A Comparison of Commercially Available Polymethylmethacrylate-Based Soft Tissue Fillers

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BACKGROUND The rapid market expansion of filler treatment options requires physicians and health care providers to fully understand differences among comparable products.

OBJECTIVE The objective was to compare commercially available polymethylmethacrylate (PMMA)-based soft tissue fillers to determine if there are meaningful variations in these products that could result in significantly different therapeutic profiles, especially with respect to safety.

METHODS AND MATERIALS PMMA particles were evaluated for size and morphology using scanning electron microscopy (SEM) techniques. PMMA microsphere soft tissue filler products from the United States, Europe, Brazil, and Canada were compared with respect to size, homogeneity/irregularity, surface smoothness/roughness, and the presence or absence of sediment and particulate debris.

RESULTS Marked differences with respect to PMMA particle morphology and related particle characteristics from a variety of products were found. Of note, some products demonstrated potentially concerning significant variability in particle size and irregular morphology.

CONCLUSION It is anticipated that the variability detected in these products, based on the literature, could result in different therapeutic profiles, especially with respect to safety. Physicians and health care providers should be aware that ''comparable'' products that at a glance appear similar may not be equal.

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The number of soft tissue filler treatment options available today is overwhelming compared to what it was just a few years ago. It is important to understand that all of these products are likely not equivalent and that regulatory approval standards across the globe can be significantly different and therefore do not assure product uniformity.

Given this rapid market expansion, physicians need to have a better understanding of the differences among these products. This need has become even more critical as physicians are required to 1) manage patients treated outside the United States with product not approved in the United States; 2) interpret medical literature that deals with categories of products that may have similar ingredients, but when sold in other countries, may have reached the market with significantly different specifications, quality or manufacturing controls, and supportive data; and 3) deal with patients treated with products imported into the United States from abroad (parallel importing of non–FDA-approved products).

Methods

Particle characteristics of implant materials have long been known to be important to the biocompatibility and performance of soft tissue filler materials.[1,2] Polymethylmethacrylate (PMMA) microsphere–containing soft tissue filler products were purchased by licensed practitioners from diverse locations across the globe (Brazil, Canada, European Union, and United States) at various times in the past 7 years. The PMMA particles in each product were evaluated for particle size and morphology using standardized scanning electron microscopy (SEM) methods.

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The following summary details the SEM techniques used. Microspheres were separated from the soft tissue filler "carrier vehicle," processed, and then evaluated by the following methods:

1. Each product was diluted with water for injection (WFI) and expressed by syringe through a 0.22-μm membrane filter mounted in clean stainless-steel filter housing to remove the carrier matrix.
2. The contents of each filter were rinsed 9 or 10 times with WFI, to wash all carrier material through the filter mesh.
3. Filter contents were then placed in a vacuum oven until they were completely dry.
4. Clean dry microspheres were then transferred to clean dry sample tubes and labeled.
5. Microsphere samples were mounted on prelabeled stainless SEM pedestals, using dual-sided adhesive mounting disks. Samples were coated with AuPd imaging powder, prepped, and then imaged using conventional SEM techniques (performed at Scripps Institute of Oceanography, University of California at San Diego, San Diego, CA).

Results

Five different PMMA soft tissue fillers were sourced and evaluated in this study. The findings are summarized in Table 1 and Figures 1 to 5 below.

Different Markets/Different Approval Requirements

Regulatory approval requirements for approval of soft tissue filler products vary across the globe and frequently change. In general, currently the premarket approval (PMA) process in the United States is the most stringent overall (nonclinical/clinical/manufacturing requirements) with respect to soft tissue fillers. The European Union (CE Mark) has historically had less stringent requirements compared to the United States. In the European Union, clinical validation of safety and efficacy of a new dosage form can be obtained from smaller human studies and/or by using supportive arguments based upon referencing clinical data for other related products in the public domain. Approval pathways outside of the United States and the European Union can vary widely from region to region and may not be as rigorous as those required in the United States or EU. cGMP-regulated facilities in the United States must also demonstrate greater process controls than the facilities in the European Union and elsewhere.

