Review Article

Physical Characteristics, Clinical Application, and Side Effects of Viscoelastics in Ophthalmology

Mehrdad Mohammadpour[1], Hassan Asadigandomani[1,2], Mehdi Aminizade[1], Saeed Raeisi[1]

[1]Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran, [2]Department of Ophthalmology, School of Medicine, Tehran University of Medical Science, Tehran, Iran

Abstract

Purpose: To explain the physical properties of ophthalmic viscoelastic devices (OVDs), covering their structural units, optimal features, existing viscoelastic materials, clinical applications, and potential side effects.

Methods: This is a narrative review on the OVDs. A literature review was conducted in PubMed, Google Scholar, and Scopus databases. Studies that investigated physical characteristics, clinical applications, OVD commercial products, and their complications were included.

Results: We included 42 articles from 2010 and discussed physical characteristics, properties of a desirable OVD, structural units of common OVDs, OVD commercial products, clinical applications, and also complications of OVDs.

Conclusions: Today, viscoelastics hold a distinct and crucial role in intraocular surgery due to their remarkable properties. These materials safeguard the endothelium and epithelium, uphold anterior chamber depth, manage intraocular bleeding, ease tissue handling, and aid intraocular lens placement. Currently, the American market features 12 prevalent viscoelastic types, including 7 sodium hyaluronate derivatives (Healon, Healon-Greater Viscosity, Healon-5, Amvisc, Amvisc Plus, Advanced Medical Optics Vitrax, and Provisc), 2 hydroxypropyl methylcellulose 2% derivatives (OcuCoat and Cellugel), and 3 combinations of sodium hyaluronate and chondroitin sulfate (Viscoat, DisCoVisc, and DuoVisc). Despite the introduction of new viscoelastic materials annually, no single material encompasses all desired properties. Surgeons must select and employ suitable viscoelastics based on surgical conditions and patient requirements. Advancements in material development and understanding of physical properties and clinical applications continue to refine viscoelastic selection.

Keywords: Cataract, Ophthalmic viscoelastic device, Phacoemulsification, Viscoelastics

Address for correspondence: Hassan Asadigandomani, Qazvin Square, Qazvin Street, 14176-13151, Tehran, Iran.
E-mail: hasanasadigandomani0800@gmail.com
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Introduction

The growing utilization of viscoelastics in ophthalmology under the designation of ophthalmic viscoelastic devices (OVDs) has substantially impacted intraocular surgery.[1] Protection of the corneal endothelium from mechanical damage, while maintaining the depth of the anterior chamber (AC) when the surgical wound is open, is one of the unique properties of viscoelastic materials.[2,3] The physical properties of OVD are the result of the chain length and intra- and interchain reactions of the molecules of these materials, which have a direct effect on its clinical capabilities.[4] A complete and correct understanding of their special features allows the surgeon to choose the optimal viscoelastic depending on the different stages of the operation, the patient's conditions, and the economic conditions of society.[5] In this article, first, we explain the physical properties of OVDs, then we introduce the structural units of viscoelastic materials, optimal features of OVD, existing viscoelastic materials, clinical applications, and also their side effects.

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Methods

A literature review was conducted in PubMed, Google Scholar, and Scopus databases on articles published until August 2023 using keywords: ophthalmic viscoelastic devices, cataract, OVD commercial products, cataract surgery, phacoemulsification, and viscoelastics. No restrictions on the journal type were used.

The first article selection was made by a quick review of the article's topics after the initial search. Second-time screening was done by reviewing their abstracts. Two authors (MM and HA) independently analyzed selected full-text articles for inclusion in the study. Articles published between January 2010 and August 2023 and in English were included.

Results

We included 42 relevant articles from 2010. We also included 10 articles before 2010. We discussed physical characteristics, properties of a desirable OVD, structural units of common OVDs, OVD commercial products, clinical applications, and also complications of OVDs.

