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Original article

Preliminary morphological characterization of injectable gels for aesthetic medicine applications

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Abstract. *Background*: Injectable gels used in aesthetic medicine for skin rejuvenation are known collectively as fillers. These gels are employed for wrinkle correction, volume restoration, and facial enhancement with some formulations predominantly providing bio-stimulating and revitalizing effects. *Aim:* This study aimed to analyze and compare the microscopic structure of various injectable gels. *Materials and Methods*: Ten products were examined, including cross-linked and non-cross-linked hyaluronic acid (HA), agarose gel, calcium hydroxyapatite combined with HA, and formulations containing collagen precursors. Smears were prepared on glass slides, air-dried, stained with Diff-Quick, and observed under optical microscopy. *Results*: Each material exhibited a distinct and reproducible microscopic morphology corresponding to its composition. *Discussion*: Microscopic analysis of injectable gels can help identify and categorize products based on their structural characteristics. This tool may assist in the identification of undocumented materials in cases of adverse reactions through fine-needle aspiration (FNA) and smear analysis. *Conclusions*: Morphological analysis may serve as a valuable framework to understanding the potential behavior and integration of gels within biological tissues. Greater attention to microscopic studies of injectable gels may enhance safety, efficacy, and complication management in aesthetic procedures.

Key words: Injectable gels, filler materials, morphological characterization, biostimulating agents, optical microscopy

Introduction

The number of procedures performed with filler materials in the field of aesthetic medicine has increased by 40% over the last 5 years. In parallel, the number of procedures aimed at removing them has increased by 46% over the same period[1].

There are different filler materials on the market that differ in terms of composition, origin, density, physical properties, mechanism of action, biodurability, and longevity[2,3]. However, knowledge regarding the morphological characterizations of these materials remains limited. When we review product technical data sheets, we encounter missing data, which hinders our ability to understand these materials and select those that offer better characteristics according to the indications for which they will be used.

Morphological study using optical microscopy can be a valuable tool for understanding the structure of different filler materials. This approach could provide better insight into how each type of filler interacts with human tissues, as well as their behavior over time and their biological compatibility.

It is important to recognize that all filler materials act primarily through space occupation, a property that varies according to their concentration and volume[4]. Secondarily, they exert their effects through a foreign-body reaction, which induces an inflammatory response and initiates additional biological processes[5,6]. The structural morphological image of each material is determinant in this process, so understanding these characteristics can help predict the integration of the filler material into dermal tissue.

Furthermore, all filler materials can present adverse effects after injection. The lack of knowledge on the type of material previously injected complicates the repair and healing process of the damage caused. Morphological characterization of different filler materials allows for identification of the injected material, thereby enabling better control over the treatment of adverse effects[7-10].

The aim of this study is to underscore the importance of microscopic morphological analysis of various filler materials for accurate structural identification, which is crucial for the appropriate management of adverse events and may provide further insight into how their morphology influences tissue integration.

Materials and Methods

Selection of gels

A total of ten injectable gels were selected for their diversity in manufacturing techniques, cross-linking methods, and hyaluronic acid combinations, as reflected in Table 1. All gels contain HA in their composition, except for Gel 9. Those containing cross-linked HA are Gels 1, 2, 3, 4, and 5. The gels that do not contain cross-linked HA are Gels 6 and 7. On the other hand, there are hybrid fillers such as Gel 8 and Gel 10. Gel 8 contains cross-linked HA and calcium hydroxyapatite microspheres. Gel 10 contains non-cross-linked HA and succinic acid.

Based on the predominant effect upon injection, we have gels with a predominant volumizing action, which are all the gels with cross-linked HA (1 to 5) and Gel 9. The gels with a predominant revitalizing or biostimulating action are all those with non-cross-linked HA (6 and 7), in addition to the hybrid Gel 10. Gel 8 has a dual effect, volumizing and revitalizing.

Table 2 provides information on the manufacturers and geographical origin of each gel product.

Procedure

Each slide was identified with the name of the corresponding gel.

