

## Review article

## Polymers in the prevention of peritoneal adhesions

Yoon Yeo <sup>a</sup>, Daniel S. Kohane <sup>b,\*</sup><sup>a</sup> School of Pharmacy and Pharmaceutical Sciences, Weldon School of Biomedical Engineering, Purdue University, West Lafayette IN, USA<sup>b</sup> Laboratory for Biomaterials and Drug Delivery, Department of Anesthesiology, Division of Critical Care Medicine, Children's Hospital, Harvard Medical School, Boston, MA, USA

Received 2 November 2006; accepted in revised form 22 March 2007

Available online 20 July 2007

---

**Abstract**

Peritoneal adhesions are serious complications of surgery, and can result in pain, infertility, and potentially lethal bowel obstruction. Pharmacotherapy and barrier devices have reduced adhesion formation to varying degrees in preclinical studies or clinical trials; however, complete prevention of adhesions remains to be accomplished. We and others have hypothesized that the limitations of the two approaches could be overcome by combining their strengths in the context of controlled drug delivery. Here we review the role of polymeric systems in the prevention of peritoneal adhesions, with an emphasis on our recent work in developing and applying polymeric drug delivery systems such as nano- or microparticles, hydrogels, and hybrid systems for peritoneal use.

© 2007 Elsevier B.V. All rights reserved.

**Keywords:** Peritoneal adhesions; Adhesion barrier; Controlled drug delivery; Particulate drug delivery system; Hydrogels

---

**1. Introduction**

Peritoneal adhesions are bands of tissue that form between structures in the abdomen and pelvis following surgery, trauma, infection, and other harmful events. The incidence of adhesions following surgery is very high; some estimate an incidence as high as 80% [1]. The consequences can be severe. Compression of the viscera can cause severe pain or infertility, and obstruction of the bowel is potentially lethal. Quite apart from the toll in human suffering and mortality, the associated health care costs are in the billions of dollars in the United States alone [1]. Consequently, adhesion prevention has been an area of absorbing interest for many years among physicians, scientists, and corporations.

Research in this field has taken a number of forms. Possibly the single largest contribution to preventing adhesions came through the development and adoption of sound sur-

gical practices, not the least of which was the use of powder-free gloves. The two other principal areas of research were directed toward the pharmacotherapy of adhesion formation, based on the understanding at the time of the pathophysiology of the condition, and the creation of biocompatible barrier devices to keep the injured surfaces separated during healing. The pathophysiology and more-or-less experimental pharmacotherapy of peritoneal adhesion formation have been reviewed extensively, as have the pros and cons of the plethora of biomaterials and barrier devices that have been employed [1–6].

**2. Pharmacological approaches to preventing peritoneal adhesions**

A wide variety of compounds which target different pathophysiological contributions to adhesion formation have been used in attempts to prevent adhesions [7]. Representative drugs are classified by their therapeutic targets in Table 1.

Injury to the peritoneum produces an inflammatory exudate and fibrin matrix [1]. One major category of drugs attempted to mitigate the effects of inflammation in

---

\* Corresponding author. Laboratory for Biomaterials and Drug Delivery, Department of Anesthesiology, Division of Critical Care Medicine, Children's Hospital, Harvard Medical School, Boston, MA 02115, USA. Tel.: +1 617 355 7327; fax: +1 617 730 0453.

E-mail address: [daniel.kohane@childrens.harvard.edu](mailto:daniel.kohane@childrens.harvard.edu) (D.S. Kohane).

Table 1  
Selected pharmacological agents for adhesion prevention

Therapeutic targets	Drug category	Examples	References
Reduce inflammation	Steroidal anti-inflammatory drugs	Dexamethasone; progesterone; hydrocortisone; prednisone	[8–11]
	Non-steroidal anti-inflammatory drugs	Ibuprofen; flurbiprofen; indomethacin; tolmetin; nimesulide	[12–16]
	Inhibitors of proinflammatory cytokines	Antibodies to transforming growth factor (TGF)- $\beta$ 1	[17]
	Antihistamine	Diphenhydramine; promethazine	[18,64]
	Free radical scavengers	Melatonin; vitamin E; superoxide dismutase	[22,65,66]
Prevent fibrin clot formation	Anticoagulants	Heparin; ancrod	[29,42]
Stimulate fibrinolysis	Proteolytic agents	Tissue-type plasminogen activator; streptokinase; urokinase; pepsin; trypsin; Neurokinin 1 receptor antagonist	[30–39,67]
Inhibit fibroblast proliferation	Antiproliferative agents	Mitomycin C	[19,41]

promoting adhesion formation. A variety of steroidal [8–11] and non-steroidal anti-inflammatory compounds [12–16] have been tested, as well as agents that interfere with specific cytokines [17] or vascular permeability [18], chemotherapeutic agents [19] and immunosuppressive drugs [20]. In a related vein, many agents that scavenge the free radicals generated by inflammation have been tested [21,22].

A separate approach targeted the apparent imbalance between the deposition of fibrin and its destruction (fibrinolysis) in the injured peritoneum. In the course of normal tissue repair, that matrix would be removed by fibrinolysis in 2–3 days post-surgery [23]. However, in the injured state, that balance is shifted to favor the formation of fibrinous strands, which eventually are infiltrated by cells and become organized, creating the nascent adhesions [5,24–28]. Pharmacotherapy of this problem has employed anticoagulants, which prevent the formation of fibrin strands [29], and fibrinolytics, which destroy them [30–36]. Less specific proteolytic agents have also been used, to a similar end [37–39]. Beyond these, a bewildering variety of agents have been used. A much more limited number of authors have incorporated compounds within hydrogels [30,40–42], microspheres [9] and similar devices. A substantial number of these investigators have reported success in using drugs to prevent adhesions in animal models.

### 3. Barrier devices

Ideally, a barrier device should be easy to use via both laparoscopic and open procedures, provide unrestricted coverage of the affected peritoneum, and remain effective throughout healing [3]. Barrier devices have been tested or commercialized in various forms including polymer solutions [43–45], solid membranes [46], pre-formed [47–49] or *in situ* cross-linkable hydrogels [41,50,51]. Solutions, mostly consisting of viscous polysaccharides, are applied by a variety of methods (spraying, pouring, extrusion from a container) at the end of the surgical proce-

dures. They may then cross-link *in situ*. Membranes or pre-formed gels are placed directly on potential sites of adhesions, but then must be fixed to the underlying tissues (e.g. by suturing). That fixation can act as a focus of adhesion formation. For laparoscopic applications or situations in which damaged areas are hard to access or predict, *in situ* cross-linkable hydrogels are attractive modalities as they can be applied as free-flowing liquids and subsequently gel in a manner that fits the topography of the injured site. Among the various devices, five were approved or cleared for sale by the Food and Drug Administration of the United States of America (U.S. FDA) and are currently in the market: regenerated cellulose (Interceed®) and expanded polytetrafluoroethylene (Preclude®), both of which are largely used in gynecological operations; hyaluronic acid–carboxymethylcellulose (Seprafilm®) which is used for general and gynecological surgery in the U.S. and Europe; polylactide membrane (Surgicel®) and, most recently, 4% icodextrin solution (Adept®). Representative barrier devices that have come as far as eliciting corporate interest are summarized in Table 2; the total list of materials that have been tested experimentally is much longer.

