



# Quality and stability of oral extemporaneous formulations developed from commercial tablets containing spironolactone

Aline Marques Rosa<sup>1</sup>; Mirella Carla Galana Gerlin<sup>1</sup>; Isabella Correa Alcântara<sup>1</sup>; Rubia Adrieli Sversut<sup>1</sup>; Teófilo Fernando Mazon Cardoso<sup>1</sup>; Patrik Oening Rodrigues<sup>1</sup>; Marcos Serrou do Amaral<sup>2</sup>; Nájla Mohamad Kassab<sup>1\*</sup>

<sup>1</sup> Centro de Ciências Biológicas e da Saúde, Universidade Federal de Mato Grosso do Sul, Campo Grande-MS, Brasil.

<sup>2</sup> Instituto de Física, Universidade Federal de Mato Grosso do Sul, Campo Grande-MS, Brasil.

## ABSTRACT

The purpose of this study was to develop extemporaneous liquid pharmaceutical formulations from commercial tablets containing spironolactone and to assess their stability for use in children or adults with difficulty in swallowing. The content and stability of spironolactone in the tablets, as well as in water, 1.5% carboxymethylcellulose (CMC) or simple syrup dispersions were determined by high performance liquid chromatography (HPLC) analysis on a C18 silica column (250 mm x 4.6 mm x 5 µm), with a mobile phase of methanol:water (75:25 v/v), flowing at 1 mL/min, and UV detection at 240 nm. The extemporaneous formulations were tested over a 35-day period at 8, 27, and 40 °C. Drug content in the aqueous dispersion was far lower than expected, with significant fluctuations at all temperatures, owing to rapid sedimentation. The content proved adequate in aqueous 1.5% CMC dispersion at 27 °C, with undesirable variations at the other temperatures. The syrup-based dispersion remained stable at all three temperatures, with suitable drug content and no significant variability. No degradation products were observed in any of the formulations. The syrup-based dispersion is easy to prepare, self-preserving, stable, palatable, offering satisfactory drug content per dose, and can therefore be recommended as an extemporaneous formulation for enhancing treatment adherence and effectiveness.

Keywords: Pediatrics. Liquid chromatography. Extemporaneous formulations. Edema. Hypertension and Dispersion.

## INTRODUCTION

Most drugs marketed in Brazil are available as tablets and capsules, while dosage forms specifically formulated for pediatric use are typically lacking. This puts children in general, as well as adults who have difficulty in swallowing, at a disadvantage, as they are unable to ingest these medications easily (Allen, 2000a). The paucity of suitable pediatric dosage forms forces physicians into prescribing dissolved or crushed tablets, or even the contents of capsules. As a result, these formulas are administered without reliable information on their bioavailability, efficacy or toxicity (Calderón-Guzmán et al., 2012).

In effect, drugs marketed for adult use end up being administered to children without regard to the original dosage forms endorsed by manufacturers. In the hospital setting, dosage forms developed for adults are often manipulated by the nursing staff or adapted by the hospital pharmacy, so as to achieve the small doses required for pediatric inpatients. This may require, for instance, splitting or crushing tablets, or even preparing dispersions or mixing drugs with other agents. Changes made to the original dose of a medicine carry a high risk of error, as they render drug bioavailability unpredictable and hard to evaluate. Furthermore, information on drug compatibility and stability under these adapted conditions is often unavailable, subjecting patients to risks of inaccurate dosing, contamination, loss of stability, incompatibility and unexpected interactions (Calderón-Guzmán et al., 2012; Costa et al., 2009a).

In the United States, off-label prescribing — indicating drug use that differs from manufacturers' guidelines — is common practice. In Brazil, where this involves disregarding the information printed on package inserts or authorized by the National Health Surveillance Agency (Anvisa), pediatric patients are frequent targets, particularly when hospitalized (Paula et al., 2011; Costa et al., 2009b; Brito, 2012). Extemporaneous formulations of spironolactone are one example of such use.

*Autor correspondente:* Nájla Mohamad Kassab – Centro de Ciências Biológicas e da Saúde, Curso de Farmácia - Laboratório de Tecnologia Farmacêutica, Universidade Federal de Mato Grosso do Sul, Caixa Postal 549, CEP 79070-900, Campo Grande-MS, Brasil.  
E-mail: nmkassab@gmail.com

Development of extemporaneous preparations has been reported for drugs commercially unavailable in liquid form. Such formulations play an important role in drug therapy, particularly in pediatrics, and even more so in children under six years of age who find it hard to swallow tablets or capsules (Allen, 2000b).

