FERTILITY AND STERILITY®
VOL. 73, NO. 4, APRIL 2000

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

Effect of Oxiplex* films (PEO/CMC) on adhesion formation and reformation in rabbit models and on peritoneal infection in a rat model

Kathleen E. Rodgers, Ph.D.,[†‡] Herbert E. Schwartz, Ph.D.,[§] Norma Roda, D.V.M.,[†] Melvin Thornton, M.D.,[‡] William Kobak, M.D.[†‡], and Gere S. diZerega, M.D.[†‡]

Livingston Research Institute, University of Southern California, Los Angeles, California; and FzioMed, Inc., San Luis Obispo, California

Objective: To assess the efficacy of Oxiplex (FzioMed, Inc., San Luis Obispo, CA) barriers.

Design: Film of polyethylene oxide and carboxymethylcellulose (Oxiplex) were tested for strength and tissue adherence. Films were selected for evaluation in models for biocompatability and adherence. Three films were selected for evaluation in efficacy studies, and one was evaluated for effects on bacterial peritonitis. Handling characteristics of Oxiplex film were evaluated via laparoscopy.

Setting: University laboratory.

Patient(s): Rabbits, rats, pigs.

Intervention(s): Placement of Oxiplex prototypes at the site of injury.

Main Outcome Measure(s): Mechanical properties, biocompatibility, tissue adherence, adhesion development, infection potentiation, and device handling.

Result(s): Mechanical tests indicated that tensile strength and elongation were inversely correlated. All films tested had excellent tissue adherence properties. Selected films, based on residence time and biocompatibility, prevented adhesion formation in all animals and were highly efficacious in preventing adhesion reformation. The optimal Oxiplex prototype prevented adhesion reformation in 91% of the animals. This Oxiplex film, dyed to allow visualization, prevented adhesion reformation and did not affect bacterial peritonitis. In a laparoscopic model, the Oxiplex film, delivered in FilmSert forceps, via a 5.0-mm trocar, rapidly unfurled and could be easily applied to tissue with strong adherence.

Conclusion(s): These data show development of an adhesion prevention material that is tissue adherent, can be placed via laparoscopy, and does not affect host resistance. (Fertil Steril® 2000;73:831–8. ©2000 by American Society for Reproductive Medicine.)

Key Words: Adhesion, carboxymethylcellulose, polyethylene, oxide, barrier

Received August 19, 1999; revised and accepted November 5, 1999.

Supported by FzioMed, Inc., San Luis Obispo, CA.

Reprint requests: Kathleen E. Rodgers, Ph.D., Livingston Research Institute, 1321 North Mission Road, Los Angeles, California 90033 (FAX: 323-222-7038; E-mail: lri1321@aol.com).

* Oxiplex, FzioMed, Inc., San Luis Obispo, California.

† Livingston Research Institute.

‡ University of Southern California.

§ FzioMed, Inc.

0015-0282/00/$20.00
PII S0015-0282(99)00642-1

Adhesion development is a major source of postoperative morbidity and mortality. The most frequent surgical procedures implicated in clinically significant adhesion formation are gynecologic, cardiovascular, and general abdominal surgery (1, 2). Complications of intraperitoneal adhesion include intestinal obstruction, chronic or recurrent pelvic pain, infertility in females, prolonged surgical time, and increased postoperative complications (3–7).

Various approaches for the prevention of adhesion development have been explored (8). Physical barriers have been used in an attempt to prevent adhesion formation by limiting tissue apposition during the critical period of peritoneal healing, thereby minimizing the development of a fibrin matrix between tissue surfaces (9). Solid barriers that have been used include oxidized regenerated cellulose (Interceed; Johnson and Johnson Medical, Arlington, TX), expanded polytetrafluorethylene (Preclude; W. L. Gore, Flagstaff, AZ) and modified hyaluronic acid and carboxymethylcellulose complex (Seprafilm; Genzyme, Inc., Cambridge, MA).

Interceed, the first product approved by the Food and Drug Administration (FDA) for adhesion prevention, has good clinical efficacy when used properly in the absence of blood.

Preclude, a barrier approved for use as a pericardial substitute, has good clinical efficacy but is not bioresorbable, requires suturing, and must be removed via a second operation. In 1996, Seprafilm was approved by the FDA for use in the reduction of adhesion development at the site of abdominal wall and uterine incisions. However, Seprafilm cannot be readily used during laparoscopic surgery because of its handling limitations.

In this report, the ability of Oxiplex film, a novel resorbable barrier made from an intermacromolecular association complex of high molecular weight polyethylene oxide (PEO) and carboxymethylcellulose (CMC; FzioMed, Inc., San Luis Obispo, CA), was evaluated for its ability to reduce adhesion formation and reformation when placed at the site of injury.

