Preformulation of a liquid dosage formulation of captopril for pediatric use: drug-excipient compatibility and stability studies

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Currently, medications used in children are typically modified from pharmaceutical dosage forms designed for adults. Captopril is widely adapted to liquid formulations for use in hospitals. Its stability in the aqueous medium is reduced since it undergoes oxidation producing captopril disulfide (its main metabolite). The aim of this formulation study was to suggest favorable conditions for the development of a stable captopril formulation. The compatibility between the drug and excipients was evaluated by differential scanning calorimetry analysis (DSC). For studies in solution, different formulations were prepared according to a factorial design varying EDTA concentration, water purity and pH. The resultant formulations were stored at 60°C and analyzed over a twelve-day period using HPLC. The DSC curves obtained suggested, although not conclusive to elucidation, interactions of captopril with citric acid and sucralose. The stability study of these solutions revealed that the variables significantly influenced captopril content, which degraded at zero order kinetics and rates differing by a factor of up to 7 times, where pH proved the most influential factor. Interactions between variables were observed. Therefore, development of a stable captopril formulation is feasible provided EDTA and a buffering agent is used at suitable concentrations (0.08% and pH 3.85).


INTRODUCTION

The available medications are mostly developed for adults. Thus, the data on safe dose is often extrapolated for pediatric use. Children are subjected to therapy risk because they have different pharmacokinetic and pharmacodynamic mechanisms according to age and compared to adults (Rosa et al, 2006; OMS, 2007; Jadhav, Kern, 2010). The lack of accurate and adequate information on the use of pediatric medicines or the lack of appropriate formulations for the indicated dosages led to the spread of the term “therapeutic orphans” when referring to children (Permala et al., 2010).

Thus, non-specific medicines for children can be classified as off-label, used with a different age, dose, frequency, presentation, other delivery route or indication to label guidelines (Carvalho et al., 2003; Rose, 2005; Costa, Lima, Coelho, 2009); or unapproved, when contraindicated or not licensed for use in children, manipulated or modified in the hospital, and with no specific dosage for children (Carvalho et al., 2003).

In various studies, captopril, an inhibitor of angiotensin converting enzyme (ECA) (Ferreira, 1998; Katzung, 2005), was cited as a necessary medicament in liquid form for the treatment of childhood arterial hypertension and heart failure (Peterlini, Chaud, Pedreira, 2003; Standing, Tuleu, 2005; Flores-Pérez, 2008; Santos et al., 2008; Costa, Lima, Coelho, 2009; Costa, Rey, Coelho, 2009). The problem of childhood hypertension has only received greater attention, so few medications have been developed and tested on children. Therefore, the antihypertensive treatment is initiated at dosages based on data obtained for adults (Salgado, Carvalhaes, 2003; Flynn, 2008).
The development of a liquid formulation of captopril for pediatric use is challenging owing to its susceptibility to oxidative degradation facilitated by high humidity and catalyzed by metal traces commonly found in excipients (Marcatto et al., 2005). Moreover, these preparations must provide safe excipients and good palatability, as the medications mostly have a bitter, sour or salty taste (Hempenstall, Tuleu, 2009).

Matthew, Das Gupta (1996) demonstrated that co-solvents, chelating agents and high concentrations of captopril favored the drug’s stability in aqueous systems. Schlatter, Sola, Saulnier (1997) evaluated the effect of pH and temperature on the stability of solutions at 1 mg/mL prepared from a captopril tablet of 25 mg. The solution prepared in citrate buffer at pH 5.0 was stable for at least 30 days at 4 °C. In extemporaneous oral liquid formulations at the same concentration containing antioxidants and chelating agents, pH did not influence the stability of captopril. However, samples stored at low temperatures were more stable and presented better microbiological quality (Escribano García et al., 2005). Furthermore, studies have shown that a pH value in the acidic range and the addition of chelating agents (e.g. EDTA) retard the oxidation of captopril (Berger-Gryllaki, 2007; Kristensen et al., 2008; Brustugun et al., 2009).

