Denture adhesives are widely used by denture wearers to improve the retention and stability of removable dental prostheses and enhance masticatory function.\textsuperscript{1,2} There are a number of attributes that contribute to the effectiveness of a denture adhesive: the fixative should provide sufficient adhesion to both the oral tissue and the denture so that the dentures can be held in place as soon as they are seated in the mouth; the mucilage of the fixative should be spread over the denture-mucosa interface to seal the denture in place; the adhesive must exhibit sufficient resistance to degradation when exposed to environmental changes that can occur in the oral cavity during common actions such as drinking hot or cold beverages; and the adhesive must be releasable so the dentures can be removed for cleaning and maintenance.\textsuperscript{3–5}

Early denture adhesives were based on highly water-soluble natural plant gums that could absorb water from saliva and swell to form a viscous, mucilaginous gel layer adhering to both the oral mucosa and the denture. Modern denture adhesives are synthesized from natural or synthetic polymers in combination with antimicrobial agents, binding agents, humectants, flavoring agents, and plasticizers.\textsuperscript{6} Today, the most common of the polymeric ingredients is the methyl vinyl ether/maleic anhydride copolymer known as Gantrez (Ashland). Current research is focused on developing different polymer systems that provide better efficacy and improved acceptability for consumers.

Key barriers to consumer adoption of Gantrez-based technologies are the poor organoleptic properties of these products and the difficulty of removing these products from the denture.

Two experimental denture adhesives based on different combinations of celluloses and medium-chain mono-, bi-, and triglycerides have been developed and tested in laboratory conditions with formulations free of Gantrez and excipients such as petrolatum, mineral oil, and alcohol. In addition, the products were formulated to be smooth, self-supporting gels rather

\textbf{Purpose:} To assess the efficacy of two experimental denture adhesive gels (adhesives 1 and 2) compared to a commercially available denture adhesive cream (positive control) and no adhesive (negative control). \textbf{Materials and Methods:} This was a single-center, randomized, four-treatment, examiner-blind, crossover study in participants with well-made and at least moderately well-fitting maxillary complete dentures. Incisal bite force until denture dislodgment was measured before application (baseline) and over the following 12 hours for each of the treatments. Between-treatment differences in the area over baseline (AOB) for the bite force at each time point were analyzed using an analysis of covariance model. \textbf{Results:} The efficacy and safety analyses were based on results from 48 participants. Compared to the negative control, adhesive 1 showed a statistically significantly higher bite force AOB over 12 hours (AOB\textsubscript{0–12h}; primary endpoint), as well as for AOB\textsubscript{0–6h} and AOB\textsubscript{0–9h} (all \(P < .05\)), but not for AOB\textsubscript{0–1h} or AOB\textsubscript{0–3h}. Adhesive 2 was not significantly different from the negative control or from adhesive 1 for any measure of AOB. The positive control was associated with a significantly higher bite force AOB than either of the experimental adhesives for all time points (\(P < .05\)). Although the positive control was well tolerated, both experimental adhesives were associated with a larger number of oral adverse events. \textbf{Conclusion:} Only adhesive 1 was significantly better than the negative control, and its performance did not match that of the positive control. Adhesives 1 and 2 showed the largest number of oral adverse events.


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than creams and were designed to optimize esthetic features while maintaining hold characteristics. The adhesive gels were evaluated in in vitro studies, the results (outcome measures turbidimetry, adhesive profile, and adhesive strength) of which demonstrated significant improvements in both appearance and hold characteristics (GSK Consumer Healthcare [GSKCH], data on file). The present clinical study was designed to ascertain whether these advantages demonstrated in vitro translated into clinical benefits.

Several recognized methods have been used to measure the effectiveness of denture adhesives, including the Kapur Index\(^7,8\) and bite force\(^9\) to measure denture retention and stability; denture dislodgment to measure denture movement in function\(^3\); and masticatory performance to assess chewing efficiency.\(^7\)

The primary objective of this proof-of-principle study was to use a bite force transducer system\(^8,10\) to compare incisal bite force until dislodgment of maxillary complete dentures for each of the two experimental adhesives compared to no adhesive (negative control) and a commercially available adhesive (positive control) over 12 hours (area over baseline \([AOB]_{p-12h}\)). The experimental formulations were compared to the negative control at the other time points up to 9 hours and to the benchmark positive control at all time points (secondary objectives).

