Dissolution and Physical Characterization of Oral Nicotine Products

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Abstract

Oral tobacco-derived nicotine (OTDN) pouches have gained popularity in recent years due to their reduced risk potential. In this study, we conducted a comprehensive analysis of seven commercially available nicotine pouch products, including on!®, Zyn®, Velo®, Dryft®, Rogue™, Volt™, and Loop® nicotine pouches. Analyses included: nicotine content, nicotine dissolution release, particle size, imaging (filler and pouch material), bulk density (tapped and untapped), true density, solubility, crystallinity, water activity, pH, OV (as measured by percent moisture content, % MC), and extract viscosity. The nicotine dissolution profiles showed a faster release for on!®, Zyn®, and Rogue™ when compared to Velo®, Dryft®, Volt™, and Loop® nicotine pouches. When all nicotine pouches release profiles were compared to on!®, only Zyn® and Rogue™ were found equivalent. Particle size analysis revealed Gaussian-like distributions for on!®, Rogue™, and Zyn® nicotine pouches. However, the remaining products displayed bimodal particle size distribution. Tapped and untapped bulk densities were measured to assess the flowability of the filler in all seven nicotine pouches. Rogue™ and Loop® nicotine pouches exhibited the highest and lowest flowabilities, respectively. Solubility data indicated that Zyn® nicotine pouches had the highest percentage of soluble components, whereas Rogue™ nicotine pouches had the lowest. Rheology results from the nicotine pouch extracts in artificial saliva showed the highest viscosity for Loop® and lowest viscosity for Volt™ and Rogue™ nicotine pouches. All products were found to have crystalline structures with both high and low-temperature melting points. Our results indicate that nicotine pouch products exhibit differences and similarities in their physicochemical properties, providing valuable insights into understanding their formulation and development. Note that trademarks used for comparison purposes only and ownership in each trademark is retained by its respective owner.

Introduction

Nicotine pouches or "tobacco-free nicotine pouches" is a growing category of oral products in may parts of the world. Nicotine pouches do not contain cut, ground, powdered, or leaf tobacco but do contain nicotine, which may be tobacco derived or synthetic. In addition to nicotine, nicotine pouches contain a base material, often cellulose based, flavors, sweeteners, and pH adjusters. Brands such as on!®, Zyn®, Velo®, Dryft®, Rogue™, Volt™, and Loop® have introduced various nicotine pouch products, each with different flavors and nicotine levels, catering to a wide range of consumer preferences.

Chemical characterization methods for the determination of nicotine, nicotine degradants, and harmful and potentially harmful constituents (HPHC) and dissolution testing of nicotine pouches were widely studied and published.[1-4] However, there is limited research on the physical properties of nicotine pouches, which may impact the dissolution rate and overall performance of the product. This study aimed to bridge this gap by examining the relationship between the chemical and physical properties of seven commercially available nicotine pouch products: on!® Mint (8 mg), Zyn® Cool Mint (6 mg), Velo® Spearmint (7 mg), Dryft® Spearmint (7 mg), Rogue™ Spearmint (6 mg), Volt™ Spearmint Breeze (Strength 3), and Loop® Mint Mania (Strength 3).