Many devices are derived from polysaccharides such as hyaluronic acid, cellulose, dextran, or chitosan. Polysaccharides are particularly popular because they either are or resemble naturally occurring biological compounds, and they have been shown to be compatible with a variety of tissues in other biomedical applications. Synthetic polymers based on polyethylene glycol or polylactic acid have also been used. Advantages of synthetic polymers include the relative ease with which their properties can be controlled, and the lower cost compared to some (but not all) natural polysaccharides that have to undergo extraction and purification processes. In many respects the specific choice of materials is empirical, often driven in part by issues of intellectual property. At this time there is no clear set of rules relating the physicochemical properties

Table 2

Barrier devices marketed or under development

Product (company)	Chemical properties	Biological properties	Disadvantages	Development status in the U.S.	References
Interceed (Ethicon)	Oxidized regenerated cellulose membrane; hydrophilic	Absorbed within 3–10 days; effective in two prospective randomized trials involving 137 patients	Limited effectiveness in presence of blood and peritoneal fluids	Marketed	[68,69]
Seprafilm (Genzyme)	Hyaluronic acid–carboxymethylcellulose membrane; hydrophilic	Absorbed within 2 weeks	Requires careful handling at open operation; difficult to use laparoscopically	Marketed	[70–72]
Sepragel (Genzyme)	Hyaluronic acid–carboxymethylcellulose gel; hydrophilic	Bioresorbable		Indicated for nasal/sinus surgery as a space-occupying gel	[49]
Sepracoat (Genzyme)	Sodium hyaluronate solution; hydrophilic	Elimination half-life in the peritoneum: ~26 h [73]	Insufficient evidence of clinical effectiveness	Not FDA approved (Marketed in Europe)	[74]
Intergel (Lifecore)	Ferric hyaluronate gel; hydrophilic	Elimination half-life of 0.5% ferric hyaluronate in the peritoneum: ~51 h [73]	Withdrawn from clinical studies due to the high morbidity associated with postoperative peritonitis and anastomotic dehiscence	Clinical study discontinued	[73,75,76]
Incert (Anika)	Chemically cross-linked hyaluronic acid; hydrophilic	Bioresorbable	Difficult to use laparoscopically	Pilot human trials in UK from 2004	[77]
Adcon-P (Gliatech Inc.)	Gelatin/proteoglycan; hydrophilic	Bioresorbable	Note FDA recall of previous product Adcon-L	Animal tests only as of 2003	[78,79]
Adept (Innovata)	Icodextrin solution; hydrophilic	A median of 40% of the instilled icodextrin was absorbed from the peritoneal solution during a 12-h dwell. Peritoneal residence time of 4% icodextrin >4 days [80]	Leakage of fluid from the surgical site; abdominal distension and discomfort	FDA approved for use in gynecological laparoscopic procedures in August 2006 (Marketed in Europe)	[81,82]
Hyskon (Medisan pharmaceuticals)	Dextran 70; hydrophilic	Bioresorbable	Local and systemic side-effects due to osmotic and antigenic properties [83,84]; not sufficient evidence of clinical effectiveness	Indicated as hysteroscopy fluid	[83–85]
NOCC (Kytogenics)	N,O-carboxymethyl chitosan; hydrophilic	Bioresorbable	Pilot clinical trial did not demonstrate significant difference between treatment and control groups in anti-adhesion efficacy [86]	Phase III clinical trial (2002)	[86–88]
FloGel (Alliance Pharm Co.)	Poloxamer 407; hydrophilic	Thermosensitive; bioresorbable	Need refrigeration	Early clinical development	[89]
SprayGel (Confluent Surgical)	<i>In situ</i> cross-linkable polyethylene glycol gel; hydrophilic	Bioresorbable in 6 days; degrades into water-soluble polyethylene glycol molecules	Need a specialized applicator and air supply	Clinical investigation	[90,91]
Surgiwrap sheet (MAST Biosurgery)	Poly lactide membrane; hydrophobic	Bioresorbable in 24 weeks; degrades into water and CO <sub>2</sub>	Need fixation	Cleared for sale by the FDA in May 2005 (Marketed in Europe)	[92]
Repel (Life Medical Sciences)	Polyethylene glycol and polylactic acid block copolymer membrane	Bioresorbable	Need fixation; difficult to use laparoscopically	Clinical studies ongoing	[93,94]
FocalGel (Focal)	Polyethylene glycol and polylactic acid	Photo-cross-linkable; bioresorbable	Need light source		[95]
Preclude (W.L. Gore)	Expanded polytetrafluoroethylene membrane; hydrophobic	Non-biodegradable	Need strict sterility; need fixation; difficult to use laparoscopically; permanent presence of a foreign body in the peritoneum	Marketed	[96]

of biomaterials to their biological effects and/or responses in the peritoneum, except in the broadest terms.

Barrier approaches have succeeded to varying degrees in preventing adhesion formation in animal models and/or clinical studies, although none of them are consistently effective in all surgical scenarios [6]. Some of the principal limitations of the existing devices include a brief residence time at the site of administration [52], difficulty in handling or fixation to tissues, and incompatibility with laparoscopic procedures [41]. Another disadvantage often related to membrane or pre-formed hydrogel forms is a relative difficulty in determining the size and shape of the area to be covered *a priori*. Therefore, the surgeon must, to some extent, predict the possible location, size and shape of potential sites of adhesion formation [5].

#### 4. Polymers for controlled drug release in the peritoneal cavity

From the above, it will be apparent that dozens of investigators have cured adhesions in one animal model or another. So why is the clinical problem not solved? It is, unfortunately, not possible to know that which is not published, and so the reasons for which so many therapies that were successful in print did not enter clinical practice are not known. However, we have hypothesized that ultimately the failure of purely pharmacological therapies lay in the

rapid clearance of drugs from the peritoneum. Conversely, the shortcomings of barrier devices – aside from physical design issues, etc. – were that they did not directly address the basic biological problems. Controlled release technology could provide sustained drug levels, and if desirable, could also provide a barrier function.

In designing a drug delivery system for the peritoneum, at least two principal approaches were apparent (Fig. 1A and B). One would be micro- or nanoparticulate, as such particles would be easy to disperse throughout the peritoneum if necessary. The other would be hydrogel-based, since it could be made out of materials that have been used in the peritoneum without significant adverse effects, such as hyaluronic acid or cellulose. *In situ* cross-linkability would make these materials easy to apply, and would make it easy to cover discrete areas of injury at the discretion of the surgeon. Alternatively, drugs could be loaded in pre-formed films of such materials. A third approach, that we will describe below, would be to combine particulate and hydrogel-based systems (Fig. 1C).

One caveat in developing peritoneal drug delivery systems, which we have found to be a much greater issue in the peritoneum than in most other anatomic locations, is that drug delivery platforms must first be evaluated as to their intrinsic potential to elicit adhesions, as that could offset the positive therapeutic effects from the pharmacological agents being delivered.

