Basics of Dermal Filler Rheology

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BACKGROUND Hyaluronic acid injectable fillers are the most widely used dermal fillers to treat facial volume deficits, providing long-term facial aesthetic enhancement outcomes for the signs of aging and/or facial contouring.

OBJECTIVES The purpose of this article was to explain how rheology, the study of the flow of matter, can be used to help physicians differentiate between dermal fillers targeted to certain areas of the face.

METHODS This article describes how rheological properties affect performance when filler is used in various parts of the face and exposed to mechanical stress (shear deformation and compression/stretching forces) associated with daily facial animation and other commonly occurring external forces.

RESULTS Improving facial volume deficits with filler is linked mainly to gel viscoelasticity and cohesivity. These 2 properties set the level of resistance to lateral and vertical deformations of the filler and influence filler tissue integration through control of gel spreading.

CONCLUSION Selection of dermal filler with the right rheological properties is a key factor in achieving a natural-looking long-lasting desired aesthetic outcome.

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Injectable dermal fillers are commonly used to treat signs of facial aging and provide facial enhancement.[1] In the United States alone, the use of fillers has more than doubled in the last decade. Over 2 million soft tissue injections were performed in 2013, of which 71% used hyaluronic acid (HA)–based fillers.[1]

Hyaluronic acid injectable fillers are the most widely used fillers, as they are a safe, effective, and reversible treatment that provides natural-looking long-term results with little downtime.[2,3] These fillers are made by attaching chains of HA together using a cross-linker such as 1,4-butanediol diglycidyl ether. This cross-linked HA can be processed in different ways to yield homogenous gels or suspensions of particles in gel carriers. Each type of HA filler has a different amount of HA and is developed using different cross-linking processes, both of which significantly affect the properties of the gel that contribute to the aesthetic outcome.[4]

Understanding the properties of fillers can help clinicians select the ideal product for each indication and region of the face.[5] A filler placed superficially in the dermis to correct fine lines will require different properties than one placed at a deeper level to restore mid-facial volume. This is because each region of the face is subjected to strains of varying frequency and intensity from overlying skin tension, muscle activity, and fat volume. These strains cause the filler to deform in various ways.

To date, a number of articles have been published on various aspects of filler rheology[6–10] (i.e., the study of how a material deforms and reacts under mechanical stress). To the best of the authors' knowledge, no article has explained the effect of rheological properties on filler performance in response to various deformations and forces.

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This article aims to overcome this gap by describing how the rheological properties of fillers affect performance when they are used in various parts of the face and exposed to mechanical stress associated with daily facial animation and other commonly occurring external forces.

Hyaluronic Acid–Based Filler Mechanical Properties

When filler is implanted into the face, it is subjected to the interplay and sum of shear stress and vertical compression/stretching forces, both of which cause the filler to deform. Shear deformation occurs when force is applied along the surface of the material by applying lateral shearing or torsion on a plane (Figure 1, left). In this case, the dimensions of the material will stay the same, but its shape will change. Compression/stretching deformation occurs when force is applied perpendicularly by stretching or compressing along an axis (Figure 1, right). In this case, the shape is retained, but the dimensions are changed as the material deforms in one direction. In certain facial areas, one type of deformation may be more dominant than the other. However, previous rheology articles have focused exclusively on shear deformation[7,10] without considering the equally important compression/stretching forces. Here, the authors describe 3 rheological properties that determine filler performance under shear and compression/stretching forces.

Viscoelasticity and Shear Deformation

Viscoelasticity is a property of an HA filler that exhibits both viscous and elastic behavior when undergoing shear deformation. Purely elastic materials deform up to a certain point under shear stress and recover when the stress is removed (e.g., a rubber band). Purely viscous materials keep deforming as long as shear stress is maintained but do not recover afterwards (e.g., honey). For HA filler to be effective, it needs to possess both of these properties because it is subjected to different types of shear force during and after the injection. During injection when high shear stress is applied (i.e., when the filler is extruded from the needle/cannula), the filler behaves almost like a purely viscous material as it flows out of the needle/cannula. However, once implanted into facial tissue, where the filler is exposed to low shearing force from soft tissue, the filler exhibits elastic behavior as it can almost recover its original shape.[6,7,10]

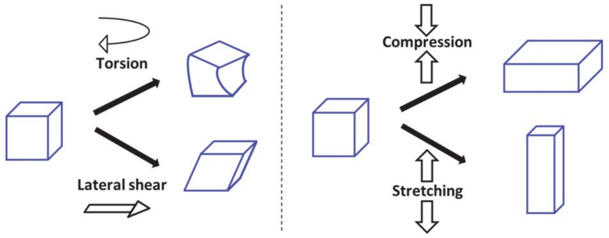

Figure 1. There are 2 types of deformation modes associated with dermal fillers: (1) lateral shear or torsion (left side) and (2) stretching/compression (right side).

