Method Comparisons for Particle Size Distributions and Nicotine Dissolution Profiles in Smokeless Tobacco Products

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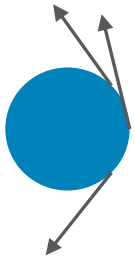
Particle Size & Dissolution in FDA Regulation

- Pharmaceutical Industry
  - Particle size assessment and dissolution testing are recommended by FDA/CDER
  - Generally recognized relationship between surface area and exposure to/release of “active” ingredient

- Tobacco Industry
  - Based on pharma, FDA/CTP has hypothesized similar relationships exist for smokeless tobacco products (STPs)
  - Currently, there is no empirical evidence in the scientific literature to support this hypothesis
  - The nature of tobacco products, manner of use for STPs, and no claim of an “active” ingredient are strikingly dissimilar from pharmaceuticals

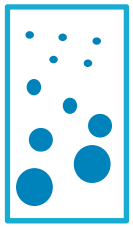
National/International Methods for Particle Size Assessment

Common Particle Size Assessment Methods



Laser Diffraction/Light Scattering

- Matrix challenges
- Distributions assessed typically assuming spherical particle shape

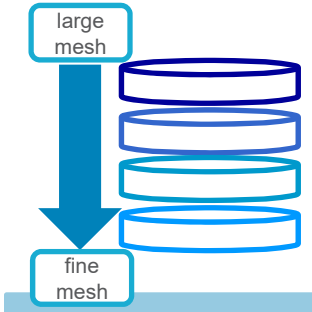


Sedimentation

- Matrix challenges
- Assumes spherical particle shape

Microscopy

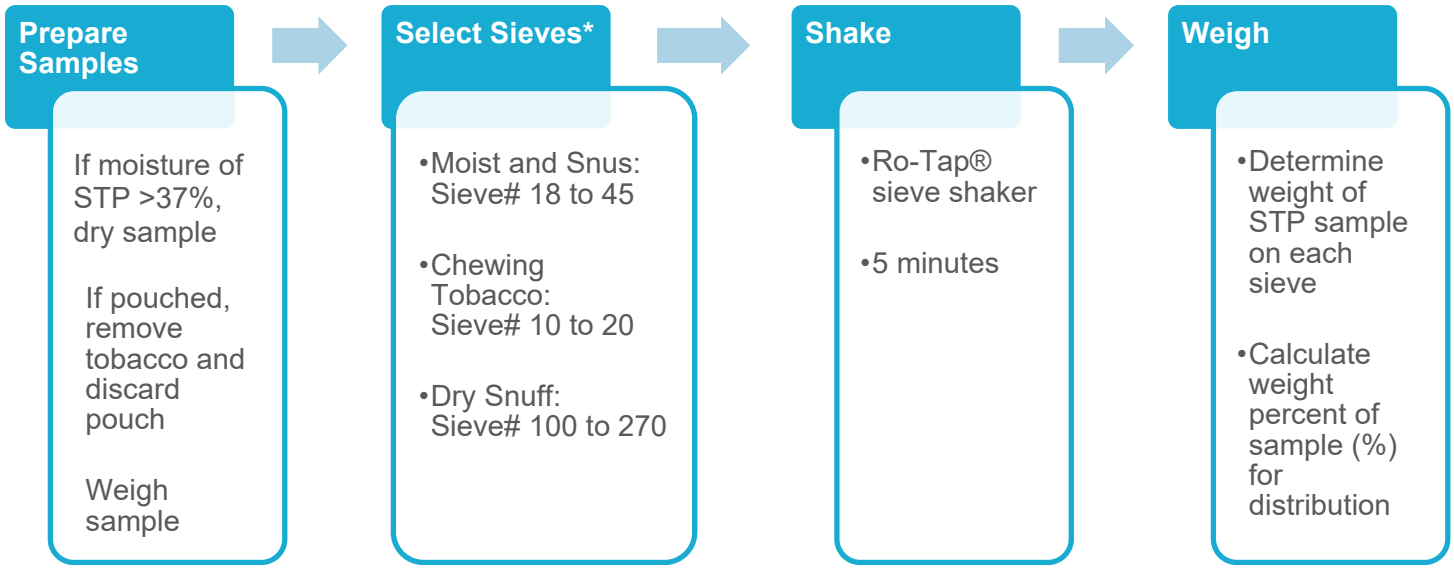
- Representative sample challenges
- Distributions assessed typically assuming spherical or regular particle shape



