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REVIEW

Dual-Polymer Carboxymethyl Cellulose and Poly(Ethylene Oxide)-Based Gels for the Prevention of Postsurgical Adhesions

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ABSTRACT

Postsurgical adhesions are a common complication associated with surgical procedures; they not only impact the patient's well-being but also impose a financial burden due to medical expenses required for reoperative surgeries or adhesiolysis. Adhesions can range from a filmy, fibrinous, or fibrous vascular band to a cohesive attachment, and they can form in diverse anatomical locations such as the peritoneum, pericardium, endometrium, tendons, synovium, and epidural and pleural spaces. Numerous strategies have been explored to minimize the occurrence of postsurgical adhesions. These strategies include surgical approaches, adhesiolysis, antiadhesive agents, and mechanical barriers which have demonstrated the most promise in terms of efficacy and breadth of indications. In this review, we discuss the use of physical/mechanical barriers for adhesion prevention and outline the most commonly used, commercially available barriers. We then focus on a synthetic, dual-polymer gel composed of carboxymethyl cellulose (CMC) and poly(ethylene oxide) [PEO], which, unlike the more commonly used single-polymer hydrogels, has demonstrated higher efficacy across a greater range of indications and surgical procedures. We review the formulation, mechanical properties, and mechanisms of action of the CMC + PEO dual-polymer gel and summarize findings from clinical studies that have assessed the efficacy of CMC + PEO gels in multiple surgical settings in clinics across the world. In conclusion, the CMC + PEO dual-polymer gel represents an approach to preventing postsurgical adhesions that has been commonly used over the last 20 years and could therefore serve as a foundation for research into improving postsurgical outcomes as well as a drug delivery device to expand the use of gels in surgical settings.

1 | Introduction

Postsurgical adhesions are one of the most prevalent complications of any surgical procedure, occurring in up to 50%–95% of postoperative patients [1, 2]. Typical surgical procedures cause ischemia, tissue trauma and desiccation, inflammation, and exposure to foreign bodies including fibers, sutures, staples, powder, lint, and, in some cases, intestinal contents [1, 3]. Postsurgical adhesions are pathological fibrotic linkages, or scar tissues, which develop following these surgery-induced tissue disturbances. These adhesions conjoin organs and the adjacent surfaces surrounding body cavities. In many cases, postsurgical adhesions are painless and cause no secondary complications; however, postsurgical adhesions can cause chronic pain,

organ failure, bowel obstruction, and, in female patients, infertility and episodic pain [1, 4, 5]. Furthermore, the reoperative surgeries required to incise or excise adhesions can be quite challenging and often lead to adhesion reformation, associated pain, reduced quality of life, notwithstanding the substantial financial burden that arises from treating these complications. Given the frequency of postsurgical adhesions and the potential consequences of both their formation and need for subsequent reoperative surgery, there is considerable interest in developing tools or methods that can prevent adhesion formation.

One of the challenges in developing effective prevention methods is that postsurgical adhesions can arise through different physiological mechanisms and can manifest differently among different patients or organs [4, 6]. Postsurgical adhesions develop when the loosely connected mesothelial cells lining internal organs are damaged by surgery-related trauma, exposing the basement membrane at the surgical site (Figure 1a) [5, 7]. This tissue insult can trigger cytokine-mediated inflammatory pathways and the prothrombin-mediated coagulation cascade [5], both of which promote fibroblast migration and fibrin deposition on the denuded organ surface [8–10] (Figure 1b,c). Under ideal conditions, fibrinolytic enzymes break down the fibrin into fibrin degradation products allowing for re-epithelialization of postsurgical tissue surfaces. However, if (i) fibrin deposition exceeds fibrinolytic activity and (ii) the damaged tissue surface is adjacent to another tissue surface, it can interconnect by a fibrin bridge (Figure 1d). The resulting adhesion may even become vascularized and, in some cases, innervated [4] within 10 days postsurgery [11]. Adhesions can range from a filmy, fibrinous, or fibrous vascular mass to a cohesive mass of fibrosis depending upon the local microenvironment. They can also be either (i) *de novo* or primary adhesions or (ii) reformed or secondary adhesions that form in the same place following adhesiolysis [12]. Any surgical approach to preventing adhesions must be able to target these multiple adhesion-forming pathways and the multiple types of adhesions.

A further challenge to effective adhesion prevention is that adhesions can occur on any internal organ, though the most

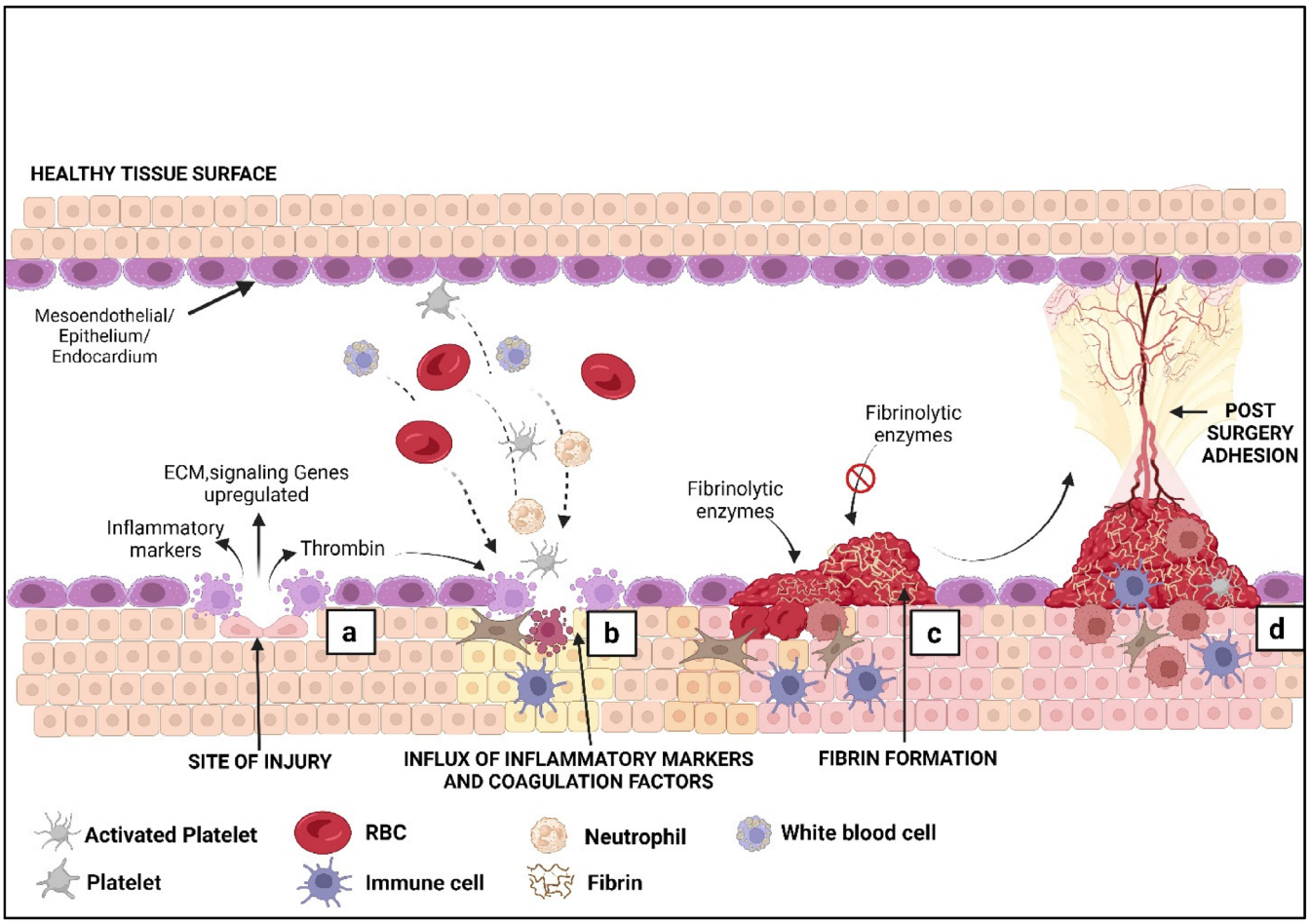


FIGURE 1 | Schematic of pathophysiology in mature stages of postsurgical adhesion formation. (a) Damage or removal of the epithelial, mesothelial, peritoneal, or endocardium layer at the site of injury triggers the adhesion process. (b) Infiltration of neutrophils, macrophages, monocytes, immune cells, inflammatory cytokines, and growth factors at the site of injury provide nidus for the healing process and promote the release of fibrin exudate. (c) Coagulation simultaneously assists in preventing blood loss and triggers fibrinogen to form fibrin monomers. The aggregation of fibrin monomers causes fibrin clot deposition and amplifies the inflammatory response. Typically, fibrinolytic and other degradative systems in the extracellular matrix degrade the fibrin clot. (d) However, with an imbalance between fibrinolysis and fibrin deposition, fibroblasts infiltrate over and within the fibrin bands or bridges and organize into permanent adhesions. The adhesion may be perfused by neovascularization and, in some cases, contain nerve tissue. (Created with BioRender.com).

extensively examined postsurgical adhesions involve the peritoneum, pericardium, epidural and intrauterine spaces, tendon synovium, pleura, and spinal nerve roots [13]. Adhesions of the peritoneal and intrauterine spaces can cause small bowel obstruction, pelvic pain, menstrual irregularities, and infertility, depending on their location and the extent of fibrous tissue involved. Adhesions often undergo neovascularization, and reports have demonstrated nerve tissue in some pelvic adhesions [14]. Conversely, adhesions of the tendon synovium can cause finger or joint stiffness and reduce the mobility of flexor tendons, resulting in the loss of a joint's normal gliding motion. In the case of surgical trauma to an intervertebral disc [15, 16], epidural adhesion to the spinal nerve roots can irritate the nerves, sensitize nociceptors and mechanoreceptors to pain, and alter nerve root excitability, all of which can cause hyperesthesia, sciatica, or lower back pain, among other complications [17, 18].

Current strategies for reducing the formation of adhesions involve a combination of surgical techniques to reduce tissue damage and pharmacological agents to inhibit inflammatory responses. First, by minimizing the amount of surgery-related tissue trauma and maintaining effective hemostasis, surgeons can reduce the amount of tissue damage and fibrin formation thereby reducing the risk of adhesion formation [19]. Ensuring that all foreign materials have been removed from the surgical site can also maximize the opportunity for healthy tissue repair mechanisms. Second, the administration of pharmacological agents that inhibit the inflammatory responses and coagulation cascade underpinning adhesion formation can further suppress adhesion formation. Despite the advantages of these techniques, the combination of minimally invasive surgery and subsequent pharmacological interventions does not appear to be adequate for preventing adhesion formation. As a result, pharmacological interventions have not yet been approved by regulatory agencies for use in reducing postsurgical adhesions. Additional techniques or interventions are therefore necessary to reduce the likelihood and potential complications of postsurgical adhesions.

