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A REVIEW ON HYALURONIC ACID USED IN PHARMACEUTICALS

¹Gaurav Jagtap, ²Gaware Prashant

¹Pharmacology,

¹Sanjivani College of Pharmaceuticals Education & Research, Kopergaon, Ahmednagar, India

Guide : Miss Gauri Borude

Abstract: Hyaluronic acid (HA) is a high molecular weight biopolysaccharide discovered by Karl Meyer and his assistant, John Palmer in 1934 from the vitreous of bovine eyes. HA is a naturally occurring biopolymer, which has important biological functions in bacteria and higher animals like mammal including humans. Hyaluronic acid is found in most connective tissues and is particularly concentrated in synovial fluid, the vitreous fluid of the cattle, umbilical cords and chicken combs. HA is naturally synthesized by a class of integral membrane proteins called hyaluronan synthases, and degraded by a family of enzymes called hyaluronidases. Hyaluronic acid has many qualities that recommend it over other substances used in skin regeneration, with moisturizing and anti-ageing effects. Its molecular weight influences its penetration into the skin and its biological activity. Considering nowadays, hyaluronic acid has a wide use and a multitude of applications (in ophthalmology, arthrology, pneumology, rhinology, aesthetic medicine, oncology, nutrition, and cosmetics). This review describes, different physiological and pathological functions, metabolism basic pharmacological properties, and the clinical use of hyaluronic acid.

Index Terms – Hyaluronic acid, History, Pharmacokinetics, Application

I. INTRODUCTION

Hyaluronic acid (HA) is a carbohydrate, more specifically biopolysaccharide occurring naturally in all living organisms. It can be several thousands of sugars (carbohydrates) long. When not bound to other molecules, it binds to water giving to stiff viscous quality similar to "Jello". The polysaccharide hyaluronan (HA) is a linear polyanion, with a poly repeating disaccharide structure $[(1 \rightarrow 3)\text{-}\beta\text{-d-GlcNAc-(1} \rightarrow 4)\text{-}\beta\text{-d-GlcA}]$. HA is found primarily in the extracellular matrix and pericellular matrix, but has also been shown to occur intracellularly. The biological functions of HA include maintenance of turgor as to viscosity of liquid connective tissues such as joint synovial and eye vitreous fluid, control of tissue hydration and water transport, supramolecular assembly of proteoglycans in the extracellular matrix, and numerous receptor-mediated role since detachment, mitosis, migration, tumor development and metastasis, and inflammation.[1] Its function in the body is, amongst other things, to bind water and to lubricate movable parts of the body, such as joints and muscles. Its consistency and tissue-friendliness allows it to be used in skin-care products as an excellent moisturizer. Hyaluronic acid is one of the mostly hydrophilic (water-loving) molecules in nature and can be described as nature's moisturizer. The unique viscoelastic nature of HA along with its biocompatibility and non-immunogenicity has led to its use in a number of clinical applications, including the supplement of joint fluid in arthritis.[2] as a surgical aid in eye surgery & to facilitate the healing and regeneration of surgical wounds. More recently, HA has been investigated as a drug delivery agent for various administration routes, including ophthalmic, nasal, pulmonary, parenteral and topical.[3]

HISTORY:

The first study that can be referred to regarding HA dates from 1880: the French scientist Portes observed that mucin from vitreous body was different from other mucoids in cornea and cartilage and called it "hyalomucine".[4] In 1934, Karl Meyer and his colleague John Palmer isolated a previously unknown chemical substance from the vitreous body of cows' eyes. They found that the substance contained two sugar molecules, one of which was uronic acid. For convenience, therefore, they proposed the name "hyaluronic acid".[5] The popular name is derived from "hyalos", which is the Greek word for glass + uronic acid. At the time, they did not know that the substance which they had discovered would prove to be one of the most interesting and useful natural macromolecules. HA was first used commercially in 1942 when Endre Balazs applied for a patent to use it as a substitute for egg white in bakery products. The first medical application of hyaluronan for humans was as a vitreous substitution / replacement during eye surgery in the late 1950s. The used hyaluronan was initially isolated from human umbilical cord, and shortly thereafter from rooster combs in a highly purified and high molecular weight form. The chemical structure of hyaluronan was essentially solved by Karl Mayer and his associate in the 1950s. It was first isolated as an acid, but under physiological conditions it behaved like a salt (sodium hyaluronate).

