

Original Research Article

Quality Assessment of Extemporaneously Compounded Carvedilol Oral Suspension for Pediatric Patients at the Hospital Pharmacy

ABSTRACT

Aims: The aim of this study was to evaluate different quality control parameters and the stability of the carvedilol compounded extemporaneous suspensions over three months at room temperature.

Methodology: The carvedilol compounded extemporaneous suspensions were prepared in our lab in a manner consistent with how they are prepared for pediatric patients at the hospital pharmacy. The suspensions were stored at room temperature and analyzed immediately and at 1, 2 and 3 months. Suspensions were monitored for changes in organoleptic properties, pH, particle size, zeta potential, viscosity, sedimentation volume, drug content and drug dissolution.

Results: The results demonstrated that the carvedilol compounding protocol used in this study was reliable and able to prepare 1.67 mg/mL of carvedilol suspension by using carvedilol commercially available tablets and Ora-blend as a suspending vehicle. Also, the extemporaneously compounded suspension maintained acceptable quality attributes when stored for three months at room temperature.

Conclusion: The extemporaneously compounded suspension enables pediatricians to administer a variable dose, which adapts to every patient's needs, and gives the possibility of treatment when the liquid dosage form is not available.

Keywords: Quality Assessment, Extemporaneous Compounding, Carvedilol, Oral Suspension, Pediatrics

1. INTRODUCTION

Carvedilol (CAR) is a third-generation beta-blocker. It was the first drug in this group to be approved by the Food and Drug Administration in 1995 for the treatment of cardiovascular diseases (heart failure and hypertension) in adult patients. Several studies report that it is effective in pediatrics with heart failure [1]. The only available oral formulation of carvedilol is the tablet dosage form. Thus, compounding extemporaneous liquid formulations is one of the most common practices employed when there is no commercially available dosage form for adjustable dosing or an appropriate dosage form for pediatric patients [2], [3].

The Saudi Food and Drug Administration (SFDA) defines pharmacy compounding under an initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice as the extemporaneous preparation, mixing, packaging, and labeling of a drug product in response to a licensed practitioner's prescription [4]. Extemporaneous compounding typically occurs when a regulatory body-approved drug is unavailable, or a licensed practitioner prescribes an appropriate dosage form for a patient's medical needs which is not available. Also, it may occur in the case of adjusting the product's strength suitable for adult use, where the prescriber needs a lower strength for pediatric patients [5]. The limited knowledge available to support the stability and shelf life of such items is a major problem emerging from this practice. When formulating extemporaneous preparations, physical, chemical, and microbiological properties must also be taken into account, as these can affect dosage uniformity, stability, and storage conditions [3].

According to the FDA survey from 2001, 34% of the 29 examined items failed quality test standards, particularly in drug content testing [6]. During the years 1999 to 2000, the improper method of compounding was reported as a pharmaceutical error 115 times (6 % of all prescription errors) in the United States [7]. Chollet and Jozwiakowski discovered that 25% of thirty compounded hydroxyprogesterone caproate injections failed to achieve the drug content standards [8]. Quality must be built-in to the extemporaneous preparation from the first steps to the final product. There are a few common rules to follow when it comes to pharmaceutical compounding. Compounding ingredients must be of suitable identity, purity, and quality, as well as be obtained from reliable sources and stored properly. Cross contamination must be avoided, and all equipment must be kept clean and utilized properly. The compounding environment must always be suitable. In the immediate area where compounding is taking place, only authorized personnel are permitted. Processes must be repeatable, compounding conditions must be sufficient to avoid errors, and all components of compounding must be properly recorded [4].

Carvedilol exhibits poor aqueous solubility (0.583 mg/L), which renders it difficult to formulate as a liquid solution [9]. For this reason, a common practice is to prepare carvedilol suspension rather than a solution in various hospitals, both in Saudi Arabia and globally. A coarse suspension is a dispersion of finely divided and insoluble particles in a liquid medium that has difficult physical stability properties [10]. One of the challenging issues in compounding oral extemporaneous suspensions is the crushing of the commercially available tablets. The time and method of grinding can influence the particle size of the resulting powder mixture. To ensure a slow rate of sedimentation and accuracy of dosing, the suspended particles should be small and uniform in size.

Many commercial suspension vehicles can be used for the preparation of oral extemporaneous suspensions. One of the commonly used suspension vehicles is Ora-blend®. It is a GMP-produced and internationally available, ready-to-use, taste-masking oral suspension vehicle. The suspending vehicle forms a structured, gellike matrix that suspends particles and allows for little settling. It is buffered to a slightly acidic pH of 4.2 to help reduce degradation of the active ingredient through oxidation. The compatibility of Ora-blend® with a large number of active pharmaceutical ingredients has already been demonstrated [11]–[15].

