# **Hyaluronic Acid**

Subjects: Polymer Science | Biochemistry & Molecular Biology Contributor: Petr Snetkov

Hyaluronic acid, as a natural linear polysaccharide, has attracted researchers' attention from its initial detection and isolation from tissues in 1934 until the present day. Due to biocompatibility and a high biodegradation of hyaluronic acid, it finds wide application in bioengineering and biomedicine: from biorevitalizing skin cosmetics and endoprostheses of joint fluid to polymeric scaffolds and wound dressings. However, the main properties of aqueous polysaccharide solutions with different molecular weights are different. Moreover, the therapeutic effect of hyaluronic acid-based preparations directly depends on the molecular weight of the biopolymer. The present entry collects the information about hyaluronic acid and its original properties. Particular emphasis is placed on the structural, physical and physico-chemical properties of hyaluronic acid in water solutions, as well as their degradability.

Keywords: biocompatibility ; degradability ; hyaluronic acid ; molecular weight ; structure ; viscosity ; water polymer solution

### 1. Introduction

Hyaluronic acid (HA), as a member of hyaluronan family, was first discovered by K. Meyer and John W. Palmer in 1934 <sup>[1]</sup>, and nowadays continues to attract careful attention on the part of chemists, biochemists, bioengineers, and other investigators from various scientific areas. HA is an essential component of the extracellular and pericellular matrixes, and can also be found inside cells <sup>[2]</sup>. The occurrence of hyaluronic acid in tissues varies: for instance, rooster's combs contain 7.50 mg/mL, human navel cords (gelatin of Wharton)—4.10 mg/mL, human joint synovial fluid—1.50–3.60 mg/mL, vitreous humor—0.14–0.34 mg/g, human dermis and epidermis—0.20–0.50 and 0.10 mg/g, respectively <sup>[3]</sup>. The turnover of hyaluronic acid in vertebrate tissues on average is equal to 5 g per day, and is provided by biosynthesis and enzymatic degradation <sup>[4]</sup>. Meanwhile, the turnover of hyaluronic acid in the blood-flow reaches 30–100 mg per day <sup>[5]</sup>.

Apart from the animal of origin, hyaluronic acid can be separated based on bacteria, for example, from Streptococcus genus (uberis, equisimilis, zooepidermicus, pyogenes, equi), Pasteurella multocida [6][Z][8][9][10], and Corynebacterium glutamicum [11]; from the green algae Chlorella purposely infected by the Chlorovirus [6][Z][12]; Saccharomycetes (Cryptococcus neoformans [6][Z]); and from molluscan shellfish, such as the bivalve mollusc Mytilus galloprovincialis [6][13]. At the same time, hyaluronic acid has not been disclosed in fungus, insects, or plants [6][14].

Note that hyaluronic acid is usually obtained from bovine vitreous humors, rooster combs, the skin of sharks, and human umbilical cords <sup>[15]</sup>. However, animal origin hyaluronic acid contains endotoxin and protein residuals, which possess immunogenic effects <sup>[14][15]</sup>. Thus, 1 mg of hyaluronic acid from human navel cord and from bovine vitreous humor could include >100.0 EU endotoxin and approximately 47.7 and 36.2 µg protein, respectively. By contrast, hyaluronic acid from rooster comb contains 23.0 EU endotoxin and 1.0 µg protein per 1 mg of polymer <sup>[16]</sup>. At the same time, bacterial technology makes it possible to obtain high-purity hyaluronic acid with low protein and endotoxin levels <sup>[15]</sup>. Therefore, bacterially derived hyaluronic acid purchased from Sigma and Genzyme includes only 1.0–1.6 µg protein and approximately 0.02 EU endotoxin per 1 mg hyaluronic acid <sup>[16]</sup>. Nevertheless, the level of immunogenic effect of protein residuals in bacterial hyaluronic acid could be greater than in animal hyaluronic acid despite the low summary protein content <sup>[17]</sup>.