The term "hyaluronan" was introduced in 1986 to conform with the international nomenclature of polysaccharides and is attributed to Endre Balazs (Balazs et al., 1986), who coined it to encompass the different forms the molecule can take, e.g., the acid form, hyaluronic acid, and the salts, such as sodium hyaluronate, which form at physiological pH (Laurent, 1989). HA was subsequently isolated from many other sources and the physicochemical structure properties, and biological role of this polysaccharide were studied in numerous laboratories.[6]

Table no. 1 History of hyaluronic acid[4,5,6]

SR.NO.	YEARS	
1	1880	mucin from vitreous body called hyalomucine
2	1934	"hyaluronic acid isolated
3	1942	HA was first used commercially
4	1950	First medically used HA for ophthalmology

Physicochemical properties of HA :

Hyaluronan, an extracellular matrix component, is a high molecular weight glycosamino-glycan composed of disaccharide repeats of N-acetylglucosamine and glucuronic acid. This relatively simple structure is conserved through out all mammals, suggesting that HA is a biomolecule of considerable importance.[7] In the body, HA occurs in the salt form, hyaluronate, and is found in high concentrations in several soft connective tissues, including skin, umbilical cord, synovial fluid, and vitreous humor. Significant amounts of HA are also found in lung, kidney, brain, and muscle & tissues.

In the physiochemical propertise of hyaluronic acid we discuss about the following headings they are as follow

1. Chemical Structure of HA acid
2. Polymer Structure
3. Aqueous HA & Its Propertise
4. Degredable propertise HA

1. Chemical Structure of HA:

The uronic acid and aminosugar in the disaccharide are D-glucuronic acid and D-N-acetylglucosamine, and are linked together through alternating β -1,4 and β -1,3 glycosidic bonds (see Figure 1). Both sugars are spatially related to glucose which in the β configuration allows all of its bulky groups (the hydroxyls, the carboxylate moiety and the anomeric carbon on the adjacent sugar) to be in sterically favorable equatorial positions while all of the small hydrogen atoms occupy the less sterically favorable axial positions. Thus, the structure of the disaccharide is energetically very stable.