Sodium CMC is an anionic polysaccharide that is available in different molecular weight ranges and degrees of substitution. The CMC has been evaluated for adhesion prevention in the form of films, gels, and sponges by various investigators (10).

PEO is a nonionic polyether used in many blood-contacting applications for its antithrombogenic properties. When used in films, PEO works by means of a surface steric exclusion mechanism to create a thromboresistant barrier, excluding the access of fibrin to protected tissues (11). Several PEO block copolymer systems have been evaluated for adhesion and scar prevention (12–15). An aqueous solution containing 20% PEO attenuated adhesion formation in rats by suppression of peritoneal inflammation and collagen incorporation (16).

Oxiplex films are produced by drying a PEO-CMC casting solution under controlled conditions. Suitable physical and chemical properties of film, such as tissue adherence, bioresorbability, tensile strength, flexibility, and elongation, are obtained by regulating the association complexation, or hydrogen bonding, between the two polymers chains in solution and by varying the amount and ratio of PEO and CMC. The association complexation is regulated by manipulating the pH of the casting solution.

This report evaluates five Oxiplex films, varying in PEO-CMC ratio and degree of complexation, for mechanical testing and for adhesion prevention in standard rabbit models.

MATERIALS AND METHODS

Animals

Female (2.4–2.7 kg) New Zealand White rabbits were used for efficacy studies and quarantined at least 2 days before surgery. Female Sprague-Dawley rats (175–225 g) were used for the infection study and were quarantined at least 2 days before surgery. Female pigs were used for the laparoscopic handling studies and quarantined at least 1 day before surgery. The animals were housed in the USC Vivarium (an Association for the Assessment and Accreditation of Laboratory Animal Care certified or accredited facility) on a 12:12 hour light-dark cycle. Food and water were available ad libitum except in the immediate postoperative interval. All procedures were approved by the Institutional Animal Care and Use Committee.

TABLE 1

Oxiplex adhesion barrier film types.

Film type	Degree of association complexation*	Weight (% PEO)	Weight (% CMC)	pH of casting solution
AC-1	+++	5	95	3.0
AC-2	++	5	95	4.0
AC-3	+	5	95	5.0
AC-4	++	23	77	4.0
AC-5	+++	23	77	3.0

Note: CMC = carboxylmethyl cellulose; PEO = polyethylene oxide.
* Degree of association complexation: +++, strong; ++, medium; +, weak.

Rodgers. Oxiplex films and adhesions. Fertil Steril 2000.

Materials

The Oxiplex films were supplied by FzioMed, Inc. and sterilized by gamma sterilization. Table 1 describes the five prototype Oxiplex films evaluated. The optimized Oxiplex film used in the final studies was made by adding an FDA-approved blue dye to film AC-4 to permit easy visualization during surgery. The desired physical and chemical properties, such as bioresorbability, tissue adherence, and handling characteristics are achieved by controlling the degree of association complexation between the polymer chains and by changing the relative percentages of the polymers (Table 1).

Mechanical Testing

Hydrated Oxiplex film was tested for tensile strength, percentage elongation, and tissue adherence with use of an LT-100 Loop Tack Tester (ChemInstruments, Fairfield, OH) equipped with a 2-kg force gauge.

The Oxiplex film specimens were prepared by cutting a "dog bone"-shaped film strip so that the narrow point was 12.7 mm wide and 10.0 cm long. Each film specimen was measured for thickness, and this value was entered into the database. Film hydration was accomplished by soaking the film for 2 minutes in balanced salt solution just before testing.

The hydrated tensile strength of the Oxiplex film was measured by mounting one end of the filmstrip securely within the lower jaws of the test device. The other end of the filmstrip was secured into the upper jaws attached to the force gauge. Applying force to the film raised the upper jaws. The gram force-to-failure of the hydrated film was recorded.

The test for percentage elongation of Oxiplex film was performed by mounting the filmstrip as in the tensile strength test procedure. Two lines, 5 mm apart, were drawn on the

film across the horizontal axis at the center of the dog bone strip. The upper jaw was raised, and the maximum distance between the lines was measured at the point of film failure. This measurement of elongation was expressed as a percentage of the original distance between the lines.

Tissue adherence testing was performed by using the LT-100 Loop Tack Tester. A 1-inch-wide test strip of Oxiplex film was prepared, bent back on itself, and joined together with a half-inch strip of masking tape. The looped Oxiplex film was inserted into the jaws of the specimen holder and then lowered to contact 1 square inch of moistened bovine intestine for 5 minutes. The tester was activated, raising the film loop from the tissue with the force gauge, recording the maximum force in grams required to separate the film from the tissue. The recorded gram release force is the measure of film adherence to tissue.

