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Quality and Stability Evaluation of Extemporaneously Compounded Losartan Potassium Oral Suspension at the Hospital Pharmacy

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Authors' contributions

This work was carried out in collaboration among all authors. Author IMA managed the literature searches, designed the study, wrote the protocol, managed the analyses of the study and wrote the first draft of the manuscript. Author NA performed the experiments, managed the literature searches, managed the analyses of the study and wrote the first draft of the manuscript. Author EE performed some experiments. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The purpose of this study was to evaluate the quality of an extemporaneous formulation of losartan potassium oral suspensions from crushed losartan potassium tablets to ensure that the compounded suspension maintained its quality attributes during its storage period.
Methodology: Losartan potassium suspensions were compounded extemporaneously in the same way they are prepared for patients at a hospital pharmacy. The suspensions were kept in the refrigerator at 4°C and evaluated immediately and after 9, 18, and 28 days. Suspension ease of redispersion, color, odor, pH, particle size, zeta potential, viscosity, and sedimentation volume were all evaluated. In addition, microbiological stability, drug content, and drug dissolution were assessed.

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Results: During the study period, the extemporaneously compounded suspension retained its color and odor, and the pH profile remained consistent. Moreover, all suspensions were easily resuspended in a homogeneous liquid with gentle shaking, and no caking was detected. Furthermore, the results of the microbiological test revealed no microbial growth. The content uniformity and dissolution test results met the pharmacopeial requirements. The findings revealed that the losartan potassium compounding procedure was reliable and capable of producing 2.5 mg/mL of losartan potassium suspension using commercially available tablets and Ora-Blend as a suspending vehicle. Furthermore, after 28 days in the refrigerator (4°C), the suspension had acceptable quality features.

Conclusion: Extemporaneously compounded suspension allows physicians to prescribe a variable dose that adjusts to each patient's needs, providing treatment when the liquid dosage form is unavailable.

Keywords: Quality control; extemporaneous; losartan potassium; suspension; stability.

1. INTRODUCTION

Losartan potassium is a nonpeptide, orally active, and highly selective type 1 angiotensin II receptor blocker (ARBs) [1]. Losartan potassium was the first orally active AT1 receptor blocker available on the market, and it is the antagonist with the highest reported clinical experience. It is among the primary agents used as first-line treatment for hypertension in adult patients [2]. Numerous studies have found losartan potassium to be effective in children aged 1 month to 16 years. Losartan potassium was the first ARB approved for high blood pressure control in children by the United States Food and Drug Administration (FDA) in 2004 in response to FDA and European Medicines Agency (EMA) regulatory initiatives for pediatric clinical trials. The recommended dose for patients >20 to 50 kg is 0.7 mg/kg/day (max 25 mg) and 50 mg/day for patients >50 kg. The dose should be adjusted based on the response [3–7]. The tablet form is the only available oral dosage form of losartan potassium. Therefore, extemporaneous compounding of losartan oral suspension is performed in various hospitals globally [8].

"Extemporaneous compounding is defined by the FDA as the act of combining, mixing, or changing substances to produce a sterile or nonsterile medicated dosage form that is customized to a patient's needs" [9]. "It is a long-standing practice to compound extemporaneous formulations when there is no commercially available dosage form for dose adjustment or an appropriate dosage form for the patient's needs" [10,11]. Extemporaneous compounding is an important part of the healthcare system because it delivers a useful service. For example, a healthcare professional may request that a pharmacist compound a liquid dosage form for a patient who is unable to swallow a medication in its commercially available form, a method approved by the FDA [12,13]. FDA-approved drugs are produced in line with good manufacturing practices standards (GMPs). The FDA regulates and audits pharmaceutical manufacturing plants on a regular basis to ensure GMP compliance. Hospital pharmacies, on the other hand, are exempt from GMP regulations and are inspected only by the authorities on rare occasions. Therefore, compared with FDA-approved medications, extemporaneously compounded formulations offer less assurance of consistent quality [9,14]. Extemporaneously compounded formulations cannot be assumed to maintain their purity and original strength over time because the expiry date of such items is not validated by testing the stability of the formulation. Furthermore, unlike generic medications, compounded products are not clinically assessed for their safety and efficacy, nor is bioequivalence testing performed [11]. When formulating extemporaneous preparations, quality must be built in from the early stages to the final product [15].