It is obvious that molecular weight of hyaluronic acid depends on the source. Consequently, hyaluronic acid from animal materials has a very high molecular weight (up to 20,000 kDa). For example, rooster combs contain hyaluronic acid with 1200 kDa, the navel cords—3400 kDa, bovine vitreous humors—770–1700 kDa. By contrast, bacterial hyaluronic acid has a molecular weight between 1000 and 4000 kDa; however, the enzymatic technique makes it possible to obtain polysaccharides with a range of molecular weight between 550 kDa and 2500 kDa <sup>[18]</sup>. The molecular weight of hyaluronic acid also depends of some other conditions: for instance, in human normal synovial fluid, it is equal to 6000–7000 kDa, while in rheumatoid fluid, the molecular weight is less, and is equal to 3000–5000 kDa <sup>[19][20]</sup>.

The biological effects of hyaluronic acid depend heavily on molecular weight. Hyaluronic acid with molecular weights from 0.4 to 4.0 kDa acts as an inducer of heat shock proteins, and has a non-apoptotic property. Polysaccharides with a molecular weight equal to 6–20 kDa possess immunostimulatory, angiogenic, and phlogotic activities. Hyaluronic acid with a molecular weight of 20–200 kDa takes part in biological processes such as embryonic development, wound healing and ovulation. By contrast, high molecular weight hyaluronic acid (>500 kDa) has anti-angiogenic activity, and can function as a space filler and a natural immunologic depressant [21].

The fact that the molecular weight of hyaluronic acid may vary its biological properties is the current subject of interest. The drastic difference in its functions is the reason that for medical applications, preference is given to low-polydispersity or monodisperse HA. Preparation of monodisperse hyaluronic acid is achieved by successive cycles of degradation and subsequent assembly of HA chains <sup>[22]</sup>. Additionally, the mechanisms of interaction of hyaluronic acid of various molecular weights with receptors on the cell surface are currently being actively studied. It has previously been suggested that HA of different MW may affect the same receptors differently; however, recent study refutes this theory <sup>[23]</sup>. On the other hand, it has been shown that HA of very high molecular weight (6000 kDa) produced by naked mole-rat suppresses the signaling of CD44, which results in altered expression of a subset of p53 target genes, thereby suggesting that HMWHA has the properties of a cytoprotective molecule <sup>[24]</sup>, but there are differences in the genes regulated by p53 between different species so this investigation is restricted to human cells.

Evidently, the structural, physical, physicochemical and degradable properties of hyaluronic acid also depend on its molecular weight. For example, the increase in the molecular weight and concentration of hyaluronic acid in polymer solutions leads to the reinforcement of the three-dimensional network of the polymer. Consequently, it results in an increase in the solution viscosity and viscoelasticity <sup>[6]</sup>. In some cases, for example, in the electrospinning process, molecular weight, concentration, and viscosity are the key parameters providing the nanofibers obtaining <sup>[25]</sup>.

There are a lot of studies dedicated to the properties of hyaluronic acid. Unfortunately, the vast majority of such papers touch upon one of several groups of polymer characteristics. Particular interest is aroused by the biological properties of materials based on hyaluronic acid. Still, for the development and technology of advanced wound healing <sup>[26]</sup>, drug delivery systems with controlled release <sup>[22]</sup>, and polymer scaffolds <sup>[28]</sup>, knowledge of the molecular weight dependency on the abovementioned properties is necessary. This entry collects brief data on the structure, viscosity, density, surface tension, cohesive/adhesive, hydrodynamic and degradable properties of hyaluronic acid.

### 2. Aqueous Hyaluronic Acid Solutions and Their Properties

Hyaluronic acid is a linear heteropolysaccharide (glucosaminoglycan, mucopolysaccharide) with high molecular weight formed by regularly repeating residues of N-acetyl-D-glucosamine and D-glucuronic acid [1][29]. In a hyaluronic acid molecule, the D-glucuronic acid is associated with amino-sugar by  $\beta$ -(1  $\rightarrow$  3)-glycosidic linking, and amino-sugar is connected with the D-glucuronic acid by a  $\beta$ -(1  $\rightarrow$  4)-glycoside tieup [17].

The existence of polar and apolar segments in the polymer structure affords hyaluronic acid the capability to chemically interact with various chemical agents  $^{[17]}$ , for instance, with metachromatic dyes, which find application in clinical examinations  $^{[30]}$ , and chitosan, which makes it possible to obtain a new class of materials based on polyelectrolyte complexes  $^{[31][32]}$ .