Conclusion

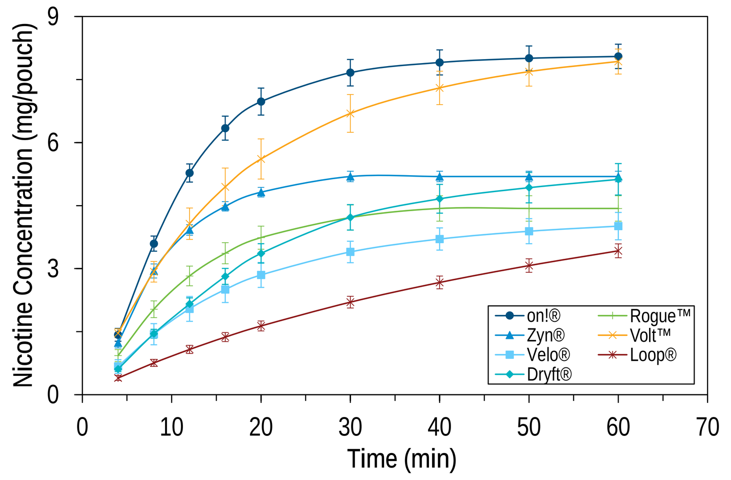
This study aimed to investigate the chemical and physical characterization of seven commercially available nicotine pouch products due to their increase in popularity in recent years and reduced risk potential. The dissolution testing was carried out using a USP-4 flow-through cell apparatus, where dissolution profiles showed a faster release for on!®, Zyn®, and Rogue™ when compared to Velo®, Dryft®, Volt™, and Loop® nicotine pouches. When all nicotine pouches release profiles were compared to on!®, only Zyn® and Rogue™ were found equivalent. The Gaussian-like particle size distributions for on!®, Rogue™, and Zyn® nicotine pouches indicate more homogenous particles compared to other products which displayed bimodal distributions. The morphology of particles was investigated by imaging using optical and scanning electron microscopy. While particle size does not appear to impact directly the dissolution rate, potential factors such as granulation process and filler composition (e.g. percent of soluble material, flavors, sweeteners, etc.) could impact particle size and dissolution in different ways. The pH values of the nicotine pouch products range from 7.6-9.0 which could have an impact on the nicotine absorption in the buccal mucosa. Using the bulk density results to estimate flowability, only Volt™ and Loop® met the criteria to be considered poorly flowing filler. In a similar manner the porosity was estimated using the true density and tapped bulk density value with Zyn® being the most porous filler (63%) and Rogue™ being the least porous (38%). Crystallinity was used to help understand the structural properties of the products with the products being grouped into high and low melting point groups (around 150°C for high melting point and below 110°C for low melting point). For the high melting point products, the crystallinity order (from highest to lowest) based on the enthalpy melting point was Dryft®, Velo®, Zyn®, and on!®. The crystallinity order for the low melting point products was Volt™, Loop®, and Rogue™. Zyn® contained the highest percent solubles in filler whereas Rogue™ had the lowest. When testing the viscosity of the extracted solution, Loop® was the most viscous while the viscosity of Volt™ and Rogue™ were close to the artificial saliva. The higher moisture content for Volt™ and Loop® is explained by both products being considered wet pouch products. Overall, this study contributes to the understanding of nicotine pouch products by providing a broad characterization of these products. The production of nicotine pouches involves various manufacturers utilizing different ingredients sourced from a variety of vendors. These ingredients can differ in their chemical composition and impurities. Additionally, manufacturers employ various granulation processes and use different materials for the pouches. As a result, a wide range of nicotine pouch products are created. Although all these products contain oral tobacco-derived nicotine, the combination of these factors leads to both similarities and differences in the physicochemical properties of the pouches. Consequently, multiple driving factors influence the nicotine release and overall performance of these pouches.