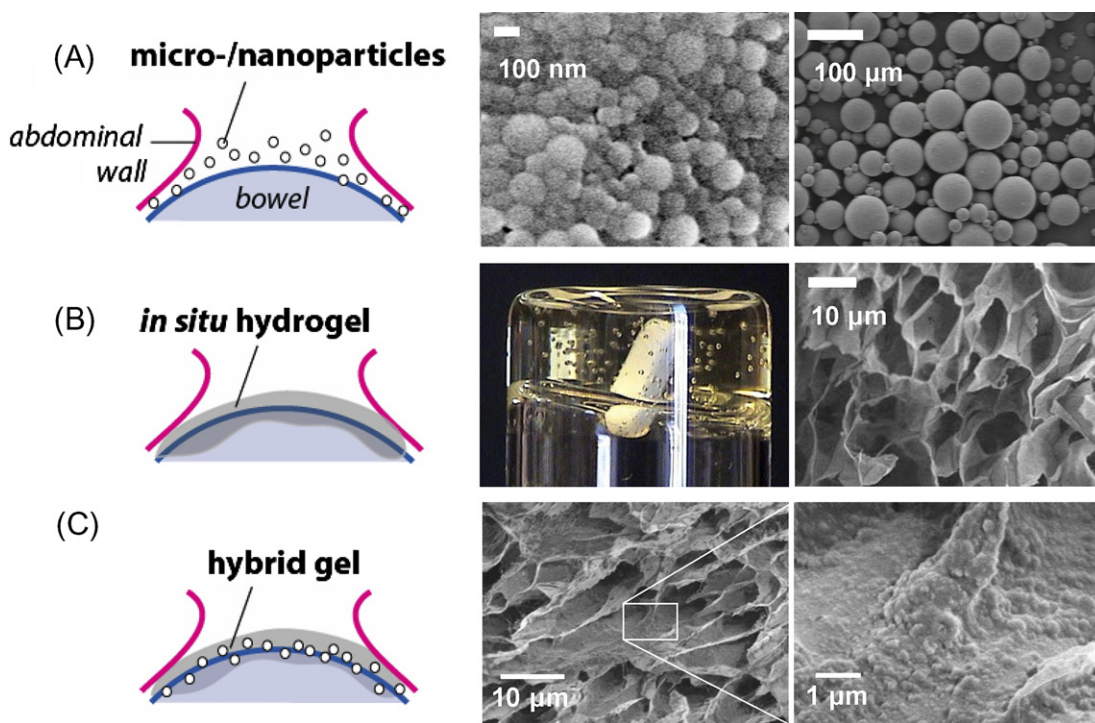


Fig. 1. Delivery systems for post-surgical adhesion prevention. Drugs can be delivered in a particulate system (A), a coating or barrier device such as a hydrogel (B), or a combination of a particulate system and a barrier device ('hybrid') (C). Scanning electron microscopic (SEM) images of nanoparticles (A, middle panel) and microparticles (A, right panel). Picture of chitosan gel cross-linked by UV irradiation (B, middle panel) and SEM of lyophilized cross-linked hyaluronan hydrogel (B, right panel). SEM images of lyophilized hybrid gel (C, middle panel) and magnified view of lyophilized hybrid gel (C, right panel). Note the roughness of the hybrid gel surface, indicating embedded nanoparticles.



#### 4.1. Poly ( $\alpha$ -hydroxy) acids

In designing a particulate drug delivery system, it seemed reasonable to begin with the poly ( $\alpha$ -hydroxy) acids, specifically the poly(lactic-co-glycolic) acids (PLGAs). These polymers had an excellent record of biocompatibility and could control the release of a wide range of drugs very effectively. They were known to degrade to lactic and glycolic acids, then to be metabolized to carbon dioxide and water. Although they caused an inflammatory response, it is transient. Even if polymeric residue and its attendant indolent chronic inflammatory response last for months, eventually tissue reaction in most tissues can resolve completely [53]. Finally, there was a large body of experience with them, and they were approved for use in humans by U.S. FDA.

The experience in the peritoneum was quite different. We injected 10 to 100 mg of particles composed of a high molecular weight (MW) poly(lactic-co-glycolic) acid into the murine peritoneum, covering a 1000-fold range of sizes from 250 nm to 250  $\mu$ m [54]. In the microparticle size range, all groups were capable of producing adhesions, although the incidence varied. Adhesions occurred most frequently on the anterior parietal peritoneum, which is the dependent portion of the peritoneum in the quadruped mouse. These findings raised the concern that in the bipedal human, even small quantities of particles would accumulate in the relatively confined lower abdomen and pelvis, causing adhesions. Nanoparticles of the same material caused almost no adhesions, but that was only because they left the peritoneum and migrated to the reticuloendothelial system, particularly the spleen. Microparticles made of lower MW PLGA caused less adhesions than those with higher MW PLGA. We speculated that the reason for the decrease in adhesions related to the more rapid degradation, with a resulting shorter tissue dwell time. Others have reduced peritoneal adhesions by using PLGA microspheres to release dexamethasone, a potent steroidal anti-inflammatory drug [9]. Interestingly, in that study, microspheres with a low loading of dexamethasone worsened adhesions, while microspheres with a high loading reduced adhesions. This suggests that the vehicle itself promoted adhesions formation, a tendency that was partly offset by the adhesion-preventing action of the drug. In furthering our work, we decided that it was best to select vehicles that had little intrinsic adhesion-forming tendency, and so decided not to use polymeric particles alone.

#### 4.2. Polysaccharide-based matrices

Others had previously used hydrogels in the peritoneum to release low [41] and high MW compounds [30], with varying degrees of effectiveness. In particular, we were interested in developing a system that would be easy to use, in addition to being biocompatible and providing adequate control of drug release.

##### 4.2.1. Chitosan

One initial approach was to use a UV-cross-linkable chitosan hydrogel [55], based on the view that chitosan was generally considered to be biocompatible [56,57]. We demonstrated *in vitro* that it had excellent properties in terms of cohesiveness and macromolecule release kinetics (data not shown). The formulation was also attractive in that it would be possible to apply *in situ*. *In vitro* cytotoxicity of cross-linked chitosan was minimal. Chitosan itself and the modified chitosan precursor to the cross-linked gel were minimally toxic to mesothelial cells. Chitosan itself, but not the modified chitosan, was quite toxic to macrophages at a relatively high concentration (2 mg/ml). The cytotoxicity of some cationic polymers (e.g. polyamines) in phagocytic cells has been documented [58]. The greater toxicity of chitosan compared to the modified chitosan in macrophages may be related to the degree of deacetylation of chitosan (i.e. the number of primary amines) [55]. However, this did not seem worrisome since the cross-linked chitosan would contain no unmodified chitosan. The *in vivo* experience was quite different. Rabbits treated with the UV-cross-linked formulation developed exuberant adhesions, even in the absence of prior peritoneal injury. The causative factor was not the UV irradiation but the material itself. Both modified and unmodified chitosan could induce adhesions. In investigating the cause of the adhesions, we found that the modified chitosan and the cross-linked gel increased the expression of proinflammatory cytokines or chemokines such as TNF- $\alpha$  and MIP-2 (a murine IL-8 analogue). Whether this explained the formation of adhesions is unclear, given that unmodified chitosan caused adhesions but did not increase cytokine release *in vitro* – although the latter could be due to its effect on cell viability.