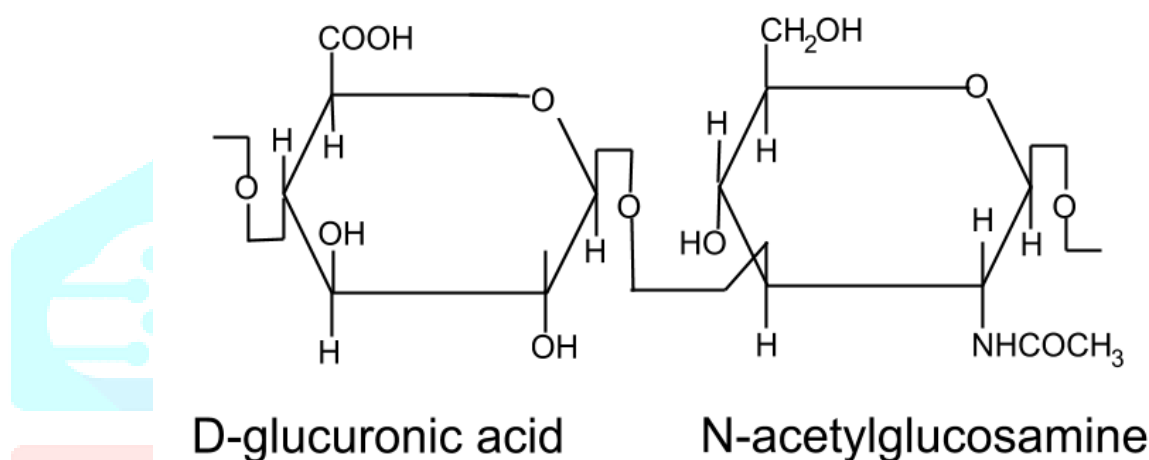


Figure 1: Chemical Structure of HA

2. Polymer Structure:

Hyaluronan synthase enzymes synthesize large, linear polymers of the repeating disaccharide structure of hyaluronan by alternating addition of glucuronic acid and N-acetylglucosamine to the growing chain using their activated nucleotide sugars (UDP – glucuronic acid and UDP-N-acetylglucosamine) as substrates.[8] The number of repeat disaccharides in a completed hyaluronan molecule can reach 10 000 or more, a molecular mass of ~4 million daltons (each disaccharide is ~400 daltons). The average length of a disaccharide is ~1nm. Thus, a hyaluronan molecule of 10 000 repeats could extend 10 μ m if stretched from end to end, a length approximately equal to the diameter of a human erythrocyte.[9]

3. Aqueous HA Solution & its properties: [21]

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. In a hyaluronic acid molecule, the D-glucuronic acid is associated with amino-sugar by β -(1 \rightarrow 3)-glycosidic linking, and amino-sugar is connected with the D-glucuronic acid by a β -(1 \rightarrow 4)-glycoside tieup. The existence of polar and a polar segments in the polymer structure affords hyaluronic acid the capability to chemically interact with various chemical agents, for instance, with meta chromatic dyes, which find application in clinical examinations, and chitosan, which makes it possible to obtain a new class of materials based on polyelectrolyte complexes. 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 . Eventually, such primary structure and hydrogen bonds help to form secondary and tertiary structure.

Table No: 2 Summary of Structural, Physical & Physicochemical Properties of HA [17,18]

PROPERTY	HA MW(kDa)	AUTHORS
Structure	2000-8000	Ribitsch et al.
	30-1700	Cleland and Wang
Rheological property	1000	Scott and Heatley
	1900	Maleki et al.
Surface tension	1630	Ribeiro et al.
Cohesive & Adhesive property	350,680,1800	Falcone et al.
	132,1500,2000	Vorvolakos et al.
Density	1500	Gómez-Alejandre et al.
Ultrasound velocity	1430	García-Abuín et al.
Osmolality and colloid osmotic pressure	1000,2000,3000	Bothner et al.
	750 (eye drop)	Aragona et al.
Hydraulic conductivity and fluid absorption rate	85,280,500	Wang et al

4. Degradable Properties:[19]

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 . 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 . 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. Hyaluronic acid undergoes degradation under the influence of ultrasound . This happens as a result of 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 . 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 and exposure to ultrasound does not lead to complete degradation. Exposure to alkali and acid also leads to the degradation of hyaluronic acid . This method leads to the complete hydrolysis of HA to oligosaccharide-hyalobiuronic acid . With the presence of acid, hydrolysis randomly occurs on glucuronic acid, and under the action of alkali, it randomly occurs on acetylglucosamine . 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. Thermal degradation mechanism is presumably a random chain scission that occurs in the HA chain .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. 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. 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 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. 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 More detailed information about the degradation dependence on the MW of hyaluronic acid is presented in the Table 2.

Table No. 3 Type of HA Degredation as per there molecular weight.

