The chromatographic analysis was conducted according to the method described previously by Rizk et al. [14]. A Water Breeze2™ HPLC system (Waters Corporation, Milford, U.S. A) with an automated sampling system (Waters™ 2695 Plus Autosampler, USA) and a photodiode array detector (Waters™ 2998) was used. The HPLC system was examined by Breeze2 (Water™) software. The pH measurements were conducted using a pH 212 meter (Hanna Instruments, Germany), while the Fourier Transform Infrared (FTIR) analysis was performed using a Nicolet 6700 FTIR spectrophotometer (Thermo Fisher Scientific. USA).

The chromatographic analysis was carried out using a Supelco RP amide C16 column (150 × 4.6 mm, 5 µm particle size). The mobile phase consisted of a mixture of methanol and phosphate buffer in a 10: 90 (v/v) ratio, with the apparent pH adjusted to 3 using ortho-phosphoric acid. Prior to use, the mobile phase was filtered through a 0.45 µm membrane filter and degassed for 30 minutes in an ultrasonic bath. The chromatographic conditions included a flow rate of 1 mL/min, UV detection at 210 nm, and an injection volume of 20 µL. All analyses were performed at ambient temperature with a run time of 5 minutes [14].

The calibration curve for mesna was prepared using a series of dilutions from a stock standard solution. Aliquots containing 0.5 to 10.0 mg of mesna were transferred to 10 mL volumetric flasks and diluted with distilled water. Each concentration was analyzed in triplicate by injecting 20 µL into the HPLC system under the previously described chromatographic conditions. The resulting peak areas were plotted against their corresponding concentrations to construct the calibration curve using linear regression analysis. HPLC method validation was conducted, and excellent linearity was demonstrated with an R^2 value of 0.9998 across the concentration range of 0.5-10 mg/mL. High accuracy was observed, with recovery rates ranging from 98.2% to 101.3%, and precision was confirmed by a relative standard deviation (RSD) of less than 2% for both intra-day and inter-day measurements.

To prepare samples for analysis, 5 mL aliquot of each formulation, equivalent to 10 mg of mesna, was accurately transferred to a 100 mL volumetric flask and diluted to volume with distilled water. This solution was then further diluted to achieve a final concentration of 0.4 mg/mL mesna. For HPLC analysis, 20 µL aliquots of this diluted sample were injected into the chromatographic system [14].

Oral Solution Preparation

Three film-coated Uromitexan® tablets (400 mg each) were finely crushed in a glass mortar to obtain a homogeneous powder. The powder was dispersed in a measured volume of water for injection and stirred for 10 minutes while being protected from light. After ensuring complete dispersion, the resulting suspension was filtered directly through a sterile 0.22 µm Millex® syringe filter into a clean glass beaker, with no pre-filtration step required. This filtration effectively removed insoluble excipients, such as magnesium stearate and titanium dioxide, resulting in a visually clear and homogeneous solution.

Following filtration, the required excipients (as specified in Table 1) were weighed separately using an analytical balance and added to the filtrate. The mixture was stirred for an additional 10 minutes, shielded from light, and the vehicle was added to achieve the desired final mesna concentration of 2 mg/mL. The solution was stirred for an additional 30 minutes in the dark until it became visually clear and homogeneous. The final preparation was

Table 1. Composition of the mesna formulations.

Formula code	Ingredients
Formulation 1 (F1)	Mesna 100 mg Vit C 250 mg Simple syrup 25 mL Purified water 25 mL
Formulation 2 (F2)	Mesna 100 mg Citric acid 250 mg Citric acid anhydrous 250 mg Vit C 250 mg Simple syrup 25 mL Purified water 25 mL
Formulation 3 (F3)	Mesna 100 mg Citric acid 250 mg Vit C 250 mg Simple syrup 25 mL Purified water 25 mL

then transferred to amber glass bottles, sealed with polypropylene caps, and stored under refrigerated conditions. These standardized formulations were used for subsequent physical, chemical, and microbiological analyses to ensure consistency and suitability for pediatric administration [18]. These prepared bottles were used for subsequent physical, chemical, and microbiological studies, ensuring a standardized and controlled sample for comprehensive analysis [19].