Sieving

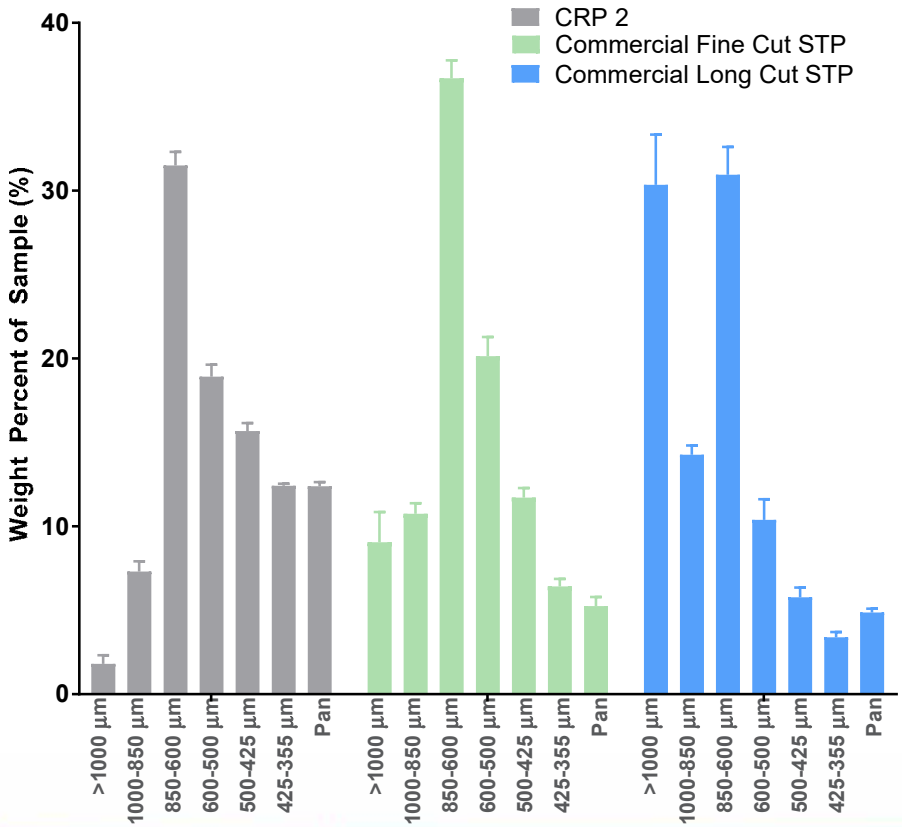
- Orientation through the screen
- Blinding

STP Particle Size Sieve Analysis Method



*U.S. Standard sieve sizes, ASTM Designation E11-17. "Standard Specifications for Woven Wire Test Sieve Cloth and Test Sieves." (2017)

Moist Snuff Product Particle Size Distributions



- Fine cut, long cut designation typically a tactile description
- Commercial Fine Cut STP distribution similar to CRP2
- Commercial Long Cut STP weight percent of sample shifted to the >1 mm particle size compared to Commercial Fine Cut STP

Comparing Particle Size Distributions

- K-S (Kolmogorov-Smirnov) two-sample test
- p-Value <0.05 indicates distributions are significantly different

Distributions Compared	p-Value
Commercial Fine Cut STP to Commercial Long Cut STP	<0.0001

National/International Methods for Dissolution

U.S. Food and Drug Administration Dissolution Methods: https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_getallData.cfm

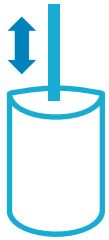
Dissolution Apparatus for Determining Release Rates of Constituents

App 1 – Basket

- Suitable for most STPs
- Sample contained
- Basket rotation necessary for STPs

App 2 - Paddle

- More challenging for STPs



App 3 – Reciprocating Cylinder

- Suitable for most STPs
- Sample contained
- Does not mimic Adult Tobacco Consumer use of STPs

