Why are T3/T4 Formulations So Difficult to Make?

Liothyronine Sodium (T3) and Levothyroxine Sodium (T4) are iodinated, modified, amino acids and are typically formulated in microgram concentrations. These active pharmaceutical ingredients (APIs) usually contain a significant amount of water: up to 4% in the T3 powder and up to 11% in the T4 powder. The primary reasons for the difficulty in preparing formulations containing T3 and/or T4 arise from these 3 issues; microgram concentrations, iodination of the compound, and water.

So, what makes these 3 issues so problematic?

1. In the preparation of, lets say, a powder blend to be use for preparation of T3/T4 capsules, typically the active(s) are mixed with microcrystalline cellulose and perhaps methyl cellulose as well, to provide the correct dilution and desired slow release properties. Sometimes a coloring agent is also included to provide a visual indication of completeness of mixing. Normally, these are blended according to the technique of geometric additions and mixed/stirred in the same fashion as many of the other capsule formulations. But, there's just one problem. In this case, we are not blending milligram amounts of an active, we are blending microgram amounts. If we can visualize how much 1 milligram of powder is, then imagine how much 1/1000th of this would be. We can begin to realize it would only take a few specks of the API powder to equal a microgram. These few specks must be evenly distributed throughout the powder blend. It may seem counterintuitive, but it actually takes longer to evenly blend micrograms of an ingredient than it does for milligrams. In addition, if the particle size of the API is significantly different from that of the other ingredients, once they are well mixed they might not stay that way. During handling, the vibrations generated in the process will cause the smaller particles to move toward the bottom of the container while the larger one will migrate to the top. (Consider what we observe when we open a new box of granola cereal. The big clusters are usually at the top while the crumbs are at the bottom).

2. Those that took general and/or organic chemistry class in school may recall the halogens, listed near the right hand column of the periodic table, tend to be strongly electronegative because of their electron rich outer shell orbital configuration. T3 and T4 both contain iodine atoms, members of this halogen group. If the powder blend described above is accomplished in a plastic container, the agitation of the cellulose along with the T3/T4 actives will develop a strong static charge on the walls of the container which will attract these microgram amounts of ingredients out of the powder and onto the surface of the container. The more rapidly the powder blend is mixed, the stronger the static charge. In our practice, we have observed a prominent light brown color of the T4 powder clinging to the white wall of the container. When we have tested the wall scrapings, they were 30-40% higher in both the T3 and the T4 than within the main volume of powder.

3. Since a fairly significant portion of the weight of the T3 and T4 powder is water (up to 4% and 11% respectively), adjustments in the desired amounts of these ingredients must be made to account for this. (See our article entitled "Water, Water Everywhere"). Unless an appropriate extra amount of the API powder is included in the formulation, the final product will be sub potent.

Bottom Line: Formulations containing microgram amounts of T3 and or T4 actives must be blended longer and more completely than usual so as to account for these very low concentrations. The blending should be accomplished in either glass or metal containers, not plastic, and should have a tumbling action of side over side and end over end to make sure the actives are well mixed. Mortar and pestle mixing seldom will be sufficient. The time required will vary depending upon batch size and mixing speed, but a 2-hour mixing time would not be unusual. Ideally, both the active and inert (excipient) ingredients are micronized to approximately the same particle size to prevent size stratification within the batch once the blend is finished. And finally, care should be taken to account for the % water content in the API powders.