Review

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Meta-Analysis of Polyethylene Glycol and Cellulose-based Polymers in Vaccine and Drug Delivery: A Comprehensive Review

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Review

Meta-Analysis of Polyethylene Glycol and Cellulose-Based Polymers in Vaccine and Drug Delivery: A Comprehensive Review

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Abstract: Due to their distinct physical, chemical, and biological characteristics, biopolymers, in particular Poly Ethylene Glycol (PEG) and Cellulose, are frequently used in biomedical medicine as drug or vaccine delivery systems. In this study, we have done a systematic review and a meta-analysis to compare current developments in many PEG and cellulose-based hydrogels, including double network hydrogels, injectable hydrogels, sliding hydrogels, conductive hydrogels, responsive hydrogels, and nanocomposite hydrogels. The pharmacokinetic properties, including physicochemical properties, biocompatibility, biodegradability, temperature, and pH, have been studied as these critical factors are to be considered for deciding the suitability of the drug for delivery. Moreover, the study has evaluated the controlled-release parameters such as half-life, circulation time, maximum release percentage of loaded drug released, burst release, maximum release, and drug-release kinetics. Finally, the efficacy and immune response of hydrogel was studied for future choice, including the cellulose hydrogel system in COVID-related long-term vaccine delivery. The finding revealed that cellulose-based hydrogel is effective for vaccine delivery.

Keywords: polyethylene glycol; cellulose; drug delivery; vaccine delivery; hydrogel; immunogenicity

Introduction

Because of their distinct features, certain biopolymers, particularly poly Ethylene Glycol (PEG) and cellulose, are frequently utilized in biomedical medicine for drug or vaccine delivery systems. Additionally, biopolymer-based drugs and vaccines have adjuvant characteristics that boost immune responses. For vaccine delivery and immunization, various delivery methods have been investigated. However, significant drawbacks include ineffective immunogenicity and unwanted inflammatory immunogenic reactions. Therefore, creating a reliable vaccination delivery system is a major challenge. A novel class of functional polymer materials called hydrogel has exciting opportunities in the biomedical sector. The effectiveness and potential of vaccine delivery systems based on polymeric hydrogel were investigated in many research [1,2]. The compelling thing about hydrogel-based systems is how well they transmit the antigen or vaccination to the desired physiological or anatomical location, demonstrating the system's efficiency as a whole [3,4]. Moreover, they might serve as adjuvants, encouraging an immunological reaction mediated by an antigen.

A drug delivery system (DDS) is a formulation or a piece of equipment that delivers a therapeutic substance to the area where it acts without harming nontarget cells, organs, or tissues. The development of vaccination as a standard drug delivery method is a remarkable accomplishment in the biomedical field [1–4]. Vaccination has prevented the spread of infectious diseases like influenza and covid that are fatal to humans. In addition to strengthening the immune system's ability to recognize and defend against infectious diseases, vaccinations also provide a passive level of community safety by promoting herd immunity [5,6]. Biotechnological methods have significantly advanced various vaccinations, such as DNA, recombinant subunits, synthetic peptide, and nano-vaccines [3,7–10]. These vaccines are intended to trigger an immunological reaction against the pathogen mediated by an antigen. Numerous vaccine delivery systems have been developed to immunize the target site and increase immunogenicity efficiently, increasing the system's

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effectiveness [11]. Multiple methods, including polymeric systems, systems based on nanoparticles, and systems based on three-dimensional scaffolds, have been described by researchers to demonstrate their effectiveness in the administration of vaccines [12–15]. Booster doses are not required because they allow for the delayed release and delivery of antigen molecules. It also shows how pathogenic antigen molecules are successfully delivered to immune cells [16].

On the other hand, demonstrating their ability to function as an "adjuvant" was also necessary for a successful vaccination delivery method. As an adjuvant, the vaccine interacts with the human immune system to induce an immunogenic response. According to prior research, these delivery systems have shortcomings, such as challenges in delivering vaccines to target sites, an inability to sustain vaccine molecule release from the delivery system, and challenges in providing "chemically diverse antigen molecules" [4,17]. Other important considerations, such as biosafety and the delivery system's degradability, are also significant concerns [15]. Therefore, a new, better delivery method is required for vaccine delivery and adequate immunization. For essential worldwide immunization coverage, improved vaccine delivery technology and vaccine administration methodologies are crucial [18].

PEG (Polyethylene glycol) and Cellulose-based polymers are often employed in drug and vaccine delivery systems because they deliver the drugs and vaccines effectively. PEG is a well-known example of a water-soluble polymer. PEG has played a significant role in drug delivery systems since it was initially discovered in the 1950s, and the first pegylation technique was introduced in the late 1970s [19]. PEG is a conjugation with FDA approval and is non-toxic, non-immunogenic, and non-antigenic. PEG is, therefore, frequently used in drug delivery systems [20,21]. PEG also be used more regularly in drug delivery systems in the future, according to the recent trend toward biotechnological medications [22].

On the other hand, many bacteria also make cellulose, an essential structural element of plant cell walls. Cellulose is created when glucose units are linked by glycosidic linkages [23]. Cellulose has been used in many goods since the 19th century, such as gels, films, and viscosities [24]. Cellulose and its derivatives are currently employed in various biological and pharmaceutical applications due to its biocompatibility. Through functionalization, the chemical structure of cellulose is easily altered, providing additional benefits for application. Two cellulose derivatives based on chemical synthesis are cellulose ether and cellulose ester.

In contrast to cellulose ester, which is found in cellulose acetate, cellulose nitrate, and cellulose sulfate, cellulose ether includes methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxymethyl cellulose, and hydroxypropyl cellulose [25]. The most readily available commercial cellulose ether derivative is carboxymethyl cellulose (CMC). Because CMC is a polyelectrolyte, it is sensitive to pH and ionic content variations, making it the ideal cellulose derivative [26]. Water-soluble CMC is produced by attaching carboxymethyl groups to anhydrous-glucose units during a chemical reaction with chloroacetic acid [27]. Specifically for the electrostatic charges of the polymer network, it is a superabsorbent polymer with exceptional swelling capacity. The polysaccharide is anionic [28]. However, due to its high hydrophilicity, it is less stable in liquid or water [29]; adding crosslinkers can overcome this instability. As crosslinking agents in cellulose-based hydrogels, epichlorohydrin, urea derivatives, aldehyde derivatives, carboxylic acids, etc., can all be used [30]. Both a CMC membrane and a citric acid crosslinked scaffold for full-thickness healing of normal and diabetic wounds, respectively, have been developed [31,32]. The creation of a superabsorbent hydrogel based on CMC for application in wound healing was also reported by Capanema et al. [33].

For the administration of vaccines, polymeric hydrogel or cellulose-based hydrogel systems have been formulated, and more recently, the effectiveness and capability of vaccine delivery systems have been investigated in various studies. The distinctiveness of hydrogel-based systems is that they demonstrate the system's effectiveness by delivering the antigen or vaccine to the intended anatomical or physiological location, which also functions as an adjuvant and may support an antigen-mediated immune response [4,15,34–44].In comparison to other types of systems, hydrogel-based delivery systems have the following advantages: These hydrogel-based systems can be used as an alternative to the traditional needle-based administration of parental vaccines because (i) they can enhance the immune response of the delivery system to the antigen compared to free antigen, (ii) the polymers used in the hydrogels can degrade within the physiological system, and (iii) the hydrogels can enhance the immune response of the delivery system to the antigen compared to free antigen.

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However, these hydrogel-based systems can be [4,18,45–48] a comparison of the effectiveness of cellulose-based polymer versus polyethylene glycol for vaccine delivery or drug delivery application has been reviewed for the perspectives mentioned above. This review examines and evaluates the most recent developments regarding the significance of various hydrogel-based delivery methods explicitly created for effective vaccine delivery.