Discussion

The literature supports the fact that microsphere-containing products may have different performance profiles from a safety perspective based on the composition, morphology, and surface characteris-

TABLE 1. Summary of SEM Findings

Product	*Country of Origin*	*SEM Analysis (Particle Shape, Surface Finish, Size, Gross Size Distribution, and Anomalies)*
ArteFill, year 2007	United States	Size ranges primarily from 30 to 50 μm, with negligible small sizes. Smooth-surfaced microspheres with scant if any sediment.
Artecoll, year 2005	Canada	Size ranges primarily from 30 to 50 μm, with negligible small sizes. Smooth-surfaced microspheres with slight surface irregularity and scant if any sediment.
Artecoll (older version), ca. 2001	EU	Size ranges primarily from 32 to 40 μm, but with larger variation in particle sizes and presence of nanoparticles on the surface of microspheres. There are sub–20 μm particles and some sub-5 μm particles noted with some sediment.
SA-1 (Metacrill), ca. 2006	Brazil	Wide variety of particle sizes 0.2–60 μm. Many sub-20 μm particles exist, and many are sub-5 μm. Many irregular shapes, some nonspherical, jagged edges, poor surface.
SA-2 (NewPlastic), ca. 2006	Brazil	Wide variety of particle sizes 0.2–70 μm. There are some oversized spheres, occasionally over 70 μm as well as very small particles. Some are nonspherical and conjoined, many small spheres and particles exist.

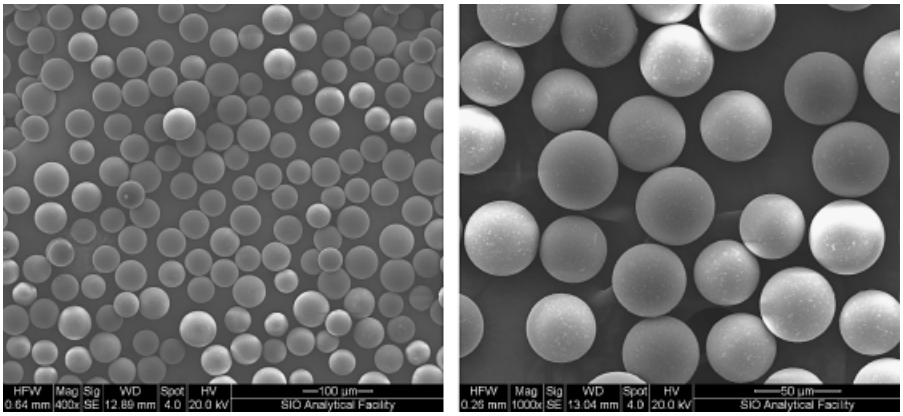

Figure 1. SEM images of PMMA from the United States, year 2007 (ArteFill).

tics of the microspheres they contain.[3] PMMA-based filler products from diverse geographic locales obtained at different points in time were evaluated in this study. The SEM images of the PMMA microspheres from these apparently "similar" products clearly demonstrated marked differences as shown in Table 1 and the corresponding SEM images as detailed in Figures 1–5.

Based on biomaterial science, it would not be surprising that such particle differences could result in significantly different product safety profiles, especially with respect to SA1 (Figure 4) and SA2 (Figure 5) in contrast to the United States (Figure 1) or even the European Union (Figure 3). Of note, the variability of the particle size, morphology, and surface characteristics seen in SA1 and SA2 are well documented in the literature to impact particle migration and overall biocompatibility.[1,2] This comparison also clearly highlights the potential differences that can be seen between analogous products obtained from diverse geographic markets (Brazil vs. the United States or Europe) at similar points in time.