The extemporaneous compounding of suspensions from tablets or capsules available on the market is a common practice in hospital pharmacies [16,17]. Oral suspension is a dispersion of finely divided particles distributed somewhat uniformly throughout a liquid medium [18]. In general, suspended particles may slowly separate during storage but are easily redispersed. In the preparation of extemporaneous compounded oral suspensions, measures should be taken to achieve a suitable and controlled particle size and, consequently, a slow rate of sedimentation and dosing consistency [19]. The crushing of tablets and selection of the suspending vehicle are

challenging issues in the extemporaneous compounding of oral suspensions. Certain characteristics should be present in an ideal suspending agent. It should generate a structured vehicle and be nontoxic. In addition, it should be compatible with other formulation constituents [20]. "Ora-Blend® is commonly used as a suspension vehicle in the extemporaneous compounding of oral suspensions and is a ready-to-use taste-masking oral liquid vehicle that is manufactured in accordance with GMP standards. The suspending vehicle creates a structured gel-like matrix that suspends particles while allowing for minimal settling. Moreover, to help minimize oxidative degradation of the active component, it is buffered to a slightly acidic pH of 4.2. Ora-Blend® has previously been shown to be compatible with a wide range of active ingredients" [21–26].

The aim of the present study was to formulate and evaluate an extemporaneous preparation of losartan potassium oral suspensions from crushed losartan potassium tablets to ensure that the compounded suspension maintained its quality attributes during its storage period.

2. MATERIALS AND METHODS

2.1 Materials

Losartan potassium tablets (Sortiva®, 50 mg, SPIMACO) were purchased from a local pharmacy. A list of excipients in the tablets formulation (Sortiva®) are as follows: microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, purified talc, magnesium stearate, polysorbate, titanium dioxide, polyethylene glycol, hydroxypropyl methylcellulose, and purified water. Losartan potassium B.P., which is the reference standard (≥99.5% purity), was obtained from SPIMACO, Qassim, Saudi Arabia. Ora-Blend® (Perrigo, Australia) was purchased from Amazon. Tryptic soya broth was purchased from Sigma-Aldrich, India, and Lennox L Broth was purchased from Invitrogen, UK. Microorganisms, including *Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis, Shigella sonnei,* and *Candida albicans,* were obtained from the United States. All materials used were of analytical grade.

2.1.1 Extemporaneous preparation of losartan potassium oral suspension

In our lab, losartan potassium compounded oral suspensions were prepared according to the method used at hospital pharmacies [27]. In brief, losartan potassium tablets (10 tablets: 1.8541 g) were crushed into a fine, uniform powder (1.8033 g) using a mortar and pestle for 2 minutes then triturated with a small amount of Ora-Blend® and diluted with Ora-Blend® into a final volume of 200 ml to produce a losartan potassium concentration of 2.5 mg/ml. Then, the suspension was poured into an amber glass bottle and stored in a refrigerator (4°C). Aliquots of the suspensions were removed and examined immediately following preparation (a fresh sample) and on days 9, 18, and 28.

2.1.2 Visual appearance and organoleptic properties

The color of the compounded suspensions was visually examined by placing the sample in a clear glass beaker against a black background. Moreover, the ease of redispersion, caking signs, and odor changes were inspected. The control was the suspension vehicle (Ora-Blend®).

2.1.3 Changes in pH value

By using a bench pH/ORP meter HI 2211 (Hanna Instruments, UK), the pH value of the compounded suspensions was determined (n=3). Before each test, the pH meter was calibrated using standard buffer solutions of pH 3.00, 4.00, 7.00, and 10.00.

2.1.4 Sedimentation volume

The sedimentation volume was calculated (n=3) as a ratio of the final volume of the sediment as the suspension settles, V_u, to the original volume of the suspension, V_o [20]. The following equation was used:

$$F = \frac{V_u}{V_0} \qquad \text{Equation (1)}$$

2.1.5 Viscosity measurements

The viscosity of the compounded suspensions was measured (n=3) using a Brookfield R/S Plus Rheometer with spindle C50-1 (Middleboro, Massachusetts, USA). At room temperature, the formulation (0.25 g) was placed on a plate, and the RPM was set at 400.