Discussion

Physical characteristics of ophthalmic viscoelastic device

Elasticity

The ability of a fluid to return to its original shape after the removal of the pressure that caused it to change its shape is elasticity. This feature preserves the depth of the AC after the removal of mechanical pressure. Other fluids such as balanced salt solution (BSS) do not have this ability. The elasticity of a fluid increases with the increase of molecular weight and the length of its molecular chain.[6,7]

Viscosity

The resistance of a fluid to flow is called viscosity, which depends on its molecular weight. The unit of fluid gravity is centistokes (cSt) or centipoise. The density of common fluids is <10000 cSt, whereas the density of viscoelastic materials is more than 10000 cSt.[8]

The rate of movement of a liquid against a constant force is called the "shearing rate", which is effective on the viscosity of the liquid. The relationship between the shearing rate and the fluid temperature is inversely proportional. The viscosity of fluids can be increased by increasing their concentration or molecular weight.[4]

Pseudoplasticity

In physical science, the word "plastic" refers to a material that has the following two properties: first, its viscosity increases as the shearing force on it decreases, and second, if the shearing force reaches zero; its viscosity increases infinitely and turns into a solid substance.[6] Since viscoelastic materials only have the first characteristic, the term pseudoplasticity is used. The ability of a fluid to change from a jelly substance to a waterier substance under pressure is called pseudoplasticity.[7,9]

Surface tension

The coating ability of a viscoelastic is determined not only by the surface tension of its material but also by the surface tension of the tissue it contacts, intraocular lens (IOL), and surgical instruments. By measuring the angle created between a drop of viscoelastic material on a smooth surface, which is called the "contact angle", it is possible to estimate the covering ability of a viscoelastic material. The lower surface tension and contact angle of OVD cause the greater covering power of that material.[10]

For example, sodium hyaluronate solution has more surface tension and a larger contact angle than chondroitin sulfate, a combination of hyaluronate and chondroitin sulfate, and hydroxypropyl methylcellulose (HPMC); hence, the covering ability of the latter materials surpasses that of sodium hyaluronate.[6]

Cohesion and dispersion

Arshinoff divided viscoelastic materials into two categories: dispersive and cohesive.[11] Aggregating materials have high viscosity and resist separation with the help of strong intermolecular junctions. Viscoelastic materials with long molecular chains are more accumulative and do not separate easily due to the junctions of their molecules into each other. These materials have higher molecular weight, more pseudoplasticity, and higher surface tension.[12] The properties of dispersive viscoelastics are just the opposite of the cohesive agents. They have less viscosity and adhere well to contact surfaces (such as tissues, surgical instruments, and IOLs). These materials have lower molecular weight and pseudoplasticity and lower surface tension and are easily separated.[12]

Another word called viscoadaptive has been proposed, which refers to the ability of viscoelastic material to adapt to different stages of surgery and special needs in each stage. This type of OVD, by compromising with the environment, can change its related variables for optimal performance. The changing component, in most conditions, is the existing degree of turbulence.[13,14]

Properties of a desirable ophthalmic viscoelastic device

It is clear that the optimum OVD must have a series of features. It should be transparent, despite the positive vitreous pressure, it should remain inside the eye during phacoemulsification and other surgeries, it should be removed from the eye easily, it should not interfere with intraocular devices and IOL, it should protect the endothelium, it should not have toxic or inflammatory properties for the eyes, it should not interfere with the outflow of the aqueous humor, and finally, it should be cost-effective.[15]

Structural units of common ophthalmic viscoelastic devices

Sodium hyaluronate

This substance is a biological polymer (biopolymer) that is present in many body tissues (including the aqueous humor and vitreous).[16,17] Its basic structural unit is a disaccharide, which is connected to each other by repetitive beta-1 and 4 glycosidic bonds, and at the end, a long unbranched chain is created.[17] This mucopolysaccharide chain, when placed in a solution such as a natural salt solution, creates an accidental spiral. By increasing the concentration of large hyaluronate molecules to more than 0.5 mg/mL, each of the spirals starts overlapping with other spirals and gets compressed. Molecular crowding increases the possibility of noncovalent chain-to-chain connections and ultimately increases the viscosity of the solution significantly.[16] In line with the increase in viscosity, the elasticity of OVD also increases.[16,17]

