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Chemical and physicochemical properties of the high cohesive silicone gel from Poly Implant Prothèse (PIP) breast prostheses after explantation: A preliminary, comparative analytical investigation

Giangiacomo Beretta [a,*], Matteo Malacco [b]

[a] Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Milan, Via Mangiagalli 25, 20133 Milan, Italy
[b] FMH Plastic, Reconstructive and Aesthetic Surgery, Lugano, Switzerland

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ABSTRACT

Aim of this work was to gain a deeper insight into the analytical profile of the macromolecular and LMW fractions of polymeric silicones present in breast implants.

The study was conducted on silicone gel samples from (i) breast prostheses (Poly Implant Prothèse, PIP) explanted from a patient that needed their therapeutical removal, (ii) from a virgin Mc Ghan 410 MX prosthesis and (iii) from a sample of technical-grade non-cohesive silicone. The gels were analysed using rheological techniques, attenuated total reflectance infrared spectroscopy (ATR-FT-IR), nuclear magnetic resonance (^{1}H NMR), gas chromatography coupled to mass spectrometry (GC–MS) and flow injection electrospray mass spectrometry (FI-ESI-MS). Our results demonstrate that, compared to the virgin McGhan gel, the silicone present the PIP prostheses lacks a significant part of the cross-linking sites necessary for the high-cohesive properties of the gel, significant amounts of cholesterol have been absorbed from the breast tissue by the silicone material, demonstrating the lack of impermeability of its elastomer shell. The potential implications and consequences of these analytical results are discussed.

1. Introduction

High-cohesive silicone gel breast implants (or prostheses) are medical devices used for breast reconstruction after mastectomy, to correct congenital defects or for breast augmentation.

They are made by an elastomer silicone shell filled with a viscous cohesive silicone gel made of a bulk of polymeric cohesive gel (cross linked polymeric silicones are considered inert materials due the durability and thermal stability of their chemical and elastic properties) in which is embedded a 1–2% of low molecular weight (LMW) silicones among which hexamethylcyclotrisiloxane (D3), octamethylcyclotetrasiloxane (D4), decamethylcyclopentasiloxane (D5), dodecamethylcyclohexasiloxane (D6) and tetradecamethylcycloheptasiloxane (D7) have been reported (D5-D7 main constituents) [1]. Previous analytical studies have shown that these LMW silicones can diffuse through the implant elastomer shell when the implant is in contact with the lipid media in the breast [1].

Flassbeck et al. reported the identification and quantification of LMW silicones (from D3 to D6) by GC–MS analysis of blood, plasma and tissues samples from women implanted with breast prostheses [2,3]. The migration of LMW silicones has been also investigated by the group of Garrido, that reported controversial results obtained working with ^{1}H NMR localized spectroscopy (STEAM) [4–10] for the in vivo measurements and liquid and liquid/solid state ^{29}Si NMR for the determination of silicone in blood and in periprosthetic capsular tissues from women implanted with silicone breast prostheses. Although the studies from these groups have been questioned by academic and industrial scientists [11a,11b,12a,12b] it seems there is enough data to raise the question whether the exposure to silicone may have consequences for the human health.

The leaking of silicone is known as implant 'bleeding'. Although the health risks or benefits associated with the local/systemic release of LMW silicones from breast implants are unknown, the development of local and systemic inflammatory responses, endocrine and autoimmune diseases after breast prostheses implantation have been observed in animal models and in several case reports, with and without implant rupture [13–20]. In these studies no informations about prostheses type and manufacturer were provided.

In this context, several concerns have arisen in the public opinion when the French health authority banned the use of implants from Poly Implant Prothèse (PIP) in 2010. This implants were fraudulently manufactured with substandard, non-medical grade silicone, and recent clinical studies evidenced a significantly higher rupture rate compared to other brands [21–23]. It has been estimated that a huge number of these adulterated implants have

* Corresponding author. Tel.: +39 0250319309; fax: +39 0250317565.
E-mail addresses: giangiacomo.beretta@unimi.it (G. Beretta), m.malacco@tin.it (M. Malacco).

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been implanted into hundreds of thousands of unknowing women around the world (around 500.000), from Europe to South America [24].

In response to this crisis, the national health authorities of the European Union (EU) and extra EU countries adopted different positions, regarding the rising requests of re-operation and substitution from women with implanted PIP breast prostheses. In Germany, France, Italy, Spain, Wales, Bolivia and Venezuela the removal and replacement of implants is supported by their respective national health systems, also for privately treated patients. The British Government deliberated: "on the basis of the evidence available to the expert group (...) there is no clear evidence that PIP implants represent a materially greater risk to health than the recognised risks of other brands of silicone gel breast implants. We therefore do not recommend that women with PIP implants should, as a routine precaution, seek to have their implants removed" [25]. The expert panel of the Australian Therapeutic Goods Administration (TGA) reiterated "its previous advice that routine explantation of PIP implants in the absence of rupture is not justified by currently available evidence, but that women with PIP implants should be strongly encouraged to undergo a full clinical assessment, including MRI" [26].

In the light of these definitely opposite conclusions and of the lack of published comparative studies on the composition and properties of high-cohesive silicone gel breast implants, aim of this work was to gain a deeper insight into the analytical profile of the macromolecular and LMW fractions of polymeric silicones present in breast implants.

The study was conducted on silicone gel samples from (i) breast prostheses (Poly Implant Prothèse, PIP) explanted from a patient that needed their therapeutical removal, (ii) from a virgin Mc Ghan 410 MX prosthesis and (iii) from a sample of technical-grade silicone. The gels were analysed using attenuated total reflectance infrared spectroscopy (ATR-IR), nuclear magnetic resonance (NMR), gas chromatography coupled to mass spectrometry (GC–MS) and flow injection electrospray mass spectrometry (FI-ESI-MS).

