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From Simple Liquids to Surgical Instruments: On the History of Ophthalmo-Viscosurgical Devices (OVD)

Od prostych płynów do narzędzi chirurgicznych: historia preparatów wiskoelastycznych (OVD)

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Summary
Nowadays, OVDs are regarded as standard tools in ophthalmic surgery. Their discovery and development started about 70 years ago, in 1934, with isolating hyaluronic acid as the substance of the vitreous body of the human eye. Sodium Hyaluronate was the first substance used as an OVD and is now the most widely used material for OVDs used in ophthalmic surgery. It has become "the gold standard" to which all other viscoelastics are compared. Since the introduction of viscoelastic substances in the 1970s the properties of these agents have improved the quality of anterior segment surgery. Therefore OVDs had — and still have — a great impact on the success of ophthalmic surgery — especially of cataract surgery and intraocular lens implantation. In vivo studies have proven that the molecular and chemical structure of hyaluronic acid is ideal. Interactions between molecules and receptor tissues and inflammatory and immunogenic reactions have also been studied extensively. This article shows the historical development of the different substances used nowadays and their properties.

Keywords: history, Ophthalmo-Viscosurgical Devices, OVD, viscoelastic substances, hyaluronic acid

Streszczenie
Preparaty wiskoelastyczne są obecnie uważane za standardowe narzędzia w operacjach okulistycznych. Ich odkrycie i rozwój zostały poprzedzone wyizolowaniem w 1934 roku kwasu hialuronowego z ciała szklistego ludzkiego oka. Hialuronian sodu był pierwszą substancją używaną w charakterze preparatu wiskoelastycznego i obecnie jest najpowszechniej używanym materiałem wiskoelastycznym w operacjach okulistycznych, stając się wzorcem, do którego porównywane są inne substancje wiskoelastyczne. Od momentu zastosowania w latach siedemdziesiątych materiały te, dzięki swoim właściwościom, przyczyniły się do poprawy wyników operacyjnych w przednim odcinku oka. Preparaty wiskoelastyczne miały i nadal mają wielki wpływ na powodzenie zabiegów okulistycznych, a zwłaszcza operacji usunięcia zaćmy i wszczepienia sztucznej soczewki wewnątrzgałkowej. Badania *in vivo* wykazały, że struktura molekularna i chemiczna kwasu hialuronowego jest idealna. Badane były również wzajemne oddziaływania między kwasem hialuronowym a tkankami oka oraz reakcje zapalne i immunologiczne. Ten artykuł przedstawia historię rozwoju obecnie stosowanych materiałów wiskoelastycznych oraz ich właściwości.

Słowa kluczowe: historia, preparaty wiskoelastyczne, OVD, substancje wiskoelastyczne, kwas hialuronowy

Introduction

Nowadays, Ophthalmo-viscosurgical devices (OVD) are regarded as standard tools in ophthalmic surgery. Their discovery and development started approximately 70 years ago, in 1934, with isolating hyaluronic acid as the substance of the vitreous body of the human eye. This article shows the historical development of today's different used substances and their properties. Today, Hyaluronic acid is more and more used in eye drops and contact lens rewetters due to its high wetting and water binding properties. Therefore, this article will review the historical development and usage of this compound in cataract surgery.

Material and Methods

The outcome of this article is based on an intensive research of current and historic literature on the topic in discussion. This article evaluates 65 scientific articles on the topics hyaluronic acid and ophthalmic viscosurgical devices.

Results

OVDs (Ophthalmic Visco-surgical Devices) [1] — formerly called viscoelastics or viscoelastic substances - are a class of non-active clear gel-like chemical compounds with viscous and elastic properties [2]. The specific physical properties make them useful e.g. for ophthalmic surgery, mainly cataract surgery [3]. (Here) they create and maintain the anterior chamber depth and visibility, protect the corneal endothelium and other intraocular tissues during surgery. OVDs minimize interaction between tissues and instruments during surgery and ensure therefore high tissue integrity [4, 5].

OVDs are essential in ophthalmic surgery today. Their use became increasingly popular for cataract surgery, glaucoma surgery, cornea surgery, trauma surgery, and vitreoretinal surgery [6, 7].

Since the introduction of viscoelastic substances in the 1970s the properties of these agents have improved the quality of anterior segment surgery.

OVDs are clear viscous fluids used in ophthalmic surgery, packed in a syringe, and are delivered through a cannula into the eye. Based on their properties, OVDs can be divided into two groups [8]:

— Cohesive agents show high viscosity, adhere to themselves, and act like a gel. The molecules are long chains, have a high molecular weight, and show high pseudoplasticity and surface tension.

— Dispersive agents show low viscosity, the molecules behave separately, they build up a solution. They show low pseudoplasticity and surface tension with short chains and low molecular weight.

Historical background

In 1934, Meyer and Palmer were able to isolate hyaluronic acid, a polysaccharide from the vitreous cortex [9, 10]. Hyaluronic acid was also purified from umbilical cord and rooster combs by Endre Balazs [11]. In 1958, he has been the first who suggested the use of hyaluronic acid as a possible vitreous substitute in the performance of complicated retinal detachment surgery [12]. In 1972, Balazs performed the first intravitreous injection of hyaluronic acid [13].

Miller and Stegman suggested the use of hyaluronic acid during the implantation of intraocular lenses [14]. Sodium hyaluronate was used in 1977 by Miller to perform experimental IOL (Intra-Ocular Lens) implantation in rabbit eyes [15]. In the same year, Fechner used a 1% solution of methylcellulose to maintain the volume of the anterior chamber [16]. Beside of Fechner different other surgeons described methylcellulose as an inexpensive alternative to hyaluronic acid used as an OVD [17, 18].

