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Review Article

Natural Polymers Used In *In Situ*gelling Systems

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ABSTRACT

In situ gelling systems have recently garnered immense interest as an innovative method for increasing drug retention time, bioavailability, and efficacy. However, among the materials used in *in situ* gel formulations, natural polymers have emerged as an innovative substitute over synthetic polymers because of their superior biocompatibility, biodegradability, and safety profile. This review emphasizes on the use of various natural polymers in *in situ* gelling systems in terms of their gelation mechanism, physicochemical characterization, and pharmaceutical properties. Case studies from recently published reports illustrating the use of such polymers have also been included. The choice of natural polymers like alginate, chitosan, pectin, gellan gum, guar gum, and xanthan gum shows potential because they have high mucoadhesive properties, toxicity, and environmental sustainability. These biomaterials can be used in all routes of drug delivery. They also have less immunogenic potential, lack chronic toxicity, are potentially compliant with increased patient safety, and are readily biodegradable in comparison with synthetic polymers. The case studies included in this review highlight the use of natural polymer-based *in situ* gels for achieving targeted and sustained drug release with enhanced durability and therapeutic effects. *In situ* gelling systems containing natural polymers constitute a safer, more environmentally friendly, and highly efficient method over synthetic polymer-based *in situ* gels.

Key-Words: *In situ* gel, Polymer, Sol-to-Gel, Stimuli responsive system, Nasal, Ocular

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INTRODUCTION

In Situ Gelling Systems (ISGS) are briskly developing systems for effective drug delivery enabling alternate routes of administration such as ocular, nasal, rectal, vaginal, etc. These systems are initially administered as a liquid that undergoes rapid gelation (liquid-gel transition) at the site of administration or site of action due to the effect of physiological factors such as changes in temperature, pH, and ionic concentration.(1) Such delivery systems are being widely used to facilitate sustained delivery of the drugs, besides aiding ease of administration and reduced frequency of administration, as well as protecting the drug from environmental degradation.(2) Conventional liquid formulations delivered via the ocular or nasal route are often associated with low bioavailability due to rapid drainage of the drug and lower residence duration at the administration site.(3) Besides the routes mentioned earlier, such formulations can also be delivered via injectable and intraperitoneal routes.(4) A key limitation recurrently faced by the pharmaceutical industry recently focuses on the development of effective treatment options that are readily available and well accepted by physicians and patients. (5)The systemic absorption of the drugs administered by alternate routes of administration could be increased by the preparation of the formulation in the form of ISGS. (6) The use of ISGS has gained importance because of the limitations of currently used conventional drug delivery methods. These limitations include poor bioavailability, rapid clearance rates, and the need for frequent administration.(7) Drug delivery systems must also translate into better therapeutic outcomes if they are to provide viable alternatives to pharmaceuticals currently administered by various routes.(8) One such system that can offer a patient-friendly and more efficient alternative for the delivery of drugs is the fabrication of ISGS.(9) Some of the other specific advantages offered by ISGS are stated in Figure 1.

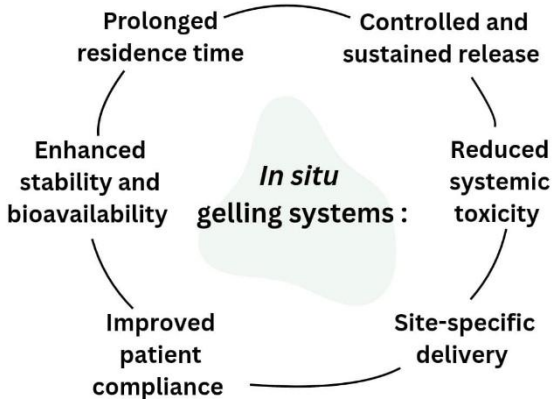

Figure 1: Need for ISGS(10)

Mechanisms of ISGS:

In situ gelling systems are stimuli-responsive preparations that transform from a liquid to a gel upon coming into contact with specific physiological conditions at the site of administration.(11) The sol-to-gel transformation occurs in response to either of the following stimuli.