Biocompatibility Model

On the day of surgery, the rabbits were anesthetized with intramuscular ketamine-xylazine (55 and 5 mg/kg, respectively) and prepared for sterile surgery. In the initial study, a midline laparotomy was performed, and five types of prototype Oxiplex films were placed on the sidewall, bowel, and uterine horns. The only injury that was performed besides the incisions was removal of the broad ligament of the rabbit uterine horns to allow the films to be wrapped around the uterine horns. After recovery, the rabbits were returned to the vivaria. At 24, 48, 72, and 96 hours after surgery, the material relative to the site of initial placement, the condition of the material, and the appearance of the tissue in contact with the material were evaluated.

Sidewall Formation Model

Rabbits were anesthetized with a mixture of 55 mg/kg of ketamine hydrochloride and 5 mg/kg of Rompum intramuscularly (17–19). After preparation for sterile surgery, a midline laparotomy was performed. The cecum and bowel were exteriorized, and digital pressure was exerted to create subserosal hemorrhages over all surfaces. The damaged intestine was then lightly abraded with a 4-inch piece of 4 × 4-ply sterile gauze until punctate bleeding was observed. The cecum and bowel were then returned to normal anatomic position. A 4 × 3-cm area in the first study and 5 × 3 cm in subsequent studies of peritoneum and transversus abdominis muscle were removed on the right lateral abdominal wall. The film was placed at the site of sidewall injury.

After 7–8 days, the rabbits were euthanized, and the percentage of the area of the sidewall injury that was involved in adhesions was determined. In addition, the tenacity of the adhesions was scored with use of the following system: 0 = no adhesions; 1 = mild, easily dissectable adhesions; 2 = moderate adhesions; nondissectable, does not tear the organ; and 3 = dense adhesions; nondissectable, tears organ when removed. Reduction in either the area or the tenacity of the adhesions was considered beneficial.

Sidewall Reformation Model

Rabbits were anesthetized, and the initial surgery was conducted as described above (18). One week later, the animals were anesthetized as described above and underwent a second laparotomy. In the rabbits that had adhesions, the adhesions were scored and lysed with use of blunt and sharp dissection. Care was taken not to injure the bowel.

The film was placed at the site after adhesiolysis. The bowel was then returned to the normal anatomic position, and the laparotomy incision was closed. After 7–10 days the rabbits were euthanized, and the percentage of the area of the sidewall injury that was involved in adhesions was determined. In addition, the tenacity of the adhesions was scored by the scoring system described above.

Rat Infection Model

Preparation of Gelatin Capsules

The cecal contents and feces from rats fed hamburger for 2 weeks were collected and mixed 1:1 with sterile peptone yeast glucose broth containing no preservatives (Allegiance Labs, Irvine, CA) and 10% barium sulfate (20). The amount of this fecal preparation that caused mortality in 0%–20% of the rats (25 μL-LD10) or 40%–60% of the rats (75 μL-LD50) was determined. The appropriate amount of material was aseptically added to a gelatin capsule (Number 1, Eli Lilly Company, Indianapolis, IN). This was referred to as a double-walled gelatin capsule. The capsules were prepared 1 week before implantation and stored under frozen conditions under quarantine until the day of surgery.

Implantation of Gelatin Capsule

The rats underwent a standardized procedure for laparotomy (intramuscular anesthesia with ketamine or rompum, shaving with animal clippers, betadine scrub, and alcohol scrub). A 2-cm incision was then made on the midline. A double-walled gelatin capsule was placed on the right side of the abdomen through the incision. In the control animals, no further treatment was given. In the animals treated with Oxiplex, the material was placed on the left side of the abdomen between the visceral and parietal peritoneum.