Evaluation of Prepared Mesna Solution Formulations

The prepared mesna solution formulations underwent comprehensive physical, chemical, and microbiological evaluations to ensure compliance with the established quality standards and suitability for clinical use. While the ICH Q1A guidelines recommend a minimum of 12 months for long-term stability studies at 5°C, our study evaluated stability over 90 days under refrigerated conditions, which aligns with the typical usage period for extemporaneous formulations in clinical practice. The study followed the ICH Q1A principles for sampling intervals, analytical method validation, and monitoring of physicochemical and microbiological parameters. The samples were analyzed at predetermined intervals (days 0, 7, 14, 28, 60, and 90) to systematically evaluate their stability over a 90-day period, ensuring the formulations maintained their integrity and efficacy throughout the study duration [20].

Physical and Chemical Examinations

Physical Evaluation

The appearance and color of the solutions were recorded immediately after preparation. After a three-month storage period under the specified conditions, the same physical assessments were conducted periodically to evaluate for any changes.

Drug Excipient Interaction Study

During the formulation process, ensuring compatibility between the drug and excipients is crucial. Fourier transform infrared (FTIR) spectroscopy was used to achieve this. This technique recorded the spectra of the newly formed combinations of the drug and excipients. The analysis was conducted using an FT-IR spectrometer equipped with an attenuated total reflectance (ATR) accessory, where the samples were placed on a cleaned ATR crystal. Spectra were obtained from 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1}, averaging between 16 and 32 scans. Data processing involved baseline correction and normalization, with characteristic peaks identified by comparison with reference data. This comprehensive approach provided valuable insights into the interactions between the drug and excipients, ensuring formulation stability and efficacy.

Drug Content Test

Five milliliters of the formulation were diluted to 100 mL with distilled water. The resulting solution was filtered through a 0.45 µm membrane. Subsequently, 1 mL of the filtrate was further diluted to 100 mL. The prepared samples were analyzed via HPLC, with three replicates conducted per batch to ensure accuracy and reproducibility.

pH Test

The samples were analyzed using a pH meter that had been previously calibrated with standard buffer solutions. The pH measurements were performed in triplicate by inserting the electrode directly into the sample at 25°C without prior dilution.

Microbiological Examination

Microbiological testing of the formulation was conducted at King Saud University's Microbiology Lab at intervals of 0, 14, 30, and 90 days, following the European Pharmacopeia guidelines for nonsterile products. The process was initiated by diluting 10 mL of the sample in 90 mL of nutrient broth and mixing thoroughly. Prepared and sterilized soybean agar and Sabouraud dextrose agar media were poured into Petri dishes, each containing 20 mL of medium. After the agar solidified, 0.1 mL of the diluted formulation was applied to the surface of each medium. The incubation conditions were as follows: casein soybean digest agar plates were incubated at 35°C for three days, whereas Sabouraud dextrose agar plates were incubated at 25°C for five days, with daily observations recorded. In addition to the samples, positive controls (*Escherichia coli* ATCC 8739) and negative controls (sterile broth) were used to confirm assay reliability. All experiments, including the controls, were conducted in duplicate. Colony counting was conducted, and the mean number of colony-forming units (CFU) per mL was calculated and documented for each formulation. To meet microbial standards, liquid oral formulations were required to have a total aerobic microbial count below 10^2 CFU/mL and a total combined mold count of less than 10^1 CFU/mL [17].

Statistical Analysis

The *in vitro* performance differences of mesna solution formulations were statistically analyzed using one-way analysis of variance (ANOVA) using statistical software. Differences were considered significant at p-values less than 0.05 ($p < 0.05$).

RESULTS AND DISCUSSION

Oral Mesna Formulation

The mesna pediatric oral solution was developed using safe excipients, including citric acid, vitamin C, and simple syrup, while avoiding harmful excipients such as benzyl alcohol, saccharin sodium, and propylene glycol (Figure 1). To enhance the water solubility of mesna, the pH of the formulation was carefully adjusted to approximately 3 by incorporating citric acid. This adjustment not only improved solubility but also provided additional benefits, as citric acid acted as an antioxidant and flavor enhancer [21]. Whereas, vitamin C contributed additional antioxidant properties and improved flavor [22]. Simple syrup was included to further enhance the taste, making the medication more acceptable for children. This careful selection of ingredients ensured the formulation's safety and efficacy, thus addressing the specific needs of pediatric patients undergoing chemotherapy. This study highlights the importance of using non-toxic excipients in developing oral solutions for children to ensure both therapeutic effectiveness and patient compliance [23]. The formulation aimed to provide an effective and palatable option for young patients who may have difficulty swallowing traditional dosage forms [24].

