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Analysis of the residual monomer content in milled and 3D-printed removable CAD-CAM complete dentures: an in vitro study

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ABSTRACT

Objective: The study aimed to quantitatively evaluate the elution of methylmethacrylate from CAD-CAM manufactured removable complete dentures (RCDs) using high performance liquid chromatography (HPLC).
Methods: Thirty-two RCDs were manufactured following either the CNC-milling (Milled: n=8) or the 3D-printing (n=24) protocols. The 3D-printed dentures were further categorized into three groups based on their post-production rinsing cycles [Extended wash cycle (EWC), Standard wash cycle (SWC), and SWC with an additional Durécon coating (SWC2)]. HPLC was used to evaluate the methylmethacrylate concentrations (MMCs) eluted from the dentures in each group for different time periods (1, 2, 4, 8, and 24 hours). Mean and standard deviations were calculated for the MMCs; data was verified for normal distribution, ANOVA and post hoc tests were applied for statistical analyses (α=0.05).
Results: The HPLC revealed that all the denture groups recorded some amounts of MMCs, with significant differences [$F(3, 31) = 23.646$, $p<0.0001$]. The milled denture group had the highest MMCs at 24 hours when compared to the EWC ($p<0.0001$), SWC ($p=0.001$), and SWC2 ($p<0.0001$) denture groups. SWC had a higher MMC than EWC ($p=0.032$) and SWC2 ($p=0.015$). No differences were found in MMCs when comparing EWC and SWC2 ($p=0.989$).
Conclusion: Methylmethacrylate concentrations were significantly lower in 3D-printed RCDs than in milled RCDs when using the resins employed in this study. Furthermore, the MMCs can be further decreased in 3D-printed RCDs when coated with an additional thin protective layer (Durécon) by following the manufacturer-recommended rinsing protocol or when an extended isopropanol wash cycle is adopted.

1. Introduction

Polymethylmethacrylate (PMMA) resin has been employed as an ideal denture base material since its clinical validation in the late 1930s [1]. Nearly a century later, this polymer still continues to be the material of choice and an established 'gold standard' for manufacturing removable complete dentures (RCDs) [2]. The PMMA resin's unparalleled popularity could be attributed to its simplicity in processing, color-stability, optical properties, compatibility, lightweight, and low cost. Despite the stated advantages, low impact strength and the release of residual methyl methacrylate (MMA) monomer are but a few of the known drawbacks of this material [3,4]. The resin's physical and mechanical properties have been successfully augmented by reinforcements with metal, fibers such as carbon/silane-treated

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glass/polyethylene, and more recently, with halloysite nanotubes [5–9].

The presence of residual monomer in dentures is detrimental to its physical properties and could alter the surface characteristics, dimensional stability, water sorption, and compatibility [10]. Furthermore, the infiltration of the monomer from the denture into the soft tissue, or its presence in the saliva may lead to a multitude of problems such as allergic reactions, stomatitis, oral ulcerations and even burning sensations [11–14]. To minimize the residual monomer content and its harmful effects, the use of heat-polymerized PMMA in combination with different polymerization techniques, extended curing times at high temperature together with the application of high pressure have been suggested [12,15-18]. However, despite all prescribed recommendations, the release of certain trace amounts of the monomer is inevitable [19].

The use of computer-aided designing and manufacturing (CAD-CAM) technology has greatly simplified the fabrication processes of RCDs. The subtractive computerized numeric control (CNC) milling technique manufactures the RCDs from a pre-polymerized PMMA billet (disk) that has been manufactured under high pressure. RCDs milled from these pre-polymerized billets (discs) in comparison to RCDs manufactured from conventional heat-polymerized PMMA are stated to exhibit improved material properties [20–23], and release relatively lower [24], or similar levels of residual monomer [25]. The additive 3D-printing technique, uses photosensitive liquid resins that are sequentially layered and then polymerized with a UV/visible light source [26,27]. Whether the process of 3D-printing minimizes the residual monomer content in the 3D-printed RCDs and is comparable to CAD-CAM milled RCDs is unknown. Moreover, the residual monomer content in 3D-printed RCDs has never been compared, nor has the effect of different rinsing cycles on the monomer release from the 3D-printed RCDs been investigated.