##### 4.2.2. Cross-linked hyaluronan matrices

We therefore turned to materials with an established track record of biocompatibility in the peritoneum [59]. We chose hyaluronan (HA) as the base material for this reason; it had also been used extensively for intraperitoneal applications. We employed a previously described synthetic method [60] to produce a cross-linkable HA hydrogel. In brief, we produced one HA derivatized to have a hydrazide moiety, and another HA derivatized to have an aldehyde. These cross-linked upon mixing, forming a slowly hydrolyzable hydrazone compound. This method had the advantage of allowing *in situ* cross-linking without the use of initiators, cross-linking chemicals, or extra equipment for cross-linking such as a light source. We had prior experience with this approach for drug delivery [61]. One early concern was whether the derivatized HAs, particularly the aldehyde derivative, would be reactive with biological components and cause toxic side-effects. It was reassuring to find that the cross-linked HA gels (HAX) showed minimal or no cytotoxicity in mesothelial cells *in vitro*, and showed excellent intraperitoneal biocompatibility in a murine screening test. This formulation was very effective in

preventing adhesions in a rabbit cecal abrasion-sidewall defect model [59] (Fig. 2). Interestingly, the cross-linked matrix itself caused a modest increase in the expression of tissue-type plasminogen activator, raising the possibility that its effectiveness in preventing adhesions might be due to an intrinsic biological effect in addition to the barrier effect.

#### 4.2.3. The hybrid system

Although the cross-linked HA performed very well, there was still room for improvement. As stated above, one hypothesis underlying our work was that barrier devices would work better if supplemented by controlled release technology. We had found that the HA-based hydrogels controlled the rate of release of proteins and other drugs only slightly [61]. While that slight difference might yet prove to be important, the release kinetics could be improved by incorporating a more hydrophobic polymeric delivery system such as PLGA micro- or nanoparticles into the hydrogel system. Thus we would be able to marry the relative strengths and weaknesses of hydrogels (excellent peritoneal biocompatibility, poor drug release kinetics) and polymeric particles (poor peritoneal biocompatibility, excellent control of release kinetics) [62]. Polymeric particles can, depending on the formulation, release

drugs for days to weeks. The exact duration will depend on the characteristics of the drug (hydrophilicity, hydrophobicity, charge, molecular weight, etc.), the polymer (type, molecular weight, etc.), and the specifics of the encapsulation method. Drug release for days to weeks has been achieved with both small molecules and macromolecules. The hybrid system is prepared simply by mixing the hydrogel precursors and nanoparticle suspensions then co-injecting them. The nanoparticles (Fig. 1A) were distributed homogeneously throughout the hydrogel matrix (Fig. 1C). We chose nanoparticles over microparticles for our initial work in this direction because they would leave the peritoneum without causing adhesions if they broke free of the gel, whereas microparticles might stay and cause adhesions [54]. These hybrid gels showed minimal cytotoxicity in mesothelial cells. Furthermore, they showed excellent biocompatibility in the murine peritoneum, with minimal adhesion formation even though nanoparticles entrapped within the hydrogel could not leave the peritoneal cavity. In a rabbit model of adhesion formation, the hybrid gels were at least as effective (and statistically significantly better) than HAX in preventing adhesions, even in the absence of any active payload (released drug). It remains to be seen whether this formulation is even more effective when loaded with active agents.

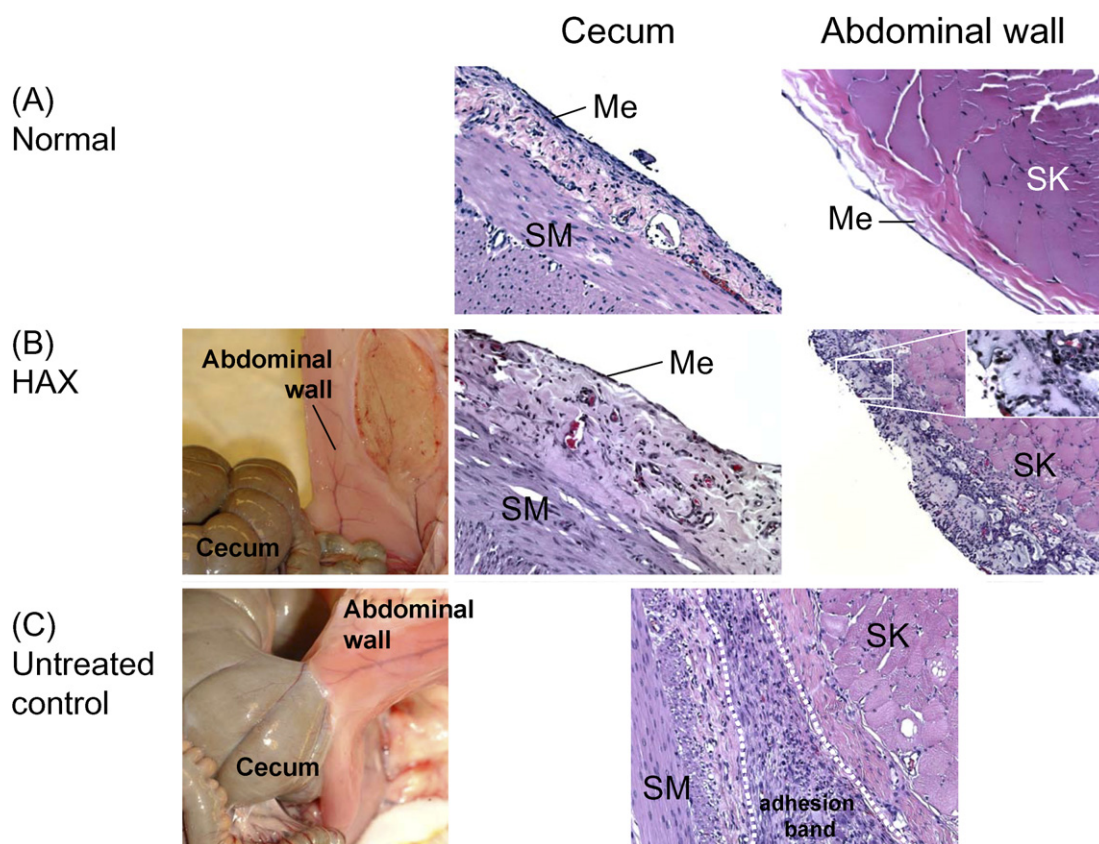


Fig. 2. Adhesion formation [59]. (A) Normal cecum (200 $\times$ ) and abdominal wall surface (400 $\times$ ). (B) Healed cecum surface (200 $\times$ ) and abdominal wall (100 $\times$ ) treated with cross-linked hyaluronan gel (HAX) one week post-surgery. Note the mesothelial layer on the treated cecum comparable to that of normal cecum, and bluish HAX residue on the treated abdominal wall. (Inset in right panel shows higher magnification of gel in area denoted by rectangle.) (C) An adhesion (200 $\times$ ) found in an injured, untreated animal. SM, smooth muscle; Me, mesothelial layer; SK, skeletal muscle of abdominal wall.

