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# Formulation and Evaluation of Extemporaneous Oral Suspension of Candesartan Cilexetil

**Anes AM Thabit*** **and Ahmed MS Al-Ghani**

*Department of Pharmacy, Medical Sciences College, Al-Razi University, Yemen*

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## ABSTRACT

**Background:** Candesartan Cilexetil is widely prescribed antihypertensive. The drug is unfortunately available in the market only as tablets which are not suitable for children and patients on nasogastric feeding.

**Objectives:** The study aimed to formulate and evaluate an appropriate extemporaneous oral suspension of candesartan Cilexetil.

**Methods:** Six oral suspension formulations of the drug were prepared from the 16 mg tablets of the innovation brand (Atacand®) of the drug. All formulations were prepared as "flocculated suspensions with a structured vehicle as a final product" with differences in the speed of mixing applied.

**Results:** Formulations with high-speed mixing were more viscous and more difficult to be poured than those prepared using low-speed mixing. Of the later, one formulation with increased amounts of flocculating agent, viscosity enhancer and wetting agents showed proper physical stability, flocculation and a shelf-life of more than 1 year.

**Conclusion:** A stable oral suspension of candesartan Cilexetil extemporaneously prepared from the drug tablets which can be easily prepared by pharmacists using available constituents, is invented in this study.

**Keywords:** Candesartan, Extemporaneous, Oral suspension, Formulation, Evaluation

## INTRODUCTION

Pharmacists are the health professionals who are trained to perform extemporaneous compounding and it is a required competency of practice for registered pharmacists in many countries [1].

Extemporaneous compounding is the preparation of a therapeutic product for an individual patient in response to an identified need. It is a practical way to have medicines supplied when there is no other option. For example, compounding may be useful for patients with dysphagia who are unable to swallow solid medications whole, when an appropriate dose or dosage form is not commercially available, when patients require an individualized dose, or when medicines must be delivered via nasogastric or gastrostomy tubes.

It should take place in community and hospital pharmacies. There are usually specialist compounding pharmacies in major towns and cities, but any pharmacy may undertake compounding as long as they have appropriate facilities according to country-based legislation [2].

For compounding, the active ingredient may be derived from commercially available medications or the pure chemical. Sometimes compounding is as simple as mixing a crushed tablet or the contents of a capsule in water to form a solution or suspension. However, this may not be suitable and depends on the solubility of the active ingredient. For example, insoluble tablet excipients can lead to blockages in enteral feeding tubes. In the majority of compounded products, additional non-active components (excipients) are included to ensure the active ingredient dissolves or remains suspended, or to adjust palatability or viscosity [3].

**Corresponding author**: Anes AM Thabit, Department of Pharmacy, Medical Sciences College, Al-Razi University, Yemen, Tel: 00967775671630; E-mail: aneesalabsi1973@gmail.com

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Risks in off-label compounding include using incorrect formulae and calculations, selecting incorrect ingredients, using incorrect quantities and producing unstable products [1]. In community compounding, if a preparation error occurs, it would only affect a limited number of patients. . Conversely, when pharmacy compounding is done at a large scale e.g. in

hospitals the error could potentially affect a large population of patients [4].

Candesartan Cilexetil [1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2¢-(1H-tetrazol-5-yl) [1, 1¢-biphenyl]-4-yl] methyl]-, 1[[cyclohexyloxyy) carbonyl] oxy] ethyl ester [5] is an oral drug belonging to the category angiotensin II receptor blockers (ARBs). It is prescribed for hypertension (adults and children) and also for congestive heart failure (adults). The dose for children (1-6 years) is 0.2 mg/kg a day or divided every 12 h, (6-17 years) 4-8 mg day. The drug is available commercially as tablets (4, 8, 16 and 32 mg) [6,7]. The drug is practically insoluble in water [8]. It has pka value of 6.0 and its partition coefficient (Octanol/aqueous) at pH 1.1, 6.9 & 8.9 is >1000 indicating high hydrophobicity character [9].

Physicians in Yemen sometimes prescribe candesartan Cilexetil for patients who cannot swallow the tablet form including children or patients on nasogastric feeding. Unfortunately, the drug is only available only as tablets. Therefore, for those patients, they recommend to crush the tablet and mix it with milk or juice and give it to the patient peroral. This is absolutely a non-evidence-based practice since no studies have revealed its validation. Hence, the need for valid extemporaneous liquid preparation of the drug becomes mandatory.