2.1.6 Particle size and zeta potential

Using photon correlation spectroscopy (PCS) with a zetasizer (Nano ZS, Malvern Instruments,

UK), the particle size, polydispersity index (PDI), and zeta potential of the compounded suspensions were measured after being adequately diluted (n=3) at room temperature.

2.1.7 Microbiological test

At each sampling point, microbiological tests of suspensions were performed in triplicate. The media were validated to ensure their competence in culturing various microorganisms [28]. Two types of media were employed. Initially, Soyabean-Casein Digest was incubated (22°C) to allow *Staphylococcus aureus, Bacillus subtilis* bacteria, and fungi to grow. The second type of media used was Fluid Thioglycollate, which was incubated at 35°C and used to culture *Shigella sonnei* bacteria. The media were examined for fermentative qualities in a growth promotion test. In each media, two tubes were infected with the specified strain (no more than 100 CFU) and incubated for 3 days [29]. From each medium, two tubes were incubated for 14 days concurrent with each inoculation, with no evidence of the microorganism's growth (negative control). Also, two tubes were inoculated with the appropriate microorganism and incubated for 3 days (positive control). At each sampling point, each aliquot of suspension was analyzed (n=3). After 14 days of incubation, 1 ml of each inoculated medium was transferred to a new vessel of the same medium and incubated for at least 4 days alongside the original because the suspension being tested made the media turbid, leading to visual inspection being unreliable in establishing the presence or absence of microbial growth [30].

2.1.8 Content uniformity test

Using the method for measuring content uniformity for liquid dosage forms described in the United States pharmacopeia, the content uniformity of the compounded suspensions was determined. The compounded suspensions were well mixed, and 30 samples were taken and examined from each container. If the acceptance value (AV) of the first 10 samples is less than L1 (L1=15), the preparation passes the test. If the AV exceeds L1, the remaining samples are tested to determine the AV. If the final AV of the 30 samples is less than L1 and none of the samples resulted in less than [1-(0.01) (L2)]M or larger than [1 + (0.01) (L2)]M, (L2=25), the preparation passes the test.

To calculate the AV, the following equation was used:

$$AV = \left|M - \overline{X}\right| + \mathrm{ks} \qquad \text{Equation (2)}$$

$\overline{X}$ is the mean of individual contents of each sample (x_1, x_2,…..x_n), which is expressed as a percentage of the label claim. When the target content (T) is ≤ 101.5, the reference value (M) is equal to ($\overline{X}$). *k* is the acceptability constant (k=2.4 when n=10 and k=2 when n=30). *s* is the sample standard deviation [31]. The drug content values were determined at 256 nm using ultraviolet (UV) spectrophotometry (Libra S22 UV/Vis. Biochrom Ltd., Cambridge, UK).

2.1.9 Dissolution test

The dissolution test was carried out according to United States pharmacopeia recommendations for losartan potassium tablets. A USP dissolution apparatus II (Pharma Test, DT 70, Hainburg, Germany) was used at 50 rpm and 37 ± 0.5°C in 900 mL deaerated distilled water and under sink conditions. Five milliliters of the suspension sample were withdrawn and placed into the dissolution medium midway between the top of the rotating blade and the surface of the dissolution medium. Aliquots were taken at predetermined times (5 min, 10 min, 20 min, and 30 min) and filtered using a 0.22 µm pore size filter. To keep the volume constant, an equivalent volume of the freshly heated dissolving medium was replaced. The samples were suitably diluted and analyzed at 256 nm using ultraviolet (UV) spectrophotometry (Libra S22 UV/Vis. Biochrom Ltd., Cambridge, UK). According to USP, the acceptance criterion for a dissolution test is a function of Q (percentage of the labeled content of drug dissolved at a given time). The dissolution test is a three-stage test. In the first stage of testing (S1), six units were examined. To pass the S1 acceptance criteria, each unit must be Q + 5% dissolved at a given time. If this condition is not met, six further units are evaluated at stage 2 (S2). To meet the S2 acceptance criterion, the average of all 12 units must equal or exceed, and no unit should have less than Q - 15%. If these conditions are not met, stage 3 (S3) testing of 12 more units is required. To pass S3, the average of all 24 units must equal or exceed Q. Two other conditions must also be met: no more than two units are less than Q - 15% dissolved, and no units are less than Q - 25% dissolved [31].

