Partial dehydration of levothyroxine sodium pentahydrate in a drug product environment: structural insights into stability

Navpreet Kaur (kauru116@umn.edu; University of Minnesota)
Victor Young Ph.D. (vyoun@umn.edu; University of Minnesota)
Yongchao Su Ph.D. (yongchao.su@merck.com; Merck & Co., Inc.)
Raj Suryanarayanan Ph.D. (surya001@umn.edu; University of Minnesota)

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Purpose. Levothyroxine sodium is one of the most prescribed drugs on the global market and, in most instances, the only treatment option available to hypothyroid patients.1-3 However, levothyroxine products are also one of the most recalled from the market, due to issues pertaining to high chemical instability.4 Despite the critical need of this drug, there is a limited understanding of the factors affecting the chemical stability of levothyroxine sodium in solid dosage forms. Our objective is to understand the structural changes, specifically dehydration of levothyroxine sodium pentahydrate, that precede chemical decomposition.5-8

Methods. Differential scanning calorimetry, thermogravimetric analysis, gravimetric water sorption/desorption, powder X-ray diffractometry (XRD; both laboratory and synchrotron sources), and spectroscopy (IR and NMR) were used for comprehensive characterization of the different solid phases of levothyroxine sodium. The dehydration phase behavior was monitored by XRD and ssNMR.

Results. We have identified two additional hydration states of levothyroxine sodium – the tetrahydrate and monohydrate, and determined the crystal structure of the monohydrate. When stored at 40 °C/0% RH, the pentahydrate converts to the monohydrate. The monohydrate, despite being highly crystalline, has a much higher chemical reactivity than the pentahydrate.6 The high chemical reactivity of the monohydrate is attributed to the “unsatisfied” coordination number of the sodium atoms, which renders the molecule susceptible to nucleophilic attack.

Conclusion. In a drug product environment, levothyroxine sodium instability can be explained by a change in the physical form from pentahydrate to monohydrate. The crystal structure of levothyroxine sodium monohydrate provided insights into its chemical reactivity. This work highlights the critical impact of physical form on the chemical stability of levothyroxine sodium in a drug product environment. Changes in the crystal structure of levothyroxine sodium during pharmaceutical processing and storage pose a potentially serious concern. Controlling the physical form of the drug substance and preventing the pentahydrate to monohydrate transition in drug products, may be the necessary steps to prepare chemically stable formulations.

References.