PCCA UniFlow™ **TECHNICAL REPORT**

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

SUMMARY: Uniformity of APIs is essential for therapeutic efficacy and patient safety. In this study, powder triturates for T3 and T4 were prepared using three mixing methods for comparison purposes and were tested for content uniformity (adapted). The powder triturates demonstrated potency within the 90-100% specification, with uniform distribution of T3 and T4 across all mixing methods, highlighting the role of the new excipient base in enhancing flow, mixing efficiency and overall formulation quality for accurate dosing.

Introduction:

Uniformity of dosage units is critically important to ensure that each individual unit (e.g., tablet, capsule) in a batch contains the intended amount of active pharmaceutical ingredient (API), within a narrow range around the label claim (90-110% specification). This guarantees both the therapeutic efficacy of the treatment and the safety of the patient by minimizing the risk of underdosing or overdosing. When preparing solid dosage forms, the powder characteristics may affect uniformity due to poor flowability, segregation or inconsistent mixing techniques.

In this study, the uniformity of powder triturates was tested to confirm the quality of the mixture prior to preparing the individual dosage units. Three mixing methods were used for comparison purposes: Mortar and Pestle (M&P), FlackTek™ and PCCA RAM™ (Fig. 1).

Figure 1. PCCA RAM™: ResonantAcoustic® Mixer.

The APIs chosen for this study were liothyronine sodium (T3) and levothyroxine sodium (T4) due to the sensitive dose-response relationship and serious consequences with small dose variations. T4 is recognized as a Narrow Therapeutic Index (NTI) drug by the FDA. The powder triturates for T3 and T4 were prepared at 1:1000 (0.1%) dilution. The corresponding PCCA formulas are as follows:

- 15642 Levothyroxine Sodium (T4) 1:1000 (0.1%)
- 15643 Levothyroxine Sodium (T4) 1:1000 (0.1%)
- 15644 Levothyroxine Sodium (T4) 1:1000 (0.1%)
- 15646 Liothyronine Sodium (T3) 1:1000 (0.1%)
- 15647 Liothyronine Sodium (T3) 1:1000 (0.1%)
- 15648 Liothyronine Sodium (T3) 1:1000 (0.1%)

UniFlow Triturations (PCCA RAM™)

Methodology:

As outlined in USP Chapter ⟨905⟩ Uniformity of Dosage Units, *Content Uniformity* is one of the two methods to demonstrate the uniformity of dosage units. When applicable to solid dosage forms, it requires individually assaying 10 units using an appropriate analytical method. For the purposes of assaying the powder triturates for T3/T4, the content uniformity method was adapted to assume that each sample drawn from the mixture corresponded to a single dose. A total of 10 samples were collected for both the T3 and T4 powder triturates. The APIs were extracted using 80% ethanol in purified water through a combination of vortex-mixing, sonication and centrifugation before transferring to HPLC vials for analysis. Standard solutions were prepared to achieve a known concentration of about 0.4 mg/mL stock, then diluted to various concentrations. The mobile phases consisted of 0.1% trifluoroacetic acid (TFA) in water (Mobile Phase A) and 0.1% TFA in acetonitrile (Mobile Phase B). Chromatographic analysis was conducted using a Waters Acquity UPLC system with reverse-phase gradient elution and a detection wavelength of 300 nm over a 2.5-minute run time. The product uniformity could be evaluated by RSD% value, which should be kept as low as possible. An RSD <5% would ensure the uniformity of the final product.

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Results and Discussion:

Potency refers to the amount of API present in a drug product compared to its label claim. For compounded preparations, USP standards dictate that the amount of API must be ±10% of the label claim, unless the monograph of the preparation states otherwise. As such, the powder triturates for T3/T4 should have potency between 90% and 110%. However, the USP monograph for the T4 capsules dictates a potency between 95% and 105%. If the corresponding powder triturates for T4 test outside this range, an adjustment must be made when preparing the capsules to meet the specifications. The potency, average, standard deviation (SD), relative standard deviation (RSD) and difference for the 10 samples of T3 and T4 powder triturates are displayed in Tables 1 and 2, respectively.

Conclusion:

It is concluded that the potency for both powder triturates was within the specifications of 90% and 110%, with acceptable standard deviations below 5.

T3 and T4 were found to be consistently distributed across the test samples, confirming the uniformity of the corresponding powder triturates regardless of the mixing method (M&P, FlackTek™ and PCCA RAM™). This consistent distribution highlights the performance of the new excipient base in enhancing flow properties and mixing efficiency, thereby minimizing the risk of segregation during compounding. These attributes contribute significantly to the overall quality, reliability and reproducibility of the powder triturates, supporting accurate and consistent dosing of T3 and T4.

Tables 1 and 2. Potency (%) of 10 samples of T3 and T4 powder triturates, respectively, obtained using the three mixing methods; average, SD and difference are displayed in the corresponding annexed tables.

Sample	M&P	FlackTek™	PCCA RAM™
1	103.980	96.978	98.207
2	103.406	97.404	101.257
3	102.205	98.576	95.834
4	101.518	102.144	95.191
5	100.847	100.578	100.676
6	101.979	98.322	97.625
7	102.470	99.337	95.698
8	103.894	96.295	95.476
9	101.114	96.785	96.046
10	101.229	99.833	97.490
Average	102.264	98.625	97.350
SD	1.351	1.927	2.213
RSD	1.321	1.954	2.273
Difference	3.133	5.849	6.066

Sample	M&P	FlackTek™	PCCA RAM™
1	98.231	94.375	98.255
2	100.513	95.510	102.623
3	99.586	99.413	102.697
4	99.661	96.480	98.247
5	101.740	98.012	99.760
6	100.003	96.921	100.787
7	100.282	97.968	98.179
8	101.350	96.834	97.567
9	100.995	96.369	102.842
10	97.947	98.060	101.206
Average	100.031	96.994	100.216
SD	1.464	1.592	2.204
RSD	1.464	1.641	2.199
Difference	3.793	5.038	5.275