In this review, we consider a third and proven effective approach to adhesion prevention: the installation of mechanical, synthetic biomaterial-based barriers to prevent direct physical contact between tissues as they heal following surgery. We discuss the general principles of antiadhesion barriers and review the types of barriers that are currently available in the field. We then focus on the advantages of a dual-polymer gel composed of the polymers carboxymethyl cellulose (CMC) and poly(ethylene oxide) (PEO). The CMC + PEO dual-polymer gel, which is marketed under the names Oxiplex, Oxiplex/IU, Intercoat, Oxiplex/SP, Interpose, MediShield, and Dynavisc, exhibits chemical properties different from other single-polymer gel-based products and has multiple indications for use in a variety of surgical procedures. Specifically, we describe the composition and mechanical properties of CMC + PEO dual-polymer gel-based barriers with an emphasis on the qualities imparted by their two component polymers. We discuss the mechanisms by which CMC + PEO dual-polymer gels reduce adhesion formation, and we then provide evidence from multiple clinical trials across a wide range of surgical procedures demonstrating the safety and efficacy of CMC + PEO dual-polymer gel.

2 | Physical Barriers for Adhesion Prevention

The use of physical barriers to reduce the risk of postsurgical adhesions is based on the principle that preventing physical contact between tissues will prevent the formation of fibrin bridges between the tissues. These barriers can include space separators, fluids, solids, or gels, any of which must (i) prevent the formation of fibrin bridges between tissues while (ii) allowing for normal postsurgical healing [20, 21]. An ideal barrier should reside at the injury site as long as required for re-epithelialization of the surgical site and then cleared from the body. Furthermore, barriers should be nonimmunogenic, biocompatible, biodegradable, and easy to use during open and endoscopic surgeries. These barriers may also be candidates for delivering antiadhesive drugs to the site of surgical injury, including fibrinolytic agents, anticoagulation agents, anesthetics, corticosteroids, antibiotics, growth factors, and anti-inflammatory agents [22]. However, the utility of physical barriers can sometimes be limited due to the lack of pliability (depending on the type of barrier), the need for absolute hemostasis, and the possible lack of compatibility with specific surgical procedures [2].

Materials that have been commonly explored as physical antiadhesion barriers include polylactic acid (PLA) [22], polyethylene glycol (PEG), PLA–PEG, hyaluronic acid (HA), alginates (ALG), oxidized regenerated cellulose (ORC), CMC, and icodextrin, a derivative of maltodextrin. Currently used physical barriers that have been approved by European regulatory bodies (i.e., Conformitè Europèene-marked) or the U.S. Food and Drug Administration (FDA) are summarized in Table 1. To date, the U.S. FDA has only approved Interceed, Seprafilm, and Adept as adhesion prevention devices, and one additional product (Intergel) that has since been withdrawn from the market. Of these, Seprafilm and Interceed have been approved for laparotomies and show an efficacy rate of 32%–55% in pre- and postmarket clinical trials [23]. However, the safety and efficacy of Seprafilm have been challenged by reports of inflammatory responses, peritonitis, foreign body reactions, and limited effectiveness in adhesion prevention [24–27], and Interceed has been reported to exhibit poor adherence to soft tissues [28] and reduced effectiveness in the presence of blood, surgical site oozing, or peritoneal fluid [29, 30]. The third FDA-approved antiadhesion barrier, ADEPT, is a colloidal osmotic agent approved for gynecological laparoscopic procedures. The FDA has not yet approved any antiadhesion product for spinal surgery. Outside the United States, commonly used barriers include Oxiplex, Dynavisc, Hyalobarrier, Hyaregen, SprayShield, Repel-CV, and Coseal [23].

2.1 | Gels

Of the various antiadhesion barriers available, gels are generally preferred over solid or membrane-based barriers due to their ease of use, viscoelasticity, biodegradability, and higher permeability to oxygen, nutrients, and waste [31, 32]. They coat exposed, denuded, or traumatized surfaces, providing improved coverage on uneven or irregular surfaces and can spatially adapt to the diverse sizes and shapes of surgical sites. Their viscoelastic properties are especially advantageous in

TABLE 1 | Commercially available physical barriers to prevent postsurgical adhesions. Barriers are listed alongside uses that have been approved by either the Conformitè Europèene (CE) or U.S. Food and Drug Administration (FDA).

Trade name (manufacturer)	Approved use in postsurgical adhesions	Consistency	Composition
Derivatives of naturally occurring polymers			
Hyalobarrier (Anika Therapeutics, Bedford, Massachusetts, USA)	Pericardium (CE)	Gel	Crosslinked hyaluronic acid
Hyaloglide (Anika Therapeutics, Massachusetts, USA; Nordic Pharma, Paris, France)	Tendon (CE)	Gel	Crosslinked hyaluronic acid
Adcon Gel (Bioscompass, Rochester, Minnesota, USA)	Tendon (CE) Peridural fibrosis (FDA)	Gel	Bioabsorbable polyglycan ester and porcine-derived gelatin
COVA + CARD (Biom'up, Lyon, France)	Pericardium, limb, and hand surgery (CE)	Solid	Bioabsorbable membranes of collagen sheets
TachoSil (Nycomed Austria GmbH, Linz, Austria)	Cardiac (FDA)	Solid	Bioabsorbable sponges of collagen (coated with human fibrinogen and human thrombin)
CorMatrix (CorMatrix, Georgia, USA)	Pericardium (FDA, CE)	Solid	Porcine extracellular matrix
Tenoglide (Integra LiveScience, New Jersey, USA)	Tendon (FDA)	Solid	Collagen-glycosaminoglycan
Interceed (Johnson & Johnson, Ohio, USA)	Peritoneum, tendon, gynecological surgeries (FDA, CE)	Solid	Oxidized regenerated cellulose absorbable adhesion barrier
Cellulose-based barriers			
Seprafilm (Sanofi Genzyme, Massachusetts, USA)	Peritoneum, pericardium, tendon (FDA, CE)	Solid	Biodegradable chemically modified sodium hyaluronate and carboxymethylcellulose (CMC)
Oxiplex (FzioMed)/Intercoat (FzioMed)/ Medishield (FzioMed, California, USA)	Peritoneal cavity, spinal, and intrauterine (CE)	Gel	CMC and poly(ethylene oxide) (PEO)
Dynavisc (FzioMed, California, USA)	Tendon/nerve (CE)	Gel	
SepraSpray (Genzyme Corporation, Massachussetts, USA)	Peritoneum	Spray	Sprayable version of Seprafilm: sodium hyaluronic acid and CMC
SprayShield (Covidien (UK)	Peritoneum	Spray	Polyethylene glycol ester amine solution and a buffer solution
Biodegradable polymers			
REPEL-CV (SyntheMed, Massachusetts, USA)	Pericardium (FDA, CE)	Solid	Polylactic acid and polyethylene glycol
SurgiWrap or CardioWrap (MastBiosurgery AG, Zurich, Switzerland)	Pericardium (FDA, CE)	Solid	Polylactic acid
Prevadh (Sofradim Production, Trevoux, France)	Abdominopelvic	Solid	Composite polymers of polylactic acid, lyophilized porcine collagen, and hydrophilic collagen
Nonbiodegradable polymeric meshes			
Gore-Tex (Gore & Associates, New Jersey, USA)	Pericardium (FDA, CE)	Solid	Expanded polytetrafluorethylene
Pegylated-based barriers			
CoSeal (Baxter Healthcare Inc., Illinois, USA)	Pericardium (FDA, CE)	Spray	Polyethylene glycol
SprayShield (Covidien-Medtronic, Minnesota, USA)	Peritoneum (CE)	Spray	Polyethylene glycol

(Continues)

TABLE 1 | (Continued)

Trade name (manufacturer)	Approved use in postsurgical adhesions	Consistency	Composition
Actamax (Actamax Surgical Materials LLC, Delaware, USA)	Abdominopelvic	Gel	Aqueous dextran aldehyde and polyethylene gylcol amine polymer
Osmotic-based barriers			
Adept (Innovata PLC., Surrey, UK; Illinois, USA)	Gynecological surgery, peritoneum (FDA, CE)	Liquid	High molecular weight dextran and 4% icodextrin
Intergel adhesion prevention solution	Withdrawn from market	Gel	Ferric hyaluronate

the unique, obstructed surgical sites involved in spine or tendon/nerve surgery, where integrating biomaterial or films can be difficult [33]. These advantages make gels one of the most versatile antiadhesion barriers, and they have been successfully used to prevent postsurgical adhesions in a variety of tissues including peritoneal, spine, intrauterine, tendon, and nerve tissues for over 20 years.

2.2 | CMC + PEO Dual-Polymer Gel

One of the more unique gel-based antiadhesion barriers is a synthetic dual-polymer gel composed of CMC and poly(ethylene oxide) (PEO), each with unique chemical properties. Like other antiadhesion barriers, the dual-polymer gel coats exposed surgical sites, thereby preventing fibrin bridge formation and connection with adjacent tissue surfaces. This gel first received European Class III Device (CE-marked) approval in July 2001, has been commercially available in Europe since 2002, and was individually approved in nearly 70 countries [19, 34].

3 | Mechanical and In Vitro Properties of CMC + PEO Dual-Polymer Gels

Unlike other gel products, which are typically based on a single polymer, CMC + PEO dual-polymer gels are a synthetic blend of the anionic polymer CMC and the neutral polymer PEO. In this section, we review the chemical composition of each of these polymers as well as the unique physicochemical properties that arise when the two polymers are mixed to form a dual-polymer gel (Table 2).

3.1 | Properties of CMC and PEO

CMC is an anionic, biodegradable linear polymer composed of repeated glucose-based units connected by 1,4-beta-glucosidic linkages. The specific physical properties of CMC depend on its degree of substitution (i.e., number of carboxymethyl groups per glucose-based unit) and corresponding molecular weight, though all forms are water-soluble, biocompatible, and classified as "generally recognized as safe" for several pharmaceutical and medical applications (Figure 2a) [19]. CMC is also a popular material in dentistry, drug delivery, and tissue engineering. It is most commonly used in its sodium salt form and has a tissue adherence property [37]. Increasing the degree of substitution increases the hydrophilicity of the CMC and disaggregation in water. In addition to different degrees of substitution, the exact formulation of CMC can vary based on the concentration of CMC in the formulation and degree of polymerization (number of repeating monomeric units) and type of molecular associations (how CMC molecules interact with other substances). The molecular weight of CMC and degree of polymerization are linked to the rheology of the solution. Polymers with a high degree of polymerization are long and complex structures and increase viscosity. The viscosity of the CMC solution also depends on the concentration or solid content of CMC used to prepare the solution and rapidly increases with the concentration. Solubilization of CMC in electrolyte media or media with solvating reduces the disaggregation and results in lower viscosity compared to those prepared in water. For instance, monovalent cations form soluble salts compared to divalent cations which form insoluble salts with trivalent cations. The texture of the gels can thereby be controlled by careful selection and addition of salts.

The second component of the dual-polymer gel, PEO, is a water-soluble, is a nonionic polymer widely used as a colloid stabilizer in pharmaceutical products (Figure 2b). Because it is hydrophilic, inert, and noninflammatory, PEO is often used as a coating for various materials and devices in medical settings [19].

Once blended together, CMC and PEO produce a gel-based antiadhesion barrier that is biocompatible, biologically inert [16, 19], and 100% synthetic [38] (Table 2). The dual-polymer gel is a viscous, flowable, lubricious, and viscoelastic material [16]. Because CMC and PEO are both water-soluble, the use of either polymer alone as an adhesion prevention system would not be feasible. However, the CMC + PEO polymer blend has unique properties that facilitate its use in surgical settings [19]. The gel is effectively retained at the application site despite patient movement or physical stress, and as described later, it effectively adheres to traumatized tissue.