## METHODS

### Materials & instrumentation

Reference standard of candesartan Cilexetil was a gift from Yemeni- Egyptian Pharma Co., Sana`a, Yemen. Atacand® (Candesartan Cilexetil 16 mg tablets; Astra-Zeneca, Switzerland) was a gift from In-patient pharmacy at Al-Thawra Public hospital. UV spectrophotometer (Shimadzu, UV-1800, Japan), high speed Lab Disperser & mixer (AD500S-P, Mxbaoheng, China).

### Assay of Candesartan Cilexetil in Atacand® tablets

The assay was conducted as described by Ravisankar P et al. [10]. A stock solution of the standard reference of the drug was prepared in methanol (100 µg/ml). Serial dilution of the stock solution was performed to yield 6 dilute standard solutions of concentrations of 10-50 µg/ml. The absorbances of the solutions were measured at 258 nm. The standard calibration curve was constructed and its linearity equation was determined. Twenty tablets of Atacand® 16 mg (theoretically contain 320 mg of Candesartan Cilexetil) were ground to powder and sieved through mesh No. 60. A quantity of the sieved powder equivalent to 16 mg of the drug was taken and dissolved in methanol up to 100 ml. Dilution of the resultant solution was made to provide a dilute solution with a theoretical concentration (Ct) of 40 µg/ml whose UV absorbance was measured at 258 nm. The test was conducted in a triplicate manner. The UV absorbance was introduced into the calibration linearity equation to calculate practical concentration of the drug (Cp). Drug content was then calculated as follows:

$$\text{Drug content \%} = 100 \times Cp / Ct$$

### Formulation of oral suspensions from Atacand® tablets

Six suspension formulations **(Table 1)** were prepared using the method of "flocculated suspension with structural vehicle" [11]. Atacand® 16 mg tablets were used as source of active ingredients. Twenty tablets were ground to powder and sieved through mesh No. 60. The powder was then levigated with glycerin and polysorbate 20. Sodium chloride (flocculating agent) was dissolved in few amount of water and then was added to the levigated mass and triturated. Then, the structured vehicle was prepared as a solution of methylcellulose in an amount of water representing two-third of the final suspension volume. All other ingredients was dissolved in the structured vehicle. The resultant solution was added into the flocculating-added levigated mass with thoroughly stirring by the mixer for 15 min. The produced suspension was transferred to a volumetric cylinder and the volume was completed to the desired volume with water.

### Evaluation of oral suspension formulation

### Drug content

To 1 ml of the suspension (theoretically contained 16 mg candesartan Cilexetil), 7 ml of water was added and the mixture was centrifuged at 2000 rpm for 12 min. The supernatant was discarded and 10 ml of methanol was added to the residue and the resultant was then filtered. The volume of filtrate was completed to 16 ml with methanol. 1 ml of this solution was then diluted to 40 ml with methanol producing a theoretical concentration (Ct) of 40 µg/ml. The UV absorbance at 258 nm of the solution was measured. The test was carried out in triplicate pattern. The drug content was then determined as described earlier in assay of the drug in Atacand tablet [10].

### Physicochemical evaluation

The particle size, sedimentation rate, pH, sedimentation volume, degree of flocculation and viscosity of the formulations were measured.

**Table 1.** Formulations of 100-ml extemporaneous oral suspensions of candesartan Cilexetil (16 mg/5 ml).

| Ingredients | Low-speed Mixing (1000 rpm) | | | High-speed Mixing (6000 rpm) | | |
|---|---|---|---|---|---|---|
| | Fa1 | Fa2 | Fa3 | Fb1 | Fb2 | Fb3 |
| **Atacand ® 16 mg tablets** | 20 tablets equivalent to 320 mg of Candesartan Cilexetil | | | | | |
| **Polysorbate 20 (ml)** | **1** | **2** | **3** | **1** | **2** | **3** |
| **Glycerin (ml)** | **5** | **7.5** | **10** | **5** | **7.5** | **10** |
| **Sodium chloride** | **0.1** | **0.3** | **0.5** | **0.1** | **0.3** | **0.5** |
| **Methyl cellulose** | **1** | **1.5** | **2** | **1** | **1.5** | **2** |
| **Sodium dihydrogen phosphate (g)** | 1.842 | 1.842 | 1.842 | 1.842 | 1.842 | 1.842 |
| **Dibasic sodium phosphate (g)** | 3.233 | 3.233 | 3.233 | 3.233 | 3.233 | 3.233 |
| **Sodium benzoate (g)** | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| **Sodium sulphite (g)** | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| **Ethyl maltol (g)** | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| **Saccharin sodium (g)** | 0.03 | 0.03 | 0.03 | 0.030.03 | 0.03 | 0.03 |
| **Sodium cyclamate (g)** | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| **Caramel E150** | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. |
| **Water (ml) ad.** | 100 | 100 | 100 | 100 | 100 | 100 |