Different conclusions arise from studies carried out under diverse conditions suggesting the influence of the factors on each other is complex. In this way, experimental planning such as factorial design has been applied as a powerful tool to understand the impact of formulation variables and preparation conditions on the stability and other properties of drug dosage forms (Padamwar, Pokharkar, 2006; Cekić et al., 2015). Besides, thermal analysis has been useful in pre-formulation studies to evaluate interactions between drug and excipients (Freire et al., 2009; Oliveira et al., 2011).

Given that liquid preparation obtained by adapting the pharmaceutical dosage form (grinding of tablets followed by dispersion in a liquid medium) may result in inaccurate dosages and inadequate stability, jeopardizing the treatment, the aim of the present study was to evaluate the influence of interactions between pH, water quality and chelating agent concentration on the stability of captopril in the preparation of a pediatric formulation.

MATERIAL AND METHODS

Raw materials and solvents

- Captopril (Galena Química e Farmacêutica Ltda);
- EDTA (Isofar - Indústria e Comércio de Produtos Químicos Ltda);
- Anhydrous citric acid and dihydrate sodium citrate (Labsynth);
- Sucralose (Embrafarma Pharmaceutical Expertise);
- Distilled water;
- Mineral water of the Indaiá brand (Composition: Chloride = 23.80 mg.L⁻¹; Sodium = 14.99 mg.L⁻¹; Nitrate = 2.9 mg.L⁻¹; Bicarbonate = 0.80 mg.L⁻¹; Sulfate = 0.8 mg.L⁻¹; Potassium = 0.79 mg.L⁻¹; Magnesium = 0.76 mg.L⁻¹; Calcium = 0.23 mg.L⁻¹; Barium = 0.027 mg.L⁻¹; Strontium = 0.006 mg.L⁻¹);
- For the preparation of the mobile phase used in the HPLC analysis: Methanol HPLC grade (VETEC Fine Chemicals Ltd), Phosphoric Acid 85% (Isofar - Industry and Chemicals Ltd) and ultra-pure water.

Study in solid phase (powder)

Determination of the drug-excipient compatibility

The compatibility between captopril and the excipients (EDTA, citric acid, dihydrate sodium citrate and sucralose) was measured by differential scanning calorimetry (DSC). The samples were obtained by physically mixing the drug and excipients at a proportion of 1:1 (m/m) with a spatula.

The DSC curves were obtained on a Shimadzu DSC-60 device, using aluminum pans with 2 mg of samples under atmospheric pressure of N₂ at a flow rate of 50 mL.min⁻¹, heating rate of 10 °C.min⁻¹ and temperature range between 25 and 400 °C.

In addition to the thermal analysis by DSC, the thermal behavior of captopril was evaluated by differential thermal analysis (DTA) and thermogravimetry (TG). Approximately 4 mg of the drug were placed in an alumina pan and analyzed on a Shimadzu DTG-60 device under an atmosphere of nitrogen at a flow rate of 50 mL.min⁻¹, heating rate of 10 °C.min⁻¹ and temperature range of between 35 and 900 °C. Both devices were calibrated with indium standards (melting point at 156 °C) and zinc (melting point at 420 °C).

Studies in liquid phase

Experimental design and statistical analysis

The formulations were developed using the minimum and maximum allowable concentration of EDTA, 0.005 and 0.1 % (m/v), respectively -1 and +1 levels, according to the Handbook of Pharmaceutical Excipients, 6th ed. (Rowe, Sheskey, Quinn, 2009), in two types of water (distilled as lower level or -1, and mineral...
- the highest level or +1) and at three pH values (2.5, 4.0 and 5.5, corresponding to levels -1, 0 and +1 respectively). Therefore, 2x3 factorial planning was used, giving a total of 12 formulations, each in triplicate, with a final volume of 500 mL. The resultant formulations are shown in Table I. Captopril concentration was fixed at 5 mg/mL.

Furthermore, sucralose was added to the formulations as a sweetener, at variable concentrations according to the pH. The concentrations used were determined according to the subjective sensory analysis, where higher concentrations of the sweetener were required in more acidic formulations. The solutions were then subjected to heating in a QUIMIS oven (MODEL: Q-317 B252) at 60 °C ± 2 °C and analyzed in alternate days for 12 days.

