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Review Article

A COMPREHENSIVE REVIEW ON APPLICATION OF HYALURONIC ACID IN DEVELOPMENT OF NOVEL DRUG DELIVERY SYSTEMS

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ABSTRACT

Hyaluronic acid is a naturally present linear polysaccharide that contributes to various structural and physiological function in the human body. Its unique properties have led to its extensive exploration in various drug delivery system, including nasal, transdermal, parenteral, pulmonary, implantable, ocular, and gene delivery. HA chemical structural modification have enabled the development of diverse formulation, such as micelles, niosomes, liposomes, solid lipid nanoparticle, microsphere, and cyclodextrin which have shown promising results in enhancing drug bioavailability, targeting specific cells, and providing sustained release. HA mucoadhesive properties, ability to interact with specific receptor, and biocompatibility have made it an attractive biomolecule for pharmaceutical and medical advancements. This abstract highlighting the versatility and potential of HA in improving therapeutic efficacy and reducing side effect in various diseases condition.

Keywords: Hyaluronic acid, Novel drug delivery system, Derivative of hyaluronic acid, micelle, Niosomes, Liposomes

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INTRODUCTION

Hyaluronic acid HA is a linear polysaccharide that occurs naturally in body that is present in extracellular matrix of connective tissue, synovial fluid, and several other body tissue. It serves multiple roles in body function and structure, such as facilitating interaction between cells and the extracellular matrix, engaging with growth factors, regulating osmotic pressure, and providing lubrication to tissues [1].

History

Hyaluronic acid, also known as hyaluronan was initially discovered by Meyer and Palmer in 1934 in the vitreous humor of bovine eyes. Because it exist as a polyanion in biological system rather than in its protonated acid form [2]. The name hyaluronic acid HA originates from Greek word hyalos, meaning glass, and reflects its glassy appearance. It consist of two sugar molecules, one of which is uronic acid [1]. This compound is found widely throughout craniate and is also a constituent of cellular outer layer in various bacterial strains, such as Streptococcus laurent1970. HA can be commercially obtained from animal origin, like joint fluid, umbilical tissue, skin, and comb of the rooster or it can be produced through bacterial fermentation or direct extraction methods [2].

Chemical structure

Hyaluronic acid (HA) a type of non-sulfated glycosaminoglycan (GAG) is commonly found within the extracellular matrix (ECM) [3]. The chemical structure of hyaluronic acid consist of repeating disaccharides units made up of D-glucuronic acid and N-acetyl-D-glucosamine a structural arrangement initially described by Weissmann and Meyer in 1954. Later studies by Laurnet and Fraser 1992 showed that this polysaccharide has a simple linear structure, where its sugar units are linked by alternating β-1,3 and β-1,4 glycosidic bonds as also noted by (Scott and Heratley1999) [2].

Reasons for modifying hyaluronic acid

Exogenous hyaluronic acid HA is rapidly broken down in the body, with a half-life ranging from 12-24 h, primarily due to hydrolytic enzymes knows as hyaluronidases. To enhance its longevity in situ, HA often undergoes chemical modification, such as derivatization or more commonly, cross-linking. These processes reduce its water solubility and improve resistance to enzymatic degradation. Currently, the market offers a variety of stabilized cross-linking and biocompatibility HA-based gels and ongoing research is focused on developing new derivative that provide improved degradation rates while maintaining the biocompatibility of the native polymer [4].

Chemical modification of hyaluronic acid HA primarily occur at two key structural sites the acidic group and alcohol groups. The carboxylic acid group can be modified through esterification as described by Benedetti *et al.* (1993) and dihydrazine reaction facilitated by carbodiimide chemistry, as reported by Luo *et al.* (2000) [5].