App 4 – Flow-Through Cell

- Suitable for most STPs
- Sample contained

STP Nicotine Dissolution Method

App 1 

phosphate buffer, pH 7.4 at 37 °C

15 rpm basket rotation

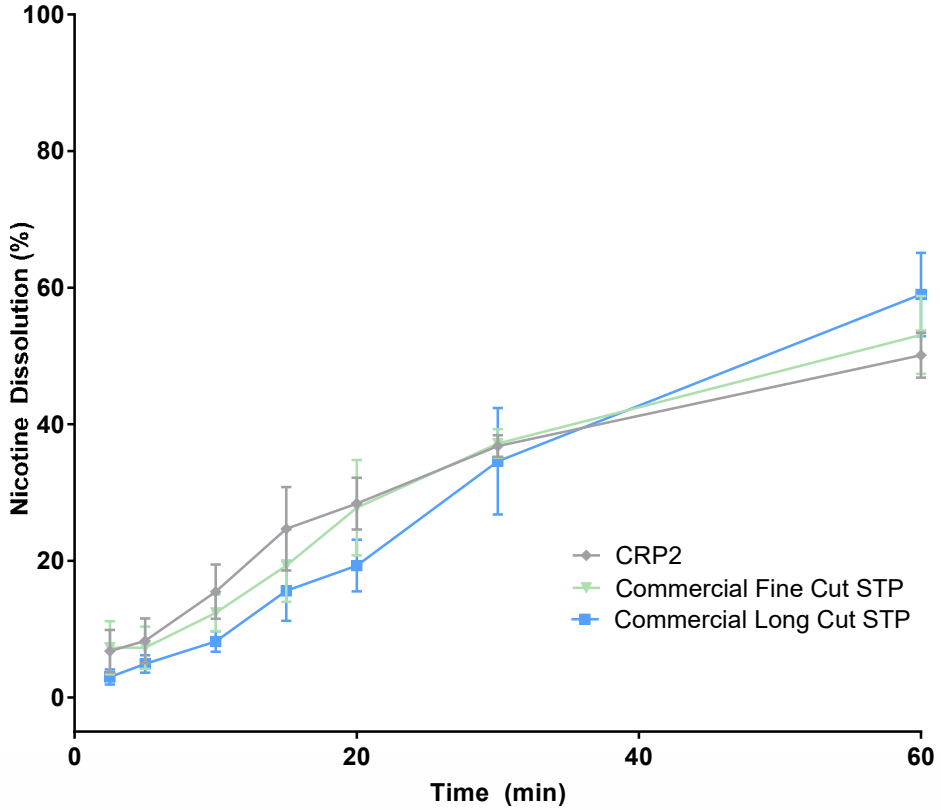
0 – 60 min. time scale

1.3 g analyzed for loose samples; pouched products analyzed as-is

t∞ 250 rpms, 15 min. after dissolution run

Sample analysis by LC

Moist Snuff Product Dissolution



Comparing Dissolution Profiles

- Similarity factor (f_2): > 50 indicates "sameness"

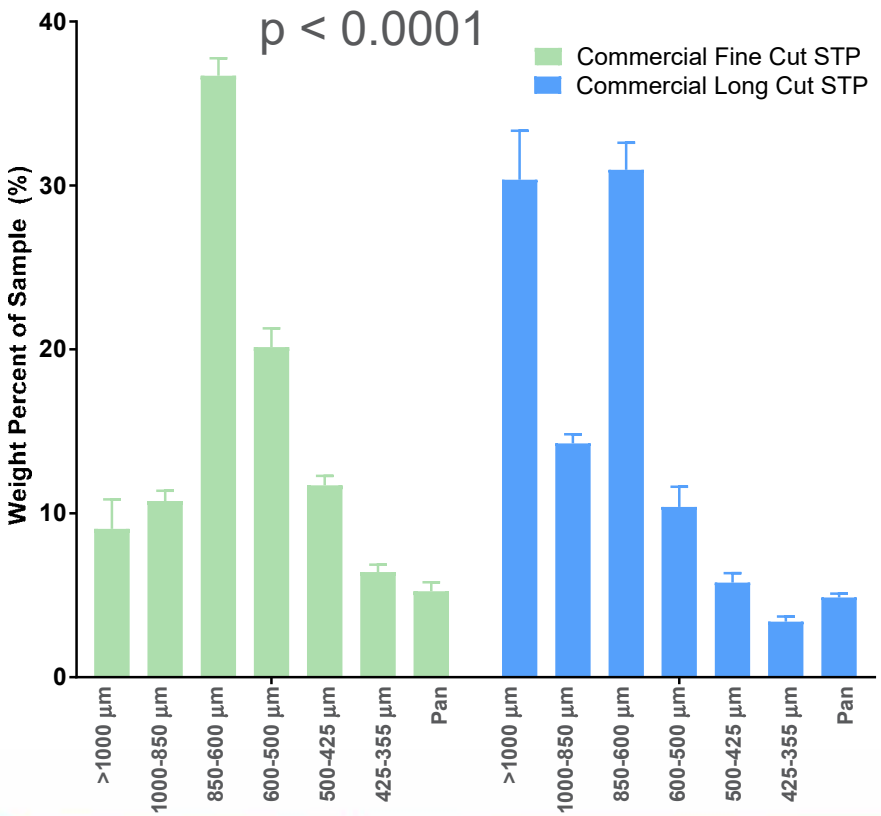
$$f_2 = 50 \times \log\left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{n}(R_t - T_t)^2}{n}}}\right]$$

