Measuring Properties of Medicated Chewing Gums and Evaluating Masticatory Efficiency for Different Frankfort-mandibular Plane Angles

Darian Zarir Irani

Abstract

Medicated Chewing Gums (MCGs) offer several advantages in oral drug delivery; however, they lack standardised testing for wider use in the pharmaceutical industry. An authorised test method backed by official pharmacopoeias has not yet been created; hence, this project uses a custom Design of Experiment (DOE) to produce a reliable and repeatable testing method for MCGs. This project also evaluates the effect of different Frankfort-mandibular plane angles (FMA) in masticatory efficiency and produces a repeatable testing method to determine the mechanical and textural properties of MCGs. A Two-bite test was carried out using an Instron compression machine, which provided the foundation for evaluating how masticatory efficiency varies for different FM angles and determining MCG properties. Adaptors and teeth used in the experiment were designed on Siemens NX and manufactured using stainless steel and aluminium materials. The MCG investigated was 'Wrigley's Extra White' chewing gum containing the active ingredient Xylitol. A sensitivity analysis and information from past researchers were implemented into the test parameters of the Instron machine to simulate human mastication as closely as experimentally possible. After carrying out ten trials of the Two-bite test for three differently angled mandible adaptors, the average Two-bite test graph using each type of adaptor was used to calculate the MCG's properties and evaluate masticatory efficiency. The design of the human replica teeth proved to have a significant impact on the accuracy of masticatory efficiency when compared to a flat compression probe used by researchers in the past. An FM angle of 29.1° proved to be more efficient in chewing than an angle of 25° due to significantly less work done in compression and the required force to compress the MCG. Several textural properties also quantified the masticatory efficiency analysis. Any further analysis into the effect of FM angles on masticatory efficiency would need to incorporate several occlusal principles that could not be implemented by the Instron compression machine.

Supervised by Dr Kazem Alemzadeh

Department of Mechanical Engineering

University of Bristol

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Keywords: Medicated Chewing Gum (MCG), Two-bite test, Mastication, Occlusion, Mandible, Maxilla, Buccal, Lingual, Texture Profile Analysis.

Declaration

This project report is submitted towards an application for a degree in Mechanical Engineering at the University of Bristol. The report is based upon independent work by the candidate. All contributions from others have been acknowledged and the supervisor is identified on the front page. The views expressed within the report are those of the author and not of the University of Bristol.
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1 Introduction

1.1 Background

Medicated Chewing Gums (MCGs) is a drug delivery system that can aid the human body's absorption of multiple active pharmaceutical ingredients, offering several advantages to traditional oral dosage forms. For example, MCGs can provide a controlled release of medication over a period, and they can also improve medication adherence for patients who dislike swallowing pills. The pleasant texture of MCGs is crucial not only for their commercial success but also for their clinical significance. The MCG texture enhances patient compliance by increasing acceptance and regular usage of the gum. This, therefore, poses a requirement for several testing procedures to determine the mechanical and textural properties of MCGs [1]. Mastication is a complex function in humans involving the collaboration of teeth, muscles, and jaws to break down food items [2]. Given that the release of any pharmaceutical ingredient in an MCG is dependent on the chewing rate, analysing the efficiency of mastication is important for optimal drug delivery relating to treatment efficacy. Additionally, by evaluating chewing efficiency, researchers can investigate how well the MCG releases active ingredients and how well they are absorbed, ultimately providing optimal therapeutical effects. The masticatory efficiency can also be quantified using mechanical and textural properties of the MCG.

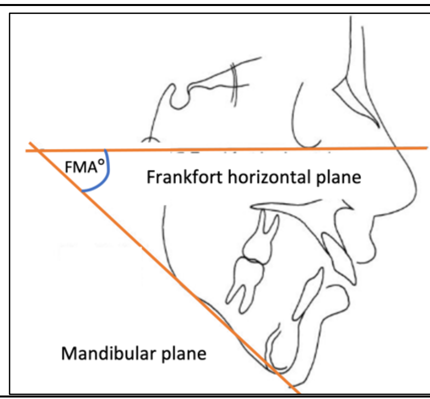

Figure 1: Frankfort-mandibular plane angle (FMA) [3].

Chewing efficiency can depend on several factors such as jaw angle & alignment, muscle function, oral sensory function, etc. Knowledge about how masticatory efficiency changes according to an individual's Frankfort-mandibular Plane Angle (FMA) is vital for the effective formulation of medicine within the gum in an MCG. The Frankfort-mandibular plane angle (FMA) is formed by the intersection of the jaw's horizontal plane acting as a datum, and the mandibular plane that is formed by the mandibular jaw [4], visualized in Figure 1.

1.2 Mechanics of Mastication

The widespread use of MCGs as a drug delivery system is also limited by the fact that there is a lack of a valid method to simulate the mastication of human teeth [5]. Mastication is composed of three food processing types: crushing, shearing, and grinding [6]. A proper simulation of human mastication would need to incorporate all three processing types, this project uses an Instron Universal Testing Machine (UTM) for the Two-bite test, which investigates the crushing and shearing processing types. Human replica molar teeth will be used as the compression probe of the Instron machine to simulate the crushing and shearing processing types. The Bennett movement of the mandible is a lateral shift in human jaws resulting from condyle movements during mastication [7]. Angled Instron machine adaptors mimicking different FM angles will be used to simulate the shearing of teeth, as the Bennett movement of the mandible cannot be carried out on the Instron machine.

1.3 Aims

This project aims to develop an experimental procedure that produces accurate, reliable, and repeatable results in measuring the mechanical and textural properties of MCGs. The mechanics of mastication will also be investigated to evaluate the chewing efficiency of MCGs for individuals with a range of different FM angles. An Instron compression machine will be used on MCGs to simulate human mastication, and a Two-bite test will be incorporated into the experiment to mimic the crushing and grinding of MCGs. A two-bite test is a valuable tool that has been used to measure the textural properties of food products by many food scientists in the past [5]. These aims require several objectives to be achieved for the successful measurement of MCG mechanical properties and evaluation of chewing efficiency.

1. Developing a reliable Two-bite test procedure using a custom Design of Experiment (DOE), inspired by past experiments and researchers.

2. Design, prototype, and manufacture adaptors for the Instron compression machine using different FM angles and then conduct Two-bite test.

3. Analysis of results from the Two-bite test for MCGs to determine their mechanical and textural properties.

4. Evaluate the impact of different FM angles on chewing efficiency by evaluating properties such as work done and hardness.

2 Literature Review

2.1 Medicated Chewing Gum

Medicated chewing gums, as defined by the European Pharmacopoeias, are solid single-dose preparations with a base consisting mainly of gum that is intended to be chewed for a certain period of time to deliver the dose, providing a slow, steady release of the medicine contained [5]. MCGs could represent an alternate and convenient dosage form to other existing oral mucosal drug delivery systems [1]. Transmucosal delivery refers to the systemic delivery of drugs through the mucous membrane of the oral cavity [8]. This drug delivery method is more efficient than traditional methods as it bypasses the digestive system and liver which normally breaks down the medication before it is absorbed into the bloodstream. Chewing the MCG also lowers the risk of drug overdose due to its relatively controlled release of the active ingredient into the bloodstream, also presenting a slow absorption option for certain medicines.

2.2 Texture Profile Analysis

Texture Profile Analysis (TPA) is an objective method that has been used by many researchers in the past to conduct a sensory analysis of food and pharmaceutical products [5]. The mechanical and textural properties of MCGs affect the overall effectiveness of drug delivery into the bloodstream and its acceptance as a valid medication delivery system in humans. A Two-bite test will form the foundation of TPA by subjecting the MCGs to a fixed compression distance. The resulting force, displacement, and time during compression provide the foundation for evaluating these properties. A variation in these properties can affect several important factors, such as the drug's release rate, palatability, and overall patient compliance towards their recommended dosage. MCGs lack acceptable testing methods that evaluate their mechanical and textural properties, and hence, it has remained a niche product in the pharmaceutical industry.

2.3 Two-bite Test

Mechanical and textural properties are determined by subjecting an MCG to two compression cycles (Two-bite) in a reciprocating motion that simulates the action of jaws [1]. This experiment generates a graph using the force, displacement, and time values from the two compression cycles, which are used to calculate the mechanical and textural properties of the MCG. The execution of the experiment is inspired by methods used by Al Hagbani, who investigated the properties of MCG tablets with high drug loadings [5]. The Two-bite test method is often used due to its simplicity in design and convenient data collection [9]. The test is conducted using a UTM that has two moving probes which simulate the maxilla and mandibular jaw movements. The probe speed and force can be controlled using various software connected to the UTM. The mandibular teeth on the lower jaw initiate chewing due to their ability to move vertically; maxilla teeth on the upper jaw are fixed and remain stationary during human mastication [10]. This project uses human replica molar teeth to model occlusion during mastication accurately.

The molar teeth are responsible for repetitive chewing due to their relatively larger occlusal contact area compared to other types of teeth that are more suited for tearing actions [11].

Conducting the Two-bite experiment on the MCG specimens allows for the production of a Force-Time graph, Figure 2 shows a typical Two-bite test graph. The mechanical and textural properties of MCGs can be calculated using equations 1 to 5, these equations use information extracted from the Two-bite test graph. Areas labelled A1 and A2 are calculated by integrating the graph with limits from A to D and B to C, respectively. All the relevant data that is needed to calculate these properties are labelled on different parts of the graph.