The noninflammatory part of sodium hyaluronate, which is used in ophthalmology, is the NIF-NaHA molecule.[17] This substance has a high molecular weight (2–5 million Daltons), low protein content (<0.5%), and only one negative charge per disaccharide unit. This composition is highly purified, sterile, nontoxic, nonantigenic, noninflammatory, and without febrile properties.[16,18]

Chondroitin sulfate

This biopolymer is one of the three main mucopolysaccharides of the cornea, which has a structure similar to hyaluronic acid and is composed of similar repeating units of disaccharides.[6] This substance has an average molecular weight of about 50,000 Daltons, and like sodium hyaluronate, it is not metabolized; however, it will be cleared from the AC within 24–30 h.[14]

Hydroxypropyl methylcellulose

It is another viscoelastic substance that is used in ophthalmology. Unlike the previous two substances, it is not found naturally in animals and is widely found in the structural material of plant fibers such as linen and wood.[14]

In the purification of this substance, special precautions are necessary to prepare high-purity products.[19] Methylcellulose is a nonphysiological compound that is not metabolized in the eye, but it is cleared from the AC of the rabbit's eye within 3 days.[19] This material is completely hydrophilic, and therefore, it can easily be washed from the eyes at the end of the procedure.[14]

Ophthalmic viscoelastic device commercial products

Healon, Healon-Greater Viscosity, and Healon-5

The first commercially available sodium hyaluronate was Healon, which was produced by Balazs, and its franchise was assigned to Pharmacia. In 1958, Balazs proposed hyaluronic acid as a vitreous substitute, and despite the mild inflammatory response it caused, it was proposed as a tolerable substitute for vitreous. In fact, surgery with viscoelastic materials was born with the appearance of Healon.[17]

This product with high concentration and molecular weight is a derivative of sodium hyaluronate, which was originally prepared from cock's crown and was purified by Balazs and introduced as a noninflammatory substance.[17] In 1972, the first intraocular injection of Healon into the vitreous and AC was reported.[20,21] By increasing the molecular weight and the concentration of Healon, Pharmacia introduced Healon-Greater Viscosity (GV) in 1992 with a static viscosity at least 10 times more than most viscoelastic materials.[14,22]

Healon-5 is another product that maintains the properties of Healon-GV during phacoemulsification, remains in the AC, and covers the endothelium. Healon-5 is known as the first viscoadaptive.[6] Healon-5 acts as a material with high viscosity and excellent adhesion similar to Healon-GV when faced with a low speed of liquid movement, and when the speed of liquid movement increases, it breaks into smaller pieces and shows a behavior similar to viscoelastic expansion.[6]

Amvisc and Amvisc Plus

Amvisc is another product of sodium hyaluronate and is prepared from cock's crown. First, Precision-Cosmet company produced this material, and now, it is supplied by Bausch and Lomb company. Amvisc is less expensive than Healon.[22] Amvisc Plus is a 1.6% sodium hyaluronate product, which has a higher viscosity than Amvisc. This higher viscosity was achieved by increasing its total concentration and made it more capable of maintaining volume and tissue manipulation than Amvisc.[6,15]

Amovitrax

It is produced by Advanced Medical Optics company and is a viscoelastic with low molecular weight but high purity and derived from NIF-NaHA solution in BSS. Despite its relatively low molecular weight, this substance is highly concentrated and, as a result, has a high viscosity. Unlike other sodium hyaluronate compounds that all need to be stored in the refrigerator, this substance can be kept at room temperature for up to 18 months. This OVD in conditions where there is no pressure on it has less viscosity than Healon. It is interesting to note that, unlike Healon, which its viscosity decreases linearly with increasing shearing force, Amovitrax maintains its viscosity.[6,14]

Provisc and DuoVisc

Provisc is produced by Alcon company. It is a sterile, nonpyrogenic substance with a high molecular weight and a highly purified derivative of NIF-NaHA, which is dissolved in a physiological sodium chloride phosphate buffer. Its material is prepared from microbial fermentation and during the purification process. Clinical tests show that the protective power of Provisc on the endothelium and its level of immunogenicity are equivalent to Healon. Like Viscoat, these materials need to be stored in the refrigerator. A combination of Provisc and Viscoat, called DuoVisc, has been produced by Alcon company, which has all the properties of shrinking and expanding in one vial.[6,14,23]