### Materials and Methods

#### Study Design

This was a single-center, proof-of-principle, randomized, four-period, four-treatment, examiner-blind, crossover clinical trial conducted in participants with well-made and at least moderately well-fitting maxillary complete dentures. The study was conducted at the Oral Health Research Institute and was approved by the Indiana University Institutional Review Board (IRB# 1509956638) before initiation. Participants were recruited from the study site’s volunteer database. Written informed consent was obtained from all participants before implementation of any study procedure. The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. There was one minor administratively well-fitting maxillary arch restored with a stable complete, partial, or implant-supported denture were included in the study. Maxillary dentures had to be at least moderately well fitting at the screening visit, as assessed by the examiner using the Olshan modification of the Kapur Index (retention score \(\geq 2\) [fair to excellent], stability score \(\geq 2\) [fair to excellent]).\(^7,8\) Dentures needed to meet this criterion because the use of denture adhesives is not recommended as a means of improving retention of poorly made or ill-fitting dentures.\(^6\) Both maxillary and mandibular dentures (if present) had to be judged by the examiner to be well made; the criteria for which included being constructed from an acceptable material, with adequate vertical dimension, freeway space, horizontal occlusal relationships, and border extension; having an acceptable contour and finish; and having acceptable porosity, tissue surfaces, polished surfaces, color, and thickness.

Eligible participants were required to have a qualifying maxillary incisal bite force measurement without adhesive of \(\leq 9\) lb (4.1 kg) at screening and at baseline for all test visits. At least two of the four qualifying bite force measurements at screening needed to be reproducible (\(\pm 2\) lb [0.9 kg]). At subsequent visits, the bite force readings had to be within 2 lb (0.9 kg) of the qualifying value for one of the three practice bites and the pretreatment baseline bite.

Participants were excluded from the study if they were pregnant or breastfeeding; had a Class III malocclusion or any clinically significant or relevant oral abnormality that could affect participation; reported having a severe dry mouth (score of 11 to 15 on a Dry Mouth Index, a modification of the Dry Mouth Inventory\(^11-13\)); had an implanted cardiac pacemaker; were taking a medication that might interfere with study participation; had an allergy or intolerance to the study materials/ingredients; or were unwilling to refrain from using tobacco products or e-cigarettes for the duration of screening and on each test day.

#### Study Procedures

At the screening visit, participants were assessed for eligibility and the ability to perform the bite force maneuver. On test days, participants were requested not to apply any adhesive to their dentures before attending the clinic. On arrival, participants removed their dentures, which were cleaned by site staff using Polident denture cleansing paste (GSKCH) and Oral B denture brushes (Procter & Gamble). An oral soft tissue (OST) examination was performed, and then, if applicable, the mandibular denture was secured with Super Poligrip Free denture adhesive cream (GSKCH) before baseline incisal bite force measurements were recorded (see below). Application was according to
manufacturer instructions; in brief, equal-sized short strips of denture adhesive cream were applied in the areas corresponding to the center, the left, and the right fitting surfaces of the dentures and to the left and right fitting surfaces of the mandibular partial dentures if necessary.

Participants with acceptable qualifying pretreatment baseline bite force measurements were randomized to receive one of four study treatments on each of the four test days:

- Experimental adhesives 1 and 2: Both experimental adhesives contained ethyl cellulose, propylene glycol dicaprylate/dicaprate, medium-chain triglyceride, carbopol, glyceryl caprylate/caprate, and glycerin in different proportions.
- Positive control: Super Poligrip Free denture adhesive cream containing polyvinylmethyl ether/maleic acid, sodium-calcium mixed partial salt, petrolatum, cellulose gum, and mineral oil.
- Negative control: No adhesive.

Participants had either a measured quantity (1 ± 0.05 g) of one of the three denture adhesives applied to their dry maxillary denture or went without adhesive (negative control) before further bite force measurements were recorded. The product was applied to the clean and dry fitting surfaces of the maxillary dentures in a pattern consistent with the instructions of the product label. Only single applications of the study treatments were permitted on each test day. As stabilization of the mandibular denture was necessary for bite force measurements to be performed, Super Poligrip Free denture adhesive cream could be reapplied to the mandibular denture a maximum of twice on each test day if the investigator deemed it necessary for bite force measurements and provided the participant had been compliant with the protocol and had not actively washed the adhesive out. After the last bite force measurement had been recorded, dentures were removed and a final OST was performed. To minimize the possibility of carryover effects, a washout period of at least 24 hours was scheduled between each test day.