#### 4.2.4. Cellulose derivatives

HA-based systems have two major drawbacks: they are costly, and they could be degraded too rapidly *in vivo* by endogenous hyaluronidase. We have hypothesized that hybridization of HA with other biocompatible polysaccharides that are not degraded enzymatically in humans could slow degradation while preserving HA's excellent biocompatibility. We synthesized aldehyde derivatives of cellulose derivatives (hydroxypropylmethylcellulose, carboxymethylcellulose, and methylcellulose), and cross-linked them to HA–dihydrazide [63]. The aldehyde–cellulose derivatives were somewhat more cytotoxic *in vitro* to mesothelial cells and peritoneal macrophages than HA–aldehyde, but showed no toxicity or adhesion formation in a murine intraperitoneal screening test. It is possible that the lack of toxicity *in vivo* reflects the rapidity of *in situ* cross-linking, which may leave little free gel precursor. All three HA–cellulose derivative gels were effective in reducing adhesions. HA–methylcellulose was slightly more effective than the others, perhaps because it degraded more slowly.

#### 4.2.5. Effect of polymeric drug delivery systems in the peritoneum

To date, there are relatively few published reports where drugs were delivered via vehicles that clearly controlled the rate of drug release, and even fewer where that control was demonstrated. However, there are studies that suggest that controlled release technology will be effective in the peritoneum. As mentioned above, polymeric microspheres containing a high loading of steroids mitigated adhesion formation [9]. Some success has also been achieved with a number of anticoagulant and fibrinolytic compounds delivered via hydrogels [29,30,42]. In the latter cases, the hydrogels themselves had independent effectiveness as barrier devices, but less than the hydrogel and drug together.

## 5. Conclusions

Despite the number of animal studies and the human experience involving biomaterials in the peritoneum, and even though we have some sense of what does work, it is difficult to point to specific material properties as explaining why some materials are biocompatible and effective in preventing adhesions and others are not. Although most materials that prevent adhesions are hydrophilic, it does not follow that hydrophobic materials cannot be used (e.g. Teflon or polylactide). Perhaps, as with some other biological properties, there is a U-shaped relation between the propensity toward adhesions and hydrophobicity. Similarly, it is difficult to make general statements about what physical properties are best. The hydrogels used in our studies have significantly lower shear moduli than that of Teflon, but both hydrogels and Teflon can be used as adhesion barriers. Quite apart from the direct physicochemical effects of the materials on their environment, little is known about the tissue responses elicited by them and the potential indirect mechanisms of injuring or healing surrounding

tissues. The design of ideal materials is complicated by the fact that our ignorance of the important parameters governing anti-adhesion devices extends to such basic questions as: how long should they persist in the peritoneum? How much of the peritoneal cavity should be covered? If controlled release of drugs is to be used, what drug or drug combination is best? Until these and other issues are resolved, a sub-optimal empiricism is going to drive research and practice.

Many materials have been tested within the peritoneum. While there can be little doubt that some materials control the rate of drug release more effectively than others, what little has been published on drug delivery in the peritoneum suggests that most materials that have been used as barriers have the potential to be used as drug delivery systems. As we have seen, some have been tried [29,30,42], although so far none have into translated clinical practice. Whether the converse is true, i.e. whether the more hydrophobic polymers used for conventional drug delivery are suitable as intraperitoneal barriers, remains to be proven.

Since the initial efforts to prevent post-surgical adhesions were made more than a century ago [6], a number of anti-adhesion devices have been developed and used, but their efficacy and scope of use still remain limited. Adhesion formation continues to be a challenge in peritoneal surgery. However, given the accumulated knowledge from research and clinical experience, and with recent advances in tissue engineering and drug delivery technology, there is reason to be optimistic that complete prevention of post-surgical adhesions is an achievable goal.

## Acknowledgements

Financial support was provided by the DuPont/MIT Alliance (to D.S.K.) and GM073626 (to D.S.K.).

## References

- [1] G.S. diZerega, Peritoneum, peritoneal healing, and adhesion formation, in: G.S. diZerega (Ed.), *Peritoneal Surgery*, Springer, New York, 2000, pp. 3–37.
- [2] H.G. Saravelos, T.C. Li, Physical barriers in adhesion prevention, *J. Reprod. Med.* 41 (1996) 42–51.
- [3] D. Al-Musawi, J.N. Thompson, Adhesion prevention: state of art, *Gynaecol. Endosc.* 10 (2001) 123–130.
- [4] L.S. Peck, E.P. Goldberg, Polymer solutions and films as tissue-protective and barrier adjuvants, in: G.S. diZerega (Ed.), *Peritoneal Surgery*, Springer, New York, 2000, pp. 499–520.
- [5] G.S. diZerega, Use of adhesion prevention barriers in pelvic reconstructive and gynecologic surgery, in: G.S. diZerega (Ed.), *Peritoneal Surgery*, Springer, New York, 2000, pp. 379–399.
- [6] D.M. Wiseman, Adhesion prevention: past the future, in: G.S. diZerega (Ed.), *Peritoneal Surgery*, Springer, New York, 2000, pp. 401–417.
- [7] K.E. Rodgers, G.S. diZerega, Developing pharmacologic agents for adhesion prevention, in: G.S. diZerega (Ed.), *Peritoneal Surgery*, Springer, New York, 2000, pp. 441–457.
- [8] T. Kucukozkan, B. Ersoy, D. Uygur, C. Gundogdu, Prevention of adhesions by sodium chromoglycate, dexamethasone, saline and aprotinin after pelvic surgery, *ANZ J. Surg.* 74 (2004) 1111–1115.