A good suspension sets slowly and is easily redispersed when the container is gently shaken. As a result, the physical stability of a suspension is usually measured by calculating the rate of sedimentation, the final volume of the sediment, and the ease with which the suspension can be redispersed. The most serious physical stability issue with suspensions is cake formation, which is characterized by the formation of a sediment that is difficult to redisperse. Physical instability not only affects the appearance but also causes dosing variability [10]. The aim of this study was to evaluate different quality control parameters and the stability of the carvedilol compounded extemporaneous suspensions over 86 days at room temperature.

2. MATERIAL AND METHODS

2.1 Materials

Carvidol® tablets, 25 mg (RIYADH PHARMA), were purchased from a local pharmacy. Ora-Blend® (Perrigo, Australia) were purchased from Amazon. Carvedilol B.P. reference standard ($\geq 99.5\%$ purity) was obtained from SPIMACO, Qassim, Saudi Arabia. All materials used were of analytical grade.

2.2 Extemporaneous preparation of carvedilol oral suspension

Carvedilol oral suspensions were prepared in our lab in a manner consistent with how they are prepared for pediatric patients at the hospital pharmacy. Briefly, oral suspensions of carvedilol 1.67 mg/ml were compounded in Ora-blend® [16]. Using a mortar and pestle, Carvidol® tablets were ground to a fine uniform powder before being mixed with a small amount of Ora-blend® and geometrically diluted with Ora-blend® to a final volume of 60 ml. The suspensions were transferred to amber glass bottles and stored at room temperature. The suspensions were sampled and analyzed immediately after compounding (a fresh sample) and after one, two and three months.

2.3 Visual Appearance and Organoleptic Properties

At each sampling point, the color of the formulations was inspected visually by placing the sample in a clear glass beaker against a black background. The odor changes, ease of redispersion and signs of caking were also investigated. The suspension vehicle (Ora-blend®) was used as the control.

2.4 pH Measurement

The pH value of the suspensions was measured in triplicate at each sampling point using a bench pH/ORP meter HI 2211 (Hanna instruments, United Kingdom). Standard buffer solutions of pH 4.00, 7.00 and 10.00 were used to calibrate the pH meter before each measurement. The results were shown as mean±standard deviation (SD).

2.5 Sedimentation volume

The sedimentation volume was calculated in triplicate at each sampling point by the following equation:

$$F = V_u / V_o \quad \text{Equation (1)}$$

Where, V_u is final volume of sediment as suspension settles, V_o is original volume of the suspension [21]. The results were shown as mean±standard deviation (SD).

2.6 Rheological properties

The viscosity of the suspensions was measured in triplicate at each sampling point using a Brookfield R/S Plus Rheometer with spindle C50-1 (Middleboro, Massachusetts, USA). About 0.25 g of the formulation was placed on a plate, and the RPM ranged from 400-900 at room temperature. The results were shown as mean±standard deviation (SD).

2.7 Particle size and zeta potential

The particle size, polydispersity index (PDI) and zeta potential were measured in triplicate on each sampling point using photon correlation spectroscopy (PCS) with a zetasizer (Nano ZS, Malvern Instruments, UK) at room temperature. The samples were placed in the appropriate cells after being adequately diluted. All measurements were reported as the mean±standard deviation (SD).

2.8 Microbiological test

Microbiological examinations of suspensions were performed in triplicate on each sampling point. Microbiological stability was confirmed if the international pharmacopeia acceptance criteria for microbiological quality of non-sterile aqueous products for oral dosage form were met. The media used were validated in order to assure their ability to cultivate different types of microorganisms [17]. Two types of media were used. First, Soyabean-Casein Digest (TSB) was incubated at 22°C to allow the growth of both aerobic bacteria and fungi. The other type of media is Fluid Thioglycollate Medium (FTG), incubated at 35°C, which is primarily intended for the culture of anaerobic bacteria (requiring the absence of oxygen). FTG will also support aerobic bacterial growth. In a growth promotion test, both types of media would be tested for their fermentative properties. Two tubes of each media were inoculated by appropriate strain (not more than 100 CFU) and incubated for 3 days [18]. For negative control, two tubes of each media were incubated for 14 days concurrent with each inoculation, with the demonstration of no growth of microorganisms. For positive control, two tubes of each media were inoculated with the appropriate strain and incubated for 3 days at the appropriate temperature. Each sample of suspension was analyzed in triplicate at each sampling point. The material being tested renders the media turbid, so that the presence or absence of microbial growth can't be readily determined by visual examination. Consequently, after 14 days of incubation, one ml of each inoculated media was transferred to a fresh vessel of the same medium and then incubated together with the original for not less than 4 days [19].