- 0.1 mL of each material was placed onto a glass slide and photographed with an iPhone 16 Pro Max camera to perform the macroscopic classification.
- Smearing: A very small amount (<0.05 mL) of the study material (selected fillers) was smeared onto another 26x76 mm glass slide. Each filler material was placed on a different slide.
- Drag: A clean glass slide was dragged over the slide containing the product under study. This distributed the product evenly across both slides to facilitate its examination. The thinner the layer of the study product on the slide, the clearer the visualization under the microscope.
- Air-drying: Both slides were air-dried for 5 minutes.
- Staining: The samples were stained with *Diff-Quick* stain (MAIM Brand, Reference B15969). The *Diff-Quick* staining kit consists of three solutions that allow for rapid staining. The samples, previously air-dried, were fixed and stained by immersion in the kit solutions.

Components:

Solution 1: Fixing solution. Contains fast green in methanol.

Solution 2: Red staining solution I. Contains eosin. –

Solution 3: Blue staining solution II. Contains thiazine stain.

Depending on the immersion time in each solution, different degrees of shading and intensity can be achieved. In this study, the following staining protocol was followed:

Table 1. Composition and HA Characteristics of Injectable Gels.

Gel/Product Name	Composition	HA Characteristics
Gel 1 (Belotero Lips Contour®)	Cross-linked sodium hyaluronate: 22.5 mg/mL Lidocaine hydrochloride: 3 mg/mL Phosphate buffer pH 7: 0.6 mL	Cross-linked DBBE CPM Technology
Gel 2 (Harmonie® 1.5%, IT Pharma)	Cross-linked sodium hyaluronate: 15 mg/mL Disodium hydrogen phosphate: 0.6 mg/mL Sodium dihydrogen phosphate: 0.05 mg/mL Sodium chloride: 8 mg/mL Water for injection	Cross-linked DBBE SARE Technology
Gel 3 (Regenovue®)	Cross-linked sodium hyaluronate: 24 mg/mL Lidocaine hydrochloride: 0.3% Phosphate saline buffer	Cross-linked DBBE
Gel 4 (Restylane Kysse®)	Cross-linked sodium hyaluronate: 20 mg/ml Lidocaine hydrochloride: 3 mg/mL Phosphate buffer pH 7	Cross-linked DBBE OBT Technology [3]
Gel 5 (Genefill Contour®)	Non-cross-linked sodium hyaluronate: 2.0 mg Cross-linked sodium hyaluronate: 20.0 mg Sodium chloride: 6.9 mg Water for injection: 1mL	Cross-linked DBBE Thixotropic technology
Gel 6 (Karisma®)	Polypeptide chain R α1 (Rh collagen) Carboxymethyl cellulose (CMC) High molecular weight hyaluronic acid (HMW-HA / 400 mg)	Non-cross-linked
Gel 7 (Croma Philart Eye®)	Polynucleotides; Sodium hyaluronate; Mannitol Water; Sodium chloride Sodium dihydrogen phosphate dihydrate Disodium phosphate dodecahydrate	Non-cross-linked
Gel 8 (HArmonyCa®,[1])	Calcium hydroxyapatite microspheres (25–45 µm diameter, 55.7%) Cross-linked sodium hyaluronate: 20 mg/mL Phosphate buffer Lidocaine hydrochloride: 3 mg/mL	Cross-linked DBBE Dual-action hybrid technology
Gel 9 (Algeness 1,5% Agarose®)	Agarose 1%; Water 88.7% Phosphate buffer 9.8%	Does not contain HA
Gel 10 (Inbiotec Amber®)	2 mL with 1.1% (22 mg) hyaluronic acid and 1.6% succinic acid	Non-cross-linked

[1] Registered trademark of Allergan.

Step 1: Each solution was poured into a container with a height of at least 10 cm.

Step 2: Each slide was immersed for 30 seconds in the fixing solution. This solution fixed the gel to the sample and helped preserve its morphology.

Step 3: The slide was immersed in the red dye solution for 20 seconds. This solution stained basic components in shades of pink or red.

Step 4: The slide was immersed in the blue dye solution for 10 seconds. This solution stained acidic components in shades of blue or purple.

Step 5: The slide was rinsed in a container of distilled water for 5 seconds.

