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Quality Control of Poly(Methyl Methacrylate) to Medical Purpose by Multiple Headspace Extraction

Lamia Zuniga Linan,*[,a] Anderson Bonon,[a] Nádson M. N. Lima,[a] Rubens Maciel Filho,[a] Flavio Manenti[b]

[a] Instituto de Biofabricação (BIOFABRIS), School of Chemical Engineering. State University of Campinas, UNICAMP, Campinas-SP, Brazil.
[b] Politecnico di Milano, CMIC Dept. "Giulio Natta", Piazza Leonardo da Vinci 32, 20133 Milano, Italy.
lazuli@feq.unicamp.br

The quality of polymers to be used for medical purposes is evaluated by the concentration of residual compounds in the polymeric matrix, especially by the amount of residual monomer. Residual components of the polymerization of monomer can cause allergies and biological complications (stomatitis, dermatitis, cheilitis, and irritability), also collateral effects for the patient which are evident from the first five years after implant placement and could remain for thirty years more. In dentures, for example, these components are dissolved by the saliva and are fixed to adjacent tissue causing allergic reactions, including burning.
Multiple headspace extraction gas chromatography (MHS-GC) has been found to be an analytical technique particularly suitable for quantification of residual monomer in process samples with complex matrix, including solids. The major advantage of MHS-GC is that there is no need to pre-treat the sample prior to analysis. In this work, the methodology used to determine the residual monomer of Methyl Methacrylate (MMA) in a polymer of Poly(Methyl Methacrylate) (PMMA) is presented. The PMMA was produced in a controlled pilot plant scale laboratory, with rigorous experimental conditions to be used for medical purposes (artificial bone). The method includes the formulation of a calibration curve which was obtained by injecting different masses (0 – 30 mg) of a standard MMA solution in the Headspace sample vials and treated at ten extraction step in the HS-GC system. The results showed that through the present method it is possible to recover 98% of MMA from a solid matrix of PMMA.

1. Introduction

Poly(Methyl Methacrylate) PMMA is an acrylic polymer, synthetic, self or thermally polymerized, which is clinically acceptable (especially in dentistry) for their properties: natural appearance, durability, low absorption and insolubility in oral fluids, absence of taste and odor and satisfactory thermal properties. (Morais et al., 2007). The powder of PMMA is one of the principal ingredients for the in-situ fabrication of bone cement. It is used as a spacer, i.e. to fill bone cavities and for general fixation of endoprosthesis (orthopaedic surgery). However, it is known that residual compounds from monomer polymerization can cause allergies and biological complications (stomatitis, Cheilitis, irritability), without considering the side effects for the patient, which are evident beginning in the early years (5 years after the implant is placed) and even after 30 years of use (Mikai et al., 2006). Also, the mechanical properties (tensile strength, modulus of elasticity, hardness) of the polymer are diminished with increasing concentration of residues (Lung and Darvell, 2005). The residual compounds of bone cement to be used in implant fixation can be listed: Methyl methacrylate (MMA); Hydroquinone (HQ); Benzoyl peroxide (BPO); Ethylene glycol dimethacrylate (EGDMA); Benzoic acid (BA); Methyl benzoate (MB); Formaldehyde (FM). (Christie e Darvell, 2004; Hasenwinkel et al., 2001; Mikai et al., 2006; Morais et al., 2007).
Generally, the concentration of these residual components of the implant decreases over time. However, Christie and Darvell (2004) reported that PMMA always contains a small amount of MMA because of the thermodynamic equilibrium between them, which is displayed during the free radical polymerization

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reaction. This portion of monomer on the PMMA is still unknown. Nevertheless, typical values, which are found in dental prosthesis, as recorded in Table 1, could be considered as reference values to evaluate the quality of PMMA synthetized in this work.