3.2 | Intermolecular H-Bonding and Stabilization

The exact mechanisms underlying the association between CMC and PEO remain unknown. The current hypothesis is that the dual-polymer gel is stabilized by intermolecular hydrogen bonds that form between the carboxyl residues of CMC and the electronegative oxygen in the ether bond of PEO (Figure 2c) [39, 40]. Water molecules can also efficiently link

TABLE 2 | Components of CMC + PEO dual-polymer gel and its associated physicochemical properties.

Components	Role
Carboxymethyl cellulose (CMC)	• Interacts with the oligosaccharide side chain of the mucin structure on mucus or tissue surface, providing stronger tissue adherence than PEO. • Higher adsorbent capacity for blood proteins relative to PEO. • May autoactivate blood clot factor XII [35, 36]. • Forms hydrogen bonds with the electronegative oxygen atom in the ether bond of PEO.
Poly(ethylene oxide) (PEO)	• Minimizes protein, fibrin, and cytokine deposition on the surfaces of damaged and adjacent tissue via a steric repulsion force generated by extensive hydration in water coupled with the dipole moment. • Separates tissues/nerves from surrounding tissue, fluid, and pain irritants, thereby reducing postoperative pain by reducing exposure to the nerve roots as well as the nerves. • Permits CMC to settle into the uneven surface of the injury or trauma region with more interpenetration on the mucosal surface and improve the tissue–surface–antiadhesive barrier surface. • Forms hydrogen bonds with the carboxyl residues of CMC.
Calcium chloride	• Maintains osmolality. • Forms ion complexes due to intra- and intermolecular electrostatic bonds with carboxylate ions in CMC. These complexes minimize the mobility of CMC and increase its viscosity, residence time, and tissue adherence.

the polymer chains via hydrogen bonds, leading to both inter- and intramolecular crosslinking and further stabilization of the dual-polymer gel. The presence of hydrogen bonding also increases the dipole moment of the molecular system. CMC + PEO dual-polymer gels are further stabilized using calcium chloride [20]. The calcium ions not only maintain osmolality but also form intra- and intermolecular electrostatic complexes with the carboxyl groups in the CMC polymer (Figure 2d). These ionic complexes minimize the mobility of CMC and increase its viscosity, residence time, and tissue adherence properties [39]. Because of its unique structure and electrostatic, reversible cross-linkages, the CMC + PEO dual-polymer gel provides effective tissue protection while still facilitating clearance in a biological environment [39].

3.3 | In Vitro Physicochemical Properties

The properties of the CMC + PEO dual-polymer gel vary with the ratio of CMC and PEO, their degrees of substitution (i.e., number of carboxymethyl groups per glucose-based unit), degree of polymerization (number of repeating monomeric units), solid content, and types of association. In general, the success of any physical barrier is dependent principally on the mechanical stability and resorption time of the gel. The CMC + PEO dual-polymer gel exhibits a consistent set of physicochemical properties that have been robustly characterized in in vitro settings.

3.3.1 | Phase Separation

The CMC + PEO dual-polymer gel is a heterogeneous mixture that can be microphase separated via centrifugation (Figure 3a). Centrifugation studies typically add methylene blue, which has more affinity for CMC than PEO, to the dual-polymer gel. Following centrifugation, methylene blue can be observed in the lower phase of the tube, while the upper PEO layer remains colorless [19].

3.3.2 | Protein Adsorption

Blood plasma proteins including albumin, fibrinogen, and gamma globulin exhibit preferential affinity for CMC over PEO. In phase separation studies, these plasma proteins overwhelmingly partition into the CMC phase, with only 0.43%, 0.24%, and 0.30% of these respective proteins detected in the PEO phase [19].

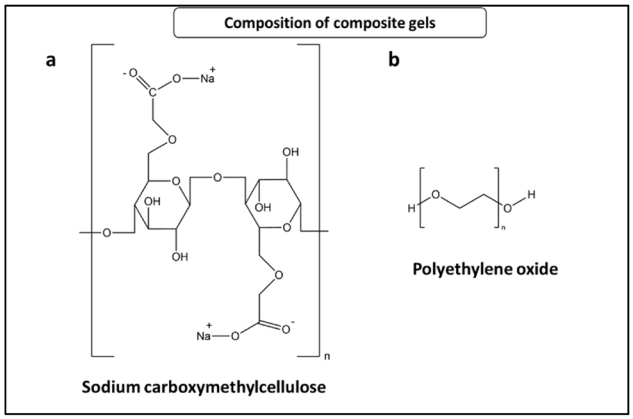
3.3.3 | Physical Transparency

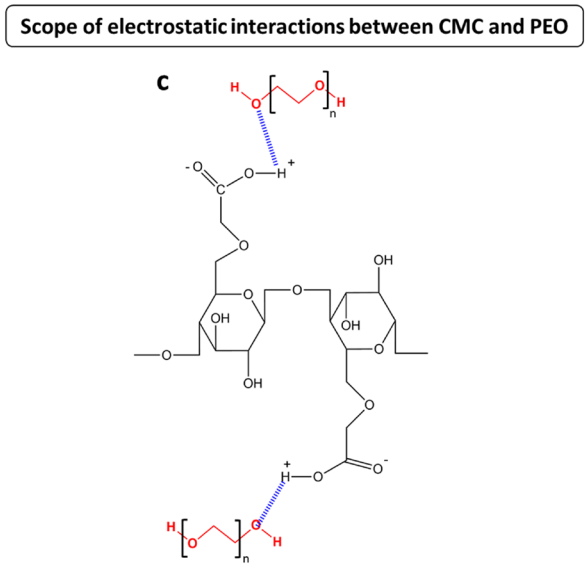
The CMC + PEO gel is transparent, allowing for easy visualization of the tissue surface below the application site (Figure 3b).

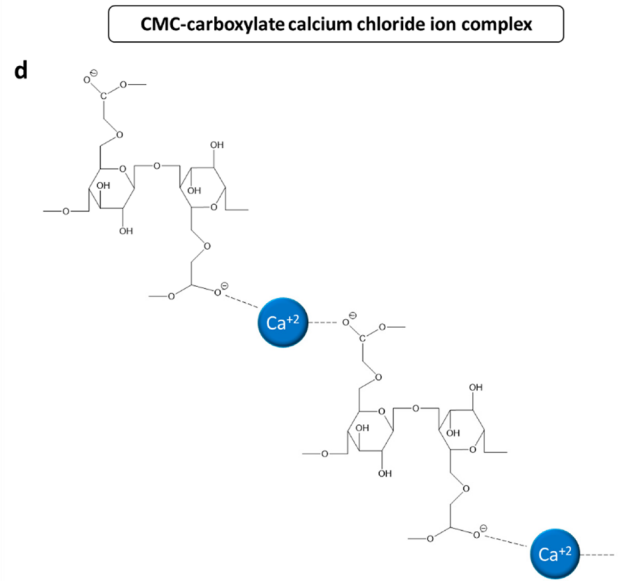
3.3.4 | Viscosity

The viscosity of the CMC + PEO dual-polymer gel depends on the PEO content, with the lowest viscosity achieved at a 1:1 ratio of CMC to PEO. Polymeric hydrogels are reported to be shear-thinning, that is, the viscosity of the material can be decreased with increasing shear. The viscosity of the gel measures the ability of the gel to resist stress and shear during injection. In its resting phase or at a zero shear rate (rate at which progressive shear strain to any material), the gel remains intact at the application site [13]. At higher shear rates, the viscosity is much lower. This shear-dependent viscosity thins the gel upon application of stress, facilitates its placement over surgical sites, that is, manipulates the gel during

injection through a small-bore cannula and permits easy gel dispersal. This property is particularly suitable for application during peridural, tendon, nerve, and peritoneal surgeries. However, upon cessation of mechanical load or removal of the stress, the gel quickly returns to a viscosity that allows it to effectively coat the site of application.







3.3.5 | Bio/mucoadhesion

The bio/mucoadhesive properties of the CMC + PEO dual-polymer gel are primarily imparted by the CMC component. Indeed, CMC-only gels have better bio- and mucoadhesive properties than PEO-only gels at equal polymer concentrations [19] (Figure 3c). For example, the force required to detach a PEO gel that is placed in between two pieces of porcine intestinal membrane is 20% of the force required to detach a CMC gel. The bio- and mucoadhesive strength of the CMC + PEO dual-polymer gel therefore decreases with an increase in the concentration of PEO.

3.3.6 | Thermal Stability

The dual-polymer CMC + PEO gel retains its heterogeneity and physical stability throughout storage at temperatures ranging from 4°C to 25°C [19].

4 | Mechanism of Action

The CMC + PEO dual-polymer gel prevents the formation of postsurgical adhesions by physically coating exposed, denuded, or traumatized tissue surfaces to create a temporary physical and mechanical barrier against contact with other tissues (Figure 4a). When placed effectively, the CMC + PEO gel separates tissues and reduces postsurgical fibrosis, thereby promoting normal healing and preventing adhesion formation [20]. Like other viscoelastic gel-based barriers, the CMC + PEO gel can also be easily applied to difficult-to-access anatomical spaces such as those involved in spine or tendon/nerve surgery. Furthermore, solubilized PEO and CMC are readily cleared from the body via diffusion for clearance by the kidneys or phagocytosis in the liver, as they are not always metabolized at the application site [32].

4.1 | Role of CMC

As noted earlier, the CMC component of CMC + PEO dual-polymer gel is primarily responsible for mucoadhesion, allowing it to adhere to the affected or injured tissue. In contrast, the PEO component helps to prevent adjacent walls or organ surfaces from adhering to each other [41]. Because CMC forms hydrogen and ionic bonds and Van der Waals interactions with mucosal surfaces, it is far more mucoadhesive than PEO [42]. Specifically, the carboxylate (COO-) molecules in the anionic CMC interact with the oligosaccharide side chain of the mucin structure on the

FIGURE 2 | The chemical composition of CMC + PEO dual-polymer gels. Chemical structures of (a) sodium carboxymethylcellulose and (b) poly(ethylene oxide). In the CMC + PEO dual-polymer gel, interlinking between CMC and PEO occurs due to (c) electrostatic linkages between the oxygen in the CMC carboxyl group and the hydrogen in PEO. (d) The CMC + PEO dual-polymer gel is further stabilized by calcium ions supplied by calcium chloride, which form an intramolecular ionic bond with the CMC carboxyl groups to create a CMC-calcium ion complex. The ionic bonds are not chemically crosslinked.

