Chemical Stability of Powder Triturates for T3/T4 Mixed with a New Excipient Base Using Variable Methods: Mortar and Pestle, FlackTek™ and PCCA RAM™

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Background

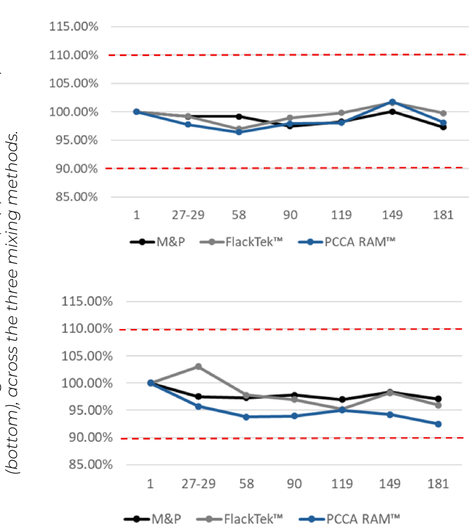
Thyroid hormones (liothyronine T3 and levothyroxine T4) are potent and low-dose active pharmaceutical ingredients (APIs), often measured in micrograms (µg) per dosing unit. As such, even slight chemical degradation can lead to clinically significant under- or overdosing, risking hypo- or hyperthyroidism. Compatibility with the new excipient base (PCCA UniFlow™) must be ensured when compounding solid dosage forms (tablets and capsules) to guarantee that there is no chemical interaction responsible for degradation of the APIs. The chemical stability of powder triturates for T3/T4 mixed with the new excipient base was evaluated when stored at both room temperature and refrigerated conditions. The powder triturates were prepared using three different methods (equipment) for comparison purposes: Mortar and Pestle (M&P), FlackTek™ and PCCA RAM™.

Materials and Methods

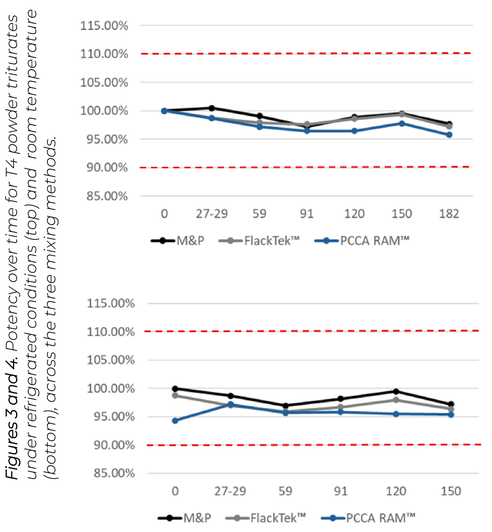
Liothyronine sodium (T3) and levothyroxine sodium (T4) USP reference standards were obtained from PCCA. Both standards were initially dissolved in 80% ethanol to prepare stock solutions at approximately 0.4 mg/mL. These stock solutions were subsequently diluted with the same solvent to produce a calibration series covering the relevant analytical range.
For sample preparation, 0.6 g of triturate was accurately weighed into a 50-mL centrifuge tube and extracted with 40 mL of 80% ethanol. The extraction procedure involved repeated cycles of vortex-mixing (15 seconds), sonication (2 minutes), vortex-mixing (15 seconds), additional sonication (1 minute), and a final vortex-mixing step (15 seconds). The resulting suspension was clarified by centrifugation at 6,000 rpm for 10 minutes, followed by a second centrifugation at 14,000 rpm for an additional 10 minutes to ensure complete removal of particulates. The supernatant was carefully transferred into HPLC vials for analysis. The extraction was designed to yield a target analyte concentration of approximately 15 µg/mL for both T3 and T4 in the final test solution.
Chromatographic analysis was performed using a Waters Acquity UPLC system equipped with a separation module (QSM), a column manager (CM) with heater/cooler, a photodiode array (PDA) detector, and an autosampler (FTN). Separation was achieved on an Acquity UPLC BEH C18 column (1.7 µm, 2.1 × 100 mm) maintained at 65 °C. The mobile phases consisted of 0.1% trifluoroacetic acid (TFA) in water (A) and 0.1% TFA in acetonitrile (B). A reverse-phase gradient elution program was employed as follows: 0.0 min, 75% A / 25% B; 1.5 min, 50% A / 50% B; 1.6 min, 75% A / 25% B; 2.5 min, 75% A / 25% B. The flow rate was set to 0.7 mL/min, the injection volume was 1 µL, and the total run time was 2.5 minutes. Detection was performed at a wavelength of 300 nm, which provided suitable sensitivity for both analytes. This methodology ensured consistent extraction of T3 and T4 from triturates and reliable quantification by UPLC under optimized chromatographic conditions.

Results and Discussion

At room temperature, both T3 and T4 powder triturates maintained their potency within ±10% of initial concentrations over 6 months and across all three mixing methods. For T3, potency values ranged from 96.96%-98.33% (M&P), 95.21%-103.05% (FlackTek™), and 92.49%-95.72% (PCCA RAM™). For T4, potency values ranged from 96.96%-99.97% (M&P), 95.94%-98.72% (FlackTek™), and 94.31%-97.18% (PCCA RAM™).
Under refrigerated conditions, the T3/T4 powder triturates showed comparable chemical stability. For T3, potency values ranged from 97.30%-100.07%(M&P), 97.01%-101.61% (FlackTek™), and 96.41%-98.10% (PCCA RAM™). For T4, potency values ranged from 97.26%-99.52% (M&P), 97.22%-99.37% (FlackTek™), and 95.77%-98.69% (PCCA RAM™).
There were no significant differences in potency across the three mixing methods, namely the traditional M&P, high shear mixing with the FlackTek™, and resonant acoustic mixing with the PCCA RAM™. Each method yielded powder triturates with comparable potency profiles, supporting the robustness and reproducibility of compounding T3/T4 with the new excipient base.



Figures 1 and 2. Potency over time for T3 powder triturates under refrigerated conditions (top) and room temperature (bottom), across the three mixing methods.



Figures 3 and 4. Potency over time for T4 powder triturates under refrigerated conditions (top) and room temperature (bottom), across the three mixing methods.

These findings support the suitability of the new excipient base for compounding T3/T4 tablets and capsules, offering flexibility for pharmacies in their choice of mixing equipment without compromising product quality.
Clinically, the demonstrated chemical stability has important implications for ensuring consistent delivery of low-dose thyroid hormones, minimizing the risk of therapeutic variability, and potentially supporting extended beyond-use dates of the final preparations when stored at both room temperature and refrigerated conditions.