Viscoat

This substance, produced by Alcon company, is a combination of chondroitin sulfate and 3% sodium hyaluronate in a one-to-three ratio. The sodium hyaluronate component is made from microbial fermentation, and the chondroitin sulfate component is extracted from shark cartilage. This composition possesses both the high viscosity and AC depth-maintaining characteristics. In addition, it exhibits a strong covering property, consequently safeguarding the endothelium.[24] In the experimental test, Koch *et al*. compared the protective effect of Healon on the endothelium during phacoemulsification on the iris plane with Viscoat and concluded that Viscoat is more effective than Healon, but if the phacoemulsification is performed behind the iris, both Healon and Viscoat have an excellent and comparable effect in protecting the endothelium.[25]

DisCoVisc

In 2005, DisCoVisc was released to the market.[26] DisCoVisc is a combination of sodium hyaluronate 1.6% and chondroitin sulfate 4%. According to its physical properties, this material has an intermediate cohesive/dispersive index, which will preserve the space of the AC and also protect the intraocular tissues.[27,28] Studies have shown that this substance will stay better in the AC during phacoemulsification and will be removed more easily compared to Healon.[27]

OcuCoat

It is produced by Bausch and Lomb and is a highly purified, nontoxic, nonprotein derivative of 2% HPMC. It has a coating property than an elastic property, and hence, it has been marketed as a viscoadherent.[29] [OcuCoat® has been marketed as a viscoadherent rather than a viscoelastic because of its significant coating ability and its relative lack of elastic properties]. OcuCoat is prepared from HPMC with very high purity and then undergoes a double purification process, and injecting it into the eye requires a larger cannula and high force. Unlike other viscoelastics, it can be sterilized in an autoclave and kept at room temperature. The cost of its preparation is less; however, the processes that are carried out for its purification may increase its cost.[6]

Cellugel

It is made by Alcon company. It is sterile, nonpyrogenic, noninflammatory, single use, and prepared from HPMC 2%. It is packed in a single-use syringe of 1 mL, inside a sterile box, and finally, it is sterilized by an autoclave. Like OcuCoat, it can be stored at room temperature, but it is 10 times more expensive and its molecular weight is 4 times more than OcuCoat. As a result, although both OVDs are HPMC 2%, the ability of Cellugel to maintain volume is higher.[14,30]

As shown in Table 1, the highest dynamic viscosity belongs to Healon-5 and Healon-GV and the lowest one belongs to OcuCoat.

Clinical applications of ophthalmic viscoelastic devices

Cataract surgery

Specular microscopic and pachymetry studies have indicated that anterior segment surgery can lead to endothelial damage at any stage of the operation.[6] Therefore, the introduction of viscoelastic substances, even if it is only considered a factor to preserve the endothelium, seems logical.[14,15]

OVD can be used outside the eye to protect the corneal epithelium and conjunctiva without obscuring the surgeon's view. Viscoelastics can serve as a mechanical barrier and aid in bleeding control both inside and outside the eye. It is possible to maintain the depth of the AC during the preparation of surgical wound incisions and intraocular manipulations by injecting OVD through a small incision. The specialized "soft tool" effect of OVD enables manipulation of the iris and other intraocular tissues, even under conditions of positive vitreous and orbital pressure or during expulsive bleeding. Finally, the use of OVD can reduce the prevalence of cystoid macular edema by maintaining appropriate intraocular pressure (IOP) and changing the refractive properties of the surgical microscope.[9,15]

The use of any of the viscoelastic materials can be associated with problems in different stages of the operation. For example, an optimal OVD, to meet a spectrum of needs in different stages of the phacoemulsification process, should have a combination of aggregation and expansion [Table 2]. Although a combination of OVDs can solve the need for accumulation and expansion in different stages of the surgery, the consumption of several OVDs is not cost-effective. Production of a viscoelastic such as Healon-5 is an attempt to provide both types of needs in a single viscoelastic.[23,24]