Table 1. Typical values of residual MMA found in dental prosthesis

Authors	Reported values of residual MMA
Christie e Darvell (2004)	0.1 to 5 % by mass (for general bone cement)
Haas et al (1975)	3.3% by mass (on Simplex P, 30 to 60 minutes after preparation of the cement).
Hasenwinkel et al. (2001)	6.86 to 16.1 % by mass (in 12 samples of bone cement prepared by the authors from commercial reagents). 4.38 ± 0.05% by mass (on Simplex P, Howmedica, Inc., Rutherford)

One of the mechanisms for quality control of polymers, for medical purposes is the determination of trace amounts of monomer in the final polymer. The polymer synthesized in this research is a complex matrix, because besides the monomer (MMA), it is accompanied by a portion of the residual solvent, ethyl acetate (EA), as a result of polymerization technique used. In this situation, the technique of Multiple Headspace Extraction (MHS-GC) is a good alternative to extract and quantify the residual compounds from the polymer matrix, without the need to prepare the sample (dissolution) (Meier, 2009; Zhong et al., 2011; Choi and Kim, 2011). The MHS-GC technique consists of exhaustive evaporation (until nothing remains) of an amount of analyte from the same solid matrix. The extraction is made by successive stages with the same experimental conditions. The results obtained are used to determine the total amount (in mass) of the analyte within the sample as a function of the peak area detected by the chromatograph. The standard is analyzed, without matrix, according to the MHS-GC technique, determining thus a response factor which permits to build up the calibration curve.

This work presents a methodology based on MHS-GC to quantify the residual monomer in a solid matrix of PMMA. The polymer of PMMA was produced in a controlled scale laboratory pilot plant, with rigorous experimental conditions to be used for medical purposes (artificial bone). Details of the reactor system including the specifications of the equipment and the process conditions can be found in our previous work (Zuniga et al., 2012; Lima et al., 2011).

2. Experimental Methodology

2.1 Construction of the calibration curve

The experimental methodology for establishing the mathematical expression, which relates the amount of residues in the final polymer and the area of the detected picks was implemented from the exhaustive extraction headspace technique (Zhong et al., 2011). The stages of the methods are described in the block diagram of Figure 1. Table 2 registers the experimental conditions for the analyses.

The preparation of the MMA standards was made according to the following way: Five vials of 20 ml, proper for analysis in Headspace were sterilized and dried to place five different amounts from MMA liquid (Aldrich, N° CAS 80-62-6, of 99% of purity and 30 ppm or less of Hydroquinone). The samples, which were measured on a micro-balance with precision $1x10^{-4}$, are registered in Table 3. The masses of MMA ranged from (0 to 30) mg because these amounts are appropriate for the test in the regime of exhausting extraction in HS/GC (Chai et al., 2004; Li et al., 2007; Li et al., 2009).

The exhaustive evaporation was carried out stage by stage at the experimental conditions of Table 2. A total of 10 extractions were made for each sample. As a result of the tests, the areas of the picks of detected signs were calculated. With this information, the profile of picks area versus the extraction stages for each sample could be defined. The results showed an exponential decreasing trend, as shown in Figure 2.

The calculation of the total area of the picks until exhaustive evaporation was made by using the linear expression, represented in Eq(1), which was formulated from results described in Figure 2.

Eq(1) permitted the prediction of the number of extraction stages need for reach the minimum value of pick area.

From previous tests, it was found that the sign of the chromatograph is a maximum of 1 pA when nothing remains in the vial (no sample). Thus, the defined areas, in each stage, until full evaporation (this is, until the pick area reaches 1 pA) were summarized to define the total area. These areas also are presented in Table 3.

Finally, the formulation of the calibration curve, Eq(2) was done considering the masses of each sample and the total peaks area, which had been estimated through Eq(1).
Figure 3 shows that there is a linear relationship between the detected signs by GC and the size of the sample in the analyzed range for 10 stages of experimental evaporation.

$$Ln(\,peak\ \ area\,) = A + B(number\ \ of\ \ extraction\ \ steps\,) \quad (1)$$

$$Area\,(pA) = 23725.04 + 39848.15 \times mass\,(mg)\,,\ \mathrm{R} = 0.9987 \quad (2)$$

Where A and B are the adjusting parameters, with defined values for each sample, as registered in Table 3 and R is the coefficient of determination obtained of the adjust of profile represented in Figure 3.

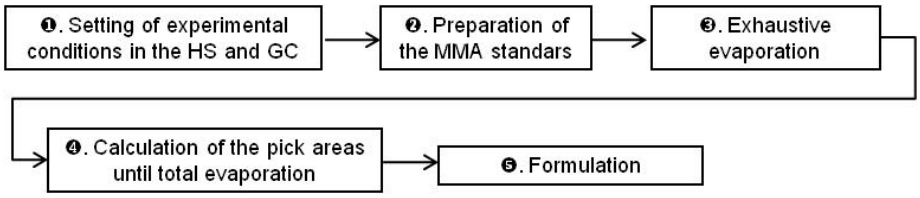

Figure 1. Experimental sequence of the exhaustive extraction headspace used for construction of the calibration curve.