Type of Degradation	HA MW (kDa)	Author
1.Ultrasound	400,1000,1200	Kubo et al.
2.Temeprature	1670,1800	Mondek et al.
3.Long-term (caused by storage time)	17, 267.2	Simulescu et al

Sources of Hyaluronic Acid :[20]

Hyaluronic Acid is present in human eye & act as cushioning agent between joints, human body produces it endogenously. HA has a property of retaining moisture within the cell. However the HA reduces over the time with ageing & poor hydration habits. In such cases human need HA from dietary sources, they are given below ;

Table No. 4 Sources of hyaluronic acid

SR. NO.	COMPONENTS	SOURCES OF HA
1	HYALURONIC ACID (HA)	Bone Broth
2		Vegetables with tubes
3		Broccoli
4		Leafy Green Vegetables
5		

PHARMACOKINETIC ACTIVITY OF HYALURONIC ACID (HA): [10 ,11]

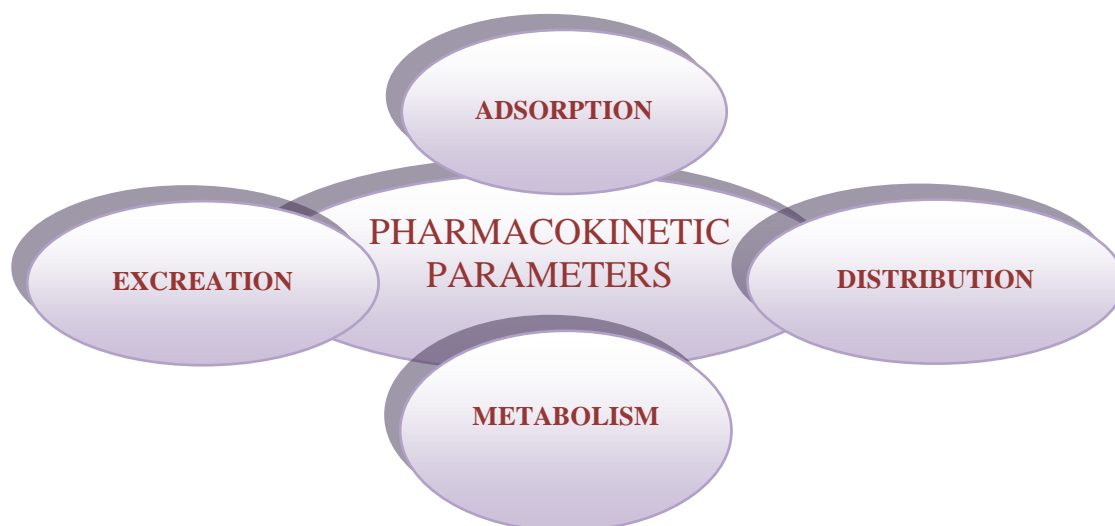


Figure 2: PHARMACOKINETIC ACTIVITY

The main objective of study is to evaluate the pharmacokinetic parameters of hyaluronic acid. In the pharmacokinetic parameters we discuss about Absorption, Distribution, Metabolism, Excretion i.e. ADME of hyaluronic acid. The limited information is available in **absorption** of HA in human body. When HA is administered orally, to a certain extent, it gets degraded by the intestinal bacteria into oligosaccharides & then absorption in the intestinal colon or subsequently distributed in different tissue and skin. The pharmacokinetic studies in dogs show the rapid Absorption & rapid Excretion. When applied topically, depending on the molecular weight of HA acid, with low molecular weight 20 -300 kDa is absorbed through the stratum corneum & the high 1000 – 1400 kDa are not penetrate through Stratum corneum. So the bioavailability of HA depends on its low molecular weight or high molecular weight.

Volume of Distribution : [10 ,11]

Volume of distribution varies according to their molecular weight. After giving dermal filler injection, HA rapidly distributed superficial & deep dermis. After intestinal breakdown by bacteria, HA gets distributed into the tissue & skin. HA gets accumulated in the kidney, thyroid gland, bladder & stomach. HA acid also gets concentrated in joints, salivary gland, vertebra within 4 hours after a single dose. HA acid also distributed in lymphatic system.