Therefore, the primary aim of this *in vitro* study was to compare the amount of residual monomer released between the CAD-CAM milled and the CAD-CAM 3D-printed RCDs. A further secondary aim of this study was to assess the effect of different rinsing cycles on the amount of residual monomer released by the 3D-printed RCDs. Hence based on these study objectives, the primary null hypothesis set for this *in vitro* study was that there will be no difference in the amount of residual monomer released from CAD-CAM milled RCDs and CAD-CAM 3D-printed RCDs. The secondary hypothesis set for this study was that there will be no effect of different rinsing cycles on the amount of residual monomer released by the 3D-printed RCDs.

2. Material & methods

This bench experiment involved no patient-based specimens or records, hence approval from the ethics committee was not required for this study.

2.1. Master reference scan

A master reference scan of a completely edentulous maxillary model which was used in our previous published similar bench experiments [26,28], was made using a high-resolution laboratory scanner that is calibrated to a precision of 6μm with a manufacturer specified nominal point spacing of 6-8μm and a repeatability of 10μm at an accuracy of 20μm (IScan D103i, Imetric 3D SA, Courgenay, Switzerland) [29]. The resultant scan (master reference scan) was stored and exported in a standard tessellation language (stl) file format for the designing and manufacturing of all the CAD-CAM maxillary RCDs that were used in this study.

2.2. CAD design of the RCD specimen

The master reference scan file was exported to the digital denture laboratory using a software (version 3.52, AvaDent^{TM} Connect, Global Dental Science Europe B. V., Tilburg, the Netherlands). This file was then imported into a design software (AvaDent^{TM} Design), and a virtual model was created on which the maxillary RCD was designed. A digital preview of the denture was generated for approval by the investigators (M.S., N.K. & F.M.). The approved design was then used for the fabrication of the required numbers of milled and the 3D-printed RCD specimens for the study.

2.3. Specimen size

An effect size (dz = 2.027727) was calculated from the results obtained from a previously published study assessing similar outcomes [25]. With the obtained effect size, the calculated specimen size was 8 specimens per group with α=0.05 for a power of 0.95 (1-β err prob), assuming a normal distribution. The specimen size was calculated using G*Power for Mac OSX (Version 3.1.9.2, Düsseldorf, Germany) [30].

2.4. Study (denture) groups

The 2 major denture (study) groups were based on the CAD-CAM manufacturing techniques, milled and 3D-printed groups. The 3D-printed group was further categorized into three sub-groups based on the rinsing cycles employed. The study groups are described as follows:

1 Group #1 (MP): n=8; milled
2 Group #2 (EWC): n=8; 3D-printed with pink resin and rinsed using an Extended Wash Cycle (EWC) protocol
3 Group #3 (SWC): n=8; 3D-printed with pink resin and rinsed using a Standard Wash Cycle (SWC) under manufacturer's recommended protocol
4 Group #4 (SWC2): n=8; 3D-printed with pink resin and rinsed using a Standard Wash Cycle (SWC) under manufacturer's recommended protocol. Post SWC, an additional protective coating was applied

A total of 32 CAD-CAM RCDs (milled: n=8; 3D-printed: n=24) were fabricated. Eight milled dentures were manufactured in entirety using pink denture base resin billets (discs) (n=8, AvaDent CAD-CAM denture base billet (disk) U, Global Dental Science Europe B. V., The Netherlands). The 3D-printed RCDs (n=24) were fabricated using a resin 3D-printer with a build platform of 110 × 62 mm that used a native pixel 29 μm 405 LED light source (RapidShape D30; Rapid Shape GmbH, Generative Production Systems). A pink monomer based on acrylic resin esters was employed for fabricating the dentures (NextDent B.V., The Netherlands). The printer was calibrated to the monomer used before the printing process was carried out. The printing orientation was vertical with a layer thickness of 50 μm per layer, and the location, as well as the number of supports, were automatically designed by the software. Post printing, the complete dentures were separated from the build platform with a putty knife and the supports were carefully removed.

Two sets of eight SWC 3D-printed RCDs were rinsed according to the manufacturer's recommended wash cycle A, while one set of eight EWC using a special wash cycle B developed by the co-investigators (E.C.C. & D.W.).

2.4.1. Wash Cycle A: Standard Wash Cycle (SWC)

In the Standard Wash Cycle (SWC), the 3D-printed RCDs were rinsed twice in a 96% isopropanol solution in an ultrasonic bath to remove the excess print material. A 3-minute initial rinse was then followed by a 2-minute second rinse in a clean 96% ethanol solution. In every rinse, a new ethanol solution was used. The combined rinse times did not exceed 5 minutes, which was as specified by the manufacturer (NextDent B. V., The Netherlands).

