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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.

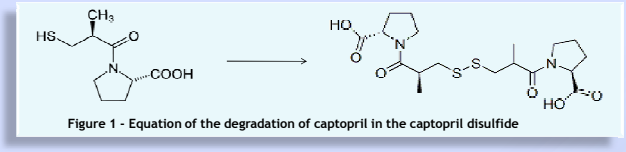


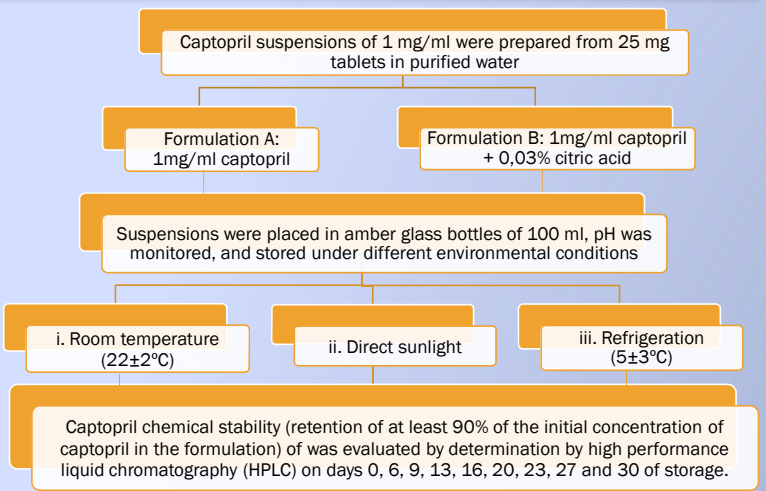
Figure 1 - Equation of the degradation of captopril in the captopril disulfide

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 1 mg/ml suspension adjuvanted with citric acid.

Materials and Methods



Results

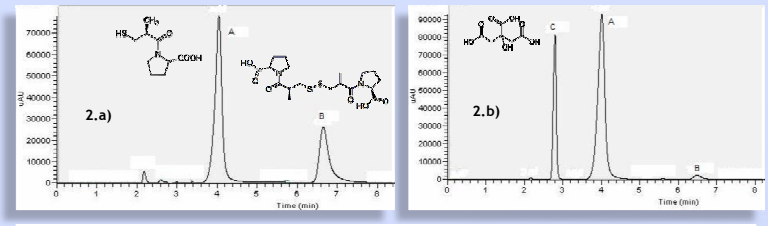


Figure 2 - HPLC chromatogram obtained after 30 days of captopril suspension storage at room temperature, protected from light. 3.a) - Formulation A; 3.b) - Formulation B. A - captopril; B - captopril disulphide; C citric acid.

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

Time	Formulation-storage conditions					
	A-i.	A-ii.	A-iii.	B-i.	B-ii.	B-iii.
Day 0	100,0% ±0,024	100,0% ±0,024	100,0% ±0,024	100,0% ±0,024	100,0% ±0,024	100,0% ±0,024
6 days	77,9% ±0,007	76,1% ±0,001	83,5% ±0,002	86,3% ±0,000	78,0% ±0,006	86,0% ±0,003
9 days	79,7% ±0,010	74,6% ±0,002	81,4% ±0,003	91,5% ±0,003	81,5% ±0,001	84,9% ±0,001
13 days	76,8% ±0,004	70,9% ±0,002	82,3% ±0,029	92,6% ±0,003	82,0% ±0,005	86,9% ±0,006
16 days	73,2% ±0,001	71,6% ±0,001	79,2% ±0,002	90,1% ±0,002	80,1% ±ND	84,2% ±0,006
20 days	73,4% ±0,001	69,2% ±0,001	75,0% ±0,006	93,1% ±0,001	80,8% ±ND	84,7% ±0,001
23 days	72,9% ±0,001	69,2% ±0,002	74,8% ±0,004	92,9% ±0,007	82,3% ±0,001	84,6% ±0,002
27 days	70,1% ±ND	68,0% ±0,004	75,6% ±0,001	92,3% ±0,001	77,9% ±ND	87,2% ±0,005
30 days	73,8% ±ND	68,6% ±0,004	76,9% ±0,001	92,9% ±0,013	81,6% ±0,001	86,1% ±0,001

Key: [a] initial concentration = 1.486 (±0,024); SD = standard deviation (n= 3, lower and upper 95% confidence limits); ND = not determined

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.

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