PEG, its derivatives, and hydrogel are often employed in drug and vaccine delivery systems because they deliver drugs and vaccines effectively. This polymer's biocompatibility led to promising vaccine delivery outcomes. PEG is a molecular Tupperware in the hydrogel system, keeping large, complicated molecules like the proteins in vaccinations, antibodies, and gene treatments apart. The PEG-based hydrogel protects proteins in vaccines against aggregation, which allows them to endure a broader range of temperature changes. By lowering the costs and health concerns connected with cold supply chains, the PEG-based hydrogel may result in financial gains, allowing more money to be allocated to developing vaccines. As most vaccines are known to be sensitive to heat and cold, this poses a significant obstacle to global immunization campaigns because the expenses associated with administering vaccination programs outweigh the costs of vaccine manufacture. Despite the many benefits, some patients who received PEG experienced anaphylactic reactions, in which the immune system creates an allergic response to the foreign substance. Anaphylaxis can cause various symptoms, from minor skin rashes to severe breathing problems, nausea, and, worst cases, unconsciousness, and instantaneous death.

On the other hand, systems with cellulose-based hydrogel have been created to administer vaccines and were recently revealed to have significant material properties. According to studies, the ability of cellulose-based hydrogels to efficiently serve as a delivery system for vaccines depends on their large cross-sectional porosity structures and viscoelastic capabilities. A vaccine molecule in the hydrogel-based approach is released once it enters the animal's body and may eventually disintegrate. The researcher has delivered the vaccine/antigen molecules using various hydrogel-based devices for transcutaneous, intramuscular, and oral immunization. It's noteworthy to note that after delivery, a cell was found to degrade the hydrogel matrix. A recent study used carboxymethyl cellulose and COVID antigenic protein at room temperature to create a microneedle-based vaccination delivery device. This technique might one day be a fascinating way to administer the COVID vaccination. This study aims to compare PEG and Cellulose-based polymers through systematic review and meta-analysis for drug/vaccine delivery systems. This review also investigated the preparation methods and properties of PEG and Cellulose-based polymers. Finally, hydrogel's efficacy and immune response were investigated to make a future decision on integrating the cellulose hydrogel system in COVID-related vaccine delivery.

Methodology

The preferred reporting items have guided a systematic review and meta-analysis to compare PEG and Cellulose-based polymers and future decision-making. The tools StArt (State of the Art through Systematic Review), R Studio, Microsoft Excel, and the recommended reporting items for systematic reviews and meta-analyses (PRISMA) statements have been utilized for modeling and data processing. The databases- Web of Science, Cumulative Index, Scopus, MEDLINE, EMBASE, The Protein Data Bank, PubMed, and Google Scholar have been utilized for the literature search. Meta-regression analyses also assess correlations between the collective prevalence and study-level covariates.

Results and Discussion

Study Design/Search Strategy: To compare Polyethylene glycol and Cellulose based polymers for vaccine delivery or drug delivery application, a systematic search strategy of a total of 702 studies, including 102 from Pub-Med, 151 from Cumulative Index, 110 from Scopus, 140 from Web of Science, 99 from Protein Data Bank, 60 from Med Line, and 40 from EMBASE, were found in publications from 1970 to 2023 (Figure 1). One hundred eight publications on inappropriate themes and of irrelevant publication type were discarded after 598 papers were screened by title and abstract after the duplicate publications had been removed. Following that, 490 studies underwent full-text screening, and 300 were disqualified for lacking experimental data. As a result, 190 papers that reported on the drug delivery method were included in the qualitative synthesis. The listed papers

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were published in various peer-reviewed scientific publications. These articles, whose publication years vary from 2000 to 2022, demonstrate a rising interest in using cellulose and cellulose derivatives as drug delivery methods.

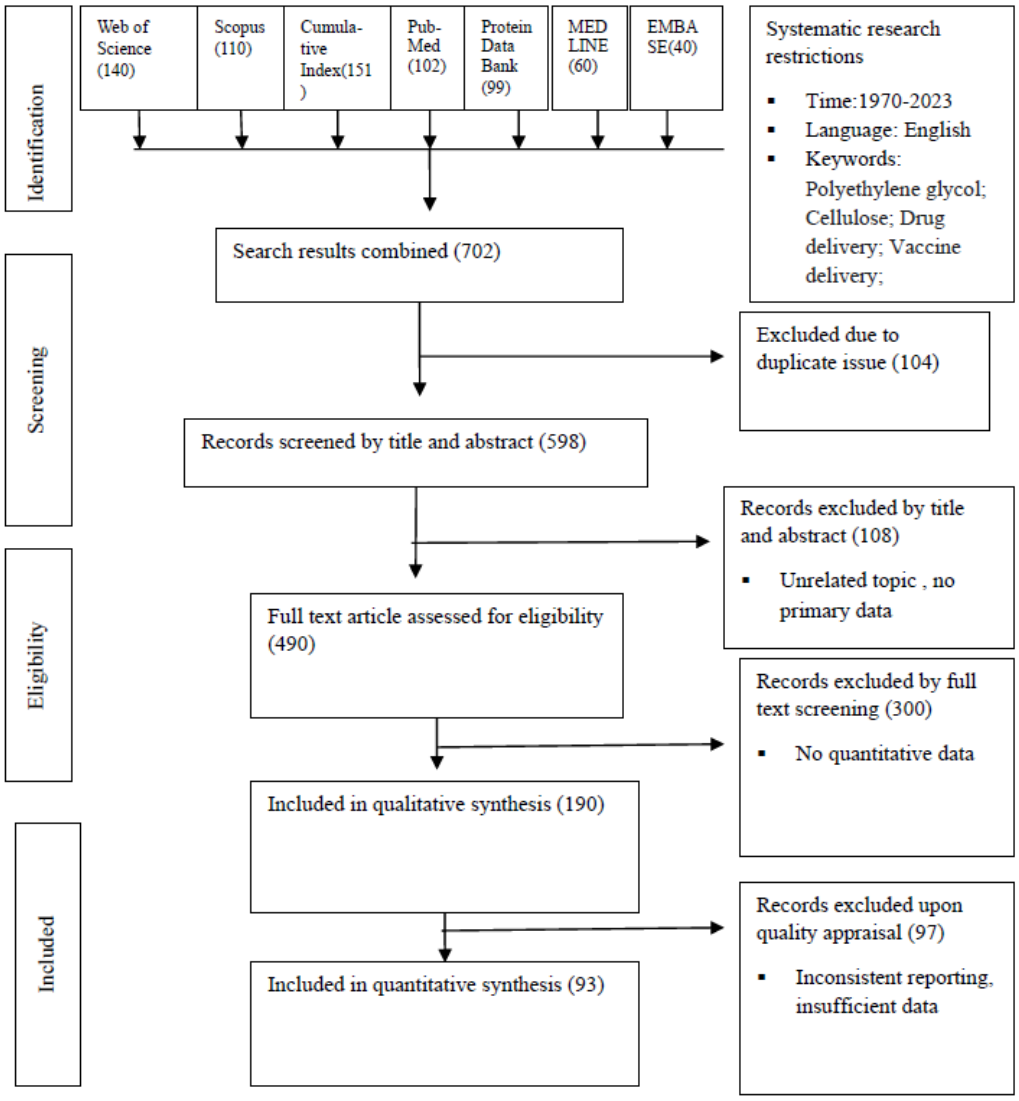

Figure 1. Systemic inclusion and search flowchart PEG and cellulose were used in drug delivery methods to date after searches in Pub-Med, Cumulative Index, Protein Data Bank, Scopus, Med Line, EMBASE, and Web of Science. Along with predetermined inclusion and exclusion criteria, every study was reviewed by its title, abstract, and full text. A further study was omitted after the experimental data quality assessment was given. The quantitative analysis comprised 93 publications, while the qualitative synthesis included 190 papers.

