ABSTRACT

KECK, MEGHAN EMILY. Tribological and Thermodynamic Analysis of Lozenge Decay during Oral Processing. (Under the direction of Dr. Christopher Daubert.)

Boiled sweets are commonly consumed worldwide in the form of candies or as medicated lozenges, such as cough drops. Despite widespread consumption, factors that contribute to boiled sweet decay rates during oral processing have not been thoroughly described in the literature. Current methods of lozenge decay rate assessments do not account for the conditions encountered during oral processing, namely the rubbing of candies against oral surfaces and continuous exposure to saliva. An appropriate analytical method to evaluate dissolution rates must include frictional wear and assessments of phase changes and thermodynamics due to the presence of saliva. Tribology, the study of friction and wear between sliding surfaces, provides a technique to evaluate the friction and wearing effects on boiled sweets during oral processing using saliva as a lubricant. Knowledge of how oral dissolution rates of boiled sweets are affected by formulation, salivation rates, and mechanical wear allows for the optimized production of sweets and lozenges with specific lifetimes in the mouth. These aspects are of particular importance for oral drug delivery design, where controlled dosage is vital. A model lozenge was selected and assessed for its surface area using image analysis. Lozenge decay was analyzed as a function of the calculated dissolved mass flux, the mass of lozenge dissolved in solution per second per lozenge surface area, to account for the effects of surface area change on the amount of lozenge mass available to dissolve into solution. Seventeen human subjects created thirty data sets assessing the breakdown of a model butterscotch candy. Salivation rates, decay rates, and changes in the surface area and volume of the lozenge were modeled as a function

of oral processing conditions. Thermodynamic tests were conducted to determine the lozenge decay performance as a function of water exposure and flow. Results indicated that the dissolved mass flux behaviors observed in the human trials could not be achieved using water flow alone and that a mechanical factor must be included to account for differences in breakdown. The average dissolved mass flux from the human oral processing tests were used to assess conditions of corresponding sliding speeds and normal loads that produce the same mass flux under mechanical processing via laboratory instrumentation. Testing conditions of 2.50 Newtons normal force and a sliding speed of 10.05 centimeters per second match the average human test data, within 95% confidence. Results from this study provide a systematic methodology for analysis and prediction of dissolution rates for any boiled sweet or lozenge, yielding a quantitative approach for product design and development.

Tribological and Thermodynamic Analysis of Lozenge Decay during Oral Processing

by
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A thesis submitted to the Graduate Faculty of
North Carolina State University
in partial fulfillment of the
requirements for the Degree of
Master of Science

Food Science

Raleigh, North Carolina

2015

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DEDICATION

To my husband, Spenser James. Thank you for your love, support, and patience. Thank you for helping me keep the big picture in mind and for supporting my dreams, even when they lead us to the other side of the continent or the world.

BIOGRAPHY

Meghan was born and raised in Rickreall, Oregon on a grass seed-sheep farm, where she first gained an appreciation for the role of agriculture and value of science and engineering in daily life. Following completion of her high school education, she moved to Los Angeles to study chemical engineering at the University of Southern California. After two years in the concrete jungle, she returned to her home state to tailor her studies for an engineering career in the agricultural sector at Oregon State University. She learned about food science at a club fair and instantly developed a passion for the field, especially for the processing of dairy products. She worked as a cheesemaker at the fledging OSU Creamery, interned at Hilmar Cheese Company, and pursued additional studies in food science. Meghan graduated from Oregon State University in June of 2013 with a Bachelor of Science degree in Chemical (Biochemical Processes) Engineering, with two minors in Food Science and Fermentation Science. Following graduation, she married and moved to Raleigh, North Carolina to pursue a Master's of Science in Food Science, under the guidance of Dr. Christopher Daubert in the Rheology Laboratory. Within her short stay at NCSU, she became the 2014-2015 President of the NCSU Food Science Club, won second place in the 2014 Dairy Research Institute Product Development Competition, and completed original research evaluating lozenge decay during oral processing. She looks forward to taking the next step in her career when she moves with her husband to Palmerston North, New Zealand to pursue a Ph.D. in Process Engineering modeling the diffusion of salt in cheeses.

ACKNOWLEDGMENTS

I would like to take this opportunity to thank my major advisor, Dr. Christopher Daubert, for his guidance, motivation, and support throughout this research project. Special thanks to Chris Pernell and for the guidance, collaboration, and help with experimental design. Thanks to Jacques Overdiep for his tireless work collecting data for me to make sure my experiments were a success. Thank you to Michael Bumgardner for his assistance with the Autodesk ® Inventor Software. Thank you to Spenser James, my husband, for the support, insight, and occasional technical and coding help. Finally, thanks to all former and current students of the department that volunteered for my human subject oral processing tests and agreed to spit for science.

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RESEARCH PREMISE AND JUSTIFICATION

1.1 Boiled Confection Industry Overview

Boiled sweets are commonly consumed worldwide in the form of candies or as medicated lozenges, such as cough drops. The landscape of the more than $339 million hard candy confectionary industry is changing to adapt to shifting consumption demographics and consumer preferences (Anonymous 2008; Kim 2012; Pacyniak 2014). Health is driving the development of new and convenient products to serve consumer demand for wholesome reduced-sugar or sugar-free alternatives to traditional products (Fuhrman 2004; Kim 2012; Pacyniak 2014). Emphasis on natural sweeteners, new flavors, and high-end quality products within the confectionary industry has required producers to reevaluate formulations, improve quality, and include new ingredients to maintain market shares (Garry 2011; Kim 2012; Pacyniak 2014). Hard candies have also been developed to capitalize on trends of increasing nutraceutical consumption by expanding into the dietary supplement industry, as seen in the expanding market of vitamin drops and NutraPop™ style dietary supplements that contain vitamins, minerals, and herbs (Vreeland 1999). Retaining profitability in an industry with significant competition and shifting consumer preferences creates challenges that require in-depth knowledge of formulation and physical properties that contribute to the dissolution of various boiled confection systems during oral processing.

Despite widespread consumption, boiled sweet dissolution rates during oral processing have not been thoroughly described in the literature. Knowledge of how oral dissolution rates of boiled sweets are affected by salivation rates, formulation, physical

geometry, and mechanical wearing during oral processing would permit optimized production of sweets and lozenges with specific lifetimes in the mouth. This aspect is of particular importance not only for traditional confection product development, but also for oral drug delivery design (Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms; United States Pharmacopeia (USP)). This research premise is important for adapting the historical hard candy and medicated lozenge industries to future industry and consumer trends.

1.1.1 Hard Candy Industry

Historically, the boiled confection business has been dominated by the hard candy industry (Manson 2010; Hartel 2014). The presence of candy-like sweets in society has been recorded since the rise of ancient civilizations, where sweets made from honey were reserved for the wealthy elites (Manson 2010). The development of products available to the less privileged consumer followed the growth and popularity of sugar (Hartel 2014). Early commercial hard candy production in the United States grew from the acquisition of cheap sugar sources and increased process mechanization (Manson 2010; Hartel 2014). Continuous development of intriguing, new flavors and candy types have led to the development of a diverse industry ranging from traditionally flavored regular hard candies, such as butterscotches and peppermints, to an array of unique gobstoppers, jawbreakers, and sugar-free variations (Hartel 2014). New flavors and means to incorporate medicinal ingredients burgeoned a new type of lozenge that would not only provide enjoyment, but also serve to treat symptoms of illness.

1.1.2 Medicated Lozenge Industry

Medicated lozenges were formally regulated by the United States Food and Drug Administration (FDA) beginning in 1938 with the passage of the Federal Food, Drug, and Cosmetic Act (Wax 1995). These lozenges include an active ingredient designed to treat a symptom of illness, most commonly cough drops, which normally incorporate menthol or another active ingredient that works as a cough suppressant or throat relaxant (Danckwerts 2003). However, medicated lozenges have extended to illness and substance abuse treatments (Reddy and others 2009). Medicated lollipops with local anesthetic or pain relief ingredients have already been developed for improved pain management and fast drug release (Danckwerts 2003; Gouin 2004; Reddy and others 2009; Hill and Schug 2009a). Another example, nicotine lozenges are a common alternative treatment for tobacco users seeking to overcome nicotine addiction. Nicotine lozenges provide a convenient method to slowly release nicotine into the system of an ex-smoker, thereby soothing a nicotine-based dependence (Shiffman and others 2003). High demand for new oral drug delivery methods requires careful assessment of active ingredient release and absorption from traditional lozenge forms (Rathbone and Hadgraft 1991; Reddy and others 2009). Unfortunately, current methods used to model breakdown rates of medicated lozenges do not adequately characterize lozenge decay under equivalent oral processing conditions.

1.2 Current Methods of Breakdown Assessment during Oral Processing

Dissolution rates are currently evaluated by placing candy samples into agitated tanks of water while documenting the time required for the sample to dissolve (Guidance for

Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms; United States Pharmacopeia (USP)). While simple, this method does not account for the conditions encountered during oral processing, namely the rubbing of candies against oral surfaces and the continuous exposure of fresh surfaces to saliva. An appropriate analytical method to evaluate dissolution rates must include frictional wear and the presence of saliva (Bongaerts, and others 2007). Tribology, the study of friction and wear between sliding surfaces, provides a technique to assess the friction and wearing effects on boiled sweets during oral processing using saliva as a lubricant (Ranc and others 2006; Bongaerts and others 2007). The development of new flavor or drug delivery systems with alternative sweeteners requires an in-depth understanding of the factors that contribute to the decay of hard candies and lozenges during oral processing.

1.3 Research Objectives and Hypotheses

The purpose of this research was to create a comprehensive, functional methodology that may be used by the confectionery or pharmaceutical industries to design hard candies or lozenges with pre-specified dissolution rates. Results from this research will improve understanding of how dissolution rates of boiled sweets and lozenges are impacted by the presence of saliva, formulation, and mechanical wear. This study also provides a systematic methodology for analysis and prediction of dissolution rates for any boiled sweet or lozenge, yielding a quantitative approach for product design and development. To achieve this goal, three hypotheses were proposed: (1) tribology, thermodynamics, and physiological responses govern the decay of hard candies and lozenges, (2) the decay rate of hard candies or lozenges

may be modeled as a function of the moving water boundary, and (3) the average decay of hard candies or lozenges can be controlled through formulation. The following chapters provide a succinct background to factors involved in lozenge oral processing and assess the decay of a model lozenge under human oral processing and laboratory tribology test conditions.

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LITERATURE REVIEW

2.1 Introduction

Boiled sweets are enjoyed worldwide in the form of hard candies or as medicated lozenges. However, despite widespread consumption, the breakdown rates of lozenges during oral processing have not been thoroughly described in the literature. Comprehension of how oral breakdown or dissolution rates of boiled sweets are affected by salivation rates, formulation, and physical geometry is necessary to optimize the production of sweets and lozenges with specific lifetimes during oral processing. The dissolution mechanism concept is important to the optimized development of new confectionary products and pharmaceutical systems (Danckwerts 2003; Gouin 2004; Hill and Schug 2009b; Hartel 2014). Oral processing is extremely complex, combining mechanical and physiological responses to reduce food particle sizes, enzymatically pre-digesting with saliva, and forming easily-swallowed boluses to aid in the breakdown of the food throughout the digestive process (Fontijn-Tekamp and others 2000; Pedersen and others 2002; Fontijn-Tekamp and others 2004; Koussoulakou and others 2009).

Understanding how the mechanisms of oral processing relate to the breakdown of foods is critical to the design of food structures that produce sensory and nutritional properties that consumers find desirable (Hartel 2014). This concept is especially true for products, such as lozenges, that last longer in the oral cavity than the majority of foods that are consumed quickly through the additional oral process of chewing. Lozenge oral processing is dominated by both the presence and flow of saliva, and mechanical wear

through rubbing on the tongue and oral surfaces. This chapter aims to provide a brief review of the three relevant subjects important to the understanding of this research by describing (1) the production, structure, and breakdown of hard candies and lozenges, (2) oral processing mechanisms and behaviors, and (3) the relevant scientific phenomena and mechanisms that contribute to the oral processing and breakdown of lozenges.

2.2 Hard Candy and Lozenge Overview

Hard candies and lozenges are produced and consumed worldwide as shelf stable sweets for enjoyment or as medicated products designed to release an active or therapeutic ingredient to alleviate ailment symptoms, as in the case of cough drops. Hard candies and lozenges are produced in a multitude of colors, flavors, shapes, and sizes, to appeal to a variety of consumers with different needs and preferences (Minifie 1999; Jeffrey 2001; Hartel 2014). Although mass production methods and ingredient types have continued to evolve along with industrial machinery and global markets, the chemistry and mechanisms that retain the shelf stability of lozenges remains well understood (Ergun and others 2011; Hartel 2014).

2.2.1 Lozenge Production

Hard candies and lozenges are brittle sugar glass structures that are created by boiling sugar or syrup mixtures to form super-saturated mixtures and then crash-cooled to form a shelf-stable glassy structure (Anonymous 1995; Hartel and others 2010; Ergun and others 2011). The principles central to the formation of stable glass structures involve solubility, colligative factors, and rapid short-range structure formation. Sugars and a variety of syrup-

like ingredients are extremely soluble in water, with sucrose dissolving at a maximum 2:1 sucrose-to-water mass ratio under room temperature conditions (Hartel and others 2010). While the maximum sugar concentration is high at this temperature, it is not sufficient to prevent the growth of microorganisms that can cause spoilage. To create a system that is shelf stable at room temperature, the water activity of the system must be significantly decreased to prevent microbial growth while maintaining a structure that can easily be handled, stored, and consumed with minimal additional resources (Slade and Levine 1991; Roos 1995; Ergun and Hartel 2009; Ergun and others 2011). This water activity stability can be achieved by forming a glassy system. In such a system, a concentrated sucrose solution or sucrose-syrup blend solution (with or without the presence of an acid for flavor or anti-graining properties) is boiled to a hard crack stage. The temperatures defining this stage typically range from 295 to 310 °F, depending on the concentration ratios of the sugars or syrups used (Hartel and others 2010). After achieving the desired temperature, and therefore desired moisture content, flavors and colors are mixed into the system before crash cooling (Roos and Karel 1991; Jeffrey 2001; Ergun and Hartel 2009; Hartel and others 2010; Ergun and others 2011). Figure 2.1 provides an example state diagram of a sucrose-water system that could be used to create stable glassy-state hard candies and lozenges for room temperature storage conditions. Increased temperature encourages increased sucrose solubility, which in turn allows the production of supersaturated solutions that may be crash-cooled to a glassy state (Hartel and others 2010). Points A and B demonstrate that

attempting to create a solution of 80 weight percent sucrose at 50 °C will yield a sucrose crystals and a 72 weight percent sucrose solution.

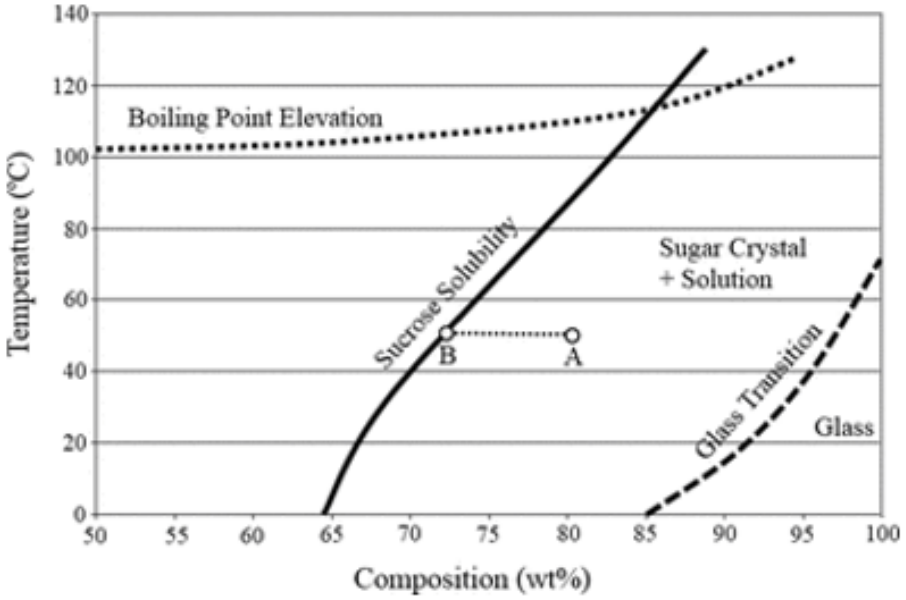

Figure 2.1: Hartel and others (2010) demonstrate the sucrose solubility, boiling point elevation, and glass transition curve in a sucrose phase diagram (Hartel and others 2010).

2.2.2 Lozenge Stability

The glassy structure that is produced after boiling past the glass transition is extremely stable under regular room temperature storage conditions (Jeffrey 2001; Ergun and Hartel 2009; Hartel and others 2010). Stability problems occur when the lozenge is exposed to optimal crystallization conditions or higher moisture conditions that can cause a phase

transition. Crystallization proves more of a risk to systems containing only one sugar type or where pre-existing crystals provide a nucleation point, often through improper dissolving of all sugar crystals ingredients (Hartel and others 2010). Crystallization is controlled by adding other syrups or acids that lead to disruptions in highly ordered crystal networks and prevent crystallization from occurring (Vink 1998).

Moisture can also affect the stability of the lozenge. Exposure to moisture allows for the glassy lozenge structure on the surface of the lozenge to be disrupted, crossing the glass transition line to create a saturated dissolved lozenge solution on the lozenge surface (Hartel and others 2010; Ergun and others 2011). This destabilization makes the surface of the lozenge sticky and undesirable if the high-moisture environment is not the mouth of the consumer (Hartel and others 2010). Elevated storage temperatures exacerbate the effect of moisture on the glass transition, requiring less moisture to undergo a glass transition. Humectant properties and the propensity to undergo phase transition during storage may be partially controlled by using different ingredients and packaging materials that limit moisture absorption or decrease exposure to moisture (Anonymous 1995; Ergun and Hartel 2009; Hartel and others 2010; Ergun and others 2011). During oral processing, conditions of elevated temperature and, more importantly, increased moisture content, create an environment that favors phase change from the stable glassy state to a rubbery state. This rubbery state eventually dissolves into a liquid solution ready for swallowing.

2.3 Oral Processing Overview

Food undergoes a combination of distinct oral processing steps as it enters the oral cavity. Most ingested solid foods undergo a well-understood set of oral processing mechanisms before proceeding to the next step in digestion (Hiiemae and others 1978; Hiiemae and Palmer 1999; Pedersen and others 2002). The majority of solid foods are processed through a series of mastication steps in a cyclical pattern until the formed bolus is ready for swallowing. Teeth chew the food to reduce the particle size and saliva mixes in to create a slick, coherent food bolus ready for swallowing (Pedersen and others 2002). Swallowing requires the use of the tongue and other muscles to squeeze and propel the bolus to the back of the throat and through the esophagus (Logemann 1983; Hiiemae and Palmer 1999; Fontijn-Tekamp and others 2004). Lozenge decay, however, is not dominated by chewing and gradually dissolves into fluids for consumption. Nevertheless, the interactions between foods and the mechanical and physiological domain of oral processing are extremely complex at the meso-scale. Significant research has been conducted to model the physiological and mechanical behaviors of the mouth during oral processing for sensory and texture studies, with limited success (Kokini and others 1977; de Wijk and others 2006; Mossaz and others 2010; Chen and Stokes 2012; Stokes 2012a). Discrepancies between benchtop assessments using rheological or tribological techniques and human sensory results may be due to the lack of distinct understanding of the governing oral processing behaviors. Specifically, these behaviors include mechanical movement by the tongue and oral surfaces and flow behaviors induced by these movements.

2.3.1 Salivation

Salivation is the physiological process whereby sublingual and mandibular glands secrete fluids to coat oral surfaces and maintain moisture. These fluids also assist with the mastication and swallowing of food and drink (Anonymous 1998; Humphrey and Williamson 2001; Bongaerts and others 2007; Drago and others 2011; Carpenter 2013). Saliva is 99.5 percent water by weight solution, with the remaining mass primarily consisting of enzymes, buffers, electrolytes, and large glycoproteins that give saliva its unique viscous behavior (Bongaerts and others 2007; Rossetti and others 2008). Saliva acts as a lubricant for the oral cavity, removing food debris and preventing tooth decay by continuously rinsing oral surfaces with fresh saliva to maintain oral health (Amerongen and Veerman 2002; Carpenter 2013). It also has unique adhesion properties that make it adsorb to oral surfaces or food products despite their varying levels of hydrophobicity (Christersson and others 2000; Ranc and others 2006; Drago and others 2011).

2.3.2 Mechanical Wear and Masticatory Performance

Masticatory performance, the ability of an individual's ability to grind and macerate food or the ability to knead and form a bolus, is commonly used to evaluate the ability of an individual to breakdown a food product during oral processing (van der Bilt and others 2010). This assessment evaluates the results of overall mastication including chewing and mechanical manipulation through distal squeezing and mechanical wearing against all oral surfaces (van der Bilt and others 2010). Although mastication from chewing is one of the primary methods to induce breakdown of a food product, the role of tongue movement and

shearing against oral surfaces is particularly important to the breakdown of products that are solid and do not undergo chewing.

2.4 Relevant Phenomena and Mechanisms to the Decay of Lozenges during Oral Processing

The physical mechanisms that contribute to oral processing are complex, consisting of a variety of wearing and flow conditions that induce the breakdown of food products and reformation into easily swallowed boluses (Logemann 1983). Furthermore, physical oral processing behaviors vary depending on the individual and the food product (Fontijn-Tekamp and others 2004). Evaluation and quantification of the average oral processing behaviors are necessary to understand the underlying mechanisms that control how a food is processed and experienced during oral processing. This section provides a brief introduction to the relevant areas of study that may contribute to understanding certain aspects of the complex mechanisms that take place during oral processing.

2.4.1 Food Rheology

Rheology, the study of flow and deformation of matter, has provided insight into the processing and oral processing qualities and performance for a variety of viscous, elastic, and viscoelastic food systems (Barnes and others 1989; Steffe 1992). However, in the case of lozenge breakdown where the lozenge is not fractured or chewed but gradually decays through phase transition into a liquid solution during oral processing, the relevant rheological properties that could be evaluated are the saliva viscosities and the amount of dissolved lozenge mass in the saliva solution. Solution viscosity plays an important role in the mass diffusivity derived from mass transfer principles, which controls the mass diffusion of

dissolved lozenge mass into the fluid saliva (Glasstone and others 1941). Saliva also has unique rheological behaviors, including its high elasticity and very low viscosity (Inoue and others 2008; Rossetti and others 2008; Stokes 2012a). These properties are a function of the dilute concentrations of mucins and other large glycoproteins that aggregate to create long molecules with strong elastic behaviors (Bansil and Turner 2006; Inoue and others 2008). Given the variety of mechanical movement and conditions lozenges and other foods experience within the oral cavity during oral processing, rheological techniques could be used to help identify average shearing behaviors during oral processing for lozenges and even a variety of other products.

2.4.2 Oral Processing Flow Conditions

The variety of tongue and jaw movements that manipulate food products during oral processing affect the flow conditions of saliva and viscoelastic products. These movements also create complex shearing conditions consisting of a combination of shear flow, narrow gap flow, and squeeze flow. This section provides a brief introduction to shear flow and squeeze flow behaviors. Figure 2.2 provides a visual depiction of the different conditions that contribute to each flow type during oral processing. It is likely that a combination of shear, narrow gap, and squeeze flow conditions are produced throughout oral processing (Stokes 2012a).

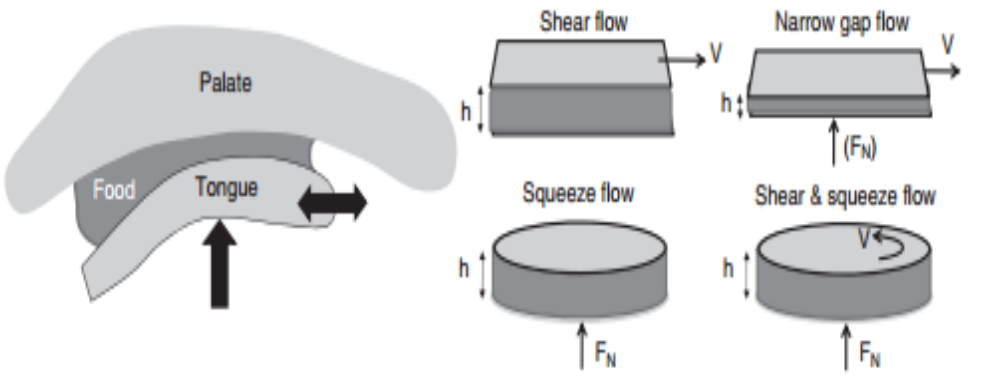

Figure 2.2: Stokes (2012a) demonstrates the various flow conditions experienced by food products during oral processing as the tongue presses and moves the food bolus against the hard palate.

2.4.2.1 Shear Flow

Shear flow conditions during oral processing are the simplest conditions to model and describe. They are modeled using the assumption that the tongue and palate are flat, non-deformable plates separated by a fluid film, similar to the design of a double plate rheometers system (Stokes 2012a). In this design, the stress at the tongue surface may be described as a function of the shear rate of the tongue. The shear rate of this system is calculated as a function of the gap distance between the tongue and palate and the velocity of the tongue movement. Equation 2.1 demonstrates this behavior:

$$\dot{\gamma} = \frac{V}{h} \qquad \text{(eq. 2.1)}$$

where $\dot{\gamma}$ is the shear rate in units of inverse seconds, V is the velocity of the tongue in meters per second, and h is the gap between the palate and tongue in units of meters (Steffe 1992;

Stokes 2012a). A solid understanding of shear rates provides a foundation for modeling flow behavior according to a variety of rheological models (Barnes and others 1989; Steffe 1992). While the shear rate is simple to calculate for a rheometer, it is difficult to identify a specific shear rate or range of shear rates representative of most oral processing shear rates. A single shear rate that is conventionally used to describe shear rate in the mouth is 50 s^{-1}, which was identified because Dr. Wood demonstrated a correlation between sensory thickness values and the viscosity of a few dilute hydrocolloid systems at 50 s^{-1} (Wood 1968). Despite the limited number of fluids tested, this particular shear rate has proven useful as a decent predictor of sensory thickness performance for liquids and is readily used in rheological-sensory assessments (Stokes 2012a). However, its value for relating sensory performance with rheological behavior of non-fluid or viscoelastic systems is suspect and requires additional investigation before it should be used to describe other food systems. Furthermore, the assumption that perceived sensory thickness is evaluated as a function of shear flow alone using the same mechanisms identified is also questionable. This assumption also requires research into other possible flow conditions that take place during oral processing, such as squeeze flow.

2.4.2.2 Squeeze Flow

Squeeze flow, simply put, is the flow behavior of a fluid film squeezed between two non-deformable plates. This action is assumed to produce flow behaviors similar to oral processing conditions where the tongue presses a food product or bolus against the hard palate (Mossaz and others 2010; Stokes 2012a). The combination of extension and possible

shearing creates a complicated system that can be difficult to model, especially when determining which slip or no-slip boundary conditions should be applied (Engmann and others 2005). Saliva complicates calculations because while it is generally assumed to act as a lubricant, it also has adhesive properties that bind food particles to form boluses during oral processing. This variation in behavior suggests that saliva may provide partial-slip conditions, depending upon the food product and plate surfaces (Stokes 2012a). Saliva further complicates lozenge modeling by causing both a phase change and dissolution to occur. These two complications make squeeze flow tests difficult to use for modeling lozenge decay behaviors during squeeze flow conditions. Nevertheless, understanding the possible flow conditions that occur during oral processing provides a framework for addressing the contribution of different flow behaviors to the breakdown of lozenges during oral processing. Shearing and squeeze flow behaviors likely occur in combination during oral processing, but the exact conditions are difficult to identify. Unless techniques such as articulography and electromyography are used to follow both tongue movements and jaw movements, it is difficult to identify the exact oral processing and possible flow behaviors of consumers. Other techniques, such as tribology, may provide more insight into the evaluation of lozenge dissolution during oral processing.

2.4.3 Food Tribology

Tribology, the study of friction, wear, and lubrication of interacting sliding surfaces, provides a relatively new means to assess food-oral surface interactions (Stokes 2012b; Stokes and others 2013). Studied in mechanical applications for decades, the principles of

tribology involve the study of hydrodynamic lubrication, where liquid becomes entrained between two sliding surfaces and produces hydrodynamic pressure (Stokes 2012b). Reynolds (1886) was the first to describe the system requirements for hydrodynamic lubrication that can carry a load: the paired surfaces must be oriented at a slight inclination and move at a sufficient velocity relative to each other to create a pressure field (Reynolds 1886). Figure 2.3 demonstrates how the lubricating film forms between two sliding surfaces and creates the pressure field.

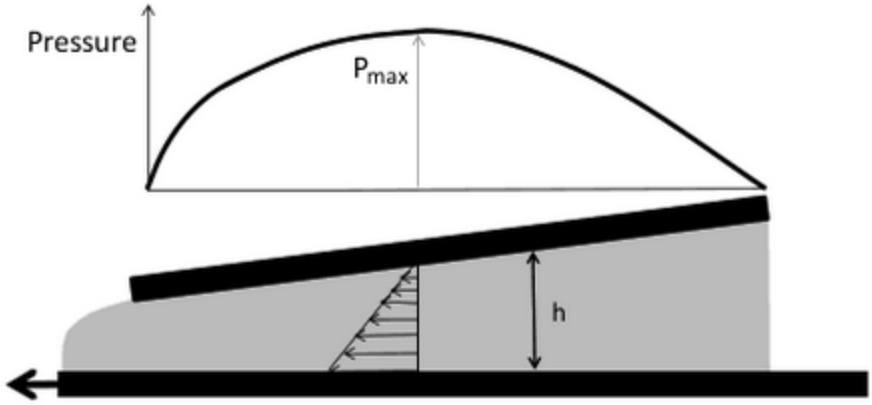

Figure 2.3: The angled gap between the sliding surfaces creates a pressure field that creates hydrodynamic lift between the surfaces at high sliding speeds. This increases the fluid film's ability to bear normal loads while maintaining separation between the two surfaces (Stokes 2012b).

The steady-state description of the Reynolds equation is derived from the Navier-Stokes continuity equations with the assumptions of constant lubricating film viscosity and a

0steady film thickness (Reynolds 1886). Equation 2.1 describes the relationship between pressure, lubricating film thickness, relative sliding speed, and apparent viscosity:

$$\frac{\partial}{\partial x}\left(h^3\frac{\partial p}{\partial x}\right)+\frac{\partial}{\partial y}\left(h^3\frac{\partial p}{\partial y}\right)=6U\eta\frac{\partial h}{\partial x} \qquad \text{(eq. 2.1)}$$

where x and y describe the distances in the direction of the flow and vertical directions, respectively, h is the film distance, p is the pressure, η is the apparent viscosity, and U is the relative sliding speed. The ability of a film layer to reduce contact between the sliding surfaces is normally shown with a Stribeck curve, where the friction coefficient is plotted with respect to the calculated film thickness (Stokes 2012b). At insufficient film thickness levels the film does not adequately separate the sliding surfaces, creating friction from the partial surface contact. However, with sufficient film thickness the friction coefficient for the system is reduced as the sliding surfaces are separated due to hydrodynamic lift. High film thickness levels begin to increase the friction coefficient for the system due to increased friction from the lubricating fluid itself, and not due to contacting sliding surfaces (de Vicente and others 2006). Figure 2.4 provides a visual example of a Stribeck curve. Tribology tests are usually conducted using a mini-traction machine or retrofitted rheometers attachment to evaluate the friction coefficient of a lubricant at different sliding speeds and controlled normal load. Under the boundary lubrication regime (BL) there are low film thickness conditions that create high friction coefficients due to the normal load support on asperity contacts. The Mixed regime creates a separation of the sliding surfaces, decreasing the friction coefficient. As the film thickness increases under the Hydrodynamic

regime the friction coefficient increases due to increased friction within the lubricating film (de Vicente and others 2006).