- [9] M. Hockel, S. Ott, U. Siemann, T. Kissel, Prevention of peritoneal adhesions in the rat with sustained intraperitoneal dexamethasone delivered by a novel therapeutic system, *Ann. Chir. Gynaecol.* 76 (1987) 306–313.
- [10] C.C. Buckenmaier, A.E. Pusateri, R.A. Harris, S.P. Hetz, Comparison of antiadhesive treatments using an objective rat model, *Am. Surg.* 65 (1999) 274–282.
- [11] J. Maurer, L. Bonaventura, The effect of aqueous progesterone on operative adhesion formation, *Fertil. Steril.* 39 (1983) 485–489.
- [12] E.K. LeGrand, K.E. Rodgers, W. Girgis, K. Struck, J.D. Campeau, G.S. diZerega, T.C. Kiorpes, Efficacy of tolmetin sodium for adhesion prevention in rabbit and rat models, *J. Surg. Res.* 56 (1994) 67–71.
- [13] T. Guvenal, A. Cetin, H. Ozdemir, O. Yanar, T. Kaya, Prevention of postoperative adhesion formation in rat uterine horn model by nimesulide: a selective COX-2 inhibitor, *Hum. Reprod.* 16 (2001) 1732–1735.
- [14] K. Nishimura, R. Nakamura, G. diZerega, Ibuprofen inhibition of postsurgical adhesion formation: a time and dose response biochemical evaluation in rabbits, *J. Surg. Res.* 36 (1984) 115–124.
- [15] G. Holtz, Failure of a nonsteroidal anti-inflammatory agent (ibuprofen) to inhibit peritoneal adhesion reformation after lysis, *Fertil. Steril.* 37 (1982) 582–583.
- [16] F. De Leon, A. Toledo, J. Sanfilippo, M. Yussman, The prevention of adhesion formation by nonsteroidal antiinflammatory drugs: an animal study comparing ibuprofen and indomethacin, *Fertil. Steril.* 41 (1984) 639–642.
- [17] P. Lucas, D. Warejcka, H. Young, B. Lee, Formation of abdominal adhesions is inhibited by antibodies to transforming growth factor-beta1, *J. Surg. Res.* 65 (1996) 135–138.
- [18] F. Avsar, M. Sahin, F. Aksoy, A. Avsar, M. Akoz, S. Hengirmen, S. Bilici, Effects of diphenhydramine HCl and methylprednisolone in the prevention of abdominal adhesions, *Am. J. Surg.* 181 (2001) 512–515.
- [19] A. Cubukcu, A. Alponat, N. Gonullu, S. Ozkan, C. Ercin, An experimental study evaluating the effect of Mitomycin C on the prevention of postoperative intraabdominal adhesions, *J. Surg. Res.* 96 (2001) 163–166.
- [20] M. Leondires, P. Stubblefield, H. Tarraza, M. Jones, A pilot study of cyclosporine for the prevention of postsurgical adhesion formation in rats, *Am. J. Obstet. Gynecol.* 172 (1995) 1537–1539.
- [21] M.M. Binda, C.R. Molinas, P.R. Koninckx, Reactive oxygen species and adhesion formation: clinical implications in adhesion prevention, *Hum. Reprod.* 18 (2003) 2503–2507.
- [22] B. Ozelik, I.S. Serin, M. Basbug, S. Uludag, F. Narin, M. Tayyar, Effect of melatonin in the prevention of post-operative adhesion formation in a rat uterine horn adhesion model, *Hum. Reprod.* 18 (2003) 1703–1706.
- [23] J. Thompson, Peritoneal fibrinolysis and adhesion formation, in: G.S. diZerega (Ed.), *Peritoneal Surgery*, Springer, New York, 2000, pp. 133–142.
- [24] K.E. Rodgers, Peritoneal tissue repair cells, in: G.S. diZerega (Ed.), *Peritoneal Surgery*, Springer, New York, 2000.
- [25] L. Holmdahl, M.-L. Ivarsson, The role of cytokines, coagulation, and fibrinolysis in peritoneal tissue repair, *Eur. J. Surg.* 165 (1999) 1012–1019.
- [26] A. Raftery, Effect of peritoneal trauma on peritoneal fibrinolytic activity and intraperitoneal adhesion formation. An experimental study in the rat, *Eur. Surg. Res.* 13 (1981) 397–401.
- [27] L. Holmdahl, E. Eriksson, M. Al-Jabreen, B. Risberg, Fibrinolysis in human peritoneum during operation, *Surgery* 119 (1996) 701–705.
- [28] L. Holmdahl, M. Falkenberg, M.L. Ivarsson, B. Risberg, Plasminogen activators and inhibitors in peritoneal tissue, *APMIS* 105 (1997) 25–30.
- [29] R.L. Reid, K. Lie, J.E. Spence, T. Tulandi, A. Yuzpe, Clinical evaluation of the efficacy of heparin-saturated interceed for prevention of adhesion reformation in the pelvic sidewall of the human, in: M.P. Diamond, G.S. diZerega, C.B. Linsky, R.L. Reid (Eds.), *Gynecologic Surgery and Adhesion Prevention*, Wiley-Liss, Inc., New York, 1993, pp. 261–264.
- [30] J.L. Hill-West, R.C. Dunn, J.A. Hubbell, Local release of fibrinolytic agents for adhesion prevention, *J. Surg. Res.* 59 (1995) 759–763.
- [31] K.J. Doody, R.C. Dunn, V.C. Buttram, Recombinant tissue plasminogen activator reduces adhesion formation in a rabbit uterine horn model, *Fertil. Steril.* 51 (1989) 509–512.
- [32] R.C. Dunn, M. Mohler, Effect of varying days of tissue plasminogen activator therapy on the prevention of postsurgical adhesions in a rabbit model, *J. Surg. Res.* 54 (1993) 242–245.
- [33] H. Orita, M. Fukasawa, W. Girgis, G.S. diZerega, Inhibition of postsurgical adhesions in a standardized rabbit model: intraperitoneal treatment with tissue plasminogen activator, *Int. J. Fertil.* 36 (1991) 172–177.
- [34] D. Menzies, H. Ellis, The role of plasminogen activator in adhesion prevention, *Surg. Gynecol. Obstet.* 172 (1991) 362–366.
- [35] R.C. Dunn, M. Mohler, Formation of adhesions after surgical injury and their prevention with tissue-type plasminogen activator in a rabbit pelvic model, *Infertility* 13 (1990) 103–111.
- [36] L.E. Holmdahl, M. Al-Jabreen, B. Risberg, Role of fibrinolysis in the formation of postoperative adhesions, *Wound Repair Regen.* 2 (1994) 171–176.
- [37] A. Ochsner, E. Garside, Peritoneal adhesions: their prevention by the use of digestive ferments, *Surg. Gynecol. Obstet.* 54 (1932) 338–361.
- [38] K. Yardumian, D. Cooper, Pepsin in the prevention of abdominal adhesions, *Arch. Surg.* 29 (1934) 264–276.
- [39] R. Walton, Trypsin preparations suitable for the prevention of adhesions, *J. Pharmacol. Exp. Ther.* 40 (1930) 403–411.
- [40] J.K. Jackson, K.C. Skinner, L. Burgess, T. Sun, W.L. Hunter, H.M. Burt, Paclitaxel-loaded crosslinked hyaluronic acid films for the prevention of postsurgical adhesions, *Pharm. Res.* 19 (2002) 411–417.
- [41] Y. Liu, H. Li, X.Z. Shu, S.D. Gray, G.D. Prestwich, Crosslinked hyaluronan hydrogels containing mitomycin C reduce postoperative abdominal adhesions, *Fertil. Steril.* 83 (2005) 1275–1283.
- [42] S.M. Chowdhury, J.A. Hubbell, Adhesion prevention with anicrod release via a tissue-adherent hydrogel, *J. Surg. Res.* 61 (1996) 58–64.
- [43] J.W. Burns, K. Skinner, J. Colt, A. Sheidlin, R. Bronson, Y. Yaacobi, E.P. Goldberg, Prevention of tissue injury and postsurgical adhesions by precoating tissues with hyaluronic acid solutions, *J. Surg. Res.* 59 (1995) 644–652.
- [44] M.M.P.J. Reijnen, E.M. Skrabut, V.A. Postma, J.W. Burns, H.V. Goor, Polyanionic polysaccharides reduce intro-abdominal adhesion and abscess formation in a rat peritonitis model, *J. Surg. Res.* 101 (2001) 248–253.
- [45] K.E. Rodgers, J. Campeau, D.B. Johns, G.S. diZerega, W. Girgis, Reproduction of adhesion formation with hyaluronic acid after peritoneal surgery in rabbits, *Fertil. Steril.* 67 (1997) 553–558.
- [46] D. Pressato, E. Bigon, M. Dona, A. Pavesio, D. Renier, L. Bonafini, P.A.D. Iaco, M. Lise, Hyaluronan derivatives in postsurgical adhesion prevention, in: J.F. Kennedy, G.O. Phillips, P.A. Williams (Eds.), *Hyaluronan: Proceedings of an International Meeting*, September 2000, North East Wales Institute, UK, Woodhead Publishing, Cambridge, England, 2002, pp. 491–499.
- [47] P.A.D. Laco, M. Stefanetti, D. Pressato, S. Piana, M. Dona, A. Pavesio, L. Bovicelli, A novel hyaluronan-based gel in laparoscopic adhesion prevention: preclinical evaluation in an animal model, *Fertil. Steril.* 69 (1998) 318–323.
- [48] J.W. Burns, K. Skinner, M.J. Colt, L. Burgess, R. Rose, M.P. Diamond, A hyaluronate based gel for the prevention of postsurgical adhesions: evaluation in two animal species, *Fertil. Steril.* 56 (1996) 814–821.
- [49] R.E. Leach, J.W. Burns, E.J. Dawe, M.D. SmithBarbour, M.P. Diamond, Reduction of postsurgical adhesion formation in the rabbit uterine horn model with use of hyaluronate/carboxymethylcellulose gel, *Fertil. Steril.* 69 (1998) 415–418.
- [50] S.L. Bennett, D.A. Melanson, D.F. Torchiana, D.M. Wiseman, A.S. Sawhney, Next-generation hydrogel films as tissue sealants and adhesion barriers, *J. Card. Surg.* 18 (2003) 494–499.