In 1979, during a symposium on ocular surgery, Balazs presented the patent of viscoelastic material with high molecular weight ("HMW VE NIF-NAHA") [19] consisting of purified hyaluronic acid, which was used in an IOL implantation procedure. At the same video symposium, a new terminology "Viscosurgery" was born, also coined by Balazs. In the same year Balazs sold his US-patent to the company *Pharmacia* which developed the first viscoelastic product (*Healon®*), also in 1979. *Healon®* is today still available distributed by AMO (*Abbott Medical Optics*).

1976 hyaluronic acid gained the US IND (Investigational New Drug) application. Miller and Stegmann submitted 1977 IND for IOL use, Pape IND for cataracts, and glaucoma and Pollach IND for corneal transplants. In 1979, *Healon®* got the 510k permission to market granted. At the AAO (American Academy of Ophthalmology) congress in November 1979, *Healon®* was first presented at a scientific exhibition. The product launch took place at the ASCRS (American Society of Cataract and Refractive Surgery) congress in April 1980. The approval of the FDA followed in January 1983.

Since the introduction of *Healon®* (sodium hyaluronate, 1%), ophthalmic viscosurgical devices have become essential tools, particularly in anterior segment surgery. The use of OVDs creates and maintains anterior chamber depth and visibility. It protects the sensitive endothelium and other intraocular tissues, and minimizes interaction between tissues and instruments during surgery [20–22]. Space and surface tactical aspects of OVD

application have first been shown by Eisner [23], techniques like visco-blockade, — tamponade or — spatula have been invented by him [24].

Therefore OVDs had — and still have — a great impact on the success of cataract surgery and intraocular lens implantation [25–30].

From 1995 to 2000 ISO developed an International Standard for the safety, performance and approval requirements for viscoelastics under a new designation of Ophthalmic Viscosurgical Devices (OVDs) [31].

Additionally, the development of new surgical techniques in cataract extraction procedures such as phacoemulsification, invented by Charles Kelman 1967, and foldable IOL implantation (since 1988) was accompanied by the development of new modalities of viscoelastics.

Viscoelastics have a wide range of features with rheologic-related properties such as viscosity, elasticity, pseudo-plasticity, cohesiveness, etc. [32–34]. Although the properties exist independently, they act synergistically. The same viscoelastic can be used as a different tool according to specific needs, such as separating or joining tissues, maintaining space, or protecting surfaces (i.e. corneal endothelium, lens capsule or anterior hyaloid) from mechanical trauma or fluids infusion.

Viscosurgery procedures are not limited to cataract surgery. They are now routinely used in anti-glaucoma filtering surgery, combined surgical interventions, keratoplasty, and anterior vitrectomy [35, 36].

In corneal surgery, Alpar observed reduced endothelial cell loss in various keratoplasty procedures performed with Healon® in 1984 [37]. Findings of reduced complication rate with OVDs have been confirmed by other studies. Beside protection, an OVD depot (dome) supports and stabilizes the donor cornea (cushion) after removal of recipient cornea, and facilitates positioning. Healon® 5, a new, high concentration viscoadaptive OVD becomes more and more popular for this procedure.

In glaucoma surgery, anterior chamber collapse during trabeculectomy is a common complication and plays an important role in cataract formation following glaucoma surgery. Also, less post-op hyphemata is observed. OVDs in other glaucoma procedures are used to improve visibility, avoid bleeding (tamponade), or open chamber angles.

In trauma surgery OVDs are used in treating perforating bulbar injuries (stabilizing anterior chamber, separating of tissue). They provide a better overview at operation site by improving the visibility of the injured anatomic structure. Furthermore, OVDs reduce intraocular bleeding, and foreign bodies can be moved/removed very safely.

The usage of OVDs in vitreoretinal surgery is related to the early history of OVDs. With new agents for the use in the posterior segment — like gases, perfluorocarbons, or silicone oil — as endotamponade, the importance of OVDs have decreased.

Substances used as ophthalmo-viscosurgical devices

Sodium Hyaluronate was the first substance used as an OVD and is now the most widely used material for OVDs used in ophthalmic surgery. It has become "the gold standard" to which all other viscoelastics are compared [38].

Hyaluronic acid (Sodium Hyaluronate, NaHa) [39–45] is a linear polysaccharide molecule of sodium glycuronate and N-acetyl glucosamine. The molecular weight may range from 100,000 to 7 million Daltons; the molecule consists of nearly 10,000 disaccharide units. Hyaluronic acid which is used in OVDs is primarily extracted from rooster combs. It is a natural biological substance in all vertebrates, humans, and also some bacteria. High concentrations are found in human connective tissue and in the eye (vitreous, cortex, and trabecular meshwork), low concentrations in aqueous humor and corneal endothelium. Hyaluronic acid seems to be recently the most widely used OVD worldwide.

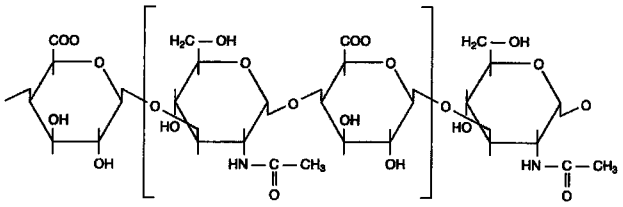

FIG. 1. Chemical structure of hyaluronic acid

Chondroitin Sulfate (CS) [46], [36] is like hyaluronic acid a biological substance in the extracellular matrix mainly in solid tissue parts like cartilage or corneal stroma. For use the as an OVD the polysaccharide is mainly extracted from shark-fin cartilage. Molecular weight is about 20,000 D, the chain length 50 nm which gives the molecule a lower viscosity and negative charge.