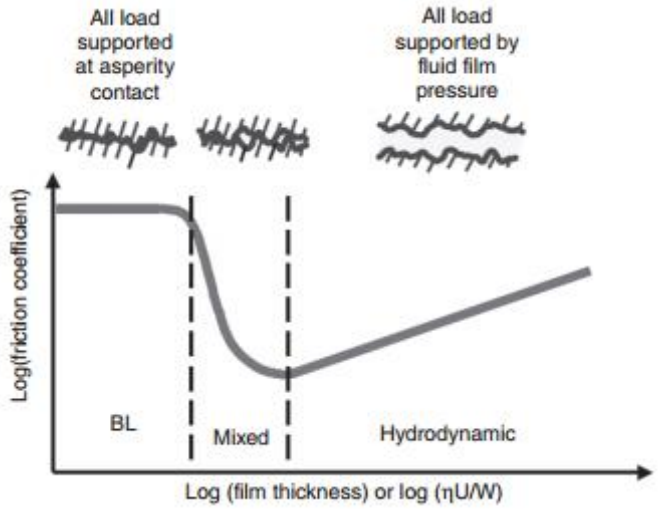

Figure 2.4: de Vicente and others (2006) uses the Stribeck curve to demonstrate the frictional behavior as a function of film thickness calculated from the sliding speed [U] in meters per second, apparent viscosity [η] in Pascal seconds, and normal load [W] in Newtons.

This information is particularly useful when creating correlations between Stribeck curve performance and sensory properties such as smoothness or slipperiness (Kokini and others 1977). Tribological analysis may provide improved understanding of the physical mechanisms that govern sensory performance, including the role of friction and interactions with saliva (Rossetti and others 2008). Tribological techniques can also be applied to model mechanical wear. The method used in this research is discussed thoroughly in the fourth chapter, where mechanical wear and breakdown of lozenges are evaluated using a lozenge-

tribopair system with water or saliva as the lubricating fluid. The lozenges are kept under constant sliding speed and normal load conditions. Tribology and the role in understanding mechanical wear pairs well with the concepts of ablation in describing decay.

2.4.4 Moving Boundary Problem

Systems that undergo phase changes that move with time are known in partial differential equation mathematical modeling as moving boundary problems. Moving boundary problems, also called Stefan problems, are used to model behavior with respect to time, where a boundary separates two different "mathematical phases" that demonstrate specific properties (Zerroukat and Wrobel 1997). A classic example involves heat transfer and the melting of ice to liquid water, where heat is transferred from the outside of the ice block to the surface, allowing melting to take place (Onuki and others 1974). The ice melt on the surface yields a fresh ice surface underneath and thereby moves the boundary of the ice surface further towards the geometric center of the ice block. Moving boundary problems may be complicated through the inclusion of additional mathematical phase changes, with multiple boundaries and phase conditions that move independently with time (Zerroukat and Wrobel 1997; Gupta and others 1998; Frauhammer and others 1998). A more complicated model of the melting ice problem would include two boundaries; one located at the ice surface separating the melted water from the solid ice, and the other located inside the ice at the location the crystalline ice starts to melt, but still maintains some crystalline properties (Onuki and others 1974; Schoof 2012). In this case, another phase exists between the melted

surface and the crystalline core: a "mushy" ice that has undergone some degree of structure disruption to make it distinct from the other two phases.

This concept of moving boundary problems is not only relevant to the study of ice melting and forming, such as in glaciology, but also to fields ranging from geology to pharmaceutical development (Verniani 1961; Nelson and Shah 1975; Schoof 2012). The moving boundary concept is not usually applied to food products during oral processing due to the lack of gradual erosive conditions when processing the majority of foods. That being said, the breakdown of lozenges due to a glass transition phase change fits the premise of a moving boundary problem. However, in the case of oral processing, the location and movement of the moving boundary may also be affected by properties other than the diffusion of water into lozenges. The presence of mechanical wear and fluid flow at the surface may affect the moving boundary if it is near the surface of the lozenge. These considerations make the moving boundary problem for a lozenge during oral processing difficult to model.

One research team attempted to model the moving boundary of a model hard candy system exposed to a constant single-directional water flow. In this research, they demonstrated the shape change and the flow behavior of the fluid moving around the surface of the lozenge (Huang and others 2015). Figure 2.5, reproduced from the research, demonstrate ablation behaviors, removal through erosive processes, of two different lozenge shapes with respect to time.

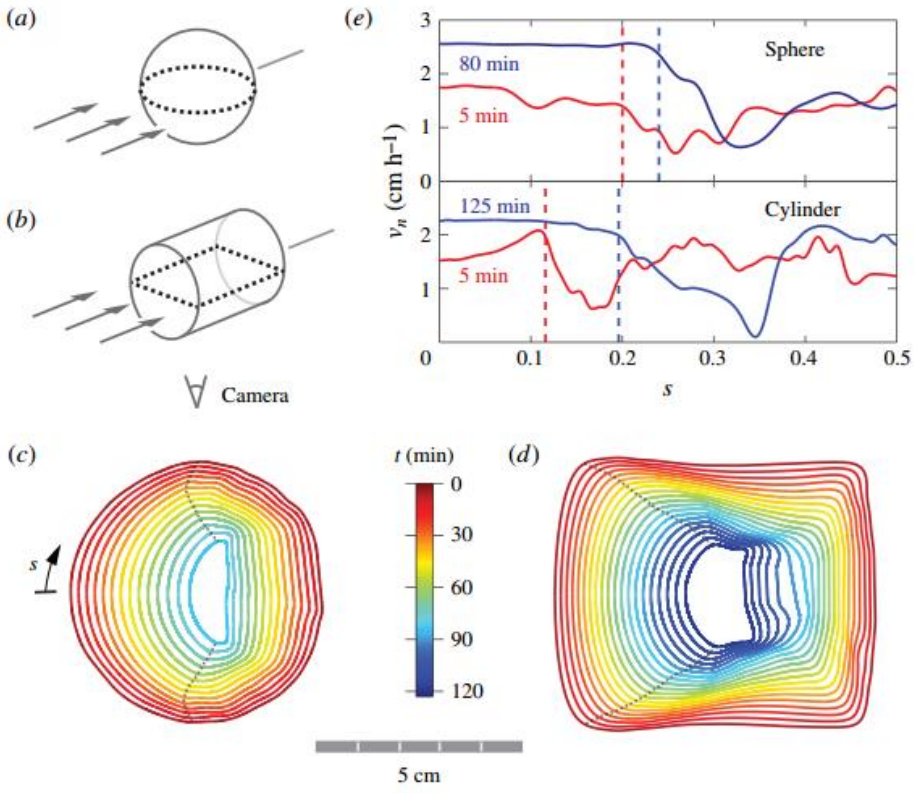

Figure 2.5: Two model lozenges with controlled shapes of (a) a perfect sphere and (b) a right cylinder were exposed to water flow of 30 centimeters per second in the directions shown. The lozenges gradually deform to create a cap-like shape for (c) the sphere and (d) the cylinder over time. The recession rate at pre-specified locations on each lozenge shape type (e) demonstrate the average overall decay rates at two different time points (Huang and others 2015).

The findings demonstrate a single boundary between the liquid and the glassy surface structure of the lozenges (Huang and others 2015). While intriguing, the gradual surface decay behavior observed under the high flow conditions is not representative of oral processing conditions that include changing flow behaviors and mechanical wearing effects.

The lack of literature investigating the factors that contribute lozenge decay during oral processing and the potential benefits to confectionery and pharmaceutical industries provided the motivation to perform this research.

2.5 Conclusions

The production, chemistry, and breakdown of boiled sweets with glassy structures are well understood; however, the amount of literature relating the lozenge structure to possible decay behavior during oral processing is extremely limited. There are several reasons for this condition, but it is primarily due to the variety of processes involved and the inconsistency of human behavior during lozenge oral processing. Mechanical wear conditions are difficult to model and to completely decouple, especially since human behavior and preferences can alter the effects of mechanical wear and salivation on lozenge decay during oral processing. The following chapters demonstrate methods to model the decay of lozenges and identify the role of mechanical wear during oral processing.

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ASSESSMENT OF MODEL LOZENGE DECAY DURING ORAL PROCESSING

3.1 Introduction

Boiled sweets are frequently consumed worldwide in the form of hard candies or as medicated lozenges. Despite extensive consumption, the factors that contribute to the decay of lozenges during oral processing have not been adequately described in literature. Lozenges experience a combination of phase change and mechanical wear during oral processing that eventually leads to their dissolution into easily consumed solutions (Chen 2009; Drago and others 2011). While the biological and non-biological mechanisms, such as increased salivation and mechanical manipulation through rubbing against oral surfaces have been addressed in literature, quantification of the exact contribution of each factor to lozenge breakdown has proven difficult to quantify (Stokes and others 2013). The difficulty in assessment is partly due to the inconsistency of human oral processing behavior (Chen 2009). However, steps can be taken towards understanding the contribution of each factor to the lozenge decay by analyzing the average of oral processing performance of a representative group of adults. The purpose of this chapter was to develop a standard methodology for the assessment of lozenge decay during oral processing and to determine the average lozenge breakdown performance from a representative sample of healthy adults. Identifying the average oral processing performance of a sample of healthy adult humans with a standard model lozenge provides the starting point to determining the average role of saliva and mechanical wear in the breakdown of lozenges during oral processing. Development of a standard method of assessment of lozenge decay by healthy adults is also useful for targeted

product development of new confections or the assessment of active ingredient release in pharmaceuticals.

3.1.1 Background

Humans generally consume lozenges and hard candies through a variety of oral processes and behaviors, including salivation, manipulation of the lozenge with the tongue against oral surfaces creating mechanical wearing conditions, and chewing in some cases near the end of lozenge breakdown (Chen 2009; Drago and others 2011). Normally during the mastication of soft or chewy foods, the combination of chewing and increased salivation leads to the rapid breakdown of the solid food into smaller pieces, followed by immediate hydration from the saliva, and the joining of the food particulates into a bolus for ease of swallowing (Prinz and Lucas 1995; Pedersen and others 2002; Chen 2009). Breakdown for hard candies and lozenges share some of the same physiological responses and behaviors, namely that upon entrance into the mouth, the salivary glands rapidly increase the production of saliva available in the oral cavity and that saliva completely coats the lozenge. A "slurping" behavior that combines high salivation rates and mechanical wear through rubbing against the tongue, hard palate, and other oral surfaces are the conditions that dominate the oral processing and breakdown of lozenges (Chen 2009; van der Bilt 2011). In the case of lozenges, the role of chewing to reduce particle size for swallowing ease is replaced with a system that slowly decays lozenges into liquid solutions for simple consumption (Prinz and Lucas 1995; Pedersen and others 2002). While lozenges only require increased moisture levels to induce the phase change from a glassy phase to a rubbery state before being

completely dissolved for easier consumption, a combination of saliva flow and mechanical wearing conditions lead breakdown during oral processing (Chen 2009; van der Bilt 2011; Ergun and others 2011).

Decoupling of the role saliva flow or mechanical wear in the oral processing of lozenges proves difficult to achieve. Part of the difficulty in identifying the contribution of each factor type lies in the variability of human physiological response to stimulus, especially in the case of salivation (Anonymous 1998; Chen 2009; Drago and others 2011; Carpenter 2013). Variation in salivation rates depend on several intrinsic physiological factors and extrinsic stimuli factors. Intrinsic factors that can affect salivation rates include general health of the subject, their age, their degree of hydration, the time of day, and their circadian rhythm, the natural behavioral, physical, and mental behaviors existing in a twenty-four hour cycle (Spence 2011). Individuals that take certain medicines, are undergoing medical treatments like cancer with drug and radiative therapies, or have other medical conditions may suffer from xerostomia, otherwise known as dry mouth (Anonymous 1985; Shern and others 1993; Spence 2011). People that suffer from dry mouth face challenges with swallowing, speaking, or maintaining proper oral health due to their insufficient salivation rates (Anonymous 1985; Shern and others 1993). Salivation rates may also be affected by extrinsic stimuli, such as mechanical jaw movement similar to chewing or exposure of dilute acids in the form of acidulant ingredients to oral surfaces (Ericson 1971; Humphrey and Williamson 2001; Gavião and others 2004). These extrinsic factors may be addressed by food processors in the design of products with unique ingredient compositions and textures.

Ingredients also affect the glass transition properties of the lozenge, thereby affecting breakdown (Ergun and others 2011). Total size, surface area, and volume may also have an effect on salivation rates and degree of mechanical manipulation during oral processing (Prinz and Lucas 1995).

A problem that has plagued the evaluation of physiological and behavioral lozenge decay during oral processing has been the inconsistency in human mechanical wear behaviors (Fontijn-Tekamp and others 2004; Engelen and others 2005). Furthermore, humans vary in their mastication style preferences. Evidence of this was provided by the Understanding and Insights Group which categorized consumers based upon their general chewing and oral processing behaviors and preferences with a selection of model foods (Chaker 2013). Arguably, a selection of consumers may not orally process strictly by "slurping" on a lozenge, but rather elect to chew and ingest the lozenge well before complete decay would be achieved by "slurping" alone (Prinz and Lucas 1995; Fontijn-Tekamp and others 2004; Engelen and others 2005). Assessing the average oral processing behavior from a selection of representative healthy adults is necessary to decouple the factors that contribute to decay from oral processing performance variability.

The main objectives of this chapter were to (1) select a model lozenge system for oral processing analysis and (2) model the average lozenge decay variables throughout oral processing. Additional experiments were designed to determine effects on lozenge decay due to formulation differences between lozenges. The last objective was to (3) determine if a moving moisture boundary condition existed in lozenge systems during oral processing. To

complete these objectives, a standard method to assessing lozenge decay was developed to account for the average oral processing behaviors such as swallowing frequency, salivation rate, dissolved lozenge mass, and solid lozenge mass under controlled and normal oral processing conditions. The standard method of analysis developed identified the critical oral processing and decay factors applicable to any lozenge system regardless of initial shape or ingredient composition, making it a universal methodology for lozenge decay assessment during oral processing.

3.1.2 Mass Flux Assessment of Breakdown

A vital first step to decoupling the critical factors that contribute to the decay of hard candies and lozenges during oral processing is to identify a model lozenge and assess its breakdown by a representative selection of healthy adults under controlled conditions. A full, human-based model demonstrating the average lozenge breakdown behaviors by a selection of adults was necessary to provide the average salivation conditions and dissolution rates of model hard candies during oral processing. To evaluate the average breakdown parameters with the full, human-based model, a method to determine the decay of lozenges throughout oral processing with respect to changing lozenge shape parameters was required. Assessment that accounts for changes in surface area provides the framework to calculate decay throughout oral processing.

A method that accounts for surface area effects is necessary for evaluating decay properties between lozenges with different surface areas or compositional differences. One method that accounts for changes in surface area and time is the dissolved mass flux, which

is a number that relates the movement of mass from an interface per unit time per unit interface area. This approach allows for simplified comparisons between data collected at different oral processing times or with lozenges with variable surface area and composition. Dissolved mass flux calculations were developed to account for shape and surface area effects while assessing breakdown during oral processing. Dissolved mass flux is denoted by the term j_n and has units of kilograms dissolved lozenge mass per second per square meter of lozenge surface area. Mass flux is defined as follows:

$$j = \lim_{A \to 0}\left(\frac{\lim_{\Delta t \to 0} \frac{\Delta m}{\Delta t}}{A}\right) \qquad \text{(eq. 2.1)}$$

where *j* is the mass flux in kilograms dissolved mass per second per square meter of surface area, Δm is dissolved mass difference in kilograms, *A* is the surface area in square meters, and Δt is the change in time in seconds. Fluxes are understood to be instantaneous estimations of mass movement in a normalized direction per unit area. A simplified flux measurement was used, assuming that the rate of surface area change between measurements and the mass loss occurred at constant rates. The equation used for analysis in section 3.3, the Results and Discussion section, is as follows:

$$j_n = \frac{m_n}{(\bar{A}_{n,n-1})(\Delta t_{n,n-1})} \qquad \text{(eq. 3.2)}$$

where j_n is the mass flux assessed at each sample *n*, m_n is the dissolved mass collected in a single sample *n*, $\bar{A}_{n,n-1}$ is the average surface area between the current sample and the previous sample, and $\Delta t_{n,n-1}$ are the is the time difference between collection of sample *n* and the previous sample. Dissolved mass flux is reported in units of kilograms of dissolved

lozenge mass per second per square meter of lozenge surface area. Calculation of dissolved mass flux was vital to the assessment of breakdown and decay in the human-based oral processing tests discussed in section 3.2, the Materials and Methods section.

3.2 Materials and Methods

This section describes techniques for model lozenge selection and key characteristics for quantifying and describing decay, discussing the tests performed with human panelists to determine the average lozenge decay performance.

3.2.1 Model Lozenge Selection

Proper selection of a model lozenge is vital to creating a methodology to study decay as a function of intrinsic physiological factors such as salivation rates, thermodynamic factors related to the lozenge ingredient composition-controlled glass transition properties, and varying human-derived mechanical wear behavioral factors. Selection of a model lozenge with a controlled composition and production eliminates variation in decay due to compositional differences that affect the glass transition properties. Ideal model lozenges must have simple formulations, containing no acidulants that may affect salivation rates. Furthermore, model lozenges should primarily consist of standard corn syrup-sucrose blends conventionally used within the confectionary industry to be applicable to the confectionery industry. Lozenge geometry should also be consistent and easily modeled with few governing dimensions. For example, methods for assessment of the decay (shape and dimensions) must be highly repeatable, reliable, and robust for efficient incorporation into human trials and assessment.

Simple, commercially produced, disk-shaped butterscotch hard candies were selected and procured (www.nuts.com) as a model lozenge from a selection of commercially marketed hard candies, because this system met all requirements desired in a model lozenge. The average physical properties of the model butterscotch lozenge are shown in Table 3.1.

Table 3.1: Physical properties of model butterscotch lozenge used during human oral processing tests

Parameters	Physical Properties ± 95% Confidence Interval
Average Dimensions	Diameter = 25.4 mm, Height = 9.0 mm
Weight	5.37 ± 0.17 grams
Density	1.34 ± 0.04 g/cm^3
Estimated Surface Area	1354 ± 38 mm^2

Preliminary assessment demonstrated the homogenous consistency, while maintaining a relatively consistent shape throughout oral processing with limited governing dimensions defining its dynamic shape: its height and the average cross-sectional diameter dimensions. Figure 3.1 demonstrates the average lozenge shape and governing dimensions using a computer generated model. The radius of curvature is calculated as equivalent to half of the lozenge height. The distance between the outer diameter and inner diameter is equivalent to the height of the lozenge. Given these observations for the average lozenge, the model to

define the system is dominated by two measurements: lozenge height and lozenge cross-sectional diameter.

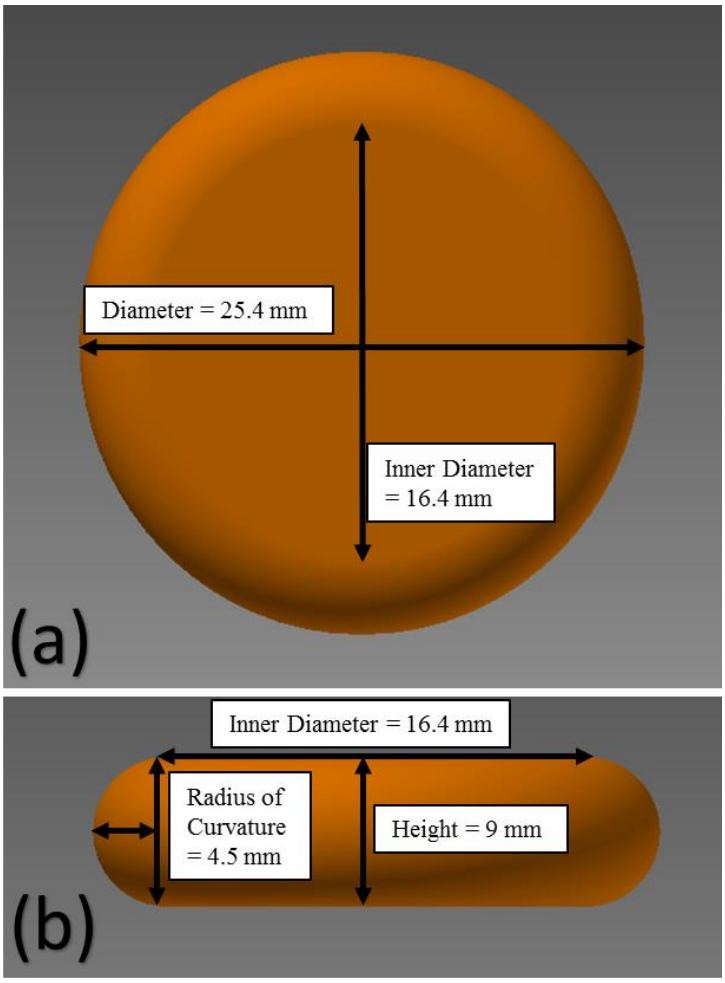


Figure 3.1: (a) The dorsal view of the lozenge disk shape is described by inner and outer diameters that govern the total width of the lozenge and the diameter of a disk of constant, maximum height. (b) The transverse view of the lozenge describes the maximum height of the lozenge, the radius of curvature for the rounded region, and the location of the inner diameter with respect to the radius of curvature.

3.2.2 Assessment of Critical Dimensions using ImageJ Image Analysis Software

The first step to rapid assessment of the model lozenge governing dimensions was the identification of a fast, highly repeatable measurement tool. Measurements needed to be made quickly and stored for analysis immediately upon capture, limiting the scope of potential platform tools. After 3D-scanning proved too time intensive and inaccurate for the lozenge system, a photographic method was developed to capture images of the lozenges throughout all tests developed. A system combining image capture using two conventional web-cameras (Logitech®, Newark, California; HP Webcam®, Palo Alto, California) and an open-source image analysis software, ImageJ (National Institutes of Health, Bethesda, Maryland) were used to determine the governing dimensions of the model lozenge. The image capture system consisted of an anchored black polypropylene pedestal to a black surface, aligned directly under one of the webcams and to the side of the second camera. Black backgrounds were included to differentiate the lozenge from the background and limit noise that could affect the software performance. Simultaneous image capture from both cameras provided a simple means to assess the governing dimensions at specific times. Images taken from the top view were used to determine the degree of ellipsoidal shape and the governing diameter dimensions, while images taken with the camera aligned with the lozenge along the transverse plane were used to determine the height and governing radius of the lozenge disk edge. Images of a standard ruler placed on the lozenge pedestal helped calibrate the image pixel to length ratios used by the ImageJ software. Following capture, images were uploaded to ImageJ and assessed for the critical dimensions using pixel

analysis. These dimensions were then uploaded in computer modeling software to determine the surface area and volume of the lozenge at each sampling point during oral processing.

3.2.3 Evaluation of Lozenge Surface Area and Volume

A disk-shaped model was constructed with Autodesk Inventor® software (Mill Valley, California) using the same governing dimensions identified in the preliminary assessment of the model lozenge critical dimensions. Additionally, a program was written to assess several dimension sets and produce the calculated surface area and volume values at a rapid rate. Next, surface area values were used to calculate the average mass flux within each oral processing time interval. Figure 3.2(a-d) demonstrates the image capture design and assessment methods. Surface area and volume were two important factors evaluated during oral processing, and these visual assessment tools combined with dissolved lozenge mass analysis were essential to the research, allowing for rapid determination of lozenge decay.

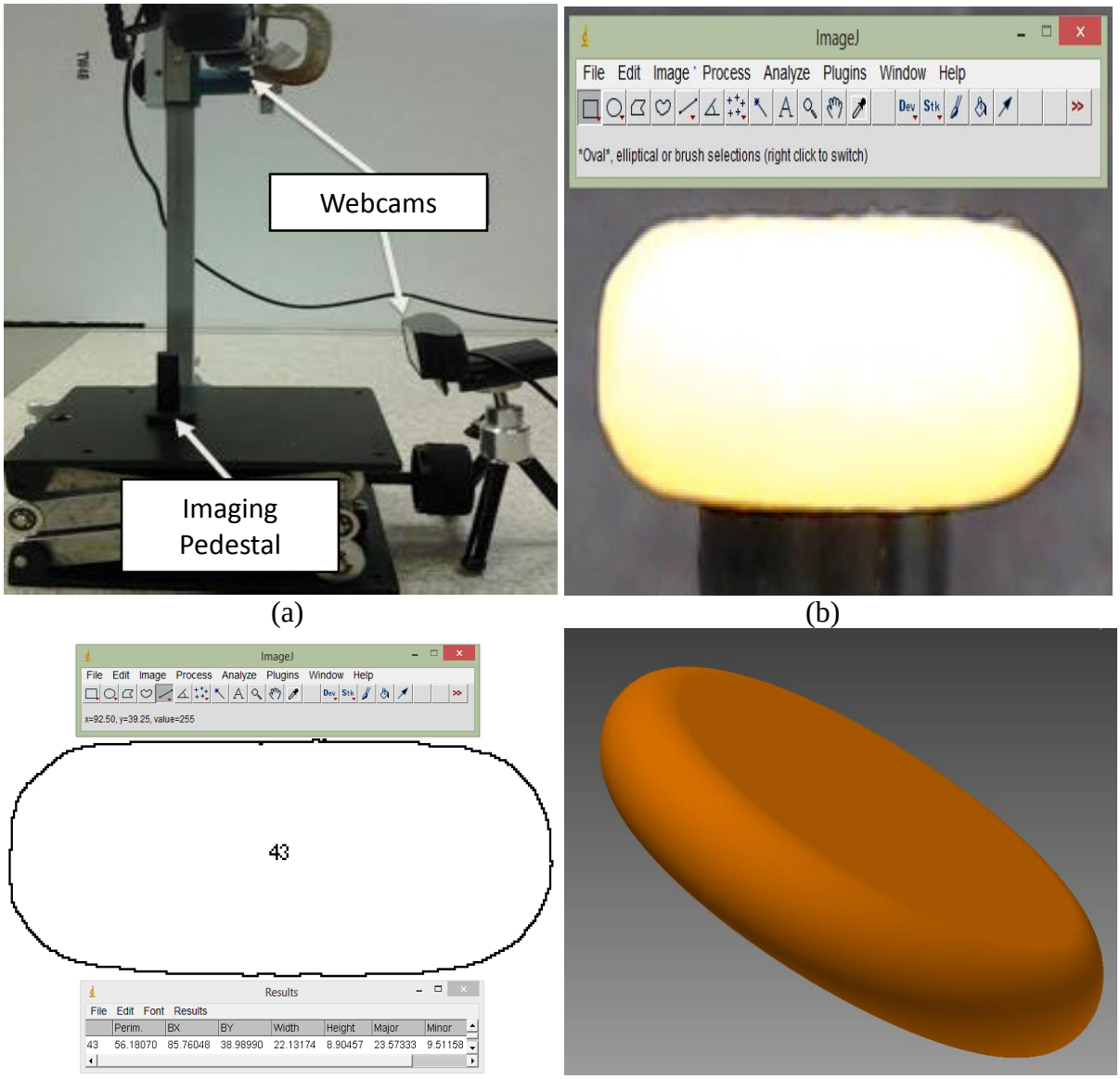


Figure 3.2: (a) Two web cameras are oriented in the dorsal and transverse plane of the imaging pedestal and model lozenge. (b) Images captured are uploaded into ImageJ for analysis. (c) ImageJ detects the lozenge edges in each image and uses pixel analysis to assess critical dimensions. (d) Critical dimensions are uploaded into an Autodesk Inventor® program, producing a visual of the model lozenge and calculating the surface area and volume in units of mm^2 and mm^3, respectively.

3.2.4 Assessment of Dissolved Lozenge Mass

Dissolved lozenge mass, the amount of solid lozenge that is converted into liquid solution during exposure to increased moisture levels, was evaluated using refractive index assessment. Solutions were prepared with varying mass percent of dissolved lozenge, ranging from 0 to 45% by weight and assessed for their refractive indices using an Anton Paar® Abbemat 500 Refractometer (Gratz, Austria), creating a standard curve. A standard curve solution was made with fresh saliva from each test from each panelist. Total dissolved mass was then determined by multiplying the solution sample mass by the corresponding mass percent derived from the refractive index standard curve. Assessment of dissolved lozenge mass was pivotal to assessing model lozenge breakdown.

3.2.5 General Oral Processing Human Subject Tests

Complete, human-based models for assessing model lozenge decay under oral processing conditions were created from lozenge mass, dissolved lozenge mass in saliva samples, and solid lozenge surface area and volume at naturally occurring and fixed time points during oral processing of panelists. Seventeen healthy adult humans who were not suffering from xerostomia or other salivation conditions were recruited for an Institutional Review Board (IRB) approved test to assess oral processing conditions of the model lozenge. Thirteen of the subjects participated in the trials twice, providing additional data to be assessed in duplicate. A total of thirty datasets were produced and analyzed. For conformity, subjects were tested individually between the hours of 7:00 AM and 11:00 AM, limiting factors associated with hunger or circadian rhythm, the biological and behavioral changes

that naturally occur in a twenty-four hour cycle. Subjects were instructed to abstain from eating or drinking anything but water for two hours prior to the trial to eliminate the effects of residual food particulates interfering with dissolved lozenge assessments or affecting salivation rates.

Three separate tests were conducted for each trial. The first test, referred to as the Salivation Test, assessed the salivation rate of each subject under mechanical stimulation, salivation due to chewing movement alone, at specified time intervals. This test served to address the average salivation rate of the subjects under minimal mechanical stimulation, thereby providing a reference for when normal salivation rates had been achieved, post-consumption of a lozenge (Pedersen and others 2002; Gavião and others 2004). The second test, referred to as the Unstructured Test, assessed the natural oral processing behaviors of the subject freely processing the model lozenge, determining the dissolved mass flux behavior in variable intervals, controlled by the subject. The purpose of the Unstructured Test was to determine the frequency of swallowing during regular oral processing and the average decay rate during normal oral processing conditions. The last test, referred to as the Full Test, assessed the oral processing behaviors of the subjects under controlled time conditions. The purpose of this test was to determine the effect of surface area change, saliva mass, and solid lozenge mass on the decay rate of model lozenge during oral processing conditions. All tests were developed independently due to the lack of standard methods provided from previous works, but were necessary to understand the average behavioral effects on the decay of

lozenges during oral processing. Table 3.2 provides a brief overview of the oral processing tests described.

Table 3.2: The Oral Processing Tests conducted to assess the average decay of a model lozenge during oral processing

Oral Processing Test	Frequency of Measurements	Factors Assessed at Each Sampling			
		Saliva Mass (Yes or No)	Dissolved Lozenge Mass (Yes or No)	Solid Lozenge Mass (Yes or No)	Lozenge Surface Area (Yes or No)
Salivation Test	Every 30 Seconds	Yes	No	No	No
Unstructured Test	Variable, dependent on subject	Yes	Yes	No	No
Full Test	Every 30 Seconds	Yes	Yes	Yes	Yes

The data from the Full test could be analyzed with greater scrutiny compared to the Unstructured Test because data was collected at regulated time points and all model dimensions, dissolved lozenge mass, and solid lozenge mass were determined at each time point. All tests were performed in the following order: Salivation Test, Unstructured Test, and Full Test. This order was done to establish salivation rates under mechanical stimulation without confounding factors concerning consumption of foods, and to limit the tendency for panelists to expectorate at thirty second intervals during the Unstructured Test as an effect of the controlled expectoration times of the Full Test. Furthermore, an additional experiment

was conducted that used all three of the tests to evaluate the dissolution of a second model lozenge to evaluate breakdown differences based on lozenge composition. This experimental procedure, called the Compositional Difference Test and described in section 3.2.6, was included to investigate the effect lozenge composition may have on the dissolved mass flux or overall lozenge decay behavior during oral processing. This study was relevant for evaluating the performance of different formulations during product development.

3.2.5.1 Salivation Test

Salivation is the biological process through which the salivary glands secrete saliva into the oral cavity to aid in mastication, swallowing, or mouth coating and oral surface hydration, thereby providing general oral health maintenance. Evaluation of the average salivation rate under only mechanical stimulation provides a baseline salivation rate for evaluating heightened salivation during oral processing of model lozenges. The method used to evaluate the mechanically stimulated flow rates was similar to the methods previously used (Gavião and others 2004).

Subjects were instructed to rinse their mouths five times with water before starting the test to remove any free food particulates. Then, the panelists received instruction to continuously masticate the bulb end of a sanitized disposable polypropylene pipette to mechanically stimulate salivation and refrain from swallowing all produced saliva. The subjects continuously chewed at their leisure in thirty second time intervals. At the end of each thirty second period, the panelist expectorated all free saliva produced. The first four free saliva samples produced were discarded to eliminate any residual water from the rinsing

step or freed food particulates. All subsequent samples were collected into a pre-weighed cup, weighed, and recorded after each interval for a total of ten minutes of mastication time. Harvested saliva was pooled and used to create the unique individual's lozenge-saliva solution refractive index standard curves. An example lozenge-saliva solution refractive index standard curves is provided in the Appendix.