- [51] A.S. Sawhney, C.P. Pathak, J.J.V. Rensburg, R.C. Dunn, J.A. Hubbell, Optimization of photopolymerized bioerodible hydrogel properties for adhesion prevention, *J. Biomed. Mater. Res.* 28 (1994) 831–838.
- [52] D. Grainger, W. Meyer, A. Decherney, M. Diamond, The use of hyaluronic-acid polymers to reduce postoperative adhesions, *J. Gynecol. Surg.* 7 (1991) 97–101.
- [53] D.S. Kohane, M. Lipp, R.C. Kinney, D.C. Anthony, D.N. Louis, N. Lotan, R. Langer, Biocompatibility of lipid–protein–sugar particles containing bupivacaine in the epineurium, *J. Biomed. Mater. Res.* 59 (2002) 450–459.
- [54] D.S. Kohane, J.Y. Tse, Y. Yeo, R. Padera, M. Shubina, R. Langer, Biodegradable polymeric microspheres and nanospheres for drug delivery in the peritoneum, *J. Biomed. Mater. Res.* 77A (2006) 351–361.
- [55] Y. Yeo, J.A. Burdick, C.B. Highley, R. Marini, R. Langer, D.S. Kohane, Peritoneal application of chitosan and UV-cross-linkable chitosan, *J. Biomed. Mater. Res.* 78A (2006) 668–675.
- [56] M. Risbud, M. Bhonde, R. Bhonde, Chitosan-polyvinyl pyrrolidone hydrogel does not activate macrophages: potentials for transplantation applications, *Cell Transplant.* 10 (2001) 195–202.
- [57] M. Prasitsilp, R. Jenwithisuk, K. Kongsuwan, N. Damrongchai, P. Watts, Cellular responses to chitosan in vitro: the importance of deacetylation, *J. Mater. Sci. Mater. Med.* 11 (2000) 773–778.
- [58] W.N. Haining, D.G. Anderson, S.R. Little, M.S.V. Berwelt-Baildon, A.A. Cardoso, P. Alves, K. Kosmatopoulos, L.M. Nadler, R. Langer, D.S. Kohane, pH-triggered microparticles for peptide vaccination, *J. Immunol.* 173 (2004) 2578–2585.
- [59] Y. Yeo, C.B. Highley, E. Bellas, T. Ito, R. Marini, R. Langer, D.S. Kohane, In situ cross-linkable hyaluronic acid hydrogels prevent post-operative abdominal adhesions in a rabbit model, *Biomaterials* 27 (2006) 4698–4705.
- [60] P. Bulpitt, D. Aeschlimann, New strategy for chemical modification of hyaluronic acid: preparation of functionalized derivatives and their use in the formation of novel biocompatible hydrogels, *J. Biomed. Mater. Res.* 47 (1999) 152–169.
- [61] X. Jia, G. Colombo, R. Padera, R. Langer, D.S. Kohane, Prolongation of sciatic nerve blockade by in situ cross-linked hyaluronic acid, *Biomaterials* 25 (2004) 4797–4804.
- [62] Y. Yeo, T. Ito, E. Bellas, C.B. Highley, R. Marini, D.S. Kohane, In situ cross-linkable hyaluronic hydrogels containing polymeric nanoparticles for preventing post-surgical adhesions, *Ann. Surg.* 245 (2007) 819–824.
- [63] T. Ito, Y. Yeo, C.B. Highley, E. Bellas, C. Benitez, D.S. Kohane, The prevention of peritoneal adhesions by in-situ cross-linking hydrogels of hyaluronic acid and cellulose derivatives, *Biomaterials* 28 (2007) 975–983.
- [64] R.L. Replogle, R. Johnson, R.E. Gross, Prevention of postoperative intestinal adhesions with combined promethazine and dexamethasone therapy: experimental and clinical studies, *Ann. Surg.* 163 (1966) 580–588.
- [65] F.d.l. Portilla, I. Ynfante, D. Bejarano, J. Conde, A. Fernández, J.M. Ortega, G. Carranza, Prevention of peritoneal adhesions by intraperitoneal administration of vitamin E: an experimental study in rats, *Dis. Colon Rectum* 47 (2005) 2157–2161.
- [66] D. Portz, T. Elkins, R. White, J. Warren, S. Adedevoh, J. Randolph, Oxygen free radicals and pelvic adhesions formation: I. Blocking oxygen free radical toxicity to prevent adhesion formation in an endometriosis model, *Int. J. Fertil.* 36 (1991) 39–42.
- [67] K.L. Reed, A.B. Fruin, A.C. Gower, A.F. Stucchi, S.E. Leeman, J.M. Becker, A neurokinin 1 receptor antagonist decreases postoperative peritoneal adhesion formation and increases peritoneal fibrinolytic activity, *Proc. Natl. Acad. Sci. USA* 101 (2004) 9115–9120.
- [68] K. Sekiba, Use of interceed(TC7) absorbable adhesion barrier to reduce postoperative adhesion reformation in infertility and endometriosis surgery. The Obstetrics and Gynecology Adhesion Prevention Committee, *Obstet. Gynecol.* 79 (1992) 518–522.
- [69] Prevention of postsurgical adhesions by INTERCEED(TC7), an absorbable adhesion barrier: a prospective randomized multicenter clinical study, INTERCEED(TC7) Adhesion Barrier Study Group, *Fertil. Steril.* 51 (1989) 933–938.
- [70] J. Becker, M. Dayton, V. Fazio, D. Beck, S. Stryker, S. Wexner, B. Wolff, P. Roberts, L. Smith, S. Sweeney, M. Moore, Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: a prospective, randomized, double-blind multicenter study, *J. Am. Coll. Surg.* 183 (1996) 297–306.
- [71] M. Diamond, Reduction of adhesions after uterine myomectomy by Seprafilm membrane (HAL-F): a blinded, prospective, randomized, multicenter clinical study. Seprafilm Adhesion Study Group, *Fertil. Steril.* 66 (1996) 904–910.
- [72] W. Vrijland, L. Tseng, H. Eijkman, W. Hop, J. Jakimowicz, P. Leguit, L. Stassen, D. Swank, R. Haverlag, H. Bonjer, H. Jeekel, Fewer intraperitoneal adhesions with use of hyaluronic acid–carboxymethylcellulose membrane: a randomized clinical trial, *Ann. Surg.* 235 (2002) 193–199.
- [73] M. Thornton, D. Johns, J. Campeau, F. Hoehler, G. DiZerega, Clinical evaluation of 0.5% ferric hyaluronate adhesion prevention gel for the reduction of adhesions following peritoneal cavity surgery: open-label pilot study, *Hum. Reprod.* 13 (1998) 1480–1485.
- [74] M. Diamond, Reduction of de novo postsurgical adhesions by intraoperative precoating with Sepracoat (HAL-C) solution: a prospective, randomized, blinded, placebo-controlled multicenter study. The Sepracoat Adhesion Study Group, *Fertil. Steril.* 69 (1998) 1067–1074.
- [75] D.M. Wiseman, Possible Intergel reaction syndrome (pIRS), *Ann. Surg.* 244 (2006) 630–632.
- [76] C.-L. Tang, D.G. Jayne, F. Seow-Choen, Y.-Y. Ng, K.-W. Eu, N. Mustapha, A randomized controlled trial of 0.5% ferric hyaluronate gel (Intergel) in the prevention of adhesions following abdominal surgery, *Ann. Surg.* 243 (2006) 449–455.
- [77] A.F. Haney, E. Doty, A barrier composed of chemically cross-linked hyaluronic acid (Incert) reduces postoperative adhesion formation, *Fertil. Steril.* 70 (1998) 145–151.
- [78] M. Oncel, F.H. Remzi, A.J. Senagore, J.T. Connor, V.W. Fazio, Liquid antiadhesive product (Adcon-p) prevents post-operative adhesions within the intra-abdominal organs in a rat model, *Int. J. Colorectal Dis.* 18 (2003) 514–517.
- [79] M. Oncel, F.H. Remzi, A.J. Senagore, J.T. Connor, V.W. Fazio, Comparison of a novel liquid (Adcon-P®) and a sodium hyaluronate and carboxymethylcellulose membrane (Seprafilm™) in postsurgical adhesion formation in a murine model, *Dis. Colon Rectum* 46 (2003) 187–191.
- [80] K. Hosie, J.A. Gilbert, D. Kerr, C.B. Brown, E.M. Peers, Fluid dynamics in man of an intraperitoneal drug delivery solution: 4% icodextrin, *Drug Deliv.* 8 (2001) 9–12.
- [81] G.S. di Zerega, S.J.S. Vercro, P. Young, M. Kettel, W. Kobak, D. Martin, J. Sanfilippo, E.M. Peers, A. Scrimgeour, C.B. Brown, A randomized, controlled pilot study of the safety and efficacy of 4% icodextrin solution in the reduction of adhesions following laparoscopic gynaecological surgery, *Hum. Reprod.* 17 (2002) 1031–1038.
- [82] D. Menzies, M.H. Pascual, M.K. Walz, J.J. Duron, F. Tonelli, A. Crowe, A. Knight, Use of icodextrin 4% solution in the prevention of adhesion formation following general surgery: from the multicentre ARIEL Registry, *Ann. R. Coll. Surg. Engl.* 88 (2006) 375–382.
- [83] C.K. Sites, B.A. Jensen, J.L. Glock, J.A. Blackman, G.J. Badger, J.V. Johnson, J.R. Brumsted, Transvaginal ultrasonographic assessment of Hyskon or lactated Ringer's solution instillation after laparoscopy: randomized, controlled study, *J. Ultrasound Med.* 16 (1997) 195–199.
- [84] J.F. Gauwerky, D. Heinrich, F. Kubli, Complications of intraperitoneal dextran application for prevention of adhesions, *Biol. Res. Pregnancy Perinatol.* 7 (1986) 93–97.
- [85] B. Larsson, O. Lalos, L. Marsk, S.E. Tronstad, M. Bygdeman, S. Pehrson, I. Joelsson, Effect of intraperitoneal instillation of 32% dextran 70 on postoperative adhesion formation after tubal surgery, *Acta Obstet. Gynecol. Scand.* 64 (1985) 437–441.