Captopril was quantified according to the methodology contained in the Brazilian Farmacopeia, i.e. by high-performance liquid chromatography in a Shimadzu chromatograph, equipped with LC-10AT pump, ultraviolet detector (SPD-M20A5), DGU-20A5 degasser and PERKIN ELMER column with length of 250 mm and an internal diameter of 4.6 mm, packed with silica chemically bonded to an octadecylsilane group (5 μm), kept at ambient temperature and mobile phase flow rate of 1 mL.min⁻¹. The mobile phase consisted of a mixture of phosphoric acid 0.11% (v/v) and methanol (45:55), filtered through an ALLCROM nylon membrane filter with pore size of 0.22 μm (Farmacopeia …, 2010).

The influence of the factors on the captopril content as a function of time was examined with the aid of the software Statistica 7.0, through Pareto diagrams (p=0.05); marginal means for analysis of interactions between factors; and response surface graphs, from which the best combination of factors to develop a stable formulation was established.

**Evaluation of the degradation kinetics**

Initially, captopril content data obtained over the 12-day test period were plotted using Microsoft Excel 2010 software to determine the order of the reaction. Data on the slope inclination, intercept and values of the coefficient of determination (R²) were derived from the equations applied for the zero, first and second order reactions (Florence, Attwood, 2003). Thus, the values of captopril content as a function of time were used, considering a direct linear relationship to zero order, the logarithmic function of the content versus the time to the first order, and in the case of the second order, inverse values of content as a function of time. The coefficients of determination (R²) derived were compared, considering the order of the reaction corresponding to the function for which the highest values were obtained.

Half-life (t₁/₂) time and the time taken for degradation of 10% of the drug (T₉₀%) were also calculated, being defined as the validity period of the solution (Florence, Attwood, 2003).

### RESULTS AND DISCUSSION

#### Studies in solid phase

**Determination of the drug-excipient compatibility**

The DSC, TG and DTA curves of captopril and DSC

#### Evaluation of the degradation kinetics

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Half-life (t₁/₂) time and the time taken for degradation of 10% of the drug (T₉₀%) were also calculated, being defined as the validity period of the solution (Florence, Attwood, 2003).

### TABLE I - Formulations combining variables at different levels submitted to stress testing at 60 °C

<table>
<thead>
<tr>
<th>Formulation</th>
<th>[EDTA]%</th>
<th>Type of water</th>
<th>pH</th>
<th>[Sucralose]%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>-</td>
<td>Distilled</td>
<td>2.73</td>
<td>-</td>
</tr>
<tr>
<td>Fa</td>
<td>0.005</td>
<td>Distilled</td>
<td>2.5</td>
<td>0.20</td>
</tr>
<tr>
<td>Fb</td>
<td>0.005</td>
<td>Distilled</td>
<td>4.0</td>
<td>0.17</td>
</tr>
<tr>
<td>Fc</td>
<td>0.005</td>
<td>Distilled</td>
<td>5.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Fd</td>
<td>0.1</td>
<td>Distilled</td>
<td>2.5</td>
<td>0.20</td>
</tr>
<tr>
<td>Fe</td>
<td>0.1</td>
<td>Distilled</td>
<td>4.0</td>
<td>0.17</td>
</tr>
<tr>
<td>Ff</td>
<td>0.1</td>
<td>Distilled</td>
<td>5.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Fg</td>
<td>0.005</td>
<td>Mineral</td>
<td>2.5</td>
<td>0.20</td>
</tr>
<tr>
<td>Fh</td>
<td>0.005</td>
<td>Mineral</td>
<td>4.0</td>
<td>0.17</td>
</tr>
<tr>
<td>Fi</td>
<td>0.005</td>
<td>Mineral</td>
<td>5.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Fj</td>
<td>0.1</td>
<td>Mineral</td>
<td>2.5</td>
<td>0.20</td>
</tr>
<tr>
<td>Fk</td>
<td>0.1</td>
<td>Mineral</td>
<td>4.0</td>
<td>0.17</td>
</tr>
<tr>
<td>Fl</td>
<td>0.1</td>
<td>Mineral</td>
<td>5.5</td>
<td>0.15</td>
</tr>
</tbody>
</table>
binary mixtures with the excipients used in this study are depicted in Figure 1.