Metabolism : [10 ,11]

Metabolism of HA is done by two methods. One is Specific Hyaluronic acid is degraded by a family of enzymes called hyaluronidases. In animals, it is metabolized into oligosaccharides by intestinal bacteria and subsequently reabsorbed in the large intestine. Hyaluronidases are the enzyme that degrades hyaluronic acid which is the constituents in part of extracellular matrix. Initially discovered in bacteria, hyaluronidases are known to be widely distributed in nature and have been found in many classes including insects, snakes, fish and mammals. In the human, six different hyaluronidases, HYAL1-4, HYAL-P1 and PH-20, have been identified. PH-20 exerts the strongest biologic activity, is found in high concentrations in the testicles and can be localized on the head and the acrosome of human spermatozoa. Other is nonspecific which is oxidative damage due to Reactive Oxygen Species (ROS). It also metabolised by lymphic blood vessels endothelial cell. Additionally, small part of HA is metabolised by endothelial cell of liver.

Route of Elimination : [10, 11]

Studies in rats and dogs administered a radio-labeled oral dose of HA showed 87-96% excretion **the feces. Excretion of hyaluronic acid is primarily extra-renal, with some contribution from the spleen.**

Table No.8 Pharmacokinetics & key points of HA

SR.NO	PHARMACOKINETICS PARAMETERS	KEY POINTS
1	Absorption	20 – 300 kDa
2	Volume of distribution	Concentrated time 4 hours
3	Plasma protein binding	Affinity toward HABP1 is glycoprotein
4	Metabolism	Metabolised by Enzymes hyaluronidases
5	Route of Excretion	87-96% excretion Through Feces
6	Half life	7 hours to 1.5days
7	Clearance	30 mg/day/kg
8	Toxicity	LD50 > 800 mg/kg

In vitro studies show that the plasma protein & HA react with each other & lead to formation of water soluble complex. Hyaluronan binding protein 1 (HABP1) is glycoprotein which having affinity toward Hyaluronic acid. originally obtain from rat tissue. some receptors & their action are given in above table.

Half life (T₅₀) :

When HA is injected intra-articular injection , than half life is 7 hours to 1.5days. the half life of high molecular weight HA is high & viceversa is true. the half life of HA in sheep is determine which is found to be 27 hours. , HA is believed to undergo rapid elimination via the blood and liver. [10]

Clearance:

There is limited information in the literature regarding the human pharmacokinetics of hyaluronic acid. In a pharmacokinetic study of rabbits, maximum clearance capacity of intravenously administered hyaluronic acid was about 30 mg/day/kg. [10]

Toxicity: [11]

Hyaluronic acid not a toxic in wide range of acute animal toxicity studies , Safety assessment of HA , potassium hyaluronate , sodium hyaluronate HA function in cosmetics as a skin conditioning agents at a concentration upto 2%. The oral LD50 of the sodium salt of hyaluronic acid is >800 mg/kg in the rat. Overdose information is not readily available in the literature. The safety profile for hyaluronic acid favourable, however, single case reports of death following vaginal injection of hyaluronic acid are published; the deaths likely occurred due to poor procedure regulation.

APPLICATION OF THE HYLURONIC ACID : [12]

The hyluronic acid are biodegradable & widely used in variety of multiple application in pharmacy field. In this review we discuss about each and every application with details.

HYLURONIC ACID IN OPHTHALMOLOGY : [12]

Hyaluronic acid (HA) is a glycosaminoglycan that are biologically safe and water retention properties, it has many ophthalmology-related applications, such as in intravitreal injection, dry eye treatment, and contact lenses. HA commonly used as an additive to their production material, surface coating, and multipurpose solution. Both low and high molecular weight HA eye drops are increasingly being used in ophthalmology. A previous clinical study has also shown that high-molecular-weight HA eye drops can be used as an alternative to autologous serum eye drops for severe dry eyes. Tear film oriented therapy has been recommended as a treatment strategy for dry eye by the Japanese Dry Eye and Asia Dry Eye Societies.