Hyaluronic acid forms hydrogen bonds, which, on the one hand, could poise the macromolecule in solutions, but, on the other hand, give rise to rigidity in the polymer system, which, finally, specify the properties of hyaluronic acid solutions. Note that an aqueous molecule could be a bridge between the two connected functional groups <sup>[17][33]</sup>. Eventually, such primary structure and hydrogen bonds help to form secondary and tertiary structures <sup>[33][34]</sup>.

Hyaluronic acid and its salt, with ammonium ions, magnesium, and alkaline metals, have good solubility in water and possess a high level of viscosity even at low polymer concentrations  $^{[17]}$ . Moreover, hyaluronic acid in solution could organize a three-dimensional cellular structure with enormous dimensions at concentrations of less than 1 µg/mL  $^{[34]}$ . By contrast, biopolymers can organize pseudo-gels when concentrations are equal to or above 1.0 wt.%  $^{[17][19][20]}$ . However, hyaluronic acid with high molecular weight equal to 5.0 MDa at concentrations greater than 0.1 mg/mL forms entangled polymer networks, but hyaluronic acid solutions do not have prolonged mechanical integrity  $^{[12]}$ . Salts of hyaluronic acid with cations possessing two and more valence numbers have substantial insolubility in water. Additionally, if such ions are introduced into hyaluronic acid solutions, intermolecular cross-links are constituted, resulting in the development of a gel with great water content  $^{[17]}$ .

It is known that the macromolecule of hyaluronic acid in solution could organize the left-oriented individual or twin spiral <sup>[34]</sup>. Study confirms that hyaluronic acid K and Na salts demonstrate a twin helix structure in solution <sup>[35]</sup>; moreover, that helix has antiparallel left-oriented strands <sup>[17][36]</sup>.

Obviously, that structure of hyaluronic acid in general specifies the other properties of biopolymer. Additional information about key hyaluronic acid properties is listed in Table 1.

Property	HA MW, kDa	Authors	Reference
Structure	2 000 – 8000	Ribitsch et al.	[ <u>37]</u>
	30 – 1700	Cleland and Wang	[ <u>38]</u>
	-	Almond et al.	<u>[39]</u>
	100, 500, 1000, 3000, 6000	Cowman et al.	[ <u>40]</u>
	-	Lapcík et al.	[41]
	1900	Maleki et al.	[42]
	-	Ghosh et al.	[43]
	1600, 1700, 4000	Morris et al.	[44]
	125, 241, 390, 598, 800, 961, 1270, 1430, 1620, 1770, 2040, 2150	Yanaki and Yamaguchi	[45]

Table 1. Summary of structural, physical, and physico-chemical properties of hyaluronic acid.

Rheological properties	1000	Scott and Heatley	[ <u>33]</u>
	-	Lapcík et al.	[ <u>41]</u>
	1900	Maleki et al.	[ <u>42]</u>
	-	Ghosh et al.	[ <u>43]</u>
	1600, 1700, 4000	Morris et al.	[ <u>44]</u>
	2000	Rwei et al.	[ <u>46]</u>
	> 1000	Gura et al.	[ <u>47]</u>
	1500	Pisárčik et al.	[ <u>48]</u>
	10, 100, 1000, 2000	Kim et al.	<u>[49]</u>
	350, 680, 1800	Falcone et al.	[ <u>50]</u>
	1000, 2000, 3000, 4000	Bothner and Wik	[ <u>51]</u>
	560, 760, 780, 1040, 1700, 1930, 1970	Kobayashi et al.	[52]
	77, 640, 1060, 2010	Rebenda et al.	[ <u>53]</u>
	125, 241, 390, 598, 800, 961, 1270, 1430, 1620, 1770, 2040, 2150	Yanaki and Yamaguchi	<u>[45]</u>
	1500	Krause et al.	[54]

