Drug Development, Hafnarfjordur, Iceland

## Enalapril maleate form II: stabilization in a tablet formulation

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*Received September 25, accepted September 30, 2002*

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*Pharmazie 58: 357 (2003)*

Enalapril maleate is unstable in solid dosage forms and the main degradation product is a diketopiperazine derivative (DKP) formed by an intramolecular cyclization reaction. This process may be prevented or minimized for example by including an alkaline reagent like sodium hydrogen carbonate in the formulation that converts the carboxylic function into a carboxylate anion [1].

Two polymorphic forms, form I and form II, of enalapril maleate have been described and characterized by spectroscopic methods [2, 3]. The X-ray powder diffraction spectra are rather similar but form II exhibits a distinctive peak of medium intensity at 13.0° 2θ whereas form I displays no peak at this position. Form II is thermodynamically more stable than form I but the energy difference between these two polymorphs has been stated to be very small or only 0.6 kcal/mol [2]. However, evidence has been presented suggesting that form II is much more unstable than form I in a tablet formulation containing sodium hydrogen carbonate as stabilizer in a practically stoichiometric amount [4].

Conceivably, less stability of form II in the tablet formulation used might be ascribed to reduced reactivity/solubility of it compared with form I, resulting in an incomplete reaction of it with the stabilizer. In order to investigate this hypothesis five tablet batches containing form II in combination with different amounts of sodium hydrogen carbonate were prepared using virtually identical processing conditions.

The enalapril maleate used in this study was practically pure form II as ascertained by X-ray powder diffraction analysis. Batch size was 5.2 kg, main excipient lactose monohydrate, tablet strength 10 mg, tablet mass 130 mg, wet granulation, drying of granulate to 1.4% (1.3–1.5%) loss on drying (IR-balance, 105 °C), compaction in a rotary tablet press. All processing steps, including packaging were performed at ambient (room) temperature and humidity (approx. 65% RH). The tablets obtained were packaged into aluminium/aluminium (Al/Al) blisters and high density polyethylene containers with desiccant (HDPE + Des) and put on stability trial at 40 °C/75% RH for one month. The results of diketopiperazine (DKP) and enalaprilate analyses performed by HPLC [5] on the tablets at the zero and one month points are displayed in the Table. Batch 1 contained sodium hydrogen carbonate in a practically stoichiometric quantity (5 mg per tablet) to enalapril maleate (10 mg per tablet) [6], the percentages shown for the other batches are relative to this amount.

These results demonstrate a dramatic decrease in DKP-content with increasing amounts of sodium hydrogen carbonate. On the other hand its effects on the content of enalaprilate seem to be marginal or non-existent. The formation of this degradate (arising from hydrolysis of the ethylester vector in the drug molecule) probably reflects residual (free) moisture in the tablets. This assumption is substantiated by the fact that significantly less degradation takes place on storage in the presence of desiccant.

**Table: Results of DKP and enalaprilate analyses**

| Batch number | | DKP-content (%) | | Enalaprilate-content (%) | |
|---|---|---|---|---|---|
| | | 0 point | 1 month | 0 point | 1 month |
| **1** | (5 mg $NaHCO_3$; + 0%) | | | | |
| | Al/Al | 0.31 | 9.31 | <0.25 | 0.44 |
| | HDPE + Des | 0.31 | 8.83 | <0.25 | 0.31 |
| **2** | (7 mg $NaHCO_3$; + 40%) | | | | |
| | Al/Al | <0.15 | 1.47 | <0.25 | 0.31 |
| | HDPE + Des | <0.15 | 1.33 | <0.25 | <0.25 |
| **3** | (8 mg $NaHCO_3$; + 60%) | | | | |
| | Al/Al | <0.15 | 1.16 | <0.25 | 0.27 |
| | HDPE + Des | <0.15 | 0.93 | <0.25 | <0.25 |
| **4** | (9 mg $NaHCO_3$; + 80%) | | | | |
| | Al/Al | <0.15 | 1.07 | <0.25 | 0.32 |
| | HDPE + Des | <0.15 | 0.98 | <0.25 | <0.25 |
| **5** | (10 mg $NaHCO_3$; + 100%) | | | | |
| | Al/Al | <0.15 | 0.17 | <0.25 | 0.26 |
| | HDPE + Des | <0.15 | <0.15 | <0.25 | <0.25 |

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