The DSC curve and the DTA of captopril (Figure 1a) shows an endothermic event with a peak at 111.83 °C (ΔH_melting = -135.24 J.g⁻¹), corresponding to the melting of the drug. A second event starts around 200 °C and is related to drug decomposition. The TG curve shows that the decomposition occurs between 170 and 449 °C, in two steps, with a 97.21% decrease in the initial mass.

In mixtures A (Figure 1b) and C (Figure 1d), the thermal events for each substance alone were observed. Moreover, the enthalpy of the first peaks of mixtures A (ΔH_melting = -58.52 J.g⁻¹) and C (ΔH_melting = -64.74 J.g⁻¹) corresponded to approximately half the value of the melting peak of the drug, confirming the absence of interaction between captopril and excipients used in these mixtures: EDTA and dehydrate sodium citrate.

In mixture B (Figure 1c), the captopril melting point was reduced to 104.53 °C with broadening of the corresponding peak while the thermal event related to citric acid melting was not observed. However, the amount of energy involved in the captopril melting process (the first event observed on DSC curve of binary mixture) close to the value of the enthalpy involved in the melting of captopril (ΔH = -82.28 J.g⁻¹) indicates no interaction between the components. Therefore, the DSC curve for mixture B suggests the dissolution of the citric acid in the molten captopril (Oliveira et al., 2011).

The DSC curve of the binary mixture between captopril and sucralose (Figure 1e) exhibited an exothermic event at 124 °C and ΔH = 29.64 J.g⁻¹ while the thermal event related to sucralose at this temperature is endothermic (ΔH_melting = -74.01 J.g⁻¹) characteristic of the melting of the substance. This change suggests an interaction between these components or dissolution of sucralose in the molten captopril.

Thermal analysis alone was not conclusive to elucidate if interactions between captopril and both citric acid and sucralose took place. Other methods should be used such as Infrared Spectrophotometry to understand the influence of those components in the solid state. Moreover, the results of the stress test provided later indicate that sucralose and citric acid were not determining factors for the decrease in captopril stability in the solutions.

Studies in liquid phase

Evaluation of stability of captopril solutions at 5 mg/mL

The 12 formulations were subjected to the stress test and the captopril content was monitored by HPLC for a 12-day period (peak at 4.0 minutes). A gradual decrease in captopril content was observed. According to Figure 2, the formulations with the lowest pH values (Fe, Fg, Fj and Fk) showed less variation in captopril content over the 12 days. Moreover, the Fc formulation stands out for the significant decrease in captopril content, showing poor stability. This solution was prepared at higher pH (5.5) and low concentrations of EDTA in distilled water, where these conditions appear to be the most unfavorable for the preparation of a stable oral solution of captopril.

In agreement with this observation, from the fourth day of analysis, the emergence of a peak can be noted on the chromatograms (t1/2 = 6.2 min, probably captopril disulfide), a phenomenon most evident in the samples of the formulations at pH 5.5 (Fc, Ff, Fi and Fl).

In general, the formulations at pH 4.0 showed minor variations in captopril content, as did formulations at the same pH value containing the highest concentration of EDTA.

When calculating the coefficient of determination (R²) for reactions of zero, first and second order, the predominance of zero-order reactions was observed for all formulations together with the highest R² values (Table II). Moreover, the R² values were lower than the expected value (0.99), particularly in formulations with mineral water, probably due to the presence of ionic species in these solutions that can interact with metals able to accelerate the degradation of captopril (Pierangeli et al., 2001).

Thus, in contrast to results reported by Berger-Gryllaki et al. (2007), Kristensen et al. (2008) and Mathew, Das Gupta (1996), the rate of the decomposition reaction proved independent of captopril concentration, where the limiting factor, in this case, may have been temperature, as the formulations were stored in an oven at 60 °C.