PEG in drug delivery system: PEG is a group of polymers that are amphiphilic [49] and have a standard structure of repeated ethylene glycol units [(CH2CH2O)n] with different molecular weights [50]. PEG is employed in medication delivery systems. PEG and its derivatives (Fig. 2A) are widely used in various fields, from cutting-edge studies in biology, pharmacology, and materials science to the large-scale manufacturing of pharmaceuticals and cosmetics. The linear PEG's functionalization category was broadened by its derivatives [51], albeit these processes may provide difficulties during synthesis. The amphiphilic copolymeric chains and other polymers created from the modified linear PEG chains were used to develop novel DDSs like polymeric micelles [52]. Peptides or other macromolecules that are vulnerable to proteolysis and have reduced immunogenicity are shielded by the "umbrella-like" structure of branched PEG structures [53] (Fig. 2 B). Multi-armed PEG blocks can be utilized to build cross-linked networks, such as hydrogels. In contrast, comb-like PEGylated

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copolymers (Fig. 2 C) have been found to enhance gas separation performance. Figs. 2 D and E shows the Y-shaped PEG and comb-like PEG copolymer.

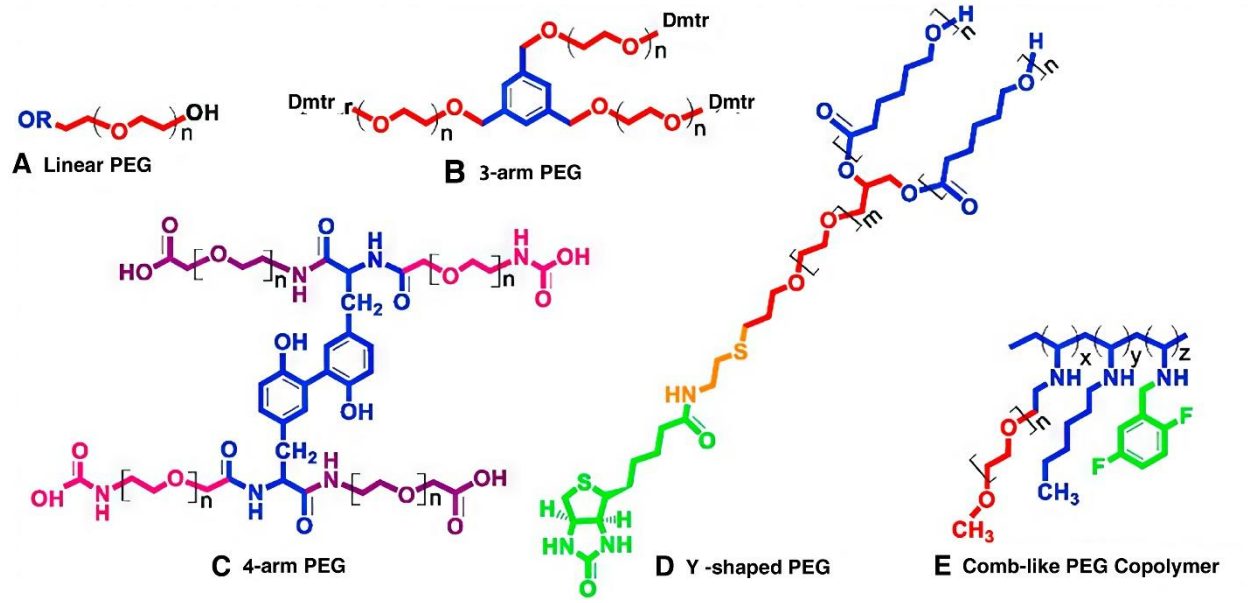

Figure 2. A. Different linking methods, including linear, armed, Y-shaped, and comb-like connections, can be used to construct different PEG variants [56]; B: Linear and branched PEG have varying enzymatic resistance; and C: Comb-like copolymeric networks containing PEG were used to generate the PES-g-PEG membrane; D: Y-shaped PEG; E: comb-like PEG copolymer [55].

With hydrogel, various vaccine delivery systems have been created. A thermosensitive hydrogel-based vaccine delivery system was developed using the polymers PLGA and PEG for the model antigen ovalbumin. For this hydrogel-based system, the sol-gel transition temperature was around 320C [57]. A hydrogel-based bio bullet for the delivery of ballistic vaccines has been developed. Thermoplastic degradable bio bullets consisting of a poly (ethylene glycol) hydrogel were synthesized utilizing photopolymerization to administer the bacterial vaccine to the bison. These hydrogel-based bio bullets have encapsulated live Brucella abortus strain vaccines and show noteworthy survival [58]. The PEG-based hydrogel has typically been regarded as an effective vaccine delivery technology [58–61]. The injectable hydrogel-based PCL and PEG administration technique developed by Wu et al. (2012) [62] showed notable antigen-mediated immunogenicity. A penta block co-polymer made of PEG, PCL, and PLA was also used to create an injectable hydrogel for prolonged vaccine release. This hydrogel demonstrated a significant ability in the context of an immunological response driven by an antigen [63]. The delivery of immunological checkpoint inhibitors, however, has been made possible by the development of a tumor vaccine that causes tumor-infiltrating CD8+ T-cells and a vaccine system with PEG-b-poly (L-alanine), both of which have been successful for immunotherapy related to B16F10 melanoma [64].

The structural aspects of PEG-based hydrogels, including swelling properties, tensile strength, and molecular transport properties, have been extensively studied. This investigation found that modest molecular weight medications could be converted into PEG-based controlled release systems containing big biomacromolecules such as nucleic acids, peptides, and proteins [65–70]. The stability and capability of releasing the correct dosage of the active substance of PEG hydrogels are necessary for obtaining a drug's desired therapeutic efficacy [71–73]. How soon an active substance is released from PEG-based hydrogels depends on several parameters, including the method used to load the drug, its size, molecular properties, the dosage required for administration, and the release profile [74–76]. The most crucial characteristic of PEG that qualifies it for usage in controlled release systems is its resistance to proteins (Figure 3) [77–79]. Due to the previously described property, PEG chains on the surface of cells slow down physiological processes such as endocytosis, phagocytosis, liver effects, and adsorptive processes, allowing therapeutic proteins to bind to them to circulate for a more extended period [83,84].