Physicochemical Properties

The oral mesna solution exhibited consistent physicochemical properties throughout the 90-day study period when stored at 2°C – 8°C as shown in Table 2. Initially, the preparation was clear with a slight yellow color and the pH of the solution was around 3. These characteristics remained stable with no noticeable changes in color or clarity. The pH of the solution showed minimal variation over time, with no statistically significant differences detected ($p > 0.05$). The overall pH change was negligible at 0.02, which did not affect the mesna concentration in the solution [25]. Importantly, the uniformity of mesna content remained robust, with the solution maintaining at least 98% of the initial drug concentration throughout the study period [25]. These results indicate that the formulated mesna oral solution demonstrated good stability under the specified storage conditions for up to 90 days [25].

Color stability was monitored throughout the study, as changes in color can signify chemical degradation or interactions within the formulation.

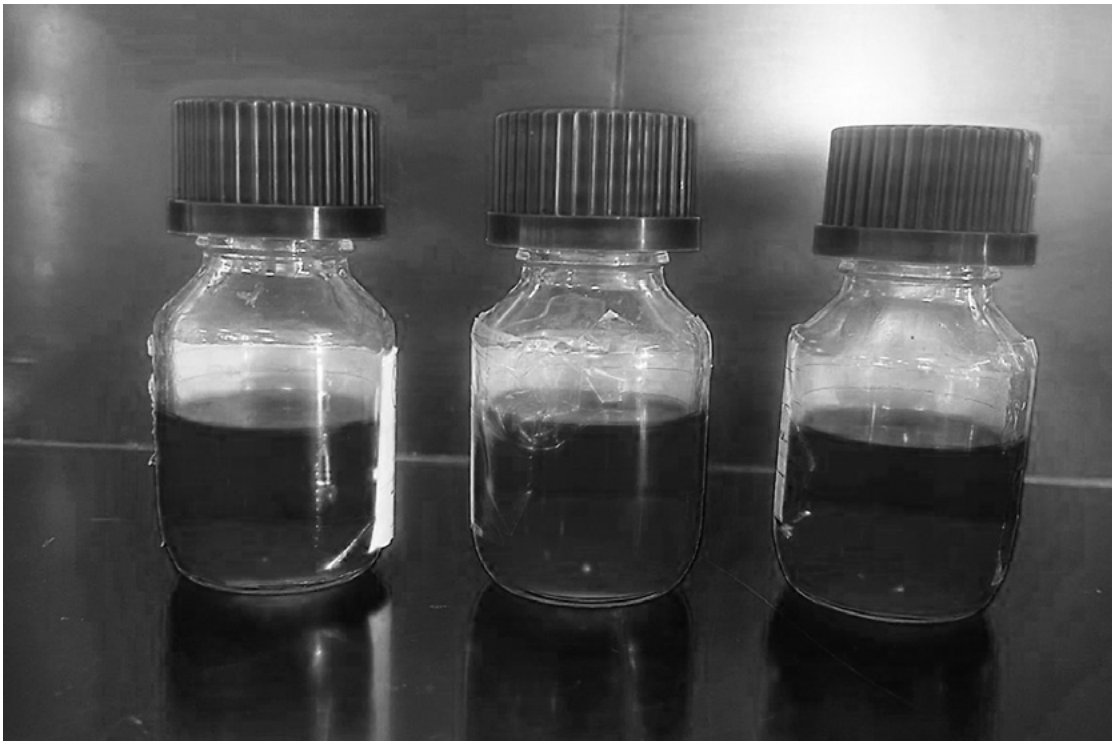

Figure 1. Photograph of prepared mesna oral solution formulations F1, F2, and F3 (from left to right).