2.4.2. Wash Cycle B: Extended Wash Cycle (EWC)

In the Extended Wash Cycle (EWC), the 3D-printed RCDs were rinsed twice in a 96% isopropanol solution in an ultrasonic bath to remove the

excess print material. A 12-minute initial rinse was then followed by an 8-minute second rinse in a clean 96% ethanol solution. In every rinse, a new ethanol solution was used. Again, the combined rinse times did not exceed 20 minutes, as specified by the manufacturer (NextDent B. V., The Netherlands).

2.4.3. Post-rinsing polymerization cycle

Post-rinsing, the RCDs were air-dried for 60 minutes and placed in an ultraviolet (UV) lightbox (LC-3DPrint Box; NextDent B.V., The Netherlands) for 30 minutes for the final polymerization to be completed. The lightbox had six UV18W lamps-71 color and six UV18W lamps-78 colors (Dulux L blue) delivering a full light spectrum with a wavelength between 300-550 nm.

2.4.4. Application of the protective coating layer

RCDs in Group 4 (SWC2) were sent to the Durécon Group, The Netherlands, for an additional thin layer coating after the final polymerization. The coating material was based on organic polysilazanes and silicone epoxy hybrids. The coating was applied evenly over the entire denture surface and left to air dry overnight.

2.5. High-performance liquid chromatography (HPLC) analysis

2.5.1. Chromatographic equipment and conditions

HPLC was employed for analysis with a Waters system equipped with a Waters 1525 quaternary pump, a Waters 2707 UV/VIS diode-array detector, and a Waters 2998 Plus automatic injector fitted with 50 µl specimen loop. Computerized data acquisition and treatment were performed with the Breeze2® software. Compounds were purchased from Waters Cromatografia, S.A. (Barcelona, Spain). The chromatographic separation of the analytes was performed at room temperature (25 ± 2) °C using a Kromasil C18 150 × 4.6mm reverse-phase column packed with 5 µm silica particles. The mobile phase consisted of a mixture of acetonitrile and pure water 50:50 (v/v). The mobile phase was filtered through a 0.45 µm ester cellulose membrane filter DURAPORE® (Millipore Corporate, Billerica, MA, USA). Analyses were run at a flow rate of 1.0 mL/min. Absorbance was measured at 230 nm. For the determination, an amendment to the method described by Mohamed et al. was used [31].

2.5.2. Methylmethacrylate quantification

A solution of methyl methacrylate (MMA) (100.12 g/mol) was prepared in a mixture of ethanol: water (80:20) to prepare the calibration curves. The analytical methods were validated with six different concentrations of MMA (0.5, 1, 5, 10, 50, 100 µg/mL). Calibration curves were obtained by the least square linear regression analysis of the peak area obtained as a function of the concentration of MMA.

2.5.3. Determination of eluted methyl methacrylate concentration (MMC) from the specimens of the prostheses

The specimens were introduced into a flow-through equipment (Erweka DT80) with 150 mL [MILLED 1-8, SWC 1-8 and EWC 17-24] and in a volume of 200 mL [EWC 3-8 and SWC 9-16] of ethanol: water (80:20) shaking at 100 rpm for 24 hours at 37°C. Specimens of 1 mL were taken at 1, 2, 4, 8, & 24 hours after immersion. After sampling, the 1 mL was replaced with an equal ethanol: water solution (80:20). The dilutes had lids to avoid evaporation of the medium, however, evaporation was still observed. The final volume was recorded after 24 hours of diffusion. A visual evaluation of the prostheses was also performed after 24 hours and differences, if any present, were noted. Chromatographic evaluation provided absorbance data that were interpolated in the MMA calibration curve to calculate the concentrations.

2.6. Statistical analysis

Normal distribution of the data was confirmed using the Kolmogorov-Smirnov test. Generalized linear regression with repeated measures, one-way ANOVA statistical models, and *post hoc* tests were applied to find any intergroup and intragroup differences with the significance set at α=0.05. All the statistical analyses were performed using the SPSS® software package (version 25.0. IBM® Corporation, Armonk, NY, USA).

3. Results

All the specimens completed the tests successfully and no specimens were lost. A summary of the chromatographic conditions for analysis of MMC by HPLC-UV is given in Table 1.

The areas under the curve (AUC) of the HPLC method for determining the MMCs is shown in Table 2. The AUC obtained from the chromatograms were represented against the concentrations and the regression was carried out by the least-squares, obtaining the following representation of the calibration curve.