Table 1. Organisms inoculated for the microbiological test validation

Organism Type	Name	Number
Gram-positive bacteria	*Staphylococcus aureus*	ATCC 25923
	Bacillus subtilis	ATCC 6633
Gram-negative bacteria	*Shigella sonnei*	ATCC 11060
	Pseudomonuas aeruginosa	ATCC 27853
Fungi	*Candida albicans*	ATCC 10231

2.1.10 Stability study

The compounded suspensions were evaluated for quality control at different time points, as described above. On the day of preparation (fresh) and on days 8, 18, and 28 after preparation and storage at 4°C, each bottle was shaken manually for 1 min, and a sample was then collected from each bottle and analyzed.

2.2 Statistical Analysis

All statistical analyses were performed using Minitab 19.1 Statistical Software (Minitab Inc., State College, Pennsylvania).

A one-way analysis of variance (ANOVA) was applied to determine statistical significance, when necessary. A *p*-value <0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Extemporaneous Preparation of Losartan Potassium Oral Suspension

The lack of a commercially available suspension of losartan potassium poses a problem for pediatric and adult patients who are unable to swallow tablets [8]. In extemporaneous compounding, an existing dosage form is modified to meet the unique needs of patients [32]. Although compounding has been a part of the pharmacist's professional skill for hundreds of years, the quality of the products being compounded has received insufficient attention [33]. The goals of the present study were to assess various quality attributes and the stability of losartan potassium extemporaneously compounded suspensions stored in refrigerators for 28 days.

3.2 Visual appearance and organoleptic properties

The extemporaneously compounded suspension retained its white color and odor during the 28-day study at 4°C. It also had an acceptable appearance. These characteristics are important because they contribute to increased patient compliance, especially for the treatment of long-standing conditions such as cardiac diseases [34].

3.3 pH measurement

Over the 28 days of the investigation, the pH of the extemporaneously compounded suspension remained consistent (4.79±0.08 to 4.81±0.14) with no significant difference ($p>0.05$) in the pH profiles. This could be attributed to the presence of sodium phosphate monobasic and citric acid (buffering system), which keeps the pH levels within the Ora-Blend® pH range (3.5–5.0) [22].

3.4 Sedimentation volume

The calculated sedimentation volume of the extemporaneously compounded suspensions remained consistent (0.7±0.04 to 0.75±0.04) over the study period, and there was no significant difference ($p>0.05$) (Fig. 1). The sedimentation volume, F, is defined by equation 1 as the ratio of the equilibrium volume of the sediment, V_u, to the total volume of the suspension, V_0. The value of F should generally be between 0 and 1, with 1 being the optimal system [20,35].

Suspensions tend to settle over time; therefore, it was important to evaluate the sedimentation volume over the study period. Sedimentation or caking may cause redispersing of the suspension difficult, resulting in an inaccurate dosing [20]. Suspensions should always be thoroughly shaken before use to ensure uniform distribution of the suspended particles in the suspending vehicles" [36]. "Throughout the 28 days of the study period, all suspensions were easily resuspended into a homogeneous liquid with gentle shaking, and no caking was detected. This attribute of compounded suspensions was because of the Ora-Blend® vehicle. Ora- Blend® is a synergistic blend of suspending ingredients (xanthan gum and carrageenan) that produce a gel-like matrix preventing suspended particles from settling [22,37].