Glaucoma surgery

One of the important applications of OVDs in ophthalmology is their use in different stages of glaucoma surgery. For example, overfiltration after trabeculectomy with mitomycin C can lead to flattening of the AC, and the incidence rate of this complication has been reported to be around 25%.[31] To treat such a situation, there are various options for treatment, which include nonsurgical treatment such as phenylephrine, atropine, and acetazolamide, as well as surgery.[32,33] Another treatment option proposed by Fisher *et al*. in 1982 was the injection of sodium hyaluronate into the AC.[34] In the following years, the use of viscoadaptive compounds such as Healon-5 as well as dispersive OVDs were also tried, and finally, studies indicated the low long-term success of OVDs for the treatment of this condition.[35]

Today, the prophylactic use of 2% HPMC in the AC during trabeculectomy is associated with a reduction in postoperative complications associated with shallow AC.[36]

Vitreoretinal surgery

One of the new applications of OVDs in ophthalmology is the use of these devices as tamponade instead of gas or silicone oil during pars plana vitrectomy surgery. Initial attempts were made in 2013 and Hirata *et al*. used dispersive OVD (Viscoat; Alcon Japan) as tamponade after vitrectomy surgery in rabbit retinal tear models.[37] In 2016, Barth *et al*. used a cross-linked

Table 1: Physical properties of common viscoelastic materials

Brand name	Molecular weight (Dalton)	Dynamic viscosity (CP)	Source	Color	Contact angle (°)	Osmolality (mOsm/kg)	Density (mg/mL)	Content
Healon	2.5×10^6	40,000	Rooster crown	Transparent	60	309	10	Sodium hyaluronate 1%
Healon-GV	5×10^6	80,000	Rooster crown	Transparent	-	302	14	Sodium hyaluronate 1.4%
Healon-5	7×10^6	60,000–80,000	Rooster crown	Transparent	-	320	23	Sodium hyaluronate 2.3%
Amvisc	2×10^6	40,000	Rooster crown	Transparent	60	318	10	Sodium hyaluronate 1%
Amvisc Plus	2×10^6	55,000	Rooster crown	Transparent	-	340	16	Sodium hyaluronate 1.6%
Amovitrax	5×10^5	30,000	Rooster crown	Transparent	-	310	30	Sodium hyaluronate 3%
Provisc	1.9×10^6	39,000	Microbial fermentation	Transparent	-	310	10	Sodium hyaluronate 1%
DuoVisc	3.75×10^6	40,000–50,000	Microbial fermentation	Transparent	-	310–325	-	Sodium hyaluronate 3% Chondroitin sulfate 4%
Viscoat	25 and 500×10^3	40,000	Microbial fermentation + Shark cartilage	Transparent	52	360	30	Sodium hyaluronate 3% Chondroitin sulfate 4%
DisCoVisc	1.65×10^6	75,000	Microbial fermentation	Transparent	66.5	298	-	Sodium hyaluronate 1.6% Chondroitin sulfate 4%
OcuCoat	8.6×10^4	4000	Wood	Transparent	52	319	20	HPMC 2%
Cellugel	3×10^5	30,000	Wood	Transparent	-	315	-	HPMC 2%
Avenile	8×10^4	4,000	Wood	Transparent	52	285±32	20	HPMC 2%
Lamean	2.5×10^6–3.5×10^6	42,000	Bacterial fermentation	Transparent	60	320	12	Sodium hyaluronate 1.2%

Healon-GV: Healon-Greater Viscosity, HPMC: Hydroxypropyl methylcellulose

Table 2: Desirable characteristics of viscoelastics in different stages of phacoemulsification surgery