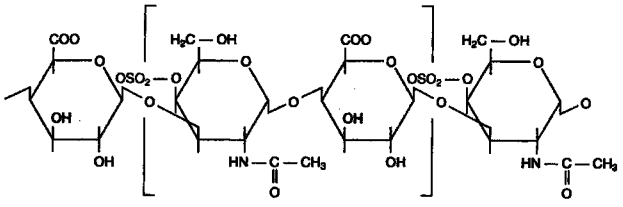

FIG. 2. Chemical structure of Chondroitin sulfate

Methylcellulose (MC) [47–49] is widely distributed in cotton and wood but not in humans or animals. It is a disaccharide (glucose units) with side chains to make the molecule more hydrophilic. In ophthalmology methylcellulose is used as a lubricant because of its good wetting and coating capacity. From an immunological aspect it is important that this substance does not occur naturally in the human body, and therefore shows a significant inflammatory potential. It will not be metabolized completely.

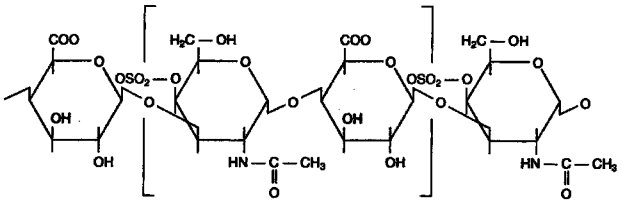

FIG. 3. Chemical structure of methylcellulose

Polyacrylamide is a synthetic polymer with a high molecular weight derived from acrylamide which consists of long carbon chains. The product was withdrawn from the market in 1991 after observing intraocular pressure elevation treated with this material. Poyacrylamid is today only of historical interest [7].

Collagen as a viscoelastic material consisting of Type IV collagen can be extracted from human tissue as well as from animal tissue (pigs). Up to now, there is less information about the ideal origin of this substance for using it as OVD [7].

Further substances as a basis for OVD were suggested but attained however no clinical relevance [50].

Rheological and physico-chemical properties of substances used as ophthalmo-viscoelastic devices

The description and characterization of different viscoelastic substances is a prerequisite for understanding their specific properties and from this their intended use. A profile of requirements for daily surgical practice can be established which indirectly presupposes the existence of certain physico-chemical characteristics. These substances must be easily and quickly injected, protect the corneal endothelium, and have the capacity to create and maintain intraocular space or compartments. It is important that optimal sight, i.e. optimal transparency of the material, is established during surgery. During the last stage of surgery the substance should be both, easily and quickly removable, or be naturally digested in the eye. In either case there should be no rise in intraocular pressure during the early postoperative phase.

Some of these functions are contradictory: Water-based solutions are most easily injectable since they offer almost no resistance. Viscous or viscoelastic substances are slower to flow through a cannula; moreover this speed is dependent on cannula diameter and pressure on the plunger.

Additionally, corneal endothelial protection presupposes a certain stickiness and adhesion of the viscous substance to the tissue, which makes the removal of the substance more difficult. A strong space-maintaining capacity can also cause problems during the removal of the substance. The characteristics mentioned before can be described by the properties of the specific visco-surgical device, like: viscosity, elasticity, viscoelasticity, pseudoplasticity, cohesion, and its contact angle.

Viscosity is a measure of fluency resistance of a fluid, indicating how viscous a substance is. Viscosity is dependent on several factors including molecular weight, molecule size, concentration, and temperature. Viscosity can be measured physically by placing the substance between two parallel plates and then moving these against each other. The "frictional resistance" of a viscoelastic can thereby be quantified. During this experiment the following terms are also interesting for day to day clinical use. The shear rate represents the speed with which the plates are shifted against each other (Unit rad/s = radiant per second or hertz =Hz, 1/second). The force needed to shift the plates per surface unit is called shear force (unit dynes/cm2). The so-called velocity gradient refers to the ratio between the relative speed of shifting the disk and thickness of the substance between the disks. This term is important since the quotient of shear force and velocity gradient is the measure of dynamic viscosity (unit N x sec x m-2 = Poise, P for Poiseuille). The quotient of dynamic viscosity and fluid density is called kinematic viscosity (unit Stokes, St).

Zero Shear Viscosity refers to viscosity at rest, i.e. at a shear rate of zero. This term is frequently seen as particularly characteristic of viscoelastics. It is interesting to note that there is practically no way in which this value can be measured and is therefore always theoretically calculated through extrapolating. This value should be surveyed censoriously and not used as an exclusive measure to judge a viscoelastic. A practical value of this measure exists nonetheless, for example good space-maintaining capacity can be achieved with a high zero shear viscosity, meaning that a deepening of the anterior chamber and the creation of space is highly successful. Comparatively, a viscoelastic with low zero shear viscosity, as in cases of high vitreous pressure can flow out of the incision.

The next term to be considered is of the term elasticity. In the physical sense, elasticity describes the ability to

offer resistance to a force and the ability of a substance to return to its original form following the removal of the force. Elasticity is also dependent on molecular weight and concentration, and is influenced by the frequency of the influencing force as well. Hyaluronic acid preparations tend to behave like viscous fluids in a low frequency range (0,1 to 10 Hertz) and more like elastic bodies at higher frequencies.