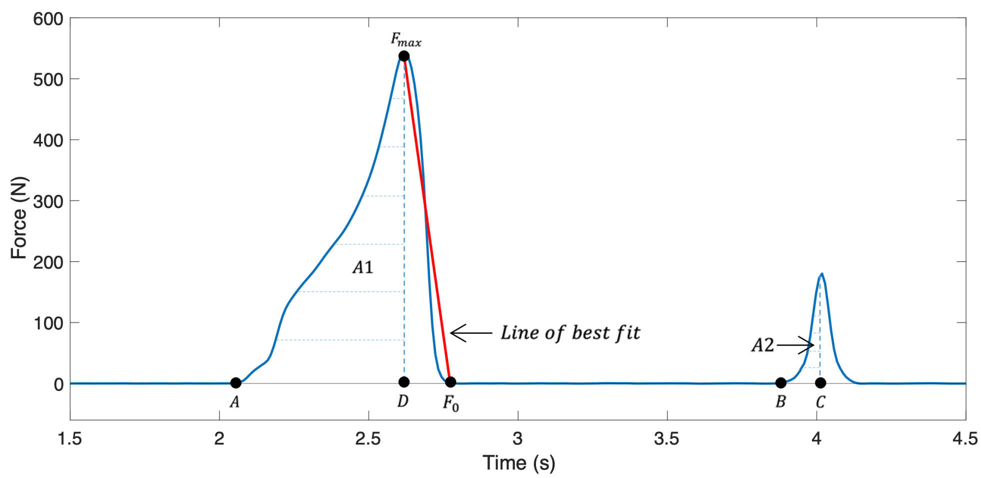

Figure 2: Typical Two-bite Force-Time graph highlighting the information needed for calculating the properties.

Considering the mechanical properties at first, the force peak on the Two-bite test graph (F_{max}) gives the hardness value of the MCG, which has a unit of N [5]. The hardness of the MCG indicates how much compressive force is required to reach a fixed depth in the MCG; this is an important parameter contributing to the evaluation of different FMA in masticatory efficiency. A high hardness value implies that a higher force is required to compress the MCG by a fixed distance, compared to a lower hardness value. The point where the force returns to zero (F_0) and force peak (F_{max}) are used to make a line of best fit, portrayed by the red line in Figure 2. The gradient of this line is defined as the Post-bite Structural Failure Rate (PSFR), which has a unit of kN/s. This parameter assesses the durability of MCGs, and it provides an indication about the likelihood of the MCG experiencing damage during mastication.

The work done during compression of the MCG is one of the most important parameters in the evaluation of different FMA in masticatory efficiency. A high work done value implies that mastication during that compression cycle is less efficient than a compression with a low work done value. Work done has a unit of J can be calculated using equation 1:

$$\text{Work done} = D1 + D2 \tag{1}$$

where, $D1$ and $D2$ are the areas under the Force-Displacement graph between times A to D, and B to C, respectively.

Now considering the textural properties of the MCG, compressibility is the ratio between the height (thickness) of the MCG after both compression cycles to their thickness before compression [5]. This parameter can provide information about a MCG's elasticity, density, and mechanical behaviour during compression. It can be calculated using equation 2 and is a ratio ranging from zero to one:

$$\text{Compressibility} = \frac{(d_{A-D} + d_{B-C})}{Original\ height} \tag{2}$$

where, d_{A-D} is the distance between points A and D, and d_{B-C} is the distance between points B and C in Figure 2. The reduction of MCG thickness after two compression cycles is given by d_{A-D} and d_{B-C}.

Cohesiveness is defined as the strength of internal bonds in the MCG. This parameter refers to the ability of the MCG substance to maintain its integrity during compression, it also provides manufacturers valuable information about the adhesion of particles within the gum after adding any active ingredients. It can be calculated by equation 3 and is a ratio ranging from zero to one:

$$\text{Cohesiveness} = \frac{A2}{A1} \tag{3}$$

where, $A1$ and $A2$ are the areas under the first and second compression cycles respectively, shown in Figure 2.

Springiness relates to the strength of the gum cell network and is used to describe the behaviour of the MCGs after the compression force was removed [5]. Like cohesiveness and compressibility, it can provide valuable information relating to the elasticity and deformation of the MCG. It is calculated by equation 4 and is a ratio ranging from zero to one:

$$\text{Springiness} = \frac{t_{B-C}}{t_{A-D}} \tag{4}$$

where, t_{B-C} is the time taken from point B to C and t_{A-D} is the time taken from point A to D in Figure 2.

Chewiness is defined as the force required to chew a solid food until it is ready and suitable for swallowing. The original equation from the Al Hagbani [5] experiment uses a constant force multiplied by cohesiveness and springiness. Since a varying force was applied to the MCG during the experiment, we use the hardness value (F_{max}) as our 'constant force'. This parameter provides important insights relating to sensory evaluation and ultimately concerns the consumer acceptance of MCGs. It is calculated by equation 5 and has a unit of N:

$$\text{Chewiness} = F_{max}\,\frac{A2}{A1}\,\frac{t_{B-C}}{t_{A-D}} \tag{5}$$

3 Design Review of Teeth and Adaptors

3.1 CAD Design and Manufacturing Process

A study led by Dr Alemzadeh (project supervisor) presented a 'humanoid chewing robot' to closely replicate the chewing motion of human jaws for drug delivery using MCGs [12]. The design of the teeth used for the Two-bite test in this project is provided by the supervisor. The maxilla and mandible teeth are designed on Siemens NX CAD software [13] and are designed so that the blunt and pointed cusp of the mandible and maxilla jaws are directly parallel and intersecting with each other to accurately mimic human teeth occlusion, as seen in Figure 3(a) and 3(b). The alignment of the buccal/facial occlusal line and central fossa line plays an invaluable role in harmonious contact of the replica teeth during mastication, visualised in Figure 3(b). This alignment also ensures the occlusal forces are evenly distributed across the MCG during contact, this also provides accurate force readings during the Two-bite test which is crucial for TPA. The molars are labelled M1, M2, and M3 from left to right in Figure 3(a) for referencing purposes within this project. They have an approximate surface area of 48mm^2. Each adaptor was threaded with a 38mm Unified National Fine (UNF) thread so that a nut could be fabricated and then used to tighten the adaptors to the Instron machine base plate and load cell.

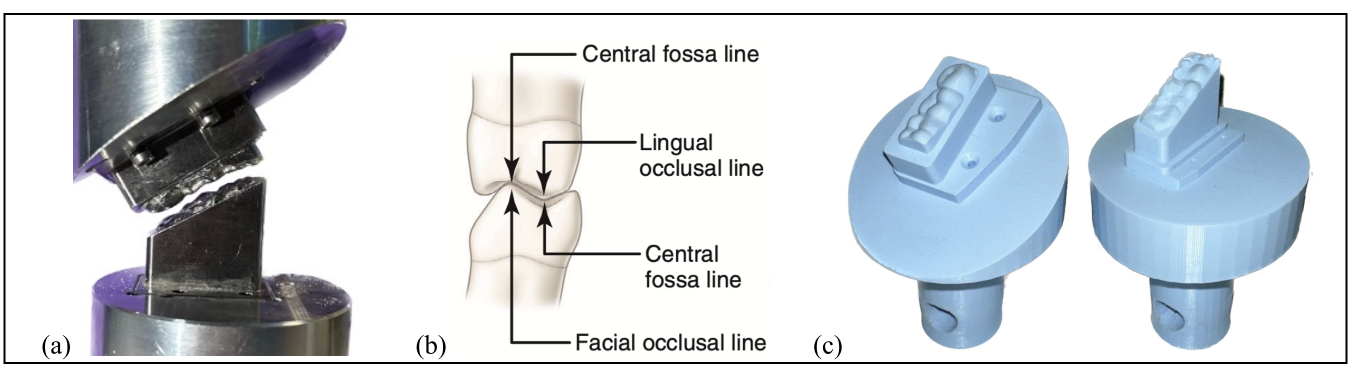

Figure 3: Maxilla and mandible (a) teeth occlusion and (b) alignment of occlusal and fossa lines [14]. (c) 3D-printed prototype of Instron machine adaptors.

In the interest of accuracy and reliability of the Two-bite test, the adaptor assembly designed on Siemens NX underwent rapid prototyping using a 3D-printed thermoplastic PLA (polylactic acid) before the adaptors were machined, as seen in Figure 3(c). The 3D-printed adaptors were then fitted onto the Instron compression machine to identify any misalignment, incorrect fitting, or irregular occlusion of the human replica teeth. The rapid prototyping of the adaptors proved to be an important measure during this project, as the 3D-printed adaptors had some misalignment issues that needed modifications on Siemens NX before the adaptors were machined. Section 3.3 provides greater detail of the errors identified in the 3D-printed model and their respective design optimisations.

The angle of the mandible adaptor had to be carefully designed on NX to accurately mimic the FM angles. Occlusal relationships of the maxilla and mandible molar teeth were maintained using the ‘assembly cut’ feature. Upon changing the angle of the adaptor, the occlusal plane angle of the teeth had to change by the same amount. Figure 4 displays the creation of a mould in preparation for the ‘assembly cut’ feature within the NX environment. This feature is a tool used to create complex cut-outs of parts within an assembly, and it is used to change the FM angle of both maxilla and mandible adaptors within the assembly. The mould is made so that an assembly cut can be performed on a blank maxilla adaptor during the creation of a specific FM angle. Several ‘assembly constraints’ were implemented into the maxilla and mandible adaptor assembly within the NX environment to ensure the human replica teeth align perfectly in all three axes and so that proper human teeth occlusion can be simulated, this is outlined in Table 1.

Table 1: Assembly constraints implemented on Siemens NX to maintain correct occlusion of maxilla and mandible teeth.