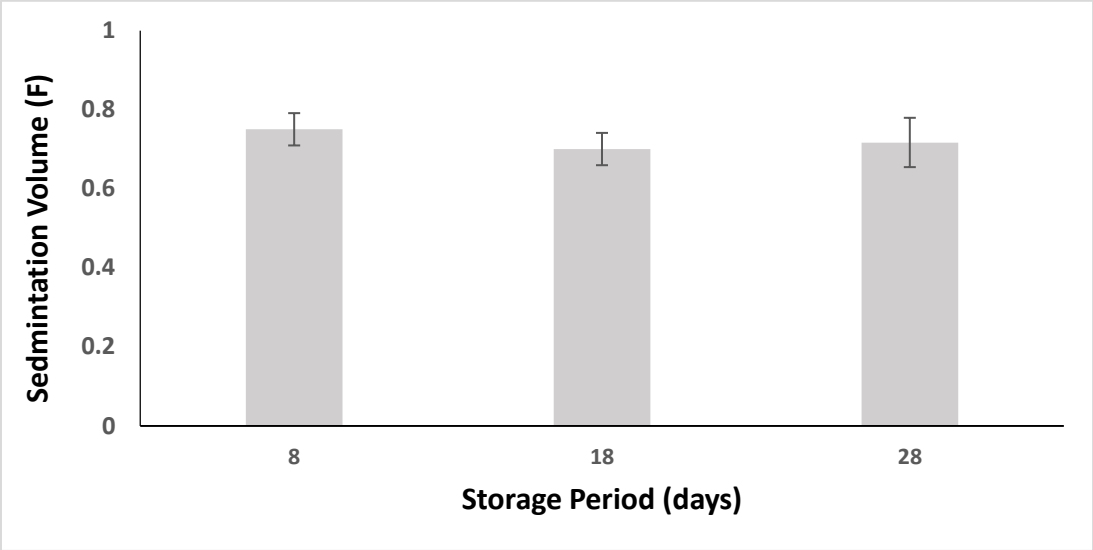

Fig. 1. The calculated sedimentation volume of extemporaneously compounded suspensions over 28 days of storage at 4°C (n=3, mean±SD, *p* > 0.05)

3.5 Viscosity Measurements

The measured viscosity of the extemporaneously compounded suspensions remained consistent (9.75±0.11 to 10.3±0.6) over the study period (Fig. 2). The changes in the viscosity of the observed suspensions were insignificant ($p>0.05$), indicating that 28 days of storage at 4°C did not affect the viscosity of the extemporaneously compounded suspensions. The viscosity of the extemporaneously compounded suspensions is critical because it affects the ease of redispersibility, pourability from the bottle, and, hence, the dosing accuracy [20]. For instance, some spironolactone suspensions have been reported to be extremely thick and difficult to pour [38].

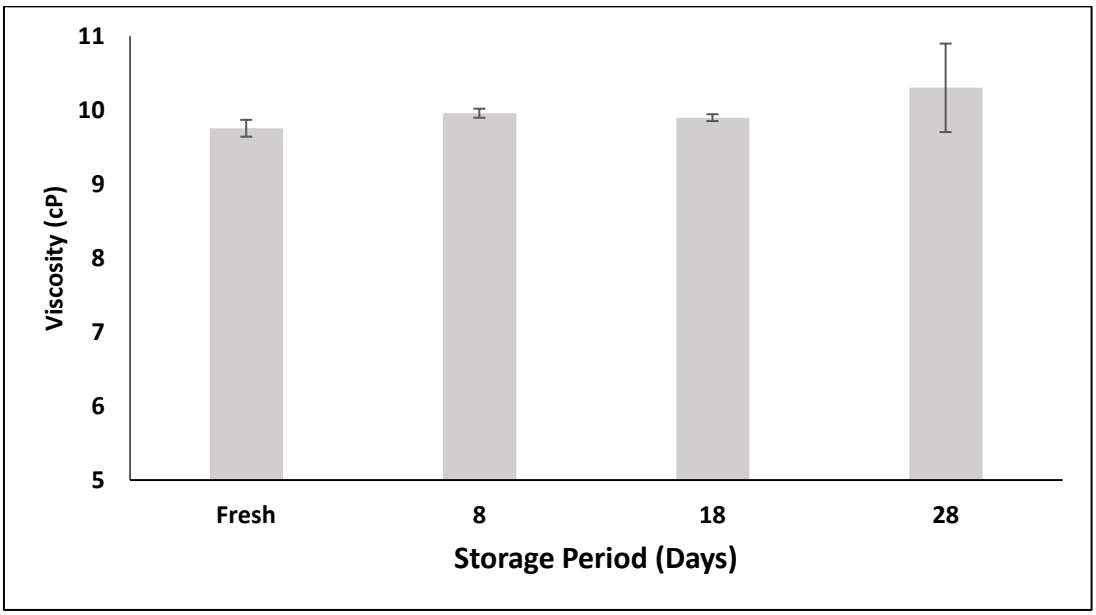

Fig. 2. The viscosity of extemporaneously compounded suspensions over 28 days of storage at 4°C (n=3, mean±SD, *p* > 0.05)