The term viscoelastic gives a name to an entire substance group. It is a term that describes substances which can behave both, viscous and elastic. Viscoelastic substances offer low resistance towards deforming forces and do not have the ability to immediately return to their original form, and indeed will never be able to fully reach their original form. This refers to relative form stability.

As a rule, all viscoelastics consist of a molecular network with varying concentrations. Most viscoelastics behave viscous if a force with low speed and low frequency act on them. The added energy is converted to heat, since the molecular chains shift against each other. At higher frequencies or fast energy impact, the viscoelastic acts like a shock absorbing gel cushion. Energy is elastically stored and dispensed with relative form stability. Which of the characteristic above prevails is dependent upon the type of force effect, and in particular the concentration and temperature. The above described characteristic of viscoelasticity is also referred to as pseudoelasticity.

Natrium hyaluronates show the highest pseudoelasticity. For practical purposes this means that they have high viscosity (zero shear viscosity) at rest. Therefore, they have good space-maintaining capabilities. Less viscous chondroitinsulfate-natrium hyaluronate combinations such as *Viscoat (Alcon)* have better coating capabilities. Low pseudoelasticity of chondroitinsulfate leads to the substance adhering longer to the corneal endothelium and therefore not being rinsed out of the eye as quickly as hyaluronic acid preparations which have the tendency to quickly rinse out of the eye "en bloc". This is a particular advantage during phacoemulsification where relatively high volumes of fluid are used.

A further term that describes the properties of viscoelastics is coating ability. This refers to the degree of adhesion of a viscoelastic on a surface. It is ascertained through the contact angle of the substance with the surface and surface tension. When a substance forms a strong curvature change on the surface, a large contact angle is formed. This points to little adhesion. For clarification, an extreme case of this would be a drop of water that repels off the surface of a Gore-Tex jacket.

Two further terms that are often associated with the characterization of viscoelastics are cohesion and dispersion. Cohesion refers to extent to which a viscoelastic substance is held together through intermolecular bindings and molecular chains. Higher molecular viscoelastics (e.g. *Healon* GV (AMO)) with long molecular chains are cohesive. A substance like this can escape or be rinsed out of the eyes "en bloc" during aspiration. Dispersive viscoelastics (e.g. *Viscoat (Alcon)*) are generally low molecular with shorter and less tightly weaved molecular chains. They do not leave the eyes "en bloc" but rather show a tendency to become glued to the structures and are therefore often difficult to aspirate. A description of cohesion and dispersion of different viscoelastics was put forth in an experimental study through means of the Cohesion-Dispersion-Index (CDI) [70]. The CDI represents the quotient of the share of the aspirated viscoelastic in percentage, measured in time and the respective aspiration setting. The faster and the more viscoelastic could (or can??) be removed, the higher the CDI. This would be e.g. 72,3 for *Healon* GV(AMO), 46 for *Provisc* (*Alcon*), 21,4 for *Healon* (AMO) and 3,4 for *Viscoat* (*Alcon*).

Most important is still the use of viscosurgical devices in cataract surgery. During the manipulation of capsulorhexis it is also important that the anterior chamber remains stable, once again making high viscosity important. While good pseudoplasticity is most important in nucleus expression, low cohesion and high dispersion are essential during phacoemulsification, preventing the viscoelastic from being rinsed out of the eye. This also applies to the steps of irrigation/aspiration during cortical cleanups. Opening and stabilizing the capsular bag for IOL-implantation requires a good space-maintaining capacity and therefore high viscosity and pseudoplasticity. Good cohesion, meanwhile, is helpful for a fast and complete removal of the substance [1, 4, 6, 7, 10, 34–36].

Viscoelastic devices used in ophthalmology

The physico-chemical properties of viscoelastics described above allow them to be used in a variety of ways and carry out a number of different functions. Particularly in cataract surgery there is a demand for the "ideal" viscoelastic which requires partly contradictory characteristics. For clinical purposes it is therefore an advantage to have in-depth knowledge of the individual properties in order to use specific substances or a combination of substances depending on the circumstances.

An integral function of viscoelastics is to maintain the anterior chamber not only during cataract surgery, but also during other corneal surgical procedures, glaucoma surgeries, trauma, and revision-surgeries in the anterior eye segment. The viscosity and elasticity of a substance determine of how well the viscoelastic is fulfilling its intended task. HPMC-preparations show little elastic-

ity; therefore they are leaving the eye relatively quickly through the incision in cases of elevated vitreous pressure. Sodium hyaluronate products, in particularly those of higher concentrations, can maintain anterior chamber depth due to their high elasticity.

A further function is the mobilization and forcing back of tissues in the anterior chamber. Examples of this in cataract surgery are the gentle loosening of synechiae between iris and lens, viscomydriasis for pupillary dilation, and filling the lens capsule prior to implantation.