2. Experimental

2.1. Patient and silicone gel-filled breast prostheses

In June 2008, a 47 years old female patient with a medical history of bilateral prophylactic skin sparing mastectomy in 2001 and immediate breast reconstruction with PIP implants (batch n. 01801 087, Poly Implant Prosthèse) complaining about continuous local pain over a few years, especially at the right breast. Further interviewing revealed no possibility for the patient to have normal sleeping in prone position, weight loss, weakness and intermittent light fever.

Clinical examination of the patient revealed: deformation of the right breast, dislocation of the implant and capsule Backer grade III contracture, bilateral local pain at manual examination, signs and symptoms of a chronic inflammatory reaction of the surrounding breast tissue.

The patient denied any physical trauma or general disease after breast reconstruction and no other abnormalities were found on general clinical examination and lab test.

MRI scan examination showed a small collection of serous exudate around the prostheses with no evident implant rupture. The patient underwent a new surgical procedure, with bilateral implants removal and substitution with Allergan style 410 MF (Allergan Inc., Rome, Italy) anatomical implants, with capsulectomy and new pocket positioning. In the immediate postoperative period and during subsequent follow up, all the clinical symptoms of general toxicity, observed before explantation, disappeared.

The virgin prosthesis was a McGhan 510 MX (batch n. 1600011, 290 g, McGhan, INAMED, Rome, Italy). The technical-grade silicone (Saratoga, Milan, Italy) was purchased in a shop in Milan.

2.2. Rheological analyses

The rheological properties of small aliquots of the silicone gels were examined using a rotational rheometer (TA AR1500ex, TA Instruments Ltd, Waters, Milan, Italy) equipped with parallel plates (d = 20 mm, inter-plate distance 1 mm). Transient shear stress experiments were done using an external shear rate of 10 s^{-1} (T = 10 s). Oscillation frequency experiments: applied angular frequency 0–16 Hz. Flow ramp experiments: applied variable shear rate from 1 s^{-1} to 1000 s^{-1}, T = 5 min.

2.3. ATR-FT-IR

ATR-FT-IR spectra were recorded using an Alpha spectrometer equipped with an ALPHA's Platinum single reflection diamond ATR unit (Bruker Optics, Milan, Italy).

2.4. ^1H NMR

^1H NMR experiments were accomplished with a Varian Mercury VX 300 spectrometer (^1H base frequency 299.96 MHz) equipped with a 5-mm probe. Silicone samples (180 mg aliquots) were extracted with 1 mL of $CDCl_3$ for NMR analysis (Sigma–Aldrich-Fluka, Milan Italy) at room temperature for t = 4 days. Spectra were done using the following acquisition parameters: relaxation delay = 1.000 s; pulse = 45°; acquisition time = 1.994 s; spectral width = 4803.1 Hz; 128 transients. Chemical shifts were referenced to the resonance frequency of residual $CHCl_3$ present in the deuterated solvent. Spectra were elaborated with the software MesTreNova v. 8.0.2 (Mestrelab Research S.L., Spain).

2.5. GC–MS

Qualitative and quantitative analysis of the LMW fraction of the silicone gels was done using a 436 Gas Chromatograph coupled to a Bruker SCION SQ^{TM} mass spectrometer system (Bruker Daltonics, Macerata, Italy), equipped with a Factor Four capillary column (VF-5 ms = 30 m; i.d. = 0.25 mm, film thickness = 0.25 mm). The oven temperature was initially set at 60 °C (hold time 3 min), with a gradient from 60 to 150 °C (3.0 °C/min, hold 1 min), and from 150 to 240 °C (10 °C/min, hold 1 min); injector temperature T = 250 °C. Column flow 1.00 mL/min. Carrier gas helium 5.5; ionization energy = 70 eV; split/splitless ratio = 1:30.

Peaks were finally confirmed by comparing the retention times with those of authentic standards when available, and final confirmation by matching with the spectra of the commercial NIST mass spectral database (NIST 11, software version 2.0 g). The percentage compositions were computed by normalization of peak areas. For the analysis, 400 mg of silicone gel were extracted with 400 μL of acetone under sonication (at maximal power for 1 h) and, after centrifugation at 10,000 g (20 min), 1 μL of this extract was submitted to GC–MS analysis. Analysis was done in triplicate.

2.6. ESI-MS

ESI/MS analyses were done on a Thermo Finnigan LCQ Advantage (Thermoquest, Milan, Italy) ion trap mass spectrometer, operating in the following conditions: capillary temperature = 250 °C; ionization voltage = 5 kV. The flow rate of the nebulizer gas (nitrogen) was 0.5 L/min. The solvent extracts used for ^1H NMR analysis were dried under nitrogen and diluted 1:10 with a isopropanol:methanol (50:50) mixture and then infused into the mass spectrometer using a Harvard syringe pump at a flow rate of

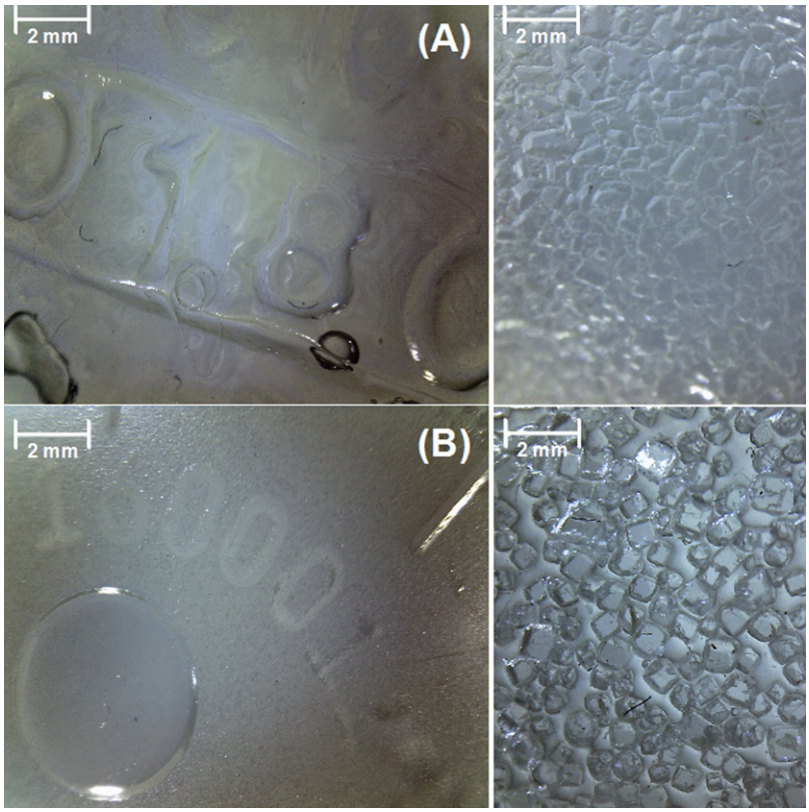

Fig. 1. Optical microscopical examination of (6× magnification) of identifier code area (left) and of the elastomer shell (right) of (A) the explanted PIP implant and of (B) the virgin McGhan implant.