As this was a crossover study, participants were assigned to the order in which they were to receive each treatment according to a computer-generated randomization schedule supplied by the Biostatistics Department of GSKCH. Randomization numbers were assigned in ascending numeric order according to the sequence in which participants were confirmed as eligible for study inclusion. To maintain blinding, denture adhesive was dispensed and applied by independent staff members who were not involved in the study assessments. The examiner was blinded to treatment allocation, and the participants were instructed not to reveal whether denture adhesive had been used to secure their maxillary denture. The study statistician, data management staff, and other employees of GSKCH who could have influenced study outcomes were also blinded to treatment allocation.

**Efficacy Measurements**

A bite force transducer system was used to measure the incisal bite force needed to dislodge the maxillary denture.\(^9\)\(^{10}\) The transducer system is comprised of two plates embedded with a strain gauge that measures displacement of the maxillary denture during biting. With the participant seated and holding their head so that the occlusal plane was parallel to the floor, a trained examiner helped the participant insert the bite force plates into their mouth. Participants were asked to first swallow and then to bite on the plates until they felt movement on the maxillary denture, at which time they were instructed to release the bite plate. The examiner ensured that each bite by a participant was made consistently at the same place on the transducer with evenly increasing force and ensured that the participants were not consciously or subconsciously holding their dentures in place. To minimize interexaminer variability, the same examiner conducted all bite force measurements for an individual participant. The examiner was a trained and calibrated dental hygienist.

During the screening visit, the examiner recorded triplicate practice bite force measurements without denture adhesive while the participant became accustomed to the equipment. Four further measurements were then recorded, two of which were required to be ≤ 9 lb (4.1 kg) and reproducible (± 2 lb [0.9 kg]) for the participant to be eligible for inclusion in the study. On each test day, the examiner initially recorded triplicate practice bite force measurements without denture adhesive while the participant refamiliarized themselves with the equipment. A fourth bite, which was required to be ≤ 9 lb (4.1 kg) and within ± 2 lb (0.9 kg) of one of the first three practice bites, was then recorded as the test day pretreatment baseline bite force. Additional bite force measurements were recorded at 0.5, 1, 3, 6, 9, and 12 hours after application of the study treatment. For those in the negative control group, bite force measurements were recorded at the same times, following insertion of the denture. At each posttreatment time point, the participant first swallowed and then bit on the transducer until the maxillary denture dislodged. No posttreatment bite force measurements were made earlier than the specified time, and all were made no later than 5 minutes after the specified time.
Participants’ preferences for the experimental adhesives with regard to flavor, texture, product ooze, and ease of denture removal was assessed as a secondary objective, but is not reported here.

Safety Assessments

Safety was assessed by OST examination findings, and adverse events (AEs) were reported by participants following treatment. AEs were categorized as oral or non-oral, and the intensity was graded as mild, moderate, or severe. AEs were deemed to be treatment emergent if they occurred after the first supervised use of the randomized treatment and up to 5 days following the last administration of the treatment product.

Statistical Analyses

It was planned to screen approximately 60 participants in order to randomize 56 participants to ensure that 46 participants completed the study. This sample size would provide 90% power to detect a between-treatment difference at 12 hours of 1.577 lb (0.7153 kg) using a two-sided t test at the 5% significance level and assuming a residual standard deviation (SD) of 2.281 lb (1.035 kg). The estimate of SD was based on a previous study (GSKCH, data on file). No sample size adjustments were made for multiplicity.

The primary efficacy variable was the incisal bite force until denture dislodgment AOB0–12h. The area under the curve (AUC) for bite force time was calculated using the trapezoidal method and using nominal timepoints from 0, 0.5, 1, 3, 6, 9, and 12 hours, respectively:

$$\text{AUC} = \frac{1}{2} \sum_{i=0}^{8} (t_{i+1} - t_i) (y_{i+1} + y_i)$$

AUC was calculated for the interval i starting at the time (t0) of the baseline reading (y0) and ending at the time (t12) of the last valid reading (y12). The transformation ([AUC/12] minus baseline) returned the measurement to the same scale as the original observations while also looking at the average amount of improved force over time (AOB) by subtracting the baseline value. Higher AOB values demonstrate a stronger bite force over time than lower values. Although a bite force measurement was recorded at 0.5 hours, this time point was not analyzed based on historical observations suggesting no expected statistical differences; however, this measurement was included in the AOB calculations for greater accuracy.