Table 1: Inoculated organisms for media validation.

Aerobic bacteria	Staphylococcus aureus	ATCC 25923
	Bacillus subtilis	ATCC 6633
Anaerobic bacterium	Shigella sonnei	ATCC 11060
Fungi	Candida albicans	ATCC 10231

2.9 Content uniformity test

At each sampling point, the content uniformity of the dosage unit was determined using the method for measuring content uniformity for liquid dosage forms defined in the USP. Thirty samples of well-mixed materials were removed from an individual container and tested. If the acceptance value (AV) of the first 10 samples is not more than L1, the preparation is said to pass the test (Table 2). If the AV is more than L1, test the remaining samples (20 samples) and calculate the AV. The preparation is said to pass the test if the final AV of the 30 samples is not more than L1, and no sample result can be less than $[1 - (0.01)(L2)]M$ or greater than $[1 + (0.01)(L2)]M$.

The AV was calculated by using the following equation:

$$|M - \bar{X}| + ks \quad \text{Equation (2)}$$

When the target content (T) is ≤ 101.5 , the reference value (M) is defined as the mean of the individual contents (\bar{X}) expressed as a percentage of the label claim. The acceptability constant k for 10 samples is 2.4 and for 30 samples is 2. The sample standard deviation is s [20]. The values of drug content were assayed using a UV-visible spectrophotometer (Libra S22 UV/Vis. Biochrom Ltd., Cambridge, England) at 242 nm.

Table 2. USP content uniformity acceptance level for immediate-release oral dosage form.

Level	Description	Value
L1	Maximum allowed acceptance value	L1 is 15 unless otherwise specified.
L2	Maximum allowed range for deviation of each dosage unit tested from the calculated value of M	L2 is 25 unless otherwise specified.

2.10 Dissolution test

The dissolution test of CAR suspension was performed using USP dissolution apparatus II (Pharma Test, DT 70, Hainburg, Germany) at 50 rpm, under sink conditions, in 900 mL of 0.1N hydrochloric acid solution, pH 1.2 and at 37 ± 0.5 °C [27]. A suspension sample of 5 mL was taken and transferred to the dissolution vessel midway between the surface of the dissolution medium and the top of the rotating blade. Samples (5 ml) were withdrawn at 5, 10, 15, 20 and 30 min and filtered using a 0.45- μ m pore size filter. An equivalent volume of the fresh heated dissolution medium was returned to keep the volume constant. The values of drug content were assayed using a UV-visible spectrophotometer (Libra S22 UV/Vis. Biochrom Ltd., Cambridge, England) at 242 nm, where the dissolution medium was used as a blank. The requirements are met if the percentage of CAR dissolved from the sample tested conforms to USP dissolution acceptance criteria for immediate-release oral dosage forms (Table 3). The acceptance criterion for a dissolution test is a function of Q, which is expressed as a percentage of the labelled content of drug dissolved at a specified time (30 min).

Table 3. USP dissolution acceptance criteria for immediate-release oral dosage form.

Stage	Number of dosage units tested	Limits
S1	6	No dosage unit is less than $Q+5\%$
S2	6	Average of the twelve dosage units $\geq Q$ and no dosage unit is less than $Q-15\%$.
S3	12	Average of the twenty-four dosage units $\geq Q$ and not more than two dosage units are less than $Q-15\%$ and no dosage unit is less than $Q-25\%$.

2.11 Statistical Analysis

Standard curves were constructed and assessed using regression analysis. A one-way analysis of variance (ANOVA) was used to assess statistical significance where required. A P -value <0.05 was considered statistically significant. All statistical analysis was performed using Minitab 19.1 Statistical Software (Minitab Inc., State College, Pennsylvania).

3. RESULTS AND DISCUSSION

Although compounding has been practiced for hundreds of years as a part of the pharmacist's professional skill, the quality of the products being compounded has received insufficient attention. Many of the medicines used in pediatric patients have not yet been licensed for this purpose, so their use is off-label or unlicensed. As a result, attempts are made to modify an existing dosage form or an active ingredient and excipients to an age-appropriate dosage form [21]. Thus, the project's aim was to evaluate different quality control parameters and the stability of the CAR compounded extemporaneous suspensions over three months at room temperature.