- Temperature-triggered systems: Gelation occurs when the liquid formulation is introduced to body temperature, resulting in polymer network formation. Polymers such as Poloxamers and Pluronics are commonly used for these systems. Such systems are further categorized into 'negatively thermal-sensible', which contract upon heating, 'positively thermal-sensible', which contract upon cooling, and thermally reversible gel.(12)
- pH-triggered systems: The system shows gel formation in response to the physiological pH which is usually neutral. Examples of polymers employed in such systems include Chitosan, Carbopol, Polymethacrylic acid, etc.(13)
- Ion-activated systems: Gelation occurs due to the interaction with ions (such as Na^+ or Ca^{2+}) readily available in body fluids, which induce the ion-mediated cross-linking in polymers, such as Gellan gum, Alginate, Hyaluronic acid, and Pectin. The gelation rate is believed to depend on the osmotic difference across the surface of the resulting gel.(14)
- Swelling: A less commonly employed mechanism of *in situ* gelation involves the use of hydrophilic polymers that absorb water present in the surrounding environment, swell, and form a viscous gel matrix.(15)
- Diffusion: Exchange of solvent or counter ions triggers polymer aggregation and gel formation. The solvent diffusion from the polymer solution into the surrounding tissue leads to the precipitation of the polymer matrix.(16)
- Enzymatic cross-linking: Enzymes naturally present in the body catalyze covalent bonds between polymer chains, leading to gel formation.(17)
- Applications of ISGS:

ISGS are widely used to enable improvement of bioavailability by prolonging the residence of the formulation at the site of action. These systems are particularly advantageous for targeted drug delivery to achieve prolonged therapeutic effects.(18) These systems are used across various routes like ocular (eye drops for glaucoma), oral (stomach gels for sustained release), nasal, rectal, vaginal, and injectable (post-surgery for tumors), offering benefits like sustained-release, better bioavailability, increased patient compliance (fewer doses), and site-specific delivery.(19) Table 1 demonstrates the different areas of drug delivery where ISGS finds application.

Table 1: Application of ISGS

Route of Administration	Advantages of using ISGS
Ocular	Enhances precorneal residence time, reduces drainage, and improves ocular bioavailability by forming a gel upon contact with tear fluid (20)
Nasal	Prolongs nasal residence time, facilitates systemic absorption and nose-to-brain delivery, and improves mucosal absorption (21)
Oral	Provides sustained and controlled drug release, reduces dosing frequency, improves gastric retention, and enhances bioavailability (22)
Buccal	Promotes prolonged mucosal adhesion for enhanced local or systemic delivery and improved therapeutic efficacy (23)
Vaginal/ Rectal	Improves local retention and drug absorption, offering a convenient alternative for systemic delivery (24)
Injectable	Forms an *in situ* depot at the injection site for long-acting and controlled drug release with reduced dosing frequency (25)
Transdermal	Provides localized and sustained drug delivery through the skin (26)

Polymers Used in ISGS:

As mentioned in the earlier section, polymers play an important role in the development of ISGS by imparting the system its stimuli-responsive nature. Synthetic and semi-synthetic polymers such as Poloxamer, Carbopol are commonly used for the development of ISGS.(27) Recently, many natural polymers have also been employed in the same field because of their sol-to-gel transitions due to the variations of temperatures, pH

levels, or composition. Naturally occurring polymers are generally free from toxic effects, making them even more suitable for ocular or nasal delivery.(28) Table 2 represents some of the significant advantages offered by natural polymers compared to their synthetic counterparts.

Table 2: Comparative Characteristics of Natural and Synthetic Polymers(29)

Characteristics	Natural Polymers	Synthetic Polymers
Biocompatibility	Structurally similar with physiological components	Cause adverse effects due to their non-physiological nature
Biodegradability	Degrade easily into non-toxic metabolites via enzymatic or hydrolytic pathways	Non-degradable or degrade into potentially toxic byproduct
Environment-friendly	Eco-friendly, renewable, and derived from sustainable resources	Typically petroleum-based, contributing to environmental pollution and carbon emissions
Non-Immunogenicity	Usually do not provoke an immune response	Often require additional modifications (e.g., PEGylation) to reduce immunogenicity
Mucoadhesive and Gelling Properties	Exhibit excellent mucoadhesive and stimuli-responsive gelation, ideal for ISGS	May require complex chemical modifications to achieve similar behavior
Safety	Exhibit proven safety records	Need extensive toxicity and long-term safety testing
Cost and Availability	Often cost-effective due to their abundance in nature	Synthesis and purification can be expensive.
Functional Versatility	Contain reactive functional groups that allow easy modification for targeted delivery, controlled release, or enhanced bioavailability	Involves more complex and costly chemical synthesis