Typically, extemporaneous formulations are prepared easily and provide dosage flexibility. They require excipients suitable for pediatric use to ensure palatability, in addition to physical, chemical, and microbiological stability (Salgado et al., 2005).

Spironolactone inhibits the action of aldosterone by binding to mineralocorticoid receptors, preventing their nuclear translocation (Bhattacharya & Alper, 2009). In pediatric practice, spironolactone is used for the treatment of hypertension, edema associated with excessive aldosterone excretion, heart failure, and hypokalemia. In the Brazilian market, however, the drug is available only as oral tablets (Pinto & Barbosa, 2008; Royal Children's Hospital, 2010).

In a study of six Spanish hospitals, spironolactone was administered to 6.1% of pediatric patients and accounted for 2.6% of prescriptions (Cortizas et al., 2003). It is the drug most often employed in dosage forms (2.5% of prescriptions) prepared as suspensions. Notwithstanding that, physicians often point to the absence of a liquid form for oral use, despite reporting the drug as necessary (10.42%), among the most prescribed (15.13%) and the most prone to underdosing (Costa et al., 2009a).

To our knowledge, only two studies have reported the preparation of liquid formulations containing spironolactone: in one of the investigations, the stability of an extemporaneous preparation was assessed at a single temperature ( $22 \pm 3$  °C) (Salgado et al., 2005); in the other, the stability of a CMC aqueous dispersion of spironolactone, developed from raw materials, was assessed at  $5 \pm 3$  °C and  $25 \pm 2$  °C (Mendes et al., 2013).

The purpose of the present study was to develop extemporaneous spironolactone formulations for oral use in children, given their absence from the market, and to assess the physical and chemical stability and the drug content of these preparations, by means of high performance liquid chromatography (HPLC).

## MATERIAL AND METHODS

### Reagents, solvents, and equipment

HPLC was employed to analyze spironolactone, first as the chemical reference substance (CRS), then in commercial tablets and dispersions prepared from them in water, aqueous 1.5% carboxymethylcellulose (CMC) dispersion and simple syrup. The procedure was performed in an Ultimate 3000 chromatograph (Dionex-ThermoFisher) coupled to a UV/VIS detector and a C18 silica column (250 mm x 4.6 mm x 5  $\mu$ m). The mobile phase consisted of methanol:water (75:25 v/v), as proposed by

Laxman et al. (2010). The detection wavelength was 240 nm and the flow rate 1.0 mL/min. The formulations were prepared from 100 mg Aldosterin® tablets (lot D709004, Cellofarm). The spironolactone CRS was purchased from Deg/Fagron (lot 100408, 98.58% purity). All solvents were of spectroscopic and analytical grade. Water was purified in a Direct-Q 3 system (Millipore).

### Construction of calibration curve

In a volumetric flask, 12.5 mg CRS was dissolved in 25 mL methanol to obtain a 500.0  $\mu$ g/mL stock solution, from which serial dilutions were prepared with the mobile phase, to yield final concentrations of 8.0, 12.0, 20.0, 28.0 and 32.0  $\mu$ g/mL. The curve was constructed from the mean of triplicate analytical results.

### Determination of mean tablet weight and active substance content

Twenty tablets were individually weighed. From these values, the average weight, standard deviation (SD) and coefficient of variation (CV%) were calculated, in compliance with the Brazilian Pharmacopoeia guidelines (Brasil, 2010). The drug content was determined in triplicate by dissolving a 45.25 mg sample from a pool of 20 crushed tablets (equivalent to 12.5 mg of drug) in methanol, in a 25-mL volumetric flask. Each flask was filled to the mark with methanol and each resulting volume was further diluted to a final concentration of 20.0  $\mu$ g/mL. From each solution, 20  $\mu$ L was injected into the chromatograph, in triplicate, with a fixed-loop injector. The amount of drug in each tablet was calculated from the straight line equation obtained for the calibration curve, as the average of triplicate HPLC results.

### Development of formulations

Three liquid dosage forms were prepared from pulverized crushed tablets.