- Drying: the slide was allowed to air dry for 5 minutes. The coverslip was then adhered to the slide.
- Observation and photography: the samples were examined under a trinocular polarizing Delphi-X Observer microscope with digital capture employing a UHD-4K-16 color camera

Table 2. Manufacturers and Countries for each Gel.

Gel/Product Name	Manufacturers	City and Country
Gel 1 (Belotero Lips Contour®)	Merz Aesthetics	Frankfurt (Germany)
Gel 2 (Harmonie® 1.5%, IT Pharma)	IT Pharma	Pamplona, Spain
Gel 3 (Regenovue®)	NeoGenesis Co., Ltd	Seúl, South Korea
Gel 4 (Restylane Kysse®)	Galderma	Uppsala, Sweden
Gel 5 (Genefill Contour®)	BioScience GmbH	Dümmer, Germany
Gel 6 (Karisma®)	Taumed SRL	Rome, Italy
Gel 7 (Croma Philart Eye®)	Croma-Pharma	Leobendorf, Austria
Gel 8 (Haymonyca®,[1])	Allergan Aesthetics	Irvine, United States of America
Gel 9 (Algeness 1,5% Agarose®)	Advanced Aesthetic Technology	Brookline, United States of America
Gel 10 (Inbiotec Amber®)	IT Pharma	Pamplona, Spain

(Euromex). The images were obtained after air-drying and staining with *Diff-Quik*. First, the slide was placed on the microscope. The image was adjusted by focusing, adjusting the lighting, and regulating the diaphragm. The appropriate magnification at which the components could be clearly identified was selected. For gels 1, 2, 3, 4, 5, and 8, a 2x magnification was used; for gels 6, 7, 9, and 10, a 10x magnification was used (Figure2). The image was captured using the microscope's built-in camera. Each image was taken digitally. Each image was saved and documented on the SD card of the integrated camera.

The measurements were performed using the digital ruler integrated into the microscope's camera system (Figure 3).

The procedure was performed in duplicate for each gel to confirm the reproducibility of the results.

Macroscopically, all gels except gel 8 exhibit transparent and translucent coloration on the microscope slides (Figure 1). Gels 1, 2, 3, 4, and 5 were denser. Gels 6, 7, 9, and 10 spread more easily on the microscope slides.

At the microscopic level, all studied gels contain a background of gelified texture. However, in gels 1, 2, 3, 4, 5, and 8, particles resembling "pearls" were additionally identified, with spherical and ovoidal morphology, constituted by a pinkish-colored nucleus (basic) with a peripheral concentric layer of purple coloration (acidic). These particles appeared to correspond to the crosslinked HA component contained in the different gels.

In gels 6, 7, 9, and 10, no recognizable particles were identified. They behaved as an amorphous matrix, which redundantly corresponds to a gel-textured material finely dispersed. Gels 6, 7, and 10 showed an overlapping morphology with an acidic, purple-colored gel texture. In gel 6 and 10, the amorphous matrix was a little bit denser. Gel 9 showed a gel texture in this case with dispersed polygonal spots of bluish coloration, indicating a more basic character.

In the gels with visible solid particles (1, 2, 3, 4, 5, and 8), the 2x objective was sufficient to identify and photograph the particle (Figure 1). In contrast, in the gels with non-particulate appearance (6 ,7 ,9, and 10), a 2x magnification was insufficient to distinguish the subtle differences in the amorphous matrix that composes these gels (Figure 2). Therefore, a 10x magnification was used, which was also used to take the micrographs in Figure 1.

The particle in gel 1 was measured using a digital millimeter ruler and found to range around 1 mm (Figure 3). The remaining gels were photographed at the same magnification, and their particles were therefore assumed to fall within the same size range.