3.1 Visual Appearance and Organoleptic Properties

The sweet cherry odor and ivory/white color did not seem to change throughout the three months of the study. The ivory/white color is caused by the original tablet film coating. The original tablet coating is Opadry yellow®, contributing to ivorysh oral liquid color.

3.2 pH Measurement

The pH of suspensions remained stable (4.68 ± 0.03 to 4.8 ± 0.02) and there was no significant difference in the pH profiles during the three months of the study ($p > 0.05$). Moreover, pH levels are maintained in the Ora-Blend buffering pH range, which is 3.5-5.0, due to the buffering system (sodium phosphate monobasic and citric acid) [12]. Thus, the buffering system of Ora-Blend® maintained a stable pH in the suspension during the three months of the study. Similarly, Stanis et al. reported that Ora-Blend® maintained the pH of cilazapril oral suspensions prepared from commercially available tablet dosage forms [12].

3.3 Sedimentation volume

There was no appearance of layering or caking of the extemporaneously compounded suspensions over the study period. Although the presence of slight sediment was noticed. Figure 1 represents the calculated sedimentation volume of compounded suspensions over the study period ($p > 0.05$). According to equation 1, the sedimentation volume, F , is the ratio of the equilibrium volume of the sediment, V_u , to the total volume of the suspension, V_0 . The value of F normally ranges from 0 to greater than 1, with F value equal to 1 being the ideal system [10], [22]. According to guidelines, suspensions should always be shaken well before use to ensure uniform distribution of the suspended particles in the suspending vehicles [23]. Over the three months of the study, all suspensions were easily resuspended into a homogeneous liquid after gentle shaking of the suspension, and no caking was observed. Such property of compounded suspensions is owing to Ora-Blend® vehicle. Ora- Blend® vehicle is composed of a synergistic mixture of suspending agents, which form a gel-like matrix, counteracting the settling down of suspended particles [12].

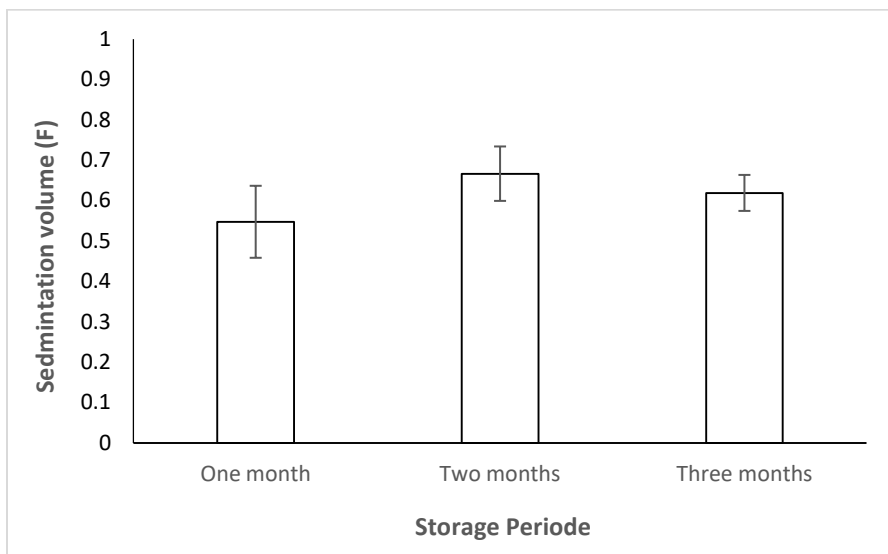


Fig. 1. The calculated sedimentation volume of compounded suspensions over the study period ($n=3$, $\text{mean} \pm \text{SD}$, $P > 0.05$).

3.4 Rheological properties

Changes in the viscosity of suspensions observed throughout the study period (Figure 2) were insignificant ($p > 0.05$) and indicated the evidence that three months of storage at room temperature did not affect the viscosity of compounded suspensions. Rheological properties of compounded suspensions are important because they permit the determination of ease of use of the compounded suspension, such as ease of pourability from the bottle and ease of redispersibility [10].