There are 4 main rheological parameters used to describe viscoelastic properties: G* (measures overall viscoelastic properties or "hardness"), G′ (measures elastic properties), G″ (measures viscous properties), and tan δ (measures the ratio between viscous and elastic properties).

G*, the "complex modulus," is the total energy needed to deform material using shear stress.[11] This term is commonly referred to as filler "hardness," representing how difficult it is to alter the shape of an individual cross-linked unit of filler. G* reflects the "hardness" of multiple units of cross-linked HA, not the hardness of the whole gel deposit. It is determined by the following formula: $|G^*| = \sqrt{(G')^2 + (G'')^2}$, in which G′ and G″ are derived from experimental testing with a rheometer.[12]

G′, the "storage/elastic modulus," represents the energy fraction of G* stored by the gel during deformation and used to recover the original shape afterwards. G′ measures the elastic behavior of a gel or how much it can recover its shape after shear deformation. For example, vulcanized rubber is a purely elastic material as it deforms instantly under stress and completely recovers its shape after the stress is removed (i.e., $G^* \approx G'$).

G″, the "loss/viscous modulus," represents the energy fraction of G* lost on shear deformation through internal friction. G″ is not directly related to viscosity because HA filler is not purely viscous. Instead, this term reflects the inability of the gel to recover its shape completely after the shear stress is removed.

Tan δ refers to the elasticity of a material. It is a measure of the ratio of viscous to elastic components of G*, defined as $\tan\delta = \frac{G''}{G'}$. Tan δ determines whether the material is mainly elastic (tan δ < 1), exhibiting a gel-like behavior (e.g., a block of gelatin), or whether it is mainly viscous (tan δ > 1), behaving more like a viscous liquid (e.g., honey). In cross-linked HA fillers, tan δ is usually low (ranging from 0.05 to 0.80), meaning that the elastic (i.e., gel-like) behavior under low shear stress is dominant over the viscous (i.e., liquid) behavior. Lower tan δ is usually associated with higher G′ because HA fillers always have low G″.

For any facial filler to be effective, it needs to be viscoelastic (Figure 2). It needs to deform enough to be injected under high strain and to be initially molded but elastic enough to provide a durable correction by resisting shear deformation forces once implanted into soft tissue. A purely elastic filler would be almost impossible to inject through a needle as it would require an immense force on the plunger to eject it in a nonreversible manner. Similarly, a purely viscous filler would irreversibly deform on stress and would not retain its shape for a significant amount of time even when the stress is removed. For example, when saline solution (i.e., a material with low viscosity and 0 elastic property) is injected, the correction is short lived because water lacks elasticity.

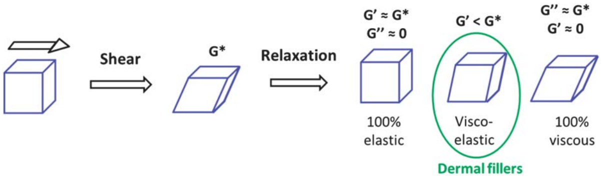

Figure 2. The effect of shear stress on elastic, viscoelastic, and viscous materials.

The viscoelastic properties of fillers are determined during the design and manufacturing process. For a given manufacturing process, the gel hardness and elastic modulus (i.e., G* and G′ values) are proportional to the level of cross-linking when all other factors are equal. The G′ values of commercial HA fillers range from 10 to 1,000 Pa depending on the manufacturing process and intended use (Table 1).[7,10,11] It is relevant to note that all HA fillers currently on the market can be considered "soft," given their elastic modulus does not exceed far beyond 10^3 Pa. Diluting a filler to reduce its HA concentration results in a decrease of G*, G′, and G″, making the gel softer, less elastic, and less viscous in addition to possibly reducing the filler's intrinsic duration.