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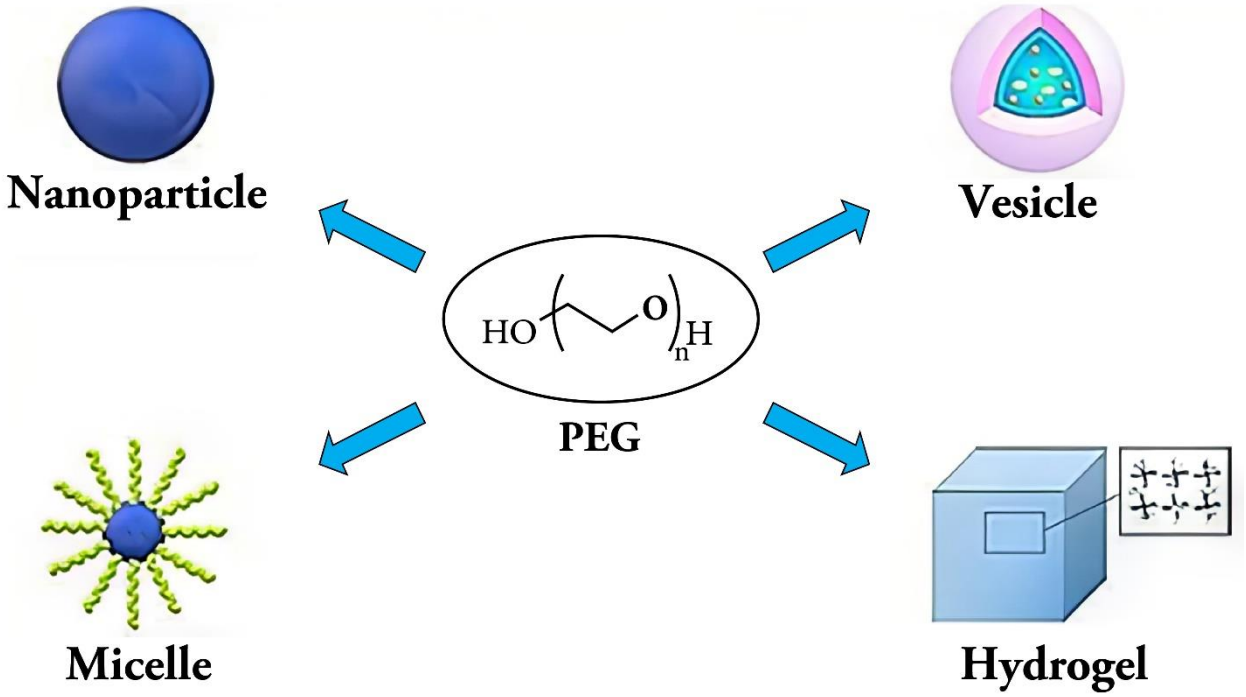

Figure 3. Controllable and sustainable antidiabetic drug delivery systems [85].

Problems with PEG Polymers

PEG and PEGylated compounds are increasingly used in pharmacological research and medical applications but also have many possible adverse effects. The following categories can be used to classify the potential negative consequences that PEG could have: The polymer itself may have undesirable side effects in the body or byproducts created during synthesis that cause hypersensitivity. Unexpected alterations in the pharmacokinetic behavior can also occur with PEG-based carriers. In addition, a conflict results from PEG's non-biodegradability combined with its very simple destruction when exposed to oxygen. Below, we will review the potential downsides and their importance to using PEG as a drug delivery mechanism.

PEG has been found to have the propensity to cause blood clotting and cell clumping, which results in embolism, according to a 1950 study. PEG has been found to have the propensity to cause blood clotting and cell clumping, which results in embolism, according to a 1950 study. According to this study, PEG and blood interact unspecific [86]. Since then, evidence has emerged demonstrating that PEG, which is not supposed to exhibit any opsonization, can also induce specific. According to research, PEG's adverse effects frequently result from complement activation, which sets off hypersensitivity reactions (HSR) that might result in anaphylactic shock[87,88]. When PEG is administered orally as an analgesic to patients in preparation for a colonoscopy, hypersensitivity responses can happen in both situations. In general, decreasing gastrointestinal adsorption can be accomplished by increasing the molar mass of PEG [86]. Another possible immunological response that can happen when PEG is present is the phenomenon of accelerated blood clearance (ABC). Dams and his team discovered the concentration of PEG liposomes in rats to be much reduced after 4 hours compared to the first injection [from (52.6-3.7)% to (0.6-0.1)% after the 2nd injection] [89]. Later, Kiwada et al. found that the ABC phenomenon also occurred when the second injection was administered within five days after the first. According to this result, injecting PEGylated liposomes first can alter the circulation time of PEG liposomes that are repeatedly injected [90].

Furthermore, it was found that previously supplied PEG-containing micelles with a minimum particle size of 30 nm may similarly promote the ABC reaction, demonstrating that the size of the

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PEGylated particles is a crucial element in the process [91]. On the other hand, extremely high doses of unprotected liposomes (5 mmol phospholipid per kg rat) have also been connected to improved blood clearance [92]. This result demonstrated that in addition to PEG, the carrier's size and surface are also considered when estimating the phenomena's induction and scope [93].

DDDs with Cellulose Bases: Contrarily, the cellulose-based hydrogel is widely and successfully utilized in various drug delivery systems. Creating cellulose-based hydrogels is made straightforward by the two methods outlined below [94].

i. Physical contacts, such as hydrogen bonds, van der Waals interactions, mechanical chain entanglements, and hydrophobic or electronic associations;

ii. Chemical cross-linking, such as utilizing crosslinking agents. Rather than cellulose-solvent interactions, preferential cellulose-cellulose contacts led to the self-association of cellulose chains. This resulted in the physical gelation, typically accompanied by a micro-phase separation. Figure 4 shows swollen, transparent, coagulated cellulose hydrogels that have undergone chemical gelation in addition to disruption of the self-association and packing of cellulose chains are more porous, have a more homogeneous morphology, have lower crystallinity, have higher swelling degrees, and have a higher affinity for water vapor adsorption.

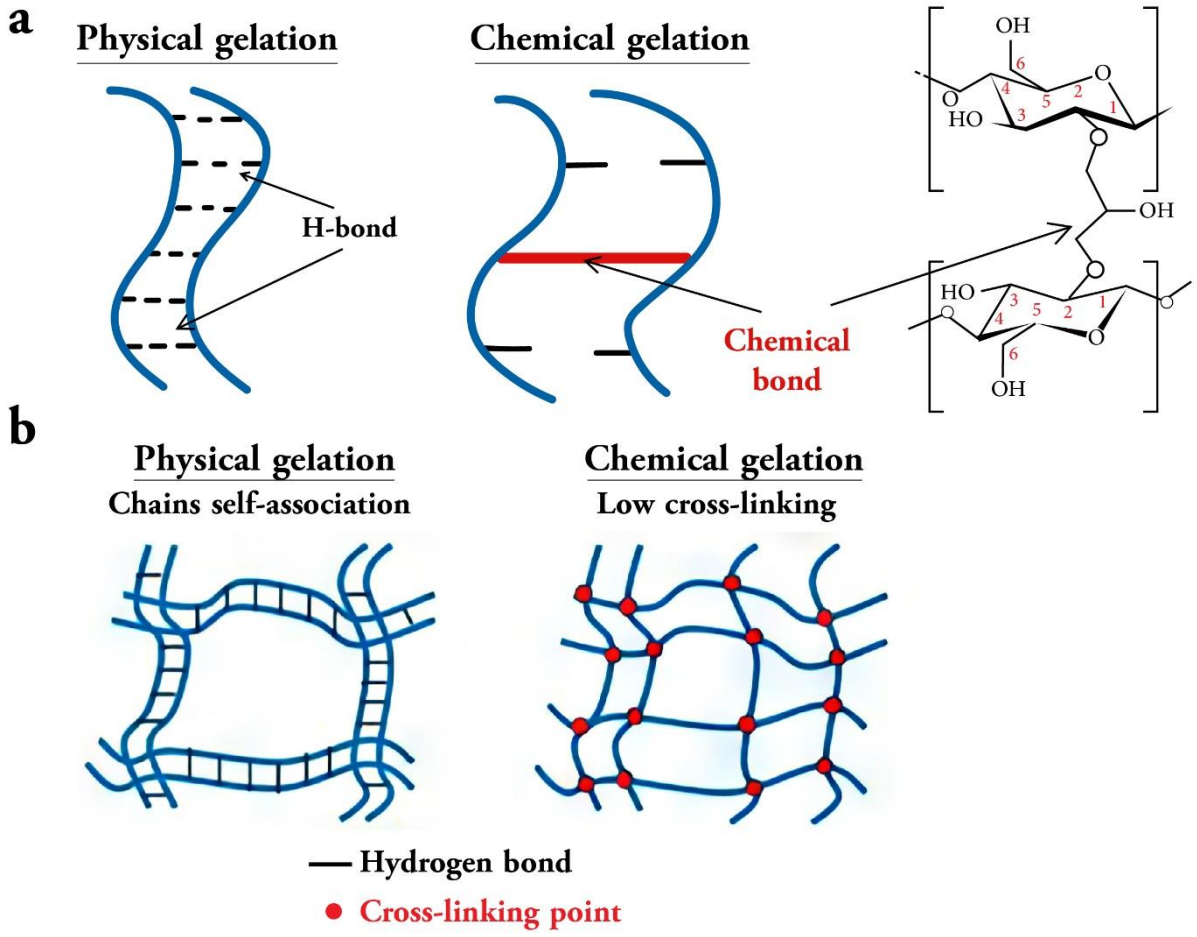

Figure 4. (a) depicts a schematic of the topology of physical and chemical cellulose gels; (b) depicts how networks emerge in cellulose solutions through physical gelation brought on by chain self-association and chemical cross-linking [95].