Sodium hyaluronate ophthalmic solutions have for many years been used to treat dry eye. In animal experiments, it has been reported that the effect on promoting wound healing in corneal erosions is higher than that of vehicles.[13]

The topical application of HA has been used to increase the secretion of water and mucin on the ocular surface. Sodium hyaluronate is a naturally occurring polymer and is ubiquitous throughout the interstitial cellular space in humans. It helps retain moisture in different types of tissue throughout the human body and aids lubrication between layers of tissue to eliminate friction – thus making it an ideal physiological tear film substitute. As a result of its coiled structure and large hydrophilic domains, HA attracts and retains a large amount of water, and therefore possesses the ability to retard water evaporation. Following instillation, SH solutions effectively moisturise the eye surface and prolong the beneficial wetting effect over time. HA gels have also been used successfully in ophthalmic surgery for many years. As a result of their unique physical and chemical properties, HA solutions are similar to natural tears. For that reason, they are widely used in ophthalmology as lubricant eye drops for the treatment of sensations of ocular dryness. The most important property of HA solutions is their viscoelasticity, which combines the viscous properties of a liquid with the elastic properties of a solid, depending on the shear stress applied. When used as an ocular lubricant, the unique viscoelastic properties of HA increase the stability of the pre-corneal tear film and maximise tear film residence time. Hyaluronic acid sodium salt (hyaluronan, HA) is commonly used as a bioavailability-enhancer in eye drops. Opsion HA Eye Drop eye drops are basically artificial tears which are required when there is a deficiency of hyaluronic acid in the eyes.

COSMETICS USED OF HYALURONIC ACID : [12,13]

HA always widely used in cosmetics product. A very low molecular weight of 5 kDa HA has the ability to [penetrate the skin](#) [Trusted Source](#), which means it can potentially carry other unwanted ingredients, chemicals, and bacteria more deeply into the skin. If you have compromised skin, this might be bad news. Thankfully, on its own, HA tends to not cause [allergic reactions](#) since our bodies also make it. HA with different molecular weights, including 50, 130, 300, 800, and 2,000 kDa.

Hyaluronic acid in arthology : : [12 ,14,15]

Hyaluronic Acid is a clear, transparent, viscous gel, [used](#) to relieve mild to moderate pain, swelling, and joint stiffness in knee caused by osteoarthritis. Chronic degenerative joint disease with painful & functional limitation are characteristics of Osteoarthritis. Hyaluronic acid injections may reduce or relieve inflammation caused by wearing of the cartilage and bone in osteoarthritic joints. In such cases intra-articular hyaluronic acid is a treatment are used.it shows following function in body such as

- **Lubrication :** Hyaluronic acid binds well to water, producing a viscous, jelly-like consistency. This viscous fluid provides lubrication and also acts as a shock absorber within the joint.
- **Growth of cartilage and bone.** Hyaluronic acid helps in the growth and development of joint's cartilage and bone by promoting the growth of new cells and tissues.
- **Reducing inflammation.** Hyaluronic acid plays an important role in reducing joint inflammation and pain caused by injury or tissue degeneration.
- **Rheumatoid arthritis.** A recent small study revealed that hyaluronic acid injections may help control inflammation and synovitis in the foot and ankle joints caused by rheumatoid arthritis.
- **Ankle sprain.** Hyaluronic acid injection in a sprained ankle joint may help decrease inflammation and reduce pain. [14]
- **Tennis elbow.** Chronic degeneration of the lateral epicondyle tendon causing tennis elbow may be treated with hyaluronic acid injection in the elbow joint.

Hyaluronic acid in oncology :[12]

- Hyaluronic (HA) acid has been widely used in delivery of anticancer drugs due to its excellent biocompatibility, biodegradability and specific targeting to cancer cells. Hyaluronic acid is a natural polysaccharide that has been widely explored for the development of anticancer therapies due to its ability to target cancer cells.

