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

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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.

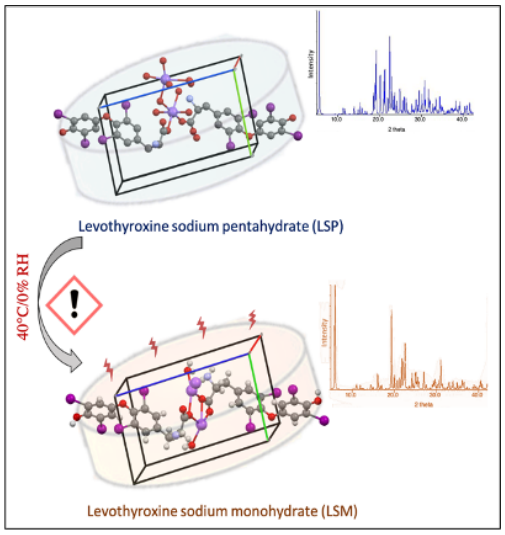

Figure. Crystal structures of levothyroxine sodium pentahydrate and monohydrate with two symmetry independent formula units in each unit cell.

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.

1. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, Cooper DS, Kim BW, Peeters RP, Rosenthal MS. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid 2014.24(12):1670-1751.
2. Levothyroxine: a review of clinical and quality considerations. https://www.gov.uk/government/publications/levothyroxine-a-review-of-clinical-and-quality-considerations. Accessed in 2019.
3. Fuentes A, Pin`eda M, Venkata K. Comprehension of top 200 prescribed drugs in the US as a resource for pharmacy teaching, training and practice. Pharmacy 2018.6(2):43.
4. Gerencer, T. Full List of All Levothyroxine Recalls, FDA 2012–2017. Available from. https://www.medprodisposal.com/levothyroxine-recall. Accessed in 2019.
5. Katrusiak A, Katrusiak A. Thyroxine revisited. J Pharm Sci 2004.93(12):3066-3075.
6. Hamad ML, Engen W, Morris KR. Impact of hydration state and molecular oxygen on the chemical stability of levothyroxine sodium. Pharm Dev Technol 2015.20(3):314-319.
7. Shah HS, Chaturvedi K, Hamad M, Bates S, Hussain A, Morris K. New insights on solid-state changes in the levothyroxine sodium pentahydrate during dehydration and its relationship to chemical instability. AAPS PharmSciTech 2019.20(1):39.
8. Kaduk J, Zhong K, Blanton T, Gates S, Fawcett T. Powder X-ray diffraction of levothyroxine sodium pentahydrate. Powder Diffr 2015.30(4):370-371.