3.2.5.2 Unstructured Test

A model lozenge butterscotch was selected, weighed, and imaged for surface area analysis. Each panelist was instructed to orally process the model lozenge naturally, with the exception of refraining from chewing the lozenge at any point while expectorating all free saliva into pre-weighed sample cups at leisure. Panelists were given no instruction concerning lozenge manipulation, prompting conditions that would match their usual oral processing preferences. Time of expectoration, sample mass, and time to complete dissolution, were recorded.

The Unstructured Test continued for two minutes post dissolution to recover any residual dissolved lozenge mass. All expectoration samples were weighed and assessed for refractive indices to determine the total mass percent of dissolved lozenge from the standard curves. Then, the panelists were instructed to rest for five minutes to return to normal salivation rates. All data was averaged and analyzed for each sample.

3.2.5.3 Full Test

The Full Test was performed to quantify the average decay behaviors and breakdown properties of model lozenges by the human subjects in controlled, oral processing time

intervals. Subjects were instructed to orally process a pre-weighed and pre-imaged model lozenge at thirty second intervals. At the end of each interval, the solid lozenge piece was weighed and imaged, and the subjects expectorated all free saliva. No chewing of the lozenge or swallowing was permitted during the test, allowing for improved dissolved mass recovery. The test continued for a total oral processing time of twelve minutes, with careful monitoring of the oral processing and non-oral processing time during the test. Time to complete dissolution was recorded, and the subjects provided free saliva samples until the end of the twelve minute test time.

The refractive index of each saliva sample was recorded and used to determine the total dissolved lozenge mass percent, as referenced against the master curve. All solid lozenge images were measured to record governing dimensions to determine the lozenge surface area and volume at each thirty second time point. Finally, the dissolved mass flux was determined at each time point according to equation 3.2. All data from individual tests were averaged and analyzed at each thirty second time point. The dissolved mass flux data was analyzed using one-way ANOVA and compared with Full Test results using a means difference t-test to determine if there were statistically significant differences in breakdown performance in and between Full Test and Unstructured Test data sets.

3.2.6 Evaluation of Lozenge Compositional Differences in Oral Processing Subject Tests

Three subjects were selected based on their availability to complete additional oral processing trials with the model lozenge and another conventional hard candy. Gobstoppers (Nestle) were selected and purchased to compare compositional effects on the breakdown

and flux behaviors of hard candy types. Gobstoppers consist of a different selection of ingredients and concentrations than the model butterscotches and maintain a relatively consistent spherical shape during oral processing. The difference in ingredients and processing from the model lozenge makes it ideal to explore the effects of composition on decay variables during oral processing. Each trial consisted of the previously described Salivation Test, Unstructured Test, and Full Test. A total of three trials were performed by each subject for each candy type, and average mass flux was calculated from the dissolved mass, sample time, and calculated surface area averages. All data were averaged at each thirty second time point during the Full Test. The dissolved mass flux data was analyzed using one-way ANOVA and compared with Full Test results using a means difference t-test to determine if there were statistically significant differences in breakdown performance in and between data sets.

3.3 Results and Discussion

Results from the Salivation Test, Full Test, and Unstructured Test demonstrate the average human behavior in oral processing. The Salivation Test specifically demonstrates the average mechanically-stimulated salivation rate using thirty second sampling times. The Unstructured and Full Tests assess the average breakdown behavior of a model lozenge at unregulated, natural sampling times and under controlled sampling times, respectively.

3.3.1 Salivation Test

The average saliva mass produced per thirty second interval for all thirty data sets produced is shown in Figure 3.3. The average salivation rate ranged between 1.1 and 1.3

grams per minute, with an average constant rate of 1.2 ± 0.02 grams per minute under strictly mechanical stimulation of salivation. The large 95% confidence interval error bars suggest that individual rates also vary between subjects and tests. The lowest and highest average salivation rate in all of the tests was 0.44 and 2.2 grams per minute, respectively. This observation implies that there is a range of salivation ranges among healthy adults, which may be a factor that contributes to breakdown rates of hard candies and lozenges. Future research that includes a larger subject base could be used to subdivide the population of healthy adults into groups with higher or lower salivation rates for targeted product development purposes. Determination of the average mechanically-stimulated salivation rate is important for determining the amount of time following oral processing of the model lozenge in the other two tests to achieve the same equilibrium non-food mechanically stimulated salivation rate.

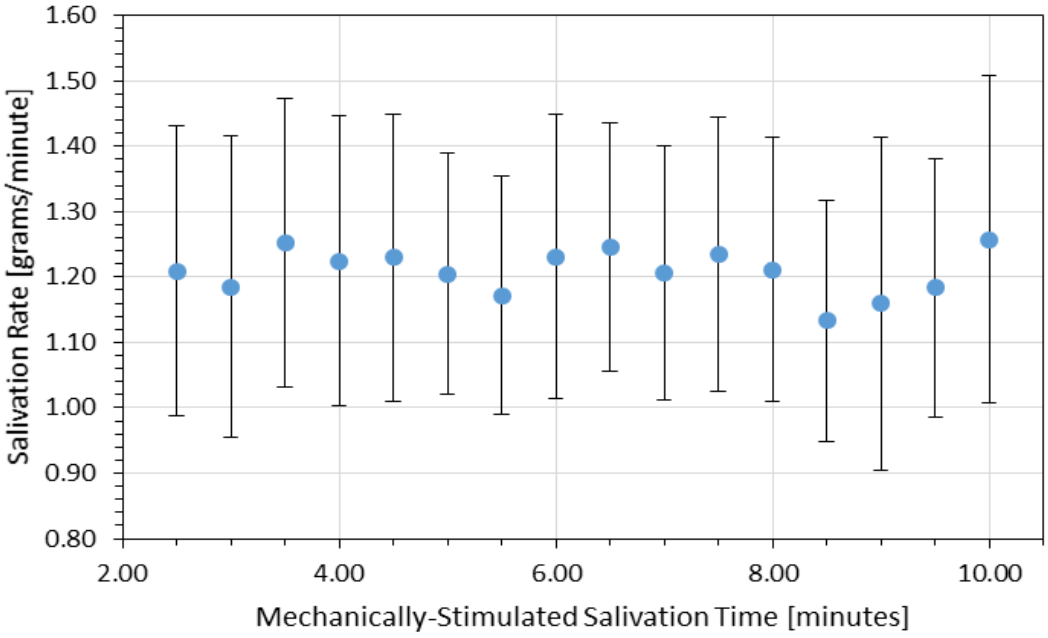


Figure 3.3: The average free salivation rates in all thirty data sets in thirty second mechanical stimulation intervals remains relatively constant at 1.2 ± 0.02 grams per minute, within 95% confidence.

3.3.2 Full Test

The Full Test was oral processing test that required panelists to orally process a pre-weighed and imaged model lozenge and assess dissolved mass, solid mass, and surface area of the model lozenge in thirty second time intervals.

3.3.2.1 Oral Processing Time to Complete Decay

The oral processing time to complete decay of the lozenge (T_D) was assessed for each of the thirty trials and used as a preliminary method to determine the relative normal distribution of the datasets. A plot was constructed to demonstrate the range and relative

distribution of time required to reach complete decay, with the accumulated percentage of subjects that had reached T_D as a function of total oral processing time. The sinusoidal shape to the curve shown in Figure 3.4 suggests there was a normal distribution of times to complete dissolution for all the Full Test data. The proximity of the average time and median time to complete dissolution of 6.0 and 6.6 minutes, respectively, demonstrate normal-like distribution, albeit with slight skewing to the right. Normally distributed data is desirable for ease of statistical analysis and making inferences about larger human population behaviors.

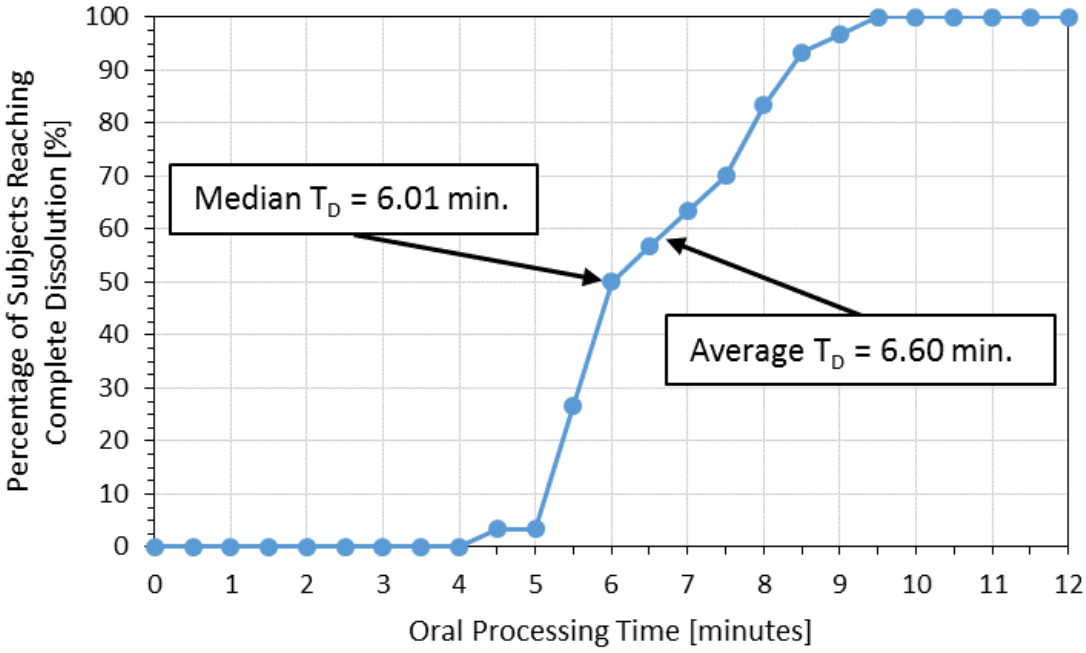
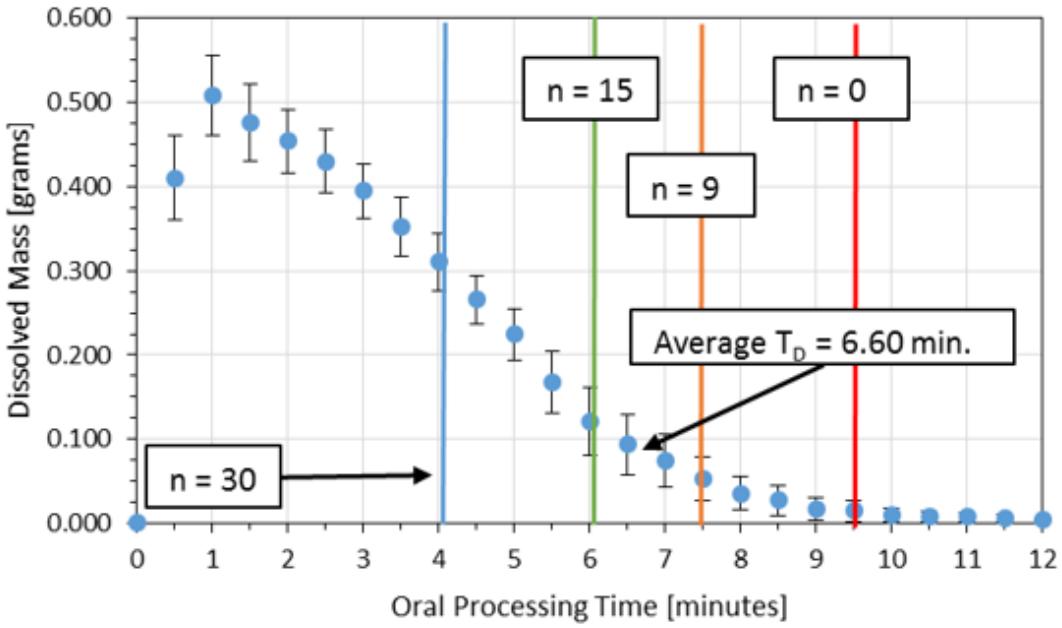


Figure 3.4: The oral processing time range, median, and average time to complete decay (T_D) for complete dissolution in all thirty tests in the Full Test.

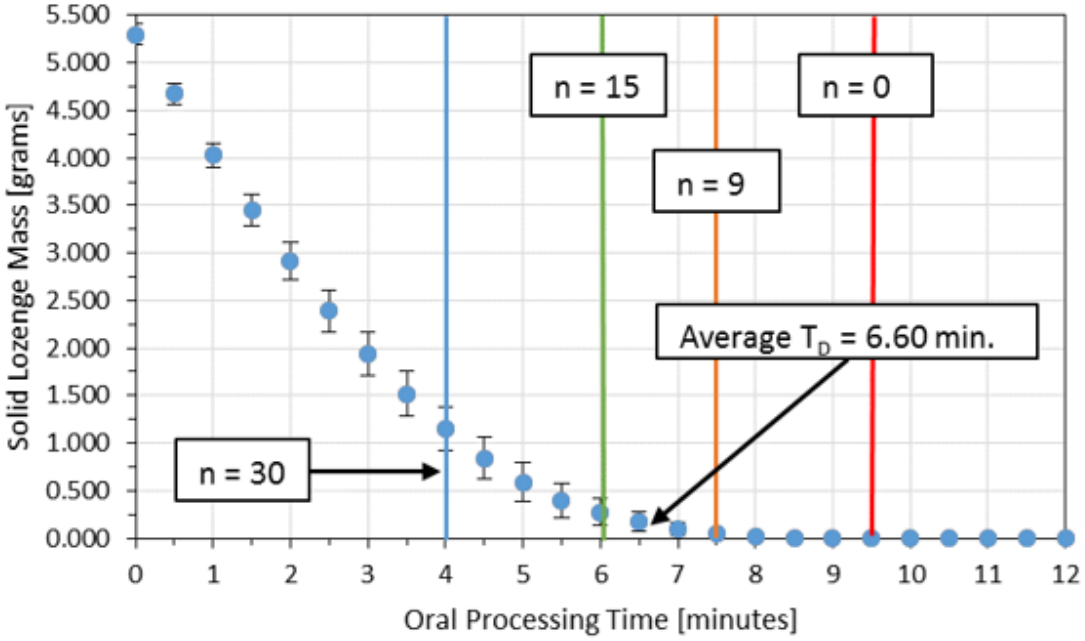
3.3.2.2 Collected Dissolved Mass, Solid Lozenge Mass, and Saliva Mass Data

The average dissolved lozenge mass, solid lozenge mass, and saliva mass data were collected at each thirty second interval to assess the breakdown conditions during oral processing. Average values from all thirty datasets were determined at each time point and plotted with respect to oral processing time in Figure 3.5 (a) through (c). Vertical lines show the change in the number of tests with solid lozenge remaining with respect to oral processing time.

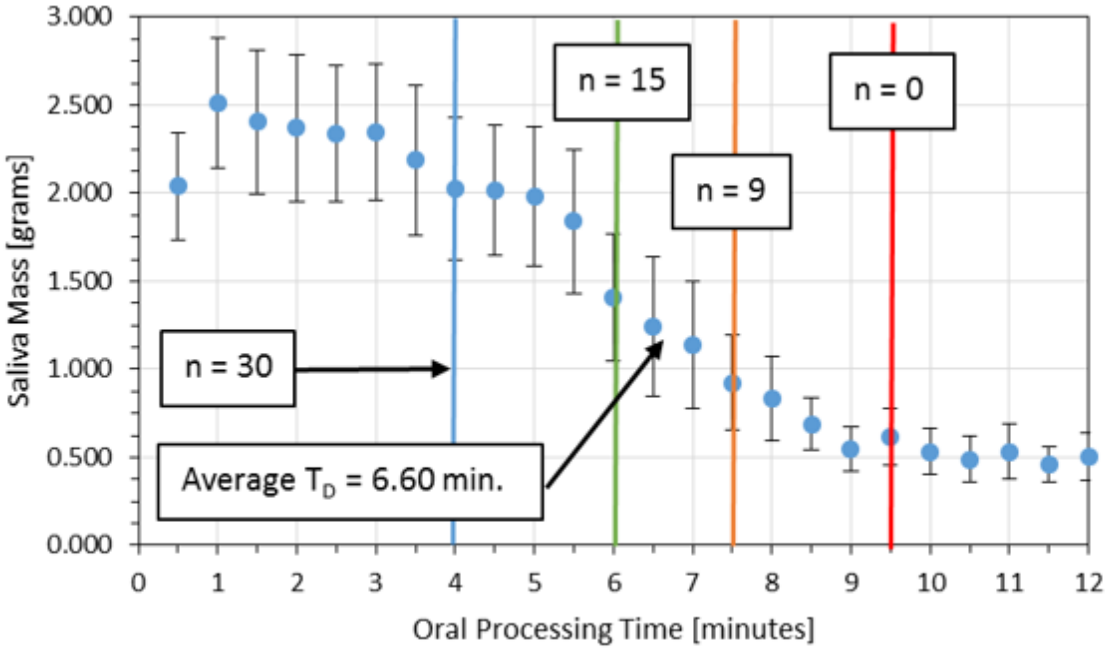
Figure 3.5: (a) The dissolved lozenge mass at each thirty second sampling time point increases quickly to a maximum at one minute before gradually decreasing. (b) The solid mass of the lozenge rapidly decreases with respect to oral processing time. (c) Free saliva mass produced increases early during oral processing and gradually decreases throughout the oral processing time.


Dissolved Mass [grams]
0.600
0.500
0.400
0.300
0.200
0.100
0.000
n = 15
n = 0
n = 9
Average T_D = 6.60 min.
n = 30
0 1 2 3 4 5 6 7 8 9 10 11 12
Oral Processing Time [minutes]

(a)


Solid Lozenge Mass [grams]
5.500
5.000
4.500
4.000
3.500
3.000
2.500
2.000
1.500
1.000
0.500
0.000
n = 15
n = 0
n = 9
Average T_D = 6.60 min.
n = 30
0 1 2 3 4 5 6 7 8 9 10 11 12
Oral Processing Time [minutes]

(b)


3.000
2.500
2.000
1.500
1.000
0.500
0.000
Saliva Mass [grams]
0
1
2
3
4
5
6
7
8
9
10
11
12
Oral Processing Time [minutes]
n = 15
n = 0
n = 9
n = 30
Average T_D = 6.60 min.

(c)

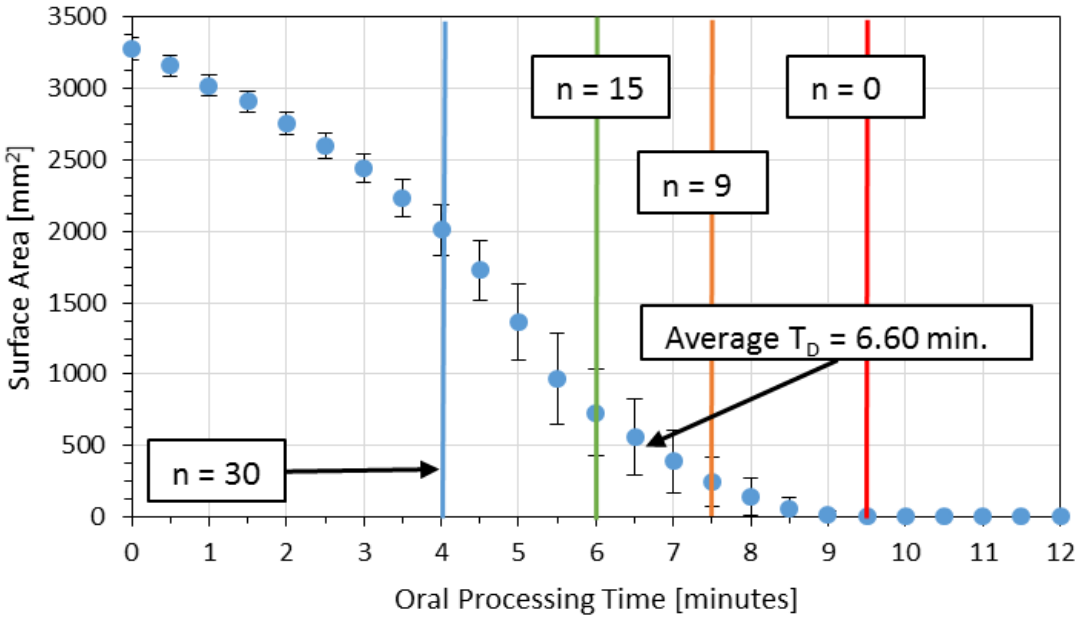
Figure 3.5 (a) shows a rapid increase in the mass of dissolved content to a peak at one minute of oral processing time, followed by a slow decrease over the course of the remaining oral processing time. It is important to note that up to the four minute time point all subjects in all tests were orally processing the solid lozenge. Shortly after that time, the number of subjects with solid lozenges decreases as each individual achieves a T_D, decreasing the average dissolved mass content. Interestingly, each test showed residual dissolved lozenge mass recovery in the samples following the complete dissolution, suggesting that residual dissolved mass remaining in the oral cavity post-oral processing. This observation may have an impact on the overall impact of the lifetime and liking of the lozenge by consumers and warrants future investigation.

Figure 3.5 (b) demonstrated that the solid lozenge mass decreased in a seemingly constant rate during oral processing throughout the majority of the test. This dissolution speed changed shortly before the average T_D was reached, where the decay rate decreased, likely a function of the number of solid lozenges remaining at each time point as oral processing progresses, increasing the average solid mass value slightly. The decreased rate may also be a function of the decreased mass or surface area of the solid lozenge. A mass balance of the dissolved mass and solid lozenge mass throughout oral processing indicated that an average 15.9% of the original lozenge mass was unrecovered at the end of the test. The amount of unrecovered mass is likely due to the presence of residual, unrecovered dissolved mass on oral surfaces or accidental swallowing by panelists.

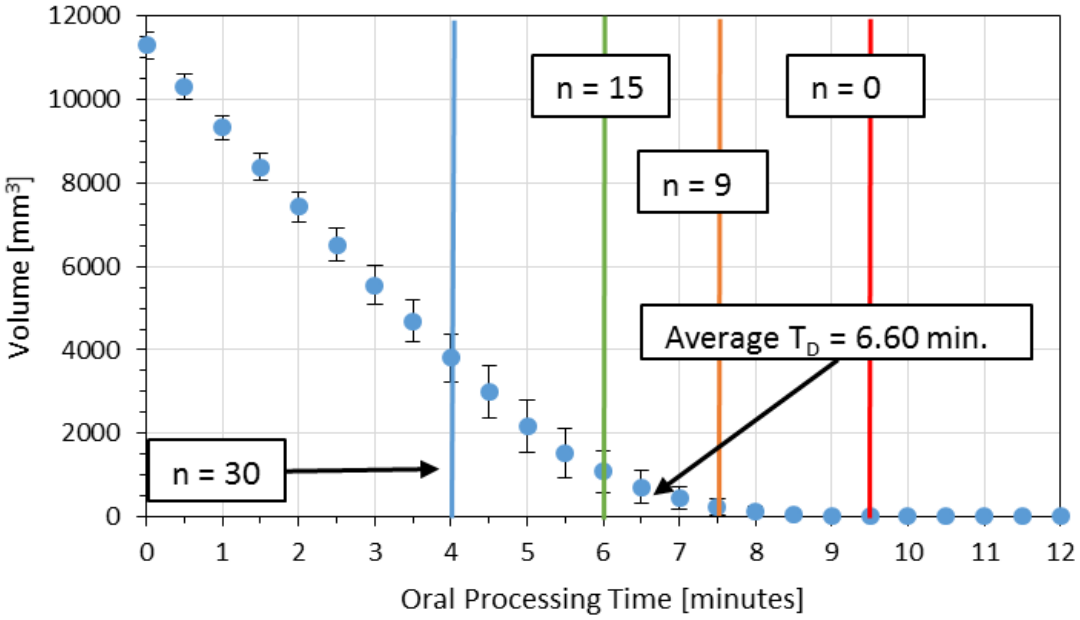
Figure 3.5 (c) shows the average saliva production at each sample point. The plot shows a rapid increase in salivation from the Mechanical Salivation Test average to a peak value over 2.5 grams of saliva (over 5.0 grams per minute) and a gradual decrease as oral processing continues. There was an observed decrease in total saliva content as the lozenge becomes smaller and the number of subjects reaching T_D increases. Shortly after T_D was met, there is no biological or mechanical stimulation to increase salivation, allowing the production rate to equilibrate to the same rate from the Salivation Test upon observation. There was also a trend showing decreased saliva production following the same decreased surface area trend of the solid lozenge.

3.3.2.3 Calculated Surface Area, Volume, and Mass Flux

Image analysis of the governing dimensions and assessment in the Autodesk Inventor® program yielded an estimated surface area and volume for each lozenge sample. Calculated surface area at each time point was important to the dissolved mass flux calculation discussed in Equation 3.2. Dissolved mass flux calculations allow for decay rate evaluation and comparisons regardless of processing time between sampling or varying surface area values. The average solid lozenge surface area and volume were plotted with respect to oral processing time in Figure 3.6 (a) and (b), respectively. Again, four vertical lines were included to demonstrate the relative change of the number of tests with solid lozenge remaining as oral processing time increases. Error bars denote the 95% confidence intervals for each measurement.



(a)

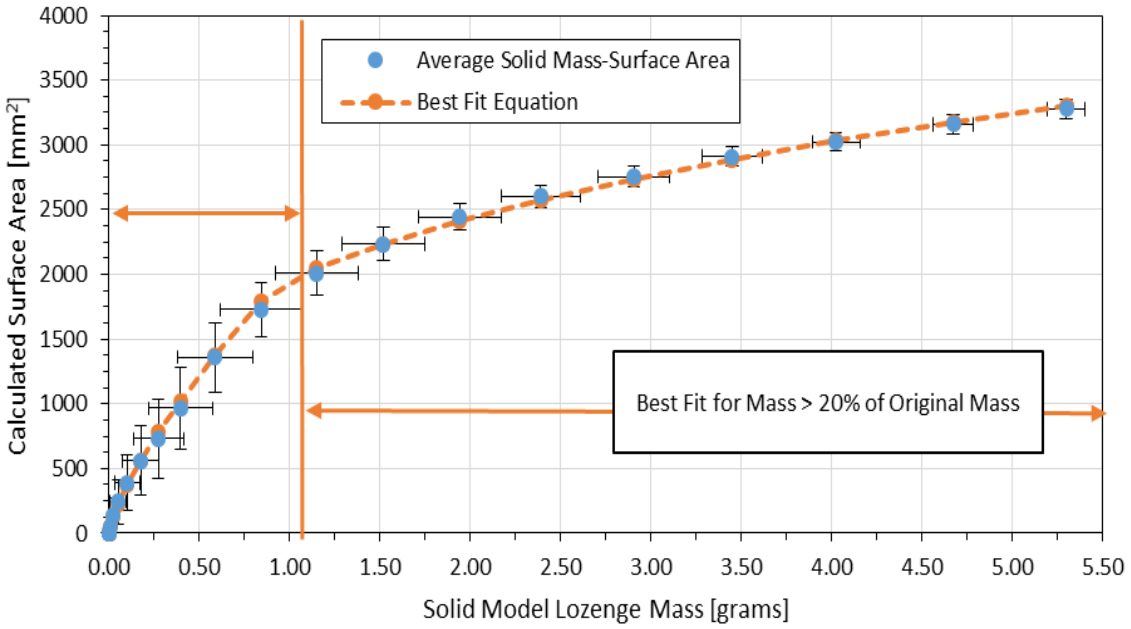


(b)

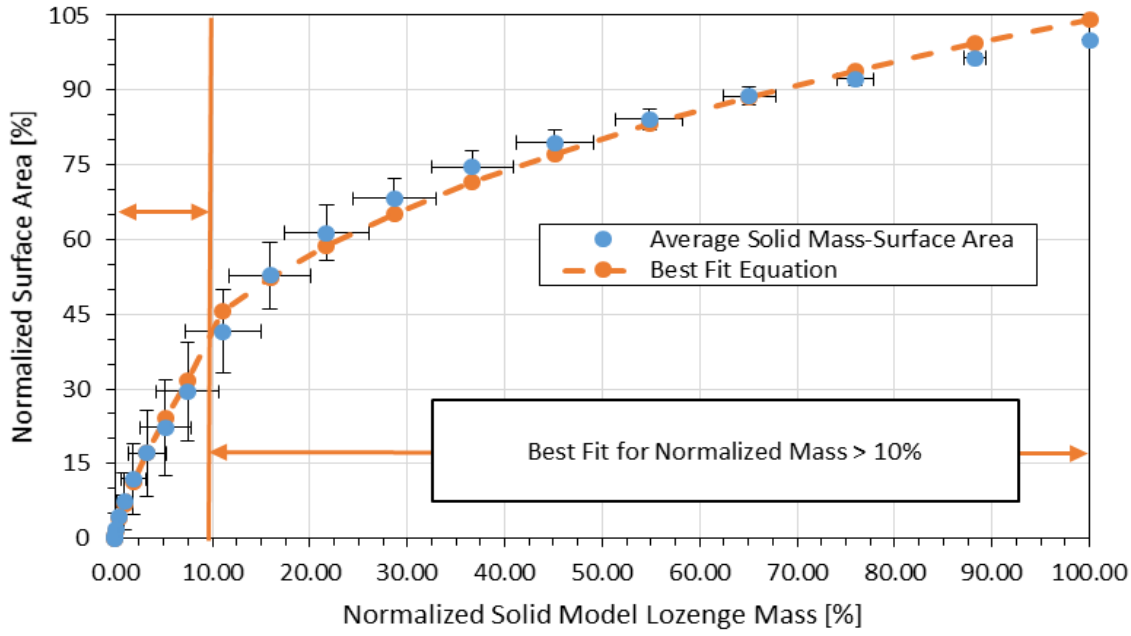
Figure 3.6: The surface area (a) and the volume (b) of the solid lozenge decreases as the mass of the lozenge decreases during oral processing. At the 9.5 minute time point, all lozenges have been completely processed.

The average surface area error bar range near the average T_D shows how the decrease in the number of solid lozenges in each of the trials may affect the average surface area, where remaining lozenges increase the average surface area. As expected, the volume data shown in Figure 3.6 (b) behaved similarly to the solid mass data. This outcome was reasonable seeing as the relative density of the lozenge is maintained throughout oral processing: changes in the volume would be proportional to changes in the solid mass to maintain the same density.

A plot was constructed to relate both the solid lozenge mass and surface area, and the normalized mass and normalized surface area of lozenges during oral processing, shown as Figures 3.6 (a) and (b), respectively. Each plot was fitted with two separate power law equations to properly describe the relationship, due to the error concerning the surface area estimation of lozenges near complete decay conditions. Two equations were necessary to describe the relative decay of the governing dimensions with respect to oral processing time. Lozenge breakdown was dominated by height loss for the majority of oral processing, until a critical height was achieved where the round, ellipsoidal shape of the lozenge started to drastically change and influence the surface area. This shape change occurs during oral processing when the lozenge has decayed to less than 20% of its original mass in Figure 3.7 (a) and less than 10% normalized mass in Figure 3.7 (b). Table 3.3 provides a simplified presentation of the relevant power law constant for the lozenge mass – surface area relationships.



(a)



(b)

Figure 3.7: (a) Solid lozenge mass may be used to predict the lozenge surface area through the relationships shown. (b) Normalized solid lozenge mass may be used to predict the normalized lozenge surface area.

Table 3.3: Power law model constants that provide the best fit parameters to relate model lozenge mass to surface area

Best Fit Model	Viable Range [Mass or % Normalized Mass]	Power Law Constant [unitless]	Power Law Coefficient	Power Law Coefficient Units	R^2
Solid Lozenge Mass - Surface Area Behavior [Figure 3.7(a)]	Mass > 20% of Starting Mass [grams]	0.3145	1957	$mm^2/grams^{0.3145}$	0.9962
	Mass < 20% of Starting Mass [grams]	0.7391	2027	$mm^2/grams^{0.7391}$	0.9969
Normalized Solid Lozenge Mass - Normalized Surface Area [Figure 3.7(b)]	Normalized Mass > 10%	0.3754	18.49	Normalized Surface Area Percent/ (Normalized Mass Percent)$^{0.3754}$	0.9755
	Normalized Mass < 10%	0.7433	7.099	Normalized Surface Area Percent/ (Normalized Mass Percent)$^{0.7433}$	0.9956

The relationships between the solid lozenge mass and surface area during oral processing were useful for estimating the approximate surface area of the lozenges during oral processing in the Unstructured Tests. The best-fit equations are included in each plot, along with the degree of fit. Horizontal error bars represent the 95% confidence intervals of the average solid lozenge mass or normalized average solid lozenge mass in Figures 3.6 (a) and (b), respectively. The vertical error bars represent the 95% confidence intervals of the average solid lozenge surface area or normalized average solid lozenge surface area in

Figures 3.6 (a) and (b), respectively. Error in surface area measurements dominates the error at low lozenge mass values while error in solid lozenge mass dominates the total error at higher mass values in the models shown.