HYALURONIC ACID AS NUTRITIONS : [12]

- Soy foods such as tofu, soy chunks, soy milk and citrus fruits such as oranges, lemons, limes, and grapefruits **contain the most hyaluronic acid**. Also, tuber vegetables such as potatoes and sweet potatoes, and green leafy vegetables are excellent sources of hyaluronic acid. Hyaluronic acid is a compound that your body produces and that is also found in many foods and supplements. It may benefit skin health, inflammation, and conditions such as acid reflux, dry eyes, and osteoarthritis. To improve skin texture and clarity with intense moisture balance & skin brightness Proven Anti-aging Properties. vegan form of *hyaluronic acid* boosts skin health, improves the overall look of skin, and adds necessary hydration.
- **HYALURONIC ACID AS ANESTHETICS : [12]**
 - The addition of hyaluronic acid in local anaesthetics drug such as prilocaine, etodacaine, bupivacaine increase the duration of the sensory & motor neurons blocking action.
- **HYALURONIC ACID USED AS PNEUMOLOGY : [12]**
 - HA is a major component of extracellular cells. Other than joint, eye, skin, it is also present in lung cells. It has a ability to retained water capacity so its having maintaining fluid level in body. So this should be used in the lung disorders such as COPD. HA aerosols used to prevent bronchoconstriction in asthmatic patients.

CURRENT STATUS OF HYALURONIC ACID : [16]

Hyaluronic Acid are naturally occurring linear polymers of repeating disaccharide units, it has a wide range of application in skin, joints, eyes etc. the main natural source of HA is Bone Broth. Bone broth is the best food source of hyaluronic acid, Organ Meats, Naringenin-Rich Foods, Citrus Fruits + Berries, Sweet potatoes. Currently it is obtained from the extracted from rooster combs & after that HA should be produced by streptococcal fermentation. Now one of the advanced technology such as recombinant system should be used due to avoidance of toxicity. Now Novozymes has produced HA with recombinant *Bacillus subtilis* on an industrial scale. The current worldwide market of HA estimated to be over \$ 1 billion. The knee osteoarthritis patient population increasing by 26 % from 15 million in 2000 to 2019 million in last ten years, the demand for viscosupplements is expected to escalate. The first single-injection HA viscosupplementation product in the US, Synvisc-One, was approved in February 2009, & the product rapidly acceptance by patients and physicians because of its convenience. In the Asia Pacific, the HA viscosupplementation market are favorably affected by both the aging and physically active demographics, as well as rising improve the treatment's benefits among both physicians and patients. Global market of dermal filler are improve toward approximately 759 million in 2009. Nowday 100 product are available in market, and are based on the HA. The dermal filler market are risen expanded more than 25% in 2011 in US & 20% over world.

The [HA Market](#) research analysis provides a contextual information of the specialized limits, various challenges, and cost adequacy that influence the overall Market of HA. It provides a review of the total Market by offering in-depth knowledge, reliable data, and complete estimates about the growth of the Hyaluronic Acid industry. The report estimates were derived from proven research techniques and assumptions. Thus, the report serves as a repository of data and research for every market area, including but not limited to regional markets, applications, types and innovation.

Regions & countries in the global Hyaluronic Acid API market report: [17]

- Europe (Germany, France, UK, Russia, Italy, Rest of Europe)
- North America (US, Canada and Mexico)
- Asia-Pacific (China, Japan, Korea, India, Southeast Asia, and Australia)
- Middle East & Africa (Saudi Arabia, UAE, Egypt, South Africa, and Rest of Middle East & Africa)
- South America (Brazil, Argentina, Colombia, and Rest of SA)

Conclusion :

It is concluded that hyaluronic acid, an essential heteropolysaccharide, is widely used in the pharmaceuticals more than the 20th century throughout the world. Because of its bioavailability, biodegradability, wide variety of uses such as cosmetics, ophthalmology, arthology, anaesthetics, oncology etc., this application depends upon the molecular weight of hyaluronic acid. It will be high molecular weight or low molecular weight. Many skin care products are available in the market and are discussed in this review article.

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