NX constraint	Affected components from the constraint	Effect of constraint on assembly design
Cylindrical Joint	Maxilla and mandible adaptors	Constraints the shaft of both adaptors to the same singular axis.
Parallel	Maxilla and mandible teeth and adaptors	Ensures the angle of the teeth component is parallel to the face of the adaptor notch where the teeth are meant to sit. It also ensures the occlusal planes of maxilla and mandible teeth are parallel.
Fix	Maxilla adaptor	Ensures that the mandible adaptor is the immobile one and that the maxilla one remains stationary during mastication.

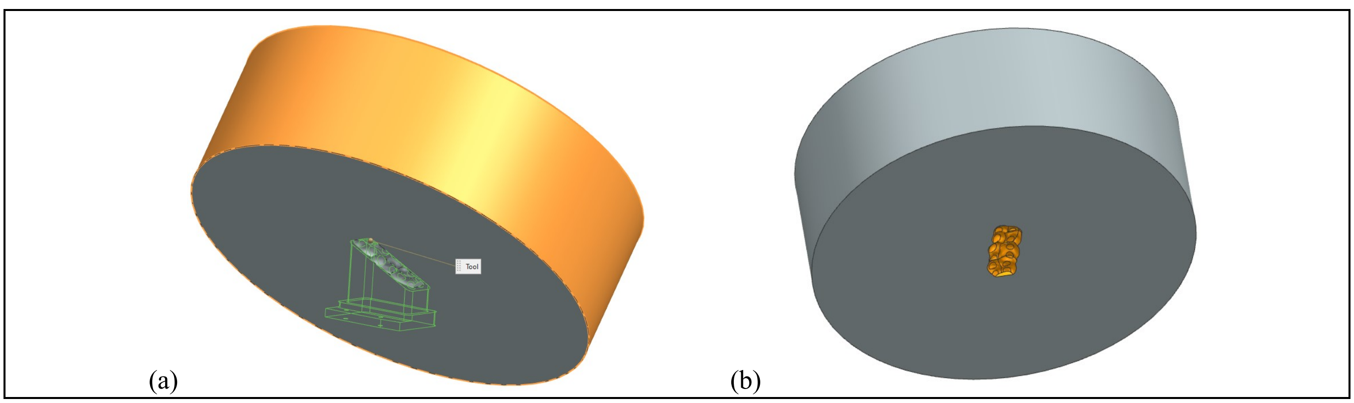

Figure 4: (a) Silhouette of maxilla teeth profile to create a (b) mould using the ‘assembly cut’ feature on Siemens NX.

After the adaptor design was optimised on Siemens NX, detailed engineering drawings of the adaptors and teeth were generated so that they could be machined in aluminium and stainless steel material. Figure 5 portrays a summary of the manufacturing process for human replica teeth and adaptors from the engineering drawings stage till the final machined product.

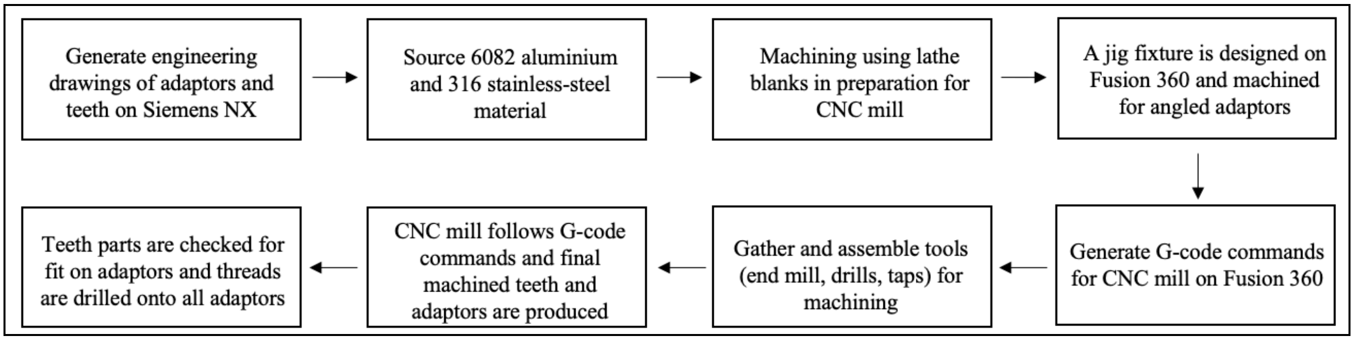

Figure 5: Overall machining process after producing engineering drawings on Siemens NX.

3.2 Frankfort-mandibular plane angle

Two mandible adaptors with angles of 25° and 29.1° each were machined to mimic two different FM angles. The masticatory efficiency of these two FM angles is evaluated in section 6. Humans tend to have FM angles ranging between 20° and 30° [4], and hence 25° was chosen as it is the midpoint between the normal range. In addition, the 'humanoid chewing robot' developed by Dr Alemzadeh [12] has a FM angle of 29.1°, hence this angle was chosen to compare masticatory efficiency. This is because the FMA and overall design of the humanoid chewing robot are taken from an actual human skull. Figure 6 displays the machined adaptors and teeth in stainless steel and aluminium material.

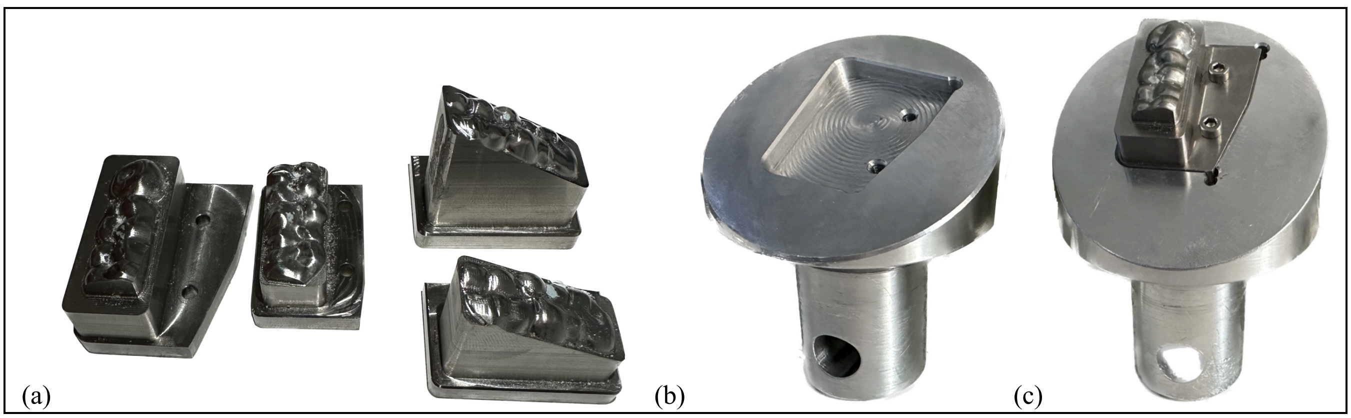

Figure 6: (a) Stainless steel human replica molar teeth, (b) 25° aluminium mandible adaptor, (c) 29.1° aluminium mandible adaptor with screwed on molar teeth.

3.3 Design optimisations

The preliminary testing of the Two-bite experiment using 3D-printed teeth and adaptor models resulted in several errors in adaptor design, which could affect the integrity of results obtained from the Two-bite test if left unchanged. Firstly, it was found that the hole dimension of the adaptor shaft and the shaft diameter were incorrect for the Instron machine's base plate, load cell, and pin that secures each adaptor in place. The dimensioning discrepancies were measured using Vernier callipers and adjusted on the NX model. Additionally, the replica teeth components were made too tight for the adaptor notch in Figure 6(b). As a result, a tolerance of +0.1 mm was added to the engineering drawings of all adaptors on the NX model. A threaded insert that uses M3x0.5mm screws with 5mm depth ensured that the teeth components were tightly fixed onto the adaptor during the experiment. The teeth were also not correctly aligned during the occlusion of an MCG, the cusps of the maxilla and mandible teeth collided incorrectly, as seen in Figure 7(a), which were later corrected and further refined. Given that the MCG is placed on the maxilla teeth, located at the bottom of the Instron testing environment, an optimised design of a sleeve was used to hold the MCG in place during occlusion whilst using angled mandible adaptors. The sleeve also ensured that the MCG was in contact with the same teeth cusps (M1 and M2) during every trial. Alternatively, to secure the MCG in a fixed position, the first design of the MCG holder used two wooden planks, a polyolefin sleeve, and a zip tie, as seen in Figure 7(b). This design was prone to lateral movement of the MCG during occlusion in the preliminary Two-bite test, which affected the force reading of the MCG. As a result, an optimised

3D-printed MCG sleeve/holder was designed on NX that prevented the lateral movement of the MCG during occlusion, as seen in Figure 7(c).