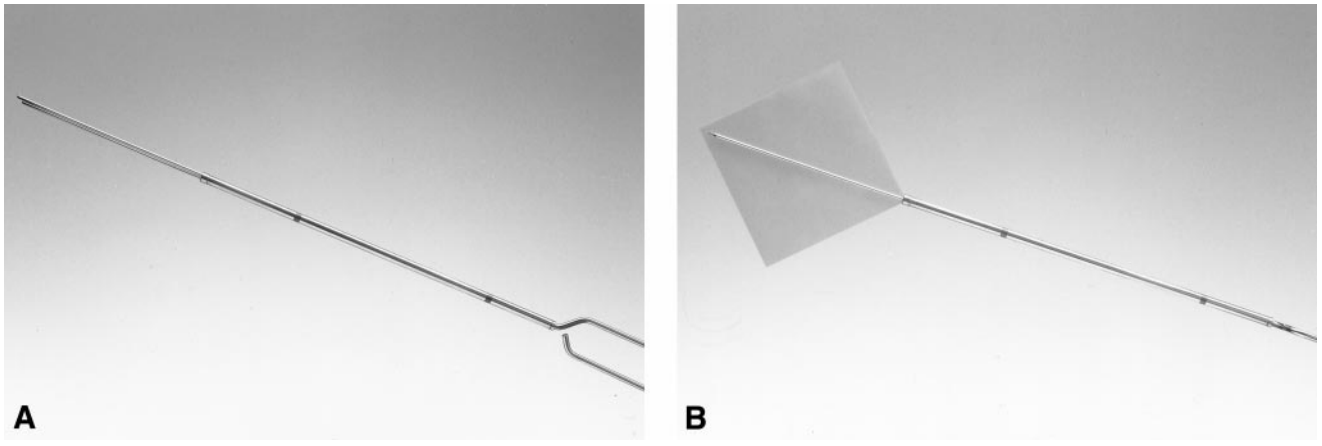
The abdominal wall and skin were then sutured closed with two layers of 4-0 Ethilon suture. After surgery, the rats received analgesic for 3 days and were observed twice daily for signs of morbidity or mortality.

Necropsy

The rats that died during the 11-day postoperative observation period were necropsied to confirm the presence of an acute bacterial infection. The rats that survived the initial acute infection were euthanized on day 11 after surgery. Four areas of the peritoneum were examined for abscess formation. These areas included the liver, abdominal wall, bowel, and omentum.

FIGURE 1

(**A**) The FilmSert instrument used to place Oxiplex barrier films via laparoscopy is shown. (**B**) The FilmSert instrument loaded with Oxiplex barrier film to be applied via laparoscopy is shown.



Rodgers. Oxiplex films and adhesions. Fertil Steril 2000.

The abscesses were scored at each site as follows:

0 No abscess present at the site
0.5 One very small abscess present at the site
1 Several small abscesses present at the site
2 Medium abscess present at the site
3 Large or several medium abscesses present at the site
4 One very large or several large abscesses present at the site

The scorings were conducted in a blinded fashion by two separate observers, and scores were recorded.

Oxiplex Barrier Handling at Laparoscopy

A pig was anesthetized with ketamine (10–20 mg/kg) and xylazine (2 mg/kg) via intramuscular injection along with sodium thiamylal (2% to effect) via intravenous infusion. When a sufficient level of anesthesia was obtained, an endotracheal tube was placed and attached to a veterinary anesthesia machine. Anesthesia was maintained for the remainder of the procedure by a semiclosed circuit inhalation of halothane. Assisted ventilation was accomplished with a ventilator.

A Verres needle or blunt trocar was inserted into the abdominal cavity at the umbilicus. The abdomen was insufflated with CO_2. Insufflation was maintained during the procedure. A 10-mm trocar was then inserted at the umbilicus. A 10-mm endoscope was inserted through this trocar and connected to a light projector and camera. Two 5-mm trocars were placed on either side of the midline.

After trocar placement, the Oxiplex film was placed in the FilmSert forceps (Fig. 1) and inserted through the 5-mm trocar. The FilmSert forceps consists of two tightly aligned metal tongs between which the film is inserted and rolled, holding the film in place during introduction into the trocar and released in the abdominal cavity. After release of the film from the FilmSert, the Oxiplex film was grasped with forceps and placed at the site of evaluation.

After the conclusion of the procedure, the pig was euthanized with an overdose of 100 mg/kg of phenobarbital.

Statistics

The area of adhesion formation or reformation and incidence of adhesion-free sidewalls were analyzed by Student's *t*-test. The mortality data and incidence of abscesses at the four evaluation sites were analyzed by χ^2 analysis. The overall abscess score (sum of abscess score at the 4 sites) was assessed by analysis of variance on the ranks. The comparisons were performed within a dose of bacterial inoculum.

Mechanical testing data were analyzed by computing the mean and standard deviation for hydrated film tensile strength, percentage elongation, and tissue adherence.

RESULTS

Mechanical Testing

In the hydrated state, Oxiplex film samples measured mean tensile strength of 17.8–175.2 g of force to failure. The two films with the highest degree of association complexation (AC-1, AC-5) had the highest hydrated tensile strength (Table 2).

Hydrated Oxiplex films displayed elongation to failure under tension in the range of 193%–483% when measured from an untensioned baseline. The highest elongation was

TABLE 2

Mechanical properties of Oxiplex film prototypes.