The HPLC revealed that MMCs were present in all the denture groups (Table 3). There was a cumulative increase in the MMCs as a function of time in the milled and SWC groups. The other two denture groups (EWC and SWC2) demonstrated a cumulative decrease in the MMCs as a function of time. The MMC amounts at 24 hours for the milled, EWC, SWC and SWC2 groups were 1.38 ± 0.65 mg, 0.154 ± 0.07 mg, 0.662 ± 0.23 mg, and 0.100 ± 0.023 mg, respectively.

HPLC-UV revealed a significant difference in the MMCs between the denture groups at 24 hours [$F(3, 31) = 23.646$, $p<0.0001$; Table 3; Fig. 1]. Post hoc tests revealed that the milled denture group demonstrated the highest MMCs as opposed to EWC ($p<0.0001$), SWC ($p=0.001$), and SWC2 ($p<0.0001$); SWC had higher MMC than SWC2 ($p=0.015$). EWC group had a lower MMC than SWC ($p=0.032$) and there was no difference when compared with SWC2 ($p=0.989$)

4. Discussion

CAD-CAM complete dentures have brought numerous novel modalities for treating edentulous patients. In the past decade, the focus has mainly been on the advantages in the reproducibility, physical properties, and biocompatibility of CAD-CAM complete denture manufactured through subtractive manufacturing (milling), whereas little is known for complete denture manufactured with 3D-printing. One of the crucial factors for the success of removable complete dentures (RCDs) is the compatibility of the denture base material, especially when it comes into a long period of contact with the patient's soft tissue. These denture base materials all undergo polymerization during different stages of fabrication. The degree of polymerization is inversely proportional to the amount of residual monomer which is left [25,32]. The residual monomers from these denture materials have cytotoxic effects which can often result in mucosal irritation and tissue sensitization [33]. However, prior to this present study, we were not aware of any literature that evaluates the residual methylmethacrylate concentration in

Table 1
Chromatographic conditions for the analysis of methylmethacrylate concentrations by HPLC-UV.

Chromatographic column: Kromasil C18 5µm 150 × 4.6mm
Mobile phase: Water: Acetonitrile = 50:50 (v/v)
Flow: 1 mL/min
Injection volume: 50 µl
Absorbance: λ = 230 nm
Methyl methacrylate retention time: 4.1 minutes
Temperature: 25 ± 2°C

HPLC-UV:High performance liquid chromatography using ultraviolet spectroscopy

Table 2
Areas under the curve (n=3) of the HPLC-UV method for determining methylmethacrylate concentrations (MMCs).

MMC (µg/mL)	AUC1	AUC2	AUC3	AUC (mean ± SD)
0.5	6822	7420	7270	7171 ± 311
1	14824	12948	15439	14404 ± 1298
5	77938	68043	62344	69442 ± 7891
10	150138	157209	153207	153518 ± 3546
50	817396	733067	761247	770570 ± 42931
100	1514760	1576577	1516755	1536031 ± 35128

HPLC-UV:High performance liquid chromatography using ultraviolet spectroscopy; AUC- Area under the curve; SD- Standard deviation

Table 3
Mean cumulative methylmethacrylate concentrations (µg) amounts as a function of time.

Time (hours)	Methylmethacrylate concentrations (MMCs) (µg) Milled mean ± SD	EWC mean ± SD	SWC mean ±SD	SWC2 mean ± SD	p-value
1	411.41 ± 187.63	198.63 ± 73.60	371.23 ± 79.92	124.12 ± 53.78	0.00003
2	387.43 ± 186.16	188.46 ± 85.33	324.26 ± 82.06	111.43 ± 43.61	0.00012
4	478.47 ± 232.15	202.79 ± 78.51	331.42 ± 97.14	130.83 ± 49.75	0.00019
8	775.28 ± 337.85	187.96 ± 75.91	383.99 ± 165.20	115.77 ± 41.55	<0.00001
24	1385.73 ± 650.97	154.00 ± 73.93	661.98 ± 227.68	100.11 ± 23.08	<0.00001

SD- Standard deviation; EWC- Extended wash cycle; SWC- Standard wash cycle; SWC2- Standard wash cycle with an additional protective coating; p-value: ANOVA, significance ($p<0.05$).

3D-printed RCDs.