Table 2. Experimental conditions defined for the MHS-GC tests.

Unit	Conditions
Headspace 7697A	Oven temperature: 105°C Needle temperature: 180°C Transfer line temperature: 200°C Injection time: 0.01 min Vial pressure: 206.9 kPa
Gas chromatograph 6850GC	Injection type: HS-Control Injector temperature: 250°C Analytical Column: 50% Cyanopropyl Phenyl Siloxane (BP225 – SGE, 25m x 0.32 mm x 0.25 µm) Carrier gas type: Hidrogen Pressure: 29 kPa Flow gas program: 2.0 ml/min. per 3.5 min. and from (2.0 to 3.0) ml/min. at 6.0 ml/min. per 10 min. Oven program :40°C per 2 min.; from (40 to 90)°C at 20°C/min. and from (90 to 230)°C at 40°/min. per 10 min.
Analysis time	35 min.

2.2 Validation of the calibration curve

The analytes (i.e. the residual compounds of the polymer) to be extracted by MHS-GC are immersed in a solid matrix of polymer. For the validation of the calibration curve, four samples of MMA immersed in a reference matrix were analyzed. The reference matrix was the PMMA polymer (Aldrich code 182230, Mw ~ 120.000,00 by GPC), which was completely dried in a vacuum cabinet (VACUCELL 22) to remove all the impurities and residues compounds. The drying program included: 378.15 °C for 9 hours (in intervals of 3 hours); 388.15 °C for 3 hours and 393.15 °C for 6 hours (in intervals of 3 hours).
The samples of MMA from (0 to 25) mg were prepared as described in Table 4. Each one was immersed in 5 mg of the reference PMMA.
The prepared samples were submitted the MHS-GC technique at the experimental conditions described in Table 2. The chromatograms generated in each extraction stage were submitted to graphic integration by using the GC Agilent Chem Station software (Rev. B.04.03[16] Copyright Agilent Technologies, 2001-2010), to estimate the detected peak area. The peak area is in direct correlation with the amount of evaporated MMA. Therefore, a high area was obtained in the first evaporation stage (which indicates larger amount of the MMA in the headspace) and a minor area at the end of extraction. This behavior can be visualized in the chromatograms of the Appendix A.
The total peaks detected for each sample were estimated as the summation of the peak areas, defined in each extraction stage. These areas are registered also in Table 4. Thus, the estimated total peak area

defined the amount of MMA in the PMMA matrix, by using the calibration curve equation (Eq.2). Also, in Table 4, the predicted and real masses of MMA immersed in the PMMA matrix are compared.

3. Results and analyses

As shown in Figure 2, the profiles of the detected peak area versus the number of extraction steps present a decreasing exponential trend, which indicates that the separation of analyte, immersed in the polymer is vigorous in the first extraction stages. Beginning with the ninth extraction stage, the efficiency of separation diminishes and the masses of MMA in the headspace remain constant.

The profile of total peak area versus the amount of analyte vaporized in headspace, for ten extraction stages has a linear trend. The linear adjust with a determination coefficient (R = 0.9987) does a good representation of these results, as is shown in Figure 3.

The results presented in Table 4 demonstrate that the implemented methodology is suitable to predict the residual monomer present in the polymer in studio. The greatest percentage of recovery (> 93%) is reached when the amount of residual monomer is larger than 10.3 mg.