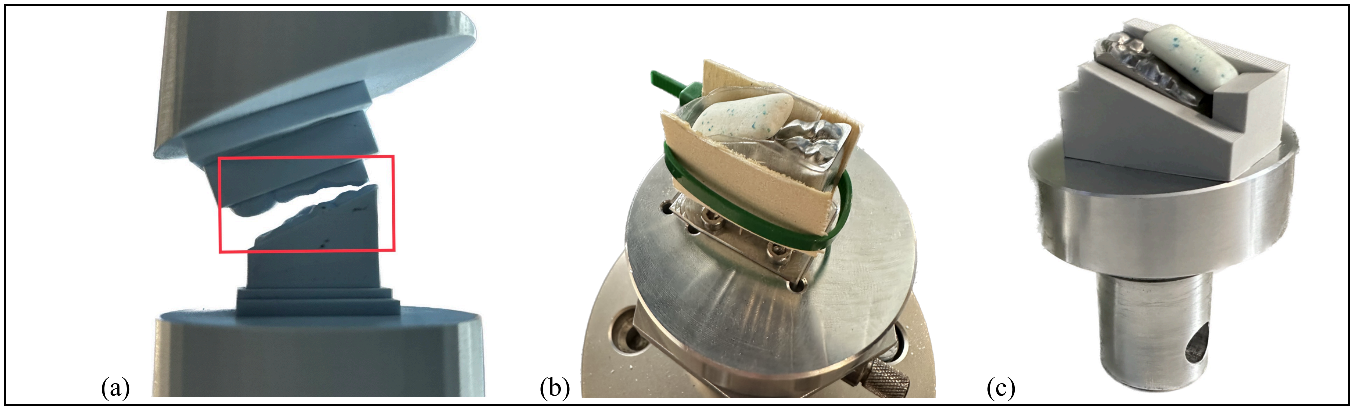

Figure 7: (a) Incorrect occlusion of maxilla and mandibular teeth, (b) preliminary design of MCG holder, and (c) optimised 3D-printed design of MCG holder.

Figure 8 outlines the step-by-step process of all the design decisions discussed in section 3 with the aim of simulating human mastication using the Two-bite test as accurately as possible.

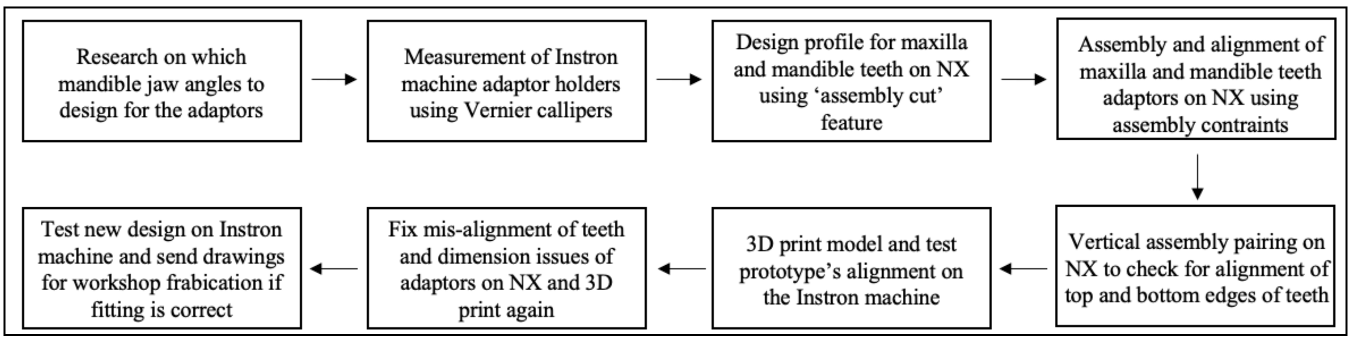

Figure 8: Overall summary of the design review for fabrication of teeth and adaptors for the Two-bite test.

4 Method – Two-bite Test Parameters

4.1 Apparatus

The Two-bite experiment was carried out using an Instron 50kN 2580 series compression machine that uses Bluehill Universal software to set test parameters and export the required data. The choice of MCG used for the experiment is 'Wrigley's Extra White chewing gum', containing 0.08 grams of the active ingredient Xylitol per gum [16]. Xylitol is an active ingredient used in chewing gums as a substitute for sugar, it provides several health benefits, such as reducing the risk of tooth decay, plaque, and ear infections [17]. Before the test parameters were set, the dimensions of the MCG specimen needed to be measured to set an appropriate compression distance. The MCG specimen has dimensions: 22.4 x 10.8 x 6.5 mm and was measured using Vernier callipers. For the Two-bite test to produce reliable and repeatable results, the compression height of the MCG and compression speed of the Instron machine probe must be set so that it mimics human mastication as closely as experimentally possible. As a result, the Two-bite test parameters were researched and tested through preliminary experimental work before conducting the actual test. Figure 9(a) displays the test assembly before occlusion for the Two-bite test using a mandible adaptor of 29.1°. Figure 9(b) displays the test assembly during occlusion (75% MCG compression) using the flat mandible adaptor.

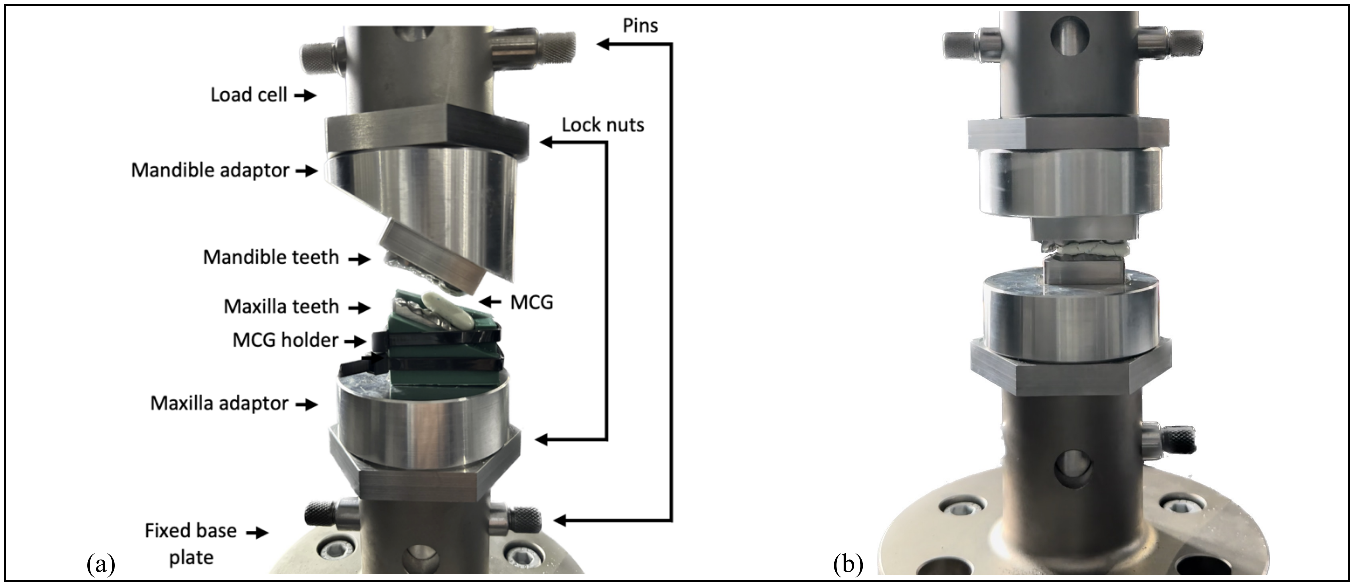

Figure 9: Apparatus of maxilla adaptor assembled with (a) 29.1° mandible adaptor at 0% MCG compression and maxilla adaptor with (b) flat mandible adaptor at 75% MCG compression.

4.2 Compression Height and Speed

During the Two-bite test, the Instron machine load cell probe (mandibular teeth) compressed the MCG by 75% of its original height (4.88mm). This compression height was chosen to ensure the MCG underwent sufficient structural breakdown for an accurate calculation during its TPA. This value was also a common deformation percentage used by many researchers in the past conducting a Two-bite test on various foods and has become the standard deformation used for this type of experiment [18].

The load cell was manually controlled until an edge of the mandible teeth touched the top of the MCG. A detection force of 1N was used to ensure the manual vertical placement of the load cell did not interfere with the structural integrity of the MCG shell before the Two-bite test was conducted. After the detection force was achieved, the compression probe was brought to a set distance of 20mm above the MCG as a starting point for the Two-bite test. The set distance of 20mm above the MCG was chosen so that the compression probe has enough travel distance to reach a constant acceleration before compressing the MCG. Differences in compression probe acceleration could cause significant discrepancies in the impact force due to changes in momentum and hence, affect the MCG's TPA.

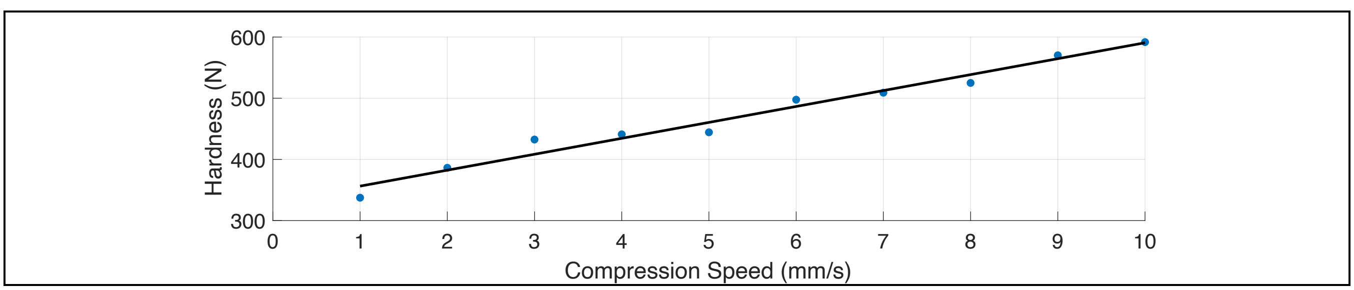

Figure 10: Graph displaying the effect of the compression probe speed on the hardness of the MCG.