Multiple studies have compared residual monomers of conventional heat processed to CAD-CAM fabricated milled complete dentures [24,25]. Ayman *et al.* reported that the residual methylmethacrylate monomer was significantly higher in the conventional heat-processed denture base when compared with the CAD-CAM milled bases. The reduction in the monomer release was associated with the high-pressure polymerization of the CAD-CAM disc [24]. In contrast, a study by Steinmassl *et al.* showed no statistical difference in the amount of residual monomer release with four different CAD-CAM milled RCDs when compared to the conventional heat-processed dentures [25]. The amount of monomer conversion during the conventional heat process and CAD-CAM milled complete denture were believed to be correlated to the application of high pressure and extended processing time for polymerization [17,19]. However, with 3D-printed denture base materials, the degree of residual monomer is unknown, as the photopolymerization fabrication mechanisms are different from those of heat-processed and milled dentures

The present study is the first to evaluate the cumulative release of methylmethacrylate (MMA) amounts from a removable complete denture. To avoid introducing additional variables during denture fabrication, both, denture teeth and the denture bases were fabricated with the the same material. The primary null hypothesis that there will be no difference in the amount of residual methylmethacrylate concentrations (MMCs) released from CAD-CAM milled RCDs and CAD-CAM 3D-printed RCDs within this *in vitro* study is rejected, because there was a significant difference between the cumulative MMC release in the CAD-CAM milled and the 3D-printed RCDs over a 24-hour period. The CAD-CAM milled RCDs exhibit minimal dimensional changes because they are milled from a homogenous billet (disk) that is manufactured under high pressure and temperature. The advantage of a homogenous billet (disk) can be explained by the longer chain of the polymer resulting in a higher degree of monomer conversion when compared with the conventional heat-processed denture [17,23,24,34]. Theoretically this feautre must also, in principle, help in elution of lower MMCs, because the polynmerisation is already complete in the billets (disks). However, the present study demonstrates that the milled RCD group still eluetd higher cumulative MMC than the 3D-printed RCDs. The reduced amount of residual monomer in 3D-printed denture base material could be attributed to the rinse cycle prior to light polymerisation; however, this is only a speculation. Another speculation is that perhaps the MMA concentrations in the 3D-printed groups were lower to begin with when

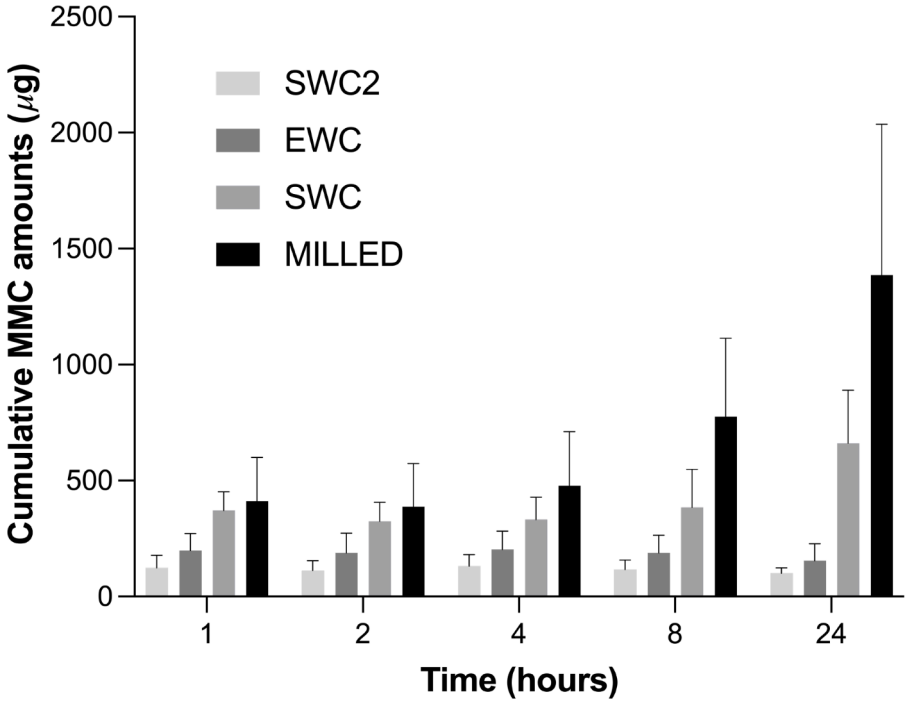

Fig. 1. Differences between the cumulative methylmethacrylate concentration (MMC) amounts as a function of time between the denture groups (EWC- extended wash cycle, SWC- standard wash cycle; SWC2- Standard wash cycle with a post wash protective coating with Durécon).