Discussion

In the field of aesthetic medicine, various types of gels are available as injectable filler materials, which must be thoroughly understood to avoid adverse effects. Although significant advances have been made

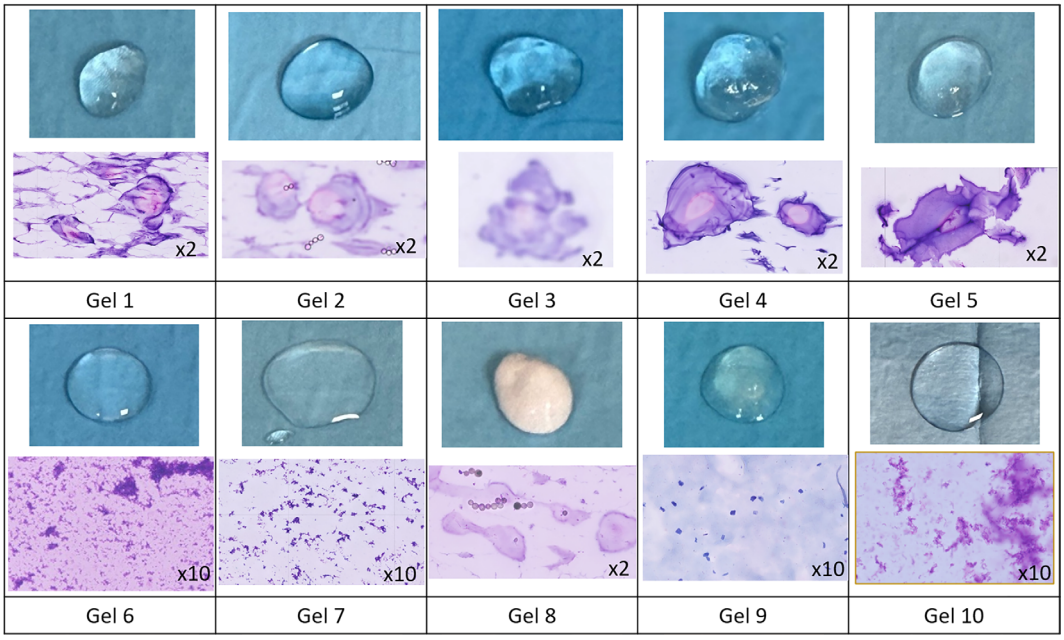

Figure 1. Macroscopic (top) and Microscopic (bottom) Morphology of the Ten Studied Gels.

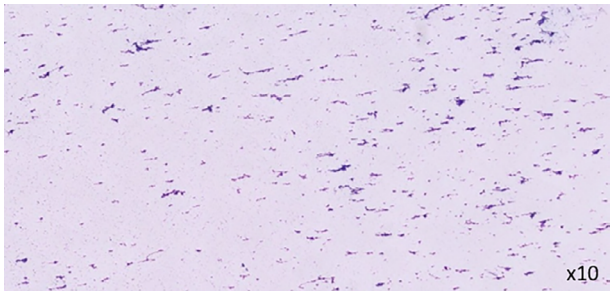

Figure 2. Example of a Micrograph of gel 7 at 12x Magnification.

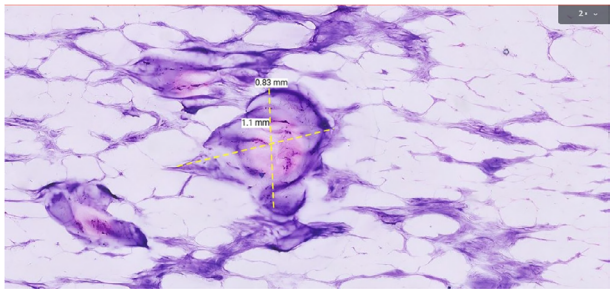

Figure 3. Measurement of one solid particle (pink circle and orange circle) from gel 1.

in the formulation and application of fillers[11,12], morphological research often receives less attention.

Despite its importance, the macro and microscopic morphological study of fillers is relatively less known and less explored in scientific literature[4]. Most studies focus on safety and efficacy from a clinical perspective[13] but are not always accompanied by a detailed morphological analysis. This creates a gap in knowledge regarding particle structure, distribution, and the nature of the surrounding matrix.

