Influence of Residual Moisture on Stability of Levothyroxine Sodium Pentahydrate Tablets

M. Koerber 1, R. Bodmeier 2

1 Pensatech Pharma GmbH, 2 Freie Universitaet Berlin

Purpose
Levothyroxine (T4) is known to be sensitive to the choice of excipients as well as to the applied storage conditions (Collier et al., 2010), and various auto-catalytically driven degradation reactions were reported (Neu et al., 2013). Effects of residual moisture levels on levothyroxine stability in pharmaceutical packaging potentially meaningful for product enhancements and/or control, have not been explored yet. The purpose of this study thus was to investigate the effect of residual moisture contents of tablets on the stability of levothyroxine sodium pentahydrate at 40°C/75% rh under closed conditions.

Methods
Tablets containing levothyroxine sodium pentahydrate at a 25 µg dose strength were prepared with microcrystalline cellulose (MCC) of different moisture contents and magnesium stearate (1% w/w) as lubricant. The moisture content of MCC was adjusted by incubating the MCC prior to tabletting at 100% relative humidity (ambient temperature) for different lengths of time, leading to an increase of the weight loss on drying at 105 °C (LOD). Tablets were immediately packaged in PVC / PVDC / alu blisters and incubated at 40 °C / 75% rh for up to 6 months.

The tablets were characterized for drug assay by HPLC after 0, 1 and 6 months storage. HPLC separation was carried out on a Shimadzu LC-10 apparatus under conditions adapted from the draft method of the British Pharmacopoeial monograph on levothyroxine tablets (Spherisorb S5-CN, 5 µm, 150 x 4.6 mm column using flow rate of 1.5 mL/min with an analysis time of 10 minutes). Compounds were eluted using a mobile phase of H2O/CH3CN/H3PO4: 70/30/5 (v/v/v). UV detection was carried out at 225 nm.

Results
Reasonably hard tablets with loss on drying values of 4.6% (untreated), 5.4%, 6.2% and 7.3% were obtained. The initial tablet potencies were all in the range of 25 – 27 µg/tablet. The initial potencies decreased within 1-month storage at 40°C / 75% rh to values between 84, 92, 86 and 82% (assay of unstored tablets = 100%), respectively. The same sequence was seen after 6 months, where recoveries of 63, 70, 64 and 62% were determined for the tablets with LOD levels of 4.6%, 5.4%, 6.2% and 7.3%, respectively. The relationship between recovery and initial moisture level was non-linear with a stability optimum at about 5%. The presence of a stability optimum for levothyroxine at intermediate moisture levels was in agreement with previous reports on storage of levothyroxine formulations at different relative humidities (US patent 8,293,272). The stability window could be attributed to a balance between hydrolysis and condensation reactions occurring during the formation of the main degradant of levothyroxine, T4-acetic acid.

Conclusion
The residual moisture level of tablets has been identified as a factor influencing the stability of levothyroxine sodium pentahydrate in the dosage form during storage under closed conditions. Careful adjustment of the residual moisture level could thus help to control and improve the storage stability.