	Hydrated tensile strength (g)	Percentage elongation of hydrated film	Tissue adherence (g)
AC-1	175 ± 24	193 ± 12	150 ± 25
AC-2	29 ± 10	300 ± 50	118 ± 36
AC-3	18 ± 5	367 ± 29	141 ± 36
AC-4	23 ± 5	483 ± 29	117 ± 28
AC-5	53 ± 6	208 ± 14	153 ± 35

Rodgers. Oxiplex films and adhesions. Fertil Steril 2000.

measured in a film (AC-4) with a relatively high PEO content and a medium level of association complexation (Table 2).

Oxiplex film tissue adherence, measured in grams of force to release, ranged from a low mean of 117 g to a high mean of 153 g. All film types exhibited good tissue adherence (Table 2). In the mechanical tests, Interceed demonstrated no measureable tissue adherence (data not shown). Seprafilm was too fragile to be mounted in the test apparatus and could not be tested.

Biocompatability and Residence Time

In the initial study, the biocompatibility and residence time of the Oxiplex film prototypes were evaluated. Most of the materials were soaked with blood at the uterine horn and were associated with a large blood clot at all times. Overall, very little inflammation was noted in association with the placed materials. At all times, the inflammation was localized and transient (noted only at 1 time point and in 1 animal per time point).

Material AC-1 was present at all sites at 24 hours. At 48 hours, the material was present at three of five sites. At 72 hours, the material was present at all sites. On the sidewall and the bowel, the material could not be seen visually, but a slippery gel-like coating was observed at the site of placement. At 96 hours, an intact piece of film was observed at the horn and on the bowel of one rabbit. On the sidewall of both rabbits and bowel of the other rabbit, small fragments and slippery gel were present at the site of placement.

Material AC-2 was present at five of six sites at 24 and 48 hours. At 48 and 72 hours, the material at the bowel was fragmented. At 96 hours, fragmented and/or gel-like material was present at five of six sites.

Material AC-3 was present at the site of placement in four of six sites at 24 hours. At 48 hours, the material was present at five of six sites and was fragmented at the bowel. At 72 hours, the material was present only at the horns (in 1 rabbit the material was fragmented). At 96 hours, the material was present at three of six sites.

Material AC-4 was present at all sites at 24 hours. At 48, 72, and 96 hours, the material was observed at five of six sites (gel-like at 3–4 of these sites).

Material AC-5 was present at four of six sites at 24 hours. At 48 and 72 hours, the material was observed at three of six sites (fragmented at bowel). At 96 hours, fragments were observed at five of six sites. At the horn, no large blood clot was observed associated with the material at the horns.

Adhesion Formation

The data from this study can be found in Figure 2. As can be seen, adhesions were found in 50% of the control rabbits. However, adhesion formation was prevented in all animals in which the three types of Oxiplex barriers were placed. This study shows a significant reduction in adhesion formation by all three Oxiplex barriers tested in this model ($P = .030$ by Student's t-test).

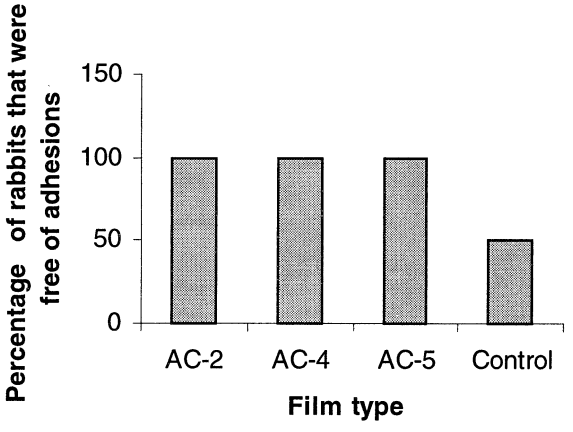
Adhesion Reformation

Because all barriers were 100% effective in the adhesion formation model, the efficacy of these Oxiplex barriers in the prevention of adhesion reformation was evaluated. All three types of Oxiplex films placed over the site of adhesiolysis were efficacious in the prevention of adhesion reformation (Fig. 3).

Furthermore, the effect of an Oxiplex film with blue dye added to aid in visualization during laparoscopy was evaluated in the animal model of adhesion reformation. As can be seen in Tables 3 and 4, the Oxiplex film AC-4 with dye added also was highly efficacious in the prevention of adhesion reformation.