A study written by A. J. Rosenthal [18] was conducted in the past to identify how the different testing parameters affect the MCG's TPA. Rosenthal claims that a compression speed more than 2 mm/s makes "little difference to hardness". To verify this statement so that an appropriate compression speed can be used, a sensitivity analysis was conducted using 75% compression of total MCG height to visualise the effect of compression speed on MCG hardness, as seen in Figure 10. The results reject Rosenthal's claim as there was a clear positive linear correlation in compression speed and the MCG's hardness. Several studies looking into the speed of biting have estimated that the human jaw moves at speeds between 33-66 mm/s [18]. The Instron compression machine used for this project's Two-bite test travels at a maximum speed of 10 mm/s. As a result, a compression speed of 10 mm/s was used for the Two-bite test to best resemble human mastication within the Instron testing environment.

4.3 Test Repetition and Delivery

The Two-bite test was repeated ten times for each of the flat, 25°, and 29.1° mandible adaptors, ultimately using thirty MCG specimens in total. Between each trial, the human replica teeth were cleaned so that any MCG residue was removed before starting the next trial. Given that the MCG sits on M1 and M2 of the replica teeth during the Two-bite test using the angled adaptors, the MCG was placed on the same two molars during the test with the flat adaptor, as seen in Figure 9. Differences in MCG placement could significantly affect force readings as the MCG's compression is very sensitive to the molar cusp's radius of curvature [19]. After the force, time, and compression probe displacement data from all the trials was extracted using the Bluehill software, the MCG's Texture Profile Analysis was carried out using equations 1 to 5 in section 2.3. Figure 11 outlines a step-by-step process for the execution of the Two-bite test using the custom DOE test parameters and designed teeth and adaptors.

Screw teeth on adaptors and secure adaptors on Instron machine base plate and load cell using pins and lock nuts → Place MCG on M1 and M2, then manually position load cell 20mm above the top shell of MCG → Re-balance the force to zero and set test parameters for 10mm/s probe speed and 4.88mm displacement

↓

Begin Two-bite test, then export force, displacement, and time data. Repeat for a total of ten trials for each mandible adaptor → Use the average force, displacement, and time values from the ten trials to plot the Force-Time graph, seen in Figure 2 → Find A1 and A2 values via integration, record F_{max}, F_0, A, B, C, D data points and conduct TPA using equations 1-5

Figure 11: Step-by-step process to conduct Two-bite test using the Instron compression machine.

5 Results

5.1 Two-bite test graphs

Figures 12, and 13, and 14 display the results of the Two-bite test for the flat, 25°, and 29.1° mandible adaptors respectively. Although ten trials were performed for each type of mandible adaptor, the graphs display the maximum, minimum, and average force peaks to visualise the variation of data between the two extremes.

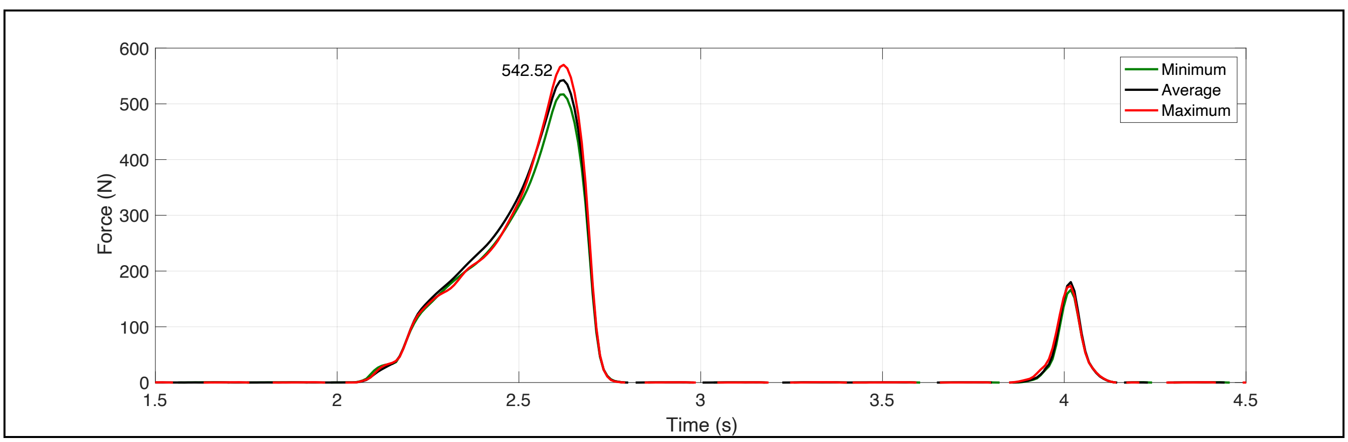

Figure 12: Two-bite test graph for flat maxilla adaptor and flat mandible adaptor displaying variation between the maximum and minimum extremes.

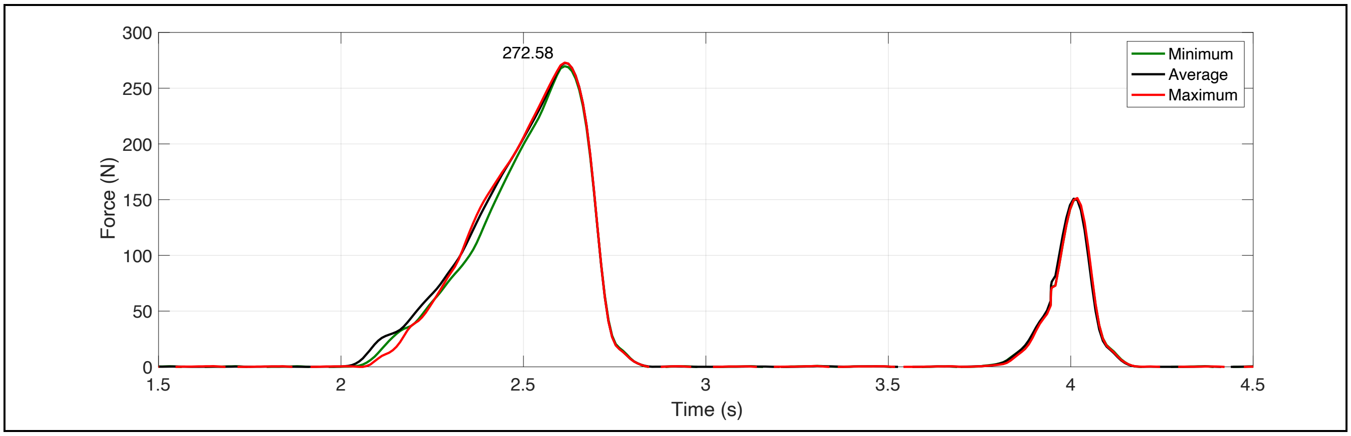

Figure 13: Two-bite test graph for flat maxilla adaptor and 25° mandible adaptor displaying variation between the maximum and minimum extremes.

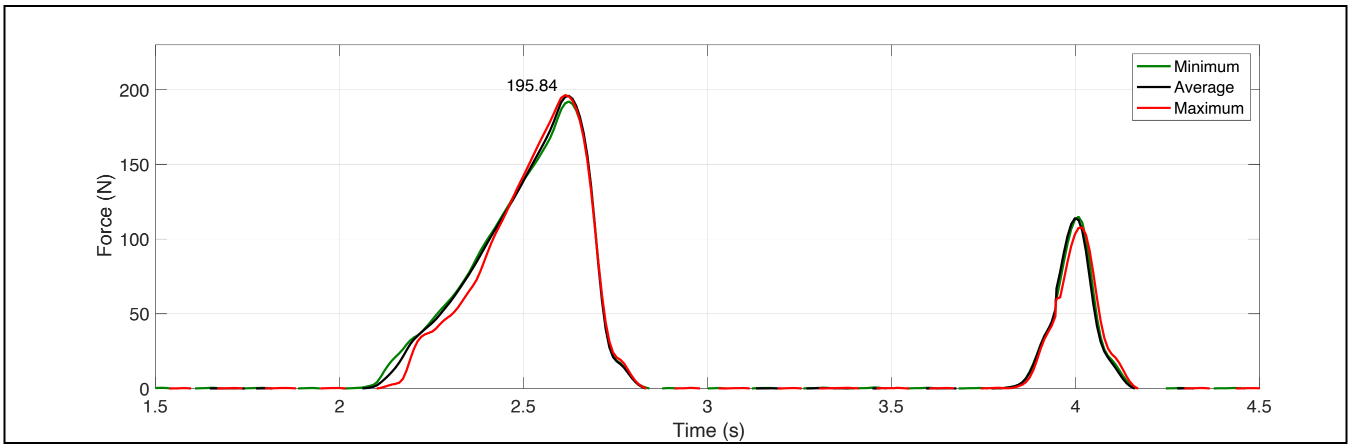

Figure 14: Two-bite test graph for flat maxilla adaptor and 29.1° mandible adaptor displaying variation between the maximum and minimum extremes.

5.2 TPA results

Figures 15, 16, and 17 provide a graphical representation of the TPA results, this analysis used the average Two-bite test graph for the three different types of mandible adaptor. Error bars are included to visualise the small uncertainties in data caused by the two extremes: maximum and minimum values from the Force-time graphs in Figures 12, 13, and 14.