Table 2. Physicochemical characteristics of mesna oral solution formulations over three months (days 0, 7, 14, 28, 60, and 90).

Time interval	Formulation 1			Formulation 2			Formulation 3		
	Color	pH	Drug content %	Color	pH	Drug content %	Color	pH	Drug content (%) ± SD
Days 0	Clear and slightly yellow	4.31	100	Clear and slightly yellow	3.34	100	Clear and slightly yellow	3.72	100 ± 0.8
Days 7		4.31	99.8		3.33	99.7		3.68	99.3 ± 0.67
Days 14		4.32	99.5		3.34	99.2		3.69	99.1 ± 1.3
Days 28		4.31	99.1		3.34	99.1		3.69	98.7 ± 0.76
Days 60		4.31	98.3		3.35	98.9		3.80	98.3 ± 1.8
Days 90		4.32	98.1		3.34	98.6		3.71	98.0 ± 1.33

Consistent coloration is not only important for patient acceptability but also serves as a visual indicator of product integrity [26]. The pH measurements were conducted regularly, as pH plays a vital role in maintaining the chemical stability of both the active ingredient and excipients. Proper pH control is essential for preserving the drug's efficacy, ensuring optimal absorption, and maintaining the overall shelf-life of the oral solution [27].

Drug content analysis was performed periodically to verify the accuracy and consistency of the active pharmaceutical ingredient concentration. This parameter is critical for ensuring that each dose delivers the intended therapeutic effect and meets the regulatory requirements for content uniformity [28]. The data demonstrated that the oral solutions consistently met the established requirements for such formulations throughout the three-month study period. This consistency in meeting quality standards is indicative of a well-formulated and stable product.

Drug Excipient Interaction Study

The FT-IR spectra of the drug and excipients are presented in Figures 2–4. The infrared spectrum of mesna features a distinctive band at 2204 cm^{-1}, attributed to the stretching vibration of the thiol group (-SH). This band is typically of weak to medium intensity and often appears as a broad peak, with its exact position subject to slight variations depending on the thiol group's environment, such as hydrogen bonding interactions. In contrast, the infrared spectrum of vitamin C is characterized by a strong, broad absorption band at 3309 cm^{-1}, which corresponds to the stretching vibration of the hydroxyl (-OH) groups present in its molecular structure. These spectral features serve as key identifiers for these compounds in infrared spectroscopic analysis. Analysis of these spectra revealed no evidence of incompatibility between the drug and the excipients. This conclusion was drawn from the absence of new peaks in the spectra of the drug-excipient mixtures. The only notable

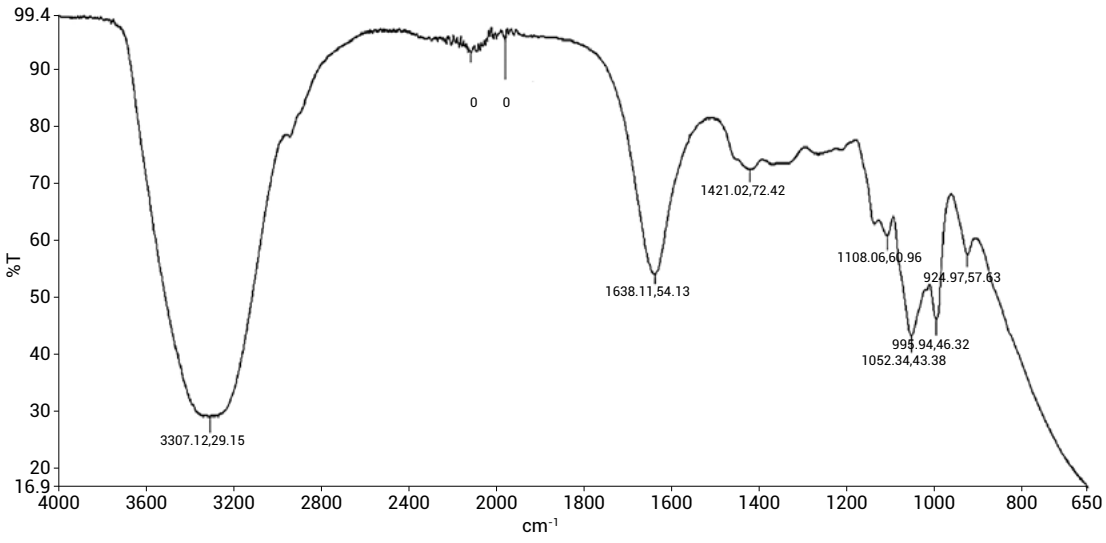

Figure 2. FTIR for formulation 1.