FIGURE 2

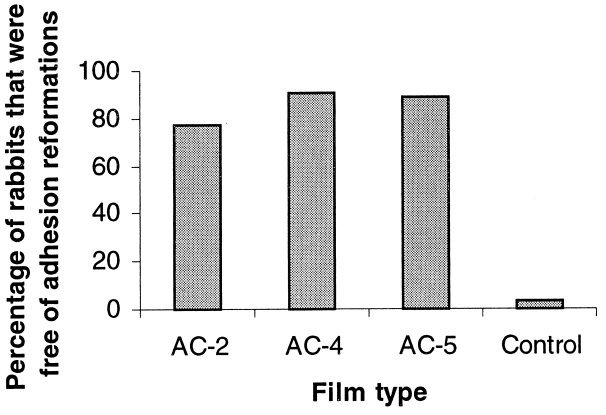
The ability of various Oxiplex prototypes to reduce adhesion formation in a rabbit adhesion formation model was evaluated. After abrasion of the bowel and cecum, a segment (4 × 3 cm) of parietal peritoneum was removed. The Oxiplex barrier films were placed over the site of sidewall injury. These data are from 10 animals per group.



Rodgers. Oxiplex films and adhesions. Fertil Steril 2000.

FIGURE 3

The ability of various Oxiplex prototypes to reduce adhesion formation in a rabbit adhesion reformation model was evaluated. After abrasion of the bowel and cecum, a segment (5 × 3 cm) of parietal peritoneum was removed. The bowel was then returned to the abdomen. One week later, the adhesions that were formed were lysed, and the Oxiplex barrier films were placed over the site of adhesiolysis. These data are from 9 to 11 animals per group.



Rodgers. Oxiplex films and adhesions. Fertil Steril 2000.

Effect of Oxiplex Film on Bacterial Peritonitis

Administration of Oxiplex film concurrent with the initiation of bacterial peritonitis did not affect the survival of the rats after injection or the formation of abscesses (Table 5) in the abdominal cavity on day 11.

Oxiplex Barrier Handling

The handling characteristics of Oxiplex barrier film were evaluated in a laparoscopic surgery porcine model. When used with the FilmSert device, the film was readily introduced into the abdominal cavity. After release into the abdomen, the film was easily placed onto tissue with good adherence. The film maintained adherence to tissue when a stream of crystalloid solution was directed over it and when bowel was placed in contact with the barrier. After placement, the film was removed to assess tissue for irritation or damage. None was evident.

TABLE 3

Effect of Oxiplex AC-4 with dye on adhesion reformation in a rabbit sidewall model.

Group	Initial area with adhesions	Necropsy	% Initial area with adhesions
Control	84.6 ± 5.5	80.0 ± 6.7	95.5 ± 7.3
Oxiplex AC-4 Blended	81.0 ± 6.2	7.0 ± 4.7	7.0 ± 4.7
P value	.668	.000	.000

Note: Values are means ± SEM of data from 10–11 rabbits per group.

Rodgers. Oxiplex films and adhesions. Fertil Steril 2000.

TABLE 4

Effect of Oxiplex AC-4 with dye on incidence of adhesion reformation in a rabbit sidewall model.

Group	No. of adhesion free rabbits/total no. of rabbits	Percentage of rabbits that were adhesion free	*P* value
Control	0/11	0	—
Oxiplex AC-4 Blended	8/10	80	0

Rodgers. Oxiplex films and adhesions. Fertil Steril 2000.

DISCUSSION

In this article, the development of a bioresorbable, site-specific adhesion prevention barrier is described. The Oxiplex Barrier film is tissue adherent, biocompatible, even in the presence of blood, and is easily introduced into the pelvic cavity in a laparoscopic procedure.

As a dry film, the Oxiplex Adhesion Barrier is strong, yet pliable, facilitating handling by the surgeon. It can be rolled with use of the FilmSert instrument and inserted into the abdomen through a 5.0-mm cannula. Testing the Oxiplex films with the loop tack tester indicated that the best combination of tensile strength, percentage elongation, and tissue adherence is achieved with film type AC-4, formulated at an intermediate level of association complexation with a relatively high weight percentage of PEO (Table 1). In the hydrated state, the Oxiplex films remain intact with good structural strength and integrity, becoming elastic and stretching as much as 500% before tearing.

The films with the highest tensile strength are those that have the highest level of association complexation. All films exhibited the strength necessary for good handling characteristics. Some compromise in strength, but not at the ex-

TABLE 5

Survival of rats after initiation of bacterial peritonitis with mixed flora.

Group	No. of rats that survived/total no. of rats	Percentage of rats that survived	Rank (mean ± SEM)
LD50-Control	9/15	60.0	35.3 ± 2.6
LD50-Oxiplex	9/15	60.0	33.4 ± 6.7
LD10-Control	13/15	86.7	14.4 ± 7.5
LD10-Oxiplex	13/15	86.7	14.2 ± 8.6

Rodgers. Oxiplex films and adhesions. Fertil Steril 2000.

pense of handling, is required to attain good wet film elongation. The best elongation was achieved with film AC-4. Elongation is desirable because of the need to have good film handling characteristics and to have the hydrated film conform to the interstices of tissues and organs.