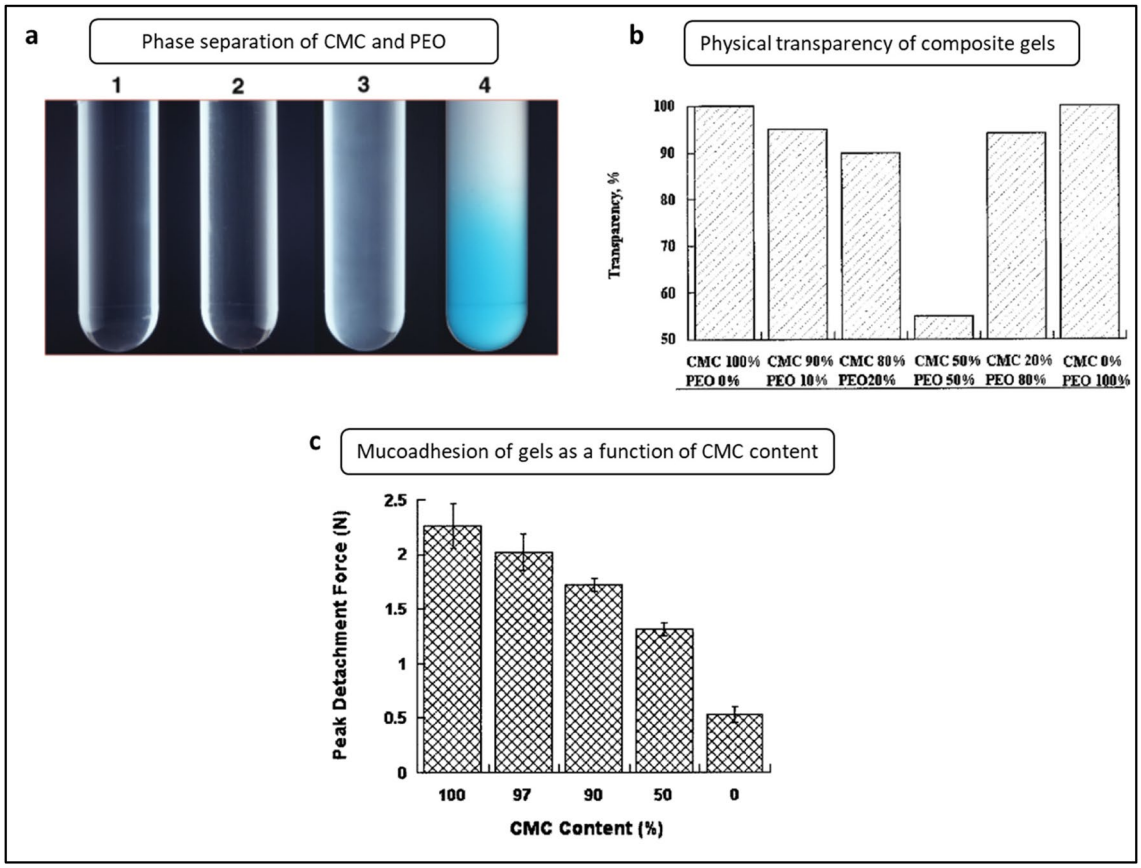


FIGURE 3 | Mechanical characterization of CMC + PEO dual-polymer gels. (a) Microphase separation of CMC/PEO gels. From left to right: 1, pure CMC solution; 2, pure PEO solution; 3, a mechanically mixed solution of CMC and PEO; and 4, a mixture of CMC, PEO, and 50 ppm methylene blue that was then centrifuged at room temperature at 3500 rpm for 20 min. Methylene blue, a CMC-specific binder, was localized in the lower layer, while the upper layer (PEO) was transparent. (b) Optical transparency, measured as absorbance at 580 nm in a UV spectrophotometer, of dual-polymer gels with different CMC:PEO ratios. (c) Mucoadhesion profile of gels with varying CMC content. Adhesion was measured as the force, in Newtons, required to detach the gel from the porcine intestine. Reprinted from [19] with permission from John Wiley and Sons.

mucus or tissue surfaces [43]. The CMC polymer chain itself is flexible, allowing it to conform to the uneven mucosal surface of the injury or trauma region, thereby increasing the total surface area of the antiadhesive barrier. Furthermore, the carboxymethyl group in CMC promotes the adsorption of blood proteins more effectively than hydrophobic adsorbents or compounds with weak Lewis acid/base groups [35], and CMC may autoactivate the blood clot factor XII allowing for its removal from the coagulation cascade early in the process thereby reducing fibrin deposition [35, 36]. Indeed, a CMC-only solution has been shown to be effective in reducing peritoneal adhesions [37].

4.2 | Role of PEO

The PEO component of the dual-polymer gel ensures its solubility and minimizes the deposition of proteins and cytokines onto the surfaces of damaged and adjacent tissue. First, the ethylene oxide monomeric units of PEO favor the polymer–solvent interaction in aqueous solutions and are thus highly water-soluble [19]. Second, the dipole moment of the ethylene oxide in PEO is maximal at room temperature. Dipole moment of any molecule is crucial for explaining dielectric properties of the material. Polarization of the molecule, that is, generation of positive and/or negative charges, or hydrogen bonding and delocalization effect increase dipole moment. Polarity allows the interaction of the molecules within the group and engages in hydrogen bonding. In the presence of an aqueous medium in the biological milieu, the electrostatic dipole moment of PEO generates a steric repulsion force between PEO and local proteins as the hydrophobic interactions between the protein molecules. This steric repulsion force, which increases with a higher molecular weight and/or increased surface area of PEO, prevents inflammatory or pain-inducing proteins and cytokines from being deposited onto the damaged tissue. Moreover, the poor partitioning of plasma proteins in PEO likely inhibits corresponding fibrin deposition. Finally, the high viscosity and osmotic pressure of PEO can increase peritoneal fluid and tissue edema, thereby decreasing the concentration of immune cells, especially leukocytes and other adhesion-promoting cells and debris, in peritoneal fluid [44].

PEO limits the diffusion of inflammatory or pain mediators into sensory nerves at the site of injury (Figure 4b,c). In cases of epidural fibrosis, nerve root tethering to a disc or pedicle can lead to nerve compression, resulting in neuropathic pain caused by the entrapment of the nerve root within fibrosis and subsequent sensitization. Further decompression surgery elevates the concentration of pain mediators, including interleukin-6, interleukin-8, and prostaglandin E2, in the epidural and disc space. These pain mediators act as nerve irritants, stimulating nociceptive sensory nerves

in the annulus fibrosus and giving rise to postsurgical lower back and leg pain [45]. Additionally, patients with herniated lumbar discs exhibit a higher density of sensory nerves in the epidural space and annulus fibrosis than those with lumbar back pain [41]. CMC + PEO dual-polymer gels thus work dually by (i) providing a physical barrier between the tissues to prevent adhesions (nerve root tethering, e.g.) and (ii) preventing pain and inflammatory mediators in the surrounding fluid from reaching the nerve roots and sensory nerve fibers, thereby reducing postoperative pain.

5 | Clinical Performance of CMC + PEO Dual-Polymer Gels

The safety and efficacy of the dual-polymer gel have been assessed in multiple preclinical studies involving peritoneal, lumbar, and tendon/nerve surgeries in mice, rats, pigs, and rabbits, as well as through blinded, randomized, controlled clinical trials performed in hospitals around the world. In this section, we review the results of clinical trials that have evaluated the use of CMC + PEO dual-polymer gel in peritoneal/intrauterine, lumbar, and tendon/nerve surgeries.

5.1 | Peritoneal and Intrauterine

CMC + PEO dual-polymer gels have been evaluated in peritoneal and intrauterine surgeries through randomized controlled clinical trials in the United States [46, 47], Europe [48, 49], Brazil [50], and Israel [51]. In these studies, the CMC + PEO gel was applied at volumes ranging from 4 to 60 mL, with an average application volume of 12 mL applied in approximately 90 s [46]. Table 3 provides an overview of these clinical trials.

One of the earliest clinical trials evaluating the dual-polymer gels was a randomized, third-party blinded, parallel-group clinical

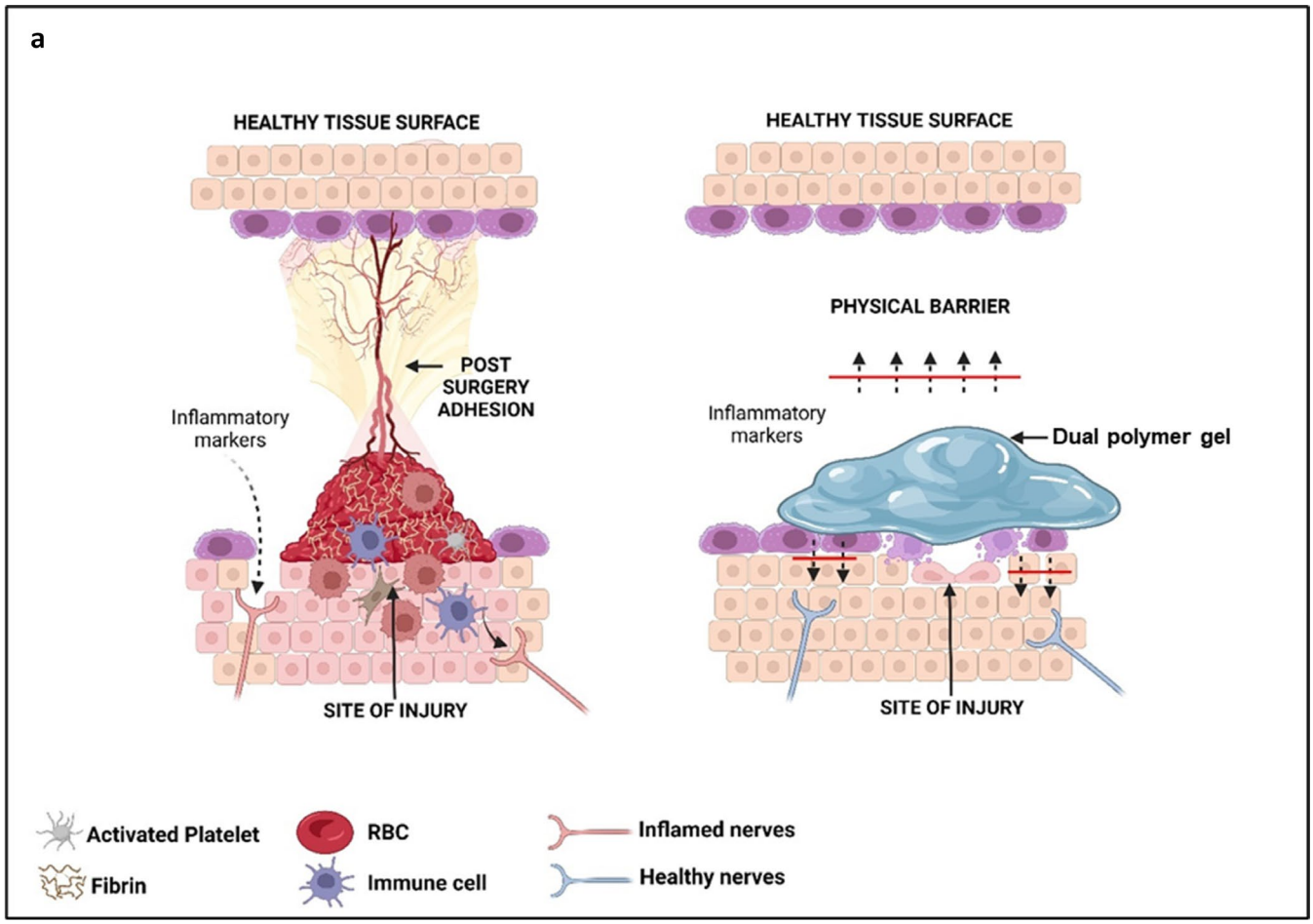


FIGURE 4 | A CMC + PEO dual-polymer gel reduces postsurgical adhesion formation in surgical settings. (a) Schematic representation showing how CMC + PEO dual-polymer gels physically coat exposed, denuded, or traumatized surfaces, including uneven or irregular surfaces, to form a temporary physical barrier between injured and healthy tissues. These gels also limit the diffusion of inflammatory or pain mediators to nerve roots at the site of injury. (b, c) Histology and Masson's trichrome staining of various surgical sites in preclinical studies confirm that CMC + PEO dual-polymer gels effectively formed a barrier between the two tissue surfaces and prevented postsurgical adhesions. (b) Epidural adhesion in rabbits, in which the dural membrane adhered to the adjacent bone following laminectomy in the control group (*left*) but not the gel-treated group (*right*). Image shown at 40× magnification. (c) Tendon adhesion in rats, in which the tenocyte showed increased proliferation and collagenization with sequestration into a peritendinous mass in the control group (*left*). In the gel-treated group (*right*), the peritendinous space was well-formed, and the synovial sheath was restored. Panel (a) was created with BioRender; panel (b) was reprinted from [20] with permission from Elsevier; and panel (c) was reprinted from [38] under Creative Commons Attribution-Non Commercial-No Derivs License.