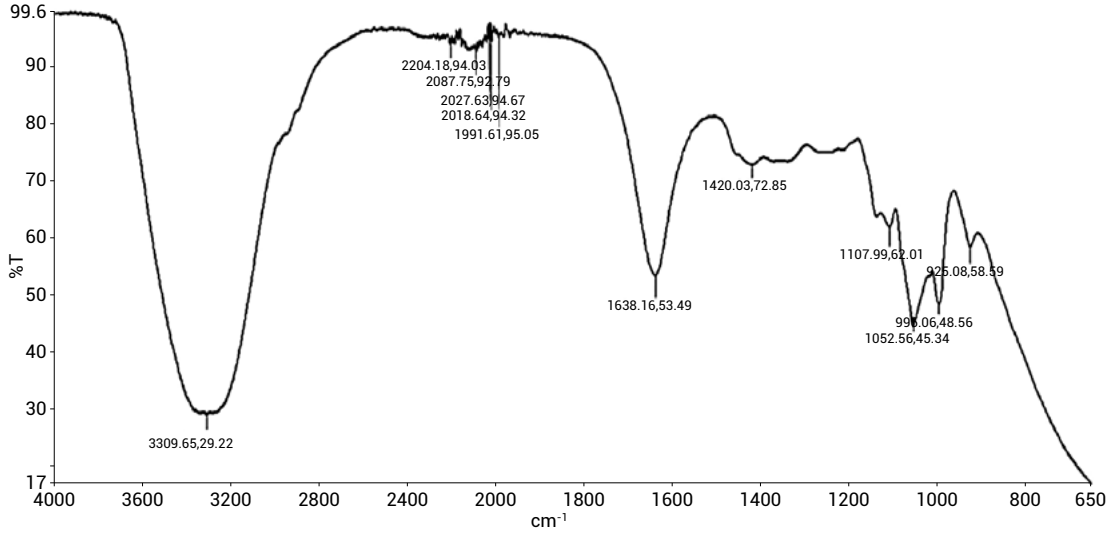

Figure 3. FTIR for formulation 2.

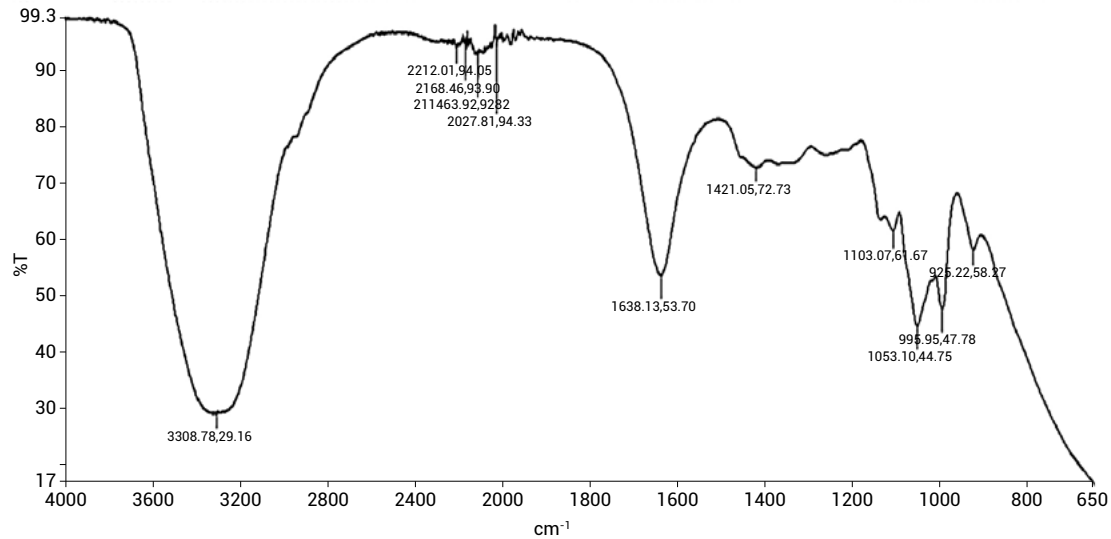

Figure 4. FTIR for formulation 3.

change observed was a reduction in the intensity of the existing peaks, which could be attributed to the dilution effect caused by mixing the drug with excipients. This dilution effect is a common and expected phenomenon in such mixtures and does not indicate any chemical interaction or incompatibility [29].