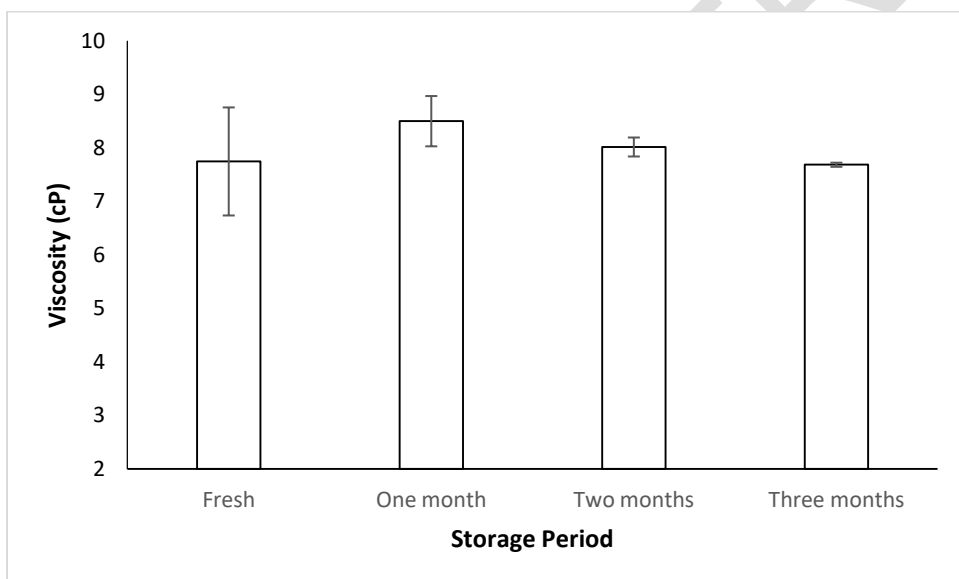


Fig. 2. The viscosity of compounded suspensions over the study period ($n=3$, $\text{mean} \pm \text{SD}$, $P > 0.05$).

3.5 Particle size and zeta potential

Figure 3 represents the particle size, polydispersity index (PDI) and zeta potential of all compounded suspensions throughout the three months of the study ($p > 0.05$). The value of zeta potential reflects the stability of the suspension, so it is monitored from time to time to ensure optimum zeta potential. To obtain a flocculated, noncaking suspension with the maximum sedimentation volume, the zeta potential must be controlled so as to lie within a certain range (generally less than 25 mV) [24]. Moreover, no aggregation of particles was observed. Crushing tablets is a critical step in the compounding of extemporaneous suspensions. The grinding technique can affect the resulting homogeneity of the suspension. Furthermore, one must consider that the suspension particles may become aggregated if they need to be

stored before the doses are dispensed [25]. Therefore, professional skills are key factors in compounding extemporaneous suspensions of good quality.

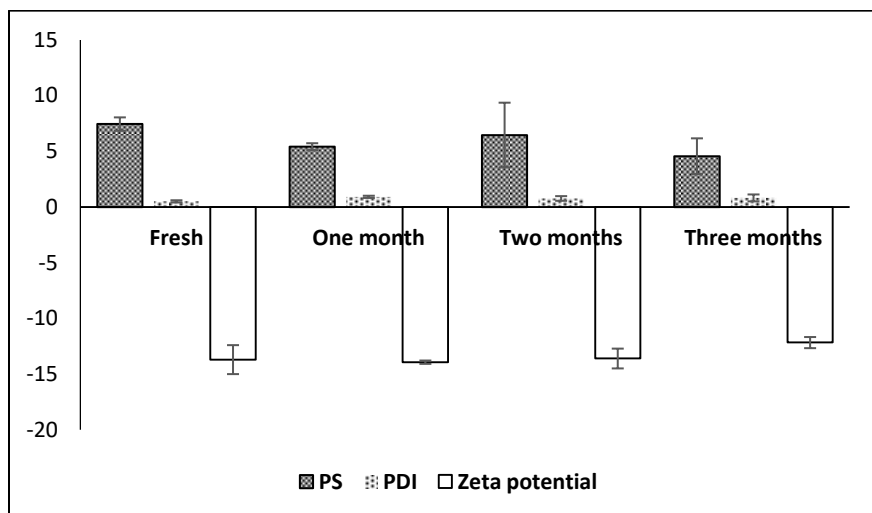


Fig. 3. The particle size, polydispersity index (PDI) and zeta potential of compounded suspensions over the study period (n=3, mean±SD, $P>0.05$).

3.6 Microbiological test

All microbial cultures were negative at each time point during the three months of storage at room temperature. The Ora-Blend® vehicle used in this work contains methylparaben and potassium sorbate preservatives, which reduce the possibility of microbial contamination [26].

3.7. Content uniformity test

One of the most important characteristics of the dosage form is the drug content uniformity to assure reproducibility of dosages, and thus the formulation is a safe and effective therapeutic preparation. Figure 4 shows the individual percentage of drug content determined. The AV, which characterizes the scatter in the drug content for samples of the tested suspensions taken separately, was calculated in order to assess quantitatively the content uniformity. Table 4 shows that all AV was no more than 15, demonstrating that all compounded suspensions met the compendial requirements. MelkouMov et al. reported that extemporaneous delayed-release suspensions of lansoprazole using Ora-Blend® vehicle maintained drug content within the acceptable range [27].