15 μL/min. Spectra were acquired in negative- and positive-ion modes, with a scan range m/z = 100–2000 (scan rate 0.5 scans/s).

3. Results

3.1. Microscopical and ATR-FT-IR observations

The microscopical examination of the PIP elastomer silicone shell (Fig. 1) evidenced (i) the presence of extensive irregularities in the area delimited by the perimeter surrounding the prostheses serial number and of its high relief characters, and (ii) an inhomogeneous distribution of its textured elastomer shell, indicating that the implants were produced under rough manufacturing procedure and/or that they underwent mechanical and/or chemical erosion during the implantation period (seven years).

ATR-IR spectroscopic analysis confirmed the polydimethylsiloxane nature of the PIP and Mc Ghan gels (Fig. 2). The spectra were almost overlapping, with slightly higher absorptions of the PIP gel at low frequencies (ν = 1079.8 cm^{-1}, ν = 864.0 cm^{-1}, ν = 700.2 cm^{-1}, ν = 661.4 cm^{-1}).

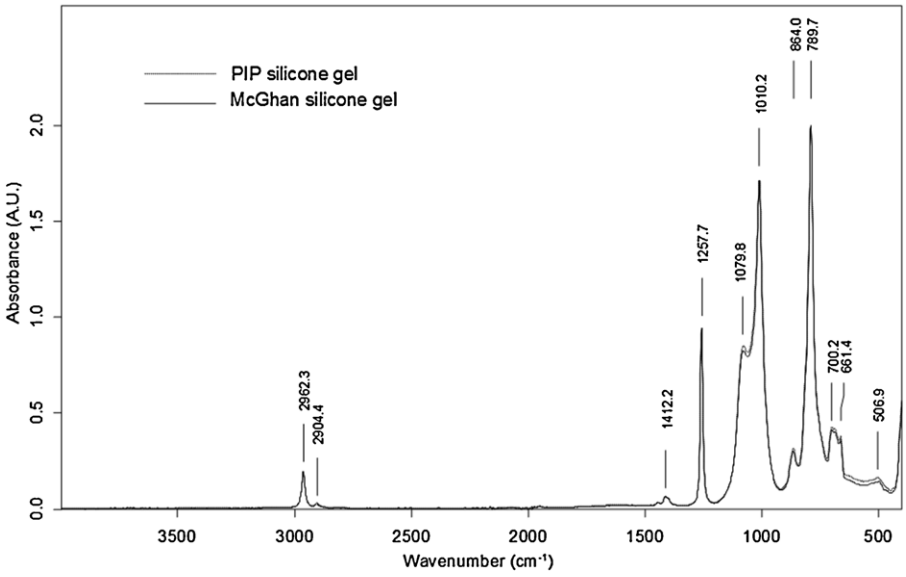

Fig. 2. ATR-FT-IR spectra of silicone gels from PIP (dotted line) and McGhan (solid line) silicone gels.

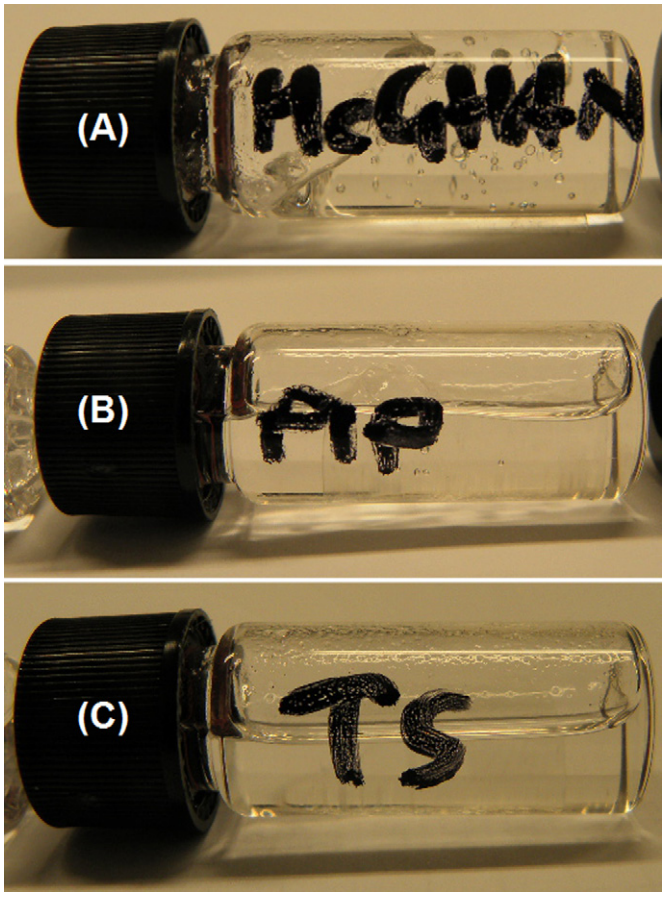

Fig. 3. Photographic comparison of the $CDCl_3$ absorbing capacity of (A) McGhan silicone gel, (B) PIP silicone gel and of (C) technical silicone (TS). Cohesiveness is almost absent in PIP gel.