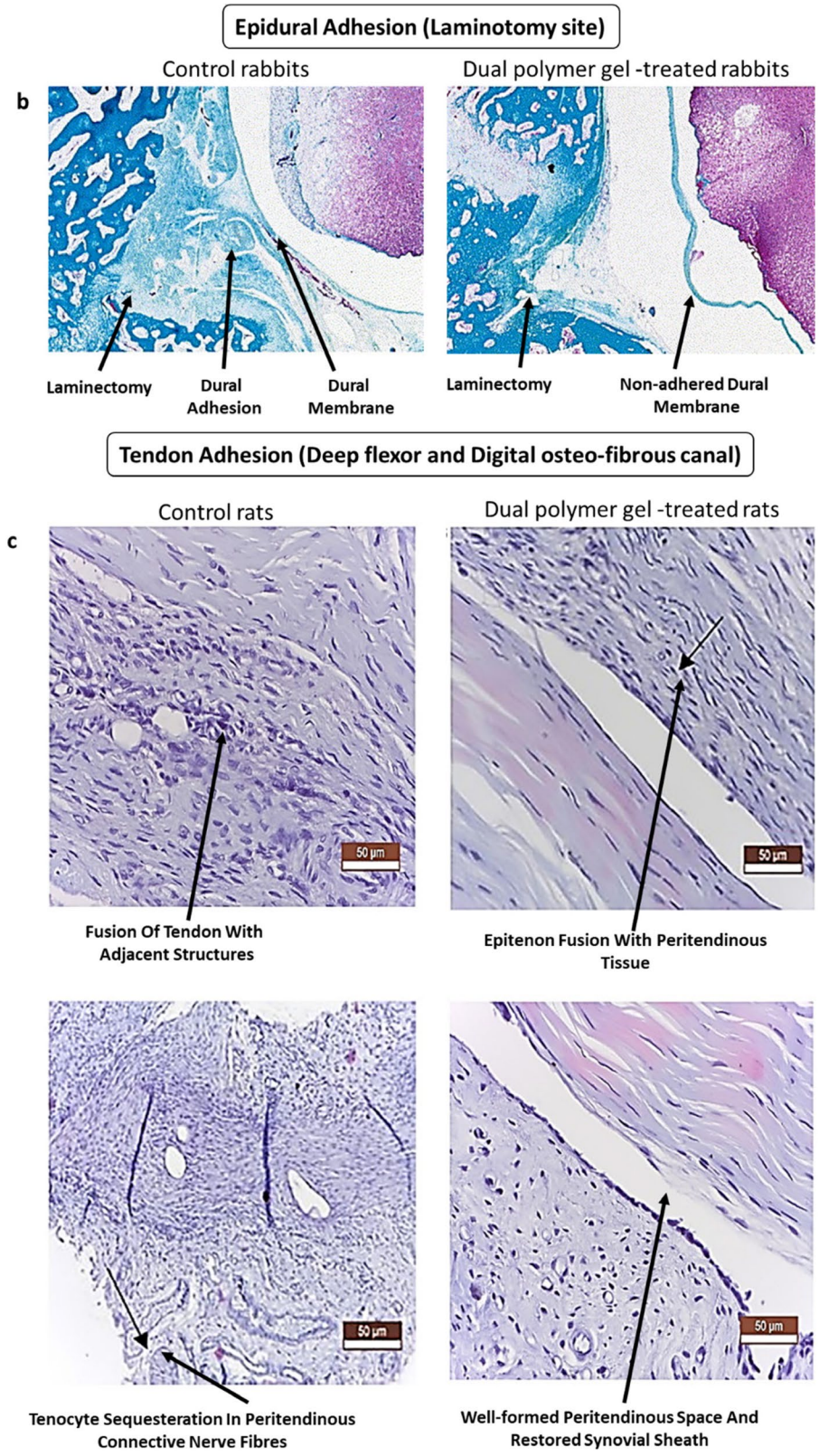


FIGURE 4 | (Continued)

trial conducted across four treatment centers in Europe with 49 female patients receiving laparoscopy. In total, 25 patients received 15 mL of CMC + PEO dual-polymer gel on a total of 45 adnexa following their surgery [48], with an average treatment time of 90 s. The other 24 patients received surgery alone across a total of 41 adnexa. All patients had undergone adhesiolysis and cystectomy for removal of ovarian endometriosis. Average American Fertility Society (AFS) adnexal adhesion scores, which measure the extent and severity of adnexal adhesions, were significantly improved in the treatment group (decreased from 11.9 to 9.1) relative to the control group (increased from 8.8 to 15.8) during a second-look laparoscopy performed 6–10 weeks

TABLE 3 | Clinical trials of CMC + PEO dual-polymer gel as antiadhesion agents in peritoneal and intrauterine surgeries.

Study design	Sample size	Country	Surgical intervention	Time points	Observation	Year	Reference
Randomized controlled, multicenter, blinded parallel	$N = 28$ (10 control, 18 treatment)	USA	Laparoscopic surgery	6–10 weeks	• Safe and easy to use with laparoscopy • Adhesion scores remained statistically identical after the first and second surgeries in the treatment group but increased in the control group	2005	[47]
Randomized, third-party, multicenter, blinded parallel	$N = 49$ (24 control, 25 treatment)	Europe, Denmark	Laparoscopic surgery	6–10 weeks	• The treatment group exhibited significantly reduced adnexal adhesions upon second-look surgeries compared to controls • Patients with grade IV endometriosis did not show any reduction in adhesion score, even in the treatment group	2005	[48]
Randomized, controlled, double-blind	$N = 37$ (17 control, 20 treatment)	USA	Laparoscopic surgical treatment of stage I–III endometriosis	6–10 weeks	• Treated patients with red lesions showed a significant decrease in adnexal adhesion scores • A positive correlation between baseline endometriosis severity and postoperative adhesion formation was seen in control patients but not in treated patients	2007	[46]
Randomized, controlled	$N = 110$ (55 control, 55 treatment)	Italy	Hysteroscopic surgery	1 month	• Gel application prevented *de novo* formation of intrauterine adhesions and improved the patency of internal uterine ostium	2011	[49]
Randomized, controlled, double-blind	$N = 52$ (26 control, 26 treatment)	Israel	Hysteroscopic surgery	6–8 weeks, 22 months	• Safe to use • After 6–8 weeks, moderate-to-severe adhesions developed in only one patient in the treatment group versus three in the control group • After 20 months, seven women in the treatment group conceived versus only three in the control group • The rate of intrauterine adhesions was not statistically significant	2014	[51]
Case reports	$N = 3$	Brazil	Hysteroscopic surgery	40 days –6 weeks	• Positive outcomes were observed in patients with septate uterus, intrauterine and pelvic adhesions, cornual pregnancy, uterine septum, amenorrhea, history of curettages, miscarriages. with no adhesions in endometrial cavities without adhesions, normalization of menstruation, and successful pregnancies	2024	[50]

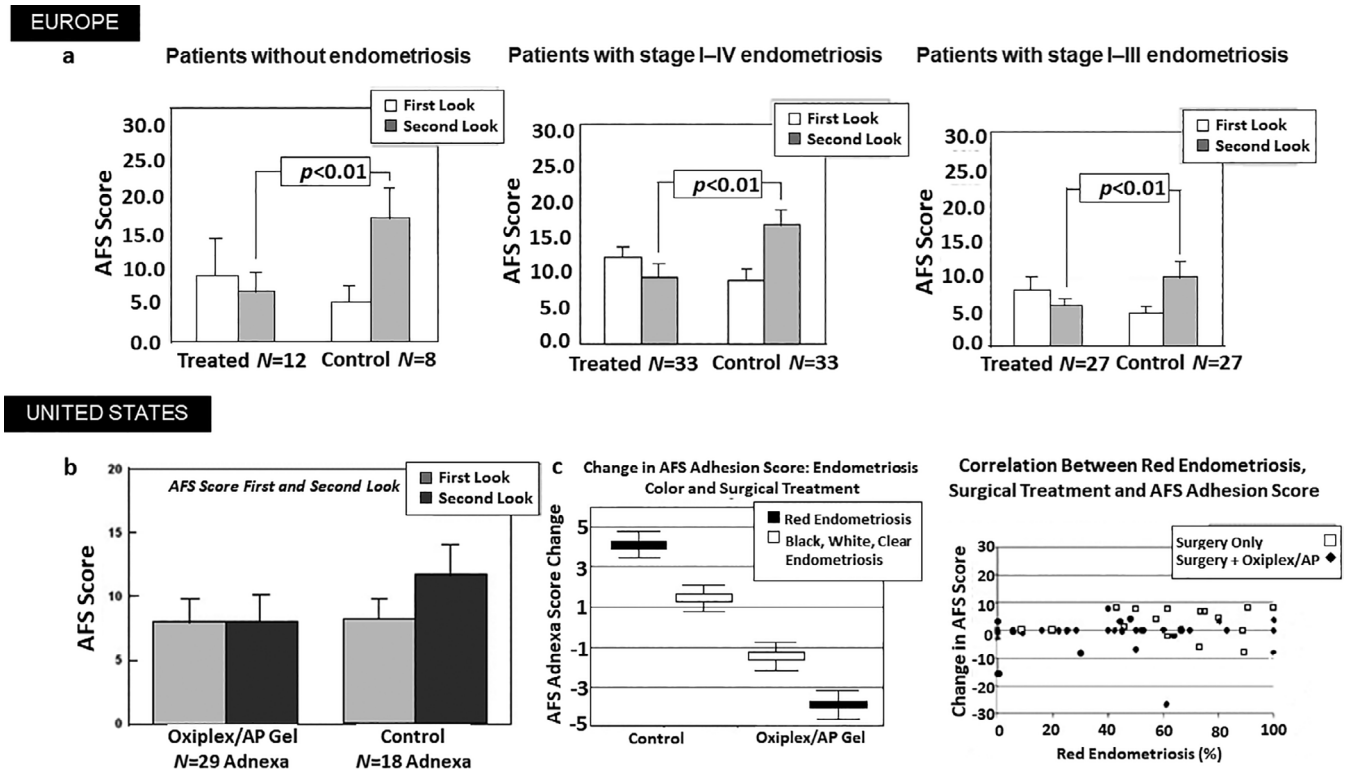


FIGURE 5 | Outcomes from clinical trials testing the efficacy of the CMC + PEO dual-polymer ger in gynecological surgeries. (a) In a European clinical trial [48], American Fertility Society (AFS) adnexal adhesion scores, which measure the extent and severity of adnexal adhesions, were significantly improved in laparoscopy patients who received the dual-polymer gel, regardless of their initial endometriosis status. (b) In a multicenter, double-blind, randomized clinical trial of 28 U.S. patients receiving laparoscopic surgery [47], patients who received the CMC + PEO dual-polymer gel showed lower AFS adnexal adhesion scores than control patients upon a second-look surgery performed 6–10 weeks postoperatively. (c) A similar U.S. clinical trial of 37 patients with stage I-III endometriosis [46] reported greater improvement in AFS adnexal adhesion scores in patients who received the dual-polymer gel (*left*). Furthermore, there was a positive correlation between baseline endometriosis severity and the extent of postoperative adhesion formation in control patients but not treatment patients (*right*). Panel (a) was reprinted from [48] with permission from Oxford University Press; panel (b) was reprinted from [47] with permission from Elsevier; and panel (c) was reprinted from [46] with permission from Elsevier.