Flux calculations were made from the estimated surface area, oral processing time between sampling, and dissolved lozenge mass in each saliva sample, and the average flux values were calculated with Equation 3.2 and plotted with respect to oral processing time in Figure 3.8. Seeing as the number of panelists with solid lozenges decreases rapidly after the four minute oral processing time point, only flux values at the four minute time point and earlier were statistically evaluated to characterize the general population oral processing behavior. After this point, the average constant flux that had been reached varies more considerably due to the decreased number of panelists with solid lozenges.

Assessment of decay prior to the four minute time point demonstrates the behavior of all panelists and tests during the majority of oral processing. Due to the variability in individual T_D for each test, it was difficult to draw complete, statistically-relevant conclusions concerning the flux behavior at oral processing times close to individual T_D values. A much larger testing base would be required to assess flux behavior at the end of oral processing. However, the analysis shown here provided insight to the average flux behavior during the early to central stages of oral processing for the model lozenge.

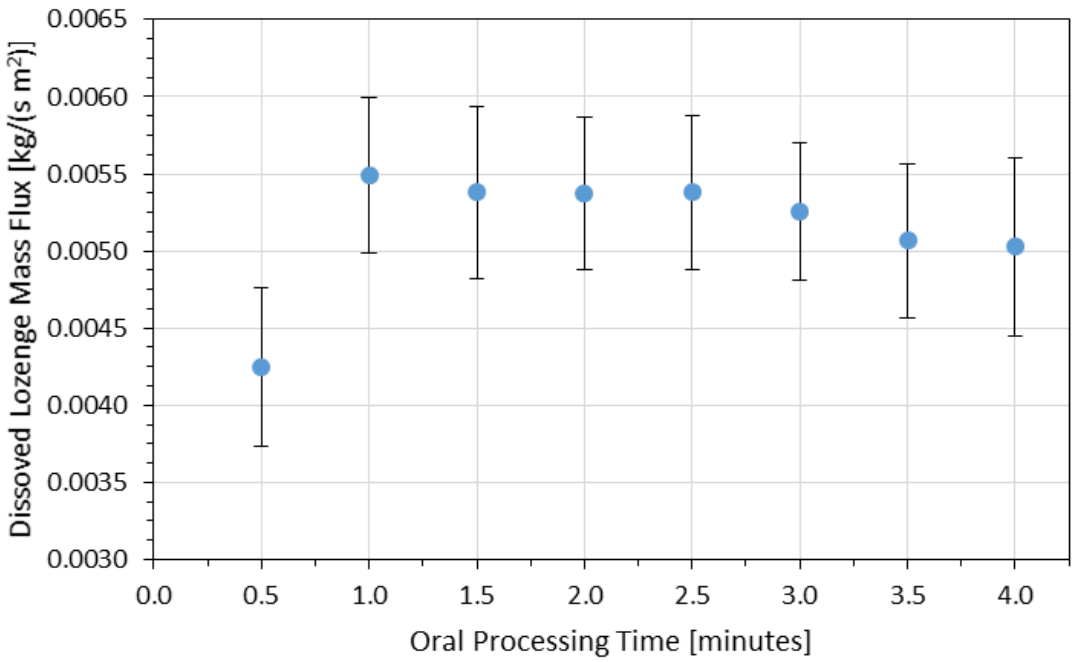


Figure 3.8: Flux values slowly increase to a peak flux value at one minute of oral processing, and then gradually decrease over the following three minutes. The first point is statistically different in value from the following seven flux values. There is no statistical difference between the flux values assessed from 1.0 to 4.0 minutes, within 95% confidence.

There is a rapid increase in the flux value during the early stages of oral processing (<1.0 minutes) to a peak value observed at the 1.0 minute sample time. A single-factor ANOVA test of all data points within the first four minutes indicated the data at the thirty second time point was not statistically the same, within 95% confidence. A second ANOVA test of only the data from the 1.0 minute time point through the 4.0 minute time point and a means difference t-test performed between each pair of mean flux values within the 0.5 and 4.0 minute time points found that all data from the 1.0 minute and 4.0 minute time point were

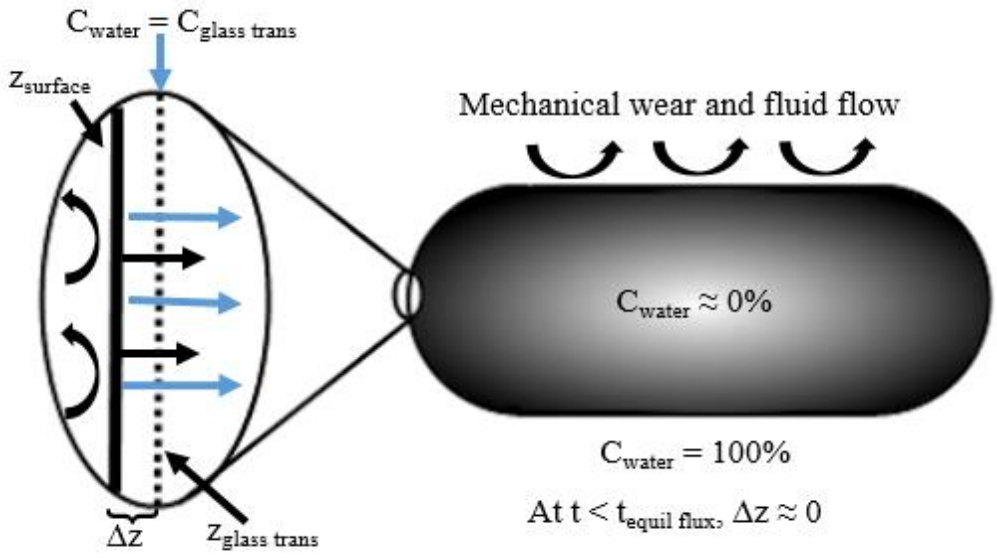
statistically equivalent, within 95% confidence. The flux value at 0.5 minute time point was found to be statistically different from all the other values, within 95% confidence. Lack of statistical difference between the flux values from the 1.0 to 4.0 minute time points allowed for an average flux value to represent the apparent average equilibrium flux reached beginning at the 1.0 minute time point. The average equilibrium flux value was determined to be $5.3 \times 10^{-3} \pm 5.1 \times 10^{-4}$ kilograms dissolved lozenge per second per square meter lozenge surface area. The average value differs by 3.9% and 4.8% from the smallest and largest flux values within the range, respectively, making it a suitable approximation for the equilibrium flux regime.

3.3.2.4 Moving Boundary Hypothesis

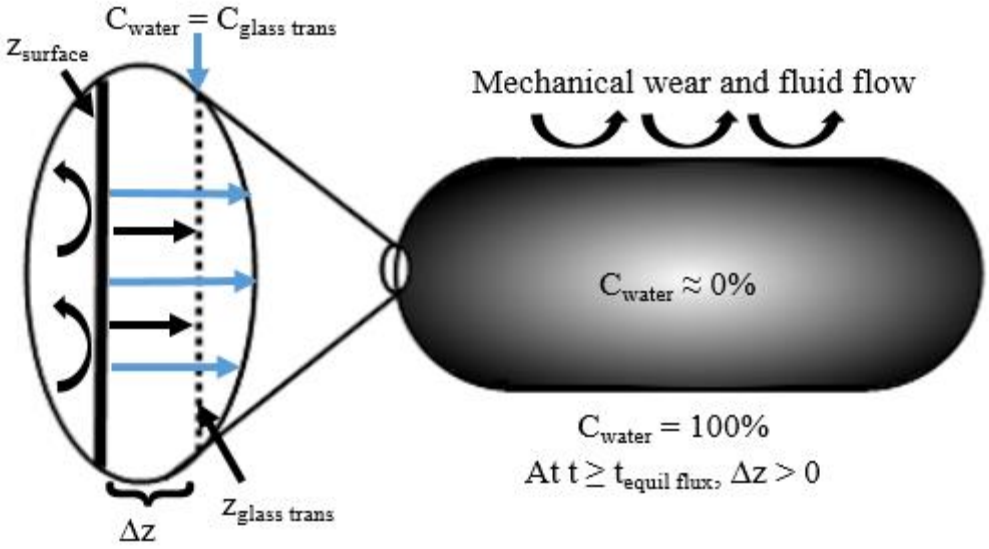
The lower flux value at the thirty second time point indicated there was a transition time required prior to attaining an equilibrium flux behavior. This transition time to equilibrium may be related to a moving water boundary condition, allowing for a phase transition to occur and dissolved mass to be swept from the surface of the lozenge. The previous chapter demonstrated the need for phase change to occur before mechanical wear or ablation, breakdown due to gradual flow related erosion can remove mass. A gradual increase in flux values to the equilibrium value likely indicate that a minimum amount of time is required for water to diffuse into the lozenge surface to achieve the phase transition from the glassy state to rubbery, preparing the mass for dissolution.

Constant equilibrium flux beginning at and beyond the 1.0 minute time point demonstrated that the rate at which the phase transition occurs was optimized to match the

mass removal rates from the lozenge surface. Beginning at this point, the moving boundary location transition rate essentially matches or exceeds the flux rate. Figure 3.9 provides a visual depiction of the expected moving boundary at different points prior to and during the equilibrium flux regime. A gradient exists during oral processing when the lozenge surface is coated with water or saliva and the center of the glassy lozenge structure remains "dry" and has not been disrupted through the migration of water. In this case, the lowest water concentration (C_{water}) exists at the geometric center of the lozenge while the surface is saturated. The critical water concentration required for glass transition moving boundary ($C_{glass\ trans}$) moves towards the center of the lozenge during oral processing as a function of diffusion. Figure 3.9 uses $z_{surface}$, $z_{glass\ trans}$, and Δz to represent the moisture concentration at the surface of the lozenge, at the distance into the lozenge for there to be sufficient water concentration to allow a glass transition to take place, and the distance between the surface and glass transition location, respectively. The *t* and $t_{equil\ flux}$ variables represent water exposure time and time required to attain equilibrium flux behavior. Blue arrows represent the movement of water while the black errors represent the movement of the lozenge surface. In Figure 3.9 (a) the moving boundary rate is closely matched by the surface wear rate (represented by mass flux in analyses) early during oral processing. In Figure 3.9 (b) the moving boundary progression rate matches or exceeds the flux rate during the equilibrium flux regime. It is assumed that Δz becomes constant when the flux is constant, but that must be confirmed with other testing, such as Magnetic Resonance Imaging.



(a)



(b)

Figure 3.9: The predicted moving boundary model for water during the (a) early oral processing times and (b) after the equilibrium flux regime is achieved.

Additional testing is required to assess the moving water boundary layer or bulk phase change to confirm this proposition. However, it is worthwhile to note that the average equilibrium flux values vary between $3.1 \times 10^{-3} \pm 6.4 \times 10^{-4}$ and $6.9 \times 10^{-3} \pm 5.2 \times 10^{-4}$ kilograms dissolved lozenge mass per second per square meter lozenge surface area. This variability in equilibrium flux values may be due to differences between each panelist's mechanical manipulation behavior or the degree of flow-induced ablation from salivation. Additional assessment of the effect of total produced free saliva is necessary to ascertain the true flux behavior with respect to relative salivation rates.

3.3.3 Unstructured Test

3.3.3.1 Oral Processing Time to Complete Decay

The oral processing time to complete decay (T_D) was assessed for each of the thirty trials and used as a preliminary method to determine the normal distribution of the datasets. A plot was constructed to demonstrate the range of times and relative frequency, with the accumulative percentage of subjects that had reached T_D as a function of total oral processing time. The sinusoidal shape to the curve shown in Figure 3.10 suggests that there was a normal appearing distribution of times to complete dissolution for all the Unstructured Test data. The proximity of the average time and median time to complete dissolution of 8.2 and 7.6 minutes, respectively, demonstrate normal-like distribution, albeit with skewing to the right. This observation is important because the normal distribution improves the relevance and application of findings to larger human populations. Assessment of the Full Test and

Unstructured T_D values with ANOVA demonstrate that the average T_D values were significantly different within 95% confidence.

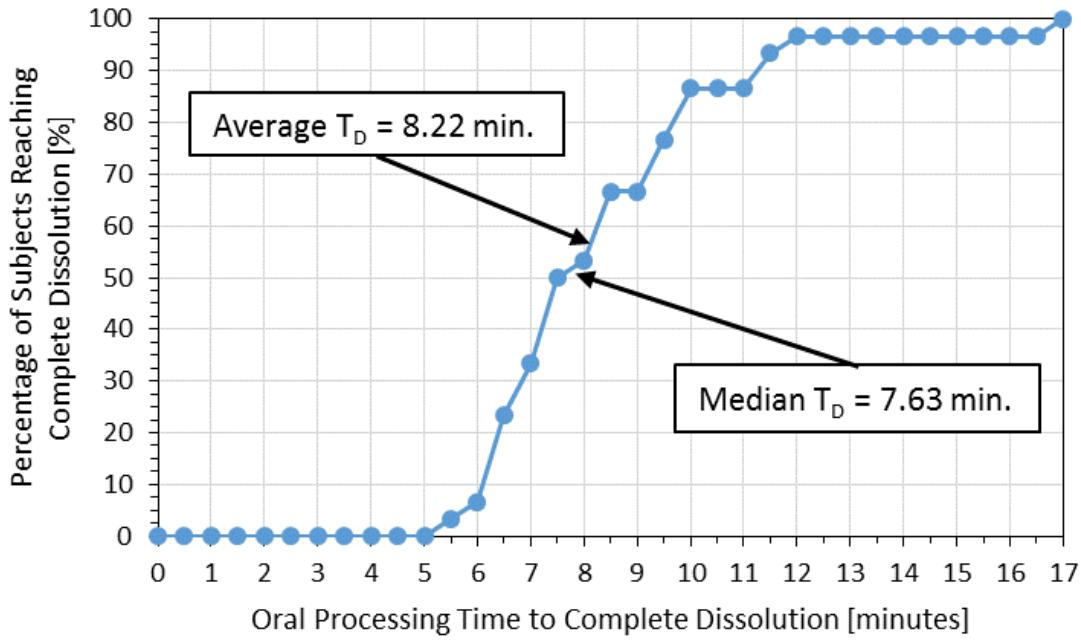


Figure 3.10: The oral processing time range, median, and average time to complete decay (T_D) for complete dissolution in all thirty tests in the Unstructured Test.

3.3.3.2 Expectoration Frequency

The Unstructured Test gave panelists the option to expectorate freely whenever they experienced an urge to swallow during oral processing, thereby representing the conditions closest to natural oral processing. Average dissolved mass and saliva mass values, however, were no longer relegated to single time points for assessment, making analysis more fraught

with error. Plotting the average oral processing time of each sample with respect to the expectoration sample number produced an average expectoration frequency, which was assumed to be reflective of the average natural swallowing frequency during oral processing.

Understanding the frequency of swallowing during oral processing may provide insight to oral processing behaviors, including salivation rates and average mechanical manipulation limitations. Figure 3.11 plots the average oral processing time for each expectoration sample produced by the panelists. The slope of the trend line represents the average time between expectorations, or the expectoration frequency. It is assumed that the average expectoration frequency provided may be related to the average swallow frequency during oral processing. It is important to note that the number of panelists with solid lozenges remaining decrease after the 5.0 minute time point relatively quickly. Three vertical lines were included to demonstrate the relative decrease in the number of tests with solid lozenge remaining with respect to oral processing time. The error bars represent the 95% confidence intervals for each sample number's average oral processing time.

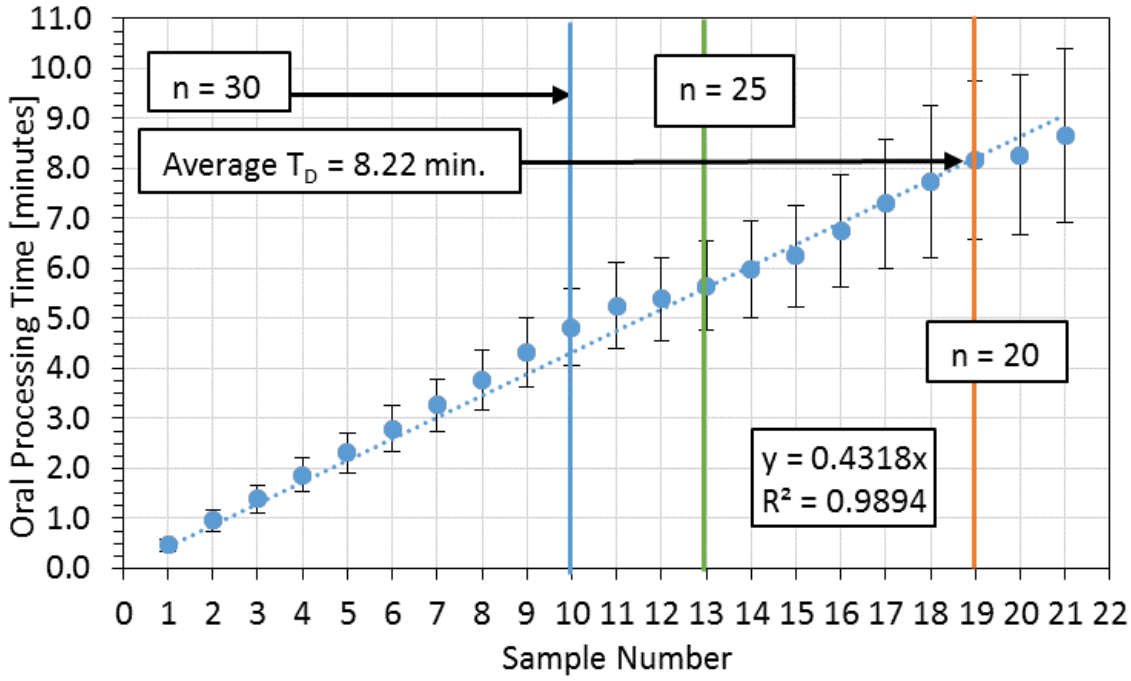
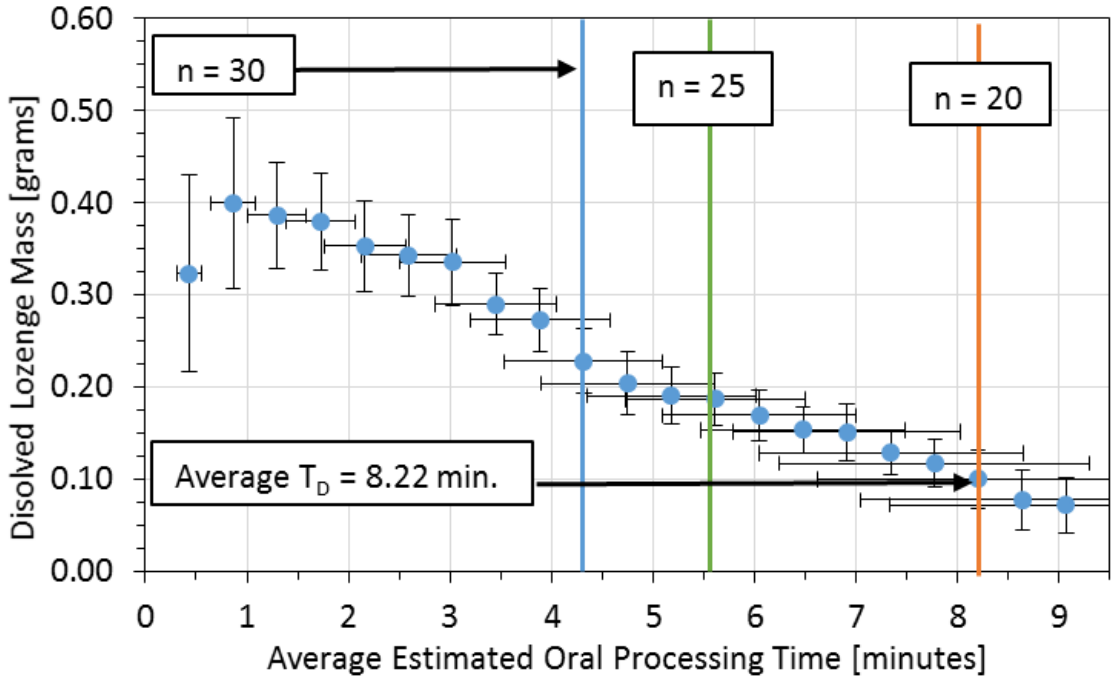


Figure 3.11: The average expectoration rate during the oral processing of the model lozenge is relatively consistent at 0.43 minutes per sample.

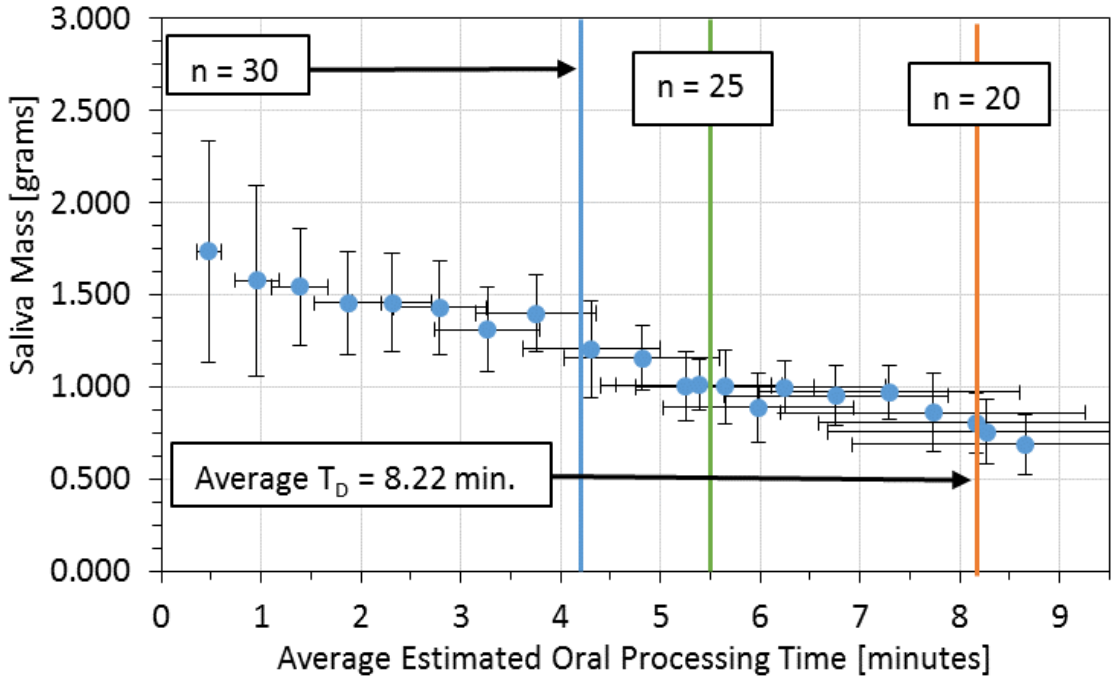
Figure 3.11 demonstrates that the average expectoration rate for all panelists was relatively consistent at 25 second intervals between expectoration. Although slightly more frequent than the controlled sampling time of the Full Test, this rate suggests that findings from the Full Test may have more relevance when determining the average healthy, adult human behavior during oral processing of the model lozenge than previously predicted. The error bars also increased in range as the number of samples increased. This result may be related to the relative lozenge decay rate near the time to complete decay.

3.3.3.3 Collected Dissolved Mass and Saliva Mass Data

The average dissolved lozenge mass and saliva mass data were collected at each sampling interval to assess the relative breakdown rates of the model lozenge during oral processing of the Unstructured Test. The average values from all thirty datasets at each sample point was plotted with respect to the average sample oral processing time in Figure 3.12 (a) and (b) to demonstrate the decay and salivation trends in conditions with the flexible timing of data collection of the Unstructured Test. Three vertical lines demonstrate the relative change of the number of tests with solid lozenge remaining as oral processing time increases. Horizontal error bars denote the 95% confidence intervals for each sample time measurement, while vertical error bars denote the 95% confidence intervals for each the dissolved lozenge mass or saliva mass at each sample collection.



(a)



(b)

Figure 3.12: The average (a) dissolved lozenge mass and (b) saliva mass assessed at each time point in the Unstructured Test.

Despite differences in the numerical findings from the Unstructured Test performance and the Full Test performance, there are commonalities observed. The rapid increase of the dissolved mass in each data point to a peak value after nearly one minute of oral processing and the gradual decrease in dissolved mass with respect to oral processing time closely matches the trends observed from the Full Test data. Likewise, the saliva mass production appears to gradually decrease as oral processing continues, similar to the observed data from the Full Test. These preliminary comparisons indicate that despite the randomness in the sampling time, lozenge breakdown trends observed in the Full test using strict sample timing are similar to the data produced using natural-like sampling times. Analysis of the dissolved mass flux can be used to confirm this claim.

3.3.3.4 Estimated Mass Flux

The average solid lozenge mass at each sample time was estimated by subtracting the accumulated mass of dissolved solid recovered from the original solid mass. This calculation was an underestimation of the mass of dissolved mass and an overestimation of the solid mass due to unrecovered residual dissolved lozenge on the oral surfaces. The calculated values, nonetheless, were used to predict the average solid lozenge mass during oral processing. Each solid lozenge mass was used to estimate the surface area of the lozenge using the functions demonstrated in Figures 3.6 (a) and (b). The dissolved lozenge mass, time between samples, and the change in the lozenge's surface area were used to calculate the approximate flux values at each time point using Equation 3.2. The first eight time points shown in Figure 3.13, display similar flux trend behaviors to the Full Test, indicating that the

controlled test parameters used in the Full Test did not affect the dissolved mass flux trends observed under the Unstructured Test conditions, which were designed to mimic decay performance under natural oral processing conditions. Flux values slowly increase to a peak flux value at 1.4 minutes of oral processing, and then gradually decrease over the following three minutes. The first point is statistically different in value from the following seven flux values, while there is no statistical difference between the flux values assessed from the second to eighth time point, within 95% confidence.

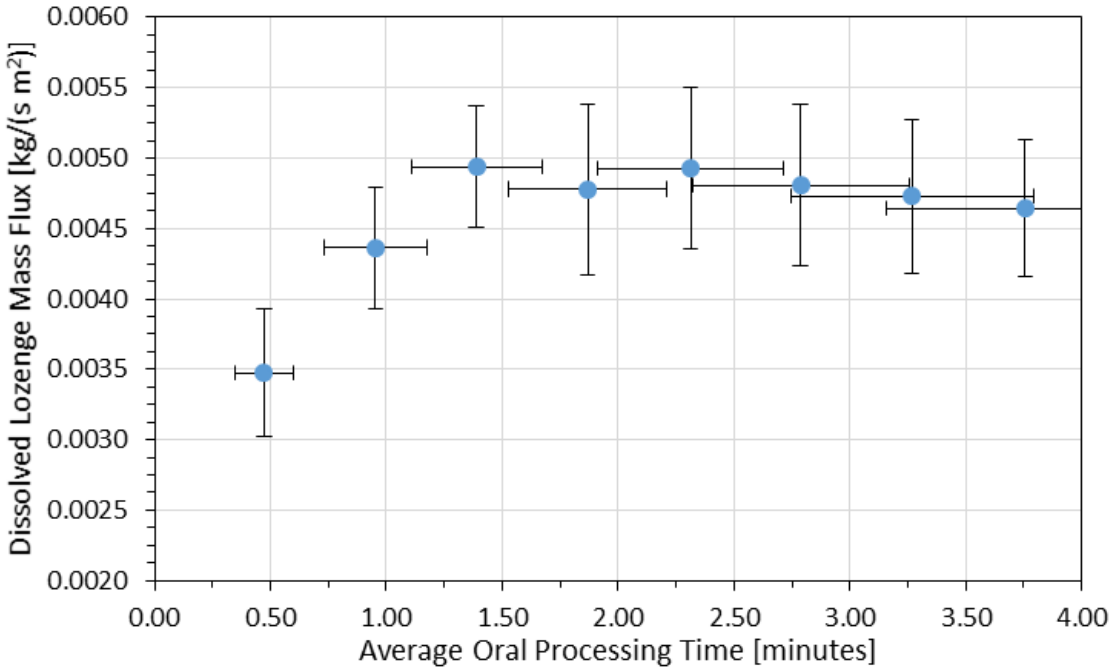


Figure 3.13: The dissolved mass flux values of the Unstructured Test plotted with respect to oral processing time.

There was a rapid increase in the flux value during the early stages of oral processing to a peak value observed at the 1.5 minute sample time. A single-factor ANOVA test of all data points within the first four minutes indicated that not all of the data was statistically the same, within 95% confidence. A second ANOVA test of only the data from the second sample time point through the eighth sample time point showed no statistical difference between the average flux value at each time point. A means difference t-test performed between each pair of average flux values within the starting 4.0 minute range confirmed this finding. All values from the 0.95 minute through the average 3.76 minute time point were found to be statistically equivalent, within 95% confidence. The flux value at 0.47 minute time point was found to be statistically different from all the other values in the evaluated test range, within 95% confidence. Since there was no statistical difference between the flux values from the second sample through the eighth sample points within 95% confidence, an average flux value was used to represent the apparent average equilibrium flux reached beginning from the 0.95 minute time point.

The average equilibrium flux value was determined to be $4.7 \times 10^{-3} \pm 5.2 \times 10^{-4}$ kilograms dissolved lozenge per second per square meter lozenge surface area. The average value differs by 4.2% and -8.0% from the largest and smallest flux values within the range, respectively, making it a reasonable estimate for the equilibrium flux regime. This calculated average equilibrium flux value was used to represent the average equilibrium dissolved mass flux value for the Unstructured Test within the first four minutes of oral processing.

The lower flux value at the 0.47 minute time point, similar to the behavior in the Full Test, indicated there was a transition time required before attaining equilibrium flux behavior. This time to equilibrium may again be related to a moving water boundary condition, introduced during the Full Test discussion and demonstrated in Figure 3.9, which allows for phase transition to occur and dissolved mass to be swept from the surface of the lozenge. The average equilibrium flux values observed in any single Unstructured Test vary between $1.5 \times 10^{-3} \pm 7.6 \times 10^{-4}$ and $6.9 \times 10^{-3} \pm 6.0 \times 10^{-4}$ kilograms dissolved lozenge mass per second per square meter lozenge surface area.

Equilibrium flux variability may be due to differences between panelist mechanical manipulation behavior or the degree of flow-induced ablation from salivation, as speculated from the Full Test data. The average equilibrium flux value of the Unstructured Test has a smaller value than the equilibrium flux value from the Full Test. This result is reasonable, seeing as the average T_D is larger in the Unstructured Test. Less mass was removed per second per lozenge surface area in the Unstructured Test, therefore more time was required to reach the average T_D. Despite differences in overall average equilibrium flux values between the Unstructured and Full Tests, both tests serve to demonstrate a common decay performance, which could be statistically related with additional panelist testing in future work.

3.3.4 Relationship between Unstructured Test and Full Test

Ascertaining meaning and relating both tests is necessary to determine the statistically relevant population behaviors during oral processing. Average flux values from the first four

minutes of oral processing in both the Unstructured and Full Tests are demonstrated in Figure 3.14. Vertical error bars signify the 95% confidence intervals of the average flux values. Horizontal error bars shown in the Unstructured Test data represent the 95% confidence intervals of the average sample time measurement. Despite the lack of perfect overlap between Unstructured Test decay data and the Full Test decay data with respect to oral processing time, both tests demonstrated similar behaviors requiring a minimum amount of oral processing time to reach the equilibrium flux value and the consistent equilibrium flux behavior previously mentioned. It is important to note that while the Unstructured Test was designed to mimic normal human oral processing conditions, assessment of the oral processing behaviors in thirty second time points in the Full Test demonstrate the same behaviors observed in the Unstructured Test.