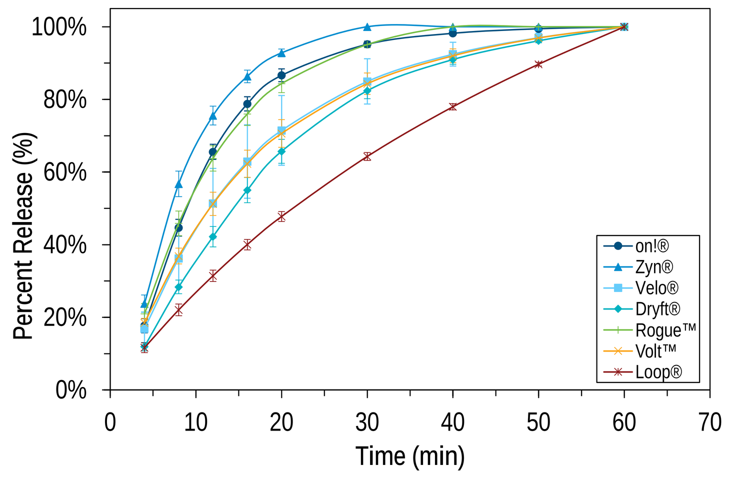
Methods

- Nicotine Determination – One gram (1 g) of filler from each pouch product was extracted in a mixture of water, sodium hydroxide (NaOH), and methyl *t*-butyl ether (MTBE) solvent with quinoline as the internal standard. The organic phase was analyzed by gas chromatography with flame ionization (GC-FID) following the CORESTA recommended method 62 (CRM 62) in triplicate.[3]
- Experimental Nicotine Dissolution - Dissolution testing was conducted following FDA guidance for industry using a USP-4 flow-through cell apparatus and twelve (12) replicates for each nicotine pouch product. Nicotine was quantified using Ultra Performance Liquid Chromatograph coupled to a photodiode array detector (UPLC-PDA). The collection of USP-4 fraction and preparation of UPLC solutions and standards were carried out according to previously published work.[1, 5-6]
- Kinetic Nicotine Model – An approach of using a first-order kinetics model to predict the nicotine content at t_∞ and estimate the total amount of nicotine available to be released within 60 minutes dissolution time was used as a second measure of the nicotine dissolution rate. This model was used to fit the nicotine dissolution cumulative release profiles for each of the twelve replicates of the seven pouch products.
- Particle Size Analysis - Particle size analysis were carried out using dynamic image analysis (DIA) conforming to ISO standards for DIA and graphical representations.[7-8] A half teaspoon of filler from each pouch products was introduced into a gravity fall system and the volume-weighted distribution of twelve (12) replicates was calculated.
- Imaging - Optical and scanning electron microscopy (SEM) imaged were taken of the filler of all products. Images were taken of pouch filler and pouch material.
- Density – Bulk density (tapped and untapped) was carried out using USP <616> method while true density was carried out using gas pycnometry. All testing was performed in triplicate.
- Crystallinity – The crystallinity was determined by differential scanning calorimetry (DSC) using 6-10 mg of filler and a 0-160°C sweep at 10 °C/Min.
- Solubility – The solubility was determined by adding 1 g of filler in 40 mL artificial saliva and filtering the solid after shaking for 10 min. The filter paper was dried at 120°C for 1 hour and once weighed used to calculate soluble mass.
- Rapid OV – Two grams (2 g) of filler was put in a halogen oven and run at 80°C for 10 min to determine percent moisture content (% MC).
- pH – The pH was determined by placing 4 pouches of on!® and 2 pouches of all other products in 20 mL of DI water and measuring the pH as the mixture was continuously stirred.
- Water Activity – One pouch was placed in a water activity meter with test performed at 25°C in triplicate.
- Viscosity – The viscosity was carried out by extracting 4 g of filler in 36 mL artificial saliva. The viscosity of the extracts was measured using a concentric cylinder at a sheer rate of 0-100 1/s and a geometry gap of 5.9171 mm.