In the biocompatibility study, film prototype AC-3 was eliminated because it was weakly complexed, rapidly turned to a gel, and was resorbed too rapidly to provide for optimal prevention of adhesion formation. Film prototype AC-1 was eliminated from further consideration because it cleared too slowly and lacked sufficient elongation. The remaining three film prototypes (AC-2, AC-4, and AC-5) were advanced to the efficacy studies.

Because all three-prototype films performed equally well in the adhesion formation model study, all films were included in the more challenging adhesion reformation model. Oxiplex film AC-4 was selected as the optimal Oxiplex film because of its superior efficacy in the adhesion reformation model, for its superior tissue adherence and handling properties, and for its clearance properties. The animals in this group were 91% adhesion free, compared to 77.7% adhesion free with film AC-2 and 88.8% free with film AC-5 (Fig. 3). Placement of the film at the site of tissue injury resulted in nearly complete prevention of adhesion formation and reformation (Tables 3 and 4). The models for adhesion formation and reformation involved significant tissue injury and bleeding.

The resorption and physical properties of the Oxiplex film are critically dependent on the pH of the casting solution from which the film is made (21). The pH affects the interpolymer complexation between the ether oxygens on the PEO and the negatively charged carboxy groups on the CMC. At a pH of approximately 3.0 (films AC-1, AC-5), the entangled polymer network is fully hydrogen bonded, resulting in low-swellable films that are relatively insoluble and resorb slowly from the body. In contrast, at pH of approximately 5.0 (film AC-3), a loosely associated network is obtained, resulting in highly swellable, readily soluble films. These films transform quickly into a gel, thus limiting the residence time of the site-specific barrier. At the intermediate pH of approximately 4.0 (film AC-4), an appropriate amount of hydration occurs, resulting in optimal film tissue adherence, residence time, strength, and flexibility.

The AC-4 film is bioadherent and does not need to be sutured in place. It sticks to tissue by means of a "wet adhesion" mechanism in which the hydrated polymer chains of the membrane are liberated to a freely moving state and are thus able to interact with "active" sites on the tissue to form cohesive bonds (22). Studies that were performed to evaluate the handling properties of the Oxiplex film indicated that it can be rapidly placed into the pelvic cavity onto injured tissue via a 5.0-mm laparoscopic port. Insertion is accomplished with use of the FilmSert forceps, an instrument engineered specifically for this purpose (Fig. 1). Once placed, the film adhered securely to tissue and did not damage contacting tissue. These properties will allow acceptable handling of this material in clinical situations, especially laparoscopic surgery.

Resorption properties of the Oxiplex film were qualitatively evaluated, and the results indicate that it remains at the site of application up to 4 days, slowly becoming a gel that is then gradually cleared from the body. Studies in the literature suggest that the high molecular weight components of Oxiplex film may be cleared by phagocytosis and removed via Kuppfer cells.

The PEO immobilized on surfaces or incorporated in biomaterials has shown reduced protein adsorption and reduced platelet, bacterial, and cellular adhesion. Barcellos et al. (23) impregnated PEO into the surface of polyethylene terephthalate (PET) films. When implanted intraperitoneally, the investigators found that the PEO-modified films stimulated less inflammation and less fibroblast overgrowth than did unmodified PET films. PEO's passivity was attributed to a possible steric stabilization or repulsive force toward proteins, platelets, and bacteria. Similar findings had been reported by Desai and Hubbell (24). Amiji (25) found that chitosan-PEO blend membranes were beneficial in reducing thrombogenicity in hemodialysis.

Because it is predicted that the Oxiplex material is cleared by phagocytosis and may, therefore, affect the initial defense against a bacterial inocula, the effect on the course of active bacterial peritonitis by this material was evaluated. These studies showed that the placement of the material in the abdominal cavity concurrent with inocula of mixed bacterial flora did not affect the course of infection or infection resolution as determined by survival and abscess formation.

In this report, the development of a biocompatible, resorbable film with good tissue adherence and the ability to be used via laparoscopy was described. A film with these desirable characteristics prevented adhesion formation and reformation in the absence of an effect on the course of bacterial peritonitis. These results, along with the lack of tissue response observed at necropsy, even in the surgical situation, suggest the chosen optimal Oxiplex film will be safe and effective in clinical use.