For a zero-order reaction, t1/2 and t90% are calculated by the equations 1 and 2 respectively:

\[
t_{1/2} = \frac{C_0}{2 \cdot k_0} \quad \text{ (equation 1)}
\]

\[
t_{90\%} = \frac{(0.1 \cdot C_0)}{k_0} \quad \text{ (equation 2)}
\]

where C₀ is the initial concentration and k₀ is the slope. The values of k₀ correspond to the percentage of drug that is degraded with time (or degradation rate) and the intercept of the line at t=0 is equal to the initial concentration.

The values of the degradation constant, half-life and shelf-life are shown in Table II. Analysis of these parameters confirms that formulations with a higher
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pH value (Fc, Ff, Fi and Fl) are less stable, showing degradation of 1.7 to 3.6 times faster than captopril alone.

On the other hand, formulations prepared using mineral water as the solvent at pH 2.5 and 4.0 (Fg, Fh, Fj and Fk) resulted in less degradation than formulations prepared with distilled water. The Fk formulation (prepared with 0.1% of EDTA in mineral water at pH 4.0) showed a lower rate of decomposition, resulting in higher stability of up to 15 days. The worst and best formulations concerning degradation rate (Fc and Fk respectively) differed by a factor of about 7 times. Kristensen et al. (2008) showed that captopril aqueous solutions at 5 mg/mL containing EDTA were more stable than those prepared at 1 mg/mL. The values found for $t_{90\%}$ were 46 and 7 days respectively at 25°C. At temperature conditions closer to that used in this study, the degradation of captopril at 5 mg/mL resulted in constants around 9 x $10^{-3}$ days$^{-1}$ at pH values below 4 (Timmins, Jackson, Wang, 1982).

No evidence was found that sucralose influences captopril stability. Sucralose concentration was much lower in the solutions compared to the rate used in solid state study. Also, the solutions with higher sucralose concentration were those with lowest pH value, the higher stability provided was attributed to pH.
Evaluation of the influence of pH, EDTA concentration and type of water on captopril content and interaction between factors

The influence of each variable, as well as their interactions, on captopril content are shown in a Pareto chart (Figure 3). The chart shows that pH influenced captopril content both positively and negatively. This is because captopril is a diprotic acid with pKa values of 3.7 and 9.8 relating to the carboxyl and thiol groups, respectively. Therefore, pH values above 3.7 promote ionization of the molecules, rendering them more reactive. However, degradation at a pH below 4.0 is independent of pH, where according to the Henderson-Hasselbalch equation, the thiol group is hardly ionized (Timmins, Jackson, Wang, 1982).

The type of water positively influenced captopril content probably due to the presence of different ionic species. The mineral water may have favored the stability of the compositions due to lower activity of metallic ions able to catalyze the oxidation of captopril, as they compete for the exchange site (Pierangeli et al., 2001).

The presence of metallic ions, such as iron and copper, increases the rate of oxidation of captopril since they act as catalysts in the oxidation reaction of the thiol group. These ions are contaminants usually found in the formulation excipients, packaging, caps and/or manufacturing equipment. For this reason, the EDTA is an interferent with a significant positive contribution to stability because it acts by sequestering metallic ions, as opposed to leaving them free to favor the degradation reaction of captopril (Timmins, Jackson, Wang, 1982).

Furthermore, the interaction between the factors is significant, since the influence of a specific variable depends on the level of the other, an effect seen in Figure 4. Thus, the assessment of interactions between the EDTA concentration and the other variables confirms that raising the concentration of the chelating agent enhances the stability of solutions only when the other conditions are unfavorable, i.e. pH 5.5 and using distilled water. Therefore, for different levels of the water type variable, the concentration of the chelator has a different influence