### Aqueous dispersion

To prepare a 4.0 mg/mL aqueous dispersion, the equivalent of 4320 mg of spironolactone was weighed from a pool of crushed tablets and transferred to a 500 mL mortar. Water was gradually added to form a paste-like mixture that was dispersed with the aid of the pistil and transferred to a beaker, where it was completed with water to a final volume of 1080 mL. The resulting dispersion was divided into 18 aliquots of 60 mL, stored separately in amber glass vials.

### Aqueous CMC dispersion

The equivalent of 1080 mg spironolactone was weighed, to prepare a 1.0 mg/mL dispersion in aqueous CMC. The preparation was similar to that of the aqueous dispersion, but employed a 1.5% dispersion of CMC as the vehicle, to give a final volume of 1080 mL. The resulting dispersion was stored in 18 amber glass vials of 60 mL capacity.

### Simple syrup dispersion

Preparation of this dosage form was similar to those described above, but simple syrup was used as the vehicle, prepared as specified in the 2nd edition of the Brazilian Pharmacopeia Formulary (Brasil, 2012) to a final concentration of 1.0 mg/mL.

### Assessment of quality and physicochemical stability of extemporaneous formulations

The physicochemical stability of the spironolactone formulations was monitored over a 35-day period. Physical appearance, color, odor, pH, presence of degradation products and drug content were recorded at three storage temperatures — namely, 8, 27 ( $\pm 2$ ), and 40 °C — for six vials of each dispersion (test vials). Only one vial was used for each CRS formulation. One vial of each dispersion was opened and tested on days 0, 7, 14, 21, 28 and 35. pH was determined with a W3B pH-meter (BEL), using a glass electrode calibrated with standard pH 4.01 and pH 7.00 buffer solutions.

After shaking the vials to redisperse the contents, the concentrations of active substance in the formulations were determined as follows:

**Aqueous dispersion:** A 5 mL aliquot (4 mg/mL) was transferred by pipette to a 100-mL volumetric flask and diluted to the mark with methanol. The resulting volume was homogenized and a 5-mL aliquot withdrawn from it, transferred to a 50-mL volumetric flask and diluted to the mark with the mobile phase, yielding a dispersion of 20  $\mu$ g/mL that was subsequently centrifuged at 3000 rpm for 3 min and filtered. The resulting filtered (20  $\mu$ L) was injected into the chromatograph in triplicate and its drug concentration were determined by comparison with the standard solution calibration curve. The procedure was repeated on all subsequent testing days.

**Aqueous 1.5% CMC dispersion:** A 5-mL aliquot (1 mg/mL) was transferred by pipette to a 50-mL volumetric flask and diluted to the mark with methanol. The resulting volume was homogenized and a 5-mL aliquot withdrawn from it, transferred to a 25-mL volumetric flask, and diluted to the mark with the mobile phase, yielding a 20- $\mu$ g/mL dispersion. The final concentration was determined as for the aqueous dispersion.

**Simple syrup dispersion:** The procedure was the same as that employed for the aqueous 1.5% CMC dispersion.

### Assessment of viability

To investigate the physicochemical viability of formulations after the vial was opened, all the vials analyzed on day 0 (control vials) were analyzed again on the remaining scheduled days.

### Calculation of the shelf life

This calculation was based on degradation kinetics (Carstensen & Rhodes, 2000).

## RESULTS

### Calibration curve

The straight calibration curve fitted the data very well (coefficient of determination  $r^2 = 0.9998$ ). The linear equation adopted to calculate drug contents in the tablets and extemporaneous formulations was  $y = 1.0842x - 0.0037$ , where  $y$  is the HPLC reading and  $x$  is the drug concentration in the injected sample.

### Mean weight and active substance content in tablets

The mean tablet weight was  $362.12 \pm 9.92$  mg. Drug content in the tablets was 104.14% of the nominal content.

### Quality and physicochemical stability of extemporaneous formulations

In all formulations, pH was measured on days 0 and 35 and remained unchanged, at 6.0, at all the temperatures evaluated.

**Aqueous dispersion:** This formulation initially appeared milky when stirred, owing to the excipients employed in the tablets, but soon after the insoluble, suspended material was left to settle, the supernatant became almost clear. Figures 1(a) and 1(b) show the aqueous dispersion chromatograms performed on days 0 and 35, respectively.