Microbiological Examination

The microbiological stability of the formulations was thoroughly evaluated over a 90-day period and yielded remarkable results. No visible bacterial or yeast growth was detected in the quality control solutions of the formulations after 90 days under various conditions. Initially, the samples were seeded using dilutions of 10^{-2} and 10^{-3}; however, due to a lack of bacterial growth, the decision was made to seed the solutions directly [30]. Even with this direct seeding approach, no microbial growth was observed under any of the tested conditions, as shown in Figures 5, 6, and 7.

The formulation's remarkable resistance to microbial contamination could be attributed to its intrinsic properties. The oral solution's composition, particularly its pH level, appears to create an environment that is highly unfavorable for microbial growth. This inherent characteristic effectively serves as a natural preservative system, inhibiting the proliferation of bacteria and yeast [31].

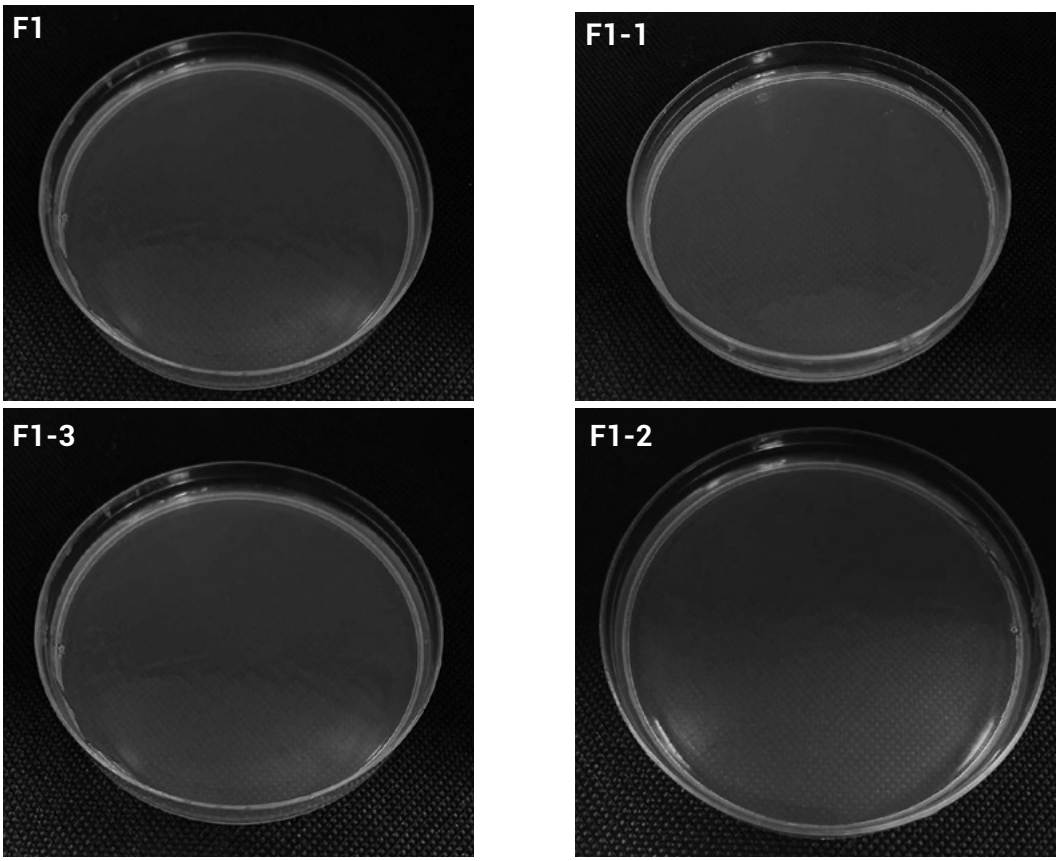

Figure 5. Microbiological testing results for oral formulation 1 (F1); the tests were conducted in triplicate.