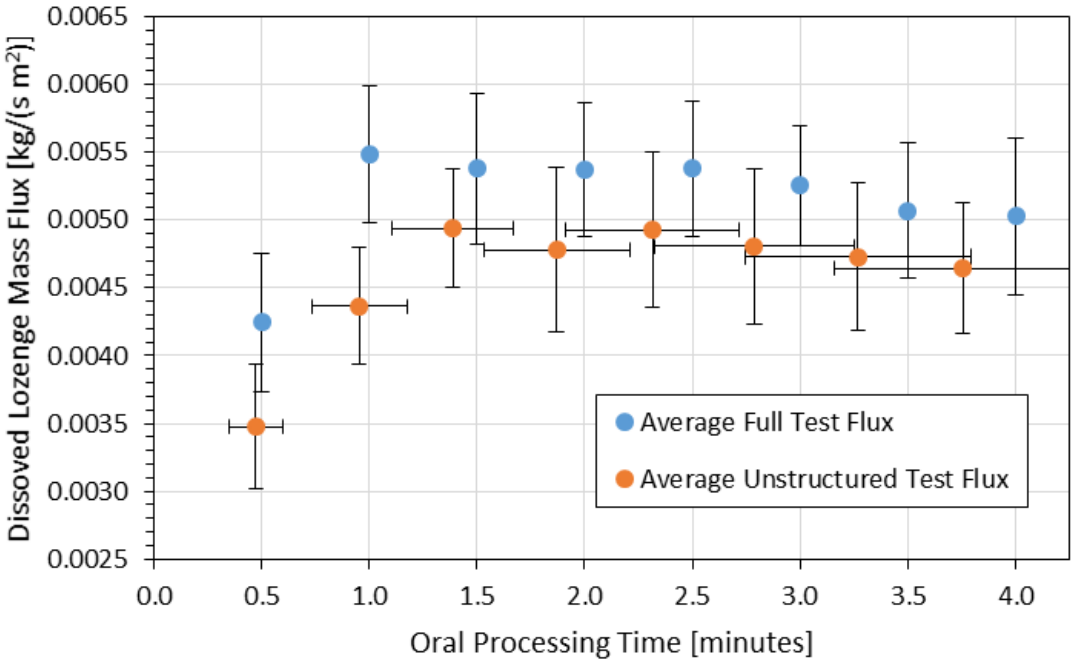


Figure 3.14: Both the average Unstructured Test and Full Test data show similar flux curve behaviors, including an average equilibrium flux and a minimum amount of time required reach equilibrium.

The mass flux in both tests gradually increased to a peak value before reaching equilibrium and maintaining levels. A means difference t-test between the corresponding average equilibrium flux values from both the Unstructured and Full Tests was performed and demonstrated that there was no difference between the equilibrium flux values in the Unstructured and Full tests within 95% confidence. Both tests showed similar trends, where the flux values reached an equilibrium level within sixty to ninety seconds of oral processing time. The differences in the equilibrium flux values and time to equilibrium may account for the differences in oral processing time required to complete dissolution. However, it is

possible that the differences may be partially due to the amount of free saliva available during oral processing or differences in average mechanical manipulation behavior.

Analysis of flux values normalized with respect to saliva mass produced in each sample was conducted for both the Unstructured and Full Tests. Figure 3.15 demonstrates the average flux per kilogram of recovered saliva in each sample with respect to oral processing time, with horizontal error bars denoting the 95% confidence intervals for each Unstructured Test average sample time measurement. No horizontal error bars were included in the Full Test data because there was no variance in oral processing time points during the Full Test. Vertical error bars denote the 95% confidence intervals for each flux calculation with respect to saliva mass recovered at each sample collection.

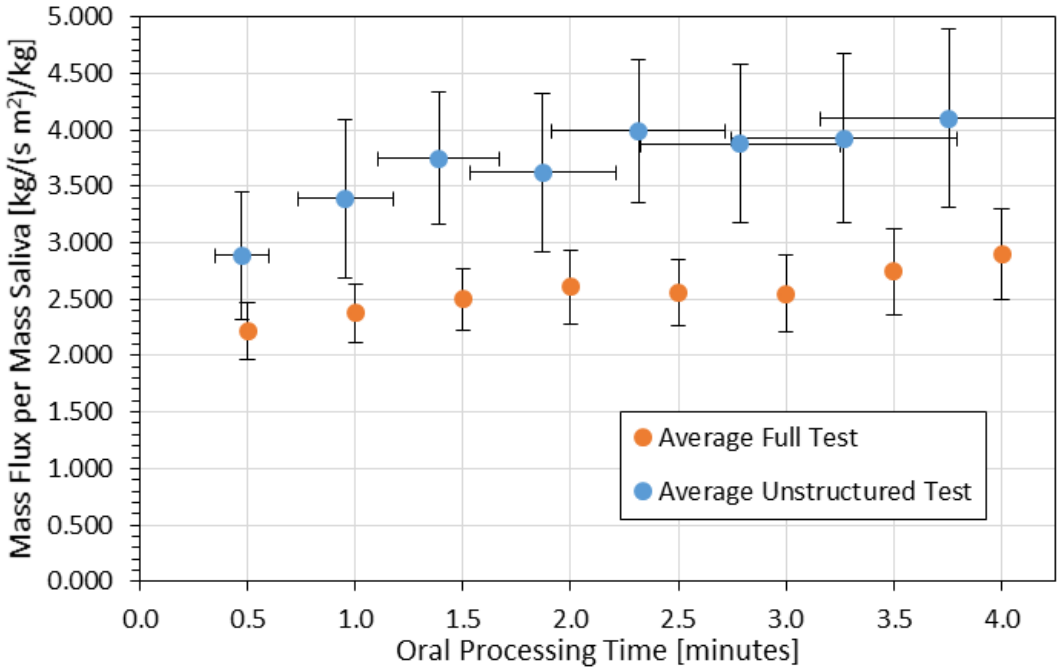


Figure 3.15: Normalizing the flux values with respect to the saliva mass produced in each sample eliminates the effect of saliva mass on the flux values with respect to oral processing time.

The normalization of the flux values with respect to saliva mass produced at each sample created a relatively flat trend for the Full Test data, correcting the lower starting flux value with respect to its lower starting saliva mass to closely match the saliva-flux behavior shown in the following seven time points. The Unstructured Test results show a slightly increasing trend, but upon analysis there was no statistical difference between all eight data points, with 95% confidence.

Figure 3.15 demonstrates that the flux was essentially constant with respect to saliva mass in the Full Test. It also shows that the average amount of collected saliva in each

sample in the Full test was larger than the average amount of saliva recovered at each time point during the Unstructured Test. This behavior was apparent because the larger Full Test flux values were over-corrected with large saliva mass samples, decreasing the saliva-flux values in comparison to the Unstructured data points where the recovered saliva mass samples tended to be lower in value.

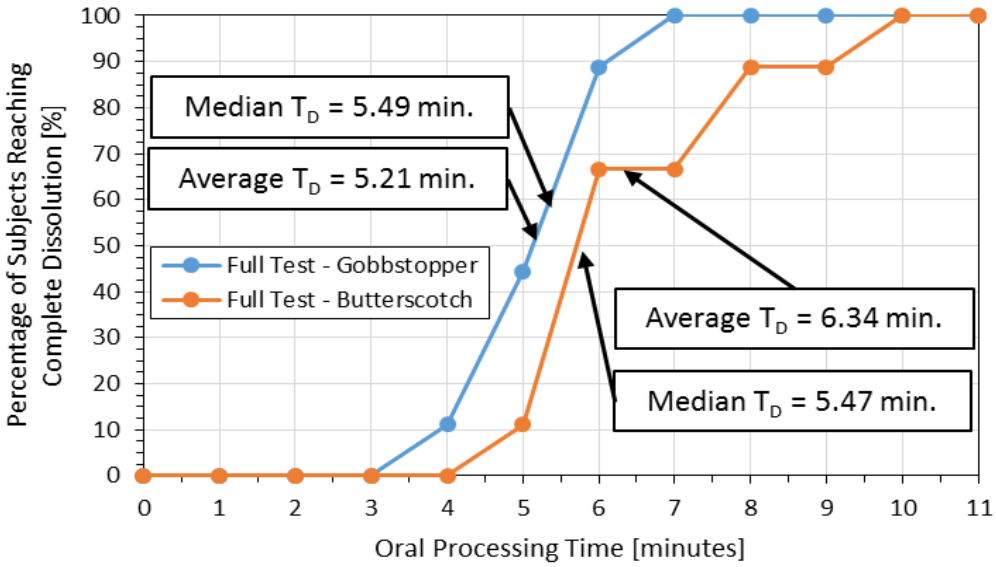
The differences in lower saliva mass values between both tests may be a contributing factor to the test decay rate differences in both test. If saliva mass had been the single factor affecting the flux values in both tests, normalization of each flux value with respect to saliva mass would have led to the overlapping of the datasets when plotted with respect to oral processing time. This supposition was obviously not the case due to the lack of overlap in the data, suggesting that differences in mechanical manipulation in addition to effects from the saliva mass may have an effect on the flux behavior. Other factors that may contribute to the differences in decay rates in both tests include differences in average mechanical manipulation, relative expectoration frequency differences, and accumulation of saliva during the Full Test during non-oral processing times where the lozenge was imaged and weighed.

Normalizing with respect to saliva and performing a single-factor ANOVA on the Unstructured and Full datasets yielded no significant differences between any of the initial eight time points assessed for each test. Assessment of all Unstructured and Full Test pooled data with ANOVA, however, demonstrated that there was a significant difference between the one average data set and the average values produced at each time point. ANOVA

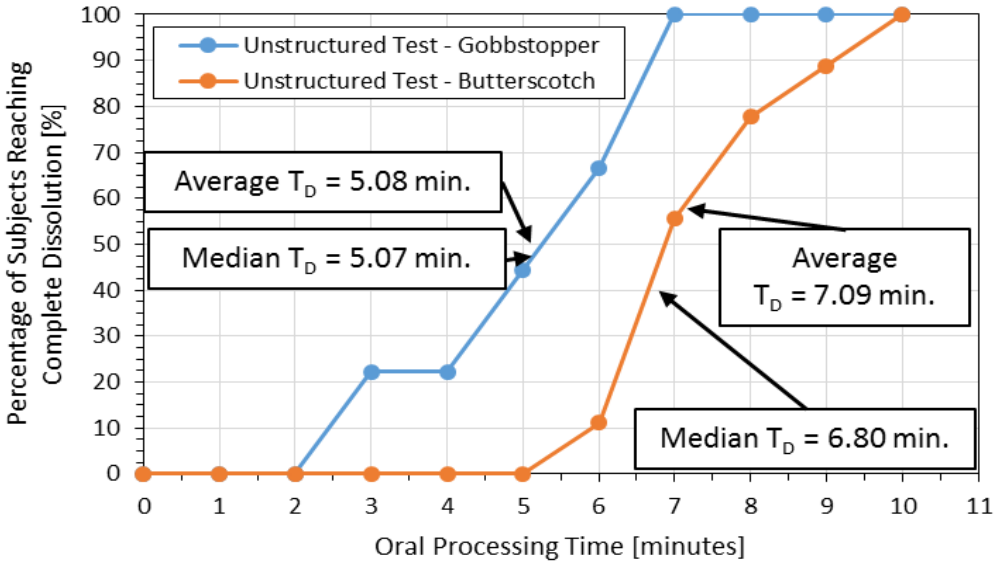
performance on the last seven data points revealed there was no significant difference, with 95% confidence, between the average values of the last seven data points. This finding suggested that the overall average value of the first data point of the pooled Unstructured and Full Test data was significantly different from the average pooled values from the following seven data points. This deviation in performance behavior was likely due to the significantly lower mass flux values of the first data points observed in the in the Full Test and Unstructured Test results, possibly due to the moving boundary condition discussed in section 3.3.2.4. The rate of the moving water boundary diffusion through the lozenge is likely a function of the lozenge composition, but investigation of mass flux for lozenges with different compositions is required to confirm the hypothesis.

3.3.5 Compositional Differences Effects Hypothesis

Complete human oral processing tests were conducted with commercially produced Gobstoppers by three panelists selected from the model lozenge decay trials. Tests were conducted in triplicate for each panelist using the same procedure from the model lozenge decay trials. The panelists also ran one more trial with the butterscotches to produce butterscotch data in triplicate. The oral processing time to complete decay (T_D) was assessed for each of the trials and used as a preliminary method to determine the normal distribution of the datasets. Figure 3.16 (a) and (b) was constructed to demonstrate the range of times and relative frequency the number of subjects had reached T_D as a function of total oral processing time for the Full and Unstructured Tests, respectively.



(a)



(b)

Figure 3.16: The oral processing time for complete dissolution in all Gobstopper and model butterscotch lozenge tests. The sigmoidal shape and the close proximity of the median and average time to complete decay (T_D) demonstrate normally distributed data sets. The average T_D for the Gobstopper tests occurs 0.85 and 2.0 minutes earlier than the T_D for the model lozenge tests in the Full test (a) and the Unstructured Test (b), respectively.

The sinusoidal shape to the curves for each lozenge type suggests the data conform to a normal distribution of time required for complete dissolution (T_D). The normal distribution of data for each lozenge T_D values indicated that enough tests were conducted to produce normalized sample performance. Gobstoppers tended to reach complete decay at a faster rate than the model Butterscotch lozenges. The difference in decay rates was likely due to several factors, including the differing ingredient compositions of each lozenge type and their relative sizes. The proximity of the Gobstopper average time and median time to complete dissolution of 5.2 and 5.5 minutes, respectively, demonstrated normal-like distribution, albeit with slight skewing to the left. This result was important because the normal behavior improves the relevance and application of findings to larger human populations.

The spherical shape of the Gobstoppers was maintained throughout oral processing, and image analysis was conducted to determine the average governing diameter for each sample time. The estimated surface area was calculated using the surface area equation for a sphere and was used to calculate the flux values shown in Figure 3.17 for the Gobstopper Full Test results.

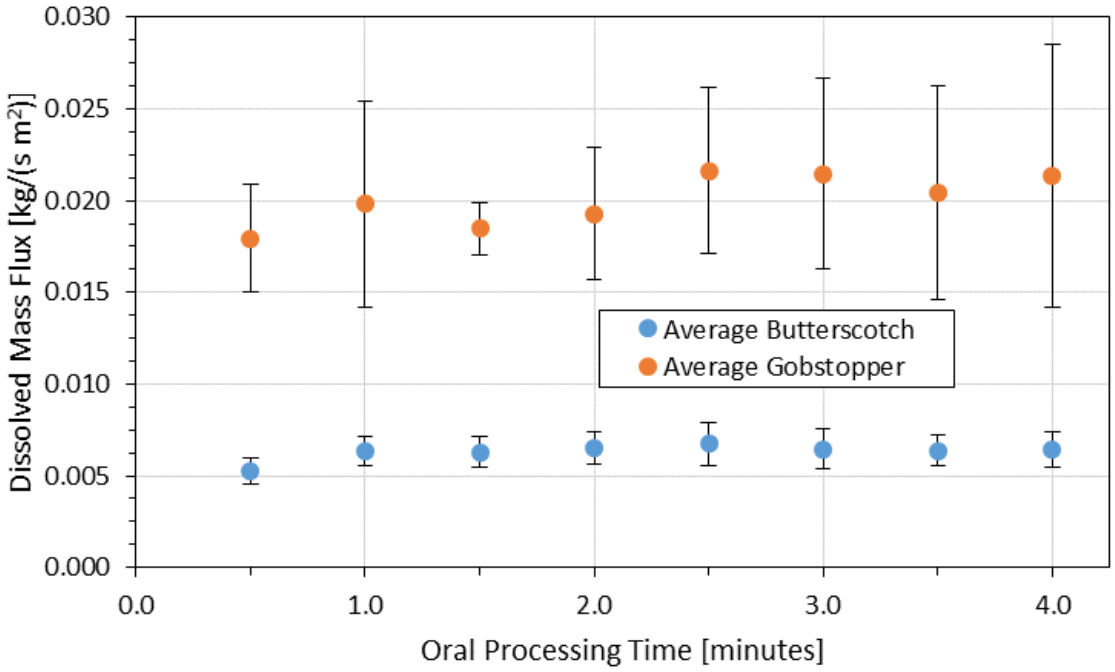


Figure 3.17: A comparison of the average dissolved mass flux values for the Gobstopper and model butterscotch with respect to oral processing time.

The same methodology used in section 3.3.3.4 was applied to estimate the solid mass and surface area of the Gobstoppers at sample points during oral processing. The calculated flux for the both the Gobstopper Unstructured and Full Tests are shown in Figure 3.18. The vertical error bars represent the 95% confidence intervals for each flux calculation at each sample collection, while the horizontal error bars represent the 95% confidence intervals for each sample time point.

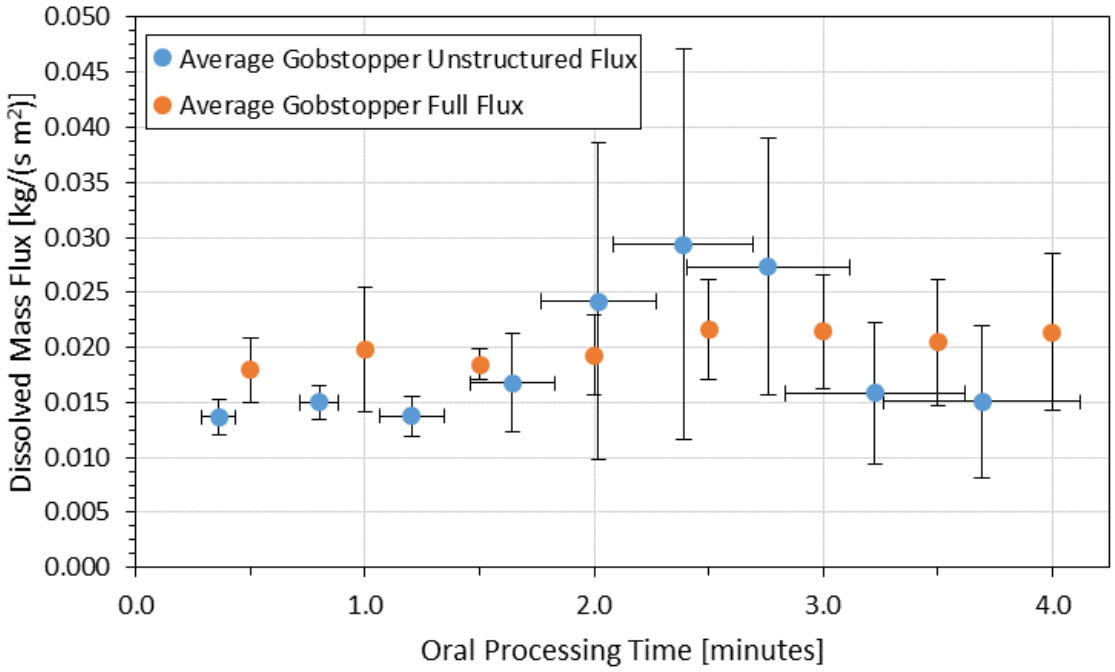


Figure 3.18: A comparison of the average dissolved mass flux values for the Gobstopper lozenges in the Unstructured Test and Full Test.

The 95% confidence intervals for the individual Unstructured data points were much larger than the confidence intervals for the Full Test. The average Unstructured Test flux values and the 95% confidence interval drastically increased between the two and three minute time points due to 22% of panelists reaching their individual T_D during this time frame. The degree of difference was likely due to the finishing of two panelists during the two to three minute oral processing time range during the Unstructured Tests. Fast decay rates may introduce error as individual test T_D are reached within the evaluation time.

A single-factor ANOVA test was conducted for the average flux value at each time point during the Full Test. It confirmed there was no statistical difference within 95%

confidence between the average flux values at each time point. Another ANOVA test of the Unstructured data showed that at least one time point's average was statistically different from the rest of the average data. This statistical finding was realistic given the obvious increase in flux between the second and third minute of oral processing of the Unstructured Test.

Interestingly, a moving boundary condition was not apparent from the mass flux results for either lozenge tested. However, this observation may be due to the measurement frequency compared to the equilibrium flux regime. A moving boundary condition may exist, but the equilibrium flux regime is achieved earlier than the first data point at thirty seconds of oral processing. Additional tests with measurements occurring more frequently would be required to confirm this proposal.

The overall implication of the Gobstopper data, from the Full Test or Unstructured Test, is that differences in formulation do have an effect on the flux and overall decay rate of lozenges during oral processing. This finding is important for the optimization of formulation designs to achieve desired lifetimes in the mouth during oral processing. It also has implications to the pharmaceutical industry, where the control of an active ingredient dosage is necessary.

3.4 Conclusion

Development of human-based models was necessary to identify the biological and physical factors that contribute to lozenge decay during oral processing. In this study, a novel methodology was developed to model the average breakdown behavior and processing

factors that contribute to the decay of model lozenges during oral processing. Assessment of the average oral processing breakdown rate by a sample population provides the means to ascertain the contribution of phase change and mechanical wear factors to breakdown throughout processing through benchtop tribology and phase change analysis tests.

Three distinct oral processing tests were used to determine the average performance of healthy adult subjects under controlled and natural-like oral processing conditions. The Salivation Test primarily served as a means to determine the range of average mechanically-stimulated salivation rates from healthy adults. The average salivation rate under mechanical stimulation was 1.2 ± 0.020 grams per minute. The large 95% confidence intervals at each measurement point indicate that humans vary in their ability to salivate, a supposition confirmed during the Full and Unstructured Tests concerning average salivation rates.

Assessment of the average model lozenge decay during the Full Test demonstrated that lozenge mass quickly decayed early during oral processing, while the surface area was maximized. Mass flux calculations confirmed that lozenge breakdown could be modeled as a function of the surface area change, dissolved mass loss, and oral processing time, regardless of starting shape or surface area. Mass flux assessment became a powerful method for determining the average breakdown performance of a model lozenge by the sample population. Average mass flux was assessed during the first four minutes of oral processing to determine decay performance during the middle of oral processing for all human subjects. Mass flux results indicated the existence of a moving boundary condition, where sufficient water diffusion must occur for phase change to occur from a stable glassy state to a rubbery

state and finally a dissolved state. After a critical oral processing time was achieved, the mass flux achieved an equilibrium state, averaging at $5.3 \times 10^{-3} \pm 5.1 \times 10^{-4}$ kilograms dissolved lozenge per second per square meter lozenge surface area.

The Unstructured Test demonstrated the range in swallowing frequencies between tests and the estimated breakdown with respect to total oral processing time and expectoration frequency. The average natural expectoration or ingestion rate was estimated at a frequency of approximately one swallow every 25 seconds during oral processing, which was slightly faster than the controlled expectoration frequency conditions of the Full Test. Furthermore, the estimated solid lozenge mass and mass flux followed similar trends observed during the Full Test, lending relevance and credibility to the findings from the Full Test. Comparison of results from both the Unstructured Test and Full Test showed there was no significant difference, within 95% confidence, between the flux values of both tests.

Mass flux assessment was also used to compare breakdown performance of lozenges with different shapes and compositions. Gobstoppers orally processed under the same testing conditions by three subjects showed a significantly different equilibrium flux value from the model lozenge, indicating that composition effects the mass flux values throughout oral processing. Results from these tests provide the framework to conduct benchtop tribology and phase change tests and decouple the contribution of each biological and physical factor to the breakdown of lozenges during oral processing.

3.5 References

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THERMODYNAMIC AND TRIBOLOGICAL WEARING ASSESSMENT OF MODEL LOZENGE

4.1 Introduction

Boiled sweets are commonly consumed worldwide in the form of candies or as medicated lozenges. Despite widespread consumption, factors that contribute to the decay of lozenges during oral processing have not been satisfactorily described. Lozenges undergo a combination of phase change and mechanical wear during oral processing that eventually results in dissolution into easily swallowed solutions (Chen 2009; Drago and others 2011). Although dissolution rates have historically been evaluated under specific fluid and agitation conditions for drug development and approval purposes, the combined role of hydration-induced phase change and mechanical wear against oral surfaces during oral processing has not been examined. This omission is partly due to the complex variability of human oral processing behavior, from a mechanical manipulation and salivation or flow behavior standpoint (Chen 2009). Tribology, the study of friction and wear between sliding surfaces, is the science to evaluate the average friction and wearing effects on boiled sweets during oral processing (Ranc and others 2006; Bongaerts and others 2007). The combination of fluid conditions observed during human trials and control of mechanical wear variables were used to assess the average effect of mechanical wear on the dissolved mass flux behaviors. The purpose of this chapter was to identify the mechanical wear conditions of sliding speed and normal force that correspond to the average lozenge dissolved mass flux behavior observed during oral processing tests. Understanding the role of mechanical wear in the

decay of lozenges allows for improved breakdown evaluation for pharmaceutical applications and design parameters for new confectionary product development.

4.1.1 Background

Humans generally consume lozenges and hard candies through gradual mastication processes, which may or may not include the action of chewing (Chen 2009; Drago and others 2011). Upon entrance into the mouth, lozenges undergo steady phase change and mechanical wearing conditions that initiate breakdown for easier consumption. Lozenges are immediately coated with moisture rich saliva (99.5% water by weight) under body temperature conditions (Bongaerts and others 2007). The high water concentration on the surface of the lozenge disrupts the glassy structure, causing the lozenge surface to undergo a transition into a rubbery state, followed by complete dissolution in saliva for swallowing (Ergun and others 2011). Lozenges undergo mechanical manipulation and wearing conditions during oral processing in addition to fluid coating and flow conditions, which is hypothesized to aid in the removal of dissolved lozenge mass from the surface of the lozenge. Despite the simplicity of the process, current evaluation methods do not account for the exact saliva flow conditions and mechanical wear contributions to dissolution during oral processing. This result creates disconnect between the tests required to determine dissolution by the FDA for drug approval and the actual dissolution behavior during oral processing.

The FDA requires extensive pharmacokinetic testing for new drugs, including evaluation of the drug's rate of liberation from the pharmaceutical formulation (Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms; United States

Pharmacopeia (USP)). The FDA evaluates the liberation rate of drugs from pharmaceutical formulations using agitated bath conditions (United States Pharmacopeia (USP)). Agilent Technologies® provides testing equipment and training for dissolution assessment of new pharmaceuticals using agitated bath conditions to model the breakdown (Agilent Technologies). Although it adheres to the testing requirements of the FDA and other international health bodies, these tests do not correspond to the conditions of oral processing, leading to the inaccuracies of the actual dissolution of lozenge formulations during oral processing (Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms). This condition is especially relevant for time-sensitive dosage products, such as nicotine lozenges used to help smokers quit smoking. Inclusion of average mechanical wear behavior observed in oral processing provides a more precise method of modeling breakdown and liberation of the active ingredients.

Estimation of the average mechanical wear effect on lozenge dissolution during oral processing requires careful observation of decay behaviors for model lozenges during oral processing and during controlled tribology or mechanical wear tests. The previous chapter demonstrated the average dissolved mass flux behavior observed during the oral processing of a model lozenge. Dissolved flux behavior observed during controlled tribology tests may be used to estimate average dissolution rates. Tribology testing conditions that yield equivalent dissolved mass flux behavior may be used to estimate the average mechanical wear contribution to lozenge dissolution during oral processing.

The main objectives of this chapter were to (1) model the contribution of fluid flow and mechanical wear parameters to overall mass decay with respect to time, and (2) determine the tribology test variables (lubricant mass, normal force, sliding speed, and time) that correspond to the average oral processing decay rates or the equivalent oral processing mass flux observed in the Full Test from the third chapter. The last objective was to (3) model the moving boundary water migration into the model lozenge under controlled lubrication and time conditions. Standard methods to identify decay during mechanical wear tests were developed to differentiate the role of mechanical wear and fluid flow in the decay of lozenges comparable to performance in the Full Tests discussed in the previous chapter.

4.2 Materials and Methods

Two separate experimental categories were conducted to address the phase change and mechanical wear effects on lozenge dissolution. The first type was designed to address decay as a function of liquid contact and its effect on phase change. These experiments, referred to as the Phase Change Experiments, address the effects of flow, agitation, and fluid volume considerations that contribute to lozenge decay rates observed in the human trials. The second category of experiments, referred to as the Tribology Experiments, use the observed lubricant masses from the human trials and controlled sliding speeds and normal loads to assess average dissolved mass flux values as a function of wearing parameters.

4.2.1 Phase Change Experiments

Three types of phase change experiments were conducted to identify the role of fluid flow in phase change, and ultimately the breakdown of lozenges. The first type of

experiment is similar to the agitated bath-condition tests required by the FDA. The second type of experiment explores the effect of single-pass flow conditions and concentration gradient effects on decay. The last experiment type identifies the effect of fluid mass under minimal agitation conditions, with or without minimal mechanical wearing. The purpose of these experiments was to demonstrate that bath-conditions or flow conditions corresponding to oral processing conditions create insufficient dissolved mass flux levels to achieve the average behavior observed during human tests.

4.2.1.1 Model Lozenge Decay in Bath Conditions

A six-hundred milliliter beaker was filled with water and preheated to 37 °C for thirty minutes. A magnetic stir bar was fixed in the beaker and used to control the relative degree of agitation in the beaker. A simple tea strainer was retrofitted to hold a single model lozenge and maintain a constant 2.5 inch height directly above the stir bar, allowing for free dissolution of a lozenge under agitated conditions. Reduction of convection at the lozenge surface due to strainer was not assessed as current testing equipment approved by the FDA to evaluate dissolution include a strainer-type basket to hold the sample which would likely have similar reduction in flow (Agilent Technologies). It was assumed that the water volume was sufficiently large enough to prevent thermodynamic equilibrium from affecting the kinetics of dissolution, as the dissolved mass concentration never exceeded 0.8% concentration even at completion of decay.

A pre-weighed and imaged model lozenge was placed in the tea strainer and was observed in three minute intervals. At the end of each interval the lozenge was removed,

gently blotted with a Kim Wipe® to remove excess liquid, weighed, and imaged for surface area analysis. It was then returned to the system to continue decay assessment in three minute intervals until the lozenge had visually dissolved. Time to complete decay was recorded, and the dissolved lozenge mass flux was calculated from the solid lozenge mass loss and the surface area change for each interval. Three treatments were designed to assess breakdown under stir bar rotational speeds of 0 (natural convection), 240 RPM, and 480 RPM. Tests were performed in triplicate for each treatment. This test was designed to mimic the tests already required by the FDA for drug approval purposes. Results were assessed using Statistical Analysis Software (SAS Institute, Inc., Cary, North Carolina) for Analysis of Variance, and general linear models to determine the significance of the variables (rotational speed, time) and any interaction effects.

4.2.1.2 Model Lozenge Decay in Flow Conditions

The purpose of this experiment was to assess the contribution of constant water flow and the effect of dissolved lozenge concentration in stock solution on the overall dissolution of model lozenges. The average maximum and minimum salivation flow rates were assessed during the Full Test during the first four minutes of the human tests, discussed in the third chapter. The maximum and minimum dissolved mass concentrations were also identified from the Full Test. An added 10% safety factor was applied to the maximum and minimum flow rates and concentrations evaluated from the Full Test data as a simple precaution to account for variation in flow rate and decay that occurs. Four treatments were designed using two stock solutions of different dissolved lozenge mass concentrations from the safety

factor-adjusted Full Test average maximum and minimum concentrations (0% and 32% by mass) and two different flow rates (0.5 and 5.0 grams per minute). Individual treatments were organized by their relative concentration and flow rate, where LC and HC denote low concentration and high concentration and LF and HF denote low and high flow rates.

A preliminary assessment was used to determine appropriate sampling frequencies. All trials except for the low concentration – high flow rate (LCHF) treatment were assessed in ten minute intervals, due to the slow decay rate. The LCHF treatment decayed at a faster rate, requiring higher frequency assessment in four minute intervals. A simple peristaltic pump was used to pump preheated water at 37 °C over a single pre-weighed and imaged model lozenge in two minute intervals. Lozenges were blotted with a Kim Wipe® to remove any free liquid, weighed, and imaged for surface area assessment at the end of each interval. The lozenge underwent continued flow intervals until the lozenge was completely dissolved upon visual assessment. The total flow time to complete dissolution was recorded, and the dissolved mass flux values were determined for each interval. All tests were performed in triplicate. Both water and a thirty-five percent dissolved lozenge stock solution were pumped over model lozenges to determine any kinetic limitations to dissolution as a function of dissolved content in lubricant.