**Aqueous 1.5% CMC dispersion:** More viscous than its aqueous counterpart, this dispersion appeared milky and free of sediment during the entire period of aliquot withdrawal. The particulate material was evenly distributed. Figures 1(c) and 1(d) show the aqueous 1.5% CMC dispersion chromatograms performed on days 0 and 35, respectively.

**Simple syrup dispersion:** More viscous than its aqueous counterpart, this dispersion was light yellowish in color, remaining unseparated for a long period. The particulate material was evenly distributed. Figures 1(e) and 1(f) show the syrup-based dispersion chromatograms performed on days 0 and 35, respectively.

### Viability

Figure 2 depicts the drug contents in the syrup-based dispersion on days 0 and 35 at 8, 27, and 40 °C.

### Shelf life

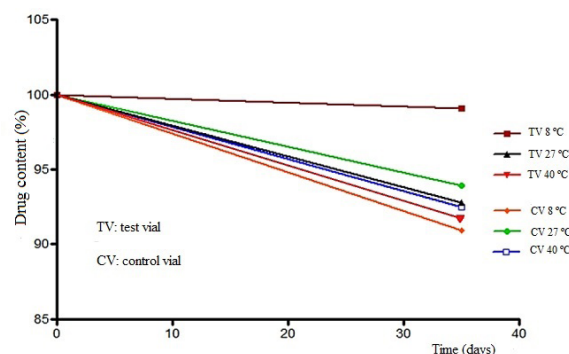


Figure 2. Drug content of syrup dispersion, stored at 3 different temperatures, on days 0 and 35.