Cohesivity and Compression/Stretching

Cohesivity characterizes how the filler behaves as a gel deposit once it is implanted in the face. It mainly relates to the degree of attraction between cross-linked HA units. It is best described as the internal adhesion forces holding together individual cross-linked HA units that compose the HA gel deposit.[13] The strength of the internal adhesion forces is a function of HA concentration and the cross-linking technology, which can yield different gel macrostructures (e.g., smooth, granular). Cohesivity can be measured as the resistance to vertical compression/stretching based on

TABLE 1. Rheological Properties of HA Dermal fillers*

Filler	*G′ (Pa)*	*G″ (Pa)*	*Tan δ*	*Compression (gmf)*
Juvéderm Ultra XC	207	80	0.39	96
Juvéderm Ultra Plus XC	263	79	0.30	112
Juvéderm Voluma XC	398	41	0.10	40
Juvéderm Volift with lidocaine†	340	46	0.14	30
Juvéderm Volbella with lidocaine†	271	39	0.14	19
Restylane-L	864	185	0.21	29
Perlane-L	977	198	0.20	32
Belotero Balance	128	82	0.64	69

*Elastic and loss moduli are given at 5 Hz with a 0.8% strain. Compression force is given from a 2-minute linear descent (2.5–0.9 mm).
†Filler is not approved in the United States.

a method adapted from a previously described assay performed on un–cross-linked HA (Figure 3).

Filler implanted in the face is constantly subjected to compression forces that affect how it performs. For example, it is subjected to force from contact with external surfaces, such as lying on a pillow, or to the force applied by skin tension over a filler placed subcutaneously. When subjected to these forces, HA filler with lower cohesivity tends to lose projection easier than filler with higher cohesivity and equivalent G′. Filler with high cohesivity can resist vertical compression and maintain the initial shape of the gel deposit (Figure 3).

Figure 4 shows a microscopic view of Filler X created using a cross-linking manufacturing process, resulting in a gel made of a suspension of highly elastic (high G′) HA cross-linked particles (here the cross-linked units are visible). This type of filler usually has low resistance to compression because the particles do not adhere (i.e., cohesivity is low). After this filler is implanted and has been subjected to repetitive compression forces in the face, the amount of projection and contour will diminish quickly. The gel deposit will lose its shape and spread until it becomes a flat layer with a thickness of only a few particles. Degree of spreading is dependent on where the product is implanted. In the dermis, where there is little space, spreading will be minimal because of the integration into the tight dermal matrix. However, in the subcutaneous level or preperiosteal plane, where there is gliding space, such filler will have tendency to spread laterally. Lack of cohesivity between the gel particles also increases the chance of particles separating from the deposit, potentially causing migration of the filler. This spreading or migration will occur regardless of the filler hardness. Therefore, with this type of low-cohesive filler, vertical projection is mainly a function of the average particle size.

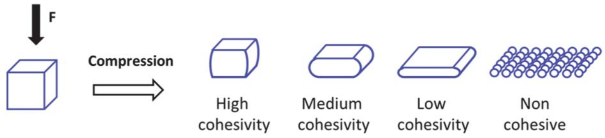

Figure 3. Compression test at constant weight designed for dermal fillers. F is the force applied by a constant weight.

Figure 5 shows Filler Y, created using a different cross-linking manufacturing technology, resulting in homogeneous cross-linked HA with higher cohesivity (the cross-linked units are shapeless and not visible). By altering HA concentration and the cross-linking manufacturing process, it is possible to dramatically change the degree of cohesivity among cross-linked HA units. The cohesivity of a filler will determine how well the cross-linked HA domains hold together when it is implanted and subjected to compression/stretching forces by the facial tissue or other external forces.

Viscosity and Extrusion Force

Viscosity is a measure of a filler's resistance to flow when shear stress is applied. As higher amounts of stress are applied, the viscosity of a filler decreases. The shear stress

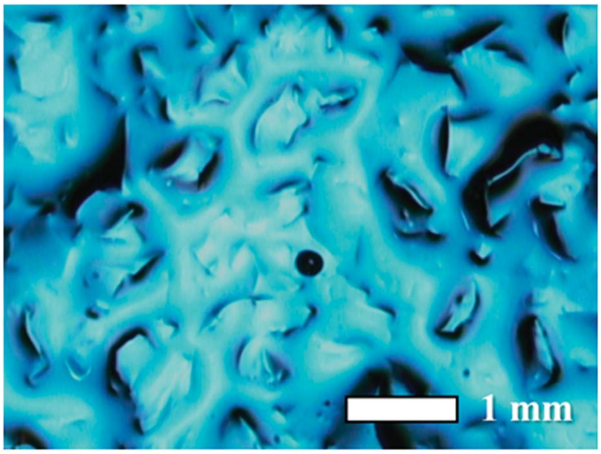

Figure 4. Microscopy image showing Filler X comprised suspended particles (original magnification ×51.7, no stain).