The rheological evaluation of the of the silicone gel gel-properties showed completely different behaviour (supplementary data), leading to the first conclusion that PIP implant filler silicone is characterized by significantly reduced viscoelastic properties compared to that of a high-cohesive silicone gel.

The reduced viscosity of the PIP gel may have two origins: (i) the first due to its manufacturing procedure: the gel already had reduced viscosity *before* implantation, and/or (ii) the silicon gel viscosity decreased during the seven years of implantation.

3.2. ^{1}H NMR experiments

As described in Section 2, prior to ^{1}H NMR analysis, the three silicone samples were left in contact with $CDCl_3$ to extract LMW silicones that may be present deeply embedded into the polydimethylsiloxane network of the implant cohesive gels.

Soon after a few minutes from the solvent addition, a strikingly different behaviour was observed comparing the McGhan and PIP cohesive gels (Fig. 3). The McGhan gel showed a fast incorporation of the solvent into its crosslinked polymeric backbone, which appeared as a solid, stable gel after approximately $t = 30$ min.

By contrast, the silicone from the PIP implant showed a dramatic loss of viscosity, appearing, already at a first visual examination, partially solubilized in the solvent. Its behaviour was alarmingly closer to that of the technical-grade silicone than to that of a high-cohesive gel such as that present in the McGhan implant.

This difference can be explained only assuming that in the PIP gel the cross-linkers necessary to obtain suitable elastic and mechanic properties are missing, supporting the first claims for which PIP implants were fraudulently filled, at least in part, with industrial, non medical-grade and cheaper silicones.

The comparison of the ^{1}H NMR spectra of the PIP and technical-grade silicone (Fig. 4) evidenced a similar profile both in quantitative and qualitative terms.

The resonances of the CH_3-Si methyl groups protons were present in the typical silicone ^{1}H spectral region, with a signal centred at $\delta = 0.08$ ppm, while the resonance typical of terminal methyl groups of $(CH_3)_3Si{-}O{-}Si(CH_3)_2{-}O{-}$ moieties were well detectable only in the PIP gel spectrum.

3.3. GC–MS analysis

The GC–MS analyses of the acetone extract of the PIP and Mc Ghan silicone gel (Fig. 5A and B) evidenced almost overlapping profiles of two major sets of peaks. Similar results were obtained working with ethylacetate or with hexane as extractor solvent (not shown).

From RT = 10.0 min to RT = 28.0 min cyclic polydimethylcyclosiloxanes from D5 to D10 were identified.

In the RT range from 34.0 min to 60.0 min a second set of major peaks with the bell shaped intensity distribution typical of polymeric higher homologues, separated by an almost constant ΔRT of around 2 min, was present.

All these compounds showed identical fragmentation patterns typical for polydimethylcyclosiloxanes, with no detectable molecular ions (even when the EI ionization potential was set as low as 1 eV, not shown). For this reason, no definitive identification of these peaks was possible on the basis of the GC–MS data only. However, these peaks were tentatively identified as the polydimethylcyclosiloxane series D11-D26 based on their almost constant RT difference. To furnish a fast confirmation of these attributions the same extract was further analysed using a soft ionization technique (ESI-MS, see next paragraph).

Four dominating peaks generated by unknown compounds U1, U2, U3 and U4 were present at RT = 29.1 min, RT = 32.2 min, RT = 35.6 min and at RT = 52.5 min (Fig. 6). In the low molecular weights regions of their fragmentation spectra, the same fragment ions at $m/z = 197.1$, $m/z = 135.1$ and $m/z = 73.1$ were present, indicating that they were structurally correlated. Interestingly, these compounds were not detectable in a sample of technical-grade silicone (Fig. 5C).

At RT = 54.5 min a peak absent in the silicone gel from the virgin McGhan implant and from technical silicone, generated by cholesterol (with minor peaks from trace amounts of cholesta-3,5-diene at RT = 50.26 min and of squalene at RT = 48.87 min) was well detectable. The intensity of this peak was found to be highly variable, depending from the sampling site in the gel three dimensional structure (with quantitative concentrations in the range 30–80 ppm, $n = 5$).

These results clearly indicated that the cohesive silicone gel in the implant is able to adsorb lipid soluble components from the surrounding adipose breast tissues. A similar cholesterol sequestering ability of silicone was previously observed by Nakamura and colleagues (GC–MS) working on silicone oil recovered after one year and seven months from its injection into the rabbit's eyes and [27].

3.4. ESI-MS

To confirm the tentative structural assignments from the GC–MS experiments, the silicone gels solvent extracts were submitted to ESI-MS analyses.

The pseudomolecular $[M+H]^+$ ions in the range from m/z 370 to m/z 1852 (Fig. 7) were a clear confirmation of the presence of heavier polydimethylcyclosiloxanes from D13 to D26.