3.6 Particle Size and Zeta Potential

The particle size measurements showed no aggregation of particles over the study period (Fig. 3, $p>0.05$). Crushing tablets is an important step in the preparation of extemporaneous suspensions. The grinding technique used can have an impact on the suspension's homogeneity. Moreover, if the suspension is required to be stored before the doses are administered, the particles may agglomerate. As a result, professional skills are critical in creating high-quality extemporaneous suspensions. The zeta potential is monitored occasionally to ensure optimum zeta potential because it is a common characterization technique that indicates the stability of the suspension. To create a flocculated, noncaking suspension with optimum sedimentation volume, the zeta potential must be controlled to stay within a range (usually less than 25 mV) [39].

3.7 Microbiological Test

The results of the microbiological test revealed no microbial growth at each time point during the 28 days of storage at 4°C. This could be attributed to the Ora-Blend® vehicle used in the present work, which contained preservatives (methylparaben and potassium sorbate) that can help reduce the possibility of microbial growth [37]. Microbial contamination could put patients at serious risk. Moreover, microbial degradation products can cause chemical changes in compounded suspensions. Furthermore, the growth of microorganisms can generate an unpleasant odor in the preparation and cause viscosity changes [40]. Microorganisms may be introduced during the compounding of extemporaneous preparations or dosing. For instance, in one case, immunocompromised patients became infected by *Candida albicans*, which was accidentally introduced into freshly prepared multidose citric acid solutions intended for oral use in cough reflex testing [41]. Even though the pharmacopeia does not demand that an oral suspension be sterile, microbial growth resistance must be maintained in accordance with the given standards. A suitable preservative must be included to prevent microbial growth development that may occur during the preparation or use [42].

3.8 Content Uniformity Test

Fig. 4 shows the determined percentage of the drug content for 10 samples. The AV characterizes the scatter in the drug content for samples of the tested suspensions taken independently; this was used to quantitatively evaluate the content uniformity. Table 2 demonstrates that the AV was less than 15, indicating that all samples met pharmacopeial standards. Content uniformity is an important quality test for the final solid dosage form because it ensures that a consistent dose of the drug is maintained between batches so that the patient receives the correct dose. When compounding extemporaneous suspensions, the uniformity of content is especially important when using tablet grinding. The active ingredient needs to be evenly distributed throughout the suspension to ensure that each dose of the suspension has an equal amount of the drug. For instance, extemporaneous amiodarone preparation was unable to control arrhythmia in patients, which was attributed to the fact that amiodarone is nearly insoluble in water, and in the absence of a suspending agent, most of the drug will be in solid form at the bottom of the measuring device [38].

3.9 Dissolution Test

A dissolution test quantifies the active ingredient released from the dosage form under controlled experimental conditions using specified dissolution equipment according to compendial specifications. The test was first designed for solid dosage forms (capsules and tablets), but it is now applicable to suspensions and other dosage forms. These compendial dissolution specifications are generally single-point dissolution tests rather than profiles performed at many sample points to determine the curve of the amount of drug dissolved versus time [43]. Fig. 5 shows that, after 30 minutes, the percentage of losartan potassium dissolved was within the established USP limits for immediate-release oral dose forms [31]. In all samples, dissolution levels of nearly 100% were achieved. The dissolution test could be used to predict in vitro bioavailability. Extemporaneously compounded suspension bioavailability was not evaluated in the present study. The absorption and therapeutic efficacy of the active ingredient in a suspension compounded from crushed tablets is unlikely to change from the original dosage form used in its compounding. In fact, because tablets or capsules containing active components are used as the drug source, most extemporaneously formulated drugs do not undergo bioavailability and pharmacokinetic studies.