For both primary and secondary variables, an analysis of covariance model was used with AOB values as the response, treatment group and period as fixed-effect factors, and participant-level baseline bite force value and period-level pretreatment baseline bite force value (parameterized as period-level baseline minus participant-level baseline) as covariates. Participant was included as a random effect. Treatment differences between groups, with 95% confidence intervals and P values, were obtained from the above model. All significance tests were conducted at the two-sided 5% significance level. Statistical and/or graphical procedures were used to assess and confirm that the assumptions of normality and homogeneity of variance were met.

The primary population for the efficacy analyses was the intent-to-treat (ITT) population, defined as all randomized participants with at least one postbaseline assessment of efficacy. The per-protocol (PP) population was a subset of the ITT population; participants with a protocol violation that was deemed to affect efficacy assessments in all study periods were excluded from the PP population. Analyses of safety were made on the safety population, defined as all participants who were randomized and received treatment at least once during the study. All statistical analyses were conducted using SAS version 9.2 (SAS Institute).

Results

The first participant was enrolled on October 15, 2015, and the last completed the study on February 18, 2016. A total of 52 participants were enrolled, 48 of whom were randomized to study treatment. One participant was withdrawn from the study after failing to produce a qualifying baseline bite force measurement on test day 3. All randomized participants were included in the ITT, PP, and safety populations (Fig 1). Participants had a mean age of 71.9 (SD 9.77) years (range 50 to 89 years), were predominantly female (60.4%), and were white (60.4%) or black/African American (39.6%). Of the 48 participants, 47 had a mandibular denture, of which 35 were complete and 15 were partial.

Efficacy

For the primary efficacy variable of incisal bite force until denture dislodgment AOB0–12h, adhesive 1 achieved a statistically significantly higher AOB0–12h compared to the negative control (P < .05; Table 1). This was not seen with adhesive 2. There was no statistically significant difference in incisal bite force AOB0–12h between adhesives 1 and 2, although both were statistically significantly inferior to the positive control (both P < .0001) (Fig 2).

Incisal bite force AOB over all other time points generally mirrored the results over 12 hours. The positive
control demonstrated a statistically significantly higher incisal bite force AOB over all time points compared to both experimental adhesives ($P < .05$). Adhesive 1 was associated with significantly higher incisal bite forces AOB$_{0-6h}$ and AOB$_{0-9h}$ than the negative control (both $P < .05$). Adhesive 2 was not significantly different from the negative control or adhesive 1 at any time point.
Effect of Denture Adhesives on Bite Force

Safety

A total of 49 treatment-emergent AEs (TEAEs) were reported by 27 participants (56.3%) (Table 2). The majority of TEAEs (40/49; 81.6%) were oral. Thirty-five of the TEAEs (33 oral, 2 non-oral) reported by 23 participants (47.9%) were considered to be treatment related, the most common of which was oral discomfort in the adhesive 1 and adhesive 2 groups. There was one treatment-related TEAE in the group receiving the positive control (gingival erythema). The two non-oral treatment-related TEAEs (nasal discomfort, throat irritation) were single instances reported with adhesive 2. All TEAEs were mild in intensity, and no participant withdrew from the study because of a TEAE. Most TEAEs were resolved by the end of the study, except for gingival erythema and decreased urine output (both with adhesive 1).

Figure 2: Mean incisal bite force (lb) until dislodgment over time (intent-to-treat population; n = 48). Data are raw mean ± standard error; data points have been offset for clarity.

Table 2: Treatment-Emergent Adverse Events (TEAEs) (Safety Population; n = 48)

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Adhesive 1 (n = 47)</th>
<th>Adhesive 2 (n = 48)</th>
<th>Positive control (n = 48)</th>
<th>Negative control (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>AE (n)</td>
<td>n (%)</td>
<td>AE (n)</td>
</tr>
<tr>
<td>At least 1 TEAE</td>
<td>12 (25.5)</td>
<td>13</td>
<td>22 (45.8)</td>
<td>30</td>
</tr>
<tr>
<td>At least 1 oral TEAE</td>
<td>10 (21.3)</td>
<td>11</td>
<td>21 (43.8)</td>
<td>25</td>
</tr>
<tr>
<td>Treatment-related TEAEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral discomfort</td>
<td>7 (14.9)</td>
<td>7</td>
<td>19 (39.6)</td>
<td>19</td>
</tr>
<tr>
<td>Oral paresthesia</td>
<td>1 (2.1)</td>
<td>1</td>
<td>4 (8.3)</td>
<td>4</td>
</tr>
<tr>
<td>Gingival erythema</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Oral pain</td>
<td>1 (2.1)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-oral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal discomfort</td>
<td>0</td>
<td>0</td>
<td>1 (2.1)</td>
<td>1</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>0</td>
<td>0</td>
<td>1 (2.1)</td>
<td>1</td>
</tr>
</tbody>
</table>
Discussion