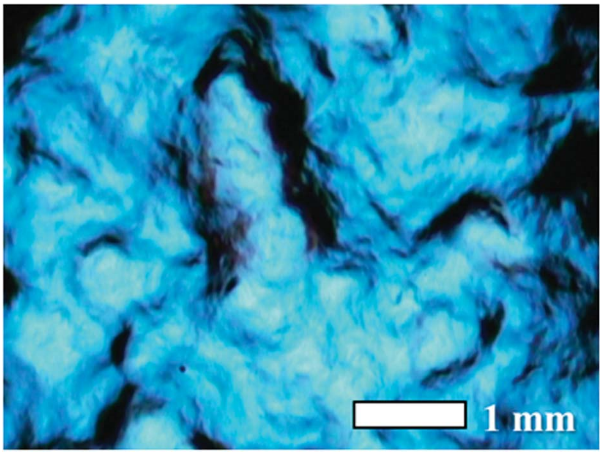

Figure 5. Microscopy image showing Filler Y, a homogeneous filler (original magnification ×51.7, no stain).

applied from overlying tissue when the filler is in the skin is low enough that the viscosity level does not allow the filler to flow. This is because at these low shear rates, filler exhibits predominantly elastic properties. Therefore, viscosity is not relevant to performance after the filler has been implanted. However, viscosity of a filler is relevant at extremely high shear rates or during the injection when it becomes an essentially viscous material.

Because a filler is subjected to high levels of shear stress during the injection, viscosity will affect extrusion force (i.e., ease-of-injection). Extrusion force is a measure of the force needed to inject a filler at a fixed rate through a needle/cannula.[14,15] This force is a function of gel viscosity provided that the syringe, needle length and diameter, and injection rate are kept constant. A highly viscous filler will require a high extrusion force, which may correspond to a difficult injection for the physician (e.g., fatigue, lack of precision), resulting in more tissue trauma at the injection site. An ideal HA filler is one with low extrusion force, allowing for ease and precise dosing during injection.

Application of Viscoelastic and Cohesive Properties to Hyaluronic Acid Fillers

The face is a complex and dynamic structure. Any filler implanted in the face will be subjected to various combinations of lateral shear and compression/stretching forces from intrinsic and extrinsic sources. Intrinsic sources include tensions and motions between bone and its overlying muscle, fat, and skin. Within each anatomic plane, filler is subjected to a complex array of forces varying in intensity and frequency. Extrinsic sources include compression/stretching and lateral shearing from normal daily activities such as resting the face on the pillow, eating, and kissing. Therefore, modern filler needs to be tailored with different mechanical properties for each specific indication and facial region (Table 2).

In fillers with a high elastic modulus, G' is nearly equal to gel hardness (G^*) because cross-linked HA fillers have low G'' at the shear rates found in facial tissues. These harder fillers are better suited for deeper placement in the subcutaneous tissue or preperiosteal so that palpability of gel particles is reduced. Lower elastic modulus/softer products are usually better suited for medium to superficial implantation such as correction of fine lines or skin folds.

Midface Fillers

For midface volumization, the aim is to provide volume restoration, projection, and 3-dimensional contouring. To achieve this, the chosen filler must maintain shape and projection by resisting the shearing and compression forces of the weight and tension of the overlying soft tissue, dynamic contraction forces of the lip and cheek elevators, and the external compression forces mentioned above. From a rheological perspective, this translates to a filler with sufficient elastic modulus (G') to withstand shearing and medium to high cohesivity to resist compression forces. Sufficient cohesivity is important for ensuring minimal separation and displacement of product because of repetitive contraction of the overlying musculature.

Fine Lines Fillers

Fillers with lower cohesivity than those used for midface volumization will provide easy molding and spread within tissue. A filler with low cohesivity combined with low to medium G^* and G' will make an ideal "nonbulking" product to treat superficial pathologies such as fine lines in the periorbital/perioral areas and volume loss in the lips. This type of filler is less likely to create visible edges and bumps. It also is suitable to be implanted in the dermis or subdermal planes.