Viscoelastics can perform a protective function through the coating of instruments, implants and tissue surfaces (e.g. corneal endothelium). Prerequisites for this are low surface tension and a small water contact angle. HPMC-preparations as well as the combination preparation *Viscoat®* (*Alcon*) containing chondroitin sulfate and sodium hyaluronate, possess significantly lower surface tension and water contact angles than pure sodium hyaluronate preparations, particularly those with high concentration and high molecular weight. Liquids spread more easily when their surface tension is lower than the critical surface tension of the tissue [63]. The critical surface tension of the corneal endothelium lies between 43 and 63 dynes/cm. The surface tension for HPMC-preparations should be at 43,0±1,41 dynes/cm, and at 62,7±6,51 dynes/cm for *Healon* [64]. Details concerning the contact angle for various preparations are provided in table 3.1.1. For this, the contact angle was measured at 35° Celsius under nitrogen on PMMA [65]. Coating the corneal epithelial surface with viscoelastic, leads to a thorough, long-lasting moistening of the cornea with corresponding positive effects on the clarity of the cornea. In addition, a drop of viscoelastic can act like a magnifying lens and therefore further improve the view in the anterior chamber. The protection of the corneal endothelium represents an important function of a viscoelastic. In contrast to the corneal epithelium, the single-layered endothelium is not capable of regeneration following damage. Various factors can lead to the damage of the endothelium during intraocular surgery. The endothelium can come in direct contact with lens fragments, instruments or the IOL. Furthermore the turbulence of the irrigation fluid can affect the endothelium. Air bubbles, free radicals, and sound waves developed during phacoemulsification can also damage endothelial cells. The space-maintaining function of viscoelastics indirectly contributes to endothelial protection because the space for intraocular manipulation is maintained. Coating of the endothelium, instruments and the IOL represent a further protective factor. Specific sodium hyaluronate binding areas were proven to be present at the endothelium [66–68]. It is assumed that sodium hyaluronate containing products are able to offer a special protective function because of this. The continuous coating of the endothelium, in particular offered by dispersive low-viscous substances, is generally seen as an important protective factor. An overly extensive removal of the viscoelastic with the corresponding irrigation/aspiration in the endothelial area may lead to endothelial damage, hence when using preparations such as *Viscoat* (*Alcon*), a thin layer can remain on the cornea.

Beside cataract surgery, viscoelastic devices are also used in other fields of ophthalmology, e.g. in keratoplasty- and glaucoma-, vitreoretinal-, and trauma surgery. Because of its extreme high ability to bind water relative to its mass this substance is therefore also used in numerous formulations of eye drops used for dry eye symptoms [10, 33–37, 45, 46].

Complications using viscoelastic substances in ophthalmology

The use of viscoelastics can also lead to intraoperative and postoperative complications. Intraocular structures can be damaged by overfilling the eye (zonular or capsular rupture) or by incomplete removal at the end of surgery (postoperative increase of intraocular pressure). An overfilling of the eye depends more on the experience of the surgeon than on the type of viscoelastic. However, viscoelastics behave very individually during the removal process. Viscoelastic that is left in the eye generally escapes as a large molecule by means of the trabecular meshwork. The ability of the viscoelastic to drain through this manner can be influenced by a variety of factors.

Hyaluronic acid used as viscoelastic substance in other areas in medicine

Hyaluronic acid is an important structure-forming matrix in the human body, particularly in the joints. There hyaluronic acid is responsible for the strength (viscosity) of joint fluid (synovial fluid) and thus also crucial for the nutrition of the cartilage. Like a film, hyaluronic acid covers the cartilage, smoothes and lubricates the surface. In osteoarthritic patients the synovial fluid shows a lower content of hyaluronic acid as in healthy patients. By this viscosity and elasticity of the synovial fluid is greatly altered. Hyaluronic acid injections replace or complement the mutated synovial fluid in osteoarthritis. These injections may stimulate the administration of hyaluronic acid in the joints and the cells of the synovium to the increased production of endogenous hyaluronic acid. Therefore hyaluronic acid is also widely used in human orthopedics as well as in veterinary medicine. Hyaluronic acid reduces the symptoms of most patients. An improvement of already existing alterations

TAB. 1. Selection of sodium hyaluronate based viscoelastics

PREPARATION	POLYMER	CONCENTRATION	MANUFACTURER/DISTRIBUTOR
Healon	Sodium hyaluronate	1.0%	AMO
Healon 5	Sodium hyaluronate	2.3%	AMO
Healon GV	Sodium hyaluronate	1.4%	AMO
Vitrax II	Sodium hyaluronate	3.0%	AMO
Amvisc	Sodium hyaluronate	1.0%	B&L
Amvisc Plus	Sodium hyaluronate	1.6%	B&L
Provisc	Sodium hyaluronate	1.0%	Alcon
Viscoat	Sodium hyaluronate Chondroitinsulfate	3.0% 4.0%	Alcon
DuoVisc	Sodium hyaluronate Chondroitinsulfate (combination package of Viscoat and Provisc)	See Viscoat and Provisc	Alcon
DisCoVisc	Sodium hyaluronate chondroitine sulfate	1.7% 4.0%	Alcon
Visthesia 1.0 and 1.5	sodium hyaluronate lidocaine (1.0) sodium hyaluronate lidocaine (1.5)	1.0% 1.0% 1.5% 1.0%	Zeiss
Rayvisc	Sodium hyaluronate	3.0%	Rayner

TAB. 2. Selection of different HPMC products

PREPARATION	POLYMER	CONCENTRATION	MANUFACTURER/DISTRIBUTOR
Adatocel	HPMC	2.0%	B&L
Coatel	HPMC	2.0%	B&L
HPMC-Ophtal H	HPMC	2.0%	Dr. Winzer
HPMC-Ophtal L	HPMC	2.0%	Dr. Winzer
La Gel	HPMC	1.8%	LA Labs
Ocucoat	HPMC	2.0%	B&L
Visco Shield 2%	HPMC	2.0%	Domilens

is not possible. Expected effects are pain reduction, improvement of quality of life through increased mobility, reduced additional pain medication, and it delays the alteration progress [62].