Such polymers, moreover, exhibit pseudo-plastic behavior, that is, their viscosity reduces with an increase in the rate of shearing, ensuring that the formulation remains viscous while at rest, and becomes thinner on application of shear.(30) This behaviour not only ensures stability of the formulation, but also increases the retention time at the site of application. The bioadhesive and mucoadhesive nature of the polymers also allows prolonged contact time and better drug absorption. These factors are crucial for improving the absorption and bioavailability of the drug from ISGS.(31) Some of the naturally occurring polymers commonly used in pharmaceutical ISGS are illustrated in Table 3

.

Table 3: Naturally derived Polymers used in Pharmaceutical ISGS

Polymers	Biological Source	Mechanisms
Alginate	Brocon Seaweed	Ion sensitive
Gellan Gum	Bacterial Fermentation (*Sphingomonas elodea*)	(Gelation in presence of (Ca^{++},Mg^{++})
Pectin	Plant Cell Walls (Citrus, Apple)	Ion sensitive
Xanthan Gum	Bacterial Fermentation (*Xanthomonas Campestris*)	pH and Thermosensitive
Carrageenan	Red Seaweed	Ion sensitive (K^{+},Ca^{++})
Chitosan	Derived from chitin(Shellfish)	Soluble in acidic pH gels at physiological pH
Guar Gum	Guar beans	Thickening agent, Supportive for Gel matrix
Gelatin	Animal collagen	Thermosensitive (Cooling agent)
Tragacanth	Exudate from Astragalus species	Swelling and mucoadhesive property
Acacia Gum	Acacia Tree Exudate	Film-forming thickener

While synthetic polymers offer precision and mechanical properties, naturally derived polymers provide unmatched biological compatibility, safety, and environmental advantages. In the context of ISGS, natural polymers, including chitosan, alginate, and gellan gum, are preferred due to their biodegradable, mucoadhesive, and eco-friendly properties, making them ideal candidates for modern pharmaceutical applications.(32)

The objective of this critical review is to draft an extensive account of the various natural polymers used for the fabrication of ISGS, with emphasis on their properties, gelling mechanisms backed by recent research citations involving the polymers.

Guar Gum:

Guar gum comes from the seeds of a plant called *Cyamopsis tetragonolobus*. It is a commonly used gelling agent that dissolves quickly, works well at different pH levels, and is biodegradable. Being uncharged, it retains stable viscosity across a wide pH range. In recent years, many studies have explored the applications of guar gum and its derivatives for targeted drug delivery, particularly for colon-specific treatments, lowering blood pressure, and delivering proteins through the skin. Besides these advantages, its affordability, flexibility, and regulatory approval make it a popular choice for effective drug delivery systems.(33)

Guar gum-based ISGS were developed for Ferulic acid, a pro-collagen compound that can mitigate cell damage and assist in repairing damaged cells. In the study cited by Akash Mondal et al., the authors aimed to synthesize ferulic acid grafted in guar gum/tamarind gum-based powder for wound healing, which could form an *in situ* gel upon contact with the wound. The ferulic acid-tamarind conjugates were synthesised *via* Steglich esterification reaction and amalgamated with guar gum, followed by lyophilization to produce dry powders. The powder absorbs the wound exudates and transforms into gels to create a defence film and a suitable ambience for wound healing. Amalgamation with guar gum improves the gel strength, hydrophilicity, and swelling ability of hydrophobic hydrogels. Guar gum facilitates gelling, adhesion to the affected area and it also has anti-inflammatory, antibacterial activity, making it a holistic gelling agent.(34)

In another study cited by Jaya Raja Kumar, et al., Fluconazole, an antifungal agent, was incorporated in guar gum, resulting in prolonged delivery in the oral cavity. The developed system reduced the systemic side-effects, while presence of Guar gum improved the viscosity of the *in situ* system. Guar gum enhances mucoadhesive strength, viscosity, and drug release profile. Thus, guar gum proved to be an essential polymer in the development of an effective mucoadhesive *in situ* gel for Fluconazole in oral thrush, validating multifunctional role of this excipient in novel drug delivery systems**.**(35)