**Particle size and sedimentation rate**

They were measured as described in literature [11, 12] by sedimentation method by standing for 24 h using Stock`s Equation as follows:

$$d = 10^4 . [(S.18.Y) / ((Ps – Po).g)]^{1/2}$$

where (d) was the particle size as diameter of dispersed particles (µm), (S) was sedimentation rate (cm/s), (Y) was viscosity of the formulation (dyne.cm$^{-2}$s), ($P_s$) was the density of dispersed particles (g.cm$^{-3}$), ($P_o$) was the density of formulation vehicle (g.cm$^{-3}$) and (g) was the acceleration due to gravity (980.7 cm.s$^{-2}$).

• **Sedimentation volume** [11] was calculated after standing for 24 h as follows:

$$F = Vs/Vo$$

where (Vs) was the sediment volume after 24 h standing and ($V_o$) was the original suspension volume.

• **Degree of flocculation [11]**

It was measured by comparing the sedimentation volume in the flocculated formulation to that of its corresponding (sodium chloride free) suspension as follows:

$$\beta = F_\infty / F$$

where (F) was the sedimentation volume of the flocculated suspension and the sedimentation volume of the suspension when deflocculated ($F_\infty$). As (β) increases (> 1) the volume of sediment in the flocculated system is greater than that in the deflocculated state which confirms the flocculation of the system.

•**Viscosity of the suspension** [13]

It was measured using Ostwald tube using $H_2O$ as reference standard ($H_2O$) which has a viscosity of (0.01 dyne cm$^{-2}$ s).
Viscosity of the suspension was calculated as follows

$$\mathcal{Y}_s = t_s \times \mathcal{Y}_w / t_w$$

where ($\mathcal{Y}_s$) and ($\mathcal{Y}_w$) were viscosity in (dyne.cm$^{-2}$s) of the suspensions and water, respectively, and ($t_s$) and ($t_w$) were flow times of the suspension and water, respectively.

**Accelerated stability study [13]**

The suspension formulation with appropriate drug content and physicochemical properties was selected for stability study in order to determine its shelf life.

A sample of 50 ml of this formulation was incubated at three different conditions 37, 50 and 75°C for 6 weeks. At intervals of 2, 4 and 6 weeks, each formulation was tested for its drug content. The results of drug content were used to predict the shelf-life using Arrhenius equation. The order of degradation reaction was determined by fitting data of drug content vs. time to zero, first and second-order models at each storage temperature. The model that showed higher correlation coefficient was the order of degradation to which data fitted at a given temperature and the rate constant of degradation (k) of that order was then determined. Arrhenius plot was constructed with ln k (at y axis) versus I/T (at x axis); where T was the temperature of storage in Kelvin. The regression equation of the plot was then determined where the slope and intercept was used to calculate the expected degradation rate constant at 25°C (K25) as follows

$$\ln K_{25} = \ln A - [(Ea/R).(1/T_{25})$$

where (ln A) was the intercept; (Ea/R) was the slope of the plot.

The expected shelf-life ($t_{90}$) was calculated as follows

$$t_{90} = (0.1 * Q_0)/K_{25}$$

where $Q_0$ was then drug content % at the beginning of the stability study.

## RESULTS

**Standard calibration curve**

A linear curve was obtained for concentrations (10-50 µg/ml) of candesartan Cilexetil standard in methanol. The linearity coefficient was 0.9988 and the curve equation was (y = 0.0245x + 0.0143).