Surgical stage	Viscoelastic initial function	Required feature	Viscoelastic group
Capsulorhexis	Maintaining the depth of the AC	High viscosity versus low shearing force, high elasticity	Cohesive
Phacoemulsification	Remaining in the eye and covering the tissues, especially the corneal endothelium	Low molecular weight, low surface tension, high viscosity against high shearing force	Dispersive
Cortical aspiration	Endothelial lining	Low surface tension	Dispersive
Opening the capsular bag and inserting the IOLs	Maintaining the depth of the capsular bag	High viscosity against low shearing force, high elasticity	Cohesive
Removal of viscoelastic at the end of the procedure	Easy and quick removal	High molecular weight and surface tension	Cohesive

AC: Anterior chamber, IOL: Intraocular lens

hyaluronic acid hydrogel called Healaflow as a substitute for vitreous in 12 samples of pigmented rabbits. Morphological and functional studies of the retina after enucleation indicated no negative effect of OVDs on the retina of rabbits if OVDs are used as a vitreous substitute.[38]

Furthermore, other animal studies showed that linearly cross-linked sodium hyaluronic acid hydrogel, as a substitute for silicone oil in rhegmatogenous retinal detachment rabbit models, can have fewer side effects, including cataracts and secondary glaucoma, in addition to proper retinal attachment. Furthermore, if hydrogels and OVDs are used, there is no need for the prone position.[39,40] Of course, the main limitation of these studies is the small sample size, as well as the lack of conducting human studies and checking the safety of these methods in patients requiring pars plana vitrectomy, which naturally, future studies should focus on these issues.

Complications of ophthalmic viscoelastic device

The most important complication is increased IOP after cataract surgery.[14,15] This complication was first reported by Healon.[41] The increase in IOP is often severe, and if the viscoelastic substance is not completely removed from the eye, IOP remains high for a significant period of time and creates a condition that was first called "Healon block glaucoma".[41] It usually takes place within the initial 6–24 h following the surgery and frequently diminishes within 72 h postoperation. This effect is mostly related to the blockage of the trabecular meshwork by the large molecules of viscoelastic material, which increases the resistance against the outflow of the aqueous humor and increases the IOP.[6] A substance with higher viscosity and lower molecular weight passes through the trabecular meshwork more quickly.[30]

Recently, greater emphasis has been placed on the immediate postoperative increase in IOP within the first 8 h. Neglecting the significant increase in eye pressure during the initial hours after the operation could occur if pressure measurements are solely taken 24 h postoperation.[30]

Various researchers have investigated the approach of diluting and aspirating viscoelastic materials at the end of surgery as a mean to decrease the risk of increasing IOP postsurgery. Nevertheless, these procedures merely mitigate the rise in IOP and do not eliminate it entirely.[3] It should also be mentioned that the total increase in IOP after surgery should not be attributed to OVD because intraocular manipulations during surgery can lead to an increase in IOP.[30]

Other side effects of OVD include postoperative inflammatory reactions. Due to the electrostatic charge and high viscosity of OVD materials, red blood cells and inflammatory cells remain suspended in the AC after the operation and create an appearance similar to anterior uveitis.[6]

Another side effect of viscoelastics is "capsular-bag distension syndrome". This syndrome usually occurs a few days to weeks after phacoemulsification, which manifests itself as the expansion of the capsular bag along with pushing forward the optics of the IOL and creating mild nearsightedness. It is thought that viscoelastic substances trapped in the capsular bag behind the optic of the lens cause this phenomenon. Creating an opening in the peripheral part of the anterior capsule with an Nd:YAG laser pulse at an energy of 1.6 millijoules to release the trapped fluid is a recommended treatment option.[42]

Calcified band keratopathy was reported as a complication of primary products of viscoelastic materials containing chondroitin sulfate. However, since modifying the chemical formulation of Viscoat, no instances of these side effects have been reported.[6,14]

The advent of OVDs has significantly impacted intraocular surgery by providing essential support and protection to delicate ocular structures. These materials play a crucial role in maintaining the integrity of the corneal endothelium, preserving AC depth, and aiding surgical maneuvers. The physical properties of OVDs, including elasticity, viscosity, pseudoplasticity, surface tension, and cohesion/dispersion characteristics, are essential factors that influence their performance in various stages of surgery. A comprehensive understanding of these properties enables surgeons to make informed decisions based on patient-specific conditions and procedural needs.

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