References

1. Strickler B, Blanco J, Fox HE. The gynecologic contribution to intestinal obstruction in females. J Am Coll Surg 1994;178:617–22.
2. Garrett HE, Mathews J. Reoperative median sternotomy. Ann Thorac Surg 1989;48:305–7.
3. Stout AL, Steege JF, Dodson WC, Hughes CL. Relationship of laparoscopic findings to self-report of pelvic pain. Am J Obstet Gynecol 1991;145:73–9.
4. Howard FM. The role of laparoscopy in chronic pelvic pain: promise and pitfalls. Obstet Gynecol Surv 1993;48:357–63.
5. DeCherney AH, Mezer HC. The nature of post-tubal pelvic adhesions determined by early and late laparoscopy. Fertil Steril 1984;41:643–6.
6. Trimbos-Kemper TCM, Trimbos JB, van Hall EV. Adhesion formation after tubal surgery: results of the eight-day laparoscopy in 188 patients. Fertil Steril 1985;43:396–400.
7. Peters AA, Trimbos-Kemper GC, Admiraal C, Trimbos JB, Hermans J. A randomized clinical trial on the benefit of adhesiolysis in patients

with intraperitoneal adhesion and chronic pelvic pain. Br J Obstet Gynaecol 1992;99:59–62.
8. diZerega GS, Rodgers KE. The Peritoneum. New York: Springer, 1992.
9. diZerega GS. Contemporary adhesion prevention. Fertil Steril 994;61: 219–35.
10. Wiseman DM. Polymers for the prevention of surgical adhesions. In: Domb AJ, ed. Polymeric site-specific pharmacotherapy. New York: John Wiley and Sons, 1994:370–400.
11. Amiji MM, Park K. Surface modification of polymeric biomaterials with PEO, a steric repulsion approach. Polymers of Biological and Bioclinical Significance. ACS Symposium Series 540, American Chemical Society, Washington DC, 1994 Ch 11:134–46.
12. Steinleitner A, Lopec G, Suarez M, Lambert H. An evaluation of Flowgel and an intraperitoneal barrier for the prevention of postsurgical adhesion reformation. Fertil Steril 1992;57:305–8.
13. Okyuyama N, Rodgers KE, Wang CY, Girgis W, Oz M, St. Amand K, et al. Prevention of retrosternal adhesion formation in a rabbit model using bioresorbable films of polyethylene glycol and polylactic acid. J Surg Res 1998;78:118–22.
14. Elbert DL, Hubbell JA. Reduction of fibrous adhesion formation by a copolymer possessing an affinity for anionic surfaces. J Biomed Mater Res 1998;42:55–65.
15. Cook SD, Prewett AB, Dalton JE, Whitecloud TS. Reduction in perineural scar formation after laminectomy with polyactive membrane sheets. Spine 1994;19:1815–25.
16. Nagelschmidt M, Minor T, Saad S. Polyethylene glycol 4000 attenuates adhesion formation in rats by suppression of peritoneal inflammation and collagen incorporation. Am J Surg 1998;176:76–80.
17. Rodgers KE, Girgis W, Campeau JD, diZerega GS. Reduction of adhesion formation by intraperitoneal administration of a recombinant hirudin analog. J Invest Surg 1996;9:388–91.
18. Rodgers KE, Girgis W, Campeau JD, diZerega GS. Reduction of adhesion formation by intraperitoneal administration of anti-inflammatory peptide 2. J Invest Surg 1997;10:31–6.
19. Rodgers KE, Girgis W, St Amand K, Campeau JD, diZerega GS. Reduction of adhesion formation in rabbits by intraperitoneal administration of lazaroid formulations. Hum Reprod 1998;13:2443–51.
20. Rodgers KE, Klykken P, Jacobs J. Immunotoxicology of medical devices. Fundam Appl Toxicol 1997;54:371–8.
21. Tsuchida E, Abe K. Interactions between macromolecules in solution and intermacromolecular complexes. Adv Poly Sci 1982;45:1–125.
22. Chen JL, Cyr GN. Compositions producing adhesion through hydration. In: Manly RS, ed. Adhesion in biological systems. New York: Academic Press, 1970;10:163–81.
23. Barcellos IO, Carobrez SG, Pires ATN, Alvarez-Silva M. In vivo and in vitro responses to polyethylene terephthalate-co-diethylene glycol terephthalate) and polyethylene oxide blends. Biomaterials 1998;19: 2075–82.
24. Desai NP, Hubbell JA. Tissue response to intraperitoneal implants of polyethylene oxide modified polyethylene terephthalate. Biomaterials 1992;13:505–10.
25. Amiji MM. Permeability and blood compatibility properties of chitosan-poly(ethylene oxide) blend membranes for haemodialysis. Biomaterials 1995;16:593–9.