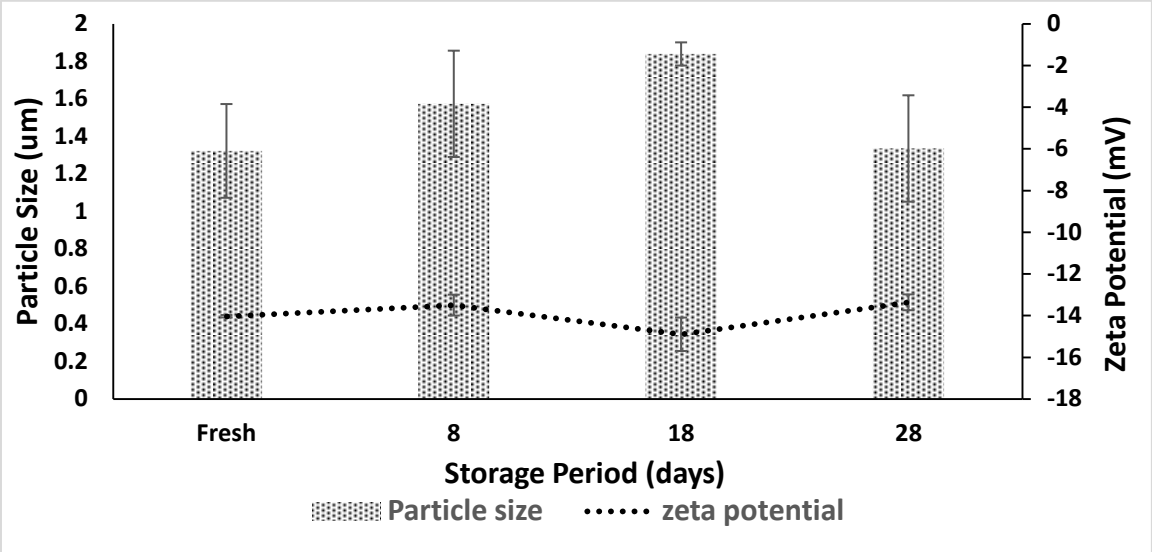

Fig. 3. The particle size and zeta potential of extemporaneously compounded suspensions over 28 days of storage at 4°C (n=3, mean±SD, *p* > 0.05)