The two preparation techniques discussed above (physically and chemically) produce hydrogels with various topologies and swelling levels, reflected in their ability to load and release drugs. Chemically crosslinked hydrogels have an advantage over physically self-assembled hydrogels; thus, they have a greater capacity for drug storage and a faster drug release rate [96]. When cellulose and the cross-linker are used in the proper proportions, it is possible to produce cellulose hydrogels with exact control over morphology and porosity.

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Depending on the type of functional groups, a cellulose derivative can produce physical hydrogels or cross-linked chemical hydrogels. Hydrogen bonds, ionic interactions, or even hydrophobic forces can induce the chains of cellulose derivatives to aggregate in a physically linked hydrogel. Chemical crosslinking of cellulose derivatives uses a variety of cross-linking agents and catalysts, the most popular of which are dialdehydes, acetals, polycarboxylic acids, epichlorohydrin, and poly epichlorohydrin [94]. Cellulose ether is the most widely used cellulose derivative in the pharmaceutical sector for the present drug formulations.

Methylcellulose (MC), carboxymethylcellulose (CMC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), and hydroxypropyl methylcellulose (HPMC) are among the excipients that are most frequently used among them [26]. Like other hydrophilic compounds, cellulose ether can gel in the presence of a lot of water. The capacity to administer the drug even in a specific environmental stimulus is another benefit of cellulose ether hydrogels [97]. They also provide the properties needed for a targeted and sustained release of the medication over an extended period. Additionally, they are biocompatible and biodegradable. Due to its main characteristics, including hydrophilicity, bioadhesive, pH sensitivity, and non-toxicity, CMC is recognized as the most often used cellulose ether in drug delivery systems and other biomedical applications. CMC in drug delivery systems can lessen the drug's crystallization or degradation and increase drug release frequency by accelerating drug diffusion or the rate of polymer erosion/degradation [98]. Ethyl cellulose (EC) is often utilized in controlled-release formulations because of its hydrophobic characteristics (Figure 5).

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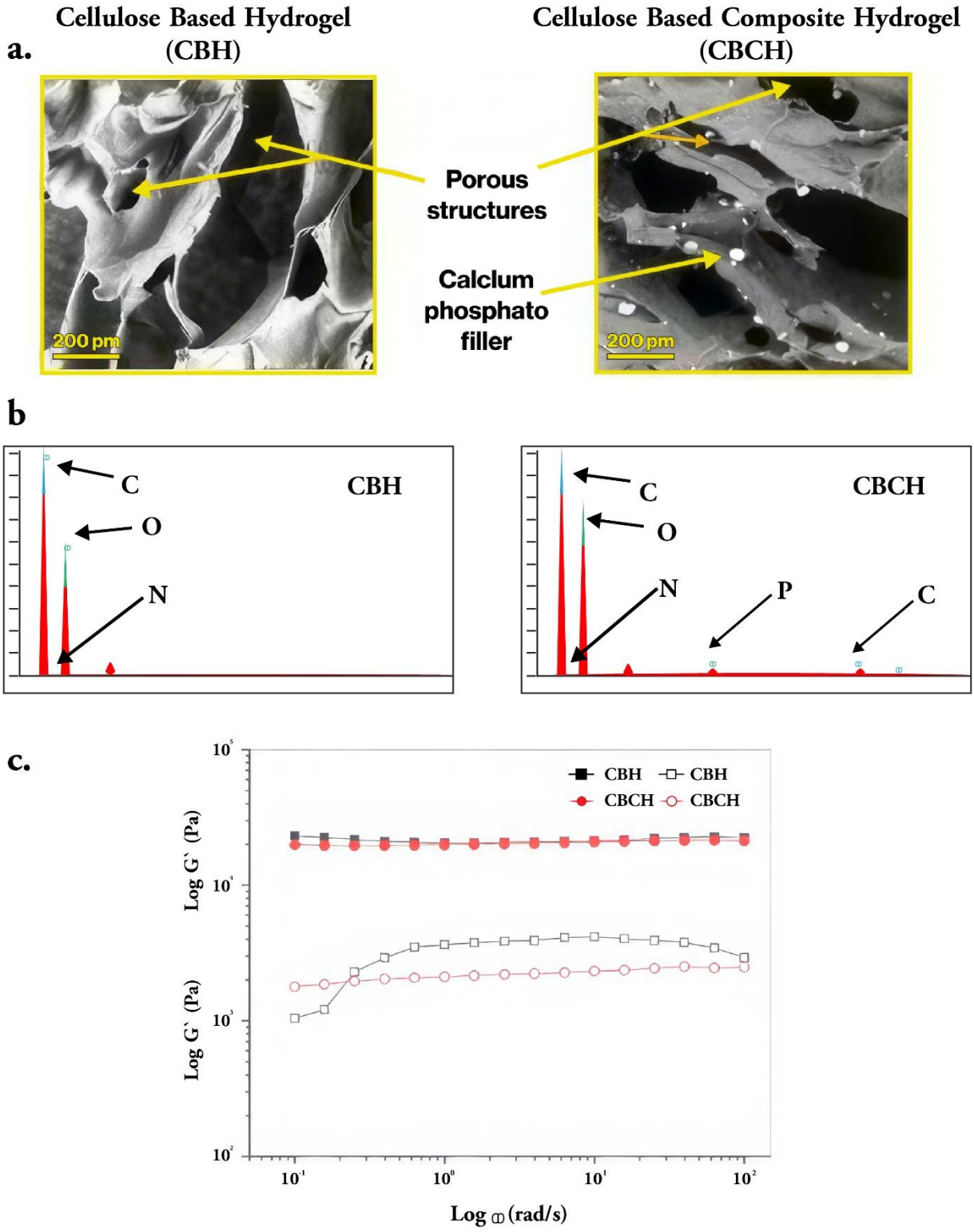

Figure 5. The characteristics of calcium-filled cellulose-based composite hydrogels (CBCH) and cellulose-based hydrogels (CBH). Using SEM cross-sectional images, porous structures are shown in (a); cellulose and calcium are confirmed to be present by SEM-EDX in (b); and the rheological properties of the hydrogels (storage modulus [filled boxes] and loss modulus [open boxes]) are shown in (c) [99].EC is frequently used as a coating agent and a biodegradable polymer in drug-release formulations, primarily for colonic diseases. The mechanical properties of films formed from various polysaccharides that exhibit increased fragility due to their highwater swelling capacity can also be improved using EC. Many pharmaceutical formulations use HPMC because it is biocompatible, has properties that make it easier to hydrate and create gels, and has regulatory approval on a global basis. Because HPMC typically extends the time of drug release, it is used in the design of

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hydrodynamically balanced systems for the particular distribution of drugs to the stomach [100]. Due to its mucoadhesive properties, have also been tested in several oral delivery systems [101].