Unfortunately, due to the low flow rates of water over the surface of the model lozenges, the lozenges did not decay evenly, making image analysis ineffective for estimating the surface area due to the degree of surface pocketing and uneven decay. Therefore, only mass values and approximate surface area values derived from the oral

processing relationships demonstrated in Figure 3.7 were used to estimate the surface area of the lozenge at the end of each interval. These surface area estimations were used in determining the dissolved mass flux at the end of each interval. Results were assessed using SAS software for Analysis of Variance to determine the significance of the variables (rotational speed, time) and any interaction effects. Assessment was conducted for simple effects using Tukey's pairwise differences and main effects using post-hoc Tukey's Honestly Significant Difference Test. Means difference t-tests were performed at each time point between treatments to determine if results from each treatment were significantly different. Each treatment was also assessed with one way-ANOVA to determine the consistency of data from the test.

4.2.1.3 Model Lozenge Decay in Minimal Volume and Agitation Conditions

Eighteen separate polypropylene one ounce cups were pre-weighed, filled with the treatment water mass, and arranged in a water bath for thirty minutes to adjust to 37 °C. Then, individual model lozenge was weighed and imaged for surface area analysis. The lozenge was placed into a cup and flipped once for even water coating. Even coating was necessary to allow for equal exposure to the water and even decay along the lozenge surface. The lozenge was then left undisturbed for fifteen seconds in contact with the water before being flipped to expose the other side to the water for an un-agitated, additional fifteen seconds. The lozenge was removed and, depending on the treatment, gently blotted with a pre-weighed Kim Wipe® to remove excess free liquid, or gently shaken with pliers to remove free liquid. The sample lozenge was then weighed and imaged before undergoing

the same treatment with a fresh cup. The procedure continued for each thirty second test for all eighteen cups for a total of nine minutes of total water contact time.

Cups with dissolved lozenge mass were weighed and assessed for dissolved lozenge mass percentage using an Anton Paar® Abbemat 550 Refractometer (Anton Paar USA Inc., Ashland, Virginia) and a standard curve of known dissolved lozenge mass concentrations versus refractive indices. Assessment of the mass percent of dissolved lozenge was multiplied by the recovered liquid mass in the cup and Kim Wipe® to determine the total dissolved mass. Dissolved lozenge mass and surface area analysis was used to determine the dissolved lozenge mass flux using Equation 3.2. Four treatments were performed in triplicate with different water masses and "wiping" combinations. The water masses tested were 2.5 grams and 1.5 grams, which included the maximum average observed saliva mass produced during the Full Test. The wiping conditions tested included the gentle blotting case and the non-blotting case, recorded as categorical variables. All four treatments were designed to determine the effect of fluid mass under minimal flow conditions and minimal mechanical removal of excess surface fluid between cups. Results were assessed using SAS software for Analysis of Variance and general linear models to determine the significance of the variables (wiping, water mass, time) and any interaction effects.

4.2.2 Tribological Wear Tests

A single type of tribological test was performed using various fluid types, fluid mass, sliding speed, and normal forces to assess model lozenge decay with respect to time. An Anton Paar® MCR 302 Rheometer (Anton Paar USA Inc, Ashland, Virginia) using a double-

ball tribometer system to conduct tribology tests. The tribopair surface consisted of a fast-set liquid rubber called Poly PT Flex 50 RTV provided by Polytek Development Corporation (Easton, Pennsylvania). This rubber, designed for use for theatrical work, was hydrophobic and maintained structure under high normal force and sliding speed conditions.

4.2.2.1 Model Lozenge Decay

Tribological wear tests were conducted using a retrofitted double ball tribometer system. For each test, two pre-weighed and imaged model lozenges were glued to laboratory tape and attached to the spindle bar at locations two centimeters from the center of the spindle. Pre-heated lubricating fluid for each treatment was pipetted and deposited on the pre-heated tribopair surface directly below the lozenges. Both deionized water and fresh, pooled saliva samples were used to model decay. Saliva was used as it was assumed that the rheological and adhesive properties may affect the dissolved mass flux differently than water, especially in the case of squeeze-flow conditions discussed in the second chapter. The spindle was lowered to contact the lubricated tribopair surface and allowed three seconds for the system to reach the preset normal force before the spindle began rotation at the preset rotational speed for a thirty second test time. Figure 4.1 shows the retrofitted tribometer system used. Two model lozenges replace the two balls for this retrofitted double-ball tribometer system. Dynamic normal force control maintains constant normal force conditions as the lozenges decrease in height due to fluid-induced dissolution and mechanical wear. The normal force was split evenly between each lozenge.

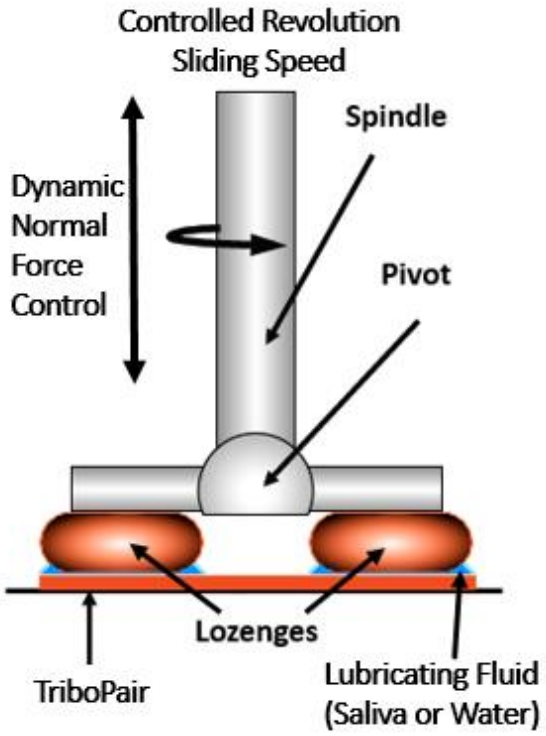

Figure 4.1: The retrofitted double-ball tribometer system used in mechanical wear tests conducted.

Normal force was maintained throughout the test, leading to a gradual spindle height loss as the solid lozenges dissolved and decreased in mass and height. The gap distance change was recorded to confirm constant mass loss from height loss. Following completion of the test, the spindle was lifted from the tribopair surface and the lozenge samples were gently blotted three times with a pre-weighed Kim Wipe® to remove any free liquid. Free liquid on the tribopair surface was collected with pre-weighed disposable pipettes into a pre-weighed cup. Residual liquid was collected in the pre-weighed Kim Wipe® previously

mentioned. The Kim Wipe®, disposable pipette, and cup of dissolved lozenge liquid were weighed to determine the recovered dissolved lozenge-lubricant mass produced during the test. Following the completion of a test, fresh lubricant was applied to the surface of the tribopair and the procedure was repeated for the test using a fresh, pre-weighed cup, Kim Wipe®, pipette with the same lozenge pair and tribopair surface.

Recovered liquid was assessed for the dissolved lozenge mass percent using an Anton Paar® Abbemat 550 Refractometer and a normal curve after each test using the procedure discussed in the second chapter. The total dissolved mass was determined by multiplying the total recovered liquid mass by the dissolved lozenge mass percentage. Each test was repeated for eight times per trial, and all trials were completed in triplicate for each treatment. The trials were designed to determine the corresponding normal load and sliding speeds that produce the same average mass flux observed at each thirty second time point during the first four minutes of oral processing in the Full Test.

Five different mechanical wear test types were conducted to evaluate the effect of sliding speed, normal force, fluid type, fluid mass, and test time on the decay of the model lozenge. All tests except for the Saliva-Water Test used water as the lubrication fluid. Tests were run at sliding speeds ranging between 0.0021 and 0.1005 meters per second and normal force values of 0.5 or 2.5 Newtons. These values were selected as the double-ball tribometer system could not adequately maintain a consistent normal force control with less than five percent deviation from the normal force set point outside of these ranges. The first test, called the Low Sliding Speed – Varying Mass Test, investigated the effects of low sliding

speeds and various fluid mass levels on the overall decay, when the fluid type was restricted to water at 37 °C and the normal force was held at 0.5 Newtons force per lozenge. Four treatments were designed using two different masses of water (1.5 and 2.5 grams) and two different sliding speeds (0.0021 and 0.0084 meters per second). The second test, called the Low Sliding Speed – Varying Force Test, investigated the effects of sliding speed and changes in normal force on the overall decay, when the fluid type was restricted to water at 37 °C and the mass of water was restricted to 2.5 grams of water. In this test, four treatments were constructed with two different sliding speeds (0.0021 and 0.0168 meters per second) and two different normal forces (0.5 and 2.5 N). The third test, called the Sliding Speed Test, investigated the effect of a variety of sliding speeds on the decay behavior, when the fluid type was restricted to water at 37 °C, mass of water was restricted to 2.5 grams, and the normal force was held at 2.5 Newtons per lozenge. Five treatments were designed to examine the breakdown differences between lozenges run at sliding speeds of 0.0021, 0.0168, 0.0670, 0.0838, and 0.1005 meters per second. The fourth test, called the Saliva – Water Test, was designed to investigate the effect of fluid type on the decay behaviors under controlled 37 °C temperature, 2.0 grams fluid, 2.5 Newton normal force, and 0.0838 meters per second sliding speed. The final test, called the High Mass – High Sliding Speed Test, investigated the effect of two different high sliding speeds and mass levels, when the conditions of fluid type were restricted to water at 37 °C and the normal force was limited to 2.5 Newtons per lozenge. This test consisted of four different treatments with two masses of water (2.0 and 2.5 grams) and two sliding speeds (0.0838 and 0.1005 meters per second).

4.2.2.2 Estimation of Lozenge Decay Parameters

Sliding speed and normal force could not be equally applied to the entire surface of the lozenge due to the limited contact area between the lozenge, lubricating fluid, and the tribopair. The lozenge, therefore, only decayed on the surface near the tribopair where lubricant was available. Testing procedure limitations also did not allow for weighing or imaging of lozenges after each thirty second interval of testing. There was also no means to determine how much each lozenge contributed to the total dissolved mass in every fluid sample collected. This means to determine the estimated dissolved mass, solid mass of the lozenge, and dissolved mass flux at the end of each thirty second test intervals, assumptions had to be made to estimate the surface area, solid mass, and contribution of each lozenge to the dissolved mass at each time point. The assumptions made were that (1) the dissolved mass contributed by each lozenge to the total dissolved mass was proportional to the total mass change of each lozenge with respect to the total mass change for both lozenges and (2) the surface area changed at a constant rate from the initial estimated contact area and the final measured contact area. It was also assumed that (3) the starting contact area for each lozenge was equivalent to half of the total lozenge starting surface area. The last assumption was made upon observation of the fluid adhering to half of the lozenge surface at the beginning of each test, regardless of the fluid mass. The relevant dissolved mass equations used for analysis of the average tribology test behaviors in the Results and Discussion section were as follows:

$$M_{Loss\ Ratio,1} = \left(\frac{M_{t=0,1} - M_{t=4,1}}{(M_{t=0,1} - M_{t=4,1}) + (M_{t=0,2} - M_{t=4,2})}\right) \qquad \text{Eq. 4.1}$$

$$M_{Loss\ Ratio,2} = 1 - M_{Loss\ Ratio,1} \quad \text{Eq. 4.2}$$

$$m_{t=n,1} = M_{Loss\ Ratio,1} m_{t=n,Total} \quad \text{Eq. 4.3}$$

$$m_{t=n,2} = M_{Loss\ Ratio,2} m_{t=n,Total} \quad \text{Eq. 4.4}$$

where $M_{Loss\ Ratio,\ 1}$ and $M_{Loss\ Ratio,\ 2}$ were the solid mass loss ratios for lozenge 1 and 2, respectively, $m_{t=n,1}$ and $m_{t=n,2}$ were the dissolved mass contributions at time *n* from lozenge 1 and 2, respectively, and $m_{t=n,Total}$ was the total dissolved mass assessed in the recovered fluid at time *n*. The mass loss ratios are unitless and the dissolved mass contributions are in units of grams. The relevant initial and final contact area equations used equations used in the Results and Discussion section were as follows:

$$A_{t=0} = 0.5 A_{t=0,total} \quad \text{Eq. 4.5}$$

$$A_{t=t_f} = A_{Tribopair} + A_{Eroded\ Side} \quad \text{Eq. 4.6}$$

where $A_{t=0}$ was the contact area at the start of the test, $A_{t=0,total}$ was the total surface area of the lozenge at the beginning of the test, $A_{t=tf}$ was the contact area at the end of the test, time t_f, $A_{Tribopair}$ was the final contact area directly on the tribopair during the test, and $A_{Eroded\ Side}$ was the final fluid contact area on the side of the lozenge not directly contacting the tribopair surface. All of these variables had units of square meters. Figure 4.2 demonstrates the approximate lozenge appearance at the start and end of each tribology test.

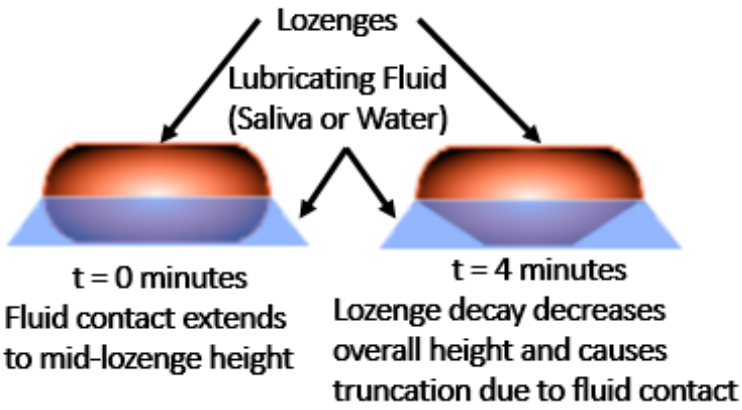

Figure 4.2: **Model lozenges undergo a truncation shape change during tribology tests as exposure to flowing fluid during the sliding process serves to assist in the breakdown.**

The estimated contact area and dissolved mass flux equations used in the Results and Discussion section were as follows:

$$\left(\frac{A_{t=t_f}-A_{t=0}}{t_f-t_0}\right)=\left(\frac{\Delta A}{\Delta t}\right)_{Avg} \quad \text{Eq. 4.7}$$

$$A_{t=0}+t_n\left(\frac{\Delta A}{\Delta t}\right)_{Avg}=A_{t=n} \quad \text{Eq. 4.8}$$

$$j_n=\frac{m_n}{(\bar{A}_{n,n-1})(\Delta t_{n,n-1})} \quad \text{Eq. 4.9}$$

where j_n was the mass flux assessed at each sample n, m_n was the dissolved mass collected in a single sample n, $\bar{A}_{n,n-1}$ was the average surface area between the current sample and the previous sample, and $\Delta t_{n,n-1}$ are the was the time difference between collection of sample n and the previous sample. Dissolved mass flux was reported in units of kilograms of dissolved lozenge mass per second per square meter of lozenge surface area. The average

solid mass and normalized solid mass equations used in the Results and Discussion section were as follows:

$$\left(\frac{M_{t=t_f}-M_{t=0}}{t_f-t_0}\right)=\left(\frac{\Delta M}{\Delta t}\right)_{Avg} \quad \text{Eq. 4.10}$$

$$M_{t=n}+t_{n+1}\left(\frac{\Delta M}{\Delta t}\right)_{Avg}=M_{t=n+1} \quad \text{Eq. 4.11}$$

$$100\%\left(\frac{M_{t=n+1}}{M_{t=0}}\right)=N_{t=n+1} \quad \text{Eq. 4.12}$$

where $M_{t=tf}$ and $M_{t=0}$ were the solid mass of the lozenge at the end of the test, t_f, and at the beginning of the test, $(\Delta M/\Delta t)_{Avg}$ was the average solid mass change per time, $M_{t=n}$ and $M_{t=n+1}$ were the solid mass values at sample *n* and *n+1*, respectively, t_{n+1} was the time of sample *n+1*, and $N_{t=n+1}$ was the normalized solid mass percent of the lozenge at sample time *n+1*. All time, solid mass, and normalized solid mass variables had units of seconds, kilograms, and no units, respectively.

The mechanical wear tests do not provide equal application of wearing conditions to the whole lozenge system. Therefore, the normalized solid mass percent of each lozenge were estimated using dissolved mass flux and normalized solid mass percent relationships observed in the Full Test. It was assumed that at equivalent times with similar dissolved mass flux values observed in both the mechanical wear tests and Full Test, the relationship would provide a reasonable estimation for the normalized solid mass percent of the lozenges from the mechanical wear tests, if the wear conditions had been applied over the entire surface of the lozenges. The relationships used in the analysis discussed in the Results and Discussion section were as follows:

$$\left(\frac{N_{t=n+1}-N_{t=n}}{j_{t=n+1}}\right)_W = \left(\frac{N_{t=n+1}-N_{t=n}}{j_{t=n+1}}\right)_F \quad \text{Eq. 4.13}$$

$$(j_{t=n+1})_W \left(\frac{N_{t=n+1}-N_{t=n}}{j_{t=n+1}}\right)_F + (N_{t=n})_W = (N_{t=n+1})_W \quad \text{Eq. 4.14}$$

where $N_{t=n}$ was the normalized solid mass percent at time *n*, $N_{t=n+1}$ was the normalized percent lozenge mass at time *n+1*, and $j_{t=n+1}$ was the dissolved mass flux in units of kilograms per second per square meter at time *n+1*. All variables subscripted with *F* and *W* were variable values from the Full Test and Mechanical Wear Tests, respectively. The estimated normalized solid mass percent for the mechanical wear tests were easily determined using the known Full Test data, mechanical wear test dissolved mass flux values, and the starting normalized solid mass percent for the mechanical wear test at one-hundred percent. These relationships serve to assess the breakdown behavior due to mechanical wear discussed in the Results and Discussion section.

4.3 Results and Discussion

4.3.1 Thermodynamic and Phase Change Tests

Results from the Phase Change Tests indicated the degree of agitation or flow and the overall fluid mass significantly affected the dissolved mass flux behavior and rate of model lozenge decay.

4.3.1.1 Model Lozenge Decay in Agitated Bath Conditions

Results indicated that dissolved mass flux values were maximized in bath conditions under high fluid agitation conditions, leading to a faster solid mass decay, and Figures 4.3 and 4.4 demonstrate the average mass flux behavior and decay of lozenges with respect to

time. As expected, fastest flow conditions produced during the 480 RPM tests produced the largest average dissolved mass flux, followed by the 240 RPM tests, and then the natural convection conditions. Natural convection, 240 RPM, and 480 RPM tests yielded average overall dissolved mass flux values of 1.9×10^{-3}, 3.2×10^{-3}, and 5.1×10^{-3} kilograms per second per square meter, respectively. These values inversely correspond to the amount of time required to reach complete dissolution, with Natural Convection, 240 RPM, and 480 RPM requiring an average time of 23, 20, and 12 minutes, respectively.

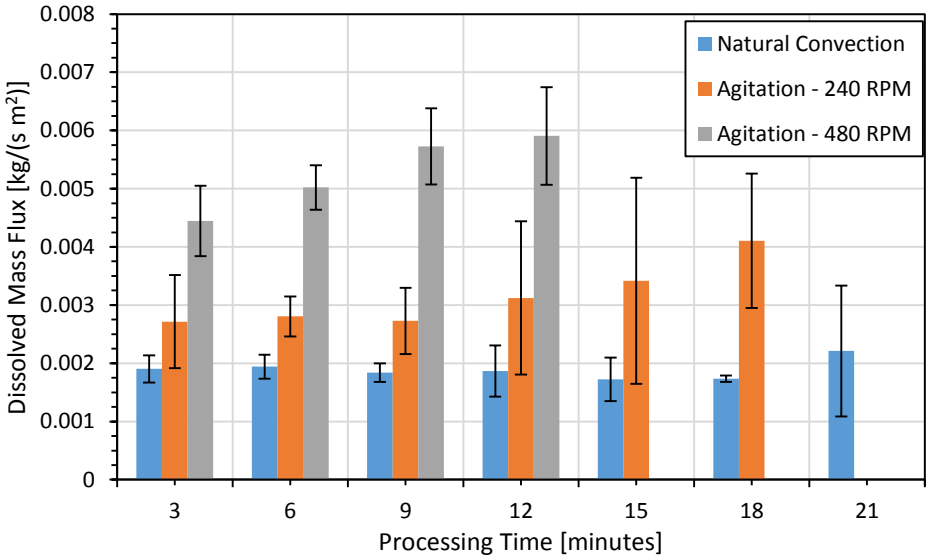

Figure 4.3: **Dissolved mass flux for the agitated bath tests demonstrate that high flux values were produced under higher relative rates of agitation. Higher flux values also corresponded to increased decay rates.**

Despite exposure to constant agitation conditions, there was a slight increase in the dissolved mass flux observed in each treatment. Statistical assessment of variable significance to the modeling of the dissolved mass flux indicated that both time and rotational speed were statistically significant variables, within 95% confidence. The interaction variable was also statistically significant, requiring analysis of the simple effects. Results indicated that the dissolved mass flux observed during the 480 RPM treatment produced statistically the same flux values at the three and six minute time points, and at the nine and twelve minute time points. The 240 RPM treatment simple effects showed that each flux value was not statistically different from the following flux value measured at the next time point. The same statistical findings are observed in the Natural Convection treatment and indicate that the gradual increase in flux values observed in Figure 4.3, is confirmed from a statistical standpoint.

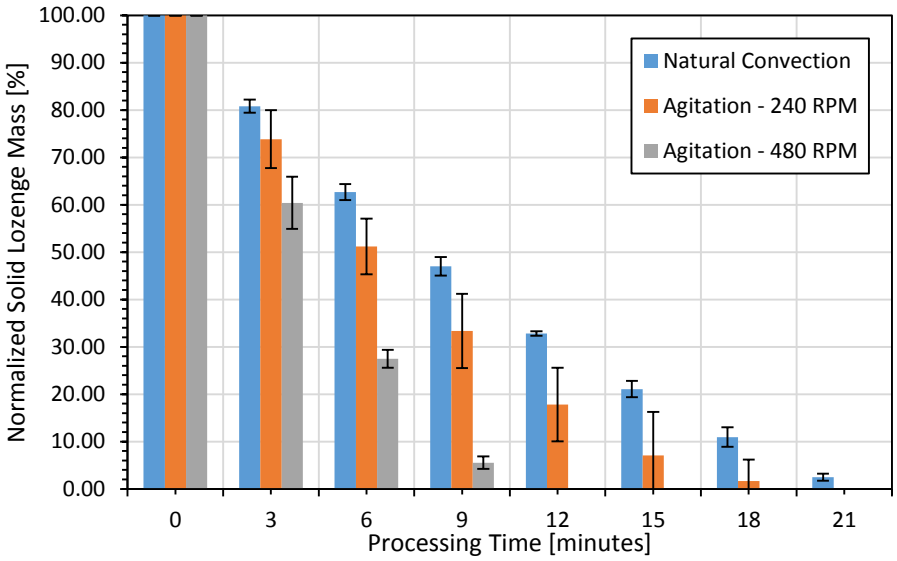

Figure 4.4: **The normalized solid lozenge mass percent for the agitated bath tests demonstrate that under faster agitation conditions, decay occurred at faster rates. Higher agitation leads to faster removal of dissolved lozenge from the surface of the lozenge, continuously renewing the surface for phase change and removal.**

None of the treatments produced a decay rate or average dissolved mass flux sufficient to achieve the same flux or decay rates observed in the Full Test. The conditions in these treatments also did not remotely correspond to the low fluid volume, high mechanical manipulation environment of oral processing, making it an inappropriate method for a true assessment for dissolution under oral processing conditions. The frequency of measurements was also low enough to make it difficult to observe the rapid increase to equilibrium flux conditions noted in the Full Test. Interestingly, there was a slight, statistically significant increase in all flux values with respect to time. This finding may suggest that the equilibrium

flux conditions had not been achieved or that the low measurement frequency decreased the ability to detect the exact equilibrium point. Future work should have assessments conducted at more frequent intervals to account for this issue.

4.3.1.2 Model Lozenge Decay in Flow Conditions

Four different flow and preliminary concentration combinations were developed to model the extreme flow and concentration conditions observed during the oral processing tests with additional safety factors. The goal of these tests, known as the Drip Tests, were to determine the effect of dissolved lozenge concentration in stock fluid on the kinetics of lozenge breakdown and the effect of extreme single-pass flow conditions on the breakdown of lozenges. Preliminary runs of all four trials indicated that both high concentration stock solution tests and the low flow rate, low concentration test could be assessed in ten minute intervals to adequately model the dissolved mass flux and solid mass change with respect to test time. The high flow rate, low concentration stock solution test, however, yielded faster decay rates and therefore required more frequent assessments of solid mass and dissolved mass flux for adequate behavior assessment. Figure 4.5 shows the average flux behavior for the HCHF, LCLF, and HCLF tests, and Figure 4.6 demonstrates the flux behavior during the LCHF test. The surface area estimation may underestimate the actual surface area, increasing the overall dissolved mass flux values. However, given the overall low magnitude of the calculated flux values, the data suggests that another variable must also be affecting flux behavior.

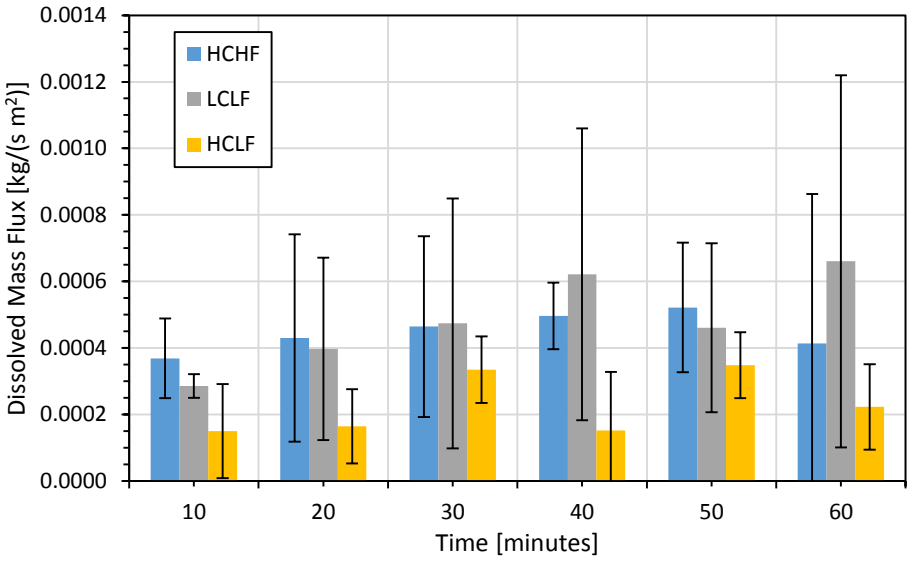

Figure 4.5: **Dissolved mass flux for the HCHF, LCLF, and HCLF Drip Test treatments with respect to processing time.**

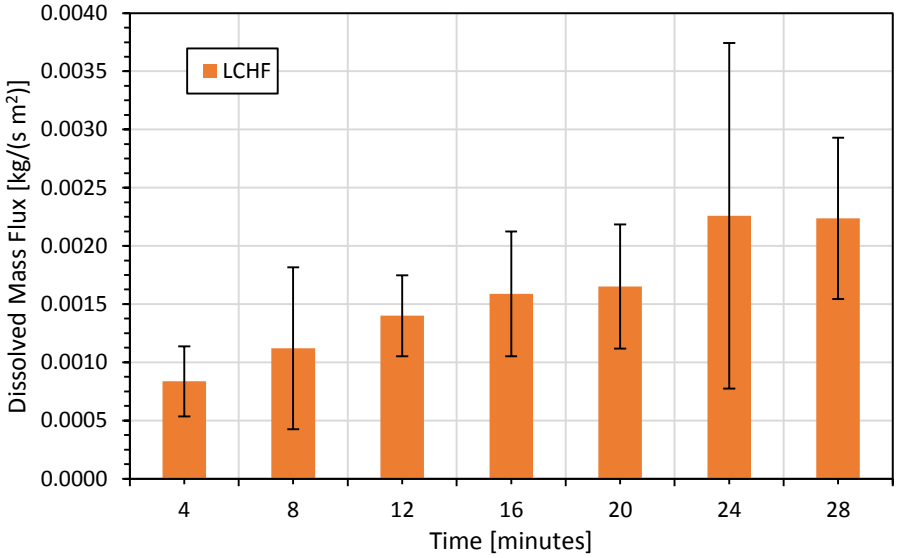

Figure 4.6: **Dissolved mass flux for the LCHF treatment demonstrate that the dissolved mass flux gradually increases with respect to time. These values are an order of magnitude larger than the values observed in the other three treatments.**

The faster flow and lower dissolved mass stock concentrations led to faster decay rates. The LCHF, LCLF, HCHF, and HCLF tests yielded average overall dissolved mass flux values of 1.6×10^{-3}, 4.5×10^{-4}, 5.1×10^{-4}, and 2.9×10^{-4} kilograms per second per square meter, respectively. These values inversely corresponded to the amount of time required to reach complete dissolution, with LCHF, LCLF, HCHF, and HCLF requiring an average time of 29, 79, 84, and 150 minutes, respectively. The longer time required to complete dissolution for the LCLF, HCHF, and HCLF treatments were realistic given that the average dissolved mass flux values were an order of magnitude lower than the values observed in the Full Test. A complete observation of the normalized lozenge mass percent for the HCHF, LCLF, and HCLF treatments is shown in Figure 4.7, while Figure 4.8 demonstrates the normalized lozenge mass percent for the LCHF treatment.

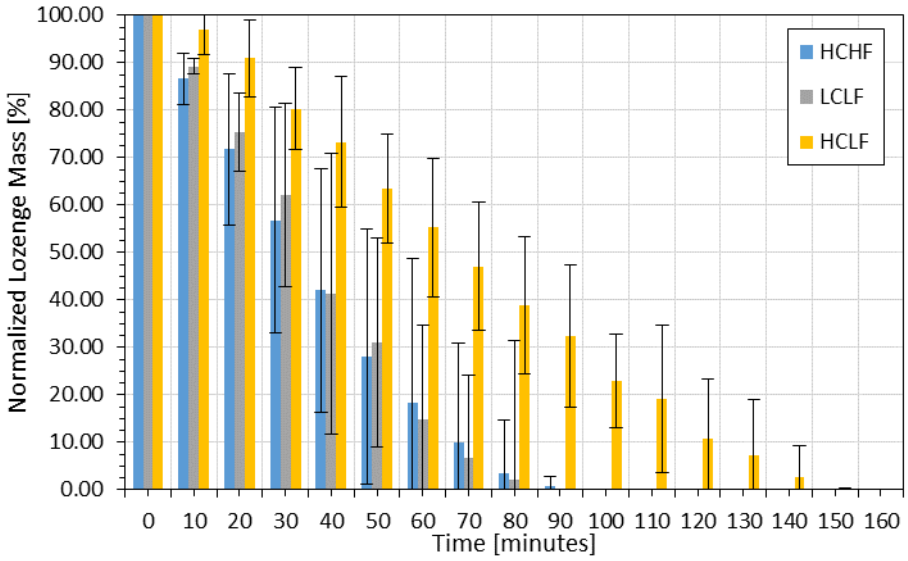

Figure 4.7: The normalized solid lozenge mass percent for the HCHF, LCLF, and HCLF Drip Test treatments with respect to processing time.