following the initial surgery ($p < 0.01$; Figure 5a). These results represent a 42% reduction in adhesion scores in the treatment group relative to the control. Furthermore, AFS score severity increased on a case-by-case basis in the control group: only 2 of the 45 adnexa treated with dual-polymer gel progressed to "moderate" or "severe" AFS scores, whereas 11 of the 41 adnexa in the control group progressed to the "moderate" or "severe" categories. Likewise, 22 of the 23 adnexa that were initially classified with "minimal" adhesion scores in the treatment group continued to exhibit minimal adhesion scores postsurgery, while only 13 of the 23 initially "minimal" adnexa in the control group remained unchanged on the second look.

To date, two clinical trials in the U.S. have demonstrated the efficacy of CMC + PEO dual-polymer gel for peritoneal/intrauterine procedures. In a multicenter, double-blind, randomized clinical trial of 28 patients ($n = 10$ control, $n = 18$ treatment), the dual-polymer gel was proven efficacious in preventing or reducing adhesion severity following laparoscopic surgery due to tubal occlusion, endometriosis, pelvic adhesions, and/or dermoids [47]. Only 34% of patients who received CMC + PEO gel showed an increase in AFS score, compared to 67% of control patients who received surgery without gel administration (Figure 5b) [47]. Another double-blind, tertiary, referral-centered clinical trial in 37 patients with stage I–III endometriosis also demonstrated positive outcomes [51]. Patients in the control group with red lesions exhibited a greater increase in ipsilateral adnexal adhesion scores than those with white, black, or clear lesions, whereas patients with red lesions who were treated with CMC + PEO dual-polymer gel showed a significant decrease in adhesion scores (Figure 5c). This latter study additionally observed a positive correlation between baseline endometriosis severity and the extent of postoperative adhesion formation in control patients, a correlation that was not observed in the treatment group.

In Italy, a randomized controlled study of 110 patients concluded that CMC + PEO dual-polymer gel was effective at reducing the rate and severity of intrauterine adhesions following hysteroscopic surgery [49]. Only 33% of patients who received the dual-polymer gel exhibited moderate-to-severe intrauterine adhesions following surgery, compared to 92% of the control patients. This study also scored the patency of internal uterine ostia and found that patency was significantly improved in 41.9% of gel-treated patients, whereas it was significantly worse in 18.2% of the control patients.

In a double-blind, randomized, controlled study conducted in Israel, 52 subjects underwent hysteroscopic treatment to remove retained products of conception [51]. For half of the patients, the CMC + PEO dual-polymer gel was then inserted into the uterine cavity until the cavity was full or until 10 mL of gel had been applied; the other half of the patients received no antiadhesion treatment. No postoperative complications were observed after the gel application. All patients were prescribed preventive antibiotics and hormone therapy during the study. After 6–8 weeks, moderate-to-severe adhesions (AFS stage 2 or 3) developed in only one subject (4%) in the treatment group compared to three subjects (14%) in the control group. By the time of a follow-up appointment, approximately 2 years later (ranging from 3 to 41 months), seven women (27%) in the treatment group had successfully conceived compared to only three subjects (14%) in the control group, though this difference was not statistically significant, perhaps due to sample size limitations. The authors concluded that, although intrauterine application of the CMC + PEO dual-polymer gel following hysteroscopy was safe, it did not significantly reduce the rate of intrauterine adhesions relative to the control groups. More extensive research will be needed to demonstrate the efficacy of the CMC + PEO dual-polymer gel in increasing pregnancy rates following hysteroscopic surgery.

5.2 | Lumbar Spine Laminectomy and Laminotomy

Biomaterials have traditionally not been successful at reducing the rate or severity of postsurgical adhesions, as well as leg and back pain in the epidural space [28], and there are currently no FDA-approved products indicated for adhesion/pain reduction following lumbar surgeries. However, clinical trials evaluating the CMC + PEO dual-polymer gel in lumbar surgery have been performed in the U.S. [33, 41, 52], Europe [34, 53, 54], and China [19, 55]. The results from an additional randomized, double-blind, multicenter-controlled clinical trial (NCT03433391) involving 135 patients with a herniated lumbar disc have yet to be published. Table 4 provides an overview of published clinical trial results evaluating the efficacy of the dual-polymer gel in lumbar surgery.

Of the trials listed in Table 4, one of the largest was a European case series of 396 patients who received the CMC + PEO dual-polymer gel following spinal microdiscectomy for one-level disc herniation [34]. No product-related complications (i.e., redness, abnormal healing, or subcutaneous collections) were observed in this patient series, and only five patients required reoperation for recurrent herniation. In the U.S., a similarly large randomized, blinded clinical trial was performed with 352 patients undergoing single-level lumbar discectomy [41]. Patients who received the CMC + PEO dual-polymer gel reported reduced back and leg pain in the Lumbar Spine Outcomes Questionnaire (LSOQ) and in clinical evaluations performed 6 months postsurgery (Figure 6b). Furthermore, patients in the treatment group exhibited less paresthesia, hypoesthesia, and sensory loss and had a lower reoperation rate than the control group, demonstrating that dual-polymer gel administration improved clinical outcomes without causing any adverse effects.

As another example, a more focused, randomized, single-blind, multicenter clinical trial of 18 U.S. patients undergoing surgery of the lumbar disc for unilateral herniation at L4-5 or L5-S1 was conducted to assess neurological function and pain using the LSOQ and clinical evaluations administered at scheduled postoperative intervals [52]. All patients presented with lower-extremity weakness and severe leg pain. The treatment group that received the CMC + PEO gel as an antiadhesion agent ($n = 11$) reported significant reductions in these symptoms at 1-, 3-, 6-, and 12-months postsurgery relative to a control group ($n = 7$) that received surgery without the dual-polymer gel (Figure 6a).

5.3 | Tendon/Nerve

CMC + PEO dual-polymer gel has also been tested for use as antiadhesion agents in tendon/nerve surgeries, though the results have been less consistent. For example, a prospective case series of 8 patients in Sweden with proximal phalanx fractures received open reduction surgery with a dorsal approach for plate fixation [56]. The dual-polymer gel was distributed between the tendon, skin, plate, and extensor tendon in all eight patients. Although there were no adverse effects of the CMC + PEO gel, the authors found that the antiadhesive effect of the gel was unconvincing: only two patients demonstrated excellent total active motion (TAM) after 3 months, with the others showing good ($n = 1$), fair ($n = 1$), or poor ($n = 4$) results. These values increased to only three patients demonstrating excellent TAM after 12 months postsurgery, with the others showing good ($n = 1$) or fair ($n = 4$) results. Median pain at rest decreased from 7 at baseline (on a scale of 100) to 0 at three- and 12-month postsurgery, and median pain at motion decreased from 50 at baseline (on a scale of 100) to 9 at 3 months and 4 at 12 months. Because the CMC + PEO dual-polymer gel is resorbed within 30 days, the authors hypothesized that the improved TAM and pain scores over their long follow-up period were due more to consistent physiotherapy than the effects of gel application.

A separate study of 39 carpal tunnel syndrome patients in France reported more positive antiadhesion effects of the CMC + PEO dual-polymer gel in tendon/nerve surgeries [57]. All patients underwent revision surgery for recurrent or resistant carpal tunnel syndrome, including one patient who received bilateral surgery (for a total of $n = 40$ hands). The revision surgery involved installation of the Canaletto implant in all 40 cases, and in 19 cases, the CMC + PEO gel was applied around the median nerve when the Canaletto was implanted. The subjects were evaluated preoperatively and postoperatively (12-month follow-up for control patients, 11-month follow-up for the treatment group) for DN4 score, pain score, Quick DASH score, grip strength, distal motor latency, and sensory nerve conduction velocity. There were no significant differences between treatment and control groups with respect to distal motor latency, rate of hypoesthesia, sensory nerve conduction velocity, or pain score; however, the treatment group showed significant improvements in other parameters (e.g., DN4 score, Quick DASH score, and grip strength) relative to the control group. The authors concluded that the postsurgery outcomes of patients who received the dual-polymer gel application were satisfactory, with minimal morbidity at the surgery site.

TABLE 4 | Overview of clinical trials and case series assessing the efficacy of the CMC + PEO dual-polymer gel as antiadhesion agents in lumbar surgeries.

Study design	Sample size	Country	Surgical intervention	Time points	Observations	Year	Reference
Randomized, single-blind, multicenter	$N = 45$ (12 control, 23 treatment)	USA	Laminectomy or laminotomy for unilateral herniation of lumbar disc	30 days 90 days 6 months	• Treatment group exhibited significantly reduced postoperative leg pain, radiculopathy scores, and lower-extremity weakness relative to baseline after 30 days • No significant differences in outcomes between the gel-treated and control patients	2003	[33]
Randomized, single-blind, multicenter	N = 18 (7 control, 11 treatment)	USA		30 days 90 days 6 months 12 months	• Gel was well-tolerated by patients • No adverse effects or clinically adverse laboratory results were observed	2004	[52]
Case series	$N = 20$	Italy	Lumbar microdiscectomy	27 days	• The CMC + PEO gel was mixed with a morphine compound • An analgesic effect was seen for 36 h • Twelve patients reported worsening lower back and radicular pain after 36 to 72 h postoperation	2005	[53]
Case series	$N = 396$	Belgium	One-level disc herniation	1 week 6 weeks	• No adverse effects were observed	2008	[34]
Randomized, controlled	$N = 70$ (35 control, 35 treatment)	Italy	Microdiscectomy with interlaminectomy for lumbar disc herniation	3 years	• No safety issues or adverse effects during the 30-day postoperative period • At the three-year follow-up, patients treated with CMC + PEO gel showed reduced disability and leg pain scores relative to control groups	2008	[54]
Randomized, controlled, multicenter	$N = 68$ (23 control, 45 treatment)	China	Decompression surgery for lumbar disc herniation at L4-L5 or L5-S1	2 months	• The treatment group showed a greater reduction in leg pain	2015	[55]
Randomized, controlled, single-blind, multicenter	$N = 93$ (33 control, 60 treatment)	China		2 months	• The treatment group reported reduced back and leg pain 30 days postoperatively, which then decreased further after 60 days. The trial may not have been randomized	2002	[19]
Randomized, blinded, multicenter	$N = 352$ (175 control, 177 treatment)	USA	Single-level lumbar discectomy (laminectomy or laminectomy)	6 months	• Treatment group reported greater satisfaction with the outcome (i.e., reduced pain and symptoms) than surgery-only control group • The treatment group reported reduced leg and back pain relative to baseline • No cerebrospinal fluid leaks or abnormal laboratory values were observed in the treatment group • Treatment group exhibited less hypoesthesia, sensory loss, and paresthesia, and required fewer reoperations	2012	[41]