Besides this, hyaluronic acid is also used as oral rinsing solution, gel or spray when dealing with oral mucositis [69]. Furthermore hyaluronic acid is also widely used in cosmetic skin preparations as moisturizer.

Mayor ophtalmo-movicosirgical products used in ophthalmology today

At present a multitude of different viscoelastics are available on the market. Most products contain sodium hyaluronate in different concentration followed by different HPMC preparations.

Viscoelastics can be classified according to their viscosity, cohesiveness and dispersiveness; it can be distinguished between the following groups [1, 36]:

High viscous-cohesive viscoelastics:
- Molecular weight 5,000,000 to 7,900,000 Dalton,
- Zero shear viscosity: > 1000,000 mPs
  (Examples: Healon GV (AMO), Healon 5 (AMO))

Viscous-cohesive viscoelastics:
- Molecular weight 100,000 to 6,100,000 Dalton,
- Zero shear viscosity: <1000,000 mPs> 100,000 mPs
  (Examples: Healon (AMO), Provisc (Alcon), Allervisc (Allergan), Amvisc (Bauch + Lomb))

Middle viscous-dispersive viscoelastics:

— Molecular weight 25,000 to 500,000 Dalton,
— Zero shear viscosity: <100,000 mPs> 10,000 mPs (Examples: Viscoat (Alcon), Cellugel (Alcon))

Low viscous-cohesive viscoelastics:
— Molecular weight 86,000 to 90,000 Dalton,
— Zero shear viscosity: <10,000 mPs > 1,000 mPs (Examples: OcuCoat (Bauch + Lomb), Adatocel (Bausch + Lomb))

As far as the authors can evaluate, mayor ophthalmoviscosurgical products on the European market are the following in regards of their ingredient(s) (table 1 and 2).

Discussion

Development, production and use of OVD require ongoing research to evaluate the biocompatibility, purity, and ocular structure protection of the materials in question [51–63]. In-vivo studies have proven that the molecular and chemical structure of hyaluronic acid is ideal, and interactions between molecules, receptor tissues [64], inflammatory and immunogenic reactions [65] have also been studied extensively.

References

1. Arshinoff S., *New Terminology:* OVD [in:] *Journal of Cataract & Refractive Surgery* 2000.

2. Abou Abboud T., *New Concept in Viscosurgery* [in:] *Medicals Int.* SARL 2001.

3. Bellucci R., *Viscoelastics in Ophthalmic Surgery*, Slack Inc., Thorofare 2000.

4. Arshinoff S., *Dispersive and Cohesive Viscoelastic Materials in Phacoemulsification Revisited 1998* [in:] *Ophthalmic Practice* 1998, 16(1), 24–32.

5. Arshinoff S., *Dispersive and Cohesive Viscoelastic Materials in Phacoemulsification* [in:] *Opthalmic Practice* 1995, 13, 98–104.

6. Berke A., Scholtz S., *Viskoelastika — Anwendung in der Ophthalmologie*, [in:] *Der Augenspiegel* 2003, 11, 18–22.

7. Dick B., Schwenn O., *Viskoelastika — eine Übersicht*, Springer Verlag 1998.

8. Tognetto D., *High Viscosity and Adhesivity Could They Coexist?*, Lecture at ASCRS Congress San Diego, 2004.

9. Meyer K., Palmer J.W., *The polysaccharide of vitreous humor* [in:] *J Biol Chem* 1934, 107, 629–634.

10. Dick B., Schwenn O., Pfeiffer N., *Einteilung der viskoelastischen Substanzen für die Ophthalmochirurgie* [in:] *Ophthalmologie* 1999, 96, 193–211.

11. Balazs E.A., Hutsch E., *Replacement of the vitreous with hyaluronic acid, collagen and other polymers* [in:] Irvine A.R., O´Malley C. (eds), *Advances in vitreous surgery*, Thomas, Springfield 1976, 601–623.

12. Balazs E.A., *Physiology of the vitreous body* [in:] Schepens C.L. (ed.), *Importance of the vitrous body in retina surgery with special emphasis on reoperations*, Mosby, St. Louis 1960, 29–48.

13. Balazs E.A., Freeman M.I., Klöti R., et al., *Hyaluronic acid and replacement of vitreous and aqueous humor* [in:] *Mod Prob Ophthalmol* 1972, 10, 3–21.

14. Stegman R., Miller D., *Extracapsular cataract extraction with hyaluronate sodium* [in:] Ann Ophtalmol 1982, 14, 813–815.

15. Miller D., O'Connor P., Williams J., *Use of Na-hyaluronate during intraocular lens implantation in rabbits* [in:] *Ophthalmic Surg* 1977, 8, 58–61.

16. Fechner P.U., Fechner M.U., *Methylcellulose and lens implantation* [in:] *Br J Ophthalmol* 1983, 67, 259–263.

17. Liesegang T.J., Bourne W.M., Ilstup D.M., *The use of hydroxy propyl methylcellulose in extracapsular cataract extraction with intraocular lens implantion* [in:] *Am J Ophthalmol* 1986, 102, 723–726.

18. Thomsen M., Simonsen A.H., Andreassen T.T., *Comparison of sodium hyaluronate and methylcellulose in extracapsular cataract extraction* [in:] *Acta Opthalmol* 1987, 65, 400–405.