Preparation and diverse application of modified hyaluronic acid HA

1. Acetylated HA

2. Thiolated HA

3. Mannose-Enhanced Hyaluronan.

Table 1: Derivative of hyaluronic acid and its application

Derivative	Application	References
Acetylated derivative	• The acetylated form of hyaluronic acid increase bioavailability compared to free form. • It shows improved radicals scavenging activity. • Enhanced anti-inflammatory effect have been observed.	[4]
Thiolated HA	• Thiolated polymer also known as have recently attracted significant interest for controlled drug delivery. • They may help address oral bioavailability challenges faced by various therapeutic agents. • Thiomers can be beneficial for delivering peptide, antisense oligonucleotides, heparin and cephalosporin	[5]
Mannose-Enhanced Hyaluronan	• Hyaluronic acid with mannose significantly enhance the uptake of nanocapsule by M2 microphages *in vitro*. • HA-Man NCs showed significantly enhanced tumor accumulation, indicating efficient targeting. • Improved biodistribution with increased accumulation in tumours rich in tumour-associated macrophages TAMs.	[6]

Application of ha in novel drug delivery system

To optimise the delivery efficacy of bioactive compound to various target areas, hyaluronic acid can be engineered using different molecular weight and chemical modification this approach enables the design of diverse delivery systems, such as micelle, Niosomes, Liposomes, Solid lipid nanoparticle, microsphere, cyclodextrin. HA enhances the use of nanomedicines by improving the biocompatibility, circulation time in the bloodstream, cellular uptake, and stability of inorganic nanoparticles [7, 8].

Micelle

Amphiphilic derivatives of hyaluronic acid (HA) have the ability to self-assemble into polymeric aggregates in specific solvents, making them promising candidates for targeted drug delivery, similar to traditional amphiphilic copolymers. The simple conjugation of hyaluronic acid (HA) with hydrophobic drugs or molecules imparts amphiphilicity, allowing the formation of micelles. These micelles can encapsulate drugs through various mechanisms, including chemical conjugation, physical absorption, and electrostatic interactions. HA micelles have the potential to serve as effective drug delivery carriers for targeting 3-cells [9, 10].

Table 2: Literature survey of hyaluronic acid by using drug for development of micelle

Drug	Conjugate/Excipient	Application	References
Curcumin	Quercetin, 3,3 Dithiodipropionic acid	HA composite microneedles loaded with nano-micelles exhibit rapid drug release due to their excellent dissolving properties, making them a promising drug delivery system for melanoma treatment.	[11]
Azithromycin, Quercetin	Soluplus, Tocopherol polyethylene glycol succinate, Polyethylene glycol-distearyl phosphatidylethanolamine.	Azithromycin and Quercetin were encapsulated in nano-micelles with HA modification, improving drug targeting and efficacy against intracellular bacterial infections. HA Azithromycin quercetin micelles shows extended circulation, targets infection sites, clears Methicillin Resistant Staphylococcus Aureus, reduces muscle damage, and has good biocompatibility, making it a promising MRSA treatment.	[12]
Harmine	Conjugate-3,5 Bis trifluromethyl benzylamine	The hyaluronic acid-loaded Harmine polymer micelles developed. That effectively target and kill breast cancer cells, while simultaneously reducing the toxicity of Harmine and enhancing its slow-release targeting.	[13]
Lipiodol	Polyethylene glycol-polycaprolactone copolymer	The micelles demonstrated high stability *in vitro* and selectively delivered a greater load to HepG2 cells, a liver cancer cell line recognized for its expression of elevated levels of CD44 and effective carrier for lipiodol.	[14]
Doxorubicin and Curcumin	Polyethylene glycol copolymer	Boosting antitumor efficacy.	[15]
Paclitaxel and Apatinib	Hyaluronic acid-g-cystamine dihydrochloride-poly benzyloxycarbonyl L-lysine	The extended blood circulation times enhanced drug accumulation at tumor sites, aiding in the effective inhibition of tumor growth. Our newly developed smart co-delivery system offers a promising approach for the clinical treatment of multidrug-resistant breast cancer.	[16]
Doxorubicin	Conjugate-tetraphenyl ethylene with glutathione	Markedly reduced tumor growth and exhibited excellent biosafety.	[15]

Niosomes

Niosomes are bilayer structure formed from non-ionic surfactant and known for their thermodynamic stability. they are created under specific condition that include the proper combination of surfactant and cholesterol, along with temperature exceeding the gel-to-liquid transition point with these bilayers, there is a central void that allow for the encapsulation of both hydrophilic and hydrophobic drug hydrophilic drug can be entrapped in the aqueous core or adsorbed onto the biliary surface while hydrophobic drug integrate into the bilayer through partitioning [16, 17].