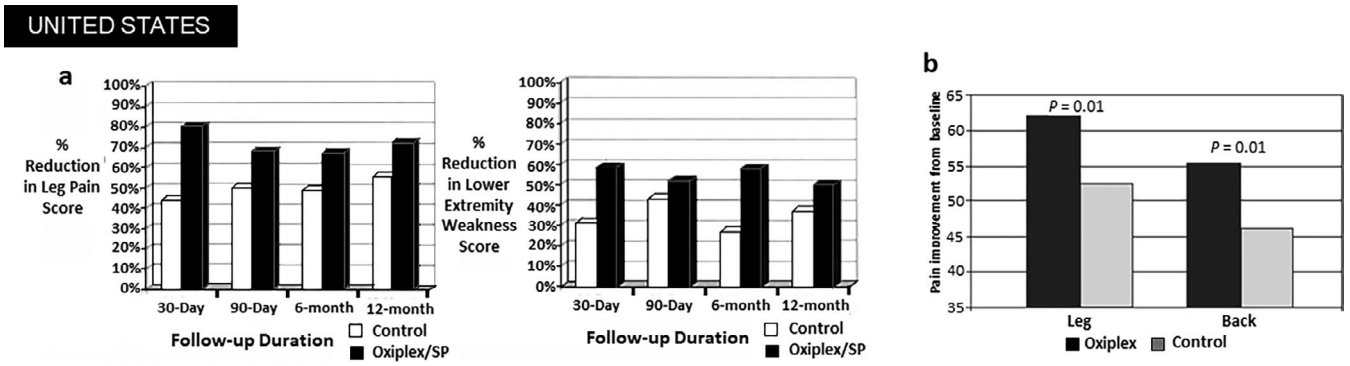


FIGURE 6 | Outcomes from a clinical trial testing the efficacy of the CMC + PEO dual-polymer gel in lumbar surgeries. (a) In a study of 18 U.S. patients undergoing surgery of the lumbar disc [52], patients who received the dual-polymer gel reported significantly greater reductions in leg pain (*left*) and lower-extremity weakness (*right*) throughout a 12-month follow-up period. (b) A larger randomized, controlled trial of 352 patients undergoing single-level lumbar discectomy [41] found that patients who received the CMC + PEO dual-polymer gel reported greater reductions in leg and back pain 6 months postoperatively relative to their preoperative baseline. Panel (a) will be reprinted from [52] after purchasing the copyright permission from the *Journal of Neuroscience* publishing group, and panel (b) was reprinted from [41] with permission from Wolters Kluwer Health Inc.

6 | Conclusion

In in vitro, preclinical, and controlled clinical trials, the CMC + PEO dual-polymer gel has demonstrated efficacy in reducing the risk, severity, and extent of postsurgical adhesions involving the spinal column [33, 34, 41, 52–54], peritoneal or intrauterine space [46–49, 51], and tendons [56, 57], though their effectiveness in tendon/nerve surgeries requires further study in different procedures to fully identify the improvement in clinical outcomes the dual-polymer gel can add. Overall, this wide breadth of applications distinguishes the broad use of dual-polymer gels from single-polymer gels, which often have more limited utility. Given their demonstrated success across this diverse array of surgeries, the CMC + PEO gel may also have potential applications in other surgical procedures. Certainly, antiadhesion barriers are needed in almost all surgical procedures, including colorectal [58], cesarean section [59], cardiac [60], pelvic [61], orthopedic [62], and other procedures involving soft tissues. Currently, clinical trials are ongoing with CMC + PEO dual-polymer gels in flexor tendon repair (NCT06582095*), hysteroscopic myomectomy, removal of septum, correction of bicornuate uterus (NCT06584344*), and revision carpal tunnel surgery (NCT06593977 [Clinical trials are registered, but enrollment not yet started]). Future research could evaluate the CMC + PEO dual-polymer gel as a drug delivery device utilizing the unique characteristics of CMC and PEO. A pharmaceutical-infused gel product could provide local and controlled postoperative drug release or even serve as a coating for devices used in reconstructive surgeries, introducing unprecedented functionality to an already-promising surgical adjuvant.

Conflicts of Interest

A.A.D. has no conflicts to declare. M.M.A. serves as an intellectual consultant of FzioMed Inc. (San Luis Obispo, CA), the developer of CMC + PEO dual-polymer gels.

Data Availability Statement

All data discussed in this review are publicly available and can be accessed through the cited references within the manuscript.

References

1. M. P. Diamond and M. L. Freeman, "Clinical Implications of Postsurgical Adhesions," *Human Reproduction Update* 7, no. 6 (2001): 567–576.

2. A. Fatehi Hassanabad, A. N. Zarzycki, K. Jeon, et al., "Prevention of Post-Operative Adhesions: A Comprehensive Review of Present and Emerging Strategies," *Biomolecules* 11, no. 7 (2021): 1027.

3. A. Fischer, T. Koopmans, P. Ramesh, et al., "Post-Surgical Adhesions Are Triggered by Calcium-Dependent Membrane Bridges Between Mesothelial Surfaces," *Nature Communications* 11, no. 1 (2020): 3068.

4. R. L. DeWilde, G. Trew, and Expert Adhesions Working Party of the European Society of Gynaecological Endoscopy (ESGE), "Postoperative Abdominal Adhesions and Their Prevention in Gynaecological Surgery. Expert Consensus Position," *Gynecological Surgery* 4, no. 3 (2007): 161–168.

5. C. N. Fortin, G. M. Saed, and M. P. Diamond, "Predisposing Factors to Post-Operative Adhesion Development," *Human Reproduction Update* 21, no. 4 (2015): 536–551.

6. Q. Hu, X. Xia, X. Kang, et al., "A Review of Physiological and Cellular Mechanisms Underlying Fibrotic Postoperative Adhesion," *International Journal of Biological Sciences* 17, no. 1 (2021): 298–306.

7. J. Chen, X. Tang, Z. Wang, et al., "Techniques for Navigating Postsurgical Adhesions: Insights Into Mechanisms and Future Directions," *Bioengineering and Translational Medicine* 8, no. 6 (2023): e10565.

8. G. Holtz, "Prevention and Management of Peritoneal Adhesions," *Fertility and Sterility* 41, no. 4 (1984): 497–507.

9. D. S. Schade and J. R. Williamson, "The Pathogenesis of Peritoneal Adhesions: An Ultrastructural Study," *Annals of Surgery* 167, no. 4 (1968): 500–510.

10. C. A. Witz, K. T. Allsup, I. A. Montoya-Rodriguez, S. L. Vaughn, V. E. Centonze, and R. S. Schenken, "Culture of Menstrual Endometrium With Peritoneal Explants and Mesothelial Monolayers Confirms

Attachment to Intact Mesothelial Cells*," *Human Reproduction* 17, no. 11 (2002): 2832–2838.

11. J. Lang, D. Ma, Y. Xiang, et al., "Chinese Expert Consensus on the Prevention of Abdominal Pelvic Adhesions After Gynecological Tumor Surgeries," *Annals of Translational Medicine* 8, no. 4 (2020): 79.

12. C. Nappi, S. A. Di Spiezio, E. Greco, M. Guida, S. Bettocchi, and G. Bifulco, "Prevention of Adhesions in Gynaecological Endoscopy," *Human Reproduction Update* 13, no. 4 (2007): 379–394.

13. G. S. diZerega, S. Cortese, K. E. Rodgers, et al., "A Modern Biomaterial for Adhesion Prevention," *Journal of Biomedical Materials Research. Part B, Applied Biomaterials* 81, no. 1 (2007): 239–250.

14. T. Tulandi, M. F. Chen, S. Al-Took, and K. Watkin, "A Study of Nerve Fibers and Histopathology of Postsurgical, Postinfectious, and Endometriosis-Related Adhesions," *Obstetrics and Gynecology* 92, no. 5 (1998): 766–768.

15. H. Wang, W. Sun, D. Fu, Y. Shen, Y. Y. Chen, and L. L. Wang, "Update on Biomaterials for Prevention of Epidural Adhesion After Lumbar Laminectomy," *Journal of Orthopaedic Translation* 13 (2018): 41–49.

16. G. S. diZerega, M. M. Traylor, L. S. Alphonso, and S. J. Falcone, "Use of Temporary Implantable Biomaterials to Reduce Leg Pain and Back Pain in Patients With Sciatica and Lumbar Disc Herniation," *Materials* 3, no. 5 (2010): 3331–3368.

17. L. S. Klopp, W. C. Welch, J. W. Tai, J. M. Toth, G. B. Cornwall, and A. S. Turner, "Use of Polylactide Resorbable Film as a Barrier to Postoperative Peridural Adhesion in an Ovine Dorsal Laminectomy Model," *Neurosurgical Focus* 16, no. 3 (2004): E2–E9.

18. K. Ido and H. Urushidani, "Fibrous Adhesive Entrapment of Lumbosacral Nerve Roots as a Cause of Sciatica," *Spinal Cord* 39, no. 5 (2001): 269–273.

19. L. S. Liu and R. A. Berg, "Adhesion Barriers of Carboxymethylcellulose and Polyethylene Oxide Composite Gels," *Journal of Biomedical Materials Research* 63, no. 3 (2002): 326–332.

20. K. E. Rodgers, J. T. Robertson, T. Espinoza, et al., "Reduction of Epidural Fibrosis in Lumbar Surgery With Oxiplex Adhesion Barriers of Carboxymethylcellulose and Polyethylene Oxide," *Spine Journal* 3, no. 4 (2003): 277–283.

21. F. Coccolini, L. Ansaloni, R. Manfredi, et al., "Peritoneal Adhesion Index (PAI): Proposal of a Score for the "Ignored Iceberg" of Medicine and Surgery," *World Journal of Emergency Surgery* 8, no. 1 (2013): 6.

22. E. Lih, S. H. Oh, Y. K. Joung, J. H. Lee, and D. K. Han, "Polymers for Cell/Tissue Anti-Adhesion," *Progress in Polymer Science* 44 (2015): 28–61.

23. R. L. De Wilde, R. Devassy, R. Broek, et al., "The Future of Adhesion Prophylaxis Trials in Abdominal Surgery: An Expert Global Consensus," *Journal of Clinical Medicine* 11, no. 6 (2022): 1476.

24. M. M. Leitao, Jr., A. Natenzon, N. R. Abu-Rustum, et al., "Postoperative Intra-Abdominal Collections Using a Sodium Hyaluronate-Carboxymethylcellulose (HA-CMC) Barrier at the Time of Laparotomy for Ovarian, Fallopian Tube, or Primary Peritoneal Cancers," *Gynecologic Oncology* 115, no. 2 (2009): 204–208.