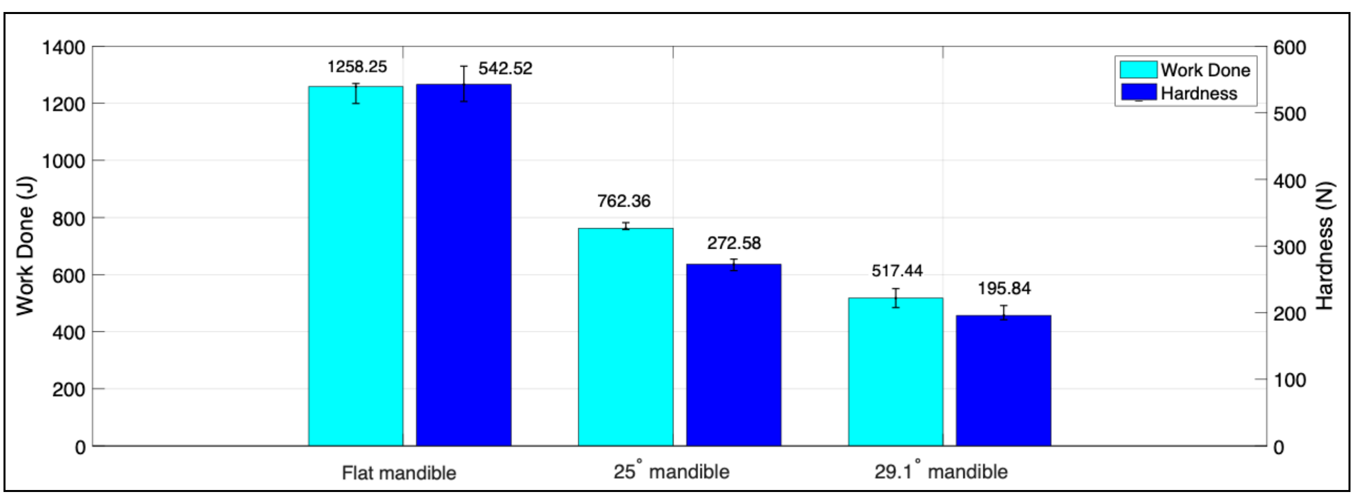

Figure 15: Work done during compression and hardness values for each type of mandible adaptor.

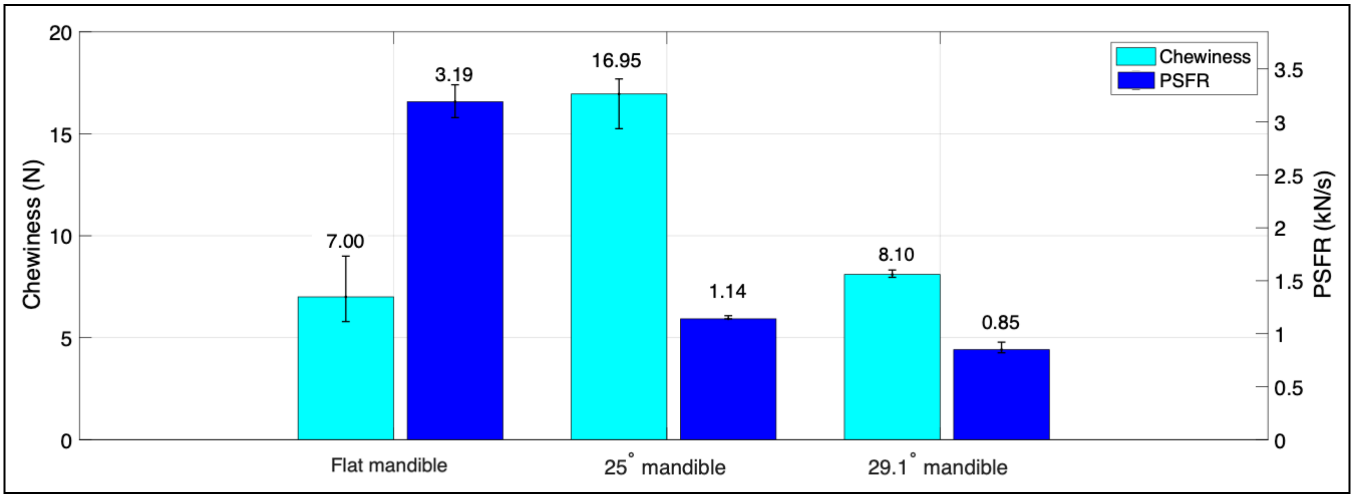

Figure 16: Chewiness and Post-bite Structural Failure Rate (PSFR) values for each type of mandible adaptor.

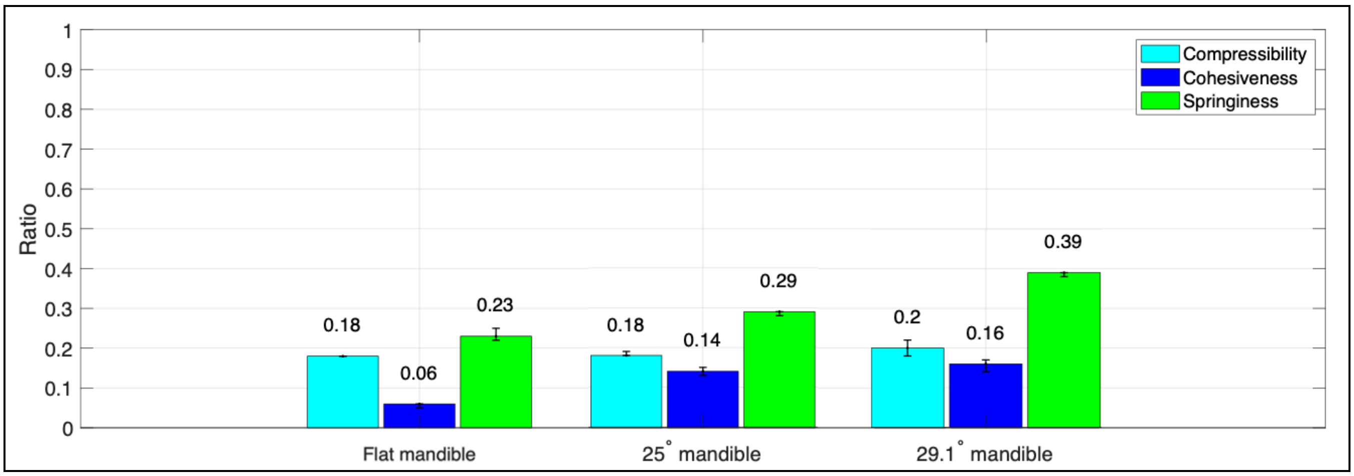

Figure 17: Compressibility, Cohesiveness, and Springiness values for each type of mandible adaptor.

6 Discussion

The formulation of a medicated chewing gum combines the elastic properties of chewable gum and the brittleness of a powdered medicated tablet. As a result, this report presents a custom DOE method using the Two-bite test to evaluate the mechanical and textural properties of MCGs. A primary challenge faced by past researchers in the development of MCGs for oral drug delivery is the attempt to balance chewing gum's texture while preserving sufficient powdered medication. The properties calculated in this project also quantify the masticatory efficiency analysis, further explained in section 6.1. Textural properties such as compressibility, cohesiveness, springiness, and chewiness are important characteristics of the MCG that would need to be examined and tested upon adding any active ingredients during the manufacturing of MCGs.

6.1 Mechanical and Textural Properties

In Figure 17, it can be observed that the Two-bite test conducted at an FM angle of 29.1° exhibits greater values for compressibility, cohesiveness, and springiness properties compared to the Two-bite test conducted at an FM angle of 25°. A higher FM angle adds more shear force to the MCG during occlusion, and hence, the polymers within the MCG are more compact. These compressed polymer chains are the reason for the higher compressibility and cohesiveness values between the two FM angles. This also implies that the MCG is likely to be more elastic, which is supported by the higher springiness value at the higher FM angle. Given that chewiness relates to the resistive force applied by the MCG during mastication, Figure 16 displays that an FM angle of 29.1° requires less force to chew the MCG by the set amount (75% compression) compared to the 25° FM angle. This is also due to the additional shear forces experienced by the MCG due to the higher FM angle. Both mandible adaptors with two different FM angles resulted in higher values for all four properties when compared to the flat mandible adaptor, therefore validating the fact that the angled adaptor design simulates the shearing forces during human mastication. This can be seen as a strength to the custom DOE of this project, as many past researchers conducted the Two-bite test with a flat compression probe [18]. Lastly, the PSFR value is synonymous with the hardness value for the three different types of mandible adaptors since the flat mandible adaptor had the highest force peak, as seen in Figures 16 and 15, respectively. A high PSFR suggests that the MCG can break apart or disintegrate more easily after several chews, meaning that the MCG was not broken down into small particles properly, there implying a lower mastication efficiency. Figure 16 shows that the 29.1° FMA is the most efficient in relation to its lowest PSFR out of the three FMA designs.

6.2 Masticatory Efficiency with FMA

Mechanical properties such as work done and hardness provide a direct indication of how different FMA affect masticatory efficiency. Figure 15 shows that work done during compression for the 29.1° mandible adaptor is 28.2% lower than that of the 25° mandible adaptor meaning that it requires less energy to chew the MCG. Given that the human replica teeth used in this project are unable to replicate the Bennett movement of the mandible [7], the two different angles of the mandible adaptors induce a shearing force accurately enough to evaluate masticatory efficiency between the 25° and 29.1° FMA. Similarly, Figure 15 also shows that the 25° mandible adaptor has a higher hardness value than the 29.1° mandible adaptor. This implies that a higher compressive force is required to compress the MCG by 75% of its original height. As a result, the combination of the crushing and shearing forces led to a higher mastication efficiency in the 29.1° mandible adaptor, evidenced by the work done and hardness values. This conclusion is supported by a study conducted by G. J. DiPietro [20] in the study of occlusion as related to the FM angle.