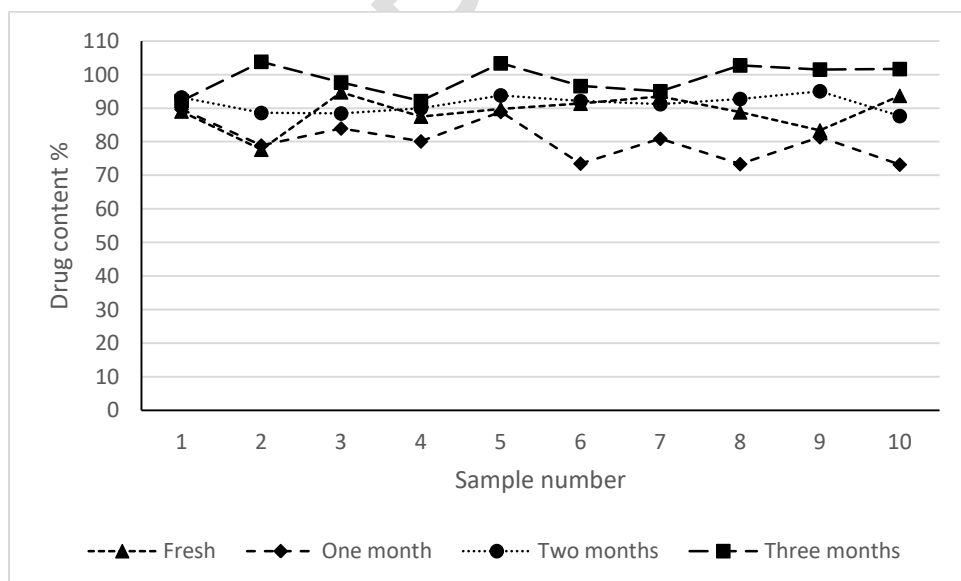


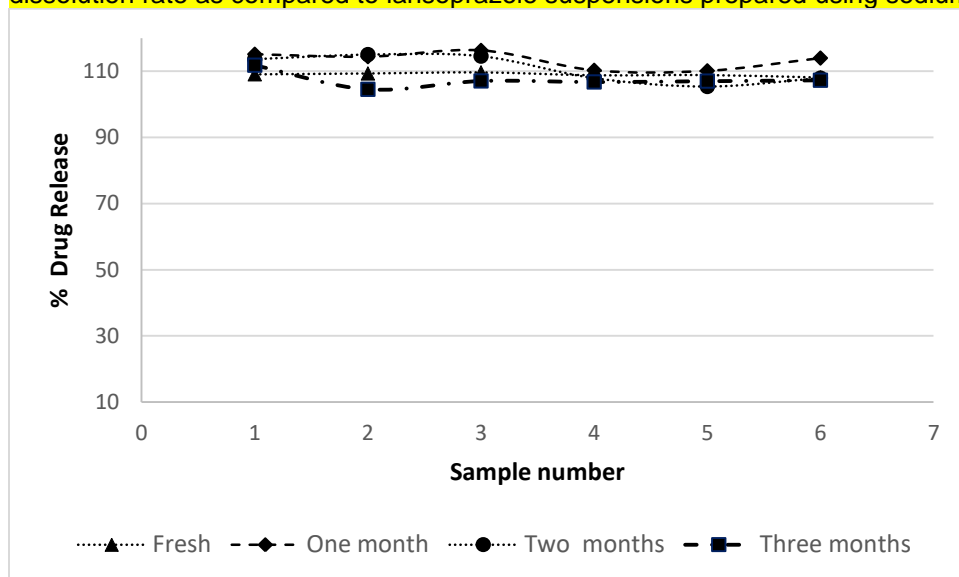
Figure 4. The individual percentage of CAR content determined of compounded suspensions over the study period (n=10).

Table 4. The calculated acceptance value of compounded suspensions over the study period.