TABLE II - Linear regression coefficient values for zero order kinetic ($R^2$), degradation rate ($k_o$), half-life time ($t_{1/2}$) and validity ($t_{90\%}$) of the analyzed formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>$R^2$</th>
<th>$k_o$ (% day$^{-1}$)</th>
<th>$t_{1/2}$ (days)</th>
<th>$t_{90%}$ (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control*</td>
<td>0.8112</td>
<td>1.22</td>
<td>40.8</td>
<td>8.2</td>
</tr>
<tr>
<td>Fa</td>
<td>0.9619</td>
<td>1.81</td>
<td>27.6</td>
<td>5.5</td>
</tr>
<tr>
<td>Fb</td>
<td>0.9031</td>
<td>1.24</td>
<td>40.2</td>
<td>8.0</td>
</tr>
<tr>
<td>Fc</td>
<td>0.9018</td>
<td>4.37</td>
<td>11.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Fd</td>
<td>0.9903</td>
<td>1.76</td>
<td>28.4</td>
<td>5.7</td>
</tr>
<tr>
<td>Fe</td>
<td>0.7074</td>
<td>0.72</td>
<td>69.2</td>
<td>13.8</td>
</tr>
<tr>
<td>Ff</td>
<td>0.9151</td>
<td>2.48</td>
<td>20.2</td>
<td>4.0</td>
</tr>
<tr>
<td>Fg</td>
<td>0.8251</td>
<td>0.75</td>
<td>67.0</td>
<td>13.4</td>
</tr>
<tr>
<td>Fh</td>
<td>0.7751</td>
<td>0.70</td>
<td>71.3</td>
<td>14.3</td>
</tr>
<tr>
<td>Fi</td>
<td>0.8789</td>
<td>2.07</td>
<td>24.1</td>
<td>4.8</td>
</tr>
<tr>
<td>Fj</td>
<td>0.7691</td>
<td>0.66</td>
<td>75.2</td>
<td>15.1</td>
</tr>
<tr>
<td>Fk</td>
<td>0.7009</td>
<td>0.64</td>
<td>77.7</td>
<td>15.5</td>
</tr>
<tr>
<td>Fl</td>
<td>0.9395</td>
<td>2.45</td>
<td>20.4</td>
<td>4.1</td>
</tr>
</tbody>
</table>

* captopril in aqueous solution (distilled water)
on the stability of the solution, showing the interaction between these factors (1Lby2L).

Regarding the relationship between water and pH, the type of water proved critical for the stability of the solutions at lowest pH values (2.5).

The surface response graphs (Figure 5) allow the optimal areas for the stability of captopril to be established. Figure 5a shows that a formulation with a pH near the central range of between 3.7 and 4.0, associated with an EDTA concentration of between 0.0525% and 0.1%, with the loss of at most 10% of captopril may be obtained.

The optimum point in the surface response graph to the type of water x concentration of EDTA (Figure 5b) is shifted to mineral water. Therefore, if mineral water associated with an EDTA concentration above 0.0525% is used, there will be a smaller loss of captopril (maximum 10%). This result support the possibility of interaction of the ionic species in the mineral water with the metallic ions, once the chelating agent can be used in the low level. Meanwhile, extremes values of pH in the range studied (2.5 or 5.5) associated with distilled water favor the captopril degradation, being more evident in the higher pH range (Figure 5c), i.e. the central zone of the graph comprises an area of lesser degradation of captopril (90% content).

From the data on surface responses, it can be stated that to develop a stable formulation of captopril, EDTA at a concentration of 0.08% (m/v) and buffering agents (anhydrous citric acid and sodium citrate dihydrate) must be added to obtain a formulation with an approximate pH of 3.85. The indicated values correspond to the average values of the ranges in which higher stability of captopril was achieved.

CONCLUSIONS

Experimental planning was a useful tool to the pre-formulation study for the development of a liquid formulation of captopril. From the results of captopril contents obtained through the stress test, it can be stated that pH is the factor that has the most influence on the stability of the solutions. The type of water also has a significant influence, where mineral water improved the stability of captopril. Among these three factors, the concentration of EDTA has an important function in preserving the captopril content when associated with other interferents.

The surface response graphs revealed the components and their optimal concentrations required to maintain the stability of captopril, data which may be used in the development of future formulations for pediatric use. Based on the results of the response surface graphs it can be concluded that a solution containing 0.08% (m/v) of EDTA at a pH of 3.85 can be considered the basis for a more stable formulation of captopril.
FIGURE 4 – Marginal means with confidence intervals (95%) for captopril content at different levels of the variables interfering the captopril degradation process: (a) EDTA; (b) water purity; (c) pH.
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REFERENCES


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