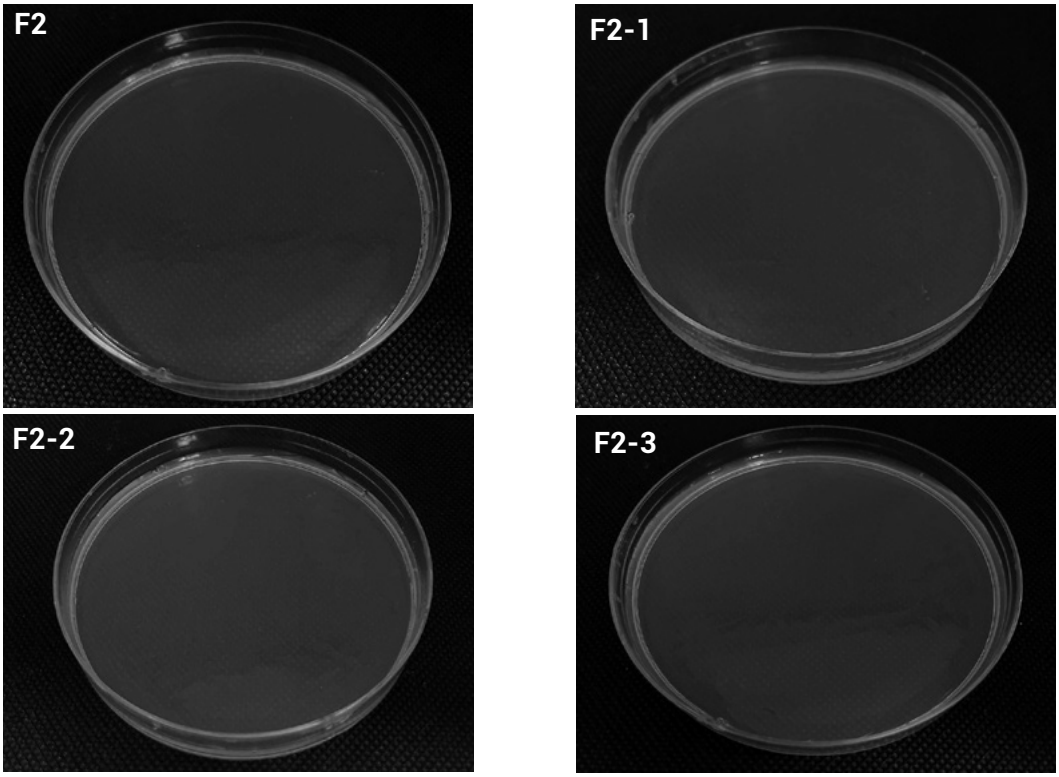

Figure 6. Microbiological testing results for oral formulation 2 (F2); the tests were conducted in triplicate.