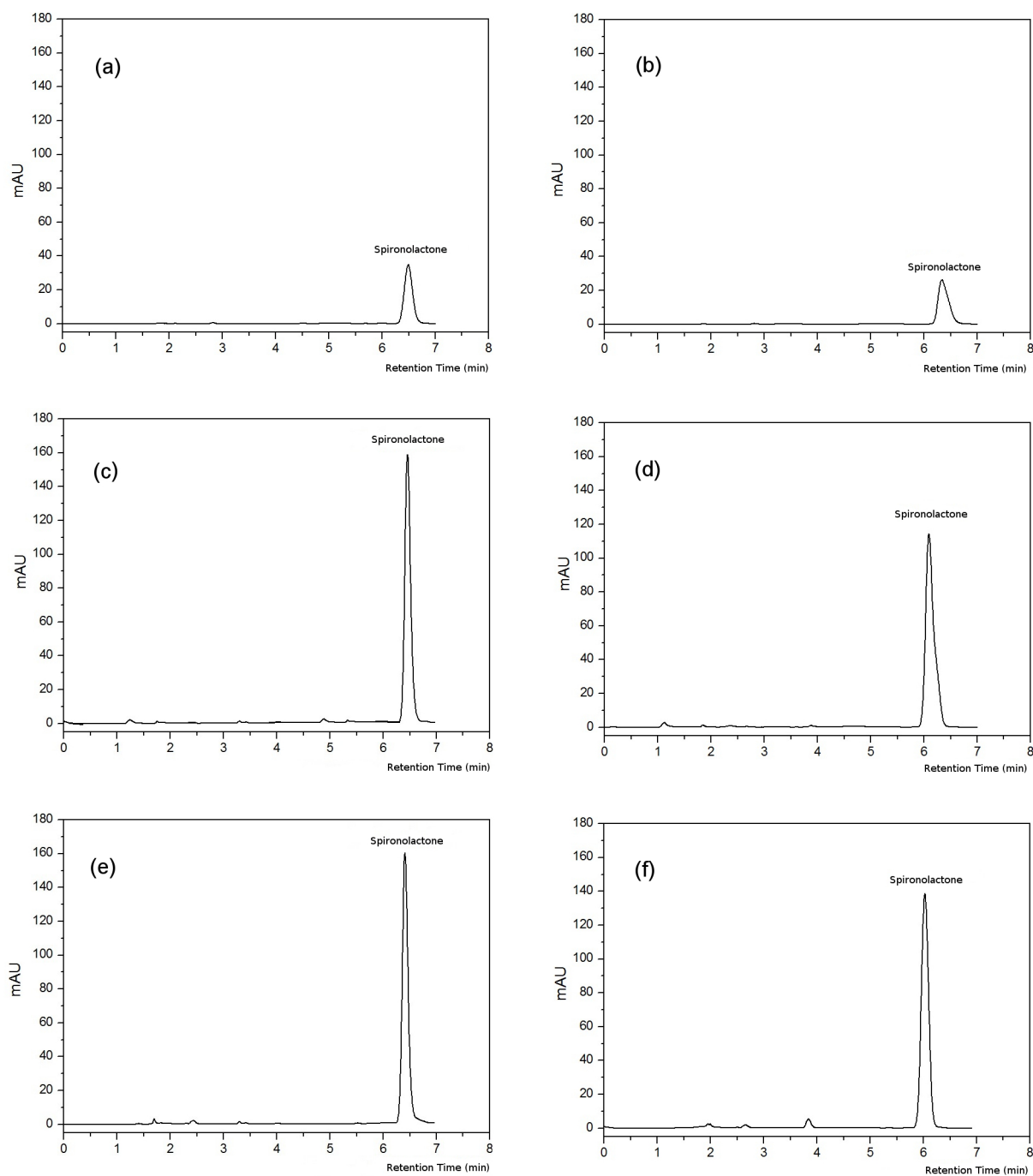


Figure 1. Chromatograms of formulated dispersions: (a, b) aqueous; (c, d) aqueous 1.5% CMC; (e, f) simple syrup; (a, c, e) day 0, (b, d, f) day 35.

Theoretical calculations of degradation kinetics for test vials indicated that simple syrup dispersions should remain viable for at least 12 months when stored at 8 °C, for 49 days at 27 °C, and for 12 months at 40 °C, whereas calculations for the control vials revealed shelf lives of 39, 57, and 47 days, respectively.

## DISCUSSION

### Calibration curve

The results revealed a linear relationship between chromatographic peak areas and the corresponding spironolactone concentrations, over the range 8 to 32 mg/mL, demonstrating that the method developed by

Laxman (2010) is reproducible and can be used reliably to determine spironolactone content in these pharmaceutical formulations.

#### Mean weight and active substance content of tablets

Tablet weight varied less than 5%, within the range allowed by the Brazilian Pharmacopeia (Brasil, 2010). Mean tablet weight was determined to ensure that the starting material for the formulations complied with pharmacopeial specifications. Drug content was in conformity with United States Pharmacopeia standards (USP 2012), partially ensuring that an adequate amount of active principle was present in the formulations.

#### Quality and physicochemical stability of extemporaneous formulations

The formulations were prepared from crushed tablets because this dosage form, typically found in essential drug lists for hospital care, is more easily acquired and stored than CRSs. The percent drug content in solutions of CRS alone was similar to that of the formulations prepared from crushed tablets, demonstrating that tablet excipients did not affect final drug concentration of the derived formulations. Only three vials containing CRS-grade spironolactone were prepared for each extemporaneous formulation—sufficient to provide a comparative standard for drug content determination.

Drug content varied more than 10% in the aqueous dispersions (Table 1), because spironolactone, being almost insoluble in water, requires a dispersing agent. Lack of this ingredient precluded homogenization of the dispersion, as could be seen by the prompt sedimentation, responsible for the low drug content observed—a property that can lead to underdosing.

Table 1. Contents (%) of active substance in extemporaneous formulations prepared from tablets containing spironolactone, during storage at three temperatures.

Extemporaneous formulation	Temperature			
	8 °C	27 °C	40 °C	
Aqueous dispersion	TV, day 0	---	29,64	---
	TV, day 35	9,91	18,52	44,66
	CV, day 35	6,89	11,85	73,88
Aqueous CMC dispersion	TV, day 0	---	100,21	---
	TV, day 35	100,49	96,14	114,17
	CV, day 35	86,22	101,78	109,41
Simple syrup dispersion	TV, day 0	---	103,88	---
	TV, day 35	102,93	96,41	102,93
	CV, day 35	94,43	97,58	96,11

TV: test vial; CV: control vial; Dash: not measured

Similar difficulties were encountered by Albuquerque (2007), while producing an extemporaneous formulation of pyrazinamide (which is also poorly soluble in water) in aqueous dispersion in the absence of a dispersant, rendering the drug difficult to dose.

In contrast, Santos et al. (2005), testing the physicochemical stability and content of folic acid (again poorly soluble in water) in extemporaneous aqueous dispersions without dispersant, found the formulation remained stable over a 14-day period, with an adequate content, at temperatures from 2 to 8 °C.