Chitosan:

Chitosan is a natural cationic polysaccharide obtained by the deacetylation of chitin, which is found in the shells of crustaceans like shrimp and crab. It is biodegradable, biocompatible, mucoadhesive, and non-toxic, leading to its wide-spread applications in pharmaceutical and biomedical field. Chitosan can bind to negatively charged biological membranes, which enhances drug absorption and permeation. It also possesses antibacterial, antifungal, and wound-healing properties, and is useful as a film-forming agent, bioadhesive polymer, and controlled drug release matrix. Its unique pH-sensitive behavior allows it to remain soluble in acidic conditions and form gels near physiological pH, making it especially valuable in ISGS, tissue engineering scaffolds, and targeted drug delivery, particularly for ocular, nasal, and gastrointestinal routes.(36)

A study cited by Maedeh Barati et al. reported incorporation of Tramadol, a synthetic semi-opioid analgesic with a short half-life, in a chitosan-based thermosensitive ISGS formulation intended for subcutaneous injection to induce a controlled release of Tramadol. Chitosan (1%) was used in combination with a synthetic thermoresponsive hydrogel Poloxamer 407 and pentasodium triphosphate (TPP) was included to induce gelation *via* ionic cross-linking. Chitosan-based *in situ* gels are gaining significance in ophthalmic formulations designed to overcome the very low systemic availability of conventional eye drops, which is typically less than 5% due to factors such as tear drainage, blinking, and limited corneal absorption. In pH-triggered gels, in combination with carbopol, chitosan-based ISGS have shown prolonged ocular retention and 24-hour sustained release of Timolol, allowing once-daily dosing making it especially valuable for long-term therapies such as glaucoma treatment.(37)

Similarly, when formulated with dextran sulphate, chitosan-based systems achieved about 83% drug entrapment and prolonged release of Ciprofloxacin, a commonly prescribed ocular antibacterial agent for approximately 21 hours.

Chitosan neutralized with β-glycerophosphate forms a thermoreversible gel with a gelation temperature in the range of 30-35°C and facilitated sustained release of 5-Fluorouracil for up to 7 hours. In ion-activated gels, chitosan is combined with polymers like sodium alginate or gellan gum, which undergoes gelation in the presence of sodium, calcium, and magnesium ions present in tears. A system containing 0.25% chitosan in addition to 0.5% gellan gum enabled easy drop instillation followed by rapid gelation on the eye surface, resulting in improved transcorneal permeability and prolonged drug retention compared to typical eye drops.This gel, made from a combination of chitosan and Pluronic F127, was designed to enhance the ocular bioavailability and retention on the ocular surface. In this study, Ciprofloxacin hydrochloride was mixed into gels with varying amounts of Pluronic F127 (between 15% and 25%) and different weights of chitosan (ranging from 0.1% to 0.3%). To understand the interplay of these factors on the gel properties, a systematic, statistical-based study was performed. They found that gels with 15% Pluronic were easy-flowing at room temperature, optimum for ocular applications. However, those with 25% Pluronic were found to be too

viscous at room temperature. The optimized formulation was composed of 15% Pluronic and 0.1% low molecular weight chitosan. This blend remained stable and effective at the physiological temperature, even when mixed with simulated tear fluid. *In vitro* release data showed slower ciprofloxacin release from systems containing higher amounts and higher molecular weights of chitosan due to increased thickness of the diffusion layer. The optimized gel formulation released 59.80% of the drug over a period of 2.30 hours and 70% of the cumulative drug release. The formulation was retained at the site of administration for more than twelve hours. Furthermore, the drug release followed diffusion-based kinetics, demonstrating a steady and controlled drug delivery pattern. Statistical evaluations revealed that the molecular weight of chitosan significantly influenced the drug release pattern. *In vitro* antibacterial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus* proved that the gel formulation was efficacious compared to the standard ciprofloxacin eye drops.(38)

Carrageenan:

Carrageenan is a natural sulfated biopolymer obtained from red seaweeds (Rhodophyceae) and is broadly used as a gelling, thickening, and stabilizing agent in the pharmaceutical and food industries. It consists of repeating galactose units and occurs in three main forms—kappa, iota, and lambda, each producing gels of different strength and texture depending on the presence of ions like potassium or calcium. Carrageenan is biocompatible, biodegradable, and non-toxic, optimising for controlled drug delivery systems such as *in situ* gels, tablets, microbeads, and wound dressings. The strong water-binding and gel-forming properties allow sustained release of drugs by forming a stable three-dimensional network, and its ability to form thermo-reversible gels makes it useful in oral, topical, and mucosal drug delivery formulations.(39)

A case-study cited by Barbara Vigani et al. focused on developing mucoadhesive ISGS using κ-carrageenan (κ-CG), hydroxypropyl cellulose (HPC), and $CaCl_2$ for oral mucositis and esophagitis, further enhanced by loading with *Hibiscus sabdariffa* (HS) hydroalcoholic extract known for its antioxidant and anti-inflammatory activity. Two formulations with 0.6% κ-CG and 0.4% κ-CG were studied, both containing 1% HPC and 0.04% $CaCl_2$. Loading the HS extract reduced viscosity, favoring easier administration. Mucoadhesion tests showed no significant change after HS loading. The developed ISGS emerged as the optimal system, combining easy administration, enhanced saliva-triggered gelation, strong mucoadhesion, high cell compatibility, antioxidant protection, and anti-inflammatory activity, thus offering a promising therapeutic option for managing oral mucositis and esophagitis.(40)

Another case-study by Pradeep Singh Rawat et al. reported design, optimization, and characterization of a dual-responsive ocular ISGS of Nebivolol (NEB) for the treatment of primary open-angle glaucoma, using thermo-responsive poloxamers (P407, P188) and ion-sensitive κ-carrageenan (κCRG). A Box–Behnken design (17 runs) optimized polymer concentrations to achieve a sol-to-gel transition close to ocular temperature with minimum viscosity. The optimized formulation contained P407 19% w/v, P188 1% w/v, and κCRG 0.3% w/v, showing a gelling temperature of 34 ± 0.5 °C, solution viscosity of 212 ± 2 cP (25 °C), pH 7.2 ± 0.5, osmolarity 285.44 mOsm/L, and drug content 96.5 ± 1%. Rheological studies confirmed synergistic thermo- and ion-triggered gelation, and mucoadhesion force increased to 0.289 N for the dual-responsive gel compared with 0.145 N for poloxamer gel alone. The optimized gel provided sustained drug release (86% over 24 h), whereas NEB suspension released completely within 30 min, following Higuchi kinetics with n = 0.77, indicating diffusion-erosion–controlled release. Safety studies showed excellent ocular compatibility with HET-CAM irritation score = 0, hemolysis 1.16%, and no corneal histopathological damage. Ocular pharmacokinetic studies in rabbits demonstrated significantly enhanced ocular bioavailability and reduced systemic exposure with the adjusted ISGS. In aqueous humor, the gel achieved a Cmax of 35.14 ± 2.25 ng/mL and $AUC_{0-\infty}$ of 381.8 ± 18.32 ng·h/mL, which were 1.2-fold and 2-fold higher, respectively, than the NEB suspension (C_{max} 28.2 ± 3.1 ng/mL; $AUC_{0-\infty}$ 194.9 ± 12.17 ng·h/mL), along with a longer $MRT_{0-\infty}$ of 8.11 ± 0.12 h versus 6.12 ± 0.18 h. In contrast, systemic exposure was markedly reduced, with plasma Cmax 0.69 ± 0.01 ng/mL and $AUC_{0-\infty}$ 8.05 ± 0.43 ng·h/mL, representing 2.7-fold and 4.1-fold reductions compared to suspension. Pharmacodynamic evaluation showed superior and sustained intra-ocular pressure reduction, with AUC_{0-12h} of 137.04 and MRT_{0-12h} of 6.1 h for the gel, compared to 74.21 and 4.06 h for the suspension (1.85-fold improvement). Overall, the dual action responsive NEB ISGS provided prolonged ocular delivery, enhanced therapeutic efficacy, and significantly reduced systemic side effects, making it a promising system for long-term glaucoma management.(41)

Pectin:

Pectin is a natural, anionic heteropolysaccharide obtained from plant cell walls; it is composed of (1,4) linked D-galacturonic acid, incorporating three structural regions: homogalacturonan and rhamnogalacturonan. The high methoxyl pectin (DE>50%) undergoes gelation in acidic conditions with sugar while the low methoxyl pectin (DE<50%) undergoes gelation in the presence of calcium ions. They are manufactured from citrus peels and apple pomace. Pectin is known as a biocompatible and non-toxic polymer which acts as a dietary fibre with prebiotic cholesterol-lowering and glucose-regulating benefits. It is also widely used in targeted drug delivery due to its mucoadhesive and biodegradable nature.(42)

In the study cited by Kunihiko Itoh et al., ISGS-based on methylcellulose/pectin system oral prolonged release gel formulations help dysphagic and geriatric patients who face difficulty in swallowing oral dosage forms. The study aimed to modify methylcellulose solution by adding pectin which forms an ion-responsive gel to prepare an ISGS for sustained drug delivery. Suitable gel strength was obtained using methylcellulose (1–2%) and pectin (0.5–2%). The addition of 1.5% pectin and 2%

methylcellulose along with 20% D-sorbitol and Ca^{+2} ions, improved gel strength, and viscosity, and afforded easy swallowing. *In situ* gels formed in the rat stomach showed good integrity, allowing sustained release. *In vitro* paracetamol release from methylcellulose (MC)/pectin gels was controlled by diffusion. Plasma drug levels after oral administration in rats (gastric pH 2.6 & 5.5) with 2% MC + 1.5% pectin showed better prolonged release compared to individual polymers. Overall addition of pectin improved viscosity, gelation, and produced ISGS suitable for dysphagic patients with an improved sustained release profile.(43)

Another case study cited by Livia Visai et.al. discussed injectable pectin-based hydrogels prepared by an internal gelation method using calcium carbonate. The gel formation takes place without the need for additional agents like δ-gluconolactone. The gelling behaviour and rheological characteristics could be modified by adjusting the pH of pectin. It was observed that increasing the pH using $NaHCO_3$ is more effective in reaching near-physiological pH than using NaOH. Pectin solutions with pH values below 5.35 showed degradation and failure to form a thick gel, while solutions in the range of 3.2–3.8 (native pH) were considered suitable for gel formation.

The rise in pH enhances the crosslinking in hydrogels, shortens the gelling time, while increasing the thickness of the gel. These changes are influenced by the concentration of calcium carbonate. Results from rheological evaluation confirmed the formation of stable gels, and the hydrogel extracts did not show cytotoxicity when tested on L-929 fibroblasts. Overall, these formulations appear promising for injectable systems, providing a supportive microenvironment for the delivery of cells, drugs, or bioactive molecules.(44)

Xanthan Gum:

Xanthan gum is known as a high-molecular-weight and anionic heteropolysaccharide obtained from *Xanthomonas campestris*. It consists of beta-(1,4)-D-glucose backbone with trisaccharide side chains containing mannose and glucuronic acid, along with acetate and pyruvate group that helps in imparting high viscosity and stability. It exhibits pseudoplastic (shear-thinning) behaviorand remains stable over a wide range of pH, temperature, and salt concentration. Xanthan gum functions as a rheology modifier in formulations, contributing to ion-triggered gelation, mucoadhesion, and synergistic gel formation with other polymers. Xanthan gum also has wide applications in pharmaceuticals, the food industry (as stabilizer E415), and cosmetics (as thickener and emulsion stabilizer).(45)

In the study cited by Bharath et al., a topical formulation for effective healing of burns has been synthesized based on the concept of ISGS. The formulation involves the use of Xanthan gum for sustained drug release for better performance. The pH value was found to be 6.8. It is skin-friendly and non-irritating. The viscosity of the formulation ranged between 2800 and 5600 cps. The values for gel strength ranged between 25-45 seconds. The drug content measured in the range of 96-99% w/w implying uniform distribution of the drug. Sustained drug release from the formulation occurred over a period of 12 hours. It is a clear demonstration that it was therapeutically effective for a considerable time. The swelling index measured between 130-150%. It is a clear demonstration that it was efficiently absorbed and retained. It is a significant aspect that is essential for skin healing. Analysis shows that antibacterial properties exist as inhibition zones are evident. It is a clear demonstration that it had significant antibacterial properties.(46)