Storage period	Fresh	One month	Two months	Three months
Acceptance value	12.49	14.39	6.06	10.92

3.8 Dissolution test

The results reported in figure 5 show that the percentage of CAR dissolved after 30 minutes was within the accepted USP limits for immediate-release oral dosage forms (Table 3). In all cases, dissolution levels greater than 100% were achieved. The dissolution test could be used as an *in vitro* tool to predict bioavailability. In this study, the bioavailability of the drug suspension was not assessed. However, the absorption and therapeutic efficacy of a drug in a suspension compounded from crushed tablets is unlikely to differ from that of the original dosage form used in its compounding. In fact, because conventional tablets or capsules containing the active ingredients are used as the drug source, most extemporaneously prepared medications do not undergo bioavailability and pharmacokinetic studies. Similarly, MelkouMov et al. reported that the lansoprazole suspensions prepared using Ora-Blend® were found to have highest dissolution rate as compared to lansoprazole suspensions prepared using sodium bicarbonate [27].

**Fig. 5. The percentage of CAR dissolved after 30 minutes of compounded suspensions over the study period (n=6).**

4. CONCLUSION

These results demonstrate that the CAR compounding protocol used in this study was reliable and able to prepare 1.67 mg/mL of CAR suspension by using CAR commercially available tablets and Ora-blend® as a suspending vehicle. This preparation may provide advantages over previous formulations that were prepared with other vehicles. Also, it was prepared from commercially available tablets as the source of the active ingredient which is readily available at the market. Moreover, the extemporaneously compounded suspension maintained acceptable quality attributes when stored for three months at room temperature. The extemporaneously compounded suspension enables pediatricians to administer a variable dose, which adapts to every patient, and gives the possibility of treatment when the liquid dosage forms are not available. Extemporaneously compounded suspension can be prepared by a hospital pharmacist using commercially available tablets as the source of the active ingredient. Scientific information and directions on how to compound commercial immediate-release tablets into a suspension, as well as information on the expiry date of the compounded suspensions, should be included in package inserts. Also, further studies are needed to compare the *in vivo* absorption of tablets with extemporaneously compounded suspensions.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

REFERENCES

- [1] S. Alabed, A. Sabouni, S. Al Dakhoul, Y. Bdaiwi, and A. K. Frobel-Mercier, "Beta-blockers for congestive heart failure in children," *Cochrane Database of Systematic Reviews*, vol. 2016, no. 1. John Wiley and Sons Ltd, Jan. 28, 2016, doi: 10.1002/14651858.CD007037.pub3.
- [2] F. Brion, A. J. Nunn, and A. Rieutord, "Extemporaneous (magistral) preparation of oral medicines for children in European hospitals," *Acta Paediatr. Int. J. Paediatr.*, vol. 92, no. 4, pp. 486–490, Apr. 2003, doi: 10.1111/j.1651-2227.2003.tb00583.x.
- [3] J. A. Giam and A. J. McLachlan, "Extemporaneous product use in paediatric patients: a systematic review," *Int. J. Pharm. Pract.*, vol. 16, no. 1, pp. 3–10, 2010, doi: 10.1211/ijpp.16.1.0002.
- [4] "Manufacturing and Compounding of Medications," 2010. https://old.sFDA.gov.sa/en/drug/resources/Guides/ManufacturingandCompoundingofMedications_v11.pdf (accessed Oct. 07, 2021).
- [5] M. M. Euphenia, S. Fatima, and G. Thirumala, "Investigating extemporaneous compounding practices in the Polokwane tertiary hospital pharmacies in South Africa - a pilot study," *African J. Pharm. Pharmacol.*, vol. 9, no. 48, pp. 1099–1105, 2015, doi: 10.5897/ajpp2015.4282.
- [6] "Report: Limited FDA Survey of Compounded Drug Products | FDA." <https://www.fda.gov/drugs/human-drug-compounding/report-limited-fda-survey-compounded-drug-products> (accessed Dec. 07, 2021).
- [7] E. Cowley, R. Williams, and D. Cousins, "Medication errors in children: a descriptive summary of medication error reports submitted to the United States pharmacopeia," *Curr. Ther. Res.*, vol. 62, no. 9, pp. 627–640, Sep. 2001, doi: 10.1016/S0011-393X(01)80069-2.
- [8] J. L. Chollet and M. J. Jozwiakowski, "Quality investigation of hydroxyprogesterone caproate active pharmaceutical ingredient and injection," *Drug Dev. Ind. Pharm.*, vol. 38, no. 5, pp. 540–549, May 2012, doi: 10.3109/03639045.2012.662511.
- [9] T. Geng, P. Banerjee, Z. Lu, A. Zoghbi, T. Li, and B. Wang, "Comparative study on stabilizing ability of food protein, non-ionic surfactant and anionic surfactant on BCS type II drug carvedilol loaded nanosuspension: Physicochemical and pharmacokinetic investigation," *Eur. J. Pharm. Sci.*, vol. 109, pp. 200–208, Nov. 2017, doi: 10.1016/j.ejps.2017.08.005.
- [10] A. K. Kulshreshtha, O. N. Singh, and G. M. Wall, *Pharmaceutical suspensions: From formulation development to manufacturing*. Springer New York, 2010.
- [11] R. F. Donnelly, E. Pascuet, C. Ma, and R. Vaillancourt, "Stability of celecoxib oral suspension," *Can. J. Hosp. Pharm.*, vol. 62, no. 6, pp. 464–468, 2009, doi: 10.4212/cjhp.v62i6.844.