Table 3. Samples of MMA standard submitted to multiple headspace extraction

Sample [a]	1	2	3	4	5
Amount (mg)	1.20	7.1	16.9	22.90	30.40
Stage of experimental evaporations	Detected sign (area in pA)				
1	11169.7	62542.7	127422.3	168315.5	194707
2	9722.7	54539.7	117954.4	152131.4	224091.6
3	8248.9	45882.3	100384.3	128671.7	162617.3
4	6821	38677.2	85033.7	108959.6	139435.9
5	5732.6	32395.9	71947.7	93287.1	117828.5
6	4779.6	27320.5	60844.7	79836.9	100677.2
7	4051.8	22877.1	51447.5	67487.8	85768.3
8	3365.4	19320.4	43698.5	57732.7	73124.4
9	2820.6	16112.3	36650.9	48388.7	61634.6
10	2342	13620.6	30815.9	41178.4	46011.4
Total area	59054.3	333288.7	726199.9	945989.8	1205896.0
Formulation	$Ln(\ peak\ \ area\ ) = A + B(number\ \ of\ \ extraction\ \ \ steps\ )$				
Parameter A	95.256	112.403	1.201.961	12.232	126.058
Parameter B	-0.1755	-0.1717	-0.16764	-0.1593	-0.1809
Coefficient of determination of the model (R)	0.9997	0.9998	0.9999	0.9994	0.9949
% Average absolute error % ($\overline{e}$)	0.1025	0.0725	0.03117021	0.1096	0.3604
Prediction of the Number of stage until exhaustive evaporation	55	65	71	77	69
Total area until exhaustive evaporation (PA)	71463.9	406560.4	909407.9	1188342.1	1504627.1

[a] It was evaluated that the sample with 0.00 mg of MMA emits a signal corresponding to 1 pA

4. Conclusion and remarks

The results obtained permitted the implementation and verification of a methodology for the determination of the residual monomer presents in a PMMA polymer, which was synthesized on a scale laboratory pilot plant. Also, these experimental campaigns optimized the drying process on the polymer, which have to be efficient to ensure the quality of the material that is going to be used in the fabrication of scaffolds.

However, additional experimental methodologies should be increased seeking to define the amounts of residual solvent (Ethyl Acetate) that could be present also in the material, as a result of the solution polymerization.

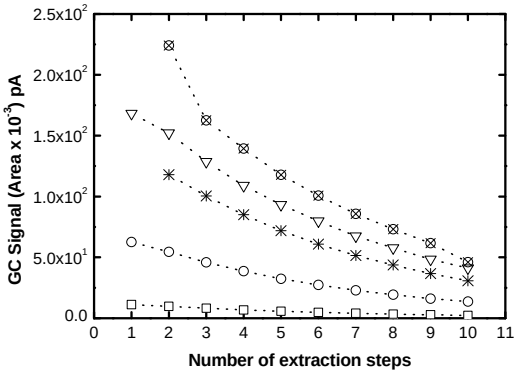

Figure 2. Representation of the detected peak area versus the extraction stages during the exhaustive evaporation of the MMA samples by MHS-GC. □ Sample 1, ○ Sample 2, ✳ Sample 3, ▽ Sample 4, ⊗ Sample 5.

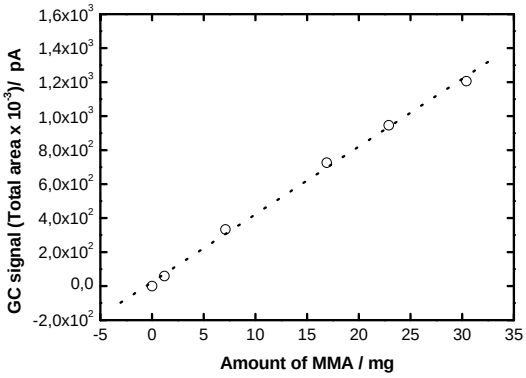

Figure 3. Profile of the detected signals as a function of the amount of MMA immersed in the PMMA matrix. ○ Total peak area for ten extraction stages; ---Linear adjusting. It was evaluated that the sample with 0.00 mg of MMA emits a signal corresponding to 1 pA

Table 4. Comparison between the amount of MMA predicted through calibration curve and detected by GC

Sample	Total peak area for 10 extraction stage (PA)	MMA (mg)		% of MMA Recovery
		Amount in the matrix	Predicted	
1	65811.0	1.6	1.1	66
2	406137.0	10.3	9.6	93
3	689391.0	15.8	16.7	106
4	950509.2	23.8	23.3	98

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APPENDIX A. VARIATION OF THE DETECTED SIGNAL BY MHS-GC AS A FUNCTION OF THE EXTRACTION STAGES

In Figures A from a) (firth extraction stage) to j) (tenth extraction stage) are presented the chromatograms, which were obtained for the sample 4 of Table 4. These results were used for the validation of the calibration curve. It is observed that the detected signals are proportional to the evaporated amount on each extraction stage, this is, the peak areas and the mass of the residual MMA decrease as a function of the number of extractions.