19. Balazs E.A., *Ultrapure hyaluronic acid and the use thereof* US patent 4 141 973 (1979).

20. Balazs E.A., *Sodium hyaluronate and viscosurgery* [in:] Miller D., Stegmann R. (eds), *Healon®, a guide to ist use in opthalmic surgery*, Wiley, New York 1983, 5–28.

21. Balazs E.A., *Pharmakologische Eigenschaften von Natrium-Hyaluronat im Auge* [in:] Meyer-Schwickerath G. (Hrsg), *Viskochirurgie des Auges*, Enke, Stuttgart 1984, 1–3.

22. Dick B., Kohnen T., Jacobi F.K., Jacobi K.W., *Long-term endothelial cell loss following phacoemulsification through temporal clear cornea incision* [in:] *J Cataract Refract Surg* 1996, 22, 63–71.

23. Eisner G., *Eye surgery. An introduction to operative technique* [in:] *Springer*, New York 1990, 171–181.

24. Eisner G., *General considerations concerning viscous materials in ophthalmic surgery* [in:] *Trans Ophthalmol Soc* UK 1983, 103, 247–253.

25. Glasser D.B., Katz H.R., Boyd J.E., Langdon J.D., Shobe S.L., Pfeiffer R.L., *Protective effects of viscous solutions in phacoemulsification and traumatic lens implantation* [in:] *Arch Ophthalmol* 1989, 107, 1047–1051.

26. Glasser D.B., Matsuda M., Edelhauser H.F., *A comparison of the efficacy and toxicity of and inttraocular pressure response to viscous solutions in the anterior chamber* [in:] *Arch Ophthalmol* 1986, 104, 1819–1824.

27. Holmberg A.S., Philipson B.T., *Sodium hyaluronate in cataract surgery. II. Report on the use of Healon® in extracapsular cataract surgery using phacoemulsification* [in:] *Ophthalmology* 1984, 91, 53–59.

28. Holmberg A.S., Philipson B.T., *Sodium hyaluronate in cataract surgery. I. Report on the use of Healon® in two different types of intracapsular cataract surgery* [in:] *Ophthalmology* 1984, 91, 45–52.

29. Polack F.M., *Healon (Na hyaluronate): A review of the literature* [in:] *Cornea* 1986, 5, 81–93.

30. Soll D.B., Harrison S.E., Arturi F.C., Clinch T., *Evaluation and protection of corneal endothelium* [in:] *J Am Intraocular Implant Soc* 1980, 6, 239–242.

31. DIN EN ISO 15798, *Ophthalmische Implantate — Viskoelastische Substanzen* (ISO 15798:2001), Deutsche Fassung EN ISO 15798:2001, Ausgabe 2001–12 (2001).

32. Buratto L., Giardini P., Bellucci R., *Viscoelastics in Ophthalmic Surgery*, Slack Inc., Thorofare 2000.

33. Arshinoff S., *Dispersive-cohesive viscoelastic soft shell technique*, [in:] *J Cataract Refract Surg* 1999, 25, 167–173.

34. Arshinoff S., *The physical properties of ophthalmic viscoelastics in cataract surgery* [in:] *Ophthalmic Pract* 1991, 9, 81–86.

35. Berke A., Scholtz S., *Viskoelastika* [in:] *Die Kontaktlinse* 2003, 5, 27–32.

36. Auffarth G.U., *Viskoelastische Substanzen in der Ophthalmochirurgie*, Uni-Med Verlag 2001.

37. Alpar J.J., *Viscoelastic surgery* [in:] *Ann Ophthalmol* 1987, 19, 350–353.

38. Hütz W., Eckardt H.B., Kohnen T., *Comparison of viscoelastic substances used in phacoemulsification* [in:] *J Cataract Refract Surg* 1996, 22, 955–959.

39. CD *Römpp Chemie Lexikon* 1995; Falbe J., Regnitz M. (ed.), *Römpp Lexikon, Chemie* 1997, 1819–1820.

40. Comper W.D., Laurent T.C., *Physiological function of connective tissue polysaccharides* [in:] *Physiol. Rev.* 1978, 58, 255–315.

41. Evered D., Whelan J. (eds), *The biology of Hyaluronan*, Ciba Foundation Symposium 143, New York, Wiley 1989.

42. Laurent T.C. (ed.), *The Chemistry, Biology and Medical Applications of Hyaluronan and Its Derivatives*, Wenner-Gren International Series No. 72, Portland Press, London 1998.

43. Laurent T.C., *Fraser* J.R.E.: *The properties and turnover of hyaluronan* [in:] Evered D., Whelan J. (eds), *Functions of the Proteoglycans*, Ciba Foundation Symposium 124, 2–29, New York, Wiley 1986.

44. Laurent T.C., [in:] Balazs E.A. (ed.), *Chemistry and molecular biology of the intercellular matrix*, vol 2, 703–732, Academic Press, London 1970.

45. Scholtz S., *Hyaluronsäure — Eigenschaften und Verwendung* [in:] DOZ 2004, 6, 62–64.

46. Hessemer V., Dick B., *Viskoelastische Substanzen in der Kataraktchirurgie* [in:] *Klinische Monatsblätter Augenheilkunde* 1996, 209, 55–61.

47. Fry L., *Postoperative intraocular pressure rises: A comparison of Healon, Amvisc, and Viscoat* [in:] *J Cataract Refract Surg* 1989, 15, 415–420.

48. Miller K., Colvard D., *Randomized clinical comparison of Healon* GV *and Viscoat* [in:] *J Cataract Refract Surg* 1999, 25, 1630–1636.