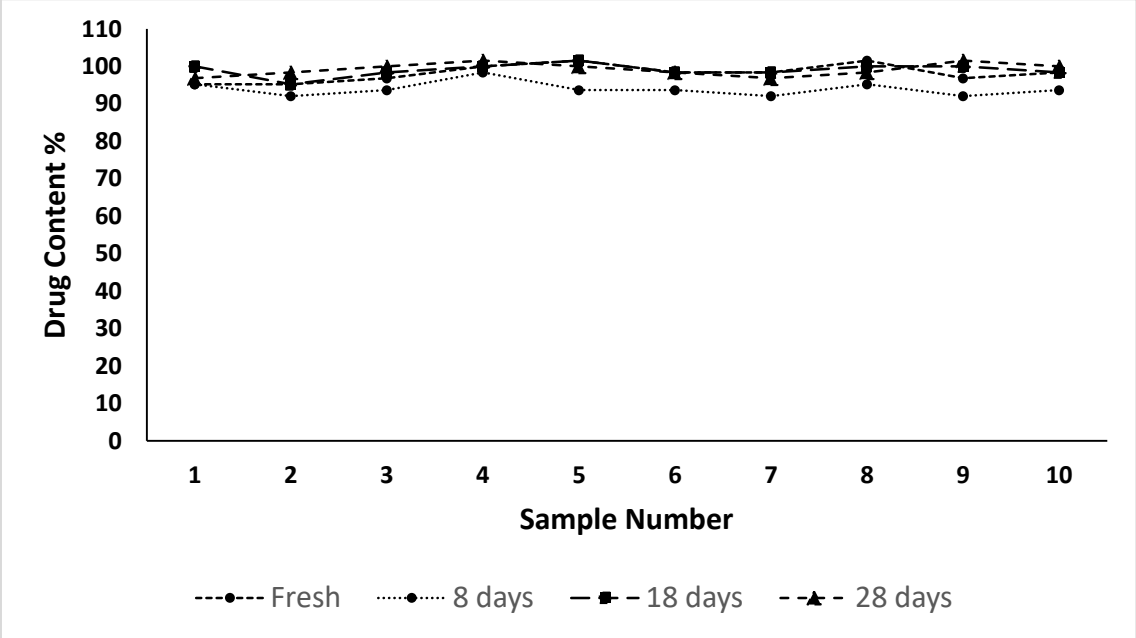

Fig. 4. The determined individual percentage of losartan potassium content in extemporaneously compounded suspensions over 28 days (n=10)

Table 2. The calculated acceptance value of extemporaneously compounded suspensions over 28 days (n=10)

Storage period	Fresh	8 days	18 days	28 days
Acceptance value	5.49	9.25	4.07	4.09

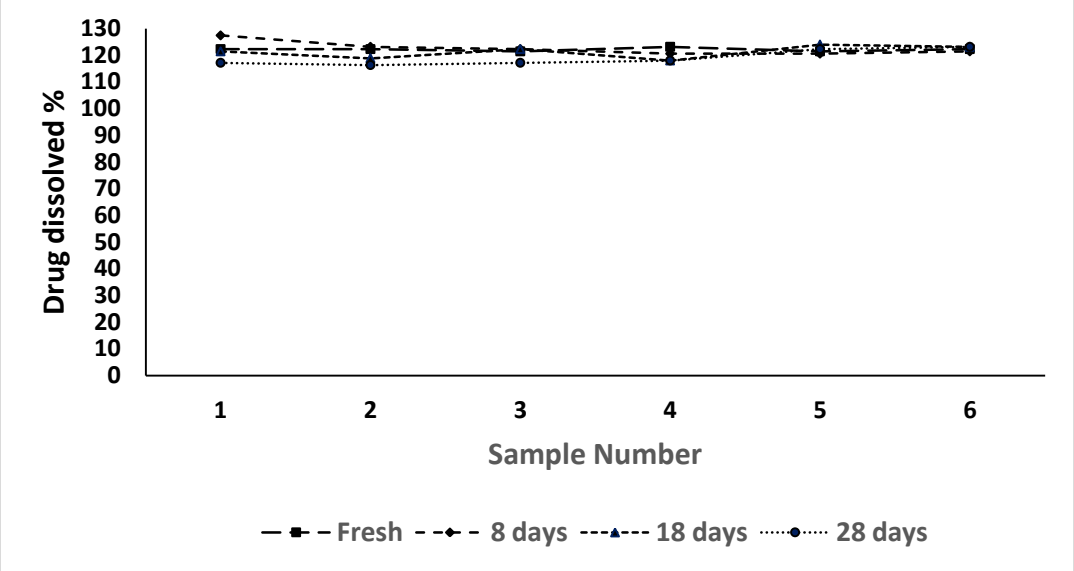

Fig. 5. The percentage of losartan potassium dissolved from extemporaneously compounded suspensions after 30 minutes over 28 days (n=6)

4. CONCLUSION

These findings show that, by using commercially available losartan potassium tablets and Ora-Blend® as a suspending vehicle, the losartan potassium compounding procedure applied in the present research was reliable and capable of producing 2.5 mg/mL of losartan potassium suspension. Moreover, after 28 days of storage at 4°C, the extemporaneously prepared suspension had acceptable quality attributes. Extemporaneously compounded suspension allows physicians to prescribe a variable dose that adjusts to the patient's needs and provides a therapy option when liquid dosage forms are unavailable. A hospital pharmacist can prepare an extemporaneously compounded suspension by employing commercially available tablets as the active ingredient source. Scientific information and directions for compounding commercial immediate-release solid dosage forms (such as tablets and capsules) into a suspension, as well as information on the expiration date of compounded suspensions, should be given in the package inserts. Also, more research is needed to compare tablet absorption to that of extemporaneously prepared suspensions in vivo. Therefore, treatments using extemporaneous preparations should be monitored to ensure the efficacy and safety of these products in patients.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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