HA-coated niosomes hold potential for a variety of applications, such as ocular drug delivery, inflammation management, and cancer treatment. They enhance the duration of drug retention in the eye, provide prolonged anti-inflammatory effects, and boost the efficiency of drug delivery to cancer cells [18].

Kong *et al.* employed the emulsion–evaporation technique to create vitamin E-loaded HA–niosomes, aiming to combine both transdermal and tumor-targeting capabilities in a single formulation [19].

Liposomes

Hyaluronic acid modified liposomes are utilized to enhance both drug encapsulation efficiency and targeting capability the hyaluronic acid coating enabled the liposomes to bind more effectively to the specific cell, allowing them to penetrate this cells more efficiently this modification makes hyaluronic acid-coated liposomes are highly effective system for targeted drug delivery [31].

Table 3: Literature survey of hyaluronic acid by using drug for development of niosomes

S. No.	Drug	Excipient	Method of HA coating	Significance	References
1.	Epirubicin	Span 60, Span 80, Span 20, Cholesterol	Physical mixing	Increase cellular uptkae	[20]
2.	Tacrolimus	Poloxamer188, Soyabean phosphatidylcholine and cholesterol	Physical Mixing	It enhanced opthalmic bioavailability and improved corneal permeability.	[21]
3.	Centella asiatica	Tween60, Span60, Cholesterol.	Thin film hydration method with HA addition	To Improve dermal absorption, permeability, and accumulation in the viable epidermis and dermis layers.	[22]
4.	Calcein	Span 20, Tween 20, Cholesterol.	Physical mixing	Enhanced active tumor targeting through nanocarrier leading to improved drug uptake.	[23]
5.	5-flurouracil	Cetyltrimethylammoniumbromide, Tetraethylorthosilicate, 3-aminopropyltriethoxy silane	Layer-by-Layer	Improved drug loading efficiency and enabled controlled drug release.	[24]
6.	Centella asiatica	Tween 60, Span 40, Span 60, Cholesterol	Post-Formation Surface modification	Improving cellular uptake and enabling sustained drug release.	[25]
7.	Fluorescein isothiocyanate	Span 20, Tween 80	Physical mixing	Effectiveness of transdermal absorption.	[26]
8.	Quercetin	Polysorbate 80, trimethylammonium bromide.	Thin film hydration	Enhance drug loading, stability, and boosts antioxidant and anti-inflammatory properties.	[27]
9.	Epirubicin	Surfactant, Cholesterol.	Thin film layer	Effectively inhibit tumor growth in mice making this nanoparticle-based system a promising approach for safe and effective breast cancer therapies.	[28]
10.	Paclitaxel	Tween 80, span 60, amidinophenyl indolecarbamidine dihydrochloride	Thin film hydration method	Enhance targeting, dual drug delivery.	[29]
11.	5-flurouracil	Span 80, Tween 80, Cholesterol	Thin film hydration	Promising approach for treating solid tumors.	[30]

Table 4: Literature survey of hyaluronic acid by using drug for development of liposomes

S. No.	Drug	Significance	References
1.	Berberine	Enhancing lipophilicity and bioavailability	[32]
2.	5-Fluorouracil	Targeting CD44 receptor.	[33]
3.	Curcumin	Intestinal delivery of curcumin Protect it from gastric condition.	[11]
4.	Doxorubicin and Paclitaxel	Enhanced stability, improved cellular effect.	[34]

Solid lipid nanoparticle

This nanoparticle feature a solid lipid core that encapsulates pharmaceutical agent, offering controlled release and improved stability the lipid matrix safeguard the encapsulated drug from degradation while enabling a sustained release profile that can be adjusted for particular therapeutic requirements. Additionally modifying solid lipid nanoparticle with hyaluronic acid boosts their targeting capacity, allowing them to selectively bind to receptor on specific cells, such as cancer cell or inflamed tissues [35].