Results

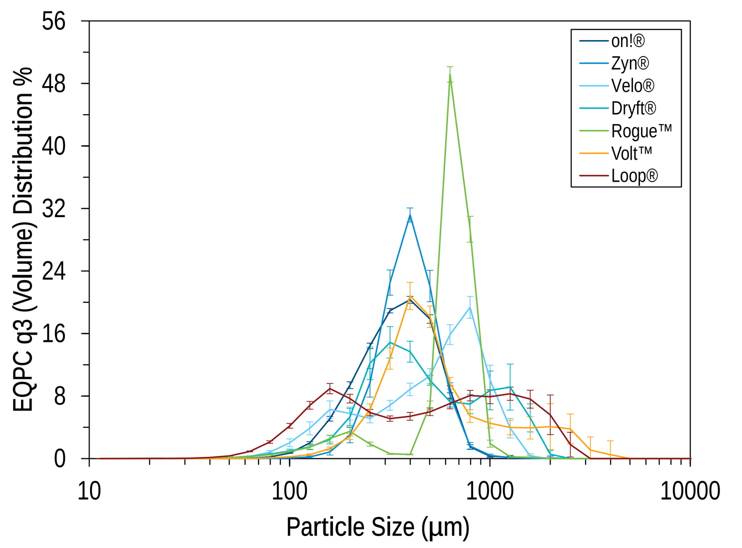
Nicotine Dissolution Release Profiles





Particle Size

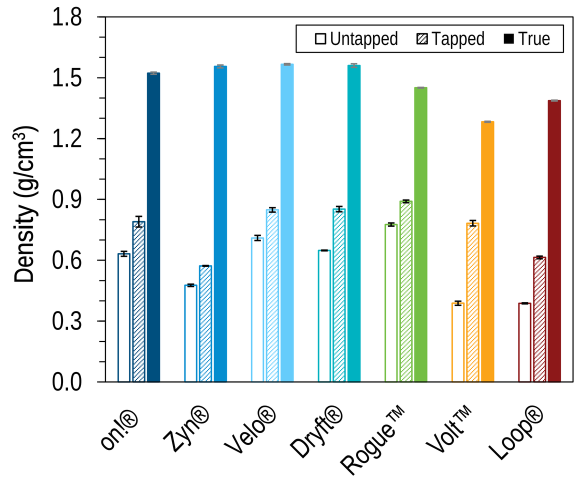
Product	Mean	d_{10}	d_{50} (Median)	d_{90}
on!®	334.45	167.20	314.11	515.85
Zyn®	367.57	233.18	352.54	511.95
Velo®	503.85	143.33	494.91	876.30
Dryft®	537.65	191.04	399.79	1121.36
Rogue™	562.28	248.44	583.91	753.03
Volt™	658.83	242.16	430.56	1543.75
Loop®	626.74	108.76	444.42	1468.33



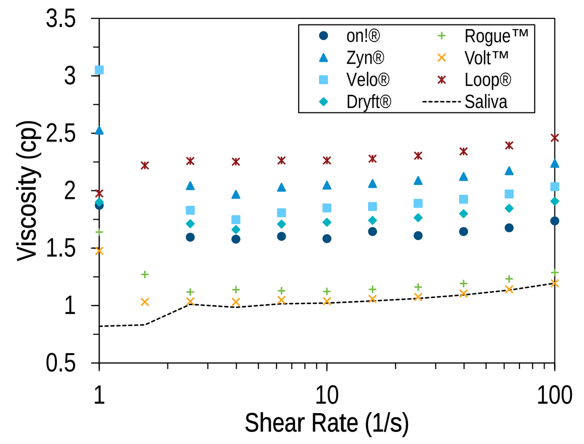
Nicotine Content and Theoretical Dissolution Rate Constants

Product	Label (mg/pouch)	Calc. Content (mg/pouch)	% of Can Label	Exp. % Released in 60 minutes	Calculated Rate Constant (k, min^{-1})	Estimated % Release from Content
on!®	8	8.2	103	98	0.080	97
Zyn®	6	5.4	90	96	0.103	97
Velo®	7	4.6	66	88	0.057	94
Dryft®	7	5.7	81	90	0.042	90
Rogue™	6	6.2	103	72	0.078	97
Volt™	8.3	8.9	107	89	0.056	96
Loop®	9.4	9.1	97	38	0.021	72