Although improvements in the PMMA component of established marketed filler products have been known to occur over time, unfortunately the potential clinical relevance of these manufacturing changes typically has not been substantiated by well-controlled trials.[4] To that end it is not uncommon for clinicians to have a common view of a product such as Artecoll, when in reality the product may have

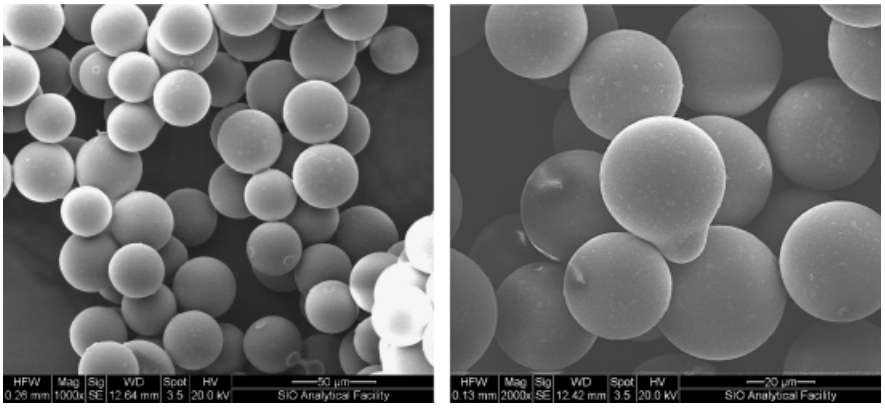

Figure 2. SEM images of PMMA from Canada, year 2005 (Artecoll).

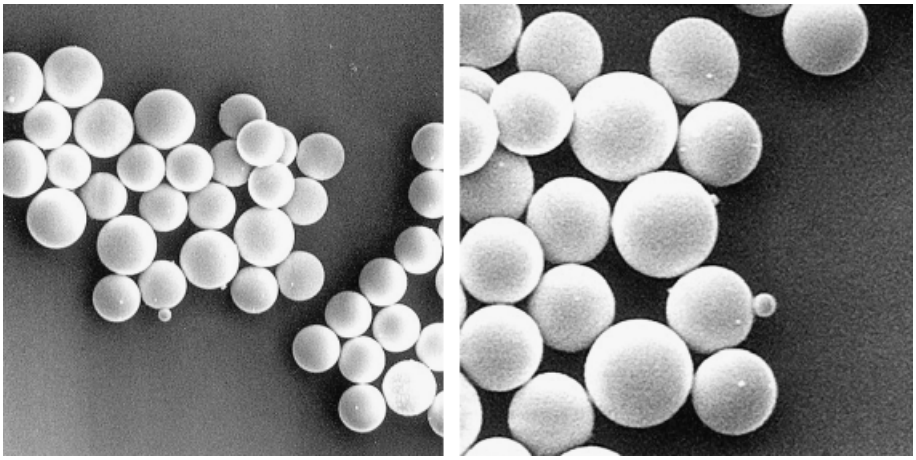

Figure 3. SEM images of PMMA from EU, ca. 2001 (Artecoll, older version).

had multiple forms over time with potentially different therapeutic features with respect to safety and efficacy. Even in the limited time period covered by this study, we can see improvements in PMMA microspheres contained in the European Union (Figure 3), which is Artecoll, an older version of a common PMMA filler, in comparison to a newer version of the product more recently distributed in Canada (Figure 2). Finally, ArteFill (United States, Figure 1) exemplifies the most recent improvement to PMMA microsphere technology, demonstrating a very high degree of microsphere uniformity with respect to size as well as topology.