Surface tension	100, 500, 4000	Knepper et al.	[ <u>55]</u>
	1630	Ribeiro et al.	[ <u>56</u> ]
	807, 4280, 5560	Silver et al.	[ <u>57][58]</u>
	1000, 5000	Nepp et al.	<u>[59]</u>
Cohesive and adhesive properties	350, 680, 1800	Falcone et al.	[50]
	132, 1500, 2000	Vorvolakos et al.	[60]
	-	Liao et al.	[ <u>61]</u>
	134, 620	Saettone et al.	[62]
	134, 620, 2200	Durrani et al.	[63]
Density	1500	Gómez-Alejandre et al.	[ <u>64]</u>
	1430	García-Abuín et al.	[ <u>65]</u>
	10–30, 110–130, 300–500, 1500–1750	Kargerová and Pekař	[66]
Ultrasound velocity	1430	García-Abuín et al.	[65]
	10–30, 110–130, 300–500, 1500–1750	Kargerová and Pekař	[ <u>66]</u>

Osmolality and colloid osmotic pressure	1000, 2000, 3000, 4000	Bothner et al.	[51]
	750 (eye drops)	Aragona et al.	[ <u>67</u> ]
	From 500 to 7900 (eye drops)	Dick et al.	<u>[68]</u>
	From 500 to 7900 (eye drops)	Dick	<u>[69]</u>
Hydraulic conductivity and fluid absorption rate	85, 280, 500, 4000	Wang et al.	<u>[70]</u>
	45.4, 81.9, 165, 196, 699, 844, 1110	Lam	<u>[71]</u>
	45.4, 81.9, 165, 196, 699, 844, 1110	Lam and Bert	[72]

## 3. Degradable Properties

The presence of hyaluronic acid in many tissues and fluids determines its widespread use in medicine and cosmetology. The biological activity of HA depends on its molecular weight [73]. It has been shown that high molecular weight HA has anti-inflammatory properties, and its rheological characteristics determine its use as a synovial fluid prosthesis in the treatment of various joint diseases, in cosmetology, and in aesthetic medicine as dermal fillers and in ophthalmology as artificial tears [6][74]. Degradation of HA leads to a decrease in the molecular weight and, consequently, to a decrease in viscosity, which is detrimental to the use of HA [40][75].

Hyaluronic acid undergoes degradation under the influence of ultrasound <sup>[76][77][78]</sup>. This happens as a result of a cleavage of the glycosidic bonds between GlcA and GlcNAc units by the free radicals OH and H, which can be generated by the action of ultrasonic waves in water and the collapse of cavitation bubbles, which causes the breakage of the macromolecule backbone in the solutions <sup>[77]</sup>. Interestingly, sonication leads to the degradation of HA in a non-random fashion. It is assumed that high molecular weight HA degrades more slowly than low molecular weight HA <sup>[76]</sup> and exposure to ultrasound does not lead to complete degradation.

Exposure to alkali and acid also leads to the degradation of hyaluronic acid [43][79][80]. This method leads to the complete hydrolysis of HA to oligosaccharide-hyalobiuronic acid [79]. With the presence of acid, hydrolysis randomly occurs on glucuronic acid, and under the action of alkali, it randomly occurs on acetylglycosamine [80]. It is hard to assume that there is any cohesion between the rate of degradation and molecular weight of HA; however, it is suggested that the pH value, as along with the concentration of HA, may affect the rate of hydrolysis [42].

Thermal degradation mechanism is presumably a random chain scission that occurs in the HA chain [81][82][83][84]. With increasing temperature, the decrease in molecular weight was more rapid for both the sample in solution and the powder. During the first three hours of heating at a temperature of 90 °C (powder and solution) and 120 °C (powder), the decrease in molecular weight was much more instantaneous than with a longer exposure to lower temperature. In general, it was concluded that degradation of HA with a lower MW occurs more quickly than with a higher MW at a moderate temperature [81].

It is known that HA degrades when exposed to reactive oxygen species. The impact of various oxidizing agents such as ozone, UV light, hydrogen peroxide and others on HA was studied [85][86][87][88][89][90][91]. Unfortunately, there is no information available about the dependence of the rate of oxidative degradation of HA on its molecular weight as only one sample of HA was studied in most articles.

Hyaluronic acid undergoes degradation under normal conditions. To minimize molecular weight loss during long-term storage, HA can be put in the refrigerator. Studies <sup>[92][93]</sup> showed that storage conditions have a greater effect on degradation than the initial molecular weight of the sample.