compared to the milled group. These speculations need to be proven in future purpose-designed studies. The results of this present study further demonstrated that there was a significant decrease in cumulative MMCs after 24 hours with the extended wash cycle (EWC) when compared with the standard wash cycle (SWC). Therefore the secondary hypothesis, that there will be no effect of different rinsing cycles on the residual monomer released by the 3D-printed RCDs, is also rejected. The extended wash cycle was four times longer than the short wash cycle. As a result, the amount of isopropanol used was the same but due to the extended wash time, the isopropanol was able to penetrate through the printed RCDs to provide a more thorough wash and a possibly a more effective elimination of the monomer. Manufacturers have suggested that over-washing the prints could lead to more porosities, decreased physical properties, and compromised color stability of the print materials. However, there is currently no literature that evaluates these suggested side-effects. In this study, we also found that applying a thin layer of coating for the SWC provided a similar result to the EWC. The coating perhaps acts as a barrier and potentially seals the porosities to create a smooth glossy surface to limit the further elution of the MMA. Although this coating could be beneficial in reducing the amount of monomer release, currently there are no studies present that have investigated if the residual monomer would eventually be released post function when the coating has worn out, or have evaluated other potential side-effects of the coating per se.

Although the present study was conducted using validated testing methods, the study may have had a few limitations. The lack of a conventional heat polymerised RCD control group could be considered a limitation in the study design. Studies exist in current literature which have evaluated this aspect and have provided evidence that the residual monomer content of the CAD-CAM milled RCDs were lower than the conventional heat polymerized RCDs [24,35]. Hence, in this study it was decided to use the milled RCDs as the control. In this study the resins used for manufacturing the 3D-printed and milled RCDs were only from one manufacturer. Furthermore, the milled RCDs were manufactured using the manufactured-recommended milling station and the 3D-printed RCDs were manufactured using the same resin manufacturer-recommended 3D-printer. Hence, it is understandable that the effect of different manufacturing units or the effect of different resins could not have been evaluated in the current study and therefore, this may be considered as a limitation of the present study. However, the current study design was deemed appropriate to study a true effect by standardizing to a single resin and a single manufacturing device. A further limitation may have been that the effect of coating was not evaluated on the milled RCDs. It would have been interesting to find out if this would have made a difference in the results for the milled RCDs, but this aspect was beyond the scope of the current study and hence was not done. Future studies aimed to evaluate this effect is warranted. Moreover, there is limited information on the possible side-effects or contraindications of this novel coating. These effects must be further explored in purposeful studies before its routine clinical application. It must be borne in mind that the findings of this study may not be generalizable for all the available resins and devices existent. Nevertheless, the current study design and the methods executed may be considered robust and the results obtained do provide novel evidence in the related field.

5. Conclusions

Within the limitation of this study, it can be concluded that the methylmethacrylate concentrations (MMCs) are significantly lower in 3D-printed removable complete detures (RCDs) than in the milled RCDs when using the resins employed in this study. Furthermore, the MMCs can be further lowered in the 3D-printed dentures when coated with an additional thin protective layer (Durécon) by following the manufacturer-recommended rinsing protocol or increasing the duration of the isopropanol wash. Further research would be needed to evaluate if the additional protective layer has an effect in decreasing the residual MMCs on milled polymethylmethacrylate materials

Clinical relevance

This study provides important information to help in the decision-making process for the clinician in selecting the right manufacturing process for fabricating removable complete dentures.

CRediT authorship contribution statement

Murali Srinivasan: Conceptualization, Methodology, Validation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. **Edward Chaoho Chien:** Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing, Project administration. **Nicole Kalberer:** Conceptualization, Methodology, Validation, Writing – review & editing. **Adrian Miguel Alambiaga Caravaca:** Methodology, Investigation, Validation, Formal analysis, Data curation, Writing – review & editing, Supervision. **Alicia López Castelleno:** Methodology, Investigation, Validation, Formal analysis, Data curation, Writing – review & editing, Supervision. **Porawit Kamnoedboon:** Conceptualization, Methodology, Validation, Writing – review & editing. **Salvatore Sauro:** Methodology, Validation, Formal analysis, Writing – review & editing, Visualization, Supervision, Resources. **Mutlu Özcan:** Methodology, Validation, Formal analysis, Writing – review & editing, Visualization, Supervision, Resources. **Frauke Müller:** Conceptualization, Methodology, Validation, Writing – review & editing, Visualization, Supervision, Project administration, Resources. **Daniel Wismeijer:** Conceptualization, Methodology, Validation, Writing – review & editing, Visualization, Supervision, Project administration, Resources.

Declaration of Competing Interest

The authors declare no conflicts of interests

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