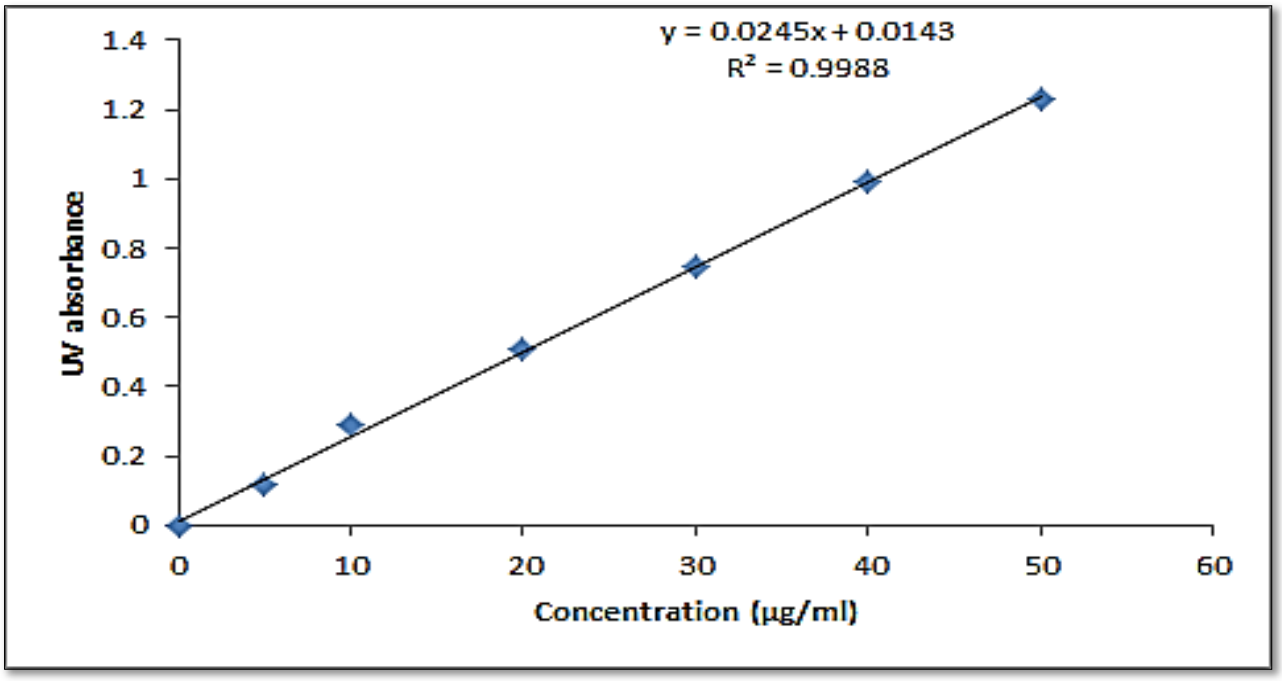


**Figure 1.** Standard calibration curve of Candesartan Cilexetil in methanol at UV 258 nm.

**Drug content in Atacand® 16 mg tablets**

The average ± SD of drug content % was 100.15 % ± 0.05 (CV was 0.05%; C.I. 95 % was (100.093 – 100.207 %).

**Evaluation of suspension formulation**

**Drug content**

The drug content of the drug in all formulations, as shown in **Table 2**, was within the range of 98.7–101% (95 % C.I. 92.422 -106.578 %). CV% (the coefficient of variation) of all measurements, within each formulation, were <5% indicating optimum precision.

**Physicochemical properties**

As shown in **Table 1**, there were two categories of formulations (Fa) with lower mixer speed and (Fb) with higher mixer speed) and each category was divided into 3 subcategories according to the amount of wetting agents, flocculating agent and suspending agent where the

formulation with the numbers 1, 2 and 3 denoting the smallest, intermediate and largest amounts of such ingredients respectively. Statistical comparison between each physicochemical property of the two categories was carried out using Chi-square method.