Moreover, HPMC can make barrier-coated reservoir-style devices for drug administration systems. When a reservoir device releases medication, the coating thickness determines the timing [102]. A biodegradable and biocompatible polymer with shape memory and a unique hydrophilic/hydrophobic transition in response to environmental factors like pH, temperature, pressure, light, magnetic fields, or electric fields is called hydroxypropyl cellulose (HPC). HPC was used to make thermoresponsive hydrogels for the controlled distribution of hydrophilic medications [103]. A strong acid catalyzes the esterification of hydroxyl groups with various organic acids to produce cellulose ester. In the pharmaceutical sector, the most often used esters include cellulose acetate (CA), cellulose nitrate, cellulose acetate phthalate (CAS), hydroxypropylmethylcellulose phthalate (HPMCP), and hydroxypropyl methylcellulose acetate succinate (HPMC-AS). These esters can create beneficial films and coatings and are insoluble in water [104]. Additionally, cellulose esters possess properties including non-toxicity, stability, gastrointestinal tract abstinence, and relatively highwater permeability that are required for drug delivery systems [105].

Drug delivery systems (DDS) use cellulose derivatives as hydrogels to enhance the controlled release of drugs, which mainly relies on external stimuli, such as body temperature and various pH ranges in different body parts [97]. Stimulus-responsive cellulose hydrogels undergo considerable changes in their network structure, swelling level, permeability, and other properties when subjected to external stimuli. Additionally, these substances display switchable sol-gel transitions. Hydrogels are often classified as physically, chemically, or physiologically sensitive based on how they react [106,107] (Figure 6). Chemical substances, ionic variables, light, pressure, temperature, and other factors are examples of physical, chemical, or biological stimuli. Proteins, enzymes, glucose are examples of biological stimuli and electric or magnetic fields are examples of physical stimuli.

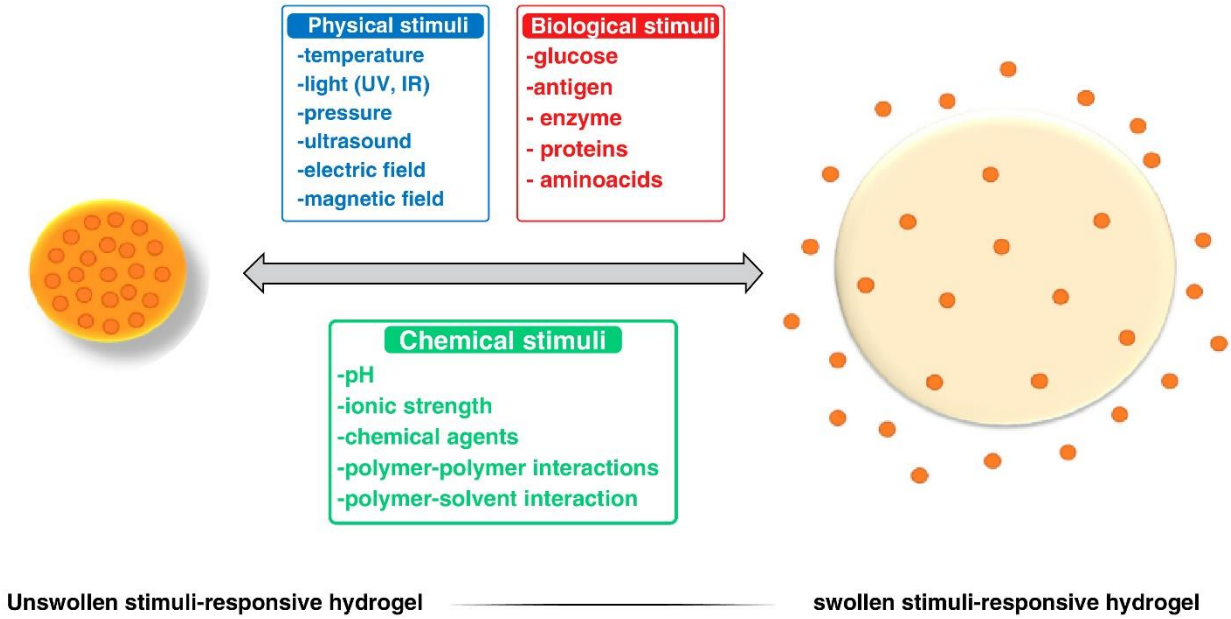

Figure 6. Hydrogels that respond to stimuli are depicted schematically [108].

Smart hydrogels' morphological and functional features, which alter in response to varied environmental stimuli, are essential for applications in drug delivery systems. These hydrogels create systems for regulated, continuous medicine delivery with few adverse effects [109–114]. Table 1 demonstrates cellulose-derived hydrogels' effectiveness in the controlled and sustained release of medicines.

Table 1.

Derivatives of Cellulose	Drugs	Action/Treatment	Ref.

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Methylcellulose	Cyclosporine	Continuous brain delivery	[115]
	Erythropoietin	After a stroke, delivery to the brain for endogenous stem cell activation	[116]
Carboxymethylcellulose	Amoxicillin	Excellent gram-positive bacterial antibiotic*Staphylococcus aureus*	[117]
	Acyclovir	regulated medication delivery systems	[118]
	Diclofenac	Skin injuries	[119]
	Nonivamide	Enhanced skin distribution and permeability	[120]
	Berberine	Safeguard healing tissue after surgery while executing a controlled medication release	[121]
	Propolis	Wound remedial	[122]
	methotrexate	Colorectal cancer	[123]
Hydroxyethyl cellulose	Eugenol	E_cientbacteriostasis against Escherichia coli	[124]
	Isoliquiritigenin	System for transdermal distribution	[125]
	Cellulose based sponges	Rehydration of vaginal cavity	[126]
Hydroxypropyl cellulose	Lidocaine	Encourage the use of a planned, regulated drug	[127]
	Ofloxacin	Gastro-retentive	[128]
Hydroxypropyl methylcellulose	Etoricoxib	Acute or chronic sickness	[129]
	Fluconazole	Fungus skin infections	[130]
	Mepivacaine	Relieve localized discomfort while executing a controlled medication release	[131]
	Propranolol	Boost percutaneous penetration	[132]
Sodium carboxymethyl cellulose	Fluorescein isothiocyanate-labeled dextran	Nasal treatment	[133]
Cellulose acetate	Nanocapsules	antimicrobial activity against Escherichia and Staphylococcus species	[134]
Cellulose acetate phthalate	Powder-form Cholera vaccination	Cholera	[135]

However, some studies have shown that cellulose-based hydrogels have developed into an efficient method for delivering vaccines since they have been shown to have significant cross-sectional porosity structures and viscoelastic properties [136,137]. To create vaccine delivery systems, such as vaccine bullets, and other biomedical systems, a variety of cellulose derivatives, such as ethyl cellulose (EC), methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), and ethyl hydroxyethyl cellulose (EHEC), have been used [138,139]. The model antigen was delivered using hydrogel microparticles composed of polyacrylic acid and ovalbumin bacterial nanocellulose. This work has reported a significant antigen-mediated immune response by producing anti-Ova-IgG in the intestinal region of mice with high entrapment efficiency and ovalbumin release by hydrogel microparticles [140]. In a similar work, an antigen-specific immune response was successfully elicited by activating cells that produce interferon using a delivery approach involving nanocellulose hydrogel and the antigen. A significant amount of cellular penetration and vaccine distribution by this nano cellulose-based technique was shown by the cell itself, which noticed that the hydrogel matrix had degraded following the delivery of the vaccine [141]. Using carboxymethyl cellulose at room temperature, Kim et al. recently created a microneedle-based vaccine delivery method for the SARS-CoV2 antigenic protein [142]. It might eventually transform into an exciting SARS-CoV2 vaccine delivery method.