Table 5: Literature survey of hyaluronic acid by using drug for development of solid lipid nanoparticle

S. No.	Drug	Significance	References
1	Paclitaxel	Lung delivery specifically targeting CD44 receptor.	[36]
2	Methotrexate	An effective treatment option for rheumatoid arthritis.	[37]
3	Vorinostat	Stayed longer in circulation, enhancing the drug chances of reaching the tumor.	[38]
4	Docetaxel	A potent drug delivery system for targeted therapy and overcoming drug resistance.	[39]

Microsphere

Microspheres are small spherical particles that are typically measured in Microns and have variety of application, including in drug delivery. naturally derived microsphere offers several advantages, such as enhancing the bioavailability of encapsulated compound. This improvement help protect the active ingredient from degradation and facilitates controlled, sustained release of the drug. Research hyaluronic acid polymer microsphere has been ongoing for nearly 10 y demonstrating their versatility in adjusting dosages, controlling release rates, and targeting specific receptors [40].

Table 6: Literature survey of hyaluronic acid by using drug for development of microsphere

S. No.	Drug	Significance	References
1.	Cyclosporin	Improve bioavailability and enhance its delivery, especially for poor water solubility.	[41]
2.	Fexofenadine HCL	Improved AUC and Cmax of nasal formulation.	[42]

Table 7: Literature survey of hyaluronic acid by using drug for development of microsphere

S. No.	Drug	Conjugate	Significance	References
1.	β-estradiol	β Cyclodextrin thioether to HA	Enhance solubility, increase intestinal transport rates.	[43]
2.	Sorafenib	γ-Cyclodextrin with HA	Enhance antiproliferative activity.	[44]
3.	Tocopherol	β-cyclodextrin grafted hyaluronic acid copolymer	Improve cosmetic and therapeutic effect.	[45]
4.	Camptothecin	β-Cyclodextrin cholic acid –hyaluronic acid polymer	Cholic acid facilitates hepatic targeting, HA targets CD44 receptor.	[46]
5.	Acyclovir	β-Cyclodextrin with HA	Exhibit strong antiviral activity with controlled release.	[47]

Application of specific drug delivery system

Nasal drug delivery system

Intranasal drug delivery has gained attention as a non-invasive method for targeting the brain, by passing the cerebrovascular barrier and avoiding presystemic metabolism by the Hepatic and digestive organ one challenge with this method is fast-acting mucociliary transport mechanism within nasal cavity requiring bio adhesive formulation to enhance drug retention. Hyaluronan HA has been used as mucoadhesive agent, increasing brain penetration of hydrophilic compounds such as peptides through the nasal route [48-50]. Research has shown that modifying HA can improve its adhesion to the nasal mucosa, enhancing drug delivery. For example, HA modified with cysteine ethyl ester hydrochloride form covalent disulfide bridges, improving its mucosal binding. Intranasal administration also offers several advantages, including being simple, non-invasive, and effective in an emergency situation, with rapid drug absorption no need for sterility. This route has potential for treating condition like rhinitis and rhinosinusitis, further highlighting its therapeutic application [51]. Casula *et al.* 2021 investigated a new eco-friendly nasal spray formulation combining hyaluronic acid and Zingiber officinalis extract as an innovative approach for treating rhinitis and rhinosinusitis [52].

According to Castellano and Mautone (2002), hyaluronic acid (HA) was effectively integrated into a topical xylometazoline formulation, enhancing its ability to relieve nasal blockage. Furthermore, Morimoto *et al.* (1991) observed that incorporating hyaluronic acid into nasal formulations significantly improved the bioavailability of vasopressin and 1-deamino-8-D-arginine vasopressin in rats-by over two-fold and 1.6-fold, respectively-compared to formulations without HA [53].

Transdermal drug delivery system

Microneedle arrays composed of hyaluronic acid (HA) have been developed for the transdermal delivery of insulin. The microneedle were capable of piercing the skin for over an hour at 75% relative humidity. Remarkably, more than 90% of insulin remained in microneedle reservoir at all temperature after being stored for month with the range of-40–40 °C demonstrating the high stability of insulin in microneedle [54]. When applied topically, these hyaluronic acid micro needle dissolve and release insulin quickly. Mechanism of action and drug movement through the body data revealed that insulin delivered via microneedle was nearly fully absorbed through skin into systemic circulation, and hypoglycemic effect was almost identical to that subcutaneous injected insulin. The HA-based microneedle provide a safe and effective approach for delivering insulin through the skin in medical application [55, 56].