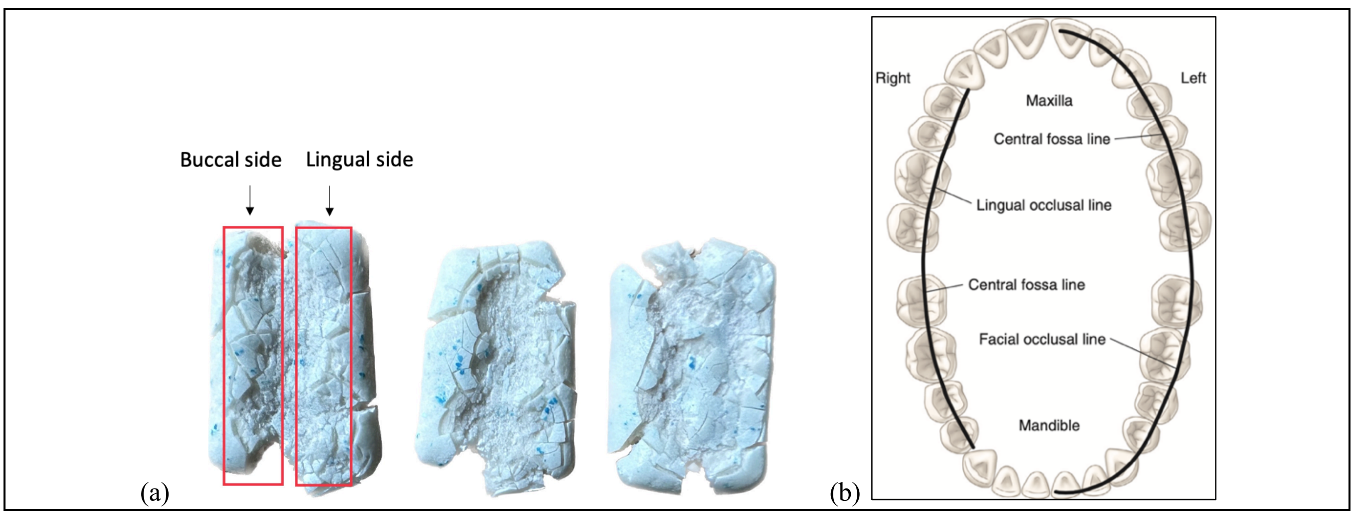

Figure 18: (a) MCG after occlusion during the Two-bite test for each type of mandible adaptor, and (b) dental arch cusp and fossa alignment [14].

Given that the design of the angled adaptors has proved to simulate the shearing forces during mastication, an evaluation of the crushing force simulated by the design of the human replica teeth is now discussed. The human replica teeth design inspired by the humanoid chewing robot developed by the project supervisor, Dr Kazem Alemzadeh, is optimised for human occlusion and hence provides a reliable simulation of human mastication. The buccal/facial and lingual sides of the three molars are designed in a way that their cusps and grooves interlock with each other, therefore providing an accurate simulation of the crushing of the MCG. This is indicated in Figure 18(a), which shows the contact of the MCG with both the buccal and lingual side of the teeth during the Two-bite test using all three types of mandible adaptor. The mandibular facial/buccal occlusal line and the maxilla central fossa line coincide, which is imperative to the accuracy of occlusion by the molars [14], visualised in Figure 18(b) below. To validate the integrity of the molar design, the hardness and work done in compression of the MCG using the flat (0°) mandible adaptor are compared to the results of Zelin Li [15], who evaluated the effect of different tooth shapes on masticatory efficiency. Zelin conducted the Two-bite test using the same test parameters, number of trials, and TPA as this project, using a flat plate design with approximately the same surface area (48 mm^2) as the human replica teeth. Table 2 displays the variation in work done and hardness using human replica teeth from this project and Zelin's flat plate compression probe. The use of human replica teeth results in a substantial decrease of 35.5% and 86.6% in the work done and hardness values, respectively. Although the Instron UTM can only perform compression loading that directly simulates crushing, the replica teeth design also simulates a shearing force due to the morphology of the teeth. The buccal (outer) side applies compressive forces relating to crushing due to the opposing buccal cusps of the maxilla and mandible molars. The lingual (inner) side applies a shearing force as the tongue pushes food into the occlusal zone of the mouth [22].

Table 2: Comparison of work done and hardness values using replica teeth and flat plate design for flat mandible adaptors.

	Work Done (J)	Hardness (N)
Human replica teeth	1258.25	542.52
Flat plate teeth	1950.6	4053.49

6.3 Strengths of the project

There are several strengths in this project's Two-bite test DOE and overall TPA that resulted in calculating the MCG properties and evaluating masticatory efficiency. Firstly, the Instron UTM was set up to mimic human mastication as closely as possible in the available testing environment. Upon carrying out a sensitivity analysis of the compression probe speed, outlined in section 4.2, it led to falsify claims made by Rosenthal [18] regarding the hardness of the MCG remaining unchanged after the compression probe speed exceeds 2mm/s. The design of the adaptors used for the Instron compression machine simulated the shearing force of the human molars well for the experiment done in vitro. This is justified by the results obtained from figures 15, 16, and 17 being in line with DiPietro's study relating to the FMA [20]. Given that the placement of the MCG on the molars plays a big role in the force values, the optimised design of the MCG holder, seen in Figure 7(c) of section 3.3, ensured that the MCG experienced occlusion on the same two molars (M1 and M2) throughout all the tests. The accuracy of the TPA carried out on the MCGs relies on the repeatability of the Two-bite test and the logic in the difference of properties for the three FMA investigated. Figures 12, 13, and 14 show that the Two-bite test resulted in a very low force variation across multiple trials, therefore proving the repeatability of the custom DOE developed in this project. The low uncertainty, represented by small error bars in Figures 15, 16, and 17, also supports this statement.

Additionally, the machine simulation of the Two-bite test via the Instron UTM ensures that the entire experiment can be carried out comprehensively without any reliance on human subjects. This also ensures that the experiment is run multiple times in a controlled environment and there is no human error affecting the integrity of the experiment.

6.4 Limitations of the project

Although this project has produced reasonable results through the evaluation of masticatory efficiency and overall TPA, any further advancements, such as calculating more properties or evaluating factors outside the FM angle affecting masticatory efficiency, would be limited to this project's custom DOE. For instance, given that human mastication reaches speeds between 33-66mm/s [18], the compression probe speed of the Instron machine is limited to 10mm/s and may not simulate human mastication very accurately. Additionally, although the angled mandible adaptors simulate enough of a shearing force to conclude that a 29.1° FMA is more efficient than a 25° FMA, any further investigation into mastication efficiency would need to incorporate the effects of the Curve of Spee. The presence of the Curve of Spee in human jaws ensures the dentition in humans resists the mechanical forces of occlusion during mastication. It is defined as the curvature of the mandibular occlusal plane [21], visualised in Figure 19(a). An optimised DOE evaluating mastication efficiency should incorporate these principles as it increases the crush/shear ratio of the force applied on MCG by the posterior molars [22].

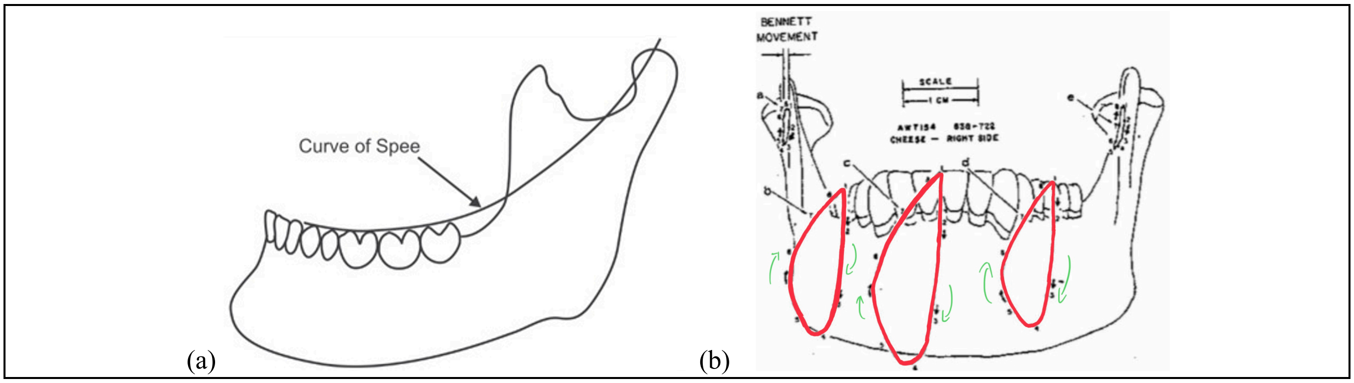

Figure 19: (a) the Curve of Spee [23] and (b) frontal trajectories due to Bennett movement during mastication [24].

Additionally, jaw movement in humans normally follows the Bennett movement, and it consists of a combined vertical and horizontal series of movements, visualised by the red trajectory in Figure 19(b). The Instron machine is limited to only vertical movement and cannot simulate actual mandibular mastication trajectories. Therefore, the force values obtained from this project's Two-bite test do not simulate masticatory forces in the human jaw with 100% accuracy. A study conducted by Estevam B. investigated the normal and lateral forces during mastication; he combined these forces into a resultant occlusal force [25]. In Estevam's study, he states that simplifying the occlusal force to just the normal (vertical) force and not considering lateral forces will induce errors in the study of the observed mechanical phenomena.

6.5 Future Work

To develop this project further in the measurement of properties and evaluation of FMA on mastication efficiency, the Two-bite test could be optimised further by incorporating several occlusion principles mentioned in sections 6.3 and 6.4. Conducting the Two-bite test with a ZwichRoell Amsler hydraulic machine will not limit the compression probe speed to 10mm/s and hence could mimic actual human mastication speeds. The torsional setting of the Roell Amsler machine would also be able to provide a more accurate effect of the Curve of Spee and crush/shear ratio. A future DOE should aim to implement the Bennett movement of the mandible; hence a 3D modelling of the masticatory forces would need to be evaluated. This could be achieved by attaching strain gauges or force transducers to the molar teeth to capture forces in all three axes, inspired by the study conducted by Estevam. These enhanced force readings during mastication could significantly improve the reliability of investigating the effect of different FMA on masticatory efficiency.