Biocompatibility and biodegradability, properties of PEG-based and Cellulose-based polymer:

Biocompatibility and Biodegradability: Biocompatibility refers to the ability of a material to interact with biological systems without causing any adverse effects. Biodegradability, on the other

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hand, refers to the power of a material to be broken down by biological processes into smaller components that can be metabolized and eliminated from the body. In drug delivery applications, biocompatibility and biodegradability are important properties that determine the safety and effectiveness of the drug delivery system.

PEG-Based Polymers: PEG-based polymers are known for their excellent biocompatibility and low toxicity, which make them attractive for drug delivery applications. PEG is a water-soluble, non-ionic polymer that is inert in biological systems, and the FDA has approved it for use in drug delivery applications. PEG-based polymers have been extensively studied for their biocompatibility in vitro and in vivo, and they have been shown to have minimal toxicity and immunogenicity. The biodegradability of PEG-based polymers is a controversial topic in the scientific community. While PEG itself is non-biodegradable, PEG-based polymers can be designed to be biodegradable by incorporating hydrolytically-cleavable linkages into the polymer backbone. However, the degradation rate of PEG-based polymers can be slow, accumulating polymer degradation products in the body. This can potentially cause toxicity issues, although the extent of this risk is still under investigation.

Cellulose-Based Polymers: Cellulose-based polymers are also known for their biocompatibility and biodegradability, which make them attractive for drug delivery applications. Cellulose is a natural polymer found in plants cell walls, and it is non-toxic and biodegradable. Cellulose-based polymers have been extensively studied for their biocompatibility in vitro and in vivo, and they have been shown to have minimal toxicity and immunogenicity. The biodegradability of cellulose-based polymers depends on the specific polymer and environmental conditions. Cellulose-based polymers can be designed to be biodegradable by incorporating hydrolytically-cleavable linkages into the polymer backbone. The degradation rate of cellulose-based polymers can be accelerated by modifying the polymer structure or using specific enzymes to catalyze the degradation process.

PEG-based and cellulose-based polymers are known for their biocompatibility and biodegradability, making them attractive for drug delivery applications. PEG-based polymers have excellent biocompatibility and low toxicity, but their biodegradability is controversial. Cellulose-based polymers are also highly biocompatible and biodegradable. Still, their degradation rate highly depends on the specific polymer used and the environmental conditions. Both polymers are widely used in drug delivery applications due to their biocompatibility and biodegradability properties.

The pharmacokinetic properties of PEG and Cellulose-based polymer:

G (polyethylene glycol) and cellulose-based polymers are widely used in pharmaceuticals as excipients, inactive substances added to a medication to improve its physical and chemical properties or aid in drug delivery. The pharmacokinetic properties of these polymers can vary depending on their molecular weight, structure, and formulation.

PEG-based polymer:

Absorption: PEG is not absorbed systemically after oral administration and has low permeability through the skin. However, it can enhance the absorption of other drugs when used as a co-solvent or surfactant.

Distribution: PEG has a considerable molecular weight and does not cross the blood-brain barrier or accumulate in most tissues. It is distributed mainly in the extracellular fluid and is eliminated primarily through the kidneys.

Metabolism: PEG is eliminated intact in the urine since the body does not digest it.

Elimination: PEG is eliminated primarily by renal clearance, with a half-life of about 4 to 6 hours.

Cellulose-based Polymers:

Absorption: After oral treatment, cellulose-based polymers are poorly absorbed from the digestive system. They can swell and form a gel-like matrix, slowing drug release and improving their bioavailability.

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Distribution: Cellulose-based polymers are not anticipated to cross the blood-brain barrier or accumulate in most tissues due to their high molecular weight. They are distributed mainly in the extracellular fluid and are eliminated primarily through the kidneys.

Metabolism: Cellulose-based polymers are not metabolized in the body and are excreted unchanged in the urine.

Elimination: Cellulose-based polymers are eliminated primarily by renal clearance, with a half-life of several hours to days, depending on the molecular weight and formulation.

PEG and cellulose-based polymers have similar pharmacokinetic properties, with low systemic absorption, mainly extracellular distribution, no metabolism, and renal elimination. However, their specific properties and effects on drug absorption and delivery can vary depending on their molecular weight, formulation, and use as pharmaceutical excipients.

Physicochemical properties of PEG and Cellulose Based Polymer:

PEG (polyethylene glycol) and cellulose-based polymers are widely used in various industries, including pharmaceuticals, food, and cosmetics. The physicochemical properties of these polymers can vary depending on their molecular weight, degree of polymerization, and formulation. Here are some of the critical physicochemical properties of PEG and cellulose-based polymers:

Solubility: PEG is soluble in various organic solvents, such as ethanol, methanol, and chloroform, as well as water. In contrast to most organic solvents, cellulose-based polymers can expand and create a gel-like matrix in water, which can be employed for the controlled release of medications.

Viscosity: PEG has a low viscosity at room temperature and can become semi-solid or liquid as its molecular weight increases. Also, cellulose-based polymers are typically high-viscosity solids at room temperature and must be heated or a plasticizer.

Thermal properties: PEG has a low melting point and can easily melt or mold into different shapes. Cellulose-based polymers have a higher melting point and are typically processed by dissolving them in a solvent and then casting or spray-drying the solution.

Chemical stability: PEG is a stable polymer resistant to chemical degradation, oxidation, and hydrolysis. Cellulose-based polymers can be susceptible to hydrolysis and enzymatic degradation in certain conditions.

Half-life, circulation time, maximum release, maximum percentage of loaded drug released, and the burst release properties of PEG and Cellulose based hydrogel:

Several studies are comparing the properties of PEG-based polymers and cellulose-based hydrogels for drug and vaccine delivery systems. Here are some key findings from these studies: **Half-life:** PEG-based polymers have a longer half-life than cellulose-based hydrogels. PEG is more resistant to enzyme degradation and other biological processes. For example, a study comparing PEG and cellulose-based hydrogels for insulin delivery found that the PEG-based system had a half-life of 16.2 hours, while the cellulose-based system had a half-life of 7.2 hours [143].

Circulation time: PEG-based polymers have a longer circulation time than cellulose-based hydrogels. This is because PEG is more hydrophilic and less likely to be cleared by the reticuloendothelial system. For example, a study comparing PEG and cellulose-based hydrogels for drug delivery found that the PEG-based system had a circulation time of 11 hours, while the cellulose-based system had a circulation time of 4 hours [144].

Maximum release: The maximum release of a drug or vaccine from a delivery system depends on several factors, including the polymer's or hydrogel's properties. In general, PEG-based polymers have a higher maximum release than cellulose-based hydrogels. For example, a study comparing PEG and cellulose-based hydrogels for vaccine delivery found that the PEG-based system had an ultimate release of 83%. In comparison, the cellulose-based system had a maximum release of 50%.

Maximum percentage of loaded drugs released: The maximum percentage of loaded drugs released from a delivery system is also higher for PEG-based polymers than for cellulose-based hydrogels. For example, a study comparing PEG and cellulose-based hydrogels for drug delivery found that the PEG-based system had a maximum percentage of loaded drug released of 70%, while the cellulose-based system had a maximum percentage of loaded drug released of 50% [144].

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Burst release properties: The burst release properties of a delivery system refer to the initial release of a large amount of drug or vaccine when the system is first administered. In general, PEG-based polymers have a lower burst release than cellulose-based hydrogels. For example, a study comparing PEG and cellulose-based hydrogels for drug delivery found that the PEG-based system had a burst release of 25%. The cellulose-based system had a burst release of 80% [144]. These studies suggest that PEG-based polymers have several advantages over cellulose-based hydrogels for drug and vaccine delivery systems. These include longer half-life, longer circulation time, higher maximum release and maximum percentage of loaded drug released, and lower burst release properties.