- [12] B. J. Stanis, S. K. Paszun, and A. Zalewska, "Stability of cilazapril in pediatric oral suspensions prepared from commercially available tablet dosage forms," *Acta Pol. Pharm. - Drug Res.*, vol. 71, no. 4, pp. 661–666, 2014.
- [13] R. F. Donnelly, E. Pascuet, M. Carmen, and R. Vaillancourt, "Stability of diclofenac sodium oral suspensions packaged in amber polyvinyl chloride bottles," *Can. J. Hosp. Pharm.*, vol. 63, no. 1, pp. 25–30, 2010, doi: 10.4212/cjhp.v63i1.865.
- [14] M. H. H. Ensom, J. Kendrick, S. Rudolph, and D. Decarie, "Stability of propranolol in extemporaneously compounded suspensions," *Can. J. Hosp. Pharm.*, vol. 66, no. 2, pp. 118–124, 2013, doi: 10.4212/cjhp.v66i2.1234.
- [15] J. Tran, M. A. Gervase, J. Evans, R. Deville, and X. Dong, "The stability of quetiapine oral suspension compounded from commercially available tablets," *PLoS One*, vol. 16, no. 8 August, pp. 1–12, 2021, doi: 10.1371/journal.pone.0255963.
- [16] E. A. Jew, Rita K, Winson Soo-Hoo, Sarah C Erush, "Handbook of Extemporaneous formulations: Extemporaneous Formulations for Pediatric, Geriatric, and Special Needs Patients," 3rd ed., ASHP, 2016.
- [17] World Health Organization, "Test for Sterility," *World Heal. Organ.*, vol. March, no. 1, pp. 571–572, 2012.
- [18] E. Santos-Fernández, K. Govindaraju, and G. Jones, "Quantity-based microbiological sampling plans and quality after inspection," *Food Control*, vol. 63, pp. 83–92, May 2016, doi: 10.1016/J.FOODCONT.2015.11.028.
- [19] Q. Mohammed Al-Khawlani, A. Kassem Alzomor, and A. Ghaleb Al-Mekhlafi, "IN-VITRO QUALITY EVALUATION OF TEN DICLOFENAC SODIUM AMPOULE BRANDS IN YEMEN," 2018, doi: 10.26479/2018.0405.37.
- [20] U.S. Pharmacopoeial Convention, "(905) Uniformity of Dosage Units. Stage 6 Harmonization.," vol. 3, pp. 4–6, 2011.
- [21] V. Patel, T. Desai, B. Chavda, and R. Katira, "Extemporaneous dosage form for oral liquids," *Pharmacophore*, vol. 2, no. 2, pp. 49–66, 2011.
- [22] J. P. Sinko, *Martin's physical pharmacy and pharmaceutical*. Lippincott Williams &Wilkins, 2013.
- [23] A. Jackson, M., & Lowey, *Handbook of Extemporaneous Preparation*, 1st ed. London: Pharmaceutical Press, 2010.
- [24] L. Felton, *Remington essentials of pharmaceuticals*, 1st ed. London: Pharmaceutical Press, 2012.
- [25] M. Helin-Tanninen, K. Autio, P. Keski-Rahkonen, T. Naaranlahti, and K. Järvinen, "Comparison of six different suspension vehicles in compounding of oral extemporaneous nifedipine suspension for paediatric patients," *Eur. J. Hosp. Pharm.*, vol. 19, no. 5, pp. 432–437, 2012, doi: 10.1136/ejhpharm-2012-000159.
- [26] K. Cutaia, L. Chablani, and F. Zhao, "Basics of Compounding: Vehicles for Compounded Oral Liquid Medications: A Review," *Int. J. Pharm. Compd.*, vol. 22, no. 6, pp. 480–489, 2018.
- [27] A. Melkoumov, A. Soukrati, I. Elkin, J. M. Forest, P. Hildgen, and G. Leclair, "Quality evaluation of extemporaneous delayed-release liquid formulations of lansoprazole," *Am. J. Heal. Pharm.*, vol. 68, no. 21, pp. 2069–2074, 2011, doi: 10.2146/ajhp100634.