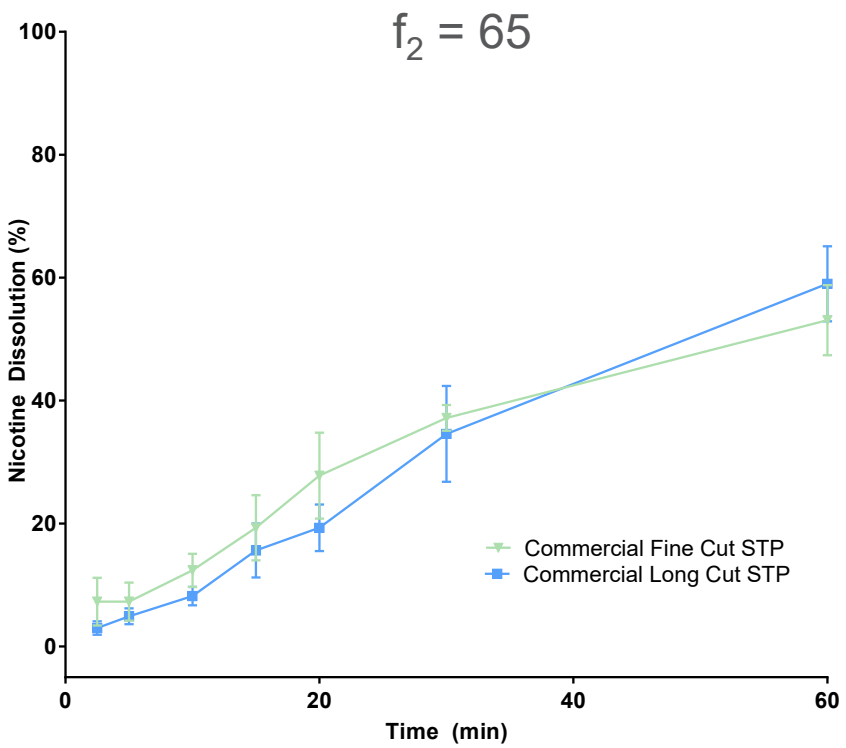
R_t = dissolution for Product 1 at time t
T_t = dissolution for Product 2 at time t
n = number of time points for which dissolution was assessed

Distributions Compared	f_2 Value
Commercial Fine Cut STP to Commercial Long Cut STP	65

Moore, JW, and Flanner, HH. "Mathematical Comparisons of Dissolution Profiles." *Pharm. Tech*. June **1996**: 64 – 74.
Ma, M-C, Wang, BC, Liu, J-P, and Tsong, Y. "Assessment of Similarity Between Dissolution Profiles." *J. Biopharma. Stat*. **2000**. 10 (2): 229 – 249.

Particle Size & Dissolution for Commercial STPs





Conclusions

- Fundamental approaches for comparing particle size distributions, and for dissolution profiles can be applied to evaluate smokeless tobacco products
- Method development requires specific considerations for smokeless tobacco products
  - Particle size
    - matrix effects
    - irregular particle shape
    - non-uniform and no “active” ingredient claim for assessment
  - Dissolution
    - samples do not disintegrate
    - numerous “ingredients” (i.e., tobacco constituents), but no “active” ingredient claim
- In these data presented, no differences were observed in nicotine release rate for products with statistically significantly different particle size distributions

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