In the present study, the aqueous 1.5% CMC dispersion was prepared at a concentration of 1 mg/mL to facilitate assaying and homogenization. The formulation proved stable when stored at 27 °C, with acceptable content variability. Storage at 40 °C led to increased drug contents, detected on day 35, possibly resulting from the increased solubility at higher temperature or from water evaporation making the dispersion more concentrated. At 8 °C, the dispersion failed to remain viable, and drug content on day 35 was unsatisfactory (Table 1).

Investigating an aqueous 0.18% CMC dispersion of spironolactone, developed from raw materials for pediatric inpatients, Mendes et al. (2013) found that it remained stable at both  $5 \pm 3$  °C and  $25 \pm 2$  °C. Preservatives, however, are known to cause allergies in many patients, especially children. Furthermore, the use of raw materials instead of crushed tablets may prove hard to implement in practice, since most hospitals acquire dosage forms rather than CRSs.

In the present syrup-based dispersion, drug content varied by no more than 10%, since the particulate material, once shaken, remained dispersed long enough for uniform aliquots to be withdrawn over 35 days. The same behavior was observed by Albuquerque (2007), while determining doses of an extemporaneous dispersion of pyrazinamide in simple syrup as the dispersant. In the present study, syrup-based dispersions were best preserved when stored at room temperature ( $27 \pm 2$  °C), relative to the other temperatures investigated (Table 1).

Similar findings were obtained by Salgado et al. (2005) while investigating the physicochemical and microbiological stability of simple syrup dispersions of spironolactone, which were found to remain stable after 60 days when stored at 5 or 22 °C.

Studies of the stability of extemporaneous syrup-based formulations of clopidogrel (at room temperature and under refrigeration) or acupril (at 5 °C) found their stability to exceed 30 days (Skillman et al., 2010; Freed et al., 2005).

A number of studies have described the development and physicochemical and microbiological stability, at various storage temperatures, of extemporaneous formulations (prepared from either raw materials or marketed dosage forms), yet to our knowledge only two of them investigated the stability of extemporaneous preparations of spironolactone. Their findings, however, cannot be extrapolated to temperature ranges other than those reported.

The chromatograms shown in Figure 1 reveal that the drug did not undergo chemical degradation in any of the formulations for at least 35 days, as shown by the absence

of new peaks that could be attributed to degradation products. The variable drug contents in dispersions in water or aqueous 1.5% CMC must therefore be attributed to poor homogeneity resulting from the physical instability of the formulations.

Out of all the formulations investigated, the syrup-based dispersion exhibited the greatest stability, maintenance of drug content and dose uniformity. It also has the advantage of being palatable, simple to prepare and self-preserving, in some cases dispensing with additional preservatives such as methylparaben or propylparaben, which can trigger adverse reactions, particularly in pediatric patients hypersensitive to them (Silva et al., 2008).

Sodium benzoate, sulfites, tartrazine yellow, sorbitol and other excipients have also been shown to cause allergic reactions in children (Tonazio et al., 2011). None of the above-mentioned excipients were present in the tablets employed in the formulations investigated in the present study, allowing their safe use in children.

The syrup-based dispersion of spironolactone has the advantage of facilitating adherence to treatment in pediatric patients, as well as in adults who have difficulty swallowing solid dosage forms.

#### Viability and shelf life of formulations

All samples were tested for drug viability, except for the aqueous dispersions, with and without 1.5% CMC, which were not tested because of their poor homogeneity and reproducibility. Given its advantages, the syrup-based dispersion was chosen for viability and shelf-life tests. As depicted in Figure 2, no significant drug losses were observed up to day 35, either in test vials or control vials: over 90% of the drug remained stable at all three temperatures investigated.

Theoretical calculations of shelf life of the syrup-based dispersion indicated physicochemical stability of both test and control samples, but at 8 and 40 °C the test samples proved superior in this respect. At room temperature, the calculations indicated similar shelf lives for all samples, at least within the 35-day period of study.

The control samples of the syrup-based dispersion had longer viability and shelf life and greater physicochemical stability, irrespective of temperature—useful features for long-term drug therapy, yet the quality of this extemporaneous spironolactone formulation remains to be tested in terms of microbiological stability.

#### ACKNOWLEDGMENTS

The authors thank CNPq and FUNDECT (Project 23/200.215/2010) for their financial support of this investigation.

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Received on August 5th, 2013

Accepted on September 19th, 2013