Lower Face Fillers

In the lower face, where there is extreme mobility (e.g., marionette lines, nasolabial folds, and accordion lines), different rheological factors need to be considered. Here, the filler needs to be placed in the deep dermal or subdermal plane; and therefore, it needs to be easily moldable, integrate well with facial movement, have minimal projection, and be nonpalpable. As the lower face is subjected to mostly shearing and some mild compression forces, the ideal filler would have moderate G' and low to medium cohesivity. However, in severe folds, a filler with high cohesivity still may provide better correction "per

TABLE 2. Definition and Clinical Relevance of Rheological Terms Related to HA-Based Dermal Fillers

Term	*Definitions Applied to Fillers*	*Clinical Relevance*
Viscoelasticity	Elastic and viscous properties of fillers	Elasticity provides a lasting filling effect; the filler must be viscous to be injectable
Complex modulus (G*)	Energy needed to deform a filler through shear stress (gel firmness or hardness)	Low G* fillers are better suited for superficial filling because they cannot be felt after implantation; High G* fillers are better suited for volumization (but optimal volumization also requires medium to high cohesivity)
Elastic modulus (G′)	Energy stored and given back after shear stress	Shear stress (lateral gliding) causes low G′ fillers to spread; higher G′ fillers will recover their shape better
Viscous modulus (G″)	Dissipated energy during shear stress due to friction	Not a measure of viscosity
Elasticity (tan δ)	Division of G″ by G′; measures whether a filler is more elastic or more viscous	When tan δ is >1, the filler is mostly viscous (uncommon for cross-linked HA fillers); when tan δ is <1, the filler is mostly elastic (common for cross-linked HA fillers); lower tan δ is usually associated with a tighter HA network*
Viscosity	Ability of a filler to resist flow (filler thickness)	Low relevance for clinical performance; high relevance for ease-of-injection
Shear stress	External force applied parallel to the surface; can be linear (gliding) or rotational (torsion)	Occurs when the filler is placed between 2 different tissue planes*
Torsion	Rotational version of shear stress	Uncommon in vivo but used with rheometers because this form of stress is easier to control than lateral shear; torsion and linear shear affect fillers similarly
Cohesivity	Adhesion between cross-linked HA domains caused by weak (noncovalent) interactions	High cohesivity helps fillers maintain vertical projection while soft tissues apply vertical stress*; medium cohesivity provides versatility by keeping a balance between vertical projection and relatively easy moldability*; low cohesivity helps the filler to form a sheet by spreading evenly on injection and makes the implant easy to mold initially*
Compression force	Force applied perpendicularly to the gel surface	Used to assess filler cohesivity; caused by soft tissues applying pressure over the implant; these forces increase when the filler is placed deep in the dermis
Spreading	Lateral distribution of the filler caused by shear and compression stress	Filler hardness influences spreading caused by lateral gliding; filler cohesivity influences spreading caused by compression/stretching forces
Extrusion force	Force needed to eject filler from a syringe through a needle/cannula at a certain rate	Highly dependent on syringe geometry and type of needle/cannula

*May contain assumptions.

injected volume," but it will be more difficult to mold on injection.

Nose and Chin Fillers

For nasal and chin projection, where the main force is compression because of skin and tight muscle tension over the prominent bony structures, the filler of choice would have high cohesivity and high G′. This type of filler will minimize lateral spreading and keep a sharp vertical projection over time. A filler in this area is not submitted to intense shear stress.

Conclusion

Viscoelasticity and cohesivity play an important role in HA filler design, selection, and clinical outcomes, as these rheological properties can make facial correction more predictable when the right product is used in the right place. These properties relate to the ability of fillers to withstand different types of deformation and forces when implanted in various facial areas and planes. Viscoelasticity is a measure of the elastic and viscous behaviors of a filler. Fillers with moderate to high elastic modulus (G′) can withstand shear stress better than those with low G′. Fillers with high G′ usually are harder (higher G*) and need to be placed in deeper planes to reduce implant palpability. Cohesivity is a measure of the ability of the gel to resist compression/stretching. This is an important concept because fillers are consisted of multiple units of cross-linked HA in the form of visible particles or discrete units that adhere through noncovalent bonds. Cohesivity affects initial spreading of the implant in a variable manner related to its depth and overlying/underlying muscle and skin compression. Fillers with high cohesivity are better suited for bulk facial volumization, whereas fillers with low cohesivity are easy to mold and tend to form thin even layers in the skin. This type of filler creates natural-looking correction of small skin folds. A better understanding of these rheological properties will guide clinicians in selecting the ideal filler for each region of the face based on pathology and the deformation forces acting in the area of interest.

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