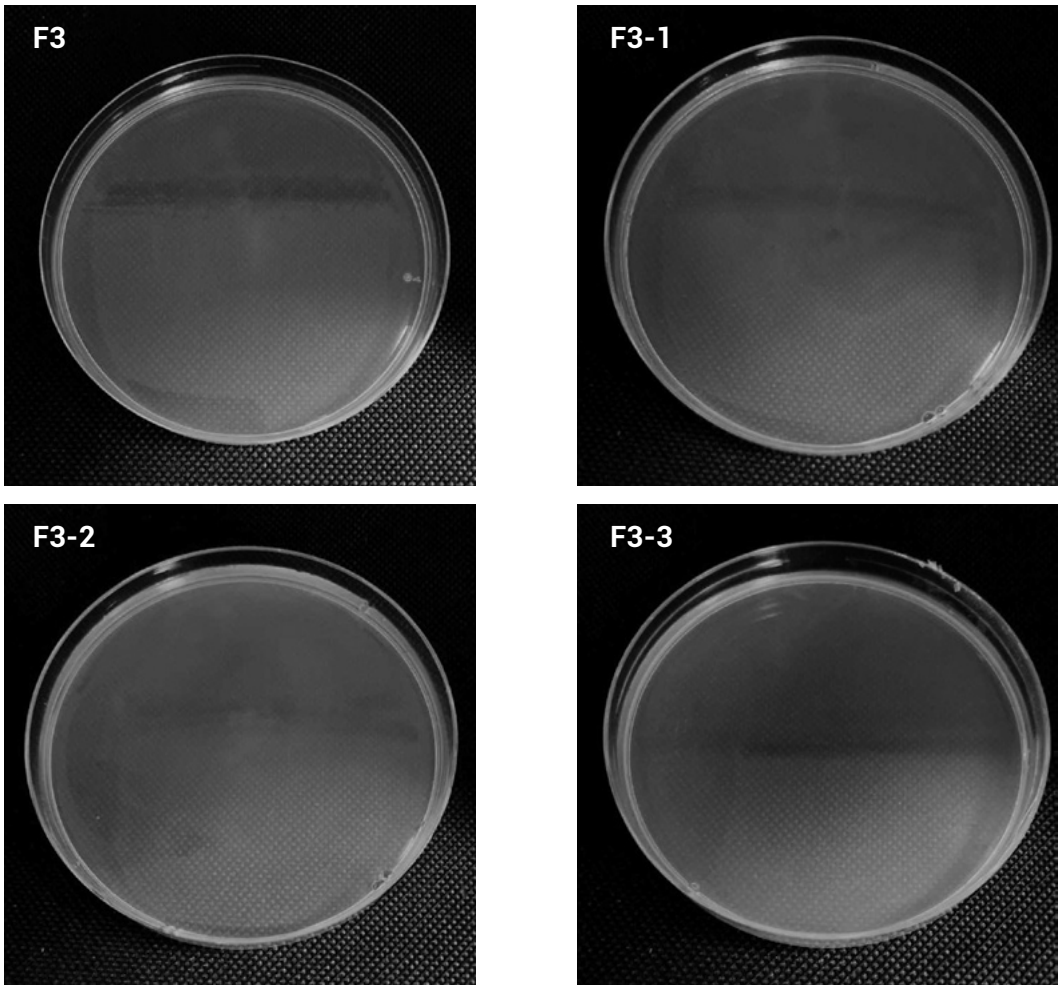

Figure 7. Microbiological testing results for oral formulation 3 (F3); the tests were conducted in triplicate.

These findings hold particular significance for liquid formulations, which are typically more vulnerable to microbial contamination than solid dosage forms [32]. The results reveal that these liquid formulations demonstrate impressive microbiological stability, effectively inhibiting microbial growth and thereby ensuring both safety and efficacy throughout their shelf life [33]. This strong microbiological profile, combined with established physicochemical stability, significantly enhances the overall quality and safety of the formulations, making them reliable options for patient use.

CONCLUSIONS

The newly developed preservative-free oral mesna solution offers a transformative approach for pediatric oncology patients, particularly those with swallowing difficulties. Unlike traditional extemporaneous preparations, which remain stable for only seven days at room temperature or 14 days refrigerated, this optimized formulation achieves a 90-day refrigerated shelf life (2°C-8°C) through sterile 0.22 μm filtration and refined storage protocols. The solution maintains ≥ 90% potency retention while complying with European Pharmacopoeia microbial standards (< 10^2 CFU/mL) and ICH Q1A stability guidelines. By replacing synthetic additives with citric acid as a natural preservative, it addresses pediatric safety concerns while providing precise dosing accuracy and a palatable slightly sweet taste. The formulation also retains room-temperature stability post-dispensing, reducing reliance on error-prone compounding and enabling flexible, body surface area-adjusted dosing. These advancements collectively enhance treatment accessibility, compliance, and safety profiles, positioning this ready-to-use liquid as a critical tool for improving outcomes in pediatric cancer care.

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Author's Contribution

Research concept and design: S.A. and A.A.;
experimental works and assembly of data: N.A.;
Data analysis and interpretation: B.A.;
Writing the article: S.A., W.S., B.A.;
Critical revision of the article: N.A.;
Final approval of the article: S.A.

Conflict of Interest Statement

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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