Double network hydrogels, injectable hydrogels, sliding hydrogels, conductive hydrogels, responsive hydrogels, and nanocomposite hydrogels:

PEG and cellulose-based hydrogels have been extensively studied and developed for various biomedical applications. Here is a comparison of these hydrogels' current development**s:** Both PEG and cellulose-based hydrogels have been developed as double network hydrogels (Fig. 7). These hydrogels have two interpenetrating networks that improve mechanical properties, such as high toughness and strength. A study reported that a PEG-based double network hydrogel showed excellent mechanical properties and biocompatibility for cartilage tissue engineering [145]. Similarly, a cellulose-based double network hydrogel showed superior mechanical properties and biocompatibility for wound healing applications [146]. Injectable hydrogels: PEG-based hydrogels have been extensively developed as injectable hydrogels due to their thermosensitive properties. They can form a gel at body temperature upon injection, allowing for minimally invasive delivery of therapeutics. A study reported that an injectable PEG-based hydrogel loaded with mesenchymal stem cells showed promising results for spinal cord injury treatment [147].

In contrast, cellulose-based hydrogels have limited applications as injectable hydrogels due to their relatively low gelation temperature. However, recent studies have reported the development of cellulose-based injectable hydrogels with improved gelation properties [148]. Sliding hydrogels: Sliding hydrogels mimic the lubrication properties of synovial fluid, reducing friction and wear between cartilage surfaces. PEG-based sliding hydrogels have been developed for cartilage tissue engineering, and studies have reported their lubrication properties and biocompatibility [149]. Similarly, cellulose-based sliding hydrogels have also been developed for cartilage tissue engineering, and studies have reported their tribological properties and biocompatibility [150].

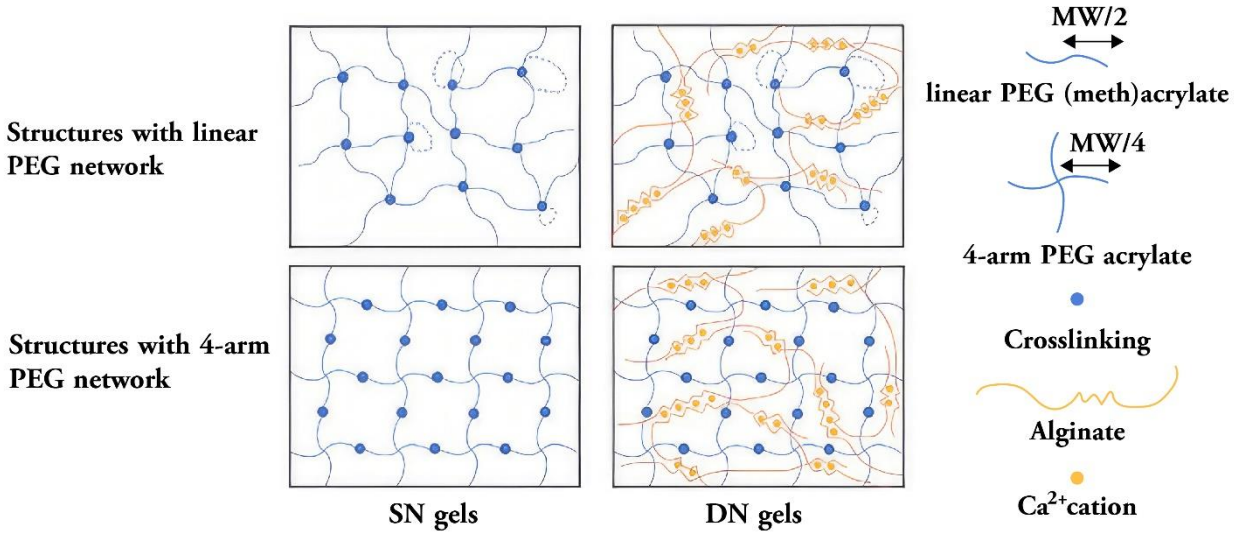

Figure 7. PEG-based Single and Double Network structures of hydrogels [151].

Conductive hydrogels: Conductive hydrogels are designed to mimic the electrical conductivity of native tissues, such as neural and cardiac tissues. PEG-based conductive hydrogels have been developed for neural tissue engineering, and studies have reported their electrical properties and biocompatibility [152]. Similarly, cellulose-based conductive hydrogels have also been developed for

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neural tissue engineering, and studies have reported their electrical properties and biocompatibility [153]. Table 2 shows the properties of PEG-based and cellulose-based hydrogels in drug and vaccine delivery systems.

Responsive hydrogels: Responsive hydrogels are designed to respond to specific stimuli, such as temperature, pH, or light. PEG-based responsive hydrogels have been developed for drug delivery and tissue engineering applications. A study reported the development of a PEG-based hydrogel that responds to near-infrared light for on-demand drug release [151]. Similarly, cellulose-based responsive hydrogels have also been developed for drug delivery and tissue engineering applications. A study reported the development of a cellulose-based hydrogel that responds to pH for sustained drug release [153].

Nanocomposite hydrogels: Nanocomposite hydrogels incorporate nanoparticles, such as graphene oxide or gold nanoparticles, to enhance their properties, such as mechanical strength, electrical conductivity, or drug release. PEG-based nanocomposite hydrogels have been developed for tissue engineering and drug delivery applications. A study reported the development of a PEG-based hydrogel incorporating graphene oxide nanoparticles for improved mechanical properties and electrical conductivity [154].

Table 2. Properties of PEG-based hydrogels and cellulose-based hydrogels in drug and vaccine delivery systems. .

Property	PEG-based hydrogels	Cellulose-based hydrogels
Half-life	Longer half-life due to resistance to degradation	Shorter half-life due to susceptibility to degradation
Circulation time	Longer circulation time	Shorter circulation time
Maximum release	Higher maximum release	Lower maximum release
Maximum % loaded drug released.	Higher maximum % loaded drug released.	Lower maximum % loaded drug released.
Burst release properties	Lower burst release properties	Higher burst release properties
Temperature properties	Good stability over a wide range of temperatures	Susceptible to temperature changes
pH properties	Good stability over a wide range of pH values	Susceptible to changes in pH
Double network hydrogels	PEG-based double network hydrogels suitable for tissue engineering[155]	Cellulose-based double-network hydrogels suitable for wound healing [146]
Injectable hydrogels	PEG-based injectable hydrogels suitable for sustained drug delivery [156].	Cellulose-based injectable hydrogels suitable for wound healing.
Sliding hydrogels	PEG-based sliding hydrogels suitable for cartilage tissue engineering.	Cellulose-based sliding hydrogels suitable for skin tissue engineering [157].
Conductive hydrogels	PEG-based conductive hydrogels suitable for cardiac tissue engineering.	Cellulose-based conductive hydrogels suitable for neural tissue engineering.
Responsive hydrogels	PEG-based thermo-responsive hydrogels are suitable for sustained drug delivery [158].	Cellulose-based pH-responsive hydrogels suitable for controlled drug delivery [159].
Nanocomposite hydrogels	PEG-based nanocomposite hydrogels suitable for drug delivery.	Cellulose-based nanocomposite hydrogels suitable for sensing of heavy metal ions [160]

Conclusion and Future Study Recommendation

Despite the achievements discussed in this review, there are still several challenges, Hypersensitivity, antagonism, ABC, etc., for using a PEG-based drug delivery system. The cost is also another fact to search for new DDSs. Creating materials with comparable prices, such as cellulose-based polymers, could be a feasible answer. Employing various reinforcements, such as nanoparticles, bacterial cellulose, calcium phosphates, and carbonates, with the hydrogel-based delivery device can increase the effectiveness of vaccine delivery systems and augment the animal's immune response. This composite hydrogel may also anticipate essential porosity and rheological

characteristics. As a result, additional research on the cellulose-based composite hydrogel system might be done to see how well it delivers a vaccine and is immunogenic.

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