25. L. S. Krill, S. M. Ueda, M. Gerardi, and R. E. Bristow, "Analysis of Postoperative Complications Associated With the Use of Anti-Adhesion Sodium Hyaluronate-Carboxymethylcellulose (HA-CMC) Barrier After Cytoreductive Surgery for Ovarian, Fallopian Tube and Peritoneal Cancers," *Gynecologic Oncology* 120, no. 2 (2011): 220–223.

26. S. Bashir, C. V. Ananth, S. N. Lewin, et al., "Utilization and Safety of Sodium Hyaluronate-Carboxymethylcellulose Adhesion Barrier," *Diseases of the Colon and Rectum* 56, no. 10 (2013): 1174–1184.

27. E. J. Flannery, *Response to Citizen Petition* (Maryland, USA: U.S. Food and Drug Administration, 2021).

28. T. Nagasaki, T. Akiyoshi, T. Mukai, Y. Hiyoshi, T. Yamaguchi, and Y. Fukunaga, "New Use of an Absorbable Adhesion Barrier (INTERCEED) for Temporary Diverting Ileostomy in Minimally Invasive Rectal Surgery," *Journal of Coloproctology* 42 (2022): 42–158.

29. D. M. Wiseman, L. E. Gottlick, and M. P. Diamond, "Effect of Thrombin-Induced Hemostasis on the Efficacy of an Absorbable Adhesion Barrier," *Journal of Reproductive Medicine* 37, no. 9 (1992): 766–770.

30. M. G. Waldron, C. Judge, L. Farina, A. O'Shaughnessy, and M. O'Halloran, "Barrier Materials for Prevention of Surgical Adhesions: Systematic Review," *BJS Open* 6, no. 3 (2022): zrac075.

31. S. Bang, Y. G. Ko, W. I. Kim, D. Cho, W. H. Park, and O. H. Kwon, "Preventing Postoperative Tissue Adhesion Using Injectable Carboxymethyl Cellulose-Pullulan Hydrogels," *International Journal of Biological Macromolecules* 105, no. Pt 1 (2017): 886–893.

32. K. E. Rodgers, H. E. Schwartz, N. Roda, M. Thornton, W. Kobak, and G. S. diZerega, "Effect of Oxiplex* Films (PEO/CMC) on Adhesion Formation and Reformation in Rabbit Models and on Peritoneal Infection in a Rat Model," *Fertility and Sterility* 73, no. 4 (2000): 831–838.

33. K. D. Kim, J. C. Wang, D. P. Robertson, et al., "Reduction of Radiculopathy and Pain With Oxiplex/SP Gel After Laminectomy, Laminotomy, and Discectomy: A Pilot Clinical Study," *Spine* 28, no. 10 (2003): 1080–1087; discussion 1087–1088.

34. P. Fransen, "Safety of Carboxymethylcellulose/Polyethylene Oxide for the Prevention of Adhesions in Lumbar Disc Herniation – Consecutive Case Series Review," *Annals of Surgical Innovation and Research* 2 (2008): 2.

35. C. H. Josh Yeh, Z. O. Dimachkie, A. Golas, A. Cheng, P. Parhi, and E. A. Vogler, "Contact Activation of Blood Plasma and Factor XII by Ion-Exchange Resins," *Biomaterials* 33, no. 1 (2012): 9–19.

36. O. D. Ratnoff, E. W. Davie, and D. L. Mallett, "Studies on the Action of Hageman Factor: Evidence That Activated Hageman Factor in Turn Activates Plasma Thromboplastin Antecedent," *Journal of Clinical Investigation* 40, no. 5 (1961): 803–819.

37. T. E. Elkins, R. J. Bury, J. L. Ritter, et al., "Adhesion Prevention by Solutions of Sodium Carboxymethylcellulose in the Rat. I," *Fertility and Sterility* 41, no. 6 (1984): 926–928.

38. A. M. Corduneanu-Luca, S. A. Pasca, C. Tamas, et al., "Improving Flexor Tendon Gliding by Using the Combination of Carboxymethylcellulose-Polyethylene Oxide on Murine Model," *Experimental and Therapeutic Medicine* 23, no. 1 (2022): 105.

39. H. E. Schwartz, J. M. Blackmore, S. M. Cortese, W. G. Oppelt, G. Dizegera, and FzioMed Inc Assignee, "Compositions of Polyacids and Polyethers and Methods for Their Use in Reducing Pain," 2004.

40. H. M. Ragab, "Optical, Thermal and Electrical Characterization of PEO/CMC Incorporated With ZnO/TiO2 NPs for Advanced Flexible Optoelectronic Technologies," *Ceramics International* 49, no. 8 (2023): 12563–12569.

41. A. L. Rhyne, S. L. Blumenthal, E. H. Frank, et al., "Oxiplex Reduces Leg Pain, Back Pain, and Associated Symptoms After Lumbar Discectomy," *Spine* 37, no. 8 (2012): 631–641.

42. S. L. Cook, S. Woods, L. Methven, J. K. Parker, and V. V. Khutoryanskiy, "Mucoadhesive Polysaccharides Modulate Sodium Retention, Release and Taste Perception," *Food Chemistry* 240 (2018): 482–489.

43. S. Javanbakht and A. Shaabani, "Carboxymethyl Cellulose-Based Oral Delivery Systems," *International Journal of Biological Macromolecules* 133 (2019): 21–29.

44. R. Schonman, R. Corona, A. Bastidas, C. De Cicco, K. Mailova, and P. R. Koninckx, "Intercoat Gel (Oxiplex): Efficacy, Safety, and Tissue Response in a Laparoscopic Mouse Model," *Journal of Minimally Invasive Gynecology* 16, no. 2 (2009): 188–194.

45. J. G. Burke, R. W. Watson, D. McCormack, F. E. Dowling, M. G. Walsh, and J. M. Fitzpatrick, "Intervertebral Discs Which Cause Low Back Pain Secrete High Levels of Proinflammatory Mediators," *Journal of Bone and Joint Surgery* 84, no. 2 (2002): 196–201.

46. G. S. diZerega, J. Coad, and J. Donnez, "Clinical Evaluation of Endometriosis and Differential Response to Surgical Therapy With and Without Application of Oxiplex/AP* Adhesion Barrier Gel," *Fertility and Sterility* 87, no. 3 (2007): 485–489.

47. P. Young, A. Johns, C. Templeman, et al., "Reduction of Postoperative Adhesions After Laparoscopic Gynecological Surgery With Oxiplex/AP Gel: A Pilot Study," *Fertility and Sterility* 84, no. 5 (2005): 1450–1456.

48. P. Lundorff, J. Donnez, M. Korell, A. J. Audebert, K. Block, and G. S. diZerega, "Clinical Evaluation of a Viscoelastic Gel for Reduction of Adhesions Following Gynaecological Surgery by Laparoscopy in Europe," *Human Reproduction* 20, no. 2 (2005): 514–520.

49. S. A. Di Spiezio, M. Spinelli, S. Bramante, et al., "Efficacy of a Polyethylene Oxide–Sodium Carboxymethylcellulose Gel in Prevention of Intrauterine Adhesions After Hysteroscopic Surgery," *Journal of Minimally Invasive Gynecology* 18, no. 4 (2011): 462–469.

50. V. M. da Cunha, W. Kondo, U. Menakaya, and G. diZerega, "Uterine Septoplasty and Adhesiolysis: Difficult Hysteroscopic Surgery and Intrauterine Carboxymethyl Cellulose + Polyethylene Oxide Dual Polymer Gel Resulted in Good Clinical Outcomes: Three Case Reports," *Journal of Clinical Obstetrics, Gynecology and Infertility* 8, no. 1 (2024): 5.

51. N. Fuchs, N. Smorgick, I. Ben Ami, et al., "Intercoat (Oxiplex/AP Gel) for Preventing Intrauterine Adhesions After Operative Hysteroscopy for Suspected Retained Products of Conception: Double-Blind, Prospective, Randomized Pilot Study," *Journal of Minimally Invasive Gynecology* 21, no. 1 (2014): 126–130.

52. K. D. Kim, J. C. Wang, D. P. Robertson, et al., "Reduction of Leg Pain and Lower-Extremity Weakness for 1 Year With Oxiplex/SP Gel Following Laminectomy, Laminotomy, and Discectomy," *Neurosurgical Focus* 17, no. 1 (2004): ECP1.

53. L. Mastronardi, M. Pappagallo, and C. Tatta, "The Oxiplex/SP Gel-Morphine Compound After Lumbar Microdiscectomy in the Management of Postoperative Pain. Report of 20 Cases," *Surgical Neurology* 64, no. 1 (2005): 75–78; discussion 78–79.

54. R. Assietti, A. Mora, and M. Brayda-Bruno, "Use of Carboxymethylcellulose/Polyethylene Oxide Gel in Microdiscectomy With Interlaminectomy: A Case Series Comparison With Long-Term Follow-Up," *Spine* 33, no. 16 (2008): 1762–1765.

55. W. Lei, R. J. Ehmsen, R. P. Chiacchierini, J. L. Krelle, and G. S. diZerega, "Reduction of Leg Pain by Oxiplex Gel After Lumbar Discectomy in Patients With Predominant Leg Pain and Elevated Levels of Lower Back Pain: A Prospective, Randomized, Blinded, Multicenter Clinical Study," *Journal of Spinal Disorders and Techniques* 28, no. 8 (2015): 301–307.

56. J. von Kieseritzky, J. Rosengren, and M. Arner, "Dynavisc as an Adhesion Barrier in Finger Phalangeal Plate Fixation-a Prospective Case Series of 8 Patients," *Journal of Hand Surgery Global Online* 2, no. 2 (2020): 109–112.

57. A. Carmona, J. J. Hidalgo Diaz, S. Facca, Y. Igeta, C. Pizza, and P. Liverneaux, "Revision Surgery in Carpal Tunnel Syndrome: A Retrospective Study Comparing the Canaletto Device Alone Versus a Combination of Canaletto and Dynavisc Gel," *Hand Surgery and Rehabilitation* 38, no. 1 (2019): 52–58.

58. P. Krielen, J. P. C. Grutters, C. Strik, R. P. G. ten Broek, H. van Goor, and M. W. J. Stommel, "Cost-Effectiveness of the Prevention of Adhesions and Adhesive Small Bowel Obstruction After Colorectal Surgery With Adhesion Barriers: A Modelling Study," *World Journal of Emergency Surgery* 14, no. 1 (2019): 41.

59. Y. Wada, H. Takahashi, H. Matsui, H. Yasunaga, H. Fujiwara, and Y. Sasabuchi, "Adhesion Barriers and Intraperitoneal or Uterine Infections After Cesarean Section: A Retrospective Cohort Study," *Surgery* 172, no. 6 (2022): 1722–1727.

60. U. U. Nkere, "Postoperative Adhesion Formation and the Use of Adhesion Preventing Techniques in Cardiac and General Surgery," *ASAIO Journal* 46, no. 6 (2000): 654–656.

61. G. Ahmad, H. O'Flynn, A. Hindocha, and A. Watson, "Barrier Agents for Adhesion Prevention After Gynaecological Surgery," *Cochrane Database of Systematic Reviews* 2015 (2015): CD000475.

62. J. S. Hayes and R. G. Richards, "Surfaces to Control Tissue Adhesion for Osteosynthesis With Metal Implants: In Vitro and In Vivo Studies to Bring Solutions to the Patient," *Expert Review of Medical Devices* 7, no. 1 (2010): 131–142.