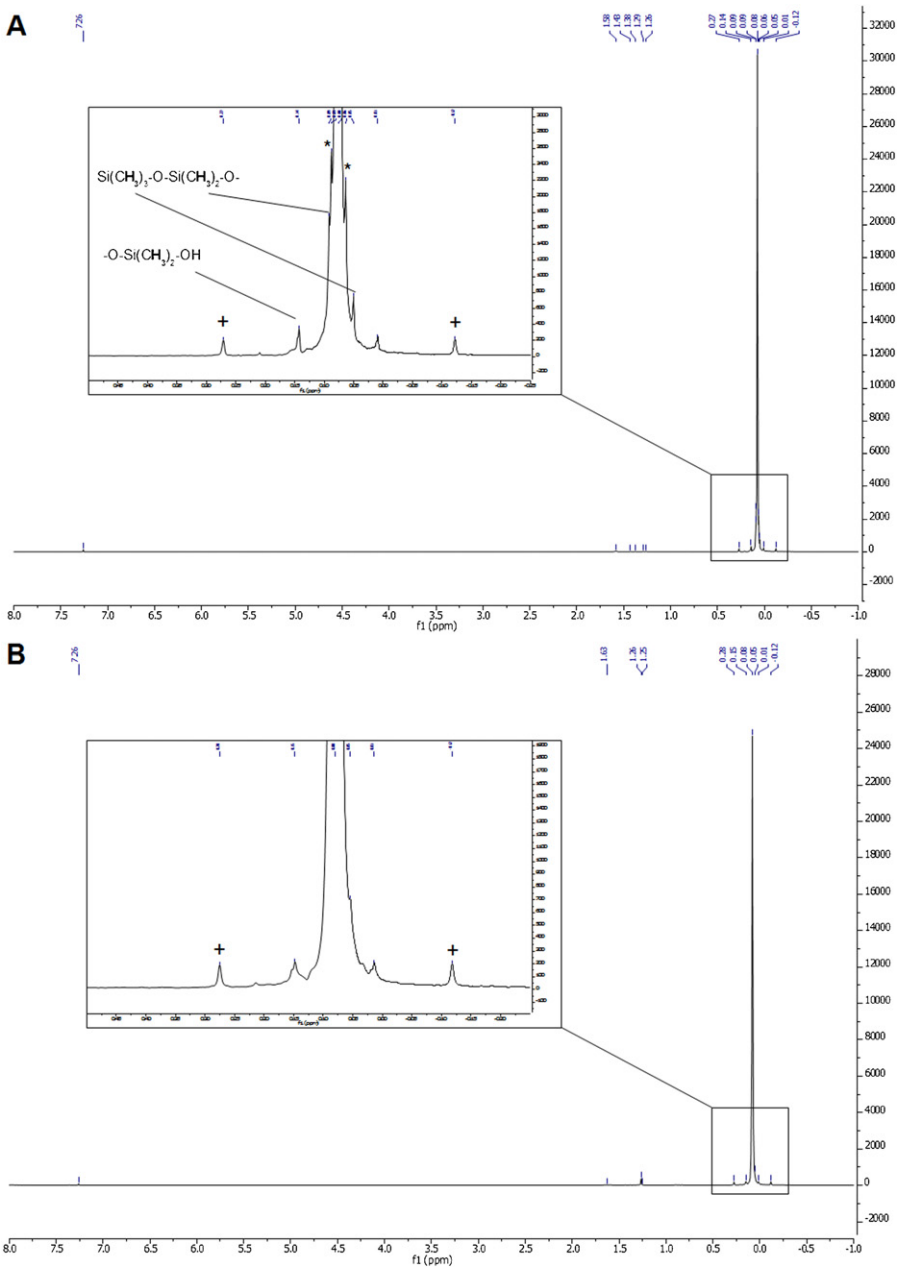

Fig. 4. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of (A) PIP silicone gel and of (B) technical silicone. Expanded spectral windows ($-0.25 < \delta < 0.60$) are in the insets. + ^{13}C satellites, * ^{1}H satellites. The ^{1}H NMR spectrum of McGhan silicone gel was not recorded due to the complete absorption of $CDCl_3$ by the sample (see Fig. 3).

4. Discussion

In March 2010 breasts implants manufactured by Poly Implant Prosthèse (PIP), the same type of prostheses explanted from our patient, were removed from the market following the discovery that non medical-grade silicone was used in prostheses implanted worldwide in at least 300,000 women [28]. The concerning conclusions of recently published clinical studies [21,22], opened a harsh international discussion about their safety [29–31].

Considering the great impact of this issue on the public opinion and in different fields of the scientific community (from plastic and reconstructive medicine to analytical chemistry and forensic analysis), it is surprising that since the publication of the first analytical studies and controversies on the LMW fraction of cohesive silicone gels during the decade 1990–2000 [1-12d], almost no further study has been focused on the detailed characterization of their chemical composition. Only recently, some data (GC–MS) have been made publicly available by manufacturers or by national official institutions.

The Therapeutic Goods Administration (TGA) group of the Australian government informed that significant amounts of D4 (0–261 ppm), D5 (0–710 ppm) and D6 (0–1005 ppm) are present in PIP prostheses, while these species are undetectable in other authorized breast implants (NUSIL) [32]. The GC–MS analyses carried out by the FDA laboratories on Sientra Silicone Gel Breast Implants identified LMW silicones from D3 to D21 (from 73 μg/g for D3 to 2563 μg/g for D17; total 27,234 μg/g) [33]. A analytical report published online on the Medicines and Healthcare products Regulatory Agency (MHRA, UK) website, has shown that the GC–MS mass chromatographic profiles of the solvent extractable fractions (hexane and ethylacetate) from $n = 5$ batches of PIP implants, were very similar to those found by us [34]. Also in this case, only

