Stability of extemporaneously prepared captopril oral liquid formulation for paediatric patients

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Introduction

Captopril, an inhibitor of angiotensin converting enzyme (ACE), is used to treat medical conditions like hypertension and heart failure, and it is usually administered in tablet form for adults. Since this dosage form is not recommended for infants and children up to 6 years, hospital pharmacies have to prepare liquid formulations for oral administration of captopril. Traditionally, concentration of captopril used in the formulations is 1mg/ml.

The problem is that captopril is prone to oxidation, and its stability in solution is affected by pH, concentration of captopril, the presence of oxygen or metal ions. The influence of different formulation ingredients on the properties of physical and chemical stability of captopril in liquid preparations has been evaluated.

Goals

• To evaluate the stability of captopril for 30 days when formulated in a 1mg/ml suspension adjuvanted with citric acid.

Materials and Methods

Captopril suspensions of 1mg/ml were prepared from 25 mg tablet form in purified water. Formulation A: 1mg/ml captopril tablets + 0.03% citric acid. Formulation B: 1mg/ml captopril + 0.03% citric acid. Suspensions were placed in amber glass bottles of 100 ml, pH was monitored, and stored under different environmental conditions: i. Room temperature (22±2ºC); ii. Direct sunlight; iii. Refrigeration (5±3ºC).

Captopril chemical stability (retention of at least 90% of the initial concentration of captopril in the formulation) was evaluated by determination by high performance liquid chromatography (HPLC) on days 0, 6, 9, 13, 16, 20, 23, 27 and 30 of storage.

Discussion: Why is this important?

1. Formulation B is more conservative than formulation A at all tested storage conditions (less degradation of captopril occurs after a 30 days period)
2. Best performance of formulation B when stored at room temperature and protected from light (92.93% of the initial concentration remaining at day 30)
3. pH remains stable below 4 during 30 days for both formulations (results not shown)
4. Exposure to light is the condition that further compromises captopril stability

The results obtained from this project demonstrate that, as long as the suspension is properly packed in brown glass flasks and stored at room temperature protected from direct light incidence:

• Citric acid is able to maintain captopril stability in 1mg/ml extemporaneous oral suspensions for 30 days without changing pH;
• When refrigeration is not available, citric acid conserves captopril in 1mg/ml suspensions better than a non adjuvanted suspension.

Discussion

Since Captopril, an inhibitor of angiotensin converting enzyme (ACE), is used to treat medical conditions like hypertension and heart failure, and it is usually administered in tablet form for adults.

Results

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Figure 2 – HPLC chromatogram obtained after 30 days of captopril suspension storage at room temperature, protected from light. 3.a) – Formulation A; 3.b) – Formulation B. A – captopril; B – captopril disulfide; C citric acid.

Table 1 - Stability of captopril 1mg/ml suspensions: percentage of initial concentration remaining (Mean ± SD)

<table>
<thead>
<tr>
<th>Time</th>
<th>Formulation-storage conditions</th>
<th>A-I</th>
<th>A-II</th>
<th>A-III</th>
<th>B-I</th>
<th>B-II</th>
<th>B-III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>100.0% ±0.024</td>
<td>100.0% ±0.024</td>
<td>100.0% ±0.024</td>
<td>100.0% ±0.024</td>
<td>100.0% ±0.024</td>
<td>100.0% ±0.024</td>
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<tr>
<td>6 days</td>
<td>77.9% ±0.007</td>
<td>76.1% ±0.001</td>
<td>83.5% ±0.002</td>
<td>86.3% ±0.000</td>
<td>78.0% ±0.006</td>
<td>86.0% ±0.003</td>
<td></td>
</tr>
<tr>
<td>9 days</td>
<td>79.7% ±0.010</td>
<td>74.6% ±0.002</td>
<td>81.4% ±0.003</td>
<td>81.5% ±0.001</td>
<td>84.9% ±0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 days</td>
<td>76.8% ±0.004</td>
<td>70.9% ±0.002</td>
<td>82.3% ±0.029</td>
<td>92.6% ±0.003</td>
<td>82.0% ±0.005</td>
<td>86.9% ±0.006</td>
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<tr>
<td>16 days</td>
<td>73.2% ±0.001</td>
<td>71.6% ±0.002</td>
<td>79.2% ±0.002</td>
<td>90.1% ±0.002</td>
<td>80.1% ±0.002</td>
<td>84.2% ±0.006</td>
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<tr>
<td>20 days</td>
<td>73.6% ±0.001</td>
<td>69.2% ±0.002</td>
<td>75.0% ±0.004</td>
<td>91.1% ±0.001</td>
<td>80.8% ±0.002</td>
<td>84.7% ±0.001</td>
<td></td>
</tr>
<tr>
<td>23 days</td>
<td>72.9% ±0.001</td>
<td>69.2% ±0.002</td>
<td>74.8% ±0.004</td>
<td>92.9% ±0.007</td>
<td>82.3% ±0.001</td>
<td>84.6% ±0.002</td>
<td></td>
</tr>
<tr>
<td>27 days</td>
<td>70.1% ±0.002</td>
<td>68.0% ±0.004</td>
<td>76.5% ±0.001</td>
<td>92.3% ±0.003</td>
<td>79.9% ±0.003</td>
<td>87.2% ±0.005</td>
<td></td>
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<tr>
<td>30 days</td>
<td>73.8% ±0.004</td>
<td>66.8% ±0.004</td>
<td>76.9% ±0.001</td>
<td>99.0% ±0.015</td>
<td>81.6% ±0.001</td>
<td>86.1% ±0.001</td>
<td></td>
</tr>
</tbody>
</table>

Key: *Initial concentration = 1.486 (±0.024); SD = standard deviation (n= 3, lower and upper 95% confidence limits); ND = not determined

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