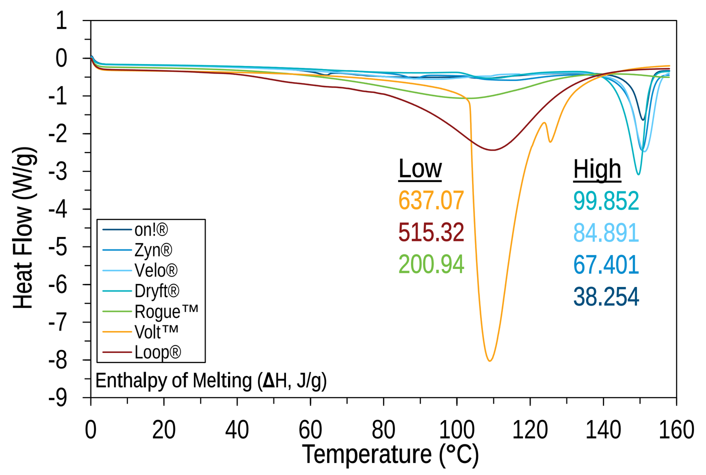
Density Measurements



Extracted Viscosity



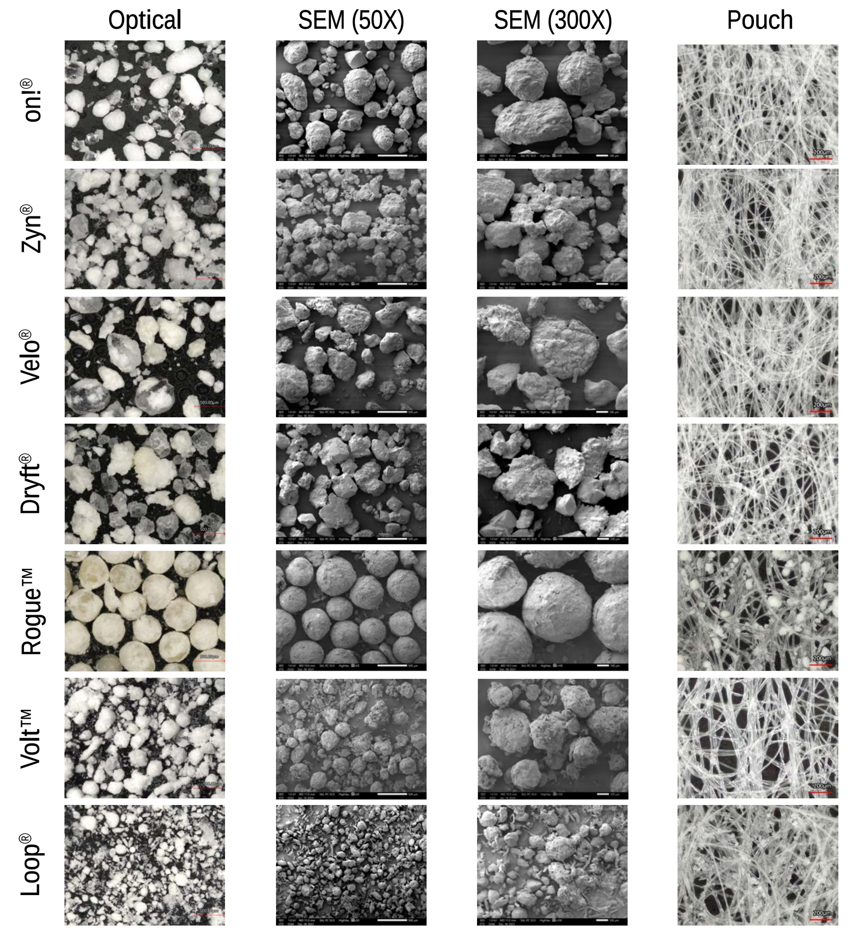
Crystallinity (DSC)



Other Physical Testing

Product	Soluble (%)	OV (% MC)	pH	Water Activity
on!®	66.35	4.48	8.617	0.5658
Zyn®	78.26	3.52	7.619	0.5561
Velo®	64.41	6.62	8.981	0.5563
Dryft®	68.03	3.71	8.305	0.5567
Rogue™	41.21	14.70	7.430	0.6542
Volt™	59.75	37.18	8.469	0.9167
Loop®	N/A	26.64	8.616	0.8747

Optical and Scanning Electron Microscopy



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