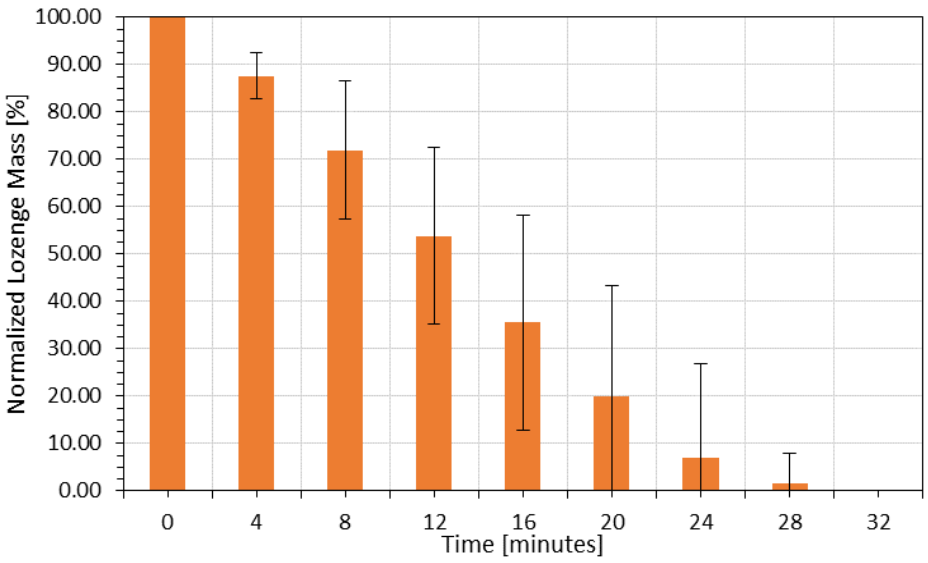

Figure 4.8: **The normalized solid lozenge mass percent for the LCHF treatment demonstrates that low concentration and high flow conditions lead to fast, relatively constant decay rates.**

The normalized solid lozenge mass percent values and rate of decay corresponded to the average dissolved mass flux behavior, as expected, with higher flux values leading to faster decay rates. Statistical analysis of the results showed that the concentration, flow rate, and time variables were statistically significant variables for modeling the system. All interaction variables were also statistically significant, within 95% confidence. Interaction effects were assessed for the concentration and flow variables and the interaction observed was quantitative, changing the magnitude of relationship between the levels of the concentration and flow factors. Time was also found to be significant due to the variability

of overall times to complete decay observed in all treatments. Therefore, it is unsurprising that the three-term interaction variable would also be statistically significant.

4.3.1.3 Model Lozenge Decay in Minimal Volume and Agitation Conditions

Wipe tests were designed to determine the effect of immersion in low water volumes under minimal agitation conditions on the overall dissolved mass flux and mass decay behavior. These experiments were developed to represent the possible extreme cases during oral processing, where the lozenge is exposed to low fluid mass under low agitation or no flow conditions. The treatments tested used fluid volumes that matched the free saliva volume conditions observed in the Full Test (2.5 grams and 1.5 grams of fluid at 1.0 and approximately at 6.0 minutes time points, respectively) described in the third chapter. The goal was to determine flux behavior under free fluid conditions observed in the Full Test, without the effects of mechanical manipulation or induced flow from mastication. Mechanical wear was briefly incorporated into the experiment in the form of gentle wiping of the lozenges at the end of each testing interval for two treatments. Although, the wiping conditions of sliding speed and normal force load were not measured, it was assumed that inclusions of any form of mechanical wear would lead to significantly higher flux values and faster decay rates. It was hypothesized that wiping would remove the concentrated surface layer of dissolved lozenge mass from the surface, thereby refreshing the surface and creating a new concentration gradient favoring dissolution. Figures 4.9, 4.10, 4.11, and 4.12 shows the findings from all treatments of this experiment, according to treatment types. Figures 4.9 and 4.10 demonstrate the effects of fluid mass under the same wiping conditions, while

Figures 4.11 and 4.12 demonstrate the effects of wiping under the controlled fluid mass conditions.

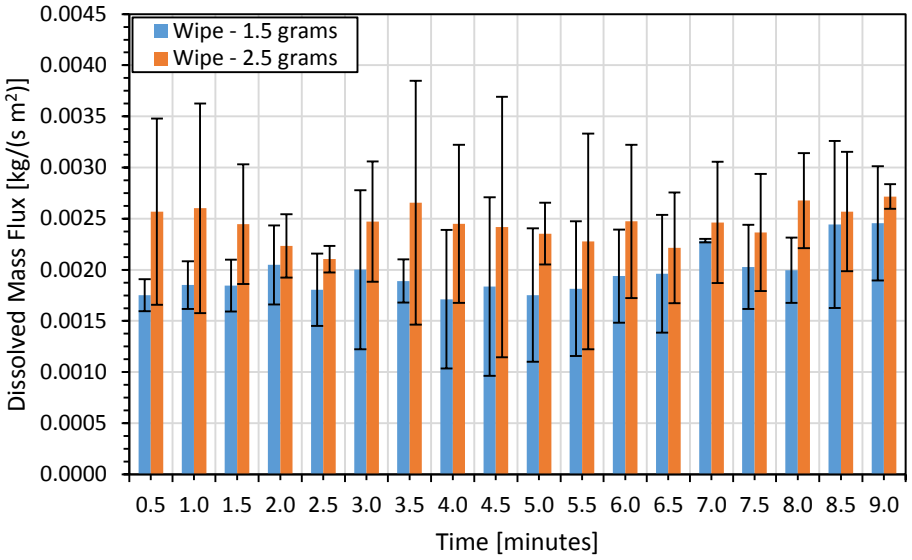

Figure 4.9: **The dissolved mass flux under wiping conditions and two water mass treatments in the Wipe Tests.**

The dissolved mass flux values showed that under the same relative agitation or mechanical action, the total mass of fluid affected the flux values. Larger fluid masses tended to lead to higher flux values. A means difference t-test confirmed that with the exception of the data at time point 8.5 minutes, there was a statistical difference between the flux values at each time point between these treatments, within 95% confidence. This finding suggests that there may have been a concentration gradient in the surrounding water

that may have deterred decay and that the natural convection of the larger mass may have decreased the gradient.

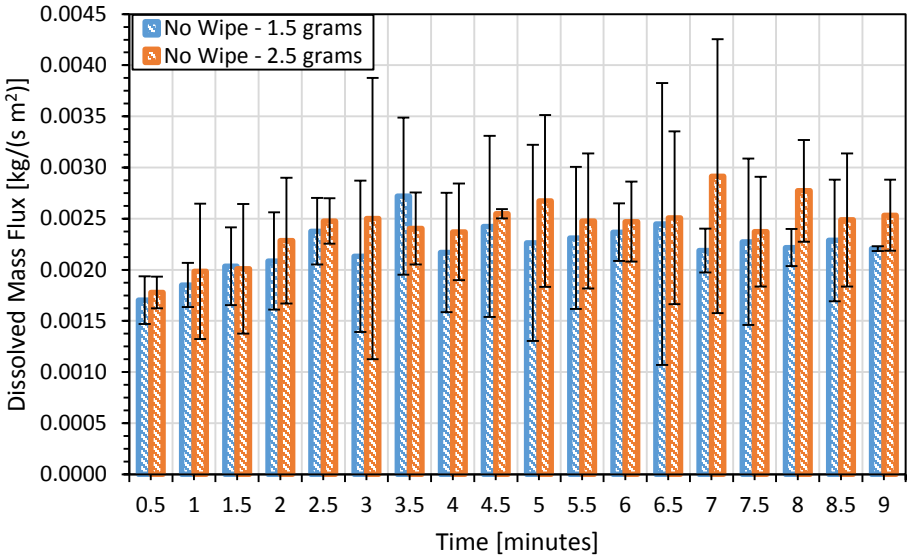

Figure 4.10: The dissolved mass flux under non-wiping conditions and two water mass treatments in the Wipe Tests.

The dissolved mass flux values showed that under no mechanical action from wiping, the total mass of fluid may affect the flux values. This behavior was likely due the dissolved mass concentration gradient in the surrounding fluid on the surface of the lozenge. A means difference t-test confirmed half of the data points were statistically different, while the data at time points 0.5, 1.0, 1.5, 2.5, 4.5, 5.5, 6.0, 6.5, and 7.5 minutes had statistically the same flux values, within 95% confidence.

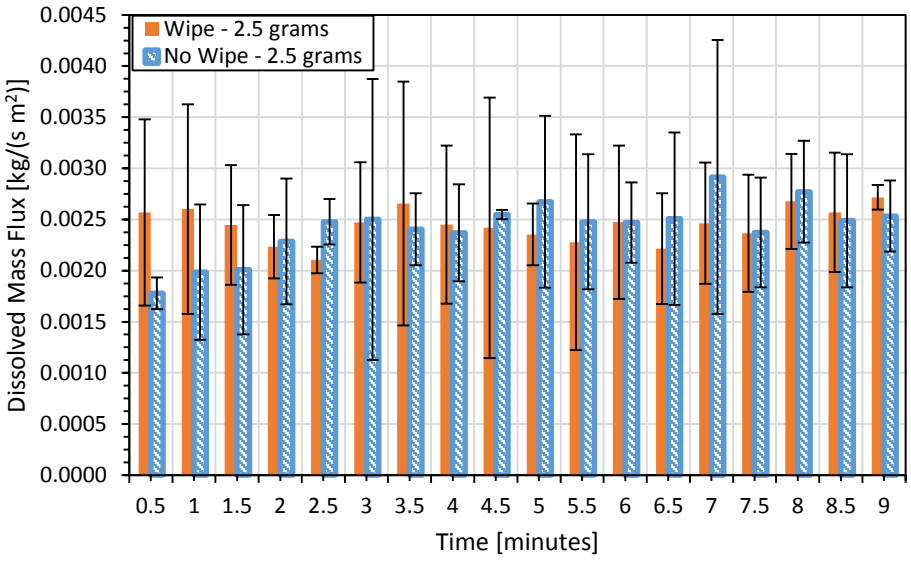

Figure 4.11: The dissolved mass flux under differing wiping and non-wiping treatments with 2.5 grams of water mass treatments.

The dissolved mass flux values demonstrated that under the same fluid mass, the presence of minimal mechanical wear or agitation may have an effect on the flux values. A means difference t-test confirmed ten of the data points were statistically different, while the data at time points 0.5, 1.0, 1.5, 2.5, 5.0, 6.5, 7.0 and 9.0 minutes had statistically the same flux values, within 95% confidence.

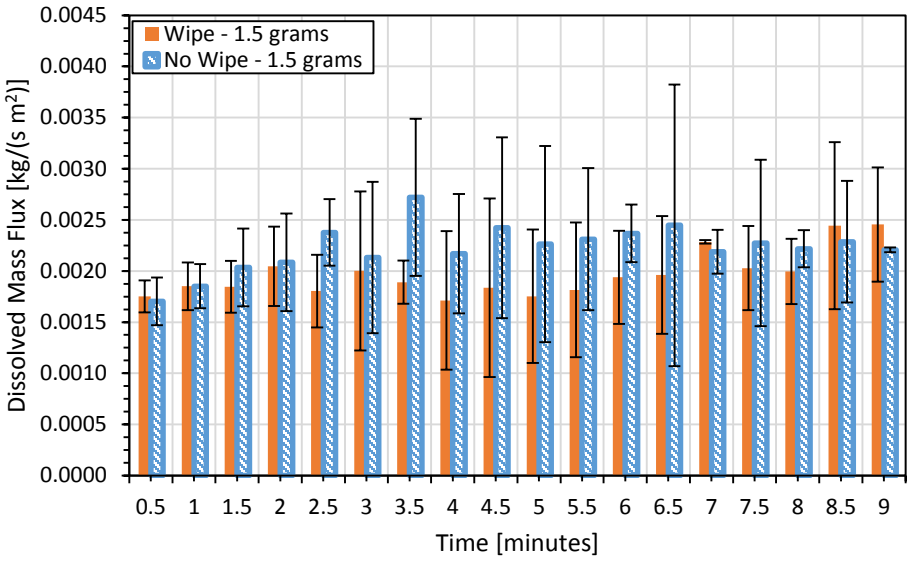

Figure 4.12: The dissolved mass flux under differing wiping and non-wiping treatments with 1.5 grams of water mass treatments.

The data showed that at low controlled mass conditions, the presence of minimal mechanical wear or fluid agitation appeared to increase values of dissolved mass flux. A means difference t-test confirmed thirteen of the data points were statistically different, while the data at time points 0.5, 1.0, 2.0, 3.0, and 8.5 minutes had statistically the same flux values, within 95% confidence.

The highest flux values were observed in cases with larger fluid mass, regardless of mechanical wear included in the test. Under low mass conditions, however, the presence of mechanical wear appeared to slightly decrease the dissolved mass flux. The two treatments that included wiping with 2.5 grams of fluid or 1.5 grams of fluid (Wipe-2.5 grams and Wipe-1.5 grams), and the two treatments that did not include wiping with 2.5 grams of fluid

or 1.5 grams of fluid (No Wipe-2.5 grams and No Wipe-1.5 grams) yielded average overall dissolved mass flux values of 2.5×10^{-3}, 2.0×10^{-3}, 2.4×10^{-3}, and 2.2×10^{-3} kilograms per second per square meter, respectively. These findings ran counter to the predicted behavior, where mechanical action was predicted to lead to higher decay and dissolved mass flux behavior.

Statistical analysis of the flux data indicated that the presence of mechanical wear in the form of a categorical variable, time, and fluid mass were all found to be statistically significant to the dissolved mass flux values, within 95% confidence. Two interaction variables between the mechanical wear and time variable, and the mechanical wear and mass variable were also found to be significant. Assessment of the simple effects indicated that there was no difference between dissolved mass flux values at 2.5 grams of water under either mechanical wiping condition. This finding suggests that there may be a limit to the effect of mechanical wear on the dissolved mass flux behavior when the mass of fluid is sufficiently large, however given the lack of control in the wiping procedure more rigorous assessment and statistical analysis would be required to confirm this hypothesis. Investigation of the other interaction variable of time and mechanical wear showed that this interaction was qualitative because it caused a change in the relationship between the levels of a factor.

Interestingly, Figure 4.13 demonstrated the normalized solid lozenge mass percent decay for all four treatments, with the treatments undergoing wiping, appear to decay faster than the treatments that did not undergo wiping. These findings suggested there may have

been small errors in the surface area or dissolved mass measurements performed, which could have affected the dissolved mass flux values. Figures 4.14, 4.15, 4.16, and 4.17 demonstrate the average normalized mass percent between two treatments with respect to time by treatment type. Figures 4.14 and 4.15 show the effects of wiping under the same fluid mass conditions, while Figures 4.16 and 4.17 display the effects of fluid mass under the same wiping conditions.

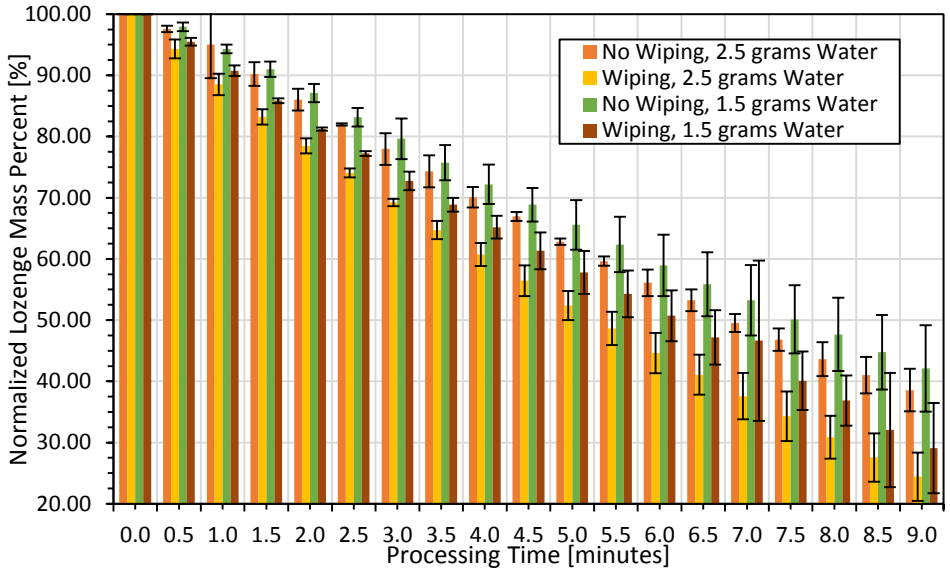

Figure 4.13: The normalized solid lozenge mass percent for all four Wipe Test Treatments with respect to processing time.

The normalized solid lozenge mass percent for the Wipe-2.5 grams, Wipe-1.5 grams, No Wipe-2.5 grams, and No Wipe-1.5 grams treatments demonstrate that higher fluid mass and wiping conditions lead to faster decay rates. Interestingly, this data suggests that the

fluid mass may have less of an effect on the overall decay rate if the mechanical wear condition is held constant.

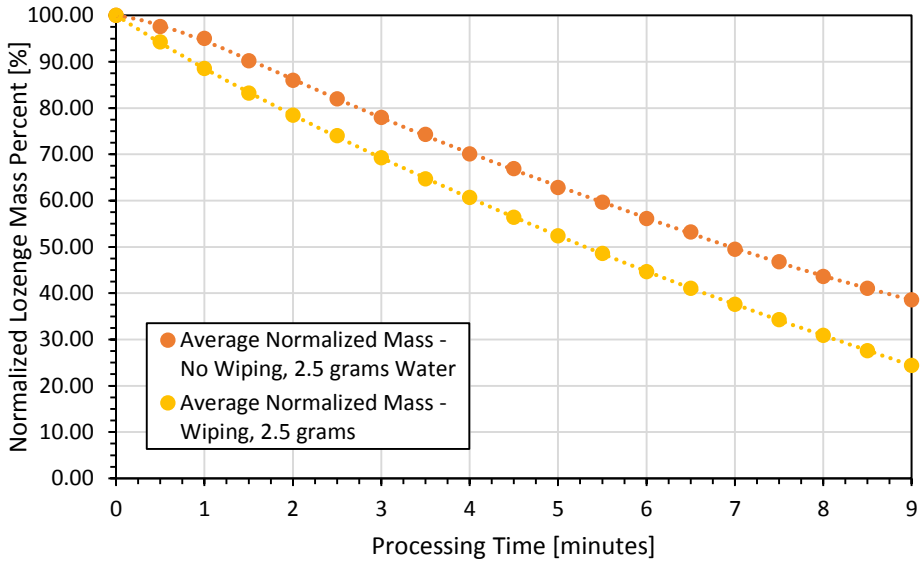

Figure 4.14: The normalized solid lozenge mass percent under differing wiping and non-wiping treatments with 2.5 grams of water mass treatments.

The normalized solid lozenge mass percent for the Wipe-2.5 grams and No Wipe-2.5 grams treatments demonstrate that under high fluid mass conditions, the presence of minimal mechanical wear increases the rate of decay. A means difference t-test for each data point confirmed that both data sets are statistically different, within 95% confidence.

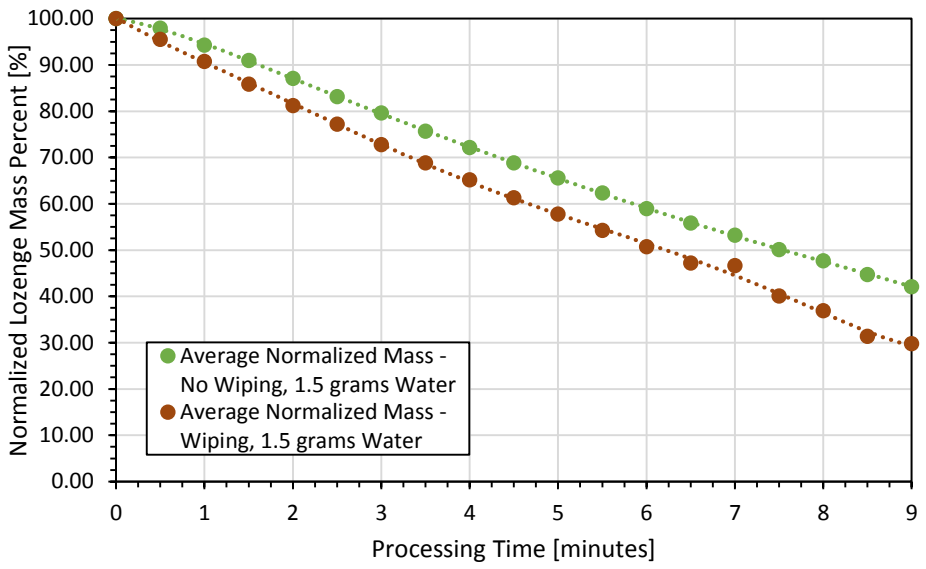

Figure 4.15: The normalized solid lozenge mass percent under differing wiping and non-wiping treatments with 1.5 grams of water mass treatments.

The normalized solid lozenge mass percent for the Wipe-1.5 grams and No Wipe-1.5 grams treatments demonstrate that under low fluid mass conditions, the presence of minimal mechanical wear increases the rate of decay, albeit not to the extreme seen at high fluid mass conditions. A means difference t-test for each data point confirmed that both data sets are statistically different, within 95% confidence.

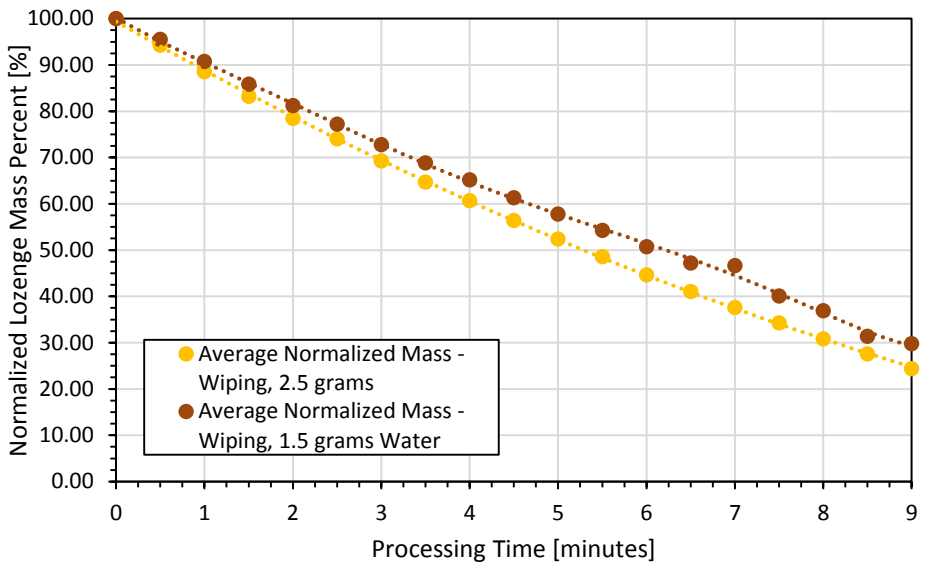

Figure 4.16: The normalized solid lozenge mass percent under differing water mass treatments with wiping during mass treatments.

The normalized solid lozenge mass percent for the Wipe-2.5 grams and Wipe-1.5 grams treatments demonstrate that under minimal mechanical wear conditions, increased fluid mass increases the rate of decay slightly. A means difference t-test confirms the difference in values, with the exception of the last two time points, where the data variability was larger. This conclusion suggests that increasing the fluid mass may yield a large gradient in sugar concentration allowing for a larger decay from a kinetic approach.

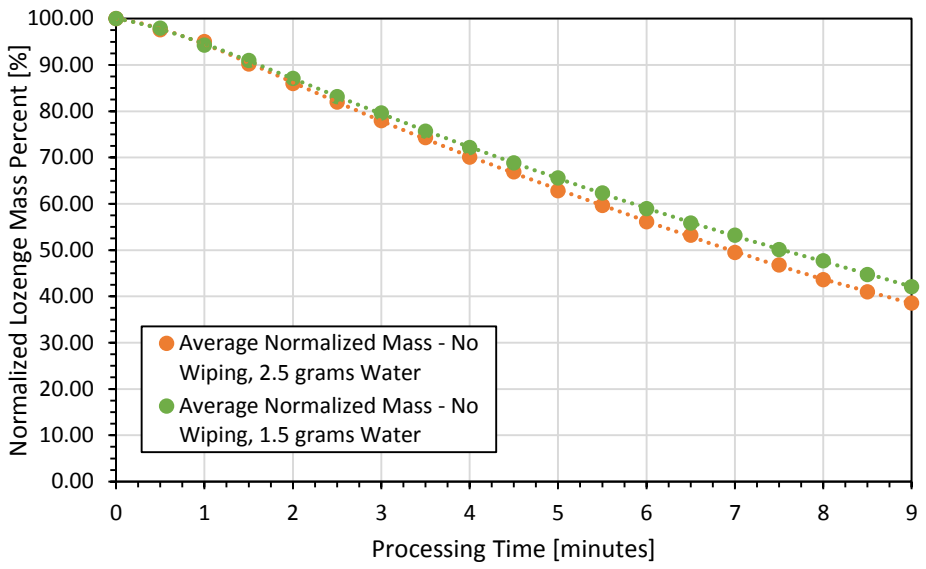

Figure 4.17: The normalized solid lozenge mass percent under differing water mass treatments with non-wiping during mass treatments.

The normalized solid lozenge mass percent for the No Wipe-2.5 grams and No Wipe-1.5 grams treatments demonstrate that, under 'no mechanical wear' conditions, increase of the fluid mass increases the rate of decay very slightly. However, a means difference t-test indicates that with the exception of the data at time points of 2.5, 4.5, and 5.0 minutes, there is no statistical difference between the treatments. This finding indicates that fluid mass, at low levels, has no effect on the decay rate under no mechanical wear conditions.

The difference in the normalized solid lozenge mass percent between the treatments shown in Figures 4.16 and 4.17 are minimal in the cases where the mechanical wear variable was controlled, and at many time points not significantly different, within 95% confidence. However, in the two cases where the fluid mass was controlled at 2.5 or 1.5 grams the space

between the lines represents the difference in the solid lozenge mass percent decay due to mechanical action. An average normalized lozenge mass difference of 4.80% and 3.62% was calculated for each time point in the 2.5 grams and 1.5 grams treatments. Although the majority of the difference was observed at later time points, these findings were relevant because they indicated the role of mechanical wear in the dissolution of lozenges during oral processing, namely that mechanical wear increases the rate of decay. These findings provided a foundation for the next series of tribological tests to determine sliding speed and normal load conditions that correlate to the oral processing lozenge decay behaviors observed during the Full Test.

4.3.2 Tribological Wear Tests

Results from the Tribological Wear Tests indicated that the overall fluid mass, fluid type, normal force, and sliding speed significantly affected the dissolved mass flux behavior and rate of model lozenge decay. Five different tests were designed to determine the effects of each variable under controlled tribology test conditions. Control of these factors eventually led to the identification of tribology test conditions that achieved the same dissolved mass flux behaviors observed during the Full Test, discussed in the third chapter. The first test discussed tested the effects of low sliding speed and changing fluid water mass.

4.3.2.1 Low Sliding Speed – Varying Mass Test

This test was designed to determine the effects of fluid mass and low sliding speeds under low normal force conditions on the overall dissolved mass flux behavior. Each treatment in this test was conducted with 0.5 Newtons per lozenge, producing roughly 2.4

kilo-Pascals of pressure or 0.34 pounds-per-square-inch, a low pressure that was likely representative of possible oral processing conditions (van der Bilt and others 2008). Results indicated that dissolved mass flux values were maximized in high sliding speed and high water mass, leading to a faster solid lozenge mass decay. Figure 4.18 demonstrated the average mass flux behavior for six treatments with respect to time. The highest dissolved mass flux values were produced with 2.5 grams of water at 0.0168 meters per second sliding speed, while the lowest flux values were produced with 1.5 grams of water at 0.0021 meters per second sliding speed. The average flux for the 1.5 grams water treatments were 0.0030, 0.0033, and 0.0039 kilograms per second per square meter for the 0.0021, 0.0084, and 0.0168 meter per second sliding speed, respectively. The average flux for the 2.5 gram water treatments were 0.0031, 0.0035, and 0.0043 kilograms per second per square meter for the 0.0021, 0.0084 and 0.0168 meter per second sliding speed, respectively.

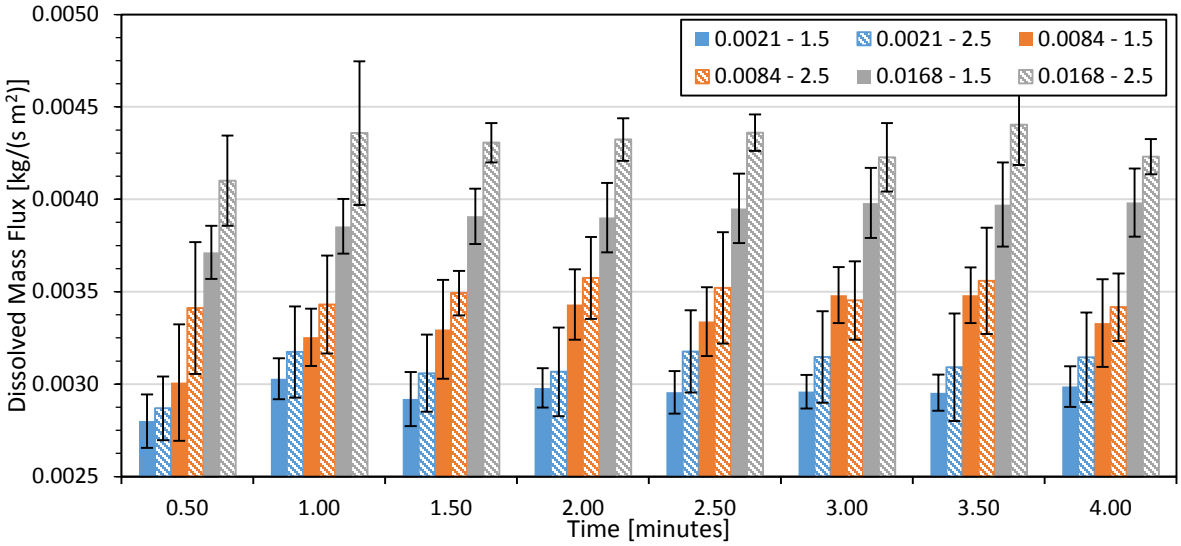

Figure 4.18: The dissolved mass flux behaviors of the treatments in the Low Sliding Speed – Varying Mass Test.

The dissolved mass flux behaviors under sliding speed conditions ranging from 0.0021 to 0.00168 meters per second and fluid mass of 1.5 and 2.5 grams, demonstrated various flux behaviors under 1.0 Newtons of normal force. A means difference t-test between the two treatments at each sliding speed indicated that with the exception of the treatments at 0.0168 meters per second sliding speed, there was no statistical difference between the treatments at each of the lower sliding speeds. This indicates that fluid mass at low levels, has a statistically minimal effect on the decay rate under slow sliding speed conditions.

Statistical analysis of the flux data indicated that sliding speed, water mass, and time were all found to be statistically significant, within 95% confidence. One interaction variable

between the sliding speed and water mass was also found to be significant. Assessment of the simple effects with Tukey's pairwise comparisons indicated that each level of interaction was significantly different, within 95% confidence. The interaction variable was quantitative because the relationship between the levels of each factor only changed in magnitude. Assessment of the main effects for the time variable using Tukey's Honest Significance Test, indicated that only the first time point data was significantly lower in value from the rest of the data. This finding follows the moving boundary hypothesis discussed in the third chapter, where a minimum amount of processing time was required to reach equilibrium flux conditions. Interestingly, ANOVA for each treatment indicated that there was no statistical difference between the dissolved mass flux values at each time point within each treatment for this test. Nonetheless, it does not detract from the observed main effect of time on the dissolved mass flux. The next test expands the findings from this test, determining the effect of the normal force control on the dissolved mass flux behavior.

4.3.2.2 Low Sliding Speed – Varying Force Test

This test was designed to determine the effects of normal force and low sliding speeds under 2.5 grams of water conditions. Each treatment in this test was conducted with 0.5 or 2.5 Newtons per lozenge, producing roughly 2.4 kilo-Pascals of pressure (0.34 pounds-per-square-inch) or 12 kilo-Pascals (1.7 pounds-per-square-inch), respectively. These pressures were likely to be representative of possible oral processing conditions, as the human jaw may produce a maximum bite force of 418 and 490 Newtons for women and men, respectively (van der Bilt and others 2008). Results indicated that dissolved mass flux values were

maximized under high sliding speed and high normal force conditions, leading to a faster solid lozenge mass decay. Figure 4.19 demonstrates the average mass flux behavior for four treatments with respect to time, where the normal forces are denoted as 1.0 or 5.0 Newtons to account for two lozenges per test. The highest dissolved mass flux values were produced with 2.5 Newtons of force at 0.0168 meters per second sliding speed, while the lowest flux values were produced with 0.5 Newtons of force at 0.0021 meters per second sliding speed. The average flux for the 0.5 Newton normal force treatments were 0.0031 and 0.0043 kilograms per second per square meter for the 0.0021 and 0.0168 meter per second sliding speed, respectively. The average flux for the 2.5 Newton normal force treatments were 0.0033 and 0.0043 kilograms per second per square meter for the 0.0021 and 0.0168 meter per second sliding speed, respectively.