One of the key components of fillers is HA. The differences between the various HAs available on the market are based on HA concentration, cross-linking type, and the product's viscoelastic properties. These characteristics influence ease of injection, long-lasting results, clinical appearance, and side effects[14]. Cross-linked HA has a structure modified through a cross-linking process, in which cross-links are created between the HA chains with the help of a cross-linking agent, making it denser and more stable. This cross-linking allows it to maintain its shape and volume longer in tissues. Non-cross-linked HA, on the other hand, lacks these cross-links, resulting in a more fluid and less stable structure that is rapidly degraded

in the body[15]. The percentage of crosslinking indicates how many disaccharides monomeric units of HA are linked by the crosslinking agent. The higher the percentage, the harder the gel and the longer it lasts. However, the higher the percentage of crosslinking, the lower the water retention and the greater the risk of rejection by the body[16].

Nicola Zerbinati et al.[17] selected seven injectable HA for optical microscopic study and evaluated their cohesivity properties. They demonstrated that the six fillers cross-linked with PEGDE showed a matrix structure resembling a "spider web". The same concept could not be demonstrated for the non-cross-linked hydrogel (18 mg/mL).

Patrick Micheels et al.[18] analyzed Belotero Balance® and Juvéderm Volbella® under microscopy, whose composition is based on cross-linked HA. The difference between both lies in the gel technology. No particles were observed in Belotero's CPM gel®, whereas they were observed in Juvéderm Volbella's Vycross technology gel®. They make no reference to the morphology of HA *in vitro*.

This study aims to demonstrate that gels containing cross-linked HA (gels 1, 2 ,3, 4, 5 and 8) have a characteristic common structure in the form of "pearls" with a size ranging between 1 and 2 mm. In contrast, gels 6, 7, and 10 contain non-cross-linked HA, which is not identifiable at the microscopic level. When immersing the preparation in a fixative, and subsequently in stains, the non-cross-linked HA can be easily detached, suggesting that these are not heavy materials, as they are easily eliminated in an aqueous medium.

Gel 9 is a purified agarose gel, which, as we can corroborate with microscopic study, resembles gels with non-cross-linked HA, so its effect when injected into tissue could be similar to that of gels 6, 7, and 10.

Regarding tissue integration of HAs, it would be expected that non-cross-linked HAs, being easily eliminated in aqueous media, would diffuse, and be eliminated easily in tissue. In contrast, the "pearls" of cross-linked HA are particles with body, which remain on the slide despite washing, suggesting that their permanence in tissue will be greater[19].

Gels containing cross-linked HA contain "solid" particles with structure and body (1, 2, 3, 4, 5, and 8). In contrast, those with gel texture (6, 7, 9, and 10) are more "liquid". When injected into the tissue, it would be expected that gels with these "solid" particles will provide more localized volume, greater water attraction, combined with a more lasting effect. Gels with "liquid" texture, when injected into tissue, will dissipate, which would correspond to an increase in volume with a more homogeneous distribution, causing a more subtle effect, and presumably less durable over time[20,21].

Hyaluronic acid fillers are classified as biphasic or monophasic according to their cross-linking process. In biphasic hyaluronic acid fillers, cross-linking is partial and localized, producing cross-linked particles suspended in a carrier of non-cross-linked HA; this design explains their high elasticity but lower cohesiveness. In contrast, monophasic fillers undergo a more extensive and homogeneous cross-linking process throughout the entire gel mass, resulting in a continuous network with greater cohesiveness, uniform integration, and enhanced resistance to enzymatic degradation[22-24]. Microscopic analysis revealed no morphological differences between the biphasic HA filler (gel 5) and the monophasic fillers (gels 1, 2, 3, 4, and 8), suggesting that our study does not support differentiation between these filler types[25].

Among the materials studied, gels 6, 7, 8, and 10 contain a combination of HA with other components. In the case of gel 6, it is with procollagen, gel 7 with polynucleotides, in gel 8 with calcium hydroxyapatite, and in the case of gel 10 with succinic acid. In the case of gels 6, 7, and 10, as previously explained, since they are composed of non-crosslinked HA, we do not observe these "pearls." What we identify as the gel component in "dust specks" in the cases of 6, 7, and 10 corresponds to the collagen, polynucleotide, and succinic acid components, respectively.

In the case of gel 8 (Figure 4), we identify the pearls that reflect the crosslinked HA. The calcium hydroxyapatite component is not observed as such in the microscopic study, but an artifact that could be attributed to this component is observed[26,27]. This artifact reflects the fact that the component is not translucent, therefore its consistency is greater. Thus, the calcium hydroxyapatite component of gel 8 is not stained or observed like the other nine gels studied, its presence can be inferred from the reflection of this artifact.