The study of the biodegradation of hydrogels of various compositions based on HA is currently receiving attention. Hydrogels of HA can be applied in different fields, including tissue engineering, drug delivery, wound dressings and regenerative medicine due to its biodegradability, biocompatibility and versatility <sup>[94]</sup>. To obtain hydrogel from HA, the latter might be crosslinked by chemical modification. In addition to creating a three-dimensional structure, chemical modification makes it possible to achieve better physicochemical characteristics in hydrogels, thereby increasing their resistance to biodegradation <sup>[95]</sup>.

More detailed information about the degradation dependence on the MW of hyaluronic acid is presented in the Table 2.

Type of Degradation	HA MW, kDa	Author	Reference
Ultrasound	400, 1000, 1200	Kubo et al.	[78]
	-	Vercruysse et al.	[76]
Temperature	1670, 1800	Mondek et al.	<u>[81]</u>
Long-term (caused by storage time)	17, 267, 752, 1000	Simulescu et al.	<u>[92]</u>
	14.3, 267.2, 1160.6	Simulescu et al.	[93]
Enzymatic	10, 50	Kim et al.	<u>[96]</u>
	200, 2000	Xue et al.	[ <u>97]</u>
	50, 350, 1100	Burdick et al.	[98]
	100, 1000, 2000	Cao et al.	[99]

Table 2. Summary of degradable properties of hyaluronic acid.

# 4. Conclusions and Perspectives

Hyaluronic acid, as a hydrophilic biopolymer with a unique set of structural, physical, physicochemical, and biodegradable properties, attracts a great deal of attention. This entry demonstrates the key properties of hyaluronic acid and gives the references on original studies. Firstly, the hyaluronic acid structure and coil overlap were discussed. However, despite comprehensive studies, this field requires more detailed analysis, for example, with respect to structural dimensions such as the diameter of the coil, etc.

Secondly, viscosity, surface tension, and density, as the key parameters, were investigated in detail. Further analysis is viable for aqueous-organic solutions of hyaluronic acid or for aqueous HA solutions with additional polymers, which are applied for electrospinning to obtain nano- and microfibers.

Thirdly, knowledge of the cohesion and adhesion properties of hyaluronic acid is necessary for the development of biomedical applications, especially for surgery, ambustial therapy, wound healing, and cell growing. Such parameters were extensively analyzed, but it is interesting to evaluate the influence of the biologically active agents used in the abovementioned applications on the cohesion and adhesion properties of the compound formed.

The next parameter, ultrasound velocity, is not important in itself. Moreover, it has been discovered that this parameter is not dependent on the molecular weight of the polymer. Nonetheless, measuring the ultrasound velocity is useful for the determination of the structural and physical properties of the polymer and their alterations.

Osmolality and colloid osmotic pressure are very important parameters of body liquids. Moreover, during the development of any kind of artificial fluids (tears, synovial fluid, etc.), it is critical to choose an osmolality that is approximately equal to the natural one. Osmolality was analyzed using eye drops, while the colloid osmotic pressure was investigated based on three fractions of hyaluronic acid. Future studies with a wider range of molecular weights could expand the fundamental scientific data in this field.

One more key parameter is hydraulic conductivity, which is as important for peritoneal fluid as it is for transport solutes. Furthermore, this parameter must be considered for the development of medical applications. Unfortunately, there are only a small number of studies in this field, and this area requires additional examination.

Study of the degradation processes of hyaluronic acid under the influence of oxidants and enzymes is necessary for assessing the half-life of drugs based on hyaluronic acid.

It was shown that HA does not degrade to oligosaccharides under the influence of ultrasound; this is in contradistinction to the action of pH and oxidants, which lead to complete hydrolysis of HA.

Moreover, long-term degradation and thermal degradation were discussed. The dependence of these parameters on the molecular weight of the HA makes it possible to choose the optimal period and temperature for storing the sample in order to avoid loss of molecular weight.

Study of the time and degree of enzymatic hydrolysis is necessary for assessing the duration of drug efficacy. It has been shown that hydrogels consisting of HA with a higher molecular weight are less susceptible to enzymatic hydrolysis, although the molecular weight of the sample is not the only factor to affect the degree of decomposition.

However, scientific studies call for further investigations for a better understanding of the relation between the degradable properties and the molecular weight of hyaluronic acid. Such investigations may create a background for development of topical and complicated drug delivery systems, scaffolds and wound dressings, which take biomedicine and bioengineering to a new level.

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