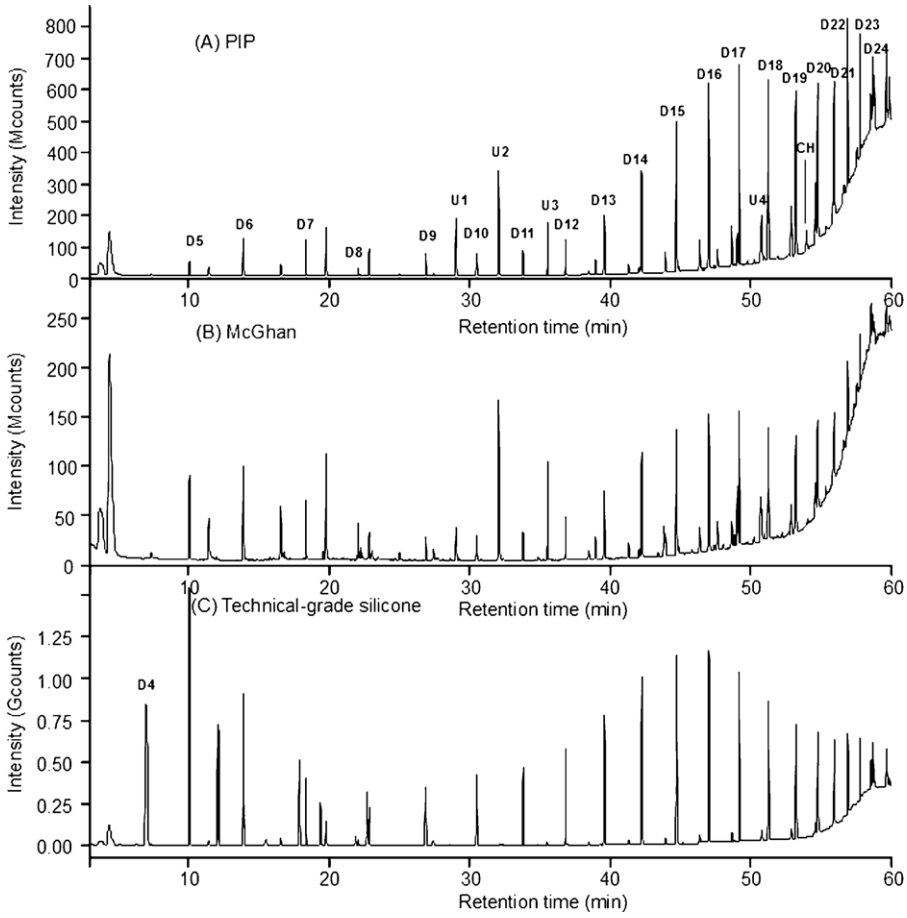

Fig. 5. GC–MS profile of the acetone extracts of (A) PIP silicone gel, (B) McGhan silicone gel and of (C) technical silicone. CH = cholesterol, U = unknown.

D4, D5 and D6 (% match 74–91%) were unambiguously identified, while astonishingly different structural attributions of the peaks at higher retention times were done. According to this report, these species were barely undetectable (or present in very low amounts) in implants from other commercial brands ($n = 6$) of undisclosed origin [34].

If some discrepancies between our results and those above reported may be reasonably explained (for instance, the different structural assignments from MHRA may arise from a low experimental spectra/spectral library match, reported in the probability range 9–50%), on the other hand they highlighted a number of critical points that we believe of fundamental importance.

It is commonly accepted that polymeric silicone and LMW silicones are not toxic to living organism and humans and, consequently, that they are of safe use in medical devices such as cohesive silicone gel breast implants. Studies from the literature or reports available online have repeatedly shown, using different experimental in vitro or in vivo models, that these materials do not elicit

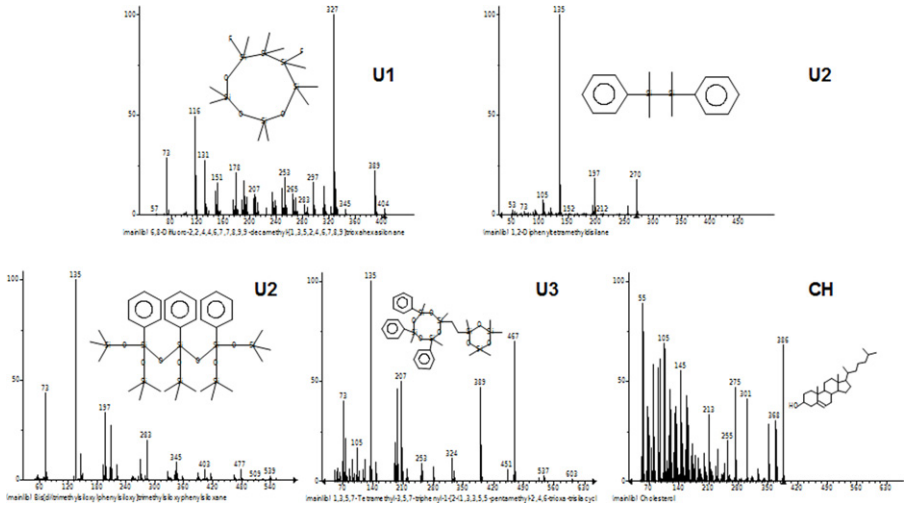

Fig. 6. Mass spectra of the unknown silicone compounds and cholesterol detected in the GC–MS chromatograms of PIP and McGhan silicone gels.

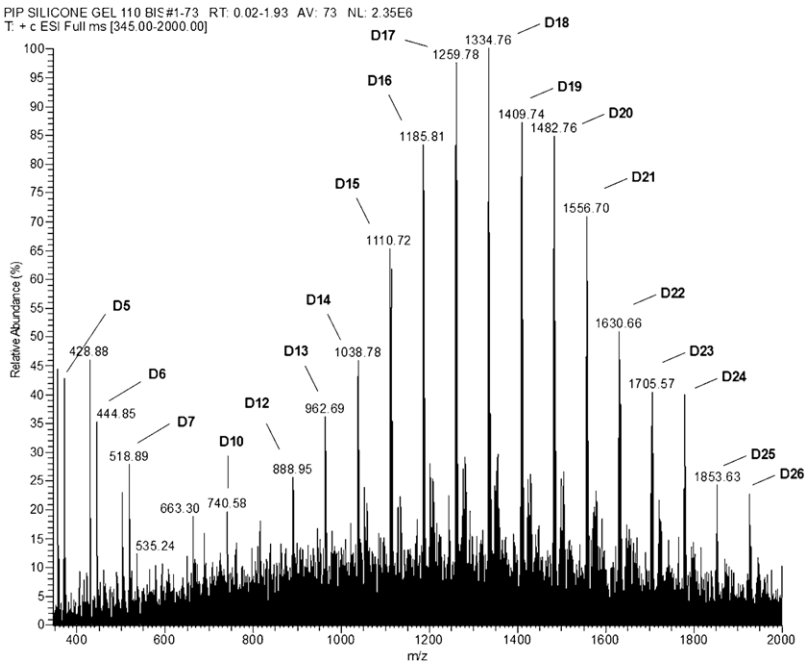

Fig. 7. Representative FI-ESI-MS spectrum of the acetone extract of PIP silicone gel.

any significant inflammatory, irritant or mutagenic effects [32–34]. However, it should be carefully considered that several previous case report studies reported the diffusion of injected silicone oil in animals [35] and its adverse effects after injection in humans in different body parts, including the breast [36].