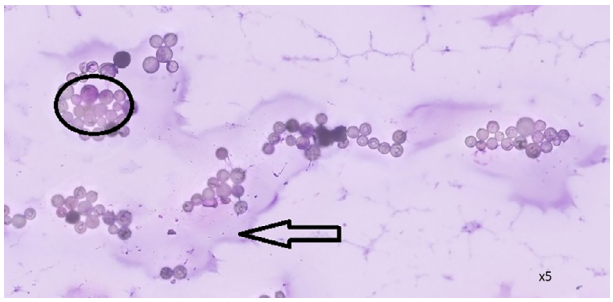

Figure 4. Gel 8, Microscopic Image with Cross-Linked HA Beads (arrow) and Non-Translucent Body Artifact in the Form of Grayish Bubbles (circle).

The morphological identification of different filler materials is helpful in resolving complications. In the event of an adverse effect from an unknown filler, we have two tools for identifying the material[28]. First, ultrasound imaging, and second, morphological analysis[29]. As part of the morphological analysis, a biopsy[30] or FNA may be performed[31].

A skin biopsy clearly shows the different structural layers of the skin: the epidermis, dermis, and hypodermis, allowing us to determine in which layer the injected filler material is deposited. In the event of an adverse effect from an unknown filler, the area could be biopsied, and the sample sent to a pathology laboratory. This sample must be processed in the laboratory before being analyzed by the pathologist. In many cases, the injected foreign material cannot be identified. It is a costly technique, requiring an external laboratory and a specialist in the field. This means that there are few histological studies of filler materials and, consequently, little experience in the histological behavior of these materials in human skin[32-36].

FNA involves inserting the needle into the lesion and aspirating the sample using negative pressure in the syringe. The material is then spread onto a slide. It is a simple, low-cost, rapid, painless technique that leaves no scar and does not require specific laboratory treatment of the sample. The main disadvantage is that the relationship between the different structures is lost, and the layers of the skin cannot be distinguished. We would only obtain a morphological image of the aspirated filler[18].

This technique could be incorporated into routine clinical practice in aesthetic medicine clinics as a first step in identifying an unknown filler. In the event of a cutaneous adverse reaction, a FNA of the lesion could be performed, and the aspirated material smeared onto a glass slide and stained following the procedures outlined in the Materials and Methods section of this study. The resulting image could then be compared with the morphological patterns described in this work to determine whether the unknown material corresponds to any of the studied fillers. This approach could support a more accurate diagnosis of the causative agent[37].

Conclusions

The morphological study of gels used as filler materials in aesthetic medicine is a field that deserves greater attention in scientific research. Different filler materials exhibit distinct microscopic morphology depending on the type of material from which they are composed.

In our study, we have been able to establish an in vitro morphological label for some of the gels available on the market. In the event of an adverse effect, FNA of the filler material and its subsequent microscopic study can be a tool for identifying injectable gels not recorded in the clinical history. Therefore, one of the immediate objectives of our work is to create an iconographic atlas of all injectable products to facilitate their diagnosis.

This study brings us closer to understanding the microstructural properties of fillers, though further studies are required to determine their behavior in tissue.

Multidisciplinary research that includes morphological study of materials could contribute significantly to the safety and efficacy of aesthetic treatments, improving the experience and outcomes for patients.

Abbreviations: BDDE: 1,4-butanediol diglycidyl ether; CMC: Carboxymethyl cellulose; CPM: Cohesive Polydensified Matrix; FNA: Fine-needle aspiration; HA: Hyaluronic acid; HMW-HA: High molecular weight hyaluronic acid.

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data curation, M.F. and M.R.; writing—original draft preparation, M.F., M.R., P.T., S.M. and M.O.; writing—review and editing, M.F., M.R., P.T., S.M. and M.O.; visualization, M.F., M.R., P.T., S.M., M.O. and S.C.; supervision, M.F., M.R. and S.C.; project administration, M.F. All authors have read and agreed to the published version of the manuscript.

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