Bonet *et al.* 2023 [57] investigated the therapeutic benefits of hyaluronic acid HA combined with three different transdermal drug delivery enhancer-protamine, Dimethyl sulfoxide DMSO and terpene in preclinical models of both inflammatory response and neurogenic pain their findings indicated that the combination of HA with either protamine or terpene significantly reduced chemotherapy-induced peripheral neuropathy and hyperalgesia more effectively than DMSO alone [58, 59]. In a separate study, Yuan *et al.* 2022 formulated that a hydrogel system incorporating HA-modified transferosomes as carrier for indomethacin. This approach enhanced as transdermal drug delivery and associated with the medication. Similarly, Son *et al.* 2017 developed HA-dodecylamine-based nanohydrogels loaded with indocyanine green as a model compound, demonstrating their potential in transdermal delivery application for both medical and cosmetic use [60, 61].

Parenteral drug delivery system

In 1991 Drobnik recognised non-immunoreactive hyaluronic acid as a active ingredient carrier for parental delivery. HA could facilitate active ingredient targeting to specific sites, such as lymphoid system by either conjugate active ingredient to HA or encapsualting them in an HA matrix. This approach could also be used for sustained release or prolonged drug retention in the body. For instance, taxol as an anti-cancer agent was covalently attached to hyaluronic acid, forming a taxol-HA conjugate selectivity targeted cancer cell lines *in vitro* [62]. The conjugation was achieved by conjugating taxol with hyaluronic acid modified using adipic dihydrazide through succinate ester. Following uptake via receptor-mediated mechanisms the drug was subsequent released by hydrolysis, achieving cytotoxicity in cancer cell [63].

Further studies by Sakurai and colleagues 1997 demonstrated that conjugating manganese and superoxide di-mutase to HA enhanced the anti-inflammatory activity of this protein in mice without eliciting immune responses. Additionally, HA has been used to achieve sustained release of human recombinant growth factor –I, with *in vitro* results showing that higher HA concentration slowed peptide diffusion, likely due to interactions between peptide and HA, which were also confirmed *in vivo* [64].

Inhalation-based therapeutic delivery

Protein and short-chain amino acid compound drug are typically administered through injection or infusion, requiring repeated injection, making non-invasive methods more appealing. Pulmonary delivery has been extensively studied for this drug to provide systemic therapeutic effects. Hyaluronic acid has been incorporated into inhaled insulin formulation to enhance absorption and ensure sustained release. According to Morimoto *et al.* (2001) found that low concentration of Hyaluronic acid in insulin solution improve absorption after intratracheal administration in rats, regardless of solution pH. In another study, spray-dried insulin with HA demonstrated improved absorption and sustained release in Beagle dogs compared to insulin alone. Incorporating zinc ions or hydroxypropyl cellulose into HA-based particle significantly enhanced insulin absorption and prolong its residence time [65, 66].

Implantable drug delivery system

Hyaluronic acid HA has been used to create implantable drug delivery system for sustained release of peptide drugs. Surini *et al.*, 2003. HA has been shown to integrate with chitosan-HA complex and forming a HA-chitosan complex that influences drug release rates, primarily through swelling effect caused by water absorption Takayama *et al.*, 1990. In study by Surini *et al.* an implant made of chitosan and HA containing insulin demonstrate a controlled, zero-order release profile. Variation in the formulation components impacted the release behaviour, such as a Chitosan-to-HA ratio and insulin content. For example, pellet with 50 mg chitosan-to-HA ratio of 3:7 released insulin three times faster than a 135 mg pellet loaded with a 16:84 chitosan-to-HA ratio [67, 68].