- [86] M.P. Diamond, A. Luciano, A. Johns, R. Dunn, P. Young, E. Bieber, Reduction of postoperative adhesions by N,O-carboxymethylchitosan: a pilot study, *Fertil. Steril.* 80 (2003) 631–636.
- [87] J. Zhou, C. Elson, T.D.G. Lee, Reduction in postoperative adhesion formation and re-formation after an abdominal operation with the use of N,O-carboxymethyl chitosan, *Surgery* 135 (2004) 307–312.
- [88] R. Kennedy, D.J. Costain, V.C. McAlister, T.D. Lee, Prevention of experimental postoperative peritoneal adhesions by N,O-carboxymethyl chitosan, *Surgery* 120 (1996) 866–870.
- [89] R. Leach, R. Henry, Reduction of postoperative adhesions in the rat uterine horn model with poloxamer 407, *Am. J. Obstet. Gynecol.* 162 (1990) 1317–1319.
- [90] R. Ferland, D. Mulani, P.K. Campbell, Evaluation of a sprayable polyethylene glycol adhesion barrier in a porcine efficacy model, *Hum. Reprod.* 16 (2001) 2718–2723.
- [91] R. Dunn, M.D. Lyman, P.G. Edelman, P.K. Campbell, Evaluation of the SprayGel(TM) adhesion barrier in the rat cecum abrasion and rabbit uterine horn adhesion models, *Fertil. Steril.* 75 (2001) 411.
- [92] H. Lamoutte, R. Chatterji, SurgiWrap(R) Mast bioresorbable sheet use for the prevention of soft tissue attachment; a two year experience, *Biomaterials/Bioresorbable Technology, Mast Biosurgery*, 2005, [http://www.mastbio.com/pdf/mast\\_wp\\_LIT\\_303\\_A.pdf](http://www.mastbio.com/pdf/mast_wp_LIT_303_A.pdf).
- [93] N. Okuyama, K. Rodgers, C. Wang, W. Girgis, M. Oz, K. St. Amand, E. Pines, A. DeCherney, E. Rose, D. Cohn, G. diZerega, Prevention of retrosternal adhesion formation in a rabbit model using bioresorbable films of polyethylene glycol and polylactic acid, *J. Surg. Res.* 78 (1998) 118–122.
- [94] K. Rodgers, D. Cohn, A. Hotovely, E. Pine, M. Diamond, G. diZerega, Evaluation of polyethylene glycol/polylactic acid films in the prevention of adhesions in the rabbit adhesion formation and reformation sidewall models, *Fertil. Steril.* 69 (1998) 403–408.
- [95] J.L. Hill-West, S.M. Chowdhury, A.S. Sawhney, C.P. Pathak, R.C. Dunn, J.A. Hubbell, Prevention of post operative adhesions in the rat by in situ photopolymerization of bioresorbable hydrogel barriers, *Obstet. Gynecol.* 83 (1994) 59–64.
- [96] An expanded polytetrafluoroethylene barrier (Gore-Tex Surgical Membrane) reduces post-myomectomy adhesion formation, The Myomectomy Adhesion Multicenter Study Group, *Fertil. Steril.* 63 (1995) 491–493.