**Table 2.** Drug content % of Candesartan Cilexetil in oral suspension formulations.

| Formulation | Drug content % (average± SD) | CV % | C.I.95 % |
|---|---|---|---|
| **Fa1** | 101 ± 3.521 | 3.486 ▲ | 97.055- 104.945 |
| **Fa2** | 99.5 ± 6.224 | 6.255 ▲ | 92.422- 106.578 |
| **Fa3** | 101 ± 1.002 | 0.992 ▲ | 99.877 - 102.123 |
| **Fb1** | 101 ± 2.451 | 2.427 ▲ | 98.254- 103.746 |
| **Fb2** | 98.7 ± 1.11 | 1.125 ▲ | 97.427- 99.973 |
| **Fb3** | 99.1 ± 0.95 | 1.085 ▲ | 98.015- 100.185 |

▲*: optimum precision (CV < 15%)*

**Table 3** demonstrates the results of physicochemical properties which showed significant smaller particle size, higher degree of flocculation and lower sedimentation rate of (Fb) formulations compared to (Fa) formulations. On the other hand, there were no significant differences between (Fa) and (Fb) formulations regarding sedimentation volume and pH. It was found that (Fb) formulations had very large viscosity that made the suspension very difficult to be poured and hence were excluded from further investigations.

**Table 3.** Physicochemical properties of Candesartan Cilexetil oral suspension formulations.

| Formulation | Average ± SD | | | | | |
|---|---|---|---|---|---|---|
| | **Viscosity (dyne cm$^{-2}$s)** | **Particle size (µm)** | **Sedimentation volume** | **Degree of flocculation** | **Sedimentation rate x 10$^{-6}$ (cm s$^{-1}$)** | **pH** |
| Fa1 | 1.01 ± 0.001 | 18.3 ± 0.016 | 0.346 ± 0.014 | 1.205 | 18.07 | 6.82 |
| Fa2 | 2.05 ± 0.002 | 14.7 ± 0.021 | 0.561 ± 0.022 | 2.312 | 5.16 | 6.84 |
| Fa3 | **3.1 ± 0.046** | **11.2 ± 0.003** | **0.798** ± 0.002 | **5.116** | **1.16** | 6.83 |
| Fb1 | 14.9 ± 0.014 | 0.992 ± 0.015 | 0.829 ± 0.004 | 12.231 | 0.53 | 6.80 |
| Fb2 | 16.5 ± 0.542 | 0.861 ± 0.011 | 0.871 ± 0.006 | 13.005 | 0.14 | 6.81 |
| Fb3 | 18.7 ± 0.63 | 0.701 ± 0.034 | 0.955 ± 0.011 | 14.112 | 0.08 | 6.83 |
| Chi-square (p value) Fa Vs. Fb | < 0.00001▲ | < 0.00001▲ | 0.806 ☼ | < 0.00001 ▲ | < 0.00001 ▲ | 0.928 ☼ |

▲*: Significant difference (p < 0.05);* ☼*: insignificant difference (p > 0.05)*

**Accelerated stability study**

The formulation (Fa3) which showed proper drug content, moderate viscosity, proper physical stability and flocculation was introduced into an accelerated stability study. The order of degradation of the drug at all the three storage temperatures fitted to first-order model. Data obtained from Arrhenius plot was demonstrated in **Table 4**. The shelf-life of the drug in that formulation was 1.27 years.

**Table 4.** Arrhenius estimates of shelf-life of (Fa3) oral suspension formulation of Candesartan Cilexetil from stability study for 6 weeks.

| Temperature | | 1/T (Kelvin $^{-1}$) | k (week$^{-1}$) | ln k |
|---|---|---|---|---|
| t (°C) | T (kelvin) | | | |
| **37** | 310 | 0.0032 | 1.025 | 0.025 |
| **50** | 323 | 0.0031 | 1.045 | 0.044 |
| **75** | 348 | 0.0029 | 1.389 | 0.329 |
| **Intercept (ln A)** | 1.0699 | | | |
| **Slope (Ea/R)** | -907.800 | | | |
| **Ln $K_{25}$** | -1.977 | | | |
| **$K_{25}$** | 0.1386 | | | |
| **t90 (shelf life) at 25°C** | 71.09 weeks=1.27 years | | | |

## DISCUSSION

Candesartan Cilexetil is yet available in the market as commercial oral suspension. Instead, the innovator (Astra Zeneca) recommends a method to prepare oral suspension from the available tablets [8]. The method requires the use of a specific vehicle products e.g. Ora plus (Perrigo, Australia) which are unavailable in the Yemeni drug market.

The vehicle is composed of many ingredients including: microcrystalline cellulose, carboxy methylcellulose, xanthan gum, carrageenan, calcium sulphate, trisodium phosphate, citric acid, dimethicone antifoam emulsion, methyl paraben and potassium sorbate [14]. Most of these ingredients are expensive and unavailable in Yemen.