Opthalmic drug delivery system

Topically applied a Ocular drug typically have low bioavailability, with most of administered dose quickly cleared from the eye, mainly due to rapid drainage through the nasolachrymal duct and absorption by the conjunctiva. This clearance can lead to systemic circulation and potential side effects. As a result, there is a need to lengthen the ocular retention time of drug and improve regional bioavailability. For ophthalmic formulation, Hyaluronic acid utilize as carrier because of its viscoelastic property and ability to adhere to mucosal surface [69]. Several studies have shown that HA can extend precorneal residence time and enhance bioavailability of various drug, including Pilocarpine, tropicamide, timolol, gentamicin, tobramycin, arecaidine propargyl ester, and S-aceclidine. The mucoadhesive property of HA, combined with its structural support, are believed to primarily contribute to prolonged residence time of drug on the corneal surface. HA interact with mucin layer of Corneal epithelium and its shear thinning behaviour ensure that it does not resist blinking, thus improving patient compliance [70, 71].

Gene delivery

Hyaluronic acid HA has been utilised in the preparation of DNA-HA matrices and microspherefor sustained gene delivery. In these system, DNA is encapsulated within HA network, which is then cross-linked with adipic dihydrazide during formulation process. Researcher have observed that the release rate of plasmid DNA from these matrices and microsphere can be regulated by adjusting the amount of DNA loaded and cross-linking method used. The release process is characterised by initial burst, followed by slower release driven by the erosion of HA Matrix which can be tailored to occur over extended periods up to two-month. The DNA trapped within the HA matrix is protected from enzymatic degradation and once released remain capable of transfecting cell *in vitro*. Additional studies by Yun *et al.* 2004 demonstrate that nucleic acid encapsulated in HA microsphere successfully delivered in skeletal muscle in living organism. Furthermore, when conjugated with recombinant antibodies, the DNA showed the ability to target specific cell receptor, with the conjugates effectively differentiating between cells expressing E-and P-selectin [72, 73].

Colon-targeted drug delivery

Colorectal cancer is leading causes of cancer death with increasing prevalence due to longer life expectancy and high-fat, low-fibre diets. Chemotherapy using FDA-approved drug life Capecitabine, irinotecan and fluorouracil is the primary treatment. However, there is need for a colon-specific drug delivery system to reduce side effect and enhance local therapeutic efficacy [74, 75].

HA-functionalized polymeric nanoparticle, like those developed by Kotla *et al.* 2019 offer solution by improving drug absorption, controlled release, and bioavailability in the colon. Liposomes with their ability to deliver both hydrophobic and hydrophilic drugs, are also studied for their potential in cancer therapy. Active targeting strategiesusing HA-conjugated liposomes take advantage of over expressed hyaluron receptor on colorectal cancer cells, enable more targeted drug delivery, minimizing harm to surrounding healthy tissue. This advanced delivery system could significantly improve colorectal cancer treatment outcomes [76, 77].

Table 8: Significance of hyaluronic acid in various drug delivery systems

S. No.	Drug delivery	Drugs	Significance	References
1.	Nasal	Vasopressin, Gentamycin, Xylometazoline	Bio-adhesion enhances drug bioavailability.	[53]
2.	Parenteral	Doxorubicin, Taxol, Human recombinant insulin-like growth factor, Superoxide dismutase.	Drug carrier for liposomal encapsulation.	[62]
3.	Pulmonary	Insulin	Absorption enhancer and dissolution modifier.	[65]
4.	Implantable	Insulin	Dissolution rate adjustment.	[68]
5.	Ophthalmic	Tropicamide, Timolol, Pilocarpine, Arecaidine polyester, S aceclidine, Tobramycin.	Enhanced ocular drug retention for improved bioavailability	[71]
6.	Gene	Plasmid DNA/monoclonal antibodies.	Dissolution rate adjustment and stabilization.	[72]

CONCLUSION

Hyaluronic acid HA plays crucial roles in various physiological and structural functions within the body. The chemical structure of HA and its modification have led to diverse application in drug delivery system, including nasal, transdermal, parenteral, pulmonary, implantable, ocular, and gene delivery. Theseapplications have shown promising results in enhancing drug bioavailability, targeting specific cells, providing sustained release, and improving therapeutic efficacy, highlighting the versatility and potential of HA in pharmaceutical and medical advancements.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICT OF INTERESTS

Authors declare that we have no conflict of interest

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