49. Pedersen O., *Comparison of the protective effects of methylcellulose and sodium hyaluronate on corneal swelling following phacoemulsification of senile cataracts* [in:] *J Cataract Refract Surg* 1990, 16, 594–596.

50. Karel I., et al., *Poly(triethylenglycol monomethacrylate) and poly(glycerol monomethacrylate) cross-linked gel as potential viscoelastics for intraoperative use* [in:] *Graefe's Archive Clin Exp Ophthalmol* 1997, 235, 186–189.

51. Arshinoff S., *Why Healon 5? The Meaning of „Viscoadaptive"* [in:] *Ophthalmic Practice* 1999, 17, 332–334.

52. Holmen J., Lundgren B., *Scheimpflug photography study of ophthalmic viscosurgical device during simulated cataract surgery* [in:] *J Cataract Refract Surg* 2003, 29, 568–574.

53. Augustin A.J., Dick B., *Oxidative tissue damage after phacoemulsification: Influence of ophthalmic viscosurgical devices* [in:] *J Cataract Refract Surg* 2004, 30, 424–427.

54. McDermott G., *What does Healon 5 have to offer?* [in:] *Review of Ophthalmology*, April 2001.

55. Holzer M., Tetz M., Auffarth G., Welt R., Völcker H.-E., *Effect of Healon 5 and 4 other viscoelastic substances on intraocular pressure and endothelium after cataract surgery* [in:] *J Cataract Refract Surg* 2001, 27, 213–218.

56. Tetz M., Holzer M., Lundberg K., Auffarth G., Burk R., Kruse F., *Clinical results of phacoemulsification with the use of Healon 5 or Viscoat* [in:] *J Cataract Refract Surg* 2001, 27, 416–420.

57. Dick B., Krummenauer F., Augustin A., Pakula T., Pfeiffer N., *Healon 5 viscoadaptive formulation: Comparison to Healon and Healon* GV [in:] *J Cataract Refract Surg* 2001, 27, 320–326.

58. Cavallini G., Campi L., Delvecchio G., Lazzerini A., Longanesi L., *Comparison of the clinical performance of Healon 5 and Healon in phacoemulsification* [in:] *European Journal of Ophthalmology* 2002, 12, 205–211.

59. Arshinoff S., *An Ophthalmic Viscoadaptive Device for Cataract Surgery — Highlights of a roundtable discussion* [in:] *Ophthalmology Times* 2001, 26, Supplement 6.

60. Rainer G., Menapace R., Findl O., Georgopoulos M., Kiss B., Petternel V., *Intraocular pressure after small incision cataract surgery with Healon 5 and Viscoat* [in:] *J Cataract Refract Surg* 2000, 26, 271–276.

61. Wolkoff L., *Viscoelastics — In search of the ideal viscosurgical device* [in:] OSN (US ed.) 2003, May 15, 2318–2322.

62. Arshinoff S.A., Albiani D., Taylor-Laporte J., *Intraocular pressure after bilateral cataract surgery using Healon, Healon 5, and Healon* GV [in:] *J Cataract Refract Surg* 2002, 28, 617–625.

63. Arshinoff A., *Understanding, retaining, and removing dispersive and pseudodispersive ophthalmic viscosurgical devices* [in:] *J Cataract Refract Surg* 2003, 29, 2318–2323.

64. Madsen K., Stenevi U., Apple D., Härfestrand A., *Histochemical and Receptor Binding Studies of Hyaluronic Acid and Hyaluronic Acid Binding Sites on Corneal Endothelium* [in:] *Ophthalmic Practice* 1989, 7, 3, 2–8.

65. Dick B., Schwenn O., *Viscoelastics in ophthalmic surgery* [in:] *Springer* 2000.

62. RECOSYN® Gebrauchsanweisung, Merckle Recordati GmbH, 5/2010.

63. Rodriquez F., *Principles of polymer systems*, Hemisphere Publishing Corporation, New York 1982, 326.

64. Silver F.H., Brizzi J., Pins G., Wang M.-C., Benedetto D., *Physical properties of hyaluonic acid and hydroxypropylmehtylcellulose in solution: evaluation of coating ability* [in:] *J Appl Biomat* 1994, 5, 89–98.

65. Burratto L., Giardini P., Bellucci R., *Viscoelastics in Ophthalmic Surgery*, SLACK Inc., Thorofare 2000.

66. Forsberg N., von Malmborg A., Madsen K., Rolfsen W., Gustafson S., *Receptors for hyaluonan on corneal endothelial cells* [in:] *Exp Eye Res* 1994, 59, 689–696.

67. Madsen K., Stenevi U., Apple D.J., Härfstrand A., *Histochemical and receptor binding studies of hyaluronic acid and hyaluronic acid binding sites on corneal endothelium* [in:] *Ophthalmic Practice* 1989, 7, 92–97.

68. Härfstrand A., Molander N., Stenevi U., Apple D., Schenholm M., Madsen K., *Evidence of hyaluornic acid and hyaluronic acid binding sites on human corneal endothelium* [in:] *J Cataract Refract Surg* 1992, 18, 265–269.

69. Bausch + Lomb, Berlin (D), product information on Bloxaphte available [online], http://www.bloxaphte.de.

70. Arshinoff S.A., Hofmann I., *Prospective, randomised trial of Microvisc and Healon in routine phacoemulsification* [in:] *J Cataract Refract Surg* 1997, 23, 761–765.