This proof-of-principle study was designed to test the efficacy of two experimental denture adhesive formulations compared to a commercially available adhesive and to no adhesive. The experimental adhesives were new gel formulations based on different combinations of ethyl celluloses and medium-chain mono-, bi-, and triglycerides. These performed well during laboratory studies, showing greatly improved adhesive strength and adhesion profile (tensile force) under a 500-N load compared to the positive control (GSKCH, data on file), which led to the decision to evaluate their effectiveness as denture adhesives in a clinical bite force study.

The positive control performed as expected, providing good adhesion as shown by the high and sustained incisal bite force values throughout the 12-hour study period, similar to published and unpublished data. While the population studied had well-made and at least moderately well-fitting maxillary complete dentures, studies have shown denture adhesives to be of use in those with poor-fitting dentures, though use of denture adhesives is not recommended as a substitute for refining fit. However, in contrast to the in vitro assessments, in the clinical setting both the experimental adhesive products were significantly less effective than the positive control in terms of incisal bite force, and adhesive 2 was no different from the negative control at any AOB time point.

While previous studies have shown the utility of in vitro models, this study highlights the limitations regarding the currently available in vitro models and their ability, in this instance, to translate to real-world retentive properties of denture adhesives. The laboratory models are often based on retention between acrylic plates and do not adequately simulate the adhesive forces in play within the oral mucosa. The reasons for this disparity are unclear, but may include participant-related factors such as salivary flow and oral contour pattern. Bite force until dislodgment as a method to assess dentures has been used in several trials and shown to be a reliable way to study changes before and after use of a denture adhesive, as well as to measure differences between denture adhesives.

Although the positive control was well tolerated, there were a considerable number of AEs associated with use of the experimental adhesives, particularly adhesive 2.

Conclusions

The present study showed that while the experimental adhesives performed well compared to each other, they did not perform as well as a marketed adhesive. Only adhesive 1 was significantly better than the negative control, and the performance did not match that of the positive control. Owing to their performance, together with the larger number of oral AEs, it is not anticipated that either experimental adhesive formulation will be developed further.

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All of the authors contributed to the design, conduct, and reporting of the study. All authors had access to the final study report, made contributions to the development of the manuscript, had final responsibility for the decision to submit, and approved the submitted version.

A.J., R.V., N.R., S.M., and R.J. are employees of GSKCH. A.G. is employed by the Indiana University School of Dentistry, which received funding for this study from GSKCH.

References


**Literature Abstract**

**Biology of Teeth and Implants: Host Factors—Pathology, Regeneration, and the Role of Stem Cells**

In chronic periodontitis and peri-implantitis, cells of the innate and adaptive immune systems are involved directly in the lesions within the tissues of the patient. Absence of a periodontal ligament around implants does not prevent a biologic process that is similar to periodontitis from affecting osseointegration. The first focus of this study was on biologic factors that are responsible for the susceptibility of individuals to chronic periodontitis and to peri-implantitis, such as genetic factors, which are of significant importance in the susceptibility to these diseases. The host's genetic factors affect the composition of the oral microbiome in the same manner that they influence other microbiomes, such as those of the intestines and lungs. The study's second focus was on the central role of stem cells in tissue regeneration, in the functioning of innate and adaptive immune systems, and in metabolism of bone. Epithelial cell rests of Malassez (ERM) are stem cells of epithelial origin that maintain the periodontal ligament as well as the cementum and alveolar bone associated with the ligament. The tissue niche within which ERM is found extends into the supracrestal areas of collagen fiber–containing tissues of the gingivae above the bony alveolar crest. Maintenance and regeneration of all periodontal tissues involves the activity of a variety of stem cells. The success of dental implants indicates that important groups of stem cells in the periodontium are active to enable that biologic success. Successful replantation of avulsed teeth and auto-transplantation of teeth are comparable to placing dental implants and so must also involve periodontal stem cells. Biology of teeth and implants represent the biology of the various stem cells that inhabit specialized niches within the periodontal tissues. Diverse biologic processes must function together successfully to maintain periodontal health. Osseointegration of dental implants does not involve formation of cementum or collagen fibers inserted into the cementum, indicating that some stem cells are not active around dental implants or that their niches are not available. Investigation of these similarities and differences between teeth and implants will help to develop a better understanding of the biology and physiologic functioning of the periodontium.