From the toxicological point of view, it can be argued that the negative/positive outcome of a predictive laboratory test does not necessarily reflect the situation occurring in vivo. To the best of our knowledge, there are no currently accepted reliable experimental models or laboratory tests for the accurate evaluation of the in situ toxicological properties of adulterated breast implants in humans. In this context, it should be kept in mind that a bleeding breast implant may represent a unique and peculiar way of delivery of its LMW silicone fraction into the body, compared to other delivery/exposure modalities (sub-cutaneous injection, ingestion or inhalation).

Finally, our results demonstrated that in the case of the PIP implants under investigation, the long 'incubation' period (seven years) inside the patient's breast induced a progressive change in their chemical composition.

According to what was reported by Birkefeld et al., that evidenced the presence of endogenous phospholipids in an explanted breast prostheses by ^{1}H and ^{13}C NMR [37], the GC–MS experiments demonstrated that the cohesive gel was able to adsorb biochemical metabolites such as cholesterol. As previously suggested by other authors, this process may lead to further significant modifications of its elastic properties and (bio)chemical composition [38] and, ultimately, to a drop of viscosity, and then to a higher rupture probability with the consequent leakage and diffusion of fluid silicone in the body.

5. Conclusions

In this study we have analysed the polydimethylsiloxane silicone gels from two different brands of breast prostheses (PIP and McGhan) by ATR-FT-IR, ^{1}H NMR, GC–MS and ESI-MS. In both cases, we observed the presence of a dominating array of LMW silicones (from D5 to D26) that, to the best of our knowledge, have been unequivocally characterized by combination of GC–MS and ESI-MS techniques in the silicone oil fraction of high-cohesive silicone gels for the first time in this work.

Since a sample of the intracapsular exudate observed during the surgery was not available, the in vivo release of LMW silicones observed by other authors cannot be confirmed only on the basis of our results. However, the appearance of significant amounts of solvent soluble lipophilic tissue derived components (squalene, cholesterol and its precursors, absent in the virgin implant), strongly suggest an exchange of LMW substances (silicones and non silicone contaminants) between the prostheses and its surrounding host tissues. Our results indicate that the releasing process may be accelerated by higher diffusivity of LMW silicones through the non cohesive silicone criminally used to fill the PIP prostheses.

In the light of these results, we believe that the highest degree of quality of silicone-based breast prostheses (and thus of safety for the patients), can be achieved only by the application of strict Hazard Analysis and Critical Control Points (HACCP) rules throughout all the implants production process (from silicone synthesis to prostheses filling) and for their validation by official health institutions before acceptance for distribution on the market.

These rules should necessarily include the application of a set of reliable laboratory tests to verify: (i) the impermeability of the elastomer implant shell, (ii) the degree of cross-linking present in the cohesive gel, and (iii) a platform of specific analytical techniques (GC–MS, ESI-MS, NMR) for the batch to batch verification of the presence of significant amounts of LMW silicones and of any other potentially diffusible contaminant material.

An expert may argue that this study, based on only two silicone gel breast implants samples from two different producers, will in no way be considered as definitively representative (e.g. no statistical evaluation of the results can be performed). However, this paper could demonstrate that in principle the basic study rationale is feasible and that further application papers based on the here proposed methodologies will be necessary, this until a firm conclusion about the potential of the method(s) to diagnose real samples and situations can be made.

Finally, it is comforting that the underlying conclusion that can be extrapolated from the present study, is in line with the position declared by the International Confederation for Plastic and

Reconstructive Surgery (IPRAS) on its website at the beginning of 2012: "There is no further room for discussion. It is mandatory to recommend the explantation of PIP (. . .) implants [39]."

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jpba.2013.01.040.