The evaluation of masticatory efficiency with a changing FMA can also be further developed by considering several clinical characteristics of the human jaw. G. J. DiPietro's study relating to the significance of FMA to prosthodontics states that there are several parts of the jaw that change simultaneously with the FMA. For example, an individual with a high FMA would have a relatively large molar size, decreased molar abrasion potential, and convex facial profile of the teeth, and vice versa for an individual with a low FMA. Employing these changing clinical characteristics in the human replica teeth and adaptor design would provide a better estimation of the FMA's effects on masticatory efficiency. Lastly, the replica molar teeth used in this project undergoes occlusion only on M1 and M2 molars for the consistency of results, a better simulation of human mastication would be to simulate occlusion randomly on all three molars, given that humans do not always chew gum on a consistent set of two molars.

7 Conclusion

Conclusively, the custom DOE for the Two-bite test carried out within this project resulted in successfully determining several mechanical and textural properties of the MCG. Test parameters such as the compression probe speed and compression distance of the MCG proved to be an important consideration in the development of the test, as the results can significantly change with different test settings. The sensitivity analysis and study about the test parameters past researchers used for the Two-bite test resulted in optimised test settings for the Two-bite test. The low standard deviation observed in Figures 12, 13, and 14 of the Two-bite test graphs is apparent. This limited variability in the data resulted in values characterised by relatively small error bars during the MCG's TPA, also seen in figures 15, 16, and 17. Moreover, the calculations involving work done and the maximum compressive force (hardness) values for mandible adaptors with FM angles of 29.1° and 25° align with previous FMA studies conducted by researchers. This validation ultimately confirms the analysis of masticatory efficiency within this project.

Considering the project's strengths and possible future advancements, it is worth noting that the Two-bite test was conducted to the best of its experimental capabilities using the Instron machine. However, there is potential for further progress in evaluating masticatory efficiency by optimising the crush/shear ratio and implementing the Curve of Spee and Bennett movement of the mandible. The angled mandible adaptors and human replica teeth simulated shearing well enough to determine that an FMA of 29.1° is more efficient than 25°. Lastly, the Two-bite test can be replicated on a Roell Amsler hydraulic machine to simulate the crushing, shearing, and grinding processing types better than the Instron machine.

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9 References

[1] T. Al Hagbani and S. Nazzal, "Medicated Chewing Gums (MCGs): Composition, Production, and Mechanical Testing," *AAPS PharmSciTech*, vol. 19, no. 7, pp. 2908–2920, Aug. 2018, doi: https://doi.org/10.1208/s12249-018-1123-z.

[2] "Mastication - an overview | ScienceDirect Topics," *www.sciencedirect.com*. https://www.sciencedirect.com/topics/immunology-and-microbiology/mastication

[3] "View Image," *www.jorthodsci.org*. https://www.jorthodsci.org/viewimage.asp?img=JOrthodontSci_2018_7_1_19_240726_f2.jpg

[4] G. J. DiPietro and J. R. Moergeli, "Significance of the Frankfort-mandibular plane angle to prosthodontics," *The Journal of Prosthetic Dentistry*, vol. 36, no. 6, pp. 624–635, Dec. 1976, doi: https://doi.org/10.1016/0022-3913(76)90026-3.

[5] T. Al Hagbani and S. Nazzal, "Development of postcompressional textural tests to evaluate the mechanical properties of medicated chewing gum tablets with high drug loadings," *Journal of Texture Studies*, vol. 49, no. 1, pp. 30–37, Aug. 2017, doi: https://doi.org/10.1111/jtxs.12287.

[6] Hiroshi Fukoe, C. P. Basili, R. Slavicek, S. Sato, and S. Akimoto, "Three-dimensional analyses of the mandible and the occlusal architecture of mandibular dentition," *International Journal of Stomatology & Occlusion Medicine*, Aug. 2012, doi: https://doi.org/10.1007/s12548-012-0053-8.

[7] E. Fanucci *et al.*, "Bennett movement of mandible: a comparison between traditional methods and a 64-slices CT scanner," *ORAL & implantology*, vol. 1, no. 1, pp. 15–20, 2008 [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3476501/

[8] J. K. W. Lam *et al.*, "Transmucosal drug administration as an alternative route in palliative and end-of-life care during the COVID-19 pandemic," *Advanced Drug Delivery Reviews*, vol. 160, pp. 234–243, 2020, doi: https://doi.org/10.1016/j.adDr2020.10.018.

[9] K. Nishinari, Y. Fang, and A. Rosenthal, "Human oral processing and texture profile analysis parameters: Bridging the gap between the sensory evaluation and the instrumental measurements," *Journal of Texture Studies*, vol. 50, no. 5, pp. 369–380, May 2019, doi: https://doi.org/10.1111/jtxs.12404.

[10] M. Komino and H. Shiga, "Changes in mandibular movement during chewing of different hardness foods," *Odontology*, vol. 105, no. 4, pp. 418–425, Feb. 2017, doi: https://doi.org/10.1007/s10266-016-0292-z.

[11] W. L. Xu, D. Lewis, J. E. Bronlund, and M. P. Morgenstern, "Mechanism, design and motion control of a linkage chewing device for food evaluation," *Mechanism and Machine Theory*, vol. 43, no. 3, pp. 376–389, Mar. 2008, doi: https://doi.org/10.1016/j.mechmachtheory.2007.03.004.

[12] K. Alemzadeh, S. B. Jones, M. Davies, and N. West, "Development of a Chewing Robot With Built-in Humanoid Jaws to Simulate Mastication to Quantify Robotic Agents Release From Chewing Gums Compared to Human Participants," *IEEE Transactions on Biomedical Engineering*, vol. 68, no. 2, pp. 492–504, Feb. 2021, doi: https://doi.org/10.1109/tbme.2020.3005863.

[13] "NX software | Siemens Software," *Siemens Digital Industries Software*. https://plm.sw.siemens.com/en-US/nx/

[14] L. W. Boushell and J. R. Sturdevant, "1 - Clinical Significance of Dental Anatomy, Histology, Physiology, and Occlusion," *ScienceDirect*, Jan. 01, 2019. https://www.sciencedirect.com/science/article/abs/pii/B9780323478335000010?via%3Dihub

[15] Zelin, L., 2023. *3rd Year Individual Research Project: Measuring mechanical property of medicated chewing gum and evaluating efficiency for different teeth shapes,* s.l.: University of Bristol

[16] N. Alshibani, M. Shalabi, K. AlMugbel, E. AlSaqer, N. AlFarraj, and E. Allam, "Xylitol content and acid production of chewing gums available in the markets of Saudi Arabia," *The Saudi Dental Journal*, Nov. 2021, doi: https://doi.org/10.1016/j.sdentj.2021.11.001.

[17] "XYLITOL: Overview, Uses, Side Effects, Precautions, Interactions, Dosing and Reviews," *www.webmd.com*. https://www.webmd.com/vitamins/ai/ingredientmono-996/xylitol#

[18] A. J. ROSENTHAL, "TEXTURE PROFILE ANALYSIS - HOW IMPORTANT ARE THE PARAMETERS?," *Journal of Texture Studies*, vol. 41, no. 5, pp. 672–684, Jul. 2010, doi: https://doi.org/10.1111/j.1745-4603.2010.00248.x.

[19] M. A. Berthaume, E. R. Dumont, L. R. Godfrey, and I. R. Grosse, "How does tooth cusp radius of curvature affect brittle food item processing?," *Journal of the Royal Society Interface*, vol. 10, no. 84, pp. 20130240–20130240, Jul. 2013, doi: https://doi.org/10.1098/rsif.2013.0240.

[20] G. J. DiPietro, "A study of occlusion as related to the Frankfort-mandibular plane angle," *The Journal of Prosthetic Dentistry*, vol. 38, no. 4, pp. 452–458, Oct. 1977, doi: https://doi.org/10.1016/0022-3913(77)90100-7.

[21] S. Tamizharasi and K. Senthil Kumar, "Significance of curve of Spee: An orthodontic review," *Journal of Pharmacy and Bioallied Sciences*, vol. 4, no. 6, p. 323, 2012, doi: https://doi.org/10.4103/0975-7406.100287.

[22] J. W. Osborn, "Orientation of the masseter muscle and the curve of Spee in relation to crushing forces on the molar teeth of primates," *American Journal of Physical Anthropology*, vol. 92, no. 1, pp. 99–106, Sep. 1993, doi: https://doi.org/10.1002/ajpa.1330920108.

[23] "JaypeeDigital | Short Notes," *www.jaypeedigital.com*. https://www.jaypeedigital.com/book/9788180614156/chapter/ch2.

[24] W. L. Xu *et al.*, "Review of the human masticatory system and masticatory robotics," *Mechanism and Machine Theory*, vol. 43, no. 11, pp. 1353–1375, Nov. 2008, doi: https://doi.org/10.1016/j.mechmachtheory.2008.06.003.

[25] E. B. de Las Casas, A. F. de Almeida, C. A. Cimini Junior, P. de T. V. Gomes, T. P. M. Cornacchia, and J. M. E. Saffar, "Determination of tangential and normal components of oral forces," *Journal of applied oral science: revista FOB*, vol. 15, no. 1, pp. 70–76, Feb. 2007, doi: https://doi.org/10.1590/s1678-77572007000100015.