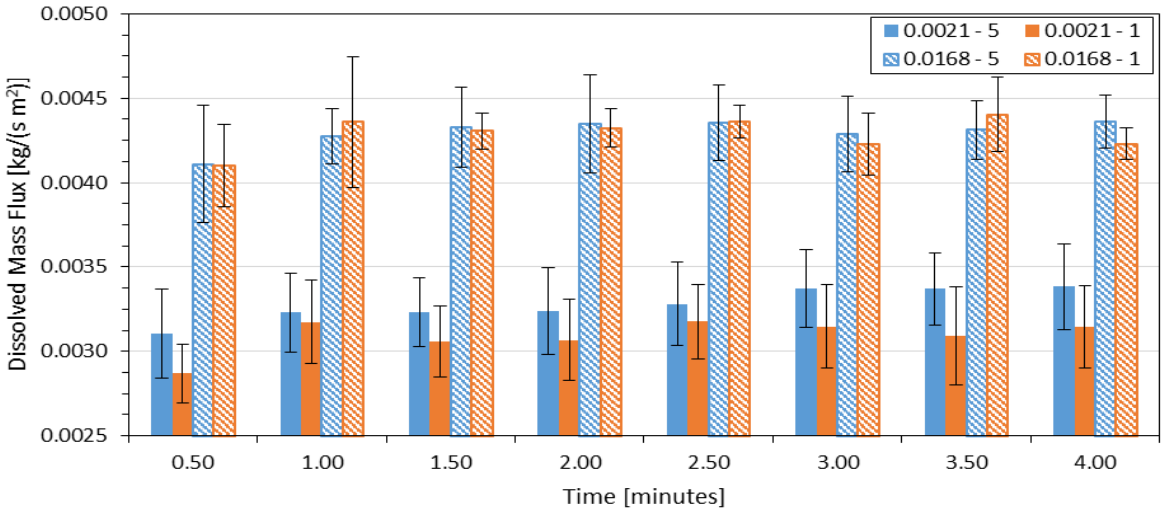

Figure 4.19: The dissolved mass flux behaviors of the treatments in the Low Sliding Speed – Varying Force Test.

The dissolved mass flux behaviors under sliding speed conditions ranging from 0.0021 to 0.00168 meters per second and fluid normal force of 0.5 and 2.5 Newtons (1.0 and 5.0 Newtons to account for two lozenges), demonstrated various flux behaviors under 2.5 grams of water. A means difference t-test between the two treatments at each normal force indicated that there is no significant difference between the treatments, within 95% confidence. This finding indicates that normal force values between 0.5 and 2.5 Newtons per lozenge, have no statistically significant effects on the decay rate under slow sliding speed and 2.5 grams of water conditions.

Statistical analysis of the flux data indicated that sliding speed, normal force, and time were all found to be statistically significant, within 95% confidence. One interaction variable between the sliding speed and normal force was also found to be significant. Assessment of the simple effects with Tukey's pairwise comparisons indicated that with the exception of the difference between the two treatments at 0.0168 meters per second, each level of interaction was significantly different, within 95% confidence. The interaction variable was quantitative because the relationship between the levels of each factor only changed in magnitude. Assessment of the main effects for the time variable using Tukey's Honest Significance Test, indicated that only the first time point data was significantly lower than the rest of the data, and that all other data points had values that were statistically the same. This finding, again follows the moving boundary hypothesis, previously proposed in the third chapter. The ANOVA for each treatment indicated there was no statistical difference between the dissolved mass flux values at each time point within each treatment

for this test. The next test expands the findings from this test, to determine the effect of a variety of sliding speeds on the dissolved mass flux behavior.

4.3.2.3 Sliding Speed Test

This test was designed to determine the effects of different sliding speeds under 2.5 grams of water and 2.5 Newton normal force conditions. Results indicated that dissolved mass flux values were maximized under high sliding speeds, as expected. Figure 4.20 demonstrates the average mass flux behavior for five treatments with respect to time. The highest dissolved mass flux values were produced with 0.1005 meters per second sliding speed, while the lowest flux values were produced with 0.0021 meters per second sliding speed. The average dissolved mass flux values for the 0.0021, 0.00168, 0.067, 0.0838, and 0.1005 meters per second sliding speed trials were 0.0031, 0.0043, 0.0046, 0.0050, and 0.0053 kilograms dissolved mass per second per square meter of surface area.

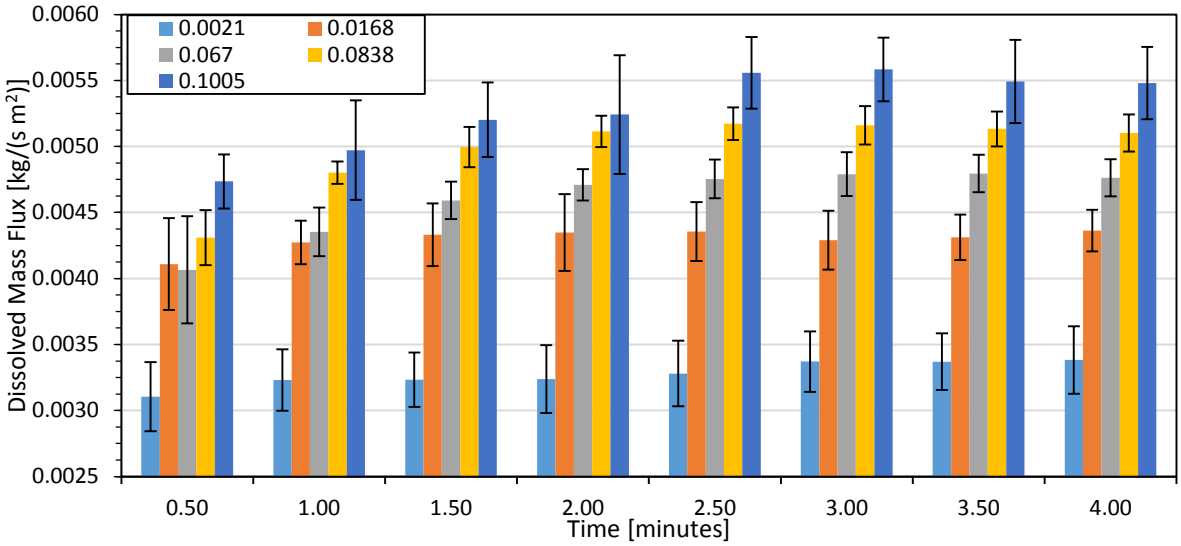

Figure 4.20: The dissolved mass flux behaviors of the treatments in the Sliding Speed Test.

The dissolved mass flux increases with the sliding speed values, under 2.5 Newton force and 2.5 grams water conditions, where the legend represents the sliding speeds for each treatment in units of meters per second. A means difference t-test indicates that with the exception of the data at time points 0.5 and 1.0 minutes, all data sets are significantly different from each other. At 0.5 and 1.0 minutes, the 0.0168 and 0.067 meters per second treatments are statistically the same. At 0.5 minutes, the 0.0168, 0.067 and 0.0838 meters per second treatments are statistically the same, within 95% confidence.

Statistical analysis of the flux data indicated that sliding speed and time were both found to be statistically significant, within 95% confidence. The interaction variable between the sliding speed and time was also found to be significant. Assessment of the simple effects

with Tukey's pairwise comparisons signified that there were several cases where the difference between values in different treatments were not statistically significant, yet the interaction variable was determined to be quantitative. The ANOVA for each treatment indicated that with the exception of the 0.0021 and 0.0168 meter per second sliding speeds, there was a statistical difference between the dissolved mass flux values of at least one time point within each treatment in this test. This outcome provides additional justification to the claim that the moving boundary hypothesis is more apparent under high sliding speed conditions, where flux values tend to be larger. The next test uses some of the data from this test to determine the effect of fluid type on the dissolved mass flux behavior, holding the normal force, sliding speed, and mass of fluid constant.

4.3.2.4 Saliva – Water Test

This test was designed to determine the effects of fluid type on the dissolved mass flux behavior under 2.5 Newtons force, 0.0838 meters per second sliding speed, and 2.5 grams total mass conditions. Each treatment in this test was conducted with deionized water or pooled fresh saliva, harvested and pooled from two adult humans using the methodology described in the third chapter. Results indicated that dissolved mass flux values were maximized using water instead of saliva, leading to a faster solid lozenge mass decay. Figure 4.21 displays the average mass flux behavior for both treatments with respect to time. The average overall dissolved mass flux values from the saliva and water treatment were 4.97×10^{-3} and 4.46×10^{-3} kilograms per second per square meter, respectively.

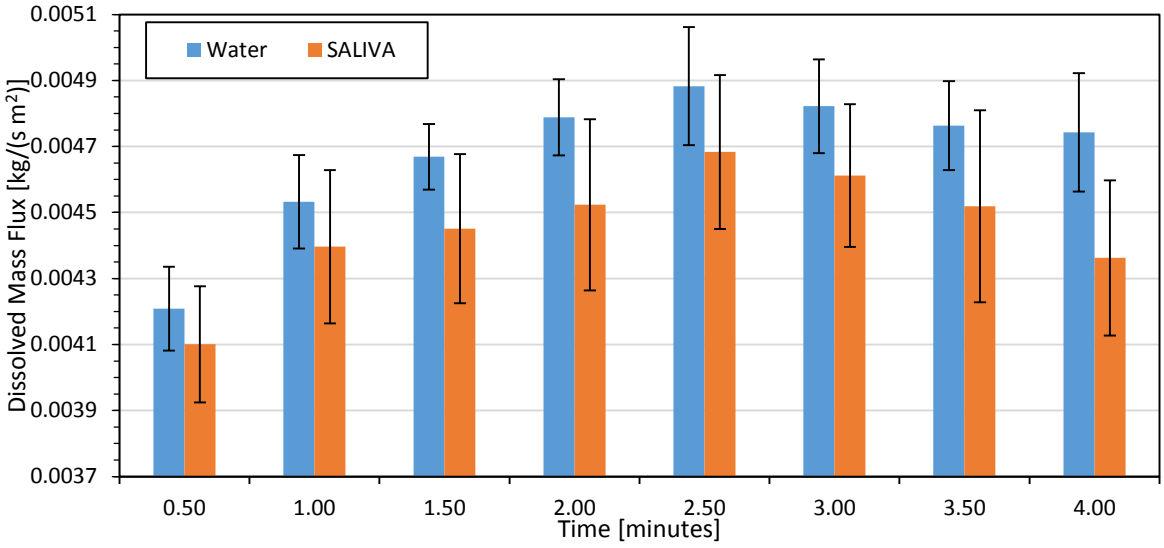

Figure 4.21: The dissolved mass flux behaviors of the treatments in the Saliva – Water Test.

The dissolved mass flux behaviors under the two different fluid type conditions vary depending on time and the fluid type, when held at a constant normal force, sliding speed, and fluid mass. A means difference t-test indicated that the data from both treatments were only significantly different at the 1.5, 2.0, and 4.0 minutes time points. Assessment of the main effects for the time and fluid type variables using Tukey's Honest Significance Test, indicated that only the first time point data was significantly lower in value from the rest of the data. This finding follows the moving boundary hypothesis, where a minimum amount of processing time was required to reach equilibrium flux conditions. An ANOVA assessment for each treatment indicated that there was a statistical difference between the dissolved mass flux values at each time point within each treatment within this test. These findings revealed

that although the use of saliva in these measurements more closely match the conditions of oral processing, it tends to not perform as consistently as water. Furthermore, it was difficult to handle, store, and standardize. Therefore, deionized water makes for an adequate fluid replacement. These findings also serve to determine the mechanical wear conditions that achieve the target dissolved mass flux values observed in the Full Test discussed in the third chapter.

4.3.2.5 High Mass – High Sliding Speed Test

This test was designed to determine the effects of fluid mass and high sliding speeds under controlled 2.5 Newton normal force conditions on the overall dissolved mass flux behavior. Furthermore, what was developed through the evaluation of previous trials to match the dissolved mass flux behavior observed during the first four minutes of oral processing for the Full Test discussed in the third chapter. All treatments were evaluated under fluid mass conditions of 2.5 and 2.0 grams of water, matching the maximum and minimum average saliva values observed in the Full Test. Furthermore, higher dynamic normal force control values limited the fluctuation of the total applied normal force to the system. Results indicated that dissolved mass flux values were maximized in high sliding speed and high water mass, as expected. Figure 4.22 demonstrated the average mass flux behavior for four treatments with respect to time. The highest dissolved mass flux values were produced with 2.5 grams of water at 0.1005 meters per second sliding speed, while the lowest flux values were produced with 2.0 grams of water at 0.0838 meters per second sliding speed. The average flux for the 2.5 grams water treatments were 0.0050 and 0.0053

kilograms per second per square meter for the 0.0838 and 0.1005 meter per second sliding speed, respectively.

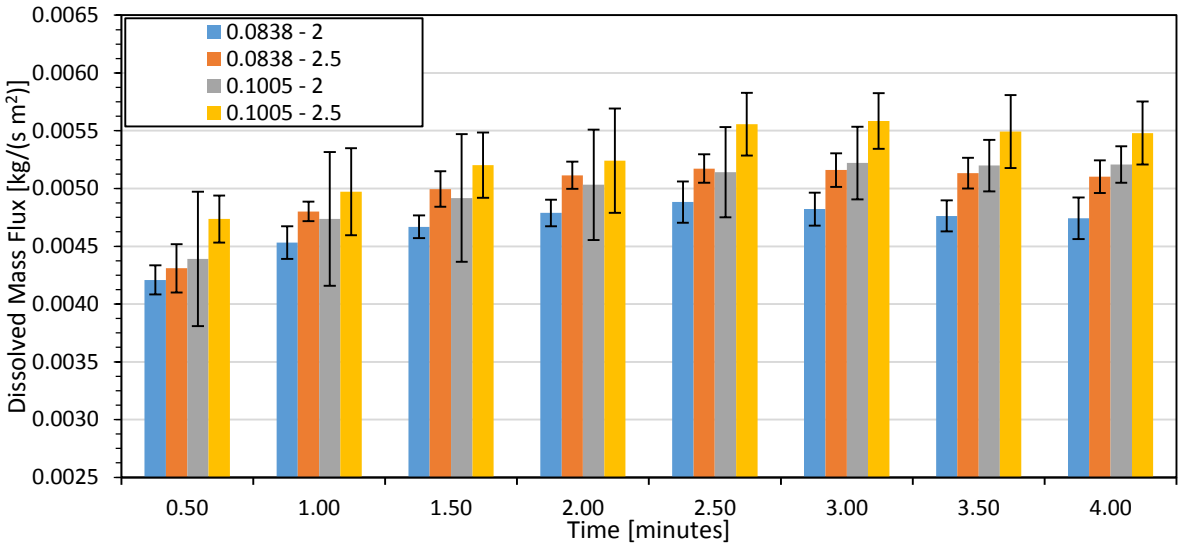

Figure 4.22: The dissolved mass flux behaviors of the treatments in the High Mass – High Sliding Speed Test.

The dissolved mass flux behaviors varies under sliding speed conditions ranging from 0.0838 to 0.1005 meters per second and fluid mass of 2.0 and 2.5 grams, when controlled at 2.5 Newtons normal force per lozenge. The average flux for the 2.0 grams water treatments were 0.0047 and 0.0050 kilograms per second per square meter for the 0.0838 and 0.1005 meter per second sliding speed, respectively. Statistical analysis of the flux data indicated that fluid mass, sliding speed, and time were all found to be statistically significant, within 95% confidence. No interaction variable was found to be statistically significant.

Assessment of the main effects using Tukey's Honestly Significant Difference Test signified that there was a significant difference between the effects of the sliding speed and mass variables, as expected. Flux values from the larger sliding speed, 0.1005 meters per second, were statistically larger than the values from treatments with the slower sliding speed of 0.0838 meters per second. The treatments with larger fluid mass levels also produced statistically larger flux values than the treatments with smaller fluid mass values. Analysis also indicated that the data at the 0.5 minute time point was statistically lower than all other data points. The 1.0 and 1.5 minute time points were statistically the same, albeit larger, and the rest of the data points were statistically the same and larger than the first three data points. The ANOVA for each treatment indicated that there was a statistical difference between the dissolved mass flux values for at least one time point within each treatment in this test. The ANOVA findings and assessment of the main effects of time provided additional evidence for the moving boundary hypothesis, where a minimum time is required to reach equilibrium dissolved mass flux values.

The results from each treatment were also compared with the Full Test values using a means difference t-test at each data point. Analysis supported that all of the results were statistically the same, within 95% confidence, for the high mass, high sliding speed treatment. The low mass, high sliding speed treatment and high mass, low sliding speed treatment were found to be statistically the same for all data points except for the data at 1.0 minutes. The low mass, low sliding speed treatment was found to have statistically the same data points as the Full Test data, with the exception of the data points from 1.0 through 2.0

minutes. These findings showed that the dissolved mass flux behavior observed in the Full Test can be matched in tribology tests, specifically with 2.5 grams water, 0.1005 meters per second sliding speed, and 2.5 Newtons normal force. It also provides an estimation of the average sliding speed and normal force that may be encountered in the mouth during oral processing of lozenges. Figure 4.23 shows the proximity of the average treatment values at each data point compared with data from the Full Test.

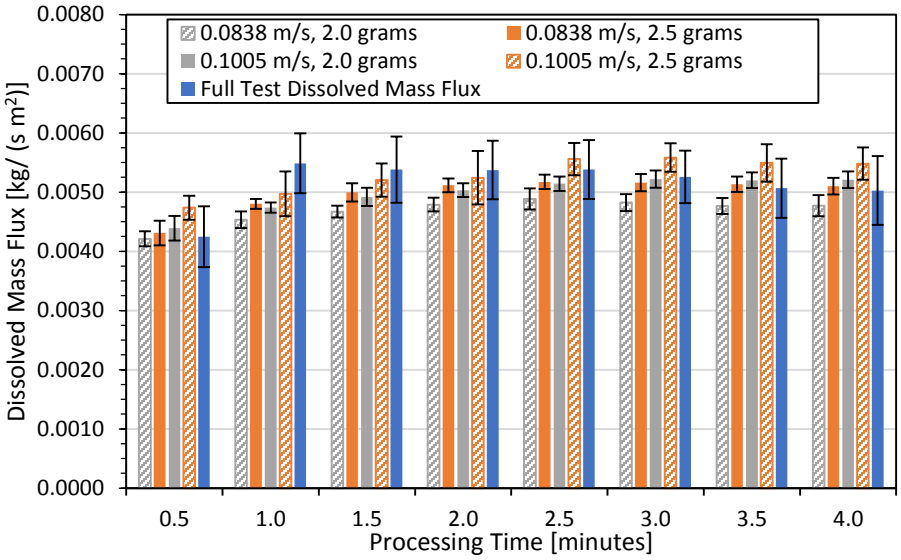

Figure 4.23: The dissolved mass flux behaviors of the treatments that produce the same dissolved mass flux behaviors observed in the oral processing Full Test.

The dissolved mass flux behaviors for four treatments producing flux behavior observed that is statistically the same to the values from the first four minutes of the Full

Test. The 0.1005 meter per second, 2.5 grams water treatment is statistically the same to the at every data point. The average estimated normalized lozenge mass percent was calculated for each treatment data point using Equations 4.13 and 4.14. The relationships shown in those equations allow for an estimation of the normalized lozenge mass percent assuming that the tribology test conditions of fluid mass, normal force, and sliding speed were equally applied over the entire surface of the lozenges tested. Figure 4.24 demonstrates the estimated normalized lozenge mass percent compared to the normalized lozenge mass percent observed in the Full Test.

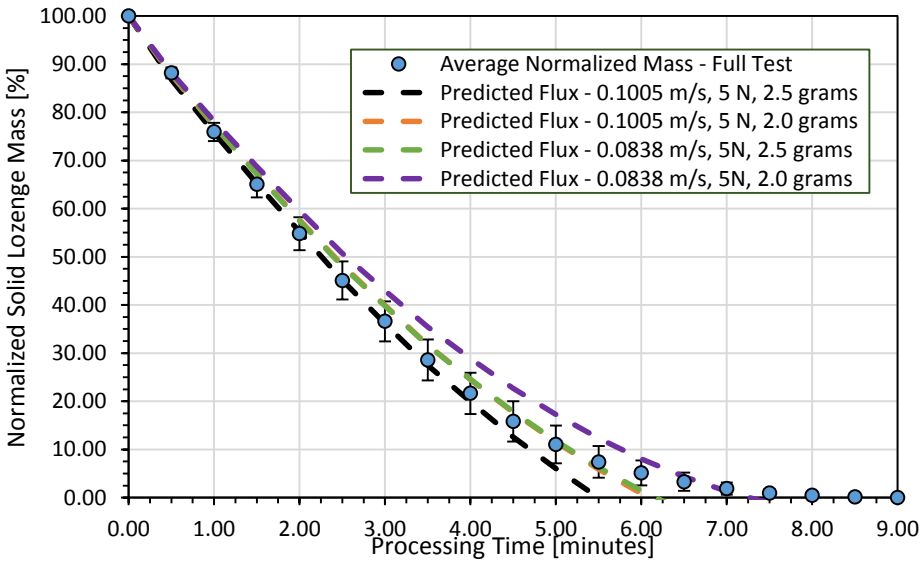

Figure 4.24: The average normalized solid lozenge mass percent from the four treatments follow the behavior of the Full Test decay behavior closely within the first four minutes of processing.

The average normalized solid lozenge mass percent from the four treatments follow the behavior of the Full Test decay behavior closely within the first four minutes of processing. Extrapolation of the performance was conducted to predict the estimated normalized solid lozenge mass percent at times exceeding the 4.0 minute tests performed. There may be validity to the trend observed, but additional tests that exceed 4.0 minutes would be required to confirm the trend. Results from the last tribology test showed that through control of tribological variables, dissolved mass flux values may be achieved that are statistically the same to the average oral processing dissolved mass flux behaviors shown in human trials. Although the data from the high mass, high sliding speed test was statistically the same to the Full Test data, the normal force and sliding speed values only create conditions that correlate to the average decay and flux behavior observed in the Full Test, and may not be exactly representative of the exact conditions during oral processing. Additional research is required to determine the range of correlating tribology test variables for a more complete understanding of the factors that contribute to the oral processing of hard candies and lozenges.

4.3.3 Summary of Tribology and Phase Change Test Findings

Analysis of the average dissolved mass flux behavior in the Phase Change Tests establish that the dissolved mass flux performance observed from the Full Test could not be achieved through fluid flow conditions inherent in oral processing alone. The tribology tests showed that mechanical wear must be included to account for the difference in flux behavior and overall rate of lozenge decay. Figure 4.25 shows the normalized solid lozenge mass

percent decay for a selection of phase change and tribology test conditions compared to the average decay from the Full Test.

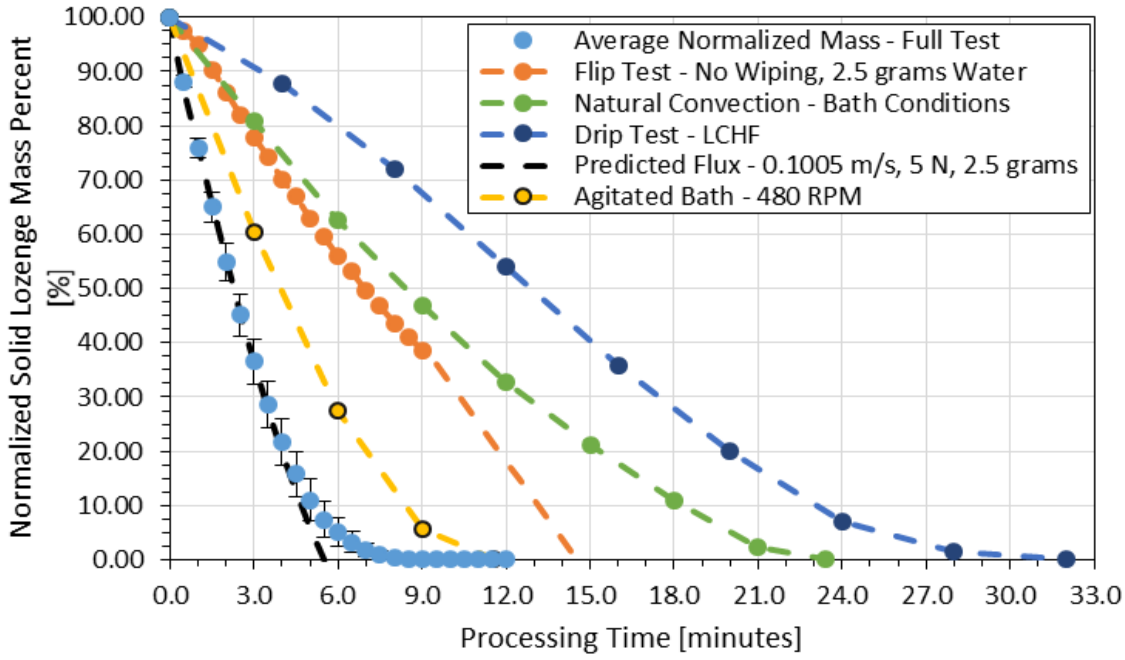

Figure 4.25: Average normalized solid lozenge mass percent from a variety of phase change and tribology test treatments compared to the Full Test decay behavior.

The average normalized solid lozenge mass percent from a variety of phase change and tribology test treatments compared to the Full Test decay behavior. The dashed orange line is an extrapolation of the Flip Test trend beyond the test that was performed. Results show that phase change and fluid flow conditions are not sufficient to match the decay

behavior observed during oral processing, with controlled fluid mass and agitation. The Drip Test data shows the limitations of slow fluid flow that corresponds to average saliva production. Flip Test data shows that under complete immersion with fluid mass levels that correspond to the human data, additional agitation or mechanical wear is required to achieve higher flux values. Only in the Tribology Test data is there an adequate combination of phase change and mechanical wear to achieve the target decay rates. The findings from these tests are important because they demonstrate that mechanical wear significantly contributes to the breakdown of lozenges during oral processing. This conclusion is important because it identifies a disruption to the current methods of confection and drug design that may have impacts on enjoyment or health conditions. Additional research is required to assess the breakdown of a variety of lozenges to determine the extent of mechanical wear and formulation effects on the lozenge decay during oral processing.

4.4 Conclusion

The combined findings from the phase change and mechanical wear tests demonstrate that both phase change and mechanical wear contribute to the breakdown of lozenges during oral processing and are therefore necessary to complete modeling and understanding of breakdown behavior during oral processing. Furthermore, this testing methodology demonstrated that the overall dissolved mass flux behavior observed in human trials may be matched in tribology tests through the control of mechanical wear variables such as sliding speed, normal force, and type of fluid and total fluid mass. Mechanical wear test conditions of 2.5 grams of water, 0.1005 meter per second sliding speed, and 2.5 Newtons normal force

yielded the same average dissolved mass flux behavior observed from the Full Test results from the third chapter. The methodology also showed the role of water in phase change and lozenge decay as a function of fluid type (water or saliva), total free mass to coat the lozenge, and flow conditions. These findings demonstrated that this methodology could be used to model the lozenge decay parameters of any homogeneous lozenge under controlled conditions. Identifying the target flux behavior may be included as a method for product development and design; thereby meeting the needs of customers in the case of a hard candy or dosing requirements stipulated by the FDA.

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OVERVIEW OF RESEARCH FINDINGS AND FUTURE WORK

5.1 Introduction

Boiled sweets are commonly consumed worldwide in the form of candies or as medicated lozenges, such as cough drops. However, despite common consumption, the factors that contribute to lozenge decay during oral processing have not been thoroughly described in literature. The original research discussed in the previous chapters was designed to identify the role of mechanical wear on the breakdown of lozenges during oral processing. A methodology for lozenge decay assessment was developed, oral processing tests with human subjects were conducted, and phase change and mechanical wear benchtop tests identified the impacts of fluid flow and mechanical wear factors on the breakdown of lozenges. Research findings and methodologies developed provide a foundation for future research to improve understanding of oral processing behaviors and the role of physiological and mechanical factors that contribute to breakdown of lozenges during oral processing. This chapter provides a brief review of the research findings and developed methodologies, their relevance to the current confectionary and pharmaceutical industries, and the future relevant research directions.

5.2 Overview of Findings

The third chapter described a novel methodology to analyze model lozenge decay through analysis of model lozenge surface area changes using image analysis techniques and refractive index assessment of dissolved mass content to calculate the dissolved mass flux at each sampling time point. This methodology allowed for decay analysis regardless of

changes in surface area properties, and created a standard means to compare decay properties of different lozenges regardless of surface area, lozenge mass, or composition. The third chapter also developed methods using human subjects to model the average dissolved mass flux behavior of model lozenges, providing a framework for analysis of mechanical wear and phase change contributions to decay during oral processing. The results demonstrated that after a minimum oral processing time, lozenge decay reached an average constant equilibrium flux regime that dominated the decay performance. Presence of a minimum amount of time to reach the equilibrium decay behavior suggests that a moving boundary condition may be limiting the decay rate early during oral processing. The third chapter also demonstrated that differing dissolved mass flux behaviors could be observed with lozenges with different formulations, suggesting that the methodology developed could be used to identify the average oral processing decay as a function of formulation differences. Adoption of a target average equilibrium dissolved mass flux could be used in product development to optimize formulations.

The fourth chapter built upon the average dissolved mass flux behaviors observed during the oral processing chapter analyses, specifically by attempting to match the average equilibrium dissolved mass flux behavior from the oral processing tests. The purpose of the fourth chapter was to decouple and identify the effects of the phase change and mechanical wear factors on the average lozenge breakdown behavior observed in the oral processing tests. Separate phase change tests were performed using agitated water bath systems, fluid flow conditions, and controlled fluid volume and agitation conditions to assess dissolved

mass flux behavior due to fluid flow alone. In all cases, the target dissolved mass flux conditions observed during the oral processing tests could not be achieved, even when the flow conditions exceeded the flow behaviors during oral processing. Inclusion of a mechanical wear factor was necessary to achieve the target dissolved mass flux behavior observed in the human subject oral processing tests. Mechanical wear test results demonstrated that the inclusion of a mechanical wear factor was necessary to achieve the target equilibrium dissolved mass flux behavior of the oral processing tests. The mechanical wear conditions that achieved the target equilibrium dissolved mass flux of 5.3×10^{-3} kilograms dissolved lozenge per second per square meter lozenge surface area were 2.5 Newtons normal load and 0.1005 meters per second sliding speed. Results from the mechanical wear tests also demonstrated that a minimum amount of time was required to reach the equilibrium decay behavior, similar to the human subject oral processing tests. This behavior suggests that a moving boundary condition may be limiting the decay rate early during oral processing. Findings and methodologies developed during this research provide a foundation for future research into the decay properties of other lozenge systems and the lozenge structural changes in the lozenge that occur due to the moving boundary that may affect decay.

5.3 Future Work

Although the dissolved mass flux behaviors, phase change factor, and mechanical wear factor effects quantified in this research are only applicable to the specific model lozenge used during the tests, the methodologies developed may be used to determine the

dissolved mass flux behaviors for other lozenge products. Furthermore, assessment of additional different products may be used to estimate the average sliding speeds encountered in the mouth during oral processing for different products. These methodologies have use in designing new confections and pharmaceutical products with specific lifetimes in the mouth. Future work will include investigation of the average human subject dissolved mass flux and salivation behaviors of other lozenge products and the equivalent mechanical wear performance that achieve the same equilibrium dissolved mass flux behaviors observed from human testing. Provided enough lozenge types are assessed, the average sliding speed behaviors may be ascertained for each style of lozenge, allowing for improved product development for confectionary and pharmaceutical products. Investigation of the effect of different non-nutritive sweeteners or ratios of corn or glucose syrups to sucrose on the decay rates is also necessary for improved product development purposes. The moving boundary hypothesis should also be confirmed using Magnetic Resonance Imaging (MRI) or other technologies to model the movement of water through the lozenge system for product design purposes.

5.4 Conclusion

The research discussed in this report has demonstrated the lack of previous investigation of lozenge decay behaviors during oral processing and developed methodologies to address the contributions of mechanical wear and phase change properties that contribute to the average overall lozenge decay during oral processing. Although the quantitative results are unique to the model lozenge tested, the methodologies developed

have merit for the decay analysis of other lozenge products. Furthermore, the methodologies provide a foundation to develop new confectionary or pharmaceutical products with specific decay properties.

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APPENDIX

I: Example refractive index-dissolved mass content calibration curve created by dissolving model lozenge in human subject saliva at 25 °C.