Significant variability in PMMA microspheres, as demonstrated in this study, leads one to conclude that adverse events previously reported with products of this type have been impacted by microspheres quality. Although microsphere quality has improved over time there is no easy mechanism to delineate the impact on adverse events since the impact of such changes is not well characterized in the literature or via standardized reporting to regulatory bodies or manufacturers. Nonetheless, a comparison of material adverse event rates between Arteplast (the first commercial PMMA product available in Europe) versus the next-generation product Artecoll has been reported to be significantly less as the product's PMMA characteristics were improved.[5] The recent United States approval of the newest-generation PMMA-based filler product has been substantiated by extensive FDA trials, which demonstrate a

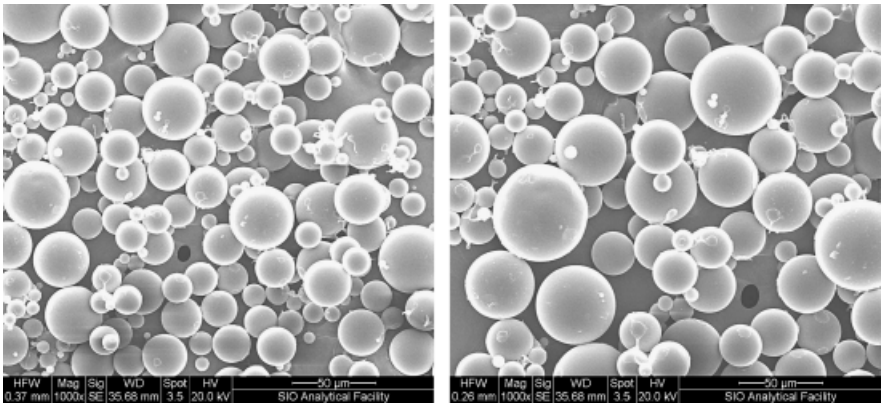

Figure 4. SA1: SEM images of PMMA from Brazil, ca. 2006 (Metacrill).

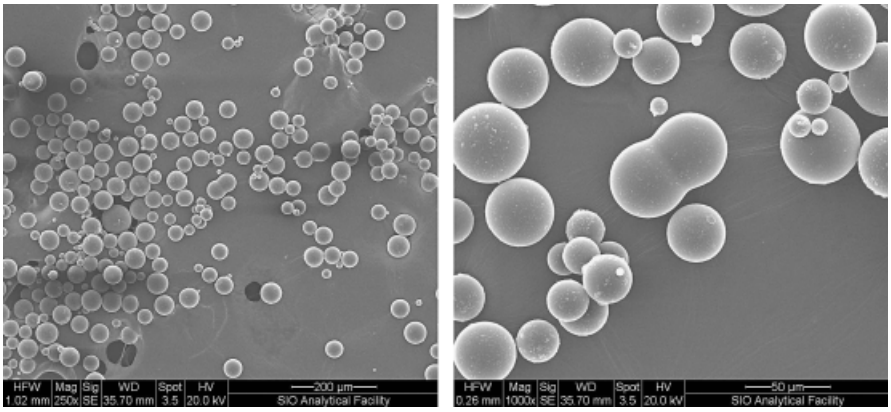

Figure 5. SA2: SEM images of PMMA from Brazil, ca. 2006 (NewPlastic).

safety profile which is consistent with other modern fillers.[6]

Summary

These findings clearly demonstrate marked differences in the quality of the microspheres in PMMA products obtained from 1) different markets (SA1/SA2) within a common time frame and 2) various time points showing improvement from older versions of ArteColl (European Union) to the newest product in this category, ArteFill (United States). It is anticipated that these differences, based on the literature, could result in significant differences in the safety profile of these products. It is also clear that although PMMA technology has improved, validation of the potential impact of such changes is not well characterized. Consequently, health care providers may have a view of PMMA microspheres that has been molded by older versions of the technology that are no longer relevant today. Unfortunately, this study has also shown that lower-quality PMMA-based product can still be found, which further complicates our ability to substantiate a clear view of the technology and emphasizes the need for clinicians not to generalize findings from one PMMA product to another.

With the rapid expansion of soft tissue filler products across the globe, health care providers need to be aware that seemingly similar products may not be equivalent. This need has become even more critical as health care providers are required to: 1) manage patients treated with products available outside the United States, 2) interpret medical literature that deals with similar products, and 3) understand the potential risks related to using similar products imported into the United States that are not FDA-approved.

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