Another report by Sethi et al. highlights the application of Xanthan gum, a natural polysaccharide, in the development of viscoelastic gels designed to stabilize iron micro- and nanoparticles. Xanthan gum was selected due to its exceptional rheological and stabilizing properties.(47)

Sodium Alginate:

Sodium alginate comes from brown algae, and is a salt derived from alginic acid, made up of a chain of two sugar components: β-D-mannuronic acid and α-L-glucuronic acid. They are linked together in a specific way. One of the neat things about sodium alginate is its ability to stick to surfaces, thanks to its carboxylic group, and it can form gels when it encounters certain ions. Plus, they are safe for the environment and break down naturally. (48)

In the study cited by Sobia Noreen, et al., sodium alginate and Terminalia arjuna gum (TAG) were used for preparing a pH-sensitive smart gel for the delivery of moxifloxacin hydrochloride (MOX-HCl). The existing eye drop formulation has limited effectiveness owing to its rapid drainage and inadequate absorption in the corneal area. The prepared smart gel demonstrated a liquid condition during installation, along with a sol-to-gel transition in tear fluid, increasing its ocular retention and bioavailability. Ex vivo corneal permeation enhanced the drug permeation without causing tissue damage. Antimicrobial assessments depicted excellent antimicrobial activity towards bacterial strains, whereas sterility and cytotoxicity assessments validated its safety for clinical applications. Irritation assessments in rabbits and HET-CAM confirmed its safety because it does not produce ocular irritation. Stability tests for six months validated its effectiveness. (49)

In another manuscript publishedby Ayat A Allamet. al., preparation of sodium alginate-based ISGS dexmedetomidine (DEX) designed for sublingual use was detailed. IV DEX, universally effective, is limited by side effects such as bradycardia and hypotension. As a remedy for the aforesaid limitation, pH-sensitive ISGS were designed using the concept of Sodium alginate, in association with a viscosifying agent, Hydroxyethyl cellulose. The *in-vitro* study of the optimized dosage form indicated sustained release of this drug following Fickian diffusion kinetics. Further, the study related to the stability test of this dosage form indicated physical and chemical stability under different conditions of storage for a period of 60 days. The kinetic studies in rabbits indicated a marked increase in bioavailability of this dosage form when administered sublingually (89.22%) in comparison with that when administered orally (43.83%),

but equal levels in blood plasma compared to IV DEX. Notably, this dosage form completely avoided the effect of the first-pass phenomenon, and this led to rapid and high absorption levels. Further, in a study concerning pharmacodynamics in rat and rabbit models, there was expression of analgesia persisting for a prolonged period, along with a lack of effect on blood pressure or heart rate, contrary to IV DEX. (50)

Gellan Gum:

Gellan gum is an anionic deacetylated exocellular polysaccharide secreted by *Pseudomonas elodea*. It demonstrates temperature-dependent or cation-induced gelling behaviour. In the study cited by Nair et al., a sustained-release ophthalmic formulation that overcomes the limitations of conventional eye drops, such as rapid precorneal elimination, was developed using a combination of gellan gum, sodium alginate, and HPMC for the delivery of Moxifloxacin (MOX). Increasing polymer concentrations raised gel strength, viscosity, and adhesive force but slowed MOX release, indicating a diffusion-controlled mechanism following the Korsmeyer–Peppas model. The optimized formulation containing all three polymers exhibited controlled drug release for up to 12 hours, high ocular bioavailability (C_{max} 727 ng/ml vs. 503 ng/ml for eye drops), and was non-irritant and stable for six months.(51)

Using the same polymer, Monica R.P. Rao et al., developed a floating ISGS of Itopride hydrochloride for controlled drug release. Apart from gellan gum, the formulation included calcium carbonate as a calcium ion source and cross-linking agent, and HPMC K100M as a viscosity enhancer and release retardant. Increasing gellan gum concentration enhanced viscosity and gel strength, leading to a denser matrix that slowed drug diffusion and achieved sustained release. The optimized gel showed immediate gelation, remained intact for over 12 hours, and followed diffusion-controlled release (Korsmeyer–Peppas model). *In vivo* studies demonstrated delayed absorption, prolonged drug action, and improved bioavailability compared to the plain drug.(52)