Crushing of Candesartan Cilexetil tablet then mixing it with fluid has been recommended by some physicians in Yemen for patients who cannot swallow tablets such as children. This practice may be associated with great risks to patients' due potential errors in formulation and stability of the drug. Therefore, the present study aimed to offer another option to physicians, patients by formulating a stable extemporaneous oral liquid of the drug which can be simply prepared by pharmacist.

Therefore, this study was undertaken in order to provide an oral suspension formulation with simple formulation from available ingredients.

The drug was formulated as an aqueous suspension owing to the numerous advantages of this liquid dosage form including the non-necessity of dissolving the drug, which is insoluble in water, the ability of suspension to mask unpleasant taste of the drug and the enhanced chemical stability of drugs when formulated as a dispersion system [13].

Prior to formulation, it was necessary to confirm the drug content in the tablets. This was carried out using the simple technique of UV spectrophotometry. A standard calibration curve was constructed and revealed high linearity **(Figure 1)** and the drug content in tablets complied the USP specifications (90-100%) [5].

The formulations were prepared from the (Atacand® 16 mg tablets) which is a brand widely available in the market. This is an advantageous point as pharmacists can prepare the drug as oral suspension whenever required with no need to import the raw material of the drug which is considered uneconomic due to limited request of the oral suspension of the drug.

As shown in **Table 1**, six suspension formulations were designed based on preformulation data of the drug and the required excipients. All formulations were prepared as "flocculated suspension in structured vehicle as final product". This system is well known with improved physical stability of the product as it prevents sediment cake

formation (flocculated system), enhances the viscosity and reduces sedimentation rate (structured vehicle) [11,13].

The differences among those formulations were in the in the speed of mixer applied (low speed 1000 rpm or high speed 6000 rpm), the amount of flocculating agent (sodium chloride), viscosity enhancer and structured vehicle (methylcellulose solution), wetting agents including the surfactant (polysorbate 20) and glycerin. Other ingredients included were of the same type and quantity in all formulations. They included sodium dihydrogen phosphate and dibasic sodium phosphate as a buffer pH 6.8, sodium benzoate as preservative, sodium sulphite as antioxidant, ethyl maltol as caramel flavor, caramel E 150 as coloring agent and saccharin sodium as sweetener [11,13].

Evaluation of the prepared formulations reveled optimum drug content in all formulations and the precision of measurements was confirmed with low CV% **(Table 2).** With respect to physicochemical properties, as shown in **Table 3**, the formulations prepared at high-speed mixing (Fb1, Fb2 & Fb3) though were of better physical stability characters with lower particle sizes and sedimentation rates, they showed very high viscosity most probably due to thixotropic phenomenon [11,13]. Accordingly, they were very difficult to be poured and as a result they were excluded from further investigations. The physicochemical properties of (Fa) formulations were within standard suspension specifications. The particles size was in the range of 11.2-18.3 µm compared to standard coarse suspension of 10-50 µm [11], the formulations viscosity was accepted (1.01-3.1 dyne $cm^{-2}$ s) as it was more than that of water (1.01-3.1 dyne $cm^{-2}$ s) [11] and the degree of flocculation was >1 within the range of (1.2-5.1) which confirmed the appropriate flocculation of the particles in the prepared suspensions [11].

Among the low-speed mixing formulations, Fa3 which contained an increased amount of flocculating agent, wetting agents and viscosity enhancer showed more appropriate characters in terms of higher viscosity, lower particle size, higher sedimentation volume, higher degree of flocculation and lower sedimentation rate than the other two formulations (Fa1 and Fa2).

In the last step of evaluation, the selected Fa3 formulation demonstrated considerably long shelf life of more than 1 year **(Table 4)** compared to only 100 days reported with the use of oral-plus as vehicle [7].

## CONCLUSION

The suspension formulation of Candesartan Cilexetil (Fa3) prepared in this study from the drug tablets using simple method and available constituents is a stable oral suspension of the drug that can be extemporaneously prepared by pharmacists whenever an oral liquid preparation of the drug is required.

## CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this article.

## AUTHOR CONTRIBUTION

The correspondent author conceived the idea and developed the theory of the presented work. All authors participated in conducting experiments, performing the calculations, discussing the results and contributing in the last manuscript.

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