References

[1] E.D. Lykissa, S.V. Kala, J.B. Hurley, R.M. Lebovitz, Release of low molecular weight silicones and platinum from silicone breast implants, Anal. Chem. 69 (1997) 4912–4916.
[2] D. Flassbeck, B. Pfleiderer, R. Grümping, A.V. Hirner, Determination of low molecular weight silicones in plasma and blood of women after exposure to silicone breast implants by GC/MS, Anal. Chem. 73 (2001) 606–611.
[3] D. Flassbeck, B. Pfleiderer, P. Klemens, K.G. Heumann, E. Eltze, A.V. Virner, Determination of siloxanes, silicon, and platinum in tissues of women with silicone gel-filled implants, Anal. Bioanal. Chem. 375 (2003) 356–362.
[4] L. Garrido, B. Pfleiderer, M. Papisov, J.L. Ackerman, In vivo degradation of silicones, Magn. Reson. Med. 29 (1993) 839–843.
[5] B. Pfleiderer, J.L. Ackerman, L. Garrido, In vivo localized proton NMR spectroscopy of silicone, Magn. Reson. Med. 30 (1993) 149–154.
[6] B. Pfleiderer, J.L. Ackerman, L. Garrido, Migration and biodegradation of free silicone from silicone gel-filled implants after long-term implantation, Magn. Reson. Med. 30 (1993) 534–543.
[7] L. Garrido, B. Pfleiderer, B.G. Jenkins, C.A. Hulka, D.B. Kopans, Migration and chemical modification of silicone in women with breast prostheses, Magn. Reson. Med. 31 (1994) 328–330.
[8] B. Pfleiderer, L. Garrido, Migration and accumulation of silicone in the liver of women with silicone gel-filled breast implants, Magn. Reson. Med. 33 (1995) 8–17.
[9] B. Pfleiderer, A. Moore, E. Tokareva, J.L. Ackerman, L. Garrido, Biodegradation of polysiloxanes in lymph nodes of rats measured with ^{29}Si NMR, Biomaterials 20 (1999) 561–571.
[10] L. Garrido, V.L. Young, Analysis of periprosthetic capsular tissue from women with silicone breast implants by magic-angle spinning NMR, Magn. Reson. Med. 42 (1999) 436–441.
[11] (a) A.L. Smith, Comments on "Determination of low molecular weight silicones in plasma and blood of women after exposure to silicone breast implants by GC/MS", Anal. Chem. 74 (2002) 1207;
(b) D. Flassbeck, B. Pfleiderer, R. Grümping, A.V. Hirner, Authors reply to comments on "Determination of low molecular weight silicones in plasma and blood of women after exposure to silicone breast implants by GC/MS", Anal. Chem. 74 (2002) 1208–1209.
[12] (a) C.T.G. Knight, Migration and chemical modification of silicone in women with breast prostheses, Magn. Reson. Med. 42 (1999) 979–980;
(b) P.M. Mcdonald, Migration and chemical modification of silicone in women with breast prostheses, Magn. Reson. Med. 42 (1999) 981–982;
(c) J.J. Kennan, R.B. Taylor, Migration and chemical modification of silicone in women with breast prostheses, Magn. Reson. Med. 42 (1999) 982–983;
(d) W.E. Hull, A critical review of MR studies concerning silicone breast implants, Magn. Reson. Med. 42 (1999) 984–996.
[13] J.F. Hayden, S.A. Barlow, Structure–activity relationships of organosiloxanes and the female reproductive system, Toxicol. Appl. Pharmacol. 21 (1972) 68–79.
[14] A.P. Prebtani, S.L. Asa, S. Ezzat, Is granulomatous thyroiditis a complication of breast implants? Endocr. Pathol. 13 (2002) 239–244.
[15] V.B. Breiting, L.R. Hölmich, B. Brandt, J.P. Fryzek, M.S. Wolthers, K. Kjøller, J.K. McLaughlin, A. Wiik, S. Friis, Long-term health status of Danish women with silicone breast implants, Plast. Reconstr. Surg. 114 (2004) 217–226.
[16] S. A: Audino, S.V. Maharaj, Prosthetic mammoplasty sensitivity syndrome: a case for causation, J. Long Term Eff. Med. Implants 21 (2011) 241–250.
[17] L.J. Jara, G. Medina, E. Gómez-Bañuelos, M.A. Saavedra, O. Vera-Lastra, Still's disease, lupus-like syndrome, and silicone breast implants. A case of 'ASIA' (Shoenfeld's syndrome), Lupus 21 (2012) 140–145.
[18] M. Caldeira, A.C. Ferreira, Siliconosis: autoimmune/inflammatory syndrome induced by adjuvants (ASIA), Isr. Med. Assoc. J. 14 (2012) 137–138.
[19] S. Kivity, M. Katz, P. Langevitz, I. Eshed, D. Olchovski, A. Barzilai, Autoimmune syndrome induced by adjuvants (ASIA) in the Middle East: morphea following silicone implantation, Lupus 21 (2012) 136–139.
[20] M. Lidar, N. Agmon-Levin, P. Langevitz, Y. Shoenfeld, Silicone and scleroderma revisited, Lupus 21 (2012) 121–127.
[21] M.G. Berry, J.J. Stanek, The PIP mammary prosthesis: a product recall study, J. Plast. Reconstr. Aesthet. Surg. 65 (2012) 697–704.
[22] A. Aktouf, I. Auquit-Auckbur, D. Coquerel-Beghin, V. Delpierre, P.Y. Milliez, Breast augmentation by Poly Implant Prothèses silicone implants: retrospective study about 99 patients, rupture analysis and management, Ann. Chir. Plast. Esthet. 57 (2012) 558–566.
[23] P. Hedén, B. Boné, D.K. Murphy, A. Slicton, P.S. Walker, Style 410 cohesive silicone breast implants: safety and effectiveness at 5 to 9 years after implantation, Plast. Reconstr. Surg. 118 (2006) 1281–1287.
[24] http://www.ipras.org/news/pip-breast-implant-scandal
[25] The government's response to the House of Commons Health committee: Sixteenth report of PIP breast implants and regulation of cosmetic interventions. Session 2010–12. Available for download at www.official-documents.gov.uk
[26] http://www.tga.gov.au/safety/alerts-device-breast-implants-pip-120525.htm
[27] K. Nakamura, M.F. Refojo, D.V. Crabtree, J. Pastor, F.L. Leong, Ocular toxicity of low-molecular-weight components of silicone and fluorosilicone oils, Invest. Ophthalmol. Vis. Sci. 32 (1991) 3007–3020.
[28] A.U. Daniels, Silicone breast implant materials, Swiss. Med. Wkly. 142 (2012) w13614.
[29] R. Horton, Offline: a serious regulatory failure, with urgent implications, Lancet 379 (2012) 106.
[30] R. Horton, Offline: the scandal of device regulation in the UK, Lancet 379 (2012) 204.
[31] K. Woods, Device regulation in the European Union: response from MHRA, Lancet 379 (2012) 515.
[32] Available online at the URL: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_134624
[33] FDA Summary of Safety and Effectiveness Data PMA P070004. Available online at: http://www.accessdata.fda.gov/cdrh_docs/pdf7/p070004b.pdf
[34] Available online at the URL: http://www.tga.gov.au/safety/alerts-device-breast-implants-pip-120402.htm
[35] S.V. Kala, E.D. Lykissa, M.W. Neely, M.W. Lieberman, Low molecular weight silicones are widely distributed after a single subcutaneous injection in mice, Am. J. Pathol. 152 (1998) 645–649.
[36] G.E. Gurvitis, Silicone pneumonitis after a cosmetic augmentation procedure, N. Engl. J. Med. 354 (2006) 211–212.
[37] A.B. Birkefeld, R. Bertermann, H. Eckert, B. Pfleiderer, Liquid- and solid-state high-resolution NMR methods for the investigation of aging processes of silicone breast implants, Biomaterials 24 (2003) 35–46.
[38] W.P. Adams, M.D. Robinson, R.D. Rohrich, Lipid infiltration as a possible biologic cause of silicone gel breast implant aging, Plast. Reconstr. Surg. 101 (1998) 64–68.
[39] Available online at the URL: http://www.ipras.org/news/pip-breast-implant-scandal