Nanaware et al. reported the development of a nasal ISGS for the controlled delivery of Sumatriptan and Naproxen. The objective was to increase the nasal residence time and improve the efficacy of the drugs by using gellan gum as an ion-reactive gelling agent and sodium carboxymethyl cellulose (CMC) as a mucoadhesive polymer with Tween 80 as a surfactant. The polymer concentration greatly influenced the gelling time, viscosity, and release of the drug. Increasing the concentration of gellan gum will increase the viscosity and gel strength, resulting in lower diffusivity and sustained release of the two drugs. The optimized formula prepared showed quick gelling within seconds after coming in contact with the simulated nasal fluid with compatibility in physiological pH values (5.8-6.8) and high mucoadhesive strongest forces that help in increasing the residence time in the nasal cavity and preventing mucociliary clearance. The in vitro release studies showed that the optimized formula helped in the controlled release of the two drugs up to six hours according to Higuchi's diffusion-controlled kinetics. Gellan gum in addition to the ion-sensitive gelation helps in the mechanical strength and bioadhesive properties of the optimized nasal formula.(53)

Challenges Associated with the Use of Natural Polymer–based ISGS:

Natural polymer–based *in situ* gel formulations, although biocompatible and biodegradable, have several drawbacks such as batch-to-batch variability in composition and molecular weight due to their biological origin, which can affect gelation behavior and drug release. They often have lower mechanical strength and viscosity stability, leading to weak or easily eroded gels. Many natural polymers are also highly sensitive to environmental conditions like pH, temperature, and ionic concentration, which may cause premature or incomplete gelation. Their limited solubility and slower hydration can create difficulties in formulation preparation. In addition, these polymers are more prone to microbial contamination and thus require strict sterilization and preservative measures, which may affect their structure. As a result, achieving consistent, predictable, and long-term controlled drug release can be challenging with natural polymer-based ISGS.(54) Despite these concerns, natural polymers have been used in a number of marketed ISGS such as Timoptic-XE (Timolol maleate ophthalmic gel forming solution) by Merck Pharmaceuticals, USA; Chitrix (Wound healing gel) by Carrington Laboratories; Gelrite (Ophthalmic gelling agent) by Kelco, USA; Lacri-Lube (Lubricant eye ointment) and Refresh Liquigel (Carboxymethyl cellulose sodium ophthalmic solution) by Allergan Inc., USA etc.

Conclusion and Future Prospects:

Naturally derived polymers have been found to have high potential in terms of being versatile, biocompatible, and highly functional for the preparation of ISGS, which can prove to be a boon in terms of drug delivery in comparison to existing methods. Being biodegradable, mucoadhesive, environmentally sensitive, and safe for use, they can specifically be employed for various applications such as ocular, nasal, oral, injectable, transdermal, and topical formulations for wound healing. It has been found out in various studies that polymers such as guar gum, chitosan, Carrageenanan, pectin, xanthan gum, sodium alginate, and gellan gum can easily be made sensitive to physiological conditions such as temperature, pH, and ionic strength. Overall, these polymers ensure that, besides offering advances in efficacy by requiring longer residence times and increasing bioavailability, they also impact patients with increased benefits of convenience owing to less frequent dosages. Even with issues like batch inconsistencies, mechanical properties, and exposure to environmental factors, ISGS derived from natural polymers are also evolving because commercial successes are available on the market.(50)

The increasing literature available indicates the growing potential of these materials in the modern pharmaceutical technology realm. With the advancement of formulation science, natural polymers are on the verge of becoming

basic materials in next-generation smart delivery systems. The role of natural polymers is well established in the development of effective in situ gelling drug delivery systems and is well emphasized in this review. Further, the future of next-generation smart gels with programmable complex biological functions and properties, through chemical modification and hybridization of the natural polymers, is considered. It is foreseen that integration of long-acting injectable depot, nanotechnology-enabled targeting, and AI-assisted formulation design will boost patient compliance and therapeutic effectiveness. The commercialization of in situ gelling drug delivery systems will also be encouraged with developments in 3D bioprinting, self-healing and bioactive gels